ESC GUIDELINES DESK REFERENCE

ESC Committee for Practice Guidelines

To improve the quality of clinical practice and patient care in Europe

CARDIOVASCULAR MEDICINE

COMPENDIUM OF ABRIDGED ESC GUIDELINES 2011

EUROPEAN SOCIETY OF CARDIOLOGY®

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Compendium of Abridged ESC Guidelines 2011

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*An updated version of these pocket guidelines on Non-ST-segment Elevation Acute Coronary Syndromes is now available. The full text of these ESC Guidelines is available on www.escardio.org/guidelines.

*An updated version of these pocket guidelines on Cardiovascular Disease during Pregnancy is now available. The full text of these ESC Guidelines is available on www.escardio.org/guidelines.

Preface

In recent years there has been an increasing tendency towards optimization of medical practice through the application of Evidence-Based Medicine. One of the consequences of this approach is an enormous increase in the number of clinical trials thus creating an environment in which keeping abreast of clinical advances, even within a single medical subspecialty, is an extremely demanding task. In this setting, clinicians have become increasingly reliant on clinical practice guidelines to help them decide on the diagnostic procedures and treatment options, which are most appropriate for the management of their patients.

The ESC is committed to reduce the burden of cardiovascular diseases in Europe and therefore considers that the development of Clinical Practice Guidelines is a strategic step to achieve this goal.

The production of ESC Clinical Practice Guidelines is coordinated by the Committee for Practice Guidelines (CPG). This committee is the body responsible for the nomination of the Task Forces, which are appointed to produce the different guidelines. The Committee selects the Task Force Members ensuring the recruitment of leading scientific experts in each field and the participation of representatives from ESC Working Groups, Associations and Councils.

The approval process for the documents includes the validation of each scientific statement by expert reviewers and ESC Board Members. In this respect, the recommendations included in the Guidelines reflect the official position of the European Society of Cardiology. ESC Guidelines are produced with the goal of covering all major topics defined in the ESC Core Curriculum.

All ESC Guidelines documents are posted on the ESC web site (http://www.escardio.org/guidelines). The original English parent document version of these guidelines are published in the European Heart Journal and are linked to an accredited Continuous Medical Education programme that allows physicians to earn CME credits online to show that they have achieved the learning objectives set for each published guidelines.

The ESC Guidelines are endorsed, translated and adopted by most of the ESC National Societies. The implementation of the Guidelines is ensured through an active partnership between the ESC and its Working Groups, Associations, Councils and National Societies.

The ESC Pocket Guidelines are a concise summary of the fundamental recommendations made in the parent guidelines documents. These pocket guidelines are highly appreciated by medical professionals and have become an important guidelines dissemination tool. In view of the utility of these documents and the strong demand for a compilation of all of the available pocket guidelines, the Committee for Practice Guidelines commissioned the production of this ESC Guidelines Compendium.

It is our hope that this 2011 edition of the Compendium of abridged ESC Guidelines will be of help to clinicians to follow the most recent recommendations in the practice of our rapidly evolving field of medicine.

Alec Vahanian, MD, FRCP
Chairperson of the ESC Committee for Practice Guidelines (CPG)
2006–2008 and 2008–2010

Jeroen Bax, MD, PhD
Chairperson of the ESC Committee for Practice Guidelines (CPG)
2010–2012

Foreword

I am pleased to announce that the European Society of Cardiology has updated the ESC Guidelines Compendium, a compilation of all current ESC Pocket Guidelines titles.

ESC Pocket Guidelines have been published as individual booklets for a few years, but as the list of titles grew, it became apparent that a compilation of all of the titles would be very useful to healthcare professionals as a resource to assist in clinical decision making at the point of care.

By definition, pocket guidelines can provide only the most important recommendations extracted from extensive and scientifically well grounded full text guidelines. In some cases, the clinician may still need to go back to these source documents in order to make a proper diagnostic or therapeutic decision.

I have no doubt that the 2011 edition, which includes the 2010 ESC Guidelines in a condensed version, will be for all of us a useful tool in our daily practice.

Michel Komajda
President of the European Society of Cardiology
(2010–2012)

Guidelines Overview

Guidelines aim to present management recommendations based on all of the relevant evidence on a particular subject. This is done in order to help physicians select the best possible management strategies for the individual patient suffering from a specific condition, taking into account the impact on outcome and also the risk:benefit ratio of a particular diagnostic or therapeutic procedure. Numerous studies have demonstrated that patient outcomes improve when guideline recommendations, based on the rigorous assessment of evidence based research, are applied in clinical practice.

A great number of Guidelines have been issued in recent years by the European Society of Cardiology (ESC) and also by other organizations or related societies. The profusion of documents can put at stake the authority and credibility of guidelines, particularly if discrepancies appear between different documents on the same issue, as this can lead to confusion in the mind of physicians. In order to avoid these pitfalls, the ESC and other organizations have issued recommendations for formulating and issuing Guidelines. The ESC recommendations for guidelines production can be found on the ESC website [http://www.escardio.org/guidelines]. It is beyond the scope of this preamble to recall all but the basic rules.

In brief, the ESC appoints experts in the field to carry out a comprehensive review of the literature, with a view to making a critical evaluation of the use of diagnostic and therapeutic procedures, and assessing the risk:benefit ratio of the therapies recommended for management and/or prevention of a given condition. Estimates of expected health outcomes are included, where data exists. The strength of evidence for or against particular procedures or treatments is weighed, according to predefined scales for grading recommendations and levels of evidence, as outlined below.

The Task Force members of the writing panels, as well as the document reviewers, are asked to provide disclosure statements of all relationships they may have which might be perceived as real or potential conflicts of interest. These disclosure forms are kept on file at the European Heart House, headquarters of the ESC, and can be made available by written request to the ESC President. Any changes in conflicts of interest that arise during the writing period must be notified to the ESC.

Guidelines and recommendations are presented in formats that are easy to interpret. They should help physicians to make clinical decisions in their daily routine practice, by describing the range of generally acceptable approaches to diagnosis and treatment. However, the ultimate judgement regarding the care of an individual patient must be made by the physician in charge of his/her care.

The ESC Committee for Practice Guidelines (CPG) supervises and coordinates the preparation of new Guidelines produced by Task Forces. The Committee is also responsible for the endorsement of these Guidelines by its National Society Member countries.

Once the document has been finalized and approved by all the experts involved in the Task Force, it is submitted to outside specialists for review. In some cases, the document can be presented to a panel of key opinion leaders in Europe, specialists in the relevant condition at hand, for discussion and critical review. If necessary, the document is revised once more and finally approved by the CPG and selected members of the Board of the ESC and subsequently published.

After publication, dissemination of the message is of paramount importance. Publication of executive summaries, the production of pocket-sized and PDA-downloadable versions of the recommendations are

helpful. However, surveys have shown that the intended end-users are often not aware of the existence of guidelines or simply don't put them into practice. Implementation programmes are thus necessary and form an important component of the dissemination of knowledge. Meetings are organized by the ESC, and directed towards its member National Societies and key opinion leaders in Europe. Implementation meetings can also be undertaken at a national level, once the guidelines have been endorsed by the ESC member societies and translated into the local language as required.

The task of writing Guidelines documentation not only involves the integration of the most recent research, but also the creation of educational tools and implementation programmes forth recommendations. The cyclical nature of clinical research, writing of guidelines and implementing them into clinical practice can then only be completed if surveys and registries are organized to verify that actual clinical practice is in keeping with what is recommended by the guidelines. Such surveys and registries also make it possible to check the impact of strict implementation of the guidelines on patient outcome.

Table 1: Classes of Recommendations

Classes of Recommendations	Definition	Suggested wording to use
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.	Is recommended/is indicated
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.	
Class IIa	*Weight of evidence/opinion is in favour of usefulness/efficacy.*	*Should be considered*
Class IIb	*Usefulness/efficacy is less well established by evidence/opinion.*	*May be considered*
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.	Is not recommended

Table 2: Level of Evidence

Level of Evidence A	Data derived from multiple randomized clinical trials or meta-analyses.
Level of Evidence B	Data derived from a single randomized clinical trial or large non-randomized studies.
Level of Evidence C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries.

Section I:
Prevention of Cardiovascular Disease

1. Cardiovascular Disease Prevention in Clinical Practice

Chapter 1
Cardiovascular Disease Prevention in Clinical Practice* 2007

Fourth Joint European Societies' Task Force on Cardiovascular Disease Prevention in Clinical Practice

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The European Heart Health Charter and the Guidelines on Cardiovascular Disease Prevention

- The European Heart Health Charter advocates the development and implementation of comprehensive health strategies, measures and policies at European, national, regional and local level that promote cardiovascular health and prevent cardiovascular disease.

- These guidelines aim to assist physicians and other health professionals to fulfil their role in this endeavour, particularly with regard to achieving effective preventive measures in day-to-day clinical practice.

* Adapted from the ESC Guidelines on the Fourth Joint European Societies' Task Force on cardiovascular disease prevention in clinical practice. Executive Summary (European Heart Journal 2007) and full text European Journal of Cardiovascular Prevention and Rehabilitation 2007;4(Suppl. 2).

- They reflect the consensus arising from a multi-disciplinary partnership between the major European professional bodies represented.

Summary Flow Chart

When do I assess total cardiovascular risk?

If the patient asks for it

If, during a consultation:
- The person is a middle aged smoker
- One or more risk factors such as a raised blood cholesterol is known about
- There is a family history of premature CVD or of major risk factors such as hyperlipidaemia
- Symptoms suggestive of CVD

Assessing risk: What do I do?

Use SCORE unless known CVD, diabetes, very high single risk factors

- History: Previous diseases, family history of premature CVD, smoking, exercise and dietary habits
- Examination: BP, HR, heart and lung auscultation, foot pulses, height, weight (Body Mass Index), waist circumference.
- Lab tests: Urine for glucose and protein. Cholesterol and fasting lipids if practicable (LDL and HDL cholesterol, triglycerides) glucose, creatinine
- ECG and exercise ECG if angina suspected
- ECG and consider echocardiogram in young or severely hypertensive persons
- Consider High sensitivity CRP, Lipoprotein (a), fibrinogen, homocysteine, specialist referral if premature CVD or family history of same

Established CVD | **DM2 or DM1 with microalbuminuria** | **Markedly elevated single risk factor** | **SCORE risk ≥ 5%** | **SCORE risk < 5%**

Lifestyle Recommendations

No Smoking

Weight reduction if BMI ≥ 25 kg/m^2 and especially if BMI ≥ 30 kg/m^2

No further weight gain if WC 80-88 cm in women and WC 94-102 cm in men. Advice weight loss if WC ≥ 88 cm in women and ≥ 102 cm in men

30 minutes of moderately vigorous exercise on most days of the week; exercise and weight reduction can prevent diabetes

Healthy Diet
- Wide variety of foods
- Energy intake adjusted to avoid overweight
- Encourage: fruits, vegetables, wholegrain cereals and bread, fish (especially oily), lean meat, low-fat dairy products
- Replace saturated fat with monounsaturated and polyunsaturated fats (vegetable and marine)
- Hypertensive subjects should reduce salt intake

Drug Treatment

More likely as SCORE risk exceeds 5% and especially as it approaches 10% or if there is end organ damage. In the elderly, drug treatment is generally not recommended below 10% risk unless a specific indication exists

- Consider BP lowering drugs when BP ≥ 140/90
- Consider statins when TC ≥ 5 or LDL ≥ 3
- In patients with CVD: Aspirin. Statins for most
- In patients with diabetes: consider glucose lowering drugs

- Lifestyle advice to maintain low risk status
- Re-assess total risk at regular intervals

Why develop a preventive strategy in clinical practice?

- Cardiovascular disease (CVD) is the major cause of premature death in Europe. It is an important cause of disability and contributes substantially to the escalating costs of health care.
- The underlying atherosclerosis develops insidiously over many years and is usually advanced by the time that symptoms occur.
- Death from CVD often occurs suddenly and before medical care is available, so that many therapeutic interventions are either inapplicable or palliative.
- The mass occurrence of CVD relates strongly to lifestyles and to modifiable physiological and biochemical factors.
- Risk factor modifications have been shown to reduce CVD mortality and morbidity, particularly in high risk subjects.

What are the objectives of these guidelines?

- To help health professionals to reduce the occurrence of coronary heart disease, stroke and peripheral artery disease and their complications.
- To achieve this by providing practical and accessible advice with regard to the rationale for prevention, priorities, objectives, risk assessment and management through lifestyle measures and selective drug usage.
- To encourage the development of national guidance through the formation of multi-disciplinary national guideline and implementation partnerships that are compatible with local, political, social, economic and medical circumstances.

People who stay healthy tend to have certain characteristics:

0 3 5 140 5 3 0	
0	No tobacco
3	Walk 3 km daily, or 30 mins any moderate activity
5	Portions of fruit and vegetables a day
140	Blood pressure less than 140 systolic
5	Total blood cholesterol < 5 mmol/L
3	LDL cholesterol < 3 mmol/L
0	Avoidance of overweight and diabetes

What are the priorities for CVD prevention in clinical practice?

Patients with established atherosclerotic CVD.

Asymptomatic individuals who are at increased risk of CVD because of:

Multiple risk factors resulting in raised total CVD risk (**≥ 5% 10 year risk of CVD death**)

Diabetes type 2 & type 1 with microalbuminuria

Markedly increased single risk factors especially if associated with end organ damage

Close relatives of subjects with premature atherosclerotic CVD or of those at particularly high risk.

What are the objectives of CVD prevention?

1. **To assist those at low risk of CVD to maintain this state lifelong, & to help those at higher increased total CVD risk to reduce it.**

2. **To achieve the characteristics of people who tend to stay healthy:**
   - No smoking
   - Healthy food choices
   - Physical activity: 30 min. of moderate activity a day
   - BMI < 25 Kg/m^2 and avoidance of central obesity
   - BP < 140/90 mmHg
   - Total cholesterol < 5 mmol/L (~ 190 mg/dL)
   - LDL cholesterol < 3 mmol/L (~ 115 mg/dL)
   - Blood glucose < 6 mmo/L (~ 110 mg/dL)

3. **To achieve more rigorous risk factor control in high risk subjects, especially those with established CVD or diabetes:**
   - Blood pressure under 130/80 mmHg if feasible
   - Total cholesterol < 4.5 mmol/L (~ 175 mg/dL) with an option of < 4 mmol/L (~ 155 mg/dL) if feasible
   - LDL- cholesterol < 2.5 mmol/L (~ 100 mg/dL) with an option of < 2 mmol/L (~ 80 mg/dL) if feasible
   - Fasting blood glucose < 6 mmol/L (~ 110 mg/dL) and HbA_{1c} < 6.5% if feasible

4. **To consider cardioprotective drug therapy in these high risk subjects especially those with established atherosclerotic CVD.**

When do I assess cardiovascular risk?

- If the patient asks for it.
- If, during a consultation:
  - The person is a middle aged smoker
  - There is obesity, especially abdominal
  - One or more risk factors such as blood pressure, lipids or glucose is raised
  - There is a family history of premature CVD or of other risk factors
  - There are symptoms suggestive of CVD. If confirmed, risk factors should be assessed but use of the SCORE chart is not necessary as the person is already at high risk

Why do the Guidelines stress the assessment of total CVD risk?

- Multiple risk factors usually contribute to the atherosclerosis that causes CVD.
- These risk factors interact, sometimes multiplicatively.
- Thus the aim should be to reduce total risk; if a target cannot be reached with one risk factor, total risk can still be reduced by trying harder with others.

How do I assess CVD risk quickly and easily?

- Those with:
  - known CVD
  - type 2 diabetes or type 1 diabetes with microalbuminuria,
  - very high levels of individual risk factors

are automatically at INCREASED CARDIOVASCULAR RISK and need management to all risk factors.

- For all other people, the SCORE risk charts can be used to estimate total risk: this is critically important because many people have mildly raised levels of several risk factors that, in combination, can result in unexpectedly high levels of total cardiovascular risk.

Assessing cardiovascular risk: What are the components?

- History: Previous CVD or related diseases, family history of premature CVD, smoking, exercise and dietary habits, social and educational status.
- Examination: BP, heart rate, heart and lung auscultation, foot pulses, height, weight (Body Mass Index), waist circumference. Fundoscopy in severe hypertension.
- Lab test: Urine for glucose and protein, microalbuminuria in diabetics. Cholesterol and if practicable, fasting lipids (LDL and HDL cholesterol, triglycerides) glucose, creatinine.
- ECG and exercise ECG if angina suspected.
- ECG and consider echocardiogram in hypertensive persons.
- Premature or aggressive CVD, especially with a family history of premature CVD: Consider High sensitivity CRP, Lipoprotein (a), fibrinogen, homocysteine and, if feasible, specialist referral.

How do I use the SCORE charts to assess CVD risk in asymptomatic persons?

1. Use the low risk chart in Belgium*, France, Greece*, Italy, Luxembourg, Spain*, Switzerland and Portugal; use the high risk chart in other countries of Europe.
   *Updated, re-calibrated charts are now available for Belgium, Germany, Greece, The Netherlands, Spain, Sweden and Poland.

2. Find the cell nearest to the person's age, cholesterol and BP values, bearing in mind that risk will be higher as the person approaches the next age, cholesterol or BP category.

3. Check the qualifiers.

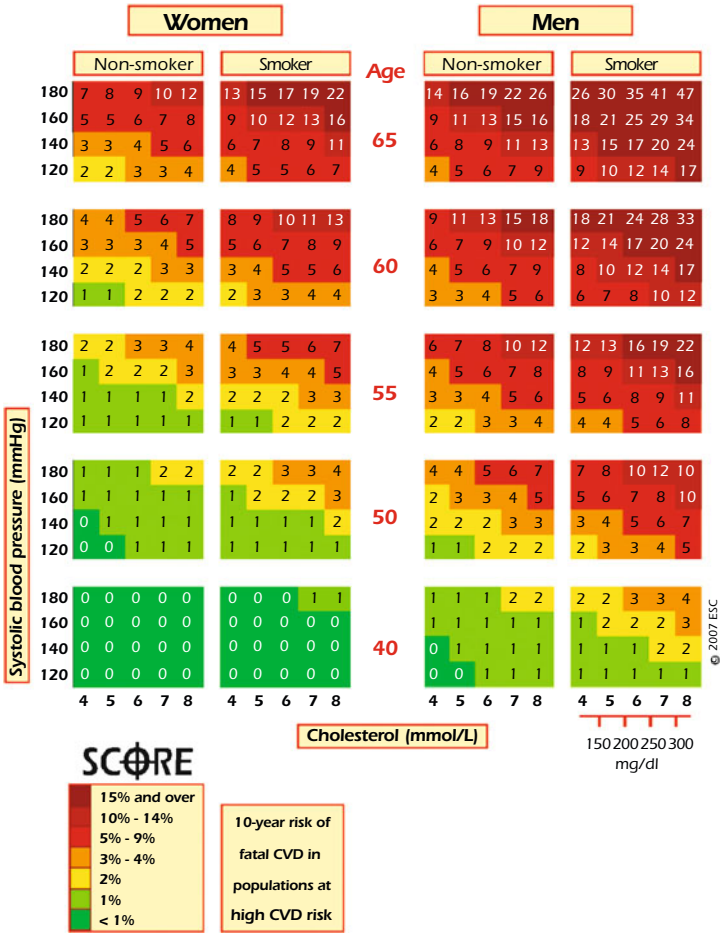
4. Establish the total 10 year risk for fatal CVD.

Note that a low total cardiovascular risk in a young person may conceal a high relative risk; this may be explained to the person by using the relative risk chart. As the person ages, a high relative risk will translate into a high total risk. More intensive lifestyle advice will be needed in such persons.

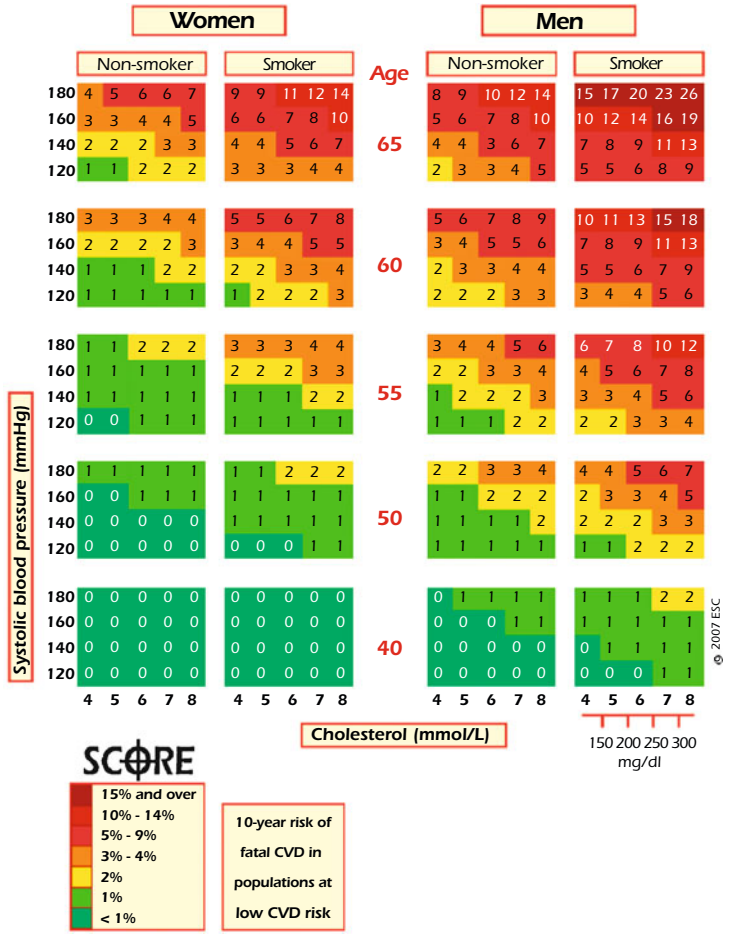
Risk estimation using SCORE: Qualifiers

- The charts should be used in the light of the clinician's knowledge and judgement, especially with regard to local conditions.
- As with all risk estimation systems, risk will be over estimated in countries with a falling CVD mortality rate, and under estimated if it is rising.
- At any given age, risk appears lower for women than men. This is misleading since, ultimately, more women than men die from CVD. Inspection of the charts shows that their risk is merely deferred by 10 years.
- Risk may be higher than indicated in the chart in:
  - Sedentary or obese subjects, especially those with central obesity
  - Those with a strong family history of premature CVD
  - The socially deprived
  - Subjects with diabetes - risk may be 5 fold higher in women with diabetes and 3 fold higher in men with diabetes compared to those without diabetes
  - Those with low HDL cholesterol or high triglycerides
  - Asymptomatic subjects with evidence of pre-clinical atherosclerosis, for example a reduced ankle-brachial index or on imaging such as carotid ultrasonography or CT scanning

10 year risk of fatal CVD in high risk regions of Europe

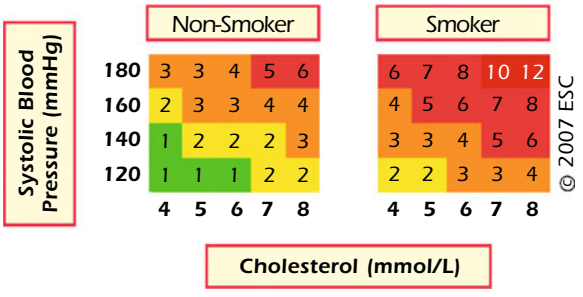


10 year risk of fatal CVD in low risk regions of Europe



Relative Risk Chart

This chart may be used to show younger people at low total risk that, relative to others in their age group, their risk may be many times higher than necessary. This may help to motivate decisions about avoidance of smoking, healthy nutrition and exercise, as well as flagging those who may become candidates for medication.



How do I manage the components of total CVD risk?

- The patient and the doctor agree that a risk assessment is indicated, and the patient is informed that the result may lead to suggestions regarding life style change and the possibility of life long medication.
- There are time and resources to discuss and follow up advice and treatment.
- The doctor should be aware of and respect the patient's own values and choices.

Total risk CVD management: A key message

- Management of the individual components of risk such as smoking, diet, exercise, blood pressure and lipids impacts on total cardiovascular risk.
- Thus, if perfect control of a risk factor is difficult (for example, blood pressure control in the elderly), total risk can still be reduced by reducing other risk factors such as smoking or blood cholesterol.

Managing total cardiovascular risk

Tips to help behaviour change

- Develop a sympathetic alliance with the patient.
- Ensure the patient understands the relationship between lifestyle and disease.
- Use this to gain commitment to lifestyle change.
- Involve the patient in identifying the risk factors to change.
- Explore potential barriers to change.
- Help design a lifestyle change plan.
- Be realistic and encouraging - "ANY increase in exercise is good and can be built on".
- Reinforce the patient's efforts to change.
- Monitor progress through follow-up contacts.
- Involve other health care staff wherever possible.

Why do people find it hard to change their lifestyle?

- **Socio-economic status:** Low SES, including low educational level and low income, impedes the ability to adopt lifestyle change.
- **Social isolation:** People living alone are more likely to have unhealthy lifestyles.
- **Stress:** Stress at work and at home makes it more difficult for people to adopt and sustain a healthy lifestyle.
- **Negative emotions:** Depression, anxiety and hostility impede lifestyle change.
- **Complex or confusing advice.**

Increased physician awareness of these factors facilitates empathy, counselling and the provision of sympathetic, simple and explicit advice.

Smoking

All smokers should be professionally encouraged to permanently stop smoking all forms of tobacco.

The 5 A's can help:

A - ASK:	systematically identify all smokers at every opportunity.
A - ASSESS:	determine the person's degree of addiction and his/her readiness to cease smoking.
A - ADVISE:	Unequivocally urge all smokers to quit.
A - ASSIST:	Agree on a smoking cessation strategy including behavioural. counselling, nicotine replacement therapy and/or pharmacological intervention.
A - ARRANGE:	a schedule of follow-up visits.

Healthy food choices

All individuals should be advised about food choices that are associated with lower CVD risk. High risk persons should receive specialist dietary advice if feasible. General recommendations should suit the local culture:

- A wide variety of foods should be eaten.
- Energy intake should be adjusted to avoid overweight.
- Encourage: Fruits, vegetables, wholegrain cereals and bread, fish (especially oily), lean meat, low fat dairy products.
- Replace saturated fat with the above foods and with monounsaturated and polyunsaturated fats from vegetable and marine sources to reduce total fat to < 30% of energy, of which less than 1/3 is saturated.
- Reduce salt intake if blood pressure is raised by avoiding table salt and salt in cooking, and by choosing fresh or frozen unsalted foods. Many processed and prepared foods, including bread, are high in salt.

Physical activity

- Stress that positive health benefits occur with almost any increase in activity; small amounts of exercise have an additive effect; exercise opportunities exist in the workplace, for example by using stairs instead of the lift.
- Try to find leisure activities that are positively enjoyable.
- 30 minutes of moderately vigorous exercise on most days of the week will reduce risk and increase fitness.
- Exercising with family or friends tends to improve motivation.
- Added benefits include a sense of well being, weight reduction and better self esteem.
- Continued physician encouragement and support may help in the long term.

Body weight

- Increasing body weight is associated with increased total and CVD mortality and morbidity, mediated in part through increases in blood pressure and blood cholesterol, reduced HDL cholesterol and an increased likelihood of diabetes.
- Weight reduction is recommended for obese people (BMI $\geq$ 30 kg/m^2) and should be considered for those who are overweight (BMI $\geq$ 25 and $<$ 30 kg/m^2).
- Men with a waist circumference of 94-102 cm and women with a waist circumference of 80-88 cm are advised not to increase their weight. Men above 102 cm and women above 88 cm are advised to lose weight.
- Restriction of total calorie intake and regular physical exercise are the cornerstones of weight control. It is likely that improvements in central fat metabolism occur with exercise even before weight reduction occurs.

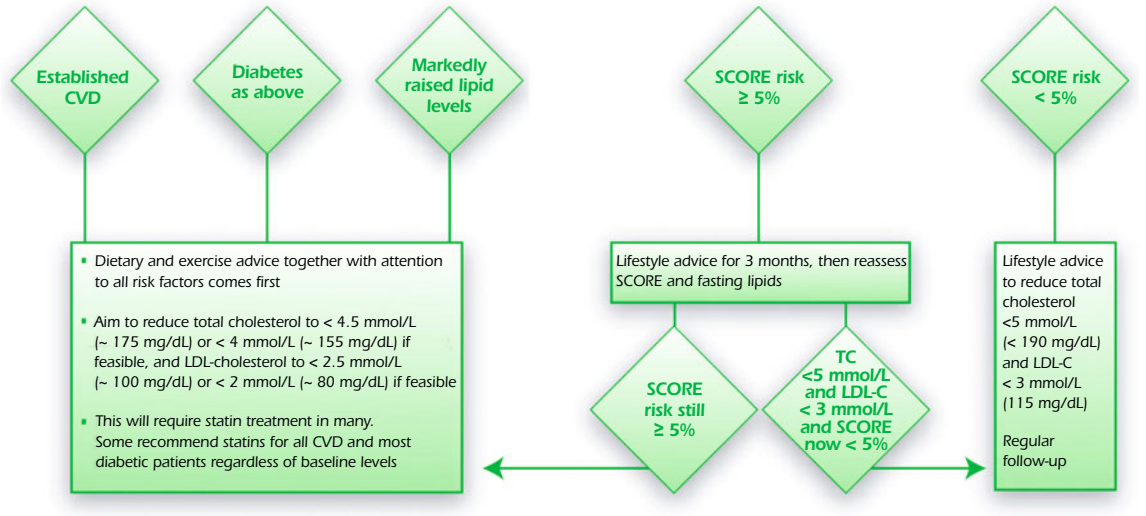
Blood pressure

In ALL cases, look for and manage all risk factors. Those with established CVD, diabetes or renal disease are at markedly increased risk and a BP of < 130/80 is desirable if feasible. For all other people, check SCORE risk. Those with target organ damage are managed as "increased risk".

SCORE CVD risk	Normal <130/85	High N 130-139/ 85-89	Grade 1 140-159/ 90-99	Grade 2 160-179/ 100-109	Grade 3 ≥ 180/110
Low < 1%	Lifestyle advice	Lifestyle advice	Lifestyle advice	Drug Rx if persists	Drug Rx
Mod 1-4%	Lifestyle advice	Lifestyle advice	+ consider drug Rx	Drug Rx if persists	Drug Rx
Increased 5-9%	Lifestyle advice	+ consider drug Rx	+ consider drug Rx	Drug Rx	Drug Rx
Markedly increased ≥ 10%	Lifestyle advice	+ consider drug Rx	Drug Rx	Drug Rx	Drug Rx

Lipids

In ALL cases, look for and manage all risk factors. Those with established CVD, diabetes type 2 or type 1 with microalbuminuria or with severe hyperlipidaemia are already at high risk. For all other people, the SCORE charts can be used to estimate total risk.



Treatment goals are not defined for HDL cholesterol and triglycerides but HDL-C < 1.0 mmol/L (40 mg/dL) for men and < 1.2 mmol/L (45 mg/dL) for women and fasting triglycerides of > 1.7 mmol/L (150 mg/dL) are markers of increased cardiovascular risk.

Treatment targets in patients with type 2 diabetes		
	Unit	**Target**
HbA_{1c} (aligned DCCT)	HbA_{1c} (%)	≤ 6.5 if feasible
Plasma glucose	Fasting/pre-prandial mmol/L (mg/dL)	< 6.0 (110) if feasible
	Post-prandial mmol/L (mg/dL)	< 7.5 (135) if feasible
Blood pressure	mmHg	≤ 130/80
Total cholesterol	mmol/L (mg/dL) mmol/L (mg/dL)	< 4.5 (175) < 4.0 (155) if feasible
LDL cholesterol	mmol/L (mg/dL) mmol/L (mg/dL)	< 2.5 (100) < 2.0 (80) if feasible

The metabolic syndrome

- The term "metabolic syndrome" refers to the combination of several factors that tend to cluster together - central obesity, hypertension, low HDL-cholesterol, raised triglycerides and raised blood sugar - to increase risk of diabetes and CVD.
- This implies that, if one component is identified, a systematic search for the others is indicated, together with an active approach to managing all of these risk factors.
- Physical activity and weight control can radically reduce the risk of developing diabetes in those with the metabolic syndrome.

Renal impairment and cardiovascular risk

- Risk of CVD rises progressively from microalbuminuria with preserved GFR to end stage renal disease, when it is 20-30x that of general population.
- Applies to apparently healthy people and those with hypertension, CVD and heart failure.
- Associated with high blood pressure, hyperlipidaemia, metabolic syndrome, uric acid, homocysteine, anaemia.
- Particularly vigorous risk factor control needed.

When to prescribe cardio-protective drugs in addition to those used to treat blood pressure, lipids and diabetes?

- Aspirin for virtually all with established CVD, and in persons at > 10% SCORE risk once blood pressure has been controlled.
- Beta-blockers after myocardial infarction and, in carefully titrated doses, in those with heart failure.
- ACE-inhibitors in those with left ventricular dysfunction and in diabetic subjects with hypertension or nephropathy.
- Anti-coagulants in those at increased risk of thrombo-embolic events, particularly atrial fibrillation.

Why screen close relatives?

- Close relatives of patients with premature CVD and persons who belong to families with inherited dyslipidaemias such as familial hypercholesterolaemia are at increased risk of developing CVD and should be examined for all cardiovascular risk factors.

What would make the practice of CVD prevention easier?

- Simple, clear, credible guidelines.
- Sufficient time.
- Positively helpful government policies (defined prevention strategy with resources, incentives including remuneration for prevention as well as treatment).
- Educational policies that facilitate patient adherence to advice.

Section II: Hypertension

1. Arterial Hypertension

Chapter 1
Arterial Hypertension*
2007

ESH–ESC Task Force on the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC)

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These pocket guidelines on the management of arterial hypertension are a concise summary of the more extensive ones prepared by a Task Force jointly appointed by the European Society of Hypertension and the European Society of Cardiology.

These guidelines have been prepared on the basis of the best available evidence on all issues deserving recommendations; their role must be educational and not prescriptive or coercive for the management of individual subjects who may differ widely in their personal, medical and cultural characteristics.

The members of the Task Force have participated independently in the preparation of these guidelines, drawing on their academic and clinical experience and by objective examination and interpretation of all available literature. A disclosure of their potential conflict of interest is reported on the websites of the ESH and the ESC.

1. Arterial hypertension

Definition and classification

Blood pressure has a unimodal distribution in the population as well as a continuous relationship with CV risk. For practical reasons the term "hypertension" is used in daily practice and patients are categorized as shown in Table 1. However the real threshold for defining "hypertension" must be considered as flexible, being high or low based on the total CV risk of each individual.

Table 1: Definitions and Classification of blood pressure (BP) levels (mmHg)

Category	Systolic		Diastolic
Optimal	< 120	and	< 80
Normal	120–129	and/or	80–84
High normal	130–139	and/or	85–89
Grade 1 hypertension	140–159	and/or	90–99
Grade 2 hypertension	160–179	and/or	100–109
Grade 3 hypertension	≥ 180	and/or	≥ 110
Isolated systolic hypertension	≥ 140	and	< 90

Isolated systolic hypertension should be graded (1,2,3) according to systolic blood pressure values in the ranges indicated, provided that diastolic values are < 90 mmHg.

* Adapted from the 2007 Guidelines for the Management of Arterial Hypertension (European Heart Journal 2007;28:1462-1536)

J. Bax et al., *Compendium of Abridged ESC Guidelines 2001*

2. Total cardiovascular (CV) risk

- All patients should be classified not only in relation to the grades of hypertension but also in terms of the total CV risk resulting from the coexistence of different risk factors, organ damage and disease.
- Decisions on treatment strategies (initiation of drug treatment, BP threshold and target for treatment, use of combination treatment, need of a statin and other non-antihypertensive drugs) all importantly depend on the initial level of risk.
- There are several methods by which total CV risk can be assessed, all with advantages and limitations. Categorization of total risk as low, moderate, high, and very high added risk has the merit of simplicity and can therefore be recommended. The term 'added risk' refers to the risk additional to the average one.
- Total risk is usually expressed as the absolute risk of having a CV event within 10 years. Because of its heavy dependence on age, in young patients absolute total CV risk can be low even in the presence of high BP with additional risk factors. If insufficiently treated, however, this condition may lead to a partly irreversible high risk condition years later. In younger subjects treatment decisions should better be guided by quantification of relative risk, i.e. the increase in risk in relation to average risk in the population.
- Using rigid cut-offs of absolute risk (e.g. > 20% within 10 years) in order to decide on treatment is discouraged.

3. Stratification of total CV risk

In Figure 1 total CV risk is stratified in four categories. Low, moderate, high and very high risks refer to 10 year risk of a fatal or non-fatal CV event. The term "added" indicates that in all categories risk is greater than average. The dashed line indicates how the definition of hypertension (and thus the decision about the initiation of treatment) is flexible, i.e. may be variable depending on the level of total CV risk.

Figure 1: Stratification of CV risk in four categories of added risk

Blood Pressure (mmHg)					
Other risk factors, OD or disease	Normal SBP 120-129 or DBP 80-84	High Normal SBP 130-139 or DBP 85-89	Grade 1 HT SBP 140-159 or DBP 90-99	Grade 2 HT SBP 160-179 or DBP 100-109	Grade 3 HT SBP ≥180 or DBP ≥110
No other risk factors	Average risk	Average risk	Low added risk	Moderate added risk	High added risk
1-2 risk factors	Low added risk	Low added risk	Moderate added risk	Moderate added risk	Very high added risk
3 or more risk factors MS, OD or Diabetes	Moderate added risk	High added risk	High added risk	High added risk	Very high added risk
Established CV or renal disease	Very high added risk	Very high added risk	Very high added risk	Very high added risk	Very high added risk

SBP = systolic blood pressure; DBP = diastolic blood pressure; CV = cardiovascular; HT = hypertension; OD = subclinical organ damage; MS = metabolic syndrome

4. Clinical variables that should be used to stratify total CV risk

Risk factors	Subclinical Organ Damage
• Systolic and diastolic BP levels • Levels of pulse pressure (in the elderly) • Age (M > 55 years; W > 65 years) • Smoking • Dyslipidaemia - TC > 5.0 mmol/L (190 mg/dL) or: - LDL-C > 3.0 mmol/L (115 mg/dL) or: - HDL-C: M < 1.0 mmol/L (40mg/dL), W < 1.2 mmol/L (46 mg/dL) or: - TG > 1.7 mmol/L (150 mg/dL) • Fasting plasma glucose 5.6-6.9 mmol/L (102-125 mg/dL) • Abnormal glucose tolerance test • Abdominal obesity (Waist circumference > 102 cm (M), > 88 cm (W)) • Family history of premature CV disease (M at age < 55 years; W at age < 65 years)	• Electrocardiographic LVH (Sokolow-Lyon > 38 mm; Cornell > 2440 mm/ms) or: • Echocardiographic LVH* (LVMI M ≥ 125 g/m^2, W ≥ 110 g/m^2) • Carotid wall thickening (IMT > 0.9 mm) or plaque • Carotid-femoral pulse wave velocity > 12 m/sec • Ankle/Brachial BP index < 0.9 • Slight increase in plasma creatinine: M: 115-133 μmol/L (1.3-1.5 mg/dL); W: 107-124 μmol/L (1.2-1.4 mg/dL) • Low estimated glomerular filtration rate** (< 60 ml/min/1.73m^2) or creatine clearance*** (< 60 ml/min) • Microalbuminuria 30-300 mg/24h or albumin-creatinine ratio: ≥ 22 (M); or ≥ 31 (W) mg/g creatinine
Diabetes Mellitus	**Established CV or renal disease**
• Fasting plasma glucose ≥ 7.0 mmol/L (126 mg/dL) on repeated measurement or: • Postload plasma glucose > 11.0 mmol/L (198 mg/dL) Note: the cluster of three out of 5 risk factors among abdominal obesity, altered fasting plasma glucose, BP ≥ 130/85 mmHg, low HDL - cholesterol and high TG (as defined above) indicates the presence of metabolic syndrome.	• Cerebrovascular disease: ischaemic stroke; cerebral haemorrhage; transient ischaemic attack • Heart disease: myocardial infarction; angina; coronary revascularization; heart failure • Renal disease: diabetic nephropathy; renal impairment (serum creatinine M > 133; W > 124 μmol/L); proteinuria (> 300 mg/24h) • Peripheral artery disease • Advanced retinopathy: haemorrhages or exudates, papilloedema

M = men; W = women; CV = cardiovascular disease; IMT = intima-media thickness; BP = blood pressure; TG = triglycerides; C = cholesterol; * = Risk maximal for concentric LVH (left ventricular hypertrophy); ** = MDRD formula; *** = Cockroft Gault formula; increased LVMI (left ventricular mass index) with a wallthickness/rasius ratio ≥ 0.42

5. Diagnostic evaluation

AIMS

- Establishing BP values
- Identifying secondary causes of hypertension
- Searching for
  a) other risk factors;
  b) subclinical organ damage;
  c) concomitant diseases;
  d) accompanying CV and renal complications.

PROCEDURES

- repeated BP measurements
- family and clinical history
- physical examination
- laboratory and instrumental investigations

6. Blood pressure (BP) measurement

When measuring BP, care should be taken to:

- Allow the patients to sit quietly for several minutes;
- Take at least two measurements spaced by 1-2 minutes;
- Use a standard bladder (12-13 cm long and 35 cm wide) but have a larger bladder available for fat arms and a smaller one for thin arms and children;
- Have the cuff at the level of the heart, whatever the position of the patient;
- Deflate the cuff at a speed of 2 mmHg/s;
- Use phase I and V (disappearance) Korotkoff sounds to identify SBP and DBP, respectively;
- Measure BP in both arms at first visit to detect possible differences due to peripheral vascular disease. In this instance, take the higher value as the reference one;
- Measure BP 1 and 5 min after assumption of the standing position in elderly subjects, diabetic patients, and when postural hypotension may be frequent or suspected;
- Measure heart rate by pulse palpation (at least 30 sec).

7. Ambulatory and home BP measurements

AMBULATORY BP

- Although office BP should be used as the reference, ambulatory BP may improve prediction of CV risk in untreated and treated patients.
- 24-h ambulatory BP monitoring should be considered, in particular, when
  - considerable variability of office BP is found
  - high office BP is measured in subjects otherwise at low total CV risk
  - there is a marked discrepancy between BP values measured in the office and at home
  - resistance to drug treatment is suspected
  - hypotensive episodes are suspected, particularly in elderly and diabetic patients
  - sleep apnoea is suspected
  - office BP is elevated in pregnant women and pre-eclampsia is suspected

Normal values for 24 hour average BP are lower than for office BP, i.e. < 125-130 mmHg systolic and < 80 mmHg diastolic. Normal values of daytime BP are < 130-135 mmHg systolic and < 85 mmHg diastolic.

HOME BP

- Self-measurement of BP at home is of clinical value. Home BP measurements should be encouraged in order to:
  - provide more information on the BP lowering effect of treatment at trough, and thus on therapeutic coverage throughout the dose-to-dose time interval
  - improve patient's adherence to treatment regimens
  - understand technical reliability/environmental conditions of ambulatory BP data

- Self-measurement of BP at home should be discouraged whenever:
  - it causes anxiety to the patient
  - it induces self-modification of the treatment regimen
- Normal values for home BP are lower than for office BP, i.e. < 130-135 mmHg systolic and < 85 mmHg diastolic

PARTICULAR CONDITIONS

Isolated office hypertension (White coat hypertension)

Office BP persistently ≥ 140/90 mmHg
Normal daytime ambulatory (< 130-135/85 mmHg) or home (< 130-135/85 mmHg) BP

In these subjects CV risk is less than in individuals with raised office and ambulatory or home BP but may be slightly greater than that of individuals with in- and out-of-office normotension

Isolated ambulatory hypertension (Masked hypertension)

Office BP persistently normal (< 140/90 mmHg)
Elevated ambulatory (≥ 125-130/80 mmHg) or home (≥ 130-135/85 mmHg) BP

In these subjects CV risk is close to that of individuals with in- and out-of-office hypertension

8. Diagnostic evaluation: medical history and physical examination

Family and clinical history
1. Duration and previous level of high BP
2. Indications of secondary hypertension
3. Risk factors
4. Symptoms of organ damage
5. Previous antihypertensive therapy (efficacy, adverse events)
6. Personal, family, environmental factors
Physical examinations
1. Signs suggesting secondary hypertension
2. Signs of organ damage
3. Evidence of visceral obesity

9. Laboratory investigation

ROUTINE TESTS
• Fasting plasma glucose
• Serum total cholesterol
• Serum LDL-cholesterol
• Serum HDL-cholesterol
• Fasting serum triglycerides
• Serum potassium
• Serum uric acid
• Serum creatinine
• Estimated creatinine clearance (Cockroft-Gault formula) or glomerular filtration rate (MDRD formula)
• Haemoglobin and haematocrit
• Urinalysis (complemented by microalbuminuria dipstick test and microscopic examination)
• Electrocardiogram
RECOMMENDED TESTS
• Echocardiogram
• Carotid ultrasound
• Quantitative proteinuria (if dipstick test positive)
• Ankle-brachial BP Index
• Fundoscopy
• Glucose tolerance test (if fasting plasma glucose > 5.6 mmol/L (100 mg/dL)
• Home and 24h ambulatory BP monitoring
• Pulse wave velocity measurement (where available)
EXTENDED EVALUATION (domain of the specialist)
• Further search for cerebral, cardiac, renal and vascular damage. Mandatory in complicated hypertension.
• Search for secondary hypertension when suggested by history, physical examination or routine tests: measurement of renin, aldosterone, corticosteroids, catecholamines in plasma and/or urine; arteriographies; renal and adrenal ultrasound; computer-assisted tomography; magnetic resonance imaging.

10. Searching for subclinical organ damage

Due to the importance of subclinical organ damage as an intermediate stage in the continuum of vascular disease and as a determinant of total CV risk, signs of organ involvement should be sought carefully by appropriate techniques:

HEART

Electrocardiography should be part of all routine assessment of subjects with high BP in order to detect left ventricular hypertrophy, patterns of "strain", ischaemia and arrhythmias. Echocardiography is recommended when a more sensitive method of detection of left ventricular hypertrophy is considered useful as well as assessment of left ventricular systolic function. Geometric patterns can be defined echocardiographically, of which concentric hypertrophy carries the worse prognosis. Diastolic dysfunction can be evaluated by transmitral Doppler.

BLOOD VESSELS

Ultrasound scanning of the extracranial carotid arteries is recommended when detection of vascular hypertrophy or asymptomatic atherosclerosis is deemed useful. Large artery stiffening (leading to isolated systolic hypertension in the elderly) can be measured by pulse wave velocity. It might be more widely recommended if its availability were greater. A low ankle-brachial BP index signals advanced peripheral artery disease.

KIDNEY

Diagnosis of hypertension-related renal damage is based on a reduced renal function or an elevated urinary excretion of albumin. Estimation from serum creatinine of glomerular filtration rate (MDRD formula, requiring age, gender, race) or creatinine clearance (Cockroft-Gault formula, requiring also body weight) should be routine procedure. Urinary protein should be sought in all hypertensives by dipstick. In dipstick negative patients low grade albuminuria (microalbuminuria) should be determined in spot urine and related to urinary creatinine excretion.

FUNDOSCOPY

Examination of eye grounds is recommended in severe hypertensives only. Mild retinal changes are largely non-specific except in young patients. Haemorrhages, exudates and papilloedema, only present in severe hypertension, are associated with increased CV risk.

BRAIN

Silent brain infarcts, lacunar infarctions, microbleeds and white matter lesions are not infrequent among hypertensives, and can be detected by MRI or CT. Availability and costs do not allow indiscriminate use of these techniques. In elderly hypertensives, cognitive tests may help to detect initial brain deterioration.

Table 2 summarizes availability, prognostic value and cost of procedures to detect subclinical organ damage.

Table 2: Availability, Prognostic Value and Cost of some markers of organ damage (scored from 1 to 4 pluses)

Markers	CV predicitive value	Availability	Cost
Electrocardiography	++	++++	+
Echocardiography	+++	+++	++
Carotid Intima-Media Thickness	+++	+++	++
Arterial stiffness (Pulse wave velocity)	+++	+	++
Ankle-Brachial index	++	++	+
Coronary calcium content	+	+	++++
Cardiac/Vascular tissue composition	?	+	++
Circulatory collagen markers	?	+	++
Endothelial dysfunction	++	+	+++
Cerebral lacunae/ White matter lesions	?	++	++++
Est. Glomerular Filtration Rate or Creatinine Clearance	+++	++++	+
Microalbuminuria	+++	++++	+

11. Evidence on the benefit of antihypertensive treatment

- Placebo controlled trials have provided uncontroversial evidence that BP lowering reduces fatal and non-fatal cardiovascular events. Beneficial effects have been found when treatment is initiated with a thiazide diuretic, a β-blocker, a calcium antagonist, an ACE-inhibitor or an angiotensin receptor blocker.

- Trials comparing different antihypertensive drugs have not been able to conclusively demonstrate that for the same reduction in BP different antihypertensive drugs (or drug combinations) reduce to different degree CV events. These trials (and their meta-analysis and meta-regressions) underline the crucial role of BP lowering in reducing all kinds of CV events, i.e. stroke, myocardial infarction and heart failure, independently of the agents used.

- BP-independent effects related to use of specific drugs have been reported for cause-specific events, e.g. stroke, heart failure and coronary events, but these effects are smaller than the dominant effect of BP lowering.

- BP-independent effects attributable to specific drugs have been more consistently shown for events that occur earlier in the continuum of CV disease, e.g. protection against subclinical organ damage and prevention of high risk conditions such as diabetes, renal failure and atrial fibrillation.

12. Initiation of BP lowering therapy

- Initiation of BP lowering therapy should be decided on two criteria:

  1. The level of SBP and DBP

  2. The level of total CV risk

  - This is detailed in Figure 2 which considers treatment based on lifestyle changes and antihypertensive drugs with, in addition, recommendations on the time delay to be used for assessing the BP lowering effects.

The following points should be emphasized:

- Drug treatment should be initiated promptly in grade 3 hypertension as well as in grade 1 and 2 when total CV risk is high or very high.

- In grade 1 or 2 hypertensives with moderate total CV risk drug treatment may be delayed for several weeks and in grade 1 hypertensives without any other risk factor for several months. However, even in these patients lack of BP control after a suitable period should lead to initiation of drug treatment.

- When initial BP is in the high normal range the decision on drug intervention heavily depends on the level of risk. In the case of diabetes, history of cerebrovascular, coronary or peripheral artery disease, the recommendation to start BP lowering drugs is justified by the results of controlled trials. Subjects with BP in the high normal range in whom total CV risk is high because of a subclinical organ damage should be advised to implement intense lifestyle measures. In these subjects BP should be closely monitored and drug treatment considered in the presence of a worsening of the clinical condition.

Figure 2: Initiation of antihypertensive treatment

	Blood Pressure (mmHg)				
Other risk factors, OD or disease	Normal SBP 120-129 or DBP 80-84	High Normal SBP 130-139 or DBP 85-89	Grade 1 HT SBP 140-159 or DBP 90-99	Grade 2 HT SBP 160-179 or DBP 100-109	Grade 3 HT SBP ≥ 180 or DBP ≥ 110
No other risk factors	No BP intervention	No BP intervention	Lifestyle changes for several months then drug treatment if BP uncontrolled	Lifestyle changes for several weeks then drug treatment if BP uncontrolled	Lifestyle changes + immediate drug treatment
1-2 risk factors	Lifestyle changes	Lifestyle changes	Lifestyle changes for several weeks then drug treatment if BP uncontrolled	Lifestyle changes for several weeks then drug treatment if BP uncontrolled	Lifestyle changes + immediate drug treatment
≥ 3 risk factors, MS or OD	Lifestyle changes	Lifestyle changes and consider drug treatment	Lifestyle changes + drug treatment	Lifestyle changes + drug treatment	Lifestyle changes + immediate drug treatment
Diabetes	Lifestyle changes	Lifestyle changes + drug treatment	Lifestyle changes + drug treatment	Lifestyle changes + drug treatment	Lifestyle changes + immediate drug treatment
Established CV or renal disease	Lifestyle changes + immediate drug treatment	Lifestyle changes + immediate drug treatment	Lifestyle changes + immediate drug treatment	Lifestyle changes + immediate drug treatment	Lifestyle changes + immediate drug treatment

13. Goals of treatment

- In hypertensive patients, the primary goal of treatment is to achieve maximum reduction in the long-term total risk of CV disease.

- This requires treatment of the raised BP *per se* as well as of all associated reversible risk factors.

- BP should be reduced to at least below 140/90 mmHg (systolic/diastolic), and to lower values, if tolerated, in all hypertensive patients.

- Target BP should be at least < 130/80 mmHg in patients with diabetes and in high or very high risk patients, such as those with associated clinical conditions (stroke, myocardial infarction, renal dysfunction, proteinuria).

- Despite use of combination treatment, reducing systolic BP to < 140 mmHg may be difficult and more so if the target is a reduction to < 130 mmHg. Additional difficulties should be expected

in elderly, in patients with diabetes, and in general, in patients with CV damage.

- In order to more easily achieve goal BP, antihypertensive treatment should be initiated before significant CV damage develops.

14. Lifestyle changes

- Lifestyle measures should be instituted, whenever appropriate, in all patients, including those who require drug treatment. The purpose is to lower BP, to control other risk factors and to reduce the number or the doses of antihypertensive drugs.

- Lifestyle measures are also advisable in subjects with high normal BP and additional risk factors to reduce the risk of developing hypertension.

- The lifestyle measures that are widely recognized to lower BP and/or CV risk, and that should be considered are:

  - smoking cessation
  - weight reduction (and weight stabilization)
  - reduction of excessive alcohol intake
  - physical exercise
  - reduction of salt intake
  - increase in fruit and vegetable intake and decrease in saturated and total fat intake

- Lifestyle recommendations should not be given as lip service but instituted with adequate behavioural and expert support, and reinforced periodically.

- Because long-term compliance with lifestyle measures is low and the BP response highly variable, patients under non-pharmacological treatment should be followed-up closely to start drug treatment when needed and in a timely fashion.

15. Choice of antihypertensive drugs

- The main benefits of antihypertensive therapy are due to lowering of BP *per se*

- Five major classes of antihypertensive agents – thiazide diuretics, calcium antagonists, ACE-inhibitors, angiotensin receptor blockers and β-blockers – are suitable for the initiation and maintenance of antihypertensive treatment, alone or in combination. β-blockers, especially in combination with a thiazide diuretic, should not be used in patients with the metabolic syndrome or at high risk of incident diabetes.

- In many patients more than one drugs is needed, so emphasis on identification of the first class of drug to be used is often futile. Nevertheless, there are conditions for which there is evidence in favour of some drugs versus others either as initial treatment or as part of a combination.

- The choice of a specific drug or a drug combination, and the avoidance of others should take into account the following:

  1. The previous favourable or unfavourable experience of the individual patient with a given class of compounds.
  2. The effect of drugs on CV risk factors in relation to the CV risk profile of the individual patient.
  3. The presence of subclinical organ damage, clinical CV disease, renal disease or diabetes, which may be more favourably treated by some drugs than others.
  4. The presence of other disorders that may limit the use of particular classes of antihypertensive drugs.
  5. The possibilities of interactions with drugs used for other conditions.
  6. The cost of drugs, either to the individual patient or to the health provider. However, cost considerations should never predominate over efficacy, tolerability, and protection of the individual patient.

- Continuing attention should be given to side-effects of drugs, because they are the most important cause of non-compliance. Drugs are not equal in terms of adverse effects, particularly in individual patients.

- The BP lowering effect should last 24 hours. This can be checked by office or home BP measurements at trough or by ambulatory BP monitoring.

- Drugs which exert their antihypertensive effect over 24 hours with a once-a-day administration should be preferred because a simple treatment schedule favours compliance.

16. Antihypertensive treatment: preferred drugs

SUBCLINICAL ORGAN DAMAGE	
LVH	ACEI, CA, ARB
Asymptomatic atherosclerosis	CA, ACEI
Microalbuminuria	ACEI, ARB
Renal dysfunction	ACEI, ARB
CLINICAL EVENT	
Previous stroke	any BP lowering agent
Previous MI	BB, ACEI, ARB
Angina pectoris	BB, CA
Heart failure	diuretics, BB, ACEI, ARB, anti-aldosterone agents
Atrial fibrillation	
Recurrent	ARB, ACEI
Permanent	BB, non-dihydropiridine CA
Tachyarrhythmias	BB
ESRD/proteinuria	ACEI, ARB, loop diuretics
Peripheral artery disease	CA
LV dysfunction	ACEI
OTHER FACTORS	
ISH (elderly)	diuretics, CA
Metabolic syndrome	ACEI, ARB, CA
Diabetes mellitus	ACEI, ARB
Pregnant women	CA, methyldopa, BB
Blacks	diuretics, CA
Glaucoma	BB
ACEI induced cough	ARB

LVH = left ventricular hypertrophy; ISH = Isolated systolic hypertension; ESRD = renal failure; ACEI = ACE-inhibitors; ARB = angiotensin receptor blockers; CA = calcium antagonists; BB = beta-blockers

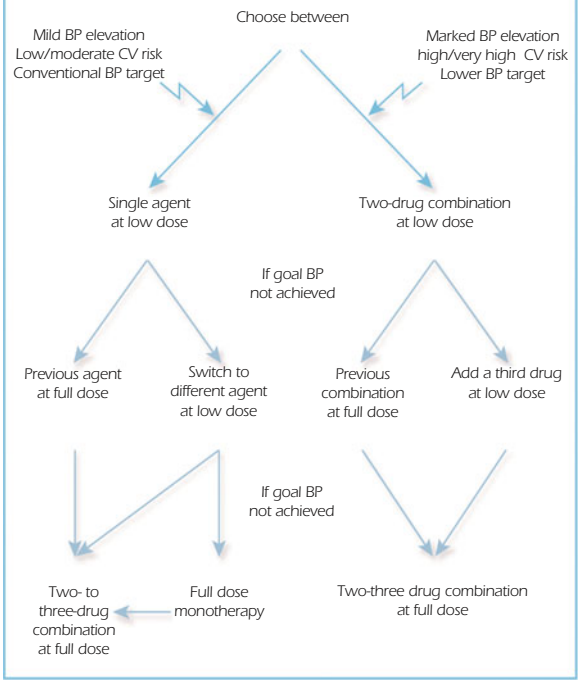
17. Contra-indications to use certain antihypertensive drugs

	Compelling contra-indications	Possible contra-indications
Thiazide diuretics	Gout	- Metabolic syndrome - Glucose intolerance - Pregnancy
Beta-blockers	Asthma A-V block (grade 2 or 3)	- Peripheral artery disease - Metabolic syndrome - Glucose intolerance - Athletes and physically active patients - Chronic obstructive pulmonary disease
Calcium antagonists (dihydropiridines)		- Tachyarrhythmias - Heart failure
Calcium antagonists (verapamil, diltiazem)	A-V block (grade 2 or 3) Heart failure	
ACE-inhibitors	Pregnancy Angioneurotic oedema Hyperkalaemia Bilate ral renal artery stenosis	
Angiotensin receptor blockers	Pregnancy Hyperkalaemia Bilateral renal artery stenosis	
Diuretics (antialdosterone	Renal failure Hyperkalaemia	

18. Monotherapy versus combination therapy

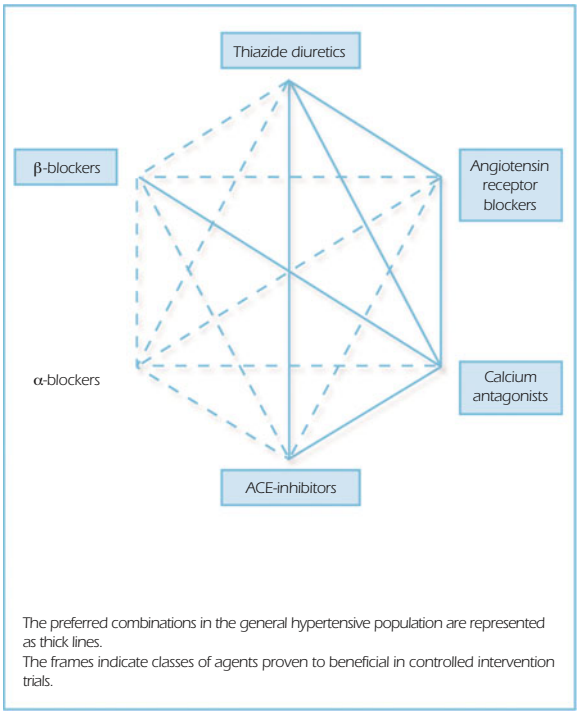
- Regardless of the drug employed, monotherapy allows to achieve BP target in only a limited number of hypertensive patients.
- Use of more than one agent is necessary to achieve target BP in the majority of patients. A vast array of effective and well tolerated combinations is available.
- Initial treatment can make use of monotherapy or combination of two drugs at low doses with a subsequent increase in drug doses or number, if needed.
- Monotherapy could be the initial treatment for mild BP elevation with low or moderate total CV risk. A combination of two drugs at low doses should be preferred as the first step in treatment when the initial BP is in the grade 2 or 3 or total CV risk is high or very high with mild BP elevation.
- Fixed combinations of two drugs can simplify the treatment schedule and favour compliance.

Monotherapy versus combination therapy strategies



- In several patients BP control is not achieved by two drugs, and a combination of three of more drugs is required.
- In uncomplicated hypertensives and in the elderly, antihypertensive therapy should normally be initiated gradually. In higher risk hypertensives, goal BP should be achieved more promptly, which favours initial combination therapy and quicker adjustment of doses.

19. Possible combinations between some classes of antihypertensive drugs



The preferred combinations in the general hypertensive population are represented as thick lines.
The frames indicate classes of agents proven to beneficial in controlled intervention trials.

20. Antihypertensive treatment in special groups

Antihypertensive treatment may differ from the one recommended in the general hypertensive population, in special groups of patients or in specific clinical conditions. The specific requirements under these circumstances are detailed below.

20.1. Elderly patients

- Drug treatment can be initiated with thiazide diuretics, calcium antagonists, angiotensin receptor blockers, ACE-inhibitors, and β-blockers, in line with general guidelines. Trials specifically addressing treatment of isolated systolic hypertension have shown the benefit of thiazides

and calcium antagonists but subanalysis of other trials also show efficacy of angiotensin receptor blockers.

- Initial doses and subsequent dose titration should be more gradual because of a greater chance of undesirable effects, especially in very old and frail subjects.

- BP goal is the same as in younger patients, i.e. < 140/90 mmHg or below, if tolerated. Many elderly patients need two or more drugs to control blood pressure and reductions to < 140 mmHg systolic may be difficult to obtain.

- Drug treatment should be tailored to the risk factors, target organ damage and associated cardiovascular and non-cardiovascular conditions that are frequent in the elderly. Because of the increased risk of postural hypotension, BP should always be measured also in the erect posture.

- In subjects aged 80 years and over, evidence for benefits of antihypertensive treatment is as yet inconclusive. However, there is no reason for interrupting a successful and well tolerated therapy when a patient reaches 80 years of age.

20.2. Diabetic patients

- Where applicable, intense non-pharmacological measures should be encouraged in all patients with diabetes, with particular attention to weight loss and reduction of salt intake in type 2 diabetes.

- Goal BP should be < 130/80 mmHg and anti-hypertensive drug treatment may be started already when BP is in the high normal range.

- To lower BP, all effective and well tolerated drugs can be used. A combination of two or more drugs is frequently needed.

- Available evidence indicates that lowering BP also exerts a protective effect on appearance and progression of renal damage. Some additional protection can be obtained by the use of a blocker of the renin–angiotensin system (either an angiotensin receptor blocker or an ACE-inhibitor).

- A blocker of the renin–angiotensin system should be a regular component of combination treatment and the one preferred when monotherapy is sufficient.

- Microalbuminuria should prompt the use of antihypertensive drug treatment also when initial BP is in the high normal range. Blockers of the renin–angiotensin system have a pronounced antiproteinuric effect and their use should be preferred.

- Treatment strategies should consider an intervention against all CV risk factors, including a statin.

- Because of the greater chance of postural hypotension, BP should also be measured in the erect posture.

20.3. Patients with renal dysfunction

- Renal dysfunction and failure are associated with a very high risk of CV events.

- Protection against progression of renal dysfunction has two main requirements: a) strict blood pressure control (< 130/80 mmHg and even lower if proteinuria is > 1g/day); b) lowering proteinuria to values as near to normal as possible.

- To achieve the BP goal, combination therapy of several antihypertensive agents (including loop diuretics) is usually required.

- To reduce proteinuria, an angiotensin receptor blocker, an ACE-inhibitor or a combination of both are required.

- There is controversial evidence as to whether blockade of the renin–angiotensin system has a specific beneficial role in preventing or retarding nephrosclerosis in non-diabetic non-proteinuric hypertensives, except perhaps in Afro-American individuals. However, inclusion of one of these agents in the combination therapy required by these patients appears well founded.

- An integrated therapeutic intervention (anti-hypertensive, statin and antiplatelet therapy) has to be frequently considered in patients with renal damage because, under these circumstances, CV risk is extremely high.

20.4. Patients with cerebrovascular disease

- In patients with a history of stroke or transient ischaemic attacks, antihypertensive treatment markedly reduces the incidence of stroke recurrence and also lowers the associated high risk of cardiac events.

- Antihypertensive treatment is beneficial in hypertensive patients as well as in subjects with

BP in the high normal range. BP goal should be < 130/80 mmHg

- Because evidence from trials suggests that the benefit largely depends on BP lowering *per se*, all available drugs and rational combinations can be used. Trial data have been mostly obtained with ACE-inhibitors and angiotensin receptor blockers, in association with or on the top of diuretic and conventional treatment, but more evidence is needed before their specific cerebrovascular protective properties are established.

- There is at present no evidence that BP lowering has a beneficial effect in acute stroke but more research is under way. Until more evidence is obtained antihypertensive treatment should start when post-stroke clinical conditions are stable, usually several days after the event. Additional research in this is necessary because cognitive dysfunction is present in about 15% and dementia in 5% of subjects aged ≥ 65 years.

- In observational studies, cognitive decline and incidence of dementia have a positive relationship with BP values. There is some evidence that both can be somewhat delayed by antihypertensive treatment.

20.5. Patients with coronary heart disease and heart failure

- In patients surviving a myocardial infarction, early administration of β-blockers, ACE-inhibitors or angiotensin receptor blockers reduces the incidence of recurrent myocardial infarction and death. These beneficial effects can be ascribed to the specific protective properties of these drugs but possibly also to the associated small BP reduction.

- Antihypertensive treatment is also beneficial in hypertensive patients with chronic coronary heart disease. The benefit can be obtained with different drugs and drug combinations (including calcium antagonists) and appears to be related to the degree of BP reduction. A beneficial effect has been demonstrated also when initial BP is < 140/90 mmHg and for achieved BP around 130/80 mmHg or less.

- A history of hypertension is common while a raised BP is relatively rare in patients with congestive heart failure. In these patients, treatment can make use of thiazide and loop diuretics, as well as of β-blockers, ACE-inhibitors, angiotensin receptor blockers and antialdosterone drugs on top of diuretics. Calcium antagonists should be avoided unless needed to control BP or anginal symptoms.

- Diastolic heart failure is common in patients with a history of hypertension and has an adverse prognosis. There is at present no evidence on the superiority of specific antihypertensive drugs.

20.6. Patients with atrial fibrillation

- Hypertension is the most important risk factor for atrial fibrillation. Atrial fibrillation markedly increases the risk of CV morbidity and mortality, particularly of embolic stroke.

- Increased left ventricular mass and left atrium enlargement are independent determinants of atrial fibrillation, and require intense antihypertensive therapy.

- Strict blood pressure control is required in patients under anticoagulant treatment to avoid intracerebral and extracerebral bleeding.

- Less new onset and recurrent atrial fibrillation has been reported in hypertensive patients treated with angiotensin receptor blockers.

- In permanent atrial fibrillation, β-blockers and non-dihydropyridine calcium antagonists (verapamil, diltiazem) help controlling ventricular rate.

21. Hypertension in women

TREATMENT

Response to antihypertensive agents and beneficial effects of BP lowering appear to be similar in women and in men. However, ACE-inhibitors and angiotensin receptor blockers should be avoided in pregnant and women planning pregnancy because of potential teratogenic effects during pregnancy.

ORAL CONTRACEPTIVES

Even oral contraceptives with low oestrogen content are associated with an increased risk of hypertension, stroke and myocardial infarction. The progestogen-only pill is a contraceptive option for women with high BP, but their influence on cardiovascular outcomes has been insufficiently investigated.

HORMONE REPLACEMENT THERAPY

The only benefit of this therapy is a decreased incidence of bone fractures and colon cancer, accompanied, however,

by increased risk of coronary events, stroke, thromboembolism, breast cancer, gallbladder disease and dementia. This therapy is not recommended for cardioprotection in postmenopausal women.

HYPERTENSION IN PREGNANCY

- Hypertensive disorders in pregnancy, particularly pre-eclampsia, may adversely affect neonatal and maternal outcomes.
- Non-pharmacological management (including close supervision and restriction of activities) should be considered for pregnant women with SBP 140-149 mmHg or DBP 90-95 mmHg. In the presence of gestational hypertension (with or without proteinuria) drug treatment is indicated at BP levels > 140/90 mmHg. SBP levels ≥ 170 or DBP ≥ 110 mmHg should be considered an emergency requiring hospitalization.
- In non-severe hypertension, oral methyldopa, labetalol, calcium antagonists and (less frequently) β-blockers are drugs of choice.
- In pre-eclampsia with pulmonary oedema, nitroglycerine is the drug of choice. Diuretic therapy is inappropriate because plasma volume is reduced.
- As emergency, intravenous labetalol, oral methyldopa and oral nifedipine are indicated. Intravenous hydralazine is no longer the drug of choice because of an excess of perinatal adverse effects. Intravenous infusion of sodium nitroprusside is useful in hypertensive crises, but prolonged administration should be avoided.
- Calcium supplementation, fish oil and low dose aspirin are not recommended. However, low dose aspirin may be used prophylactically in women with a history of early onset pre-eclampsia.

22. The metabolic syndrome

- The metabolic syndrome is characterized by the variable combination of visceral obesity and alterations in glucose metabolism, lipid metabolism and BP. It has a high prevalence in the middle age and elderly population.
- Subjects with the metabolic syndrome also have a higher prevalence of microalbuminuria, left ventricular hypertrophy and arterial stiffness than those without metabolic syndrome. Their CV risk is high and the chance of developing diabetes markedly increased.
- In patients with metabolic syndrome diagnostic procedures should include a more in-depth assessment of subclinical organ damage. Measuring ambulatory and home BP is also desirable.
- In all individuals with metabolic syndrome intense lifestyle measures should be adopted. When there is hypertension drug treatment should start with a drug unlikely to facilitate onset to diabetes. Therefore a blocker of the renin–angiotensin system should be used and followed, if needed, by the addition of a calcium antagonist or a low-dose thiazide diuretic. It appears desirable to bring BP to the normal range.
- Lack of evidence from specific clinical trials prevents firm recommendations on use of antihypertensive drugs in all metabolic syndrome subjects with a high normal BP. There is some evidence that blocking the renin-angiotensin system may also delay incident hypertension.
- Statins and antidiabetic drugs should be given in the presence of dyslipidemia and diabetes, respectively. Insulin sensitizers have been shown to markedly reduce new onset diabetes, but their advantages and disadvantages in the presence of impaired fasting glucose or glucose intolerance as a metabolic syndrome component remain to be demonstrated.

23. Resistant hypertension

DEFINITION:

BP ≥ 140/90 mmHg despite treatment with at least three drugs (including a diuretic) in adequate doses and after exclusion of spurious hypertension such as isolated office hypertension and failure to use large cuffs on large arms.

CAUSES:

- Poor adherence to therapeutic plan;
- Failure to modify lifestyle including:
  - weight gain
  - heavy alcohol intake (NB: binge drinking);
- Continued intake of drugs that raise blood pressure (liquorice, cocaine, glucocorticoids, non-steroid anti-inflammatory drugs, etc.);
- Obstructive sleep apnea;

- Unsuspected secondary cause;
- Irreversible or limited reversibility of organ damage;
- Volume overload due to:
  - inadequate diuretic therapy
  - progressive renal insufficiency
  - high sodium intake
  - hyperaldosteronism

TREATMENT

- Adequate investigation of causes
- If necessary, use of more than three drugs, including an aldosterone antagonist

24. Hypertensive emergencies

Hypertensive Emergencies
• Hypertensive encephalopathy • Hypertensive left ventricular failure • Hypertension with myocardial infarction • Hypertension with unstable angina • Hypertension and dissection of the aorta • Severe hypertension associated with subarachnoid haemorrhage or cerebrovascular accident • Crisis associated with phaeochromocytoma • Use of recreational drugs such as amphetamines, LSD, cocaine or ecstasy • Hypertension perioperatively • Severe pre-eclampsia or eclampsia

25. Treatment of associated risk factors

LIPID LOWERING AGENTS

- All hypertensive patients with established CV disease or with type 2 diabetes should be considered for statin therapy aiming at serum total and LDL cholesterol levels of, respectively, $<$ 4.5 mmol/L (175 mg/dL) and $<$ 2.5 mmol/L (100 mg/dL), and lower, if possible.
- Hypertensive patients without overt CV disease but with high CV risk ($\geq$ 20% risk of events in 10 years) should also be considered for statin treatment even if their baseline total and LDL serum cholesterol levels are not elevated.

ANTIPLATELET THERAPY

- Antiplatelet therapy, in particular low-dose aspirin, should be prescribed to hypertensive patients with previous CV events, provided that there is no excessive risk of bleeding.
- Low-dose aspirin should also be considered in hypertensive patients without a history of CV disease if older than 50 years and with a moderate increase in serum creatinine or with a high CV risk. In all these conditions, the benefit-to-risk ratio of this intervention (reduction in myocardial infarction greater than the risk of bleeding) has been proven favourable.
- To minimize the risk of haemorrhagic stroke, antiplatelet treatment should be started after achievement of BP control.

GLYCAEMIC CONTROL

- Effective glycaemic control is of great importance in patients with hypertension and diabetes.
- In these patients dietary and drug treatment of diabetes should aim at lowering plasma fasting glucose to values 6 mmol/L (108 mg/dL) and at a glycated haemoglobin of $<$ 6.5%.

26. Patients' follow-up

- Effective and timely titration to BP control requires frequent visits in order to timely modify the treatment regimen in relation to BP changes and the appearance of side-effects.
- Once the target BP has been reached, the frequency of visits can be considerably reduced. However, excessively wide intervals between visits are not advisable because they interfere with a good doctor-patient relationship, which is crucial for patient's compliance.
- Patients at low risk or with grade 1 hypertension may be seen every 6 months and regular home BP measurements may further extend this interval. Visits should be more frequent in high or very high risk patients. This is the case also in patients under non-pharmacological treatment alone due to the variable antihypertensive response and the low compliance to this intervention.
- Follow-up visits should aim at maintaining control of all reversible risk factors as well as at checking the status of organ damage. Because treatment-induced changes in left ventricular mass and carotid artery wall thickness are slow, there is no reason to perform these examinations at less than 1 year intervals.

- Treatment of hypertension should be continued for life because in correctly diagnosed patients cessation of treatment is usually followed by return to the hypertensive state. Cautious downward titration of the existing treatment may be attempted in low risk patients after long-term BP control, particularly if non-pharmacological treatment can be successfully implemented.

27. How to improve compliance with blood pressure lowering therapy

- Inform the patient of the risk of hypertension and the benefit of effective treatment.
- Provide clear written and oral instructions about treatment.
- Tailor the treatment regimen to patient's lifestyle and needs.
- Simplify treatment by reducing, if possible, the number of daily medicaments.
- Involve the patient's partner or family in information on disease and treatment plans.
- Make use of self measurement of BP at home and of behavioural strategies such as reminder systems.
- Pay great attention to side-effects (even if subtle) and be prepared to timely change drug doses or types, if needed.
- Dialogue with patient regarding adherence and be informed of his/her problems.
- Provide reliable support system and affordable prices.
- Arrange a schedule of follow-up visits.

Section III:
Diabetic Heart Disease

1. Diabetes, Pre-diabetes and Cardiovascular Diseases

Chapter 1
Diabetes, Pre-diabetes and Cardiovascular Diseases*
2007

The Task Force on Diabetes and Cardiovascular Diseases of the European Society of Cardiology (ESC) and of the European Association for the Study of Diabetes (EASD)

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1. Preamble

The ESC Committee for Practice Guidelines (CPG) supervises and coordinates the preparation of new Guidelines and Expert Consensus Documents produced by Task Forces, expert groups, or consensus panels. The chosen experts in these writing panels are asked to provide disclosure statements of all relationships they may have, which might be perceived as real or potential conflicts of interest. These disclosure forms are kept on file at the European Heart House, headquarters of the ESC. The Committee is also responsible for the endorsement of these Guidelines and Expert Consensus Documents or statements.

Guidelines and Expert Consensus documents aim to present patients management recommendations based on all of the relevant evidence on a particular subject in order to help physicians to select the best possible management strategies for the individual patient, suffering from a specific condition, taking into account not only the impact on outcome, but also the risk benefit ratio of a particular diagnostic or therapeutic procedure.

The Task Force has classified and ranked the usefulness or efficacy of the recommended procedures and/or treatments and their levels of evidence as indicated in the tables overleaf.

*Adapted from the ESC Guidelines on Diabetes, Pre-diabetes, and Cardiovascular Diseases, Executive Summary (European Heart Journal (2007); 28: 88-136) and Full Text (European Heart Journal 2007;9 (Suppl. C):1-74 and http://www.easd.org)

J. Bax et al., *Compendium of Abridged ESC Guidelines 2001*

Classes of Recommendations

Class I	Evidence and/or general agreement that a given diagnostic procedure/treatment is beneficial, useful and effective.
Class II Class IIa Class IIb	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the treatment or procedure. Weight of evidence/opinion is in favour of usefulness/efficacy. Usefulness/efficacy is less well established by evidence/opinion.
Class III	Evidence or general agreement that the treatment or procedure is not useful/effective and, in some cases, may be harmful.

Levels of Evidence

Level of Evidence A	Data derived from multiple randomized clinical trials or meta-analyses
Level of Evidence B	Data derived from a single randomized trial or large non-randomized studies
Level of Evidence C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries

2. Introduction

Diabetes and cardiovascular diseases (CVD) often appear as two sides of a coin. Diabetes mellitus (DM) has been rated as an equivalent of coronary heart disease, and conversely, many patients with established coronary heart disease suffer from diabetes or its pre-states. Thus, it is high time that diabetologists and cardiologists join their forces to improve the quality management in diagnosis and care for the millions of patients who have coexisting cardiovascular and metabolic diseases.

An algorithm (Figure 1) has been developed to help discover the alternate cardiovascular diseases in patients with diabetes, and vice versa, the metabolic diseases in patients with coronary heart disease, setting the basis for appropriate joint therapy. The cardio-diabetological approach not only is of utmost importance for the sake of patient management, but is also instrumental for further progress in the fields of cardiology, diabetology and prevention. Treatment targets for life style counselling, glycemic control, blood pressure and blood lipids are discussed in different chapters. To give the reader a comprehensive overview they are summarised in Table 1.

Figure 1. Investigational algorithm for patients with coronary artery disease (CAD) and diabetes mellitus (DM)

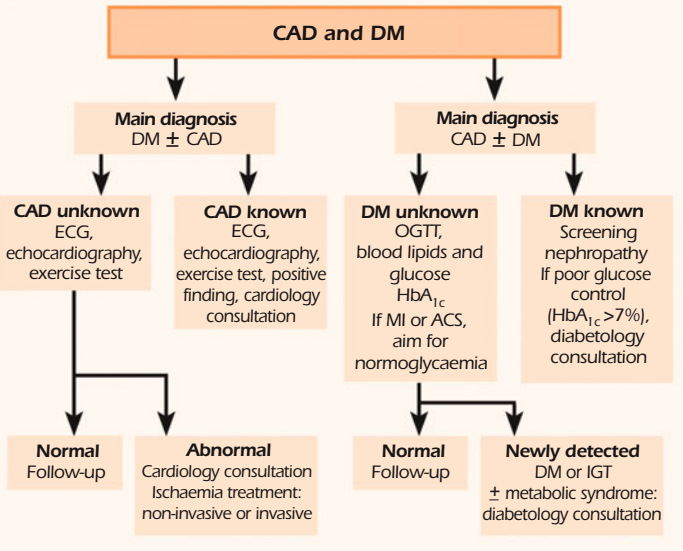


Table 1. Recommended treatment targets for patients with diabetes and CAD

	Variable	Treatment target
Blood pressure	Systolic/diastolic (mm Hg)	< 130/80
	In case of renal impairment or proteinuria > 1 g/24 h	< 125/75
Glycaemic control	HbA_{1c} (%)*	≤ 6.5
	Glucose (venous plasma; mmol/L) mg/dL	
	Fasting	< 6.0 (108)
	Post-prandial (peak)	
	Type 1 diabetes	7.5-9.0 (135-160)
	Type 2 diabetes	< 7.5 (135)
Lipid profile (mmol/L) (mg/dL)	Total cholesterol	< 4.5 (175)
	LDL cholesterol	≤ 1.8 (70)
	HDL cholesterol	
	Men	> 1.0 (40)
	Women	> 1.2 (46)
	Triglycerides**	< 1.7 (150)
	Total/HDL cholesterol**	< 3
Life style counselling	Smoking cessation	Obligatory
	Regular physical activity (min/day)	> 30-45
	Weight control BMI (kg/m^2)	< 25
	In case of overweight, weight reduction (%)	10
	Waist circumference (optimum; ethnic specific; cm)	
	Men (European)	< 94
	Women (European)	< 80
	Dietary habits	
	Salt intake (g/day)	< 6
	Fibre intake	> 30 g per day
	Liquid mono- and disaccharides	avoid
	Fat intake (% of dietary energy)	≤ 30-35
	Saturated	< 10
	Trans-fat	< 2
	Polyunsaturated n-6	4-8
	Polyunsaturated n-3	2 g/day of linolenic acid and 200 mg/day of very long chain fatty acids

* DCCT-Standardized for recalculation formula for some national standards in Europe. ** Not recommended for guiding treatment, but recommended for metabolic/risk assessment.

3. Definition, classification, and screening of diabetes and pre-diabetic glucose abnormalities

Recommendation	Class	Level
The definition and diagnostic classification of diabetes and its pre-states should be based on the level of the subsequent risk of cardiovascular complications.	I	B
Early stages of hyperglycaemia and asymptomatic type 2 diabetes are best diagnosed by an oral glucose tolerance test (OGTT) that gives both fasting and 2 h post-load glucose values.	I	B
Primary screening for the potential type 2 diabetes can be done most efficiently by using a non-invasive risk score, combined with a diagnostic OGTT in people with high score values.	I	A

Definition and classification

Diabetes mellitus is a metabolic disorder characterised by chronic hyperglycaemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects of insulin secretion, insulin action, or a combination of both. Type 1 diabetes is due to a lack of endogenous pancreatic insulin production while the increase in blood glucose in type 2 diabetes results from more complex processes.

Traditionally, diabetes was diagnosed based on symptoms due to hyperglycaemia, but during the last decades emphasis has been placed on the need to identify diabetes and other forms of glucose abnormalities in asymptomatic subjects.

Diabetes mellitus is associated with development of long-term organ damage including retinopathy, nephropathy, neuropathy and autonomic dysfunction. Patients with diabetes are at a particularly high risk for cardiovascular, cerebrovascular and peripheral artery disease.

Four main aetiology categories of diabetes have been identified as diabetes type 1, type 2, other specific types such as Maturity-Onset Diabetes in the Young (MODY) or secondary to other conditions or diseases e.g. surgery and gestational diabetes.

The current classification criteria (Table 2) have been issued by World Health Organisation (WHO) and American Diabetes Association (ADA). The WHO recommendations for glucometabolic classification are based on measuring both fasting and two hour post-load glucose concentrations and recommend that a standardised 75 g

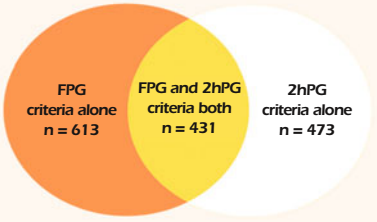
Table 2. Criteria used for glucometabolic classification from WHO (1999 and 2006) and ADA (1997 and 2003)

Glucometabolic category	Source	Classification criteria Venous plasma glucose mmol/L (mg/dL)
Normal glucose regulation (NGR)	WHO	FPG < 6.1 (110) + 2 h PG < 7.8 (140)
	ADA (1997)	FPG < 6.1 (110)
	ADA (2003)	FPG < 5.6 (100)
Impaired fasting glucose (IFG)	WHO	FPG ≥ 6.1 (110) and < 7.0 (126) + 2 h PG < 7.8 (140)
	ADA (1997)	FPG ≥ 6.1 (110) and < 7.0 (126)
	ADA (2003)	FPG ≥ 5.6 (100) and < 7.0 (126)
Impaired glucose tolerance (IGT)	WHO	FPG < 7.0 (126) + 2 h PG ≥ 7.8 and < 11.1 (200)
Impaired glucose homeostasis (IGH)	WHO	IFG or IGT
Diabetes mellitus (DM)	WHO	FPG ≥ 7.0 (126) or 2 h PG ≥ 11.1 (200)
	ADA (1997)	FPG ≥ 7.0 (126)
	ADA (2003)	FPG ≥ 7.0 (126)

FPG = fasting plasma glucose; 2-h PG=two-hour post-load plasma glucose (1 mmol/L = 18 mg/dL).

IGT can only be diagnosed by OGTT. OGTT is performed in the morning, after 8–14 h fast; one blood sample is taken before and one 120 min after intake of 75 g glucose dissolved in 250–300 mL water for 5 min (timing is from the beginning of the drink).

Figure 2. Fasting and post-load glucose levels identify different individuals with asymptomatic diabetes. FPG, fasting plasma glucose; 2hPG, 2 h post-load plasma glucose (adapted from the DECODE Study Group).



oral glucose tolerance test (OGTT) should be performed in the absence of overt hyperglycaemia.

The use of an OGTT for glucometabolic classification is recommended. As shown in Figure 2 FPG and 2 h post-load PG may identify the same individuals but they do often not coincide.

Glycated haemoglobin (HbA_{1c}) is a useful measure of metabolic control and the efficacy of glucose lowering treatment in people with diabetes. It represents a mean value of blood glucose during the preceding six to eight weeks (life span of erythrocytes). HbA_{1c} is not recommended as a diagnostic test for diabetes. It is insensitive in the low range and a normal value does not exclude diabetes or impaired glucose tolerance.

Detection of people at high risk for diabetes

The approaches for early detection are for:

1) measuring blood glucose to determine prevalent impaired glucose homeostasis;

2) using demographic, clinical characteristics and previous laboratory tests to determine the likelihood of future incident diabetes;

3) collecting questionnaire based information on aetiological factors for type 2 diabetes.

The two latter are cost-efficient screening tools. Option two is suited for certain groups with pre-existing cardiovascular disease and women who have had gestational diabetes while the third option is better suited for the general population.

Glycaemic testing (OGTT) is always necessary as a secondary step to accurately define impaired glucose homeostasis. Glucometabolic abnormalities are common in patients with CVD and an OGTT should be carried out in them.

Figure 3. FINnish Diabetes Risk SCore (FINDRISC) to assess the 10 year risk of type 2 diabetes in adults. Available at www.diabetes.fi/english

Type 2 diabetes risk assessment form

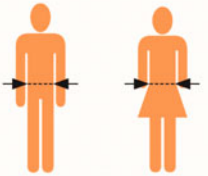
Circle the right alternative and add up your points.

1. Age
0 p. Under 45 years
2 p. 45-54 years
3 p. 55-64 years
4 p. Over 64 years

2. Body mass index
0 p. Lower than 25 kg/m²
1 p. 25-30 kg/m²
3 p. Higher than 30 kg/m²

3. Waist circumference measured below the ribs (usually at the level of the navel)

	MEN	WOMEN
0 p.	Less than 94 cm	Less than 80 cm
3 p.	94-102 cm	80-88 cm
4 p.	More than 102 cm	More than 88 cm



4. Do you usually have daily at least 30 min of physical activity at work and/or during leisure time (including normal daily activity)?
0 p. Yes
2 p. No

5. How often do you eat vegetable, fruit, or berries?
0 p. Every day
1 p. Not every day

6. Have you ever taken anti-hypertensive medication regularly?
0 p. No
2 p. Yes

7. Have you ever been found to have high blood glucose (e.g. in a health examination, during an illness, during pregnancy)?
0 p. No
5 p. Yes

8. Have any of the members of your immediate family or other relatives been diagnosed with diabetes (type 1 or type 2)?
0 p. No
3 p. Yes: grandparent, aunt, uncle, or first cousin (but no own parent, brother, sister or child)
5 p. Yes: parent, brother, sister, or own child

Total risk score

The risk of developing type 2 diabetes within 10 years is

Lower than 7	Low: estimated one in 100 will develop disease
7-11	Slightly elevated: estimated one in 25 will develop disease
12-14	Moderate: estimated one in 6 will develop disease
15-20	High: estimated one in three will develop disease
Higher than 20	Very High: estimated one in two will develop disease

Test designed by Professor Jaakko Tuomilehto. Department of Public Health, University of Helsinki, and Dr Jaana Lindström, MFS, National Public Health Institute.

In the general population the appropriate strategy is to start with risk assessment as the primary screening tool combined with subsequent glucose testing (OGTT) of individuals identified to be at a high risk. An example of such screening tool is shown in Figure 3.

4. Epidemiology of diabetes, IGH, and cardiovascular risk

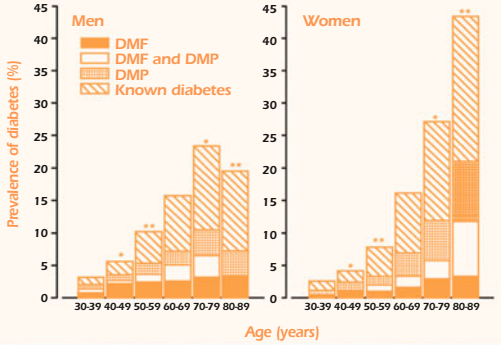
Recommendation	Class	Level
The relationship between hyperglycaemia and CVD should be seen as a continuum. For each 1% increase of HbA_{1c}, there is a defined increased risk for CVD.	I	A
The risk of CVD for people with overt diabetes is increased by two to three times for men and three to five times for women compared with people without diabetes.	I	A
Information on post-prandial (post-load) glucose provides better information about the future risk for CVD than fasting glucose, and elevated post-prandial (post-load) glucose also predicts increased cardiovascular risk in subjects with normal fasting glucose levels.	I	A
Glucometabolic perturbations carry a particularly high risk for cardiovascular morbidity and mortality in women, who in this respect need special attention.	IIa	B

Prevalence of diabetes in relation to age

The age-specific prevalence of diabetes rises with age in both men and women (Figure 4). The lifetime risk of diabetes in European people has been estimated to 30-40%. Approximately half of those affected are unaware of their condition. Among middle aged Europeans the prevalence of impaired glucose tolerance is about 15% increasing to 35-40% in the elderly.

Figure 4. Age- and gender-specific prevalence of diabetes in 13 European population-based cohorts included in the DECODE study.

DMF, diabetes determined by FPG ≥ 7.0 mmol/L and 2 h plasma glucose < 11.1 mmol/L; DMP diabetes determined by 2 h plasma glucose ≥ 11.1 mmol/L, and FPG < 7.0 mmol/L; DMF and DMP, diabetes determined by FPG ≥ 7.0 mmol/L and 2 h plasma glucose ≥ 11.1 mmol/L; known diabetes, previously diagnosed diabetes.
*P < 0.05 and **P < 0.001 for the difference in prevalence between men and women, respectively.



Diabetes, impaired glucose tolerance and coronary artery disease

The most common cause of death in European adults with diabetes is CAD. Their risk is two to three times higher than that among people without diabetes. The combination of type 2 diabetes and previous CAD identifies patients with particularly high risk for coronary deaths. The relative effect of diabetes is larger in women than men. The reason for this gender difference is so far not clear. There is also convincing evidence for a relation between IGT and an increased CAD risk. Following adjustment for major cardiovascular risk factors, mortality and cardiovascular morbidity is predicted by elevated 2-hour post-load plasma glucose, however, not by fasting glucose. Thus hyperglycaemia in itself is very important for the increased risk. Although some evidence points in this direction it remains to be proven if lowering of high post-load glucose will reduce this risk. Studies are underway and a meta-analysis of seven long-term studies using acarbose is promising, but data are scarce.

The risk for cerebrovascular morbidity and mortality is also magnified by diabetes while considerably less is known about the frequency of asymptomatic diabetes and impaired glucose tolerance in patients with stroke.

5. Identification of subjects at high risk for CVD or diabetes

Recommendation	Class	Level
The metabolic syndrome identifies people at a higher risk of CVD than the general population, although it may not provide a better or even equally good prediction of cardiovascular risk than scores based on the major cardiovascular risk factors (blood pressure, smoking, and serum cholesterol).	II	B
Several cardiovascular risk assessment tools exist and they can be applied to both non-diabetic and diabetic subjects.	I	A
An assessment of predicted type 2 diabetes risk should be part of the routine health care using the risk assessment tools available.	II	A
Patients without known diabetes but with established CVD should be investigated with an OGTT.	I	B
People at high risk for type 2 diabetes should receive appropriate lifestyle counselling and, if needed, pharma-cological therapy to reduce or delay their risk of developing diabetes. This may also decrease their risk to develop CVD.	I	A
Diabetic patients should be advised to be physically active in order to decrease their cardiovascular risk.	I	A

The metabolic syndrome

There has been an interest in the clustering factors, each one associated with increased risk for CVD, to what has become known as the "metabolic syndrome". It is debated whether such clustering represents a disease entity in its own, but it helps identifying individuals at high risk for cardiovascular disease and type 2 diabetes. Currently there are several definitions. The most recent has been issued by the International Federation of Diabetes (Table 3). The pathogenesis of the metabolic syndrome and its components is complex and not well understood. However, central obesity and insulin resistance are important causative factors. Abdominal circumference is the clinical screening factor for the metabolic syndrome, much more associated with metabolic risk than body mass index.

Table 3. International Diabetes Federation: Metabolic Syndrome Definition

Central Obesity (defined as waist circumference ≥ 94 cm for Europid men and ≥ 80 cm for Europid women, with ethnicity specific values for other groups)
plus any two of the following four factors:

- **Raised TG level:** ≥ 1.7 mmol/L (150 mg/dL), **or specific treatment for this lipid abnormality**.
- **Reduced HDL cholesterol:** < 1.03 mmol/L (40 mg/dL) in males and < 1.29 mmol/L (50 mg/dL) in females, **or specific treatment for this lipid abnormality**.
- **Raised blood pressure:** systolic BP ≥ 130 or diastolic BP ≥ 85 mmHg, **or treatment of previously diagnosed hypertension**.
- **Raised fasting plasma glucose (FPG)** ≥ 5.6 mmol/L (100 mg/dL), **or previously diagnosed type 2 diabetes**.

If above 5.6 mmol/L or 100 mg/dL, OGTT is strongly recommended but is not necessary to define presence of the syndrome.

Various risk charts or scores have been developed to assess the risk for non-fatal or fatal cardiovascular events within a given time frame in individuals without a previous cardiovascular diagnosis. The European Heart Score (1) takes CVD risk into account. It does, however, only include traditional risk factors while diabetes has not yet been taken into account. FINDRISC (Figure 3) predicts the risk for developing type 2 diabetes with great accuracy, including asymptomatic diabetes and abnormal glucose tolerance and in addition the incidence of myocardial infarction and stroke.

Preventing progression to diabetes

The development of type 2 diabetes is preceded by altered metabolic states, including glucose intolerance and insulin resistance, and normally present years before overt type 2 diabetes. Although not all patients with such abnormalities progress to diabetes, their risk of developing the disease is significantly enhanced. A poor diet and a sedentary lifestyle have a major impact on this risk. Effective lifestyle interventions (Table 4) can prevent or at least delay the progression to type 2 diabetes in such individuals.

If life style interaction fails, pharmacological therapy may be used as an alternative. The following compounds are of proven value: acarbose, metformin and rosiglitazone. When metformin was compared with life-style interaction the number needed to treat to save one case of diabetes was 50% lower with lifestyle than metformin. The combined use of these two measures does not improve preventive efficacy.

Table 4. Summary of findings in some lifestyle intervention studies aiming at preventing type 2 diabetes in people with impaired glucose tolerance.

Study	Cohort size	Mean BMI (kg/m^2)	Duration (years)	RRR (%)	ARR (%)	NNT
Malmö	217	26.6	5	63	18	28
DPS	523	31.0	3	58	12	22
DPP	2161*	34.0	3	58	15	21
Da Qing	500	25.8	6	46	27	25

RRR=Relative risk reduction; ARR=absolute risk reduction/1000 person-years; NNT=numbers needed to treat to prevent one case of diabetes over 12 months.

* Combined numbers for placebo and diet and exercise groups.

6. Treatment to reduce cardiovascular risk

Recommendation	Class	Level
Structured patient education improves metabolic and blood pressure control.	I	A
Non-pharmacological life style therapy improves metabolic control.	I	A
Self-monitoring improves glycaemic control.	I	A
Near normoglycaemic control ($HbA_{1c} \leq 6.5\%$*). reduces microvascular complications. reduces macrovascular complications.	 I I	 A A
Intensified insulin therapy in type 1 diabetes reduces morbidity and mortality.	I	A
Early escalation of therapy towards predefined treatment targets improves a composite of morbidity and mortality in type 2 diabetes.	IIa	B
Early initiation of insulin should be considered in patients with type 2 diabetes failing glucose target.	IIb	C
Metformin is recommended as first line drug in overweight type 2 diabetes.	IIa	B

* Diabetes Control and Complication Trial-standardized.

Lifestyle and comprehensive management

Non-pharmacological therapy as outlined in Table 1 is essential for a successful glucose lowering regimen especially at early stages of diabetes. Life style measures are at least as effective as any glucose lowering drug therapy, which yields a mean HbA_{1c} decrease of 1.0-1.5% in placebo controlled randomized studies.

Glycaemic control

Treatment aiming at lowering haemoglobin HbA_{1c} towards the normal range is associated with a reduction of microvascular and neuropathic complications in people with type 1 and type 2 diabetes. A 1.0% lower HbA_{1c} seems associated with a 25% decline in the risk of microvascular complications with a rather low absolute risk at HbA_{1c} levels below 7.5%.

Microvascular complications at the kidney and eye level, warrant meticulous therapeutic measures, including adequate control of blood pressure with the use of ACE-inhibitors and/or angiotensin II receptor blockers.

Accordingly screening for microalbuminuria and retinopathy is mandatory on an annual basis. The relation between macrovascular disease and hyperglycaemia is less clear than the relation to microangiopathy, however, rather suggestive.

In type 1 diabetes, the gold standard is insulin therapy based on appropriate nutrition and blood glucose self-monitoring, aiming at HbA_{1c} below 7%. The risk for hypoglycaemic episodes needs to be titrated against this goal and severe episodes should be few. In type 2 diabetes, a common pharmacologic treatment approach is less well accepted. Some aspects on the choice of drug are given in Table 5 and recommended treatment targets in Table 1.

Combination therapy including early escalation to insulin, if oral drugs in appropriate doses and combinations fail, is advocated to maximize efficacy and minimize side-effects. A medium dose of an oral agent yields about 80% of the glucose-lowering effect, minimizing potential side-effects (Tables 6 and 7).

Table 5. Suggested policy for the selection of glucose-lowering therapy according to the glucometabolic situation

Glucometabolic situation	Policy
Post-prandial hyperglycaemia	Alpha-glucosidase inhibitors, short-acting sulphonylureas, glinides, short-acting regular insulin, or insulin analogs
Fasting hyperglycaemia	Biguanides, long acting sulphonylureas, glitazones, long-acting insulin or insulin analogs
Insulin resistance	Biguanides, glitazones, alpha-glucosidase inhibitors
Insulin deficiency	Sulphonylureas, glinides, insulin

Table 6. Mean efficacy of pharmacological treatment options in patients with type 2 diabetes

Pharmacological agent	Mean lowering of initial HbA_{1c} (%)
Alpha-glucosidase inhibitors	0.5–1.0
Biguanides	1.0–1.5
Glinides	0.5–1.5
Glitazones	1.0–1.5
Insulin	1.0–2.0
Sulphonylurea derivatives	1.0–1.5

Table 7. Potential downsides of pharmacological treatment modalities in patients with type 2 diabetes

Potential problems*	Avoid or reconsider
Unwanted weight gain	Sulphonylureas, glinides, glitazones, insulin
Gastrointestinal symptoms	Biguanides, alpha-glucosidase inhibitors
Hypoglycaemia	Sulphonylureas, glinides, insulin
Impaired kidney function	Biguanides, sulphonylureas
Impaired liver function	Glinides, glitazones, biguanides, alpha-glucosidase inhibitors
Impaired cardio-pulmonary function	Biguanides, glitazones

* Oedema or lipid disorders may need further considerations

Dyslipidaemia

Recommendation	Class	Level
Elevated LDL and low HDL cholesterol are important risk factors for CVD in people with diabetes.	I	A
Statins are first-line agents for lowering LDL cholesterol in diabetic patients.	I	A
In diabetic patients with CVD, statin therapy should be initiated regardless of baseline LDL cholesterol, with a treatment target of < 1.8–2.0 mmol/L (< 70–77 mg/dL).	I	B
Statin therapy should be considered in adult patients with type 2 diabetes, without CVD, if total cholesterol > 3.5 mmol/L (> 135 mg/dL), with a treatment targeting an LDL cholesterol reduction of 30–40%.	IIb	B
Given the high lifetime risk of CVD, it is suggested that all type 1 patients over the age of 40 years should be considered for statin therapy. In patients 18–39 years (either type 1 or type 2), statin therapy should be considered when other risk factors are present, e.g. nephropathy, poor glycaemic control, retinopathy, hypertension, hypercholesterolaemia, features of the metabolic syndrome, or family history of premature vascular disease.	IIb	C
In diabetic patients with hypertriglyceridaemia > 2 mmol/L (177 mg/dL) remaining after having reached the LDL cholesterol target with statins, statin therapy should be increased to reduce the secondary target of non-HDL cholesterol. In some cases, combination therapy with the addition of ezetimibe, nicotinic acid, or fibrates may be considered.	IIb	B

Dyslipidaemia and vascular risk

Dyslipidaemia is part of the metabolic syndrome and the pre-diabetic state. It persists despite instigation of hypoglycaemic therapy and requires specific therapy with life style interaction and drugs. Typically in type 2 diabetes there is moderate hypertriglyceridaemia, low high density lipoprotein (HDL) cholesterol and abnormal post-prandial lipidaemia. Total and low density lipoprotein (LDL) cholesterol levels are similar to those in subjects without

Table 8. Subgroups of patients with DM in the major secondary prevention trials with statins and the proportionate risk reduction in patients with and without diabetes

Variables			Proportion of events (%)		Relative risk reduction (%)	
Trial	Type of event	Treatment	Diabetes present No	Yes	Type of patients All	Diabetes
4S Diabetes n = 202	CHD death or non-fatal MI	Simvastatin Placebo	19 27	23 45	32	55
4S Reanalysis Diabetes n = 483	CHD death or non-fatal MI	Simvastatin Placebo	19 26	24 38	32	42
HPS Diabetes n = 3050	Major coronary event, stroke, or revascularization	Simvastatin Placebo	20 25	31 36	24	18
CARE Diabetes n = 586	CHD death or non-fatal MI	Pravastatin Placebo	12 15	19 23	23	25
LIPID Diabetes n = 782	CHD death, non-fatal MI, revascularization	Pravastatin Placebo	19 25	29 37	24	19
LIPS Diabetes n = 202	CHD death, non-fatal MI, revascularization	Fluvastatin Placebo	21 25	22 38	22	47
GREACE Diabetes n = 313	CHD death, non-fatal MI, UAP, CHF, revascularization, stroke	Atorvastatin Standard care	12 25	13 30	51 -	58 -

diabetes, however, LDL particles are small and dense, which relates to increased atherogenicity.

Statins

Statins, whether used for primary or secondary prevention, show similar benefits in reducing cardiovascular events in patients with and without diabetes. Since the absolute risk is higher in patients with diabetes the number needed to treat becomes lower (Table 8). There is strong support for aggressive LDL cholesterol lowering in this patient category as detailed in Table 1. Evidence favors the use of statins for primary prevention in diabetic patients with a total cholesterol > 3.5 mmol/L (> 135 mg/dL), targeting a LDL reduction of 30-40% from the actual one.

Fibrates

Less information is available on the benefits of fibrates. Given this information gap the guidelines are less specific with regard to targets for HDL cholesterol and triglycerides. They do, however, recognize low HDL cholesterol (< 1 mmol/L (39 mg/dL) in men and < 1.2 mmol/L (46 mg/dL) in women) and fasting triglycerides > 1.7 mmol/L (151 mg/dL) as markers of increased vascular risk.

If triglycerides remain > 2.0 mmol/L (> 177 mg/dL) after having reached the LDL cholesterol target with statins, a secondary treatment target of non-HDL cholesterol (total cholesterol minus HDL cholesterol) is suggested with a goal 0.8 mmol/L (31 mg/dL) higher that the identified LDL cholesterol goal. This may require the addition of ezetimibe, fibrates or nicotinic acid.

Blood pressure

Recommendation	Class	Level
In patients with diabetes and hypertension, the recommended target for blood pressure control is <130/80 mm Hg.	I	B
The cardiovascular risk in patients with diabetes and hypertension is substantially enhanced. The risk can be effectively reduced by blood pressure-lowering treatment.	I	A
The diabetic patient usually requires a combination of several anti-hypertensive drugs for satisfactory blood pressure control.	I	A
The diabetic patient should be prescribed a renin–angiotensin–system inhibitor as part of the blood pressure-lowering treatment.	I	A
Screening for microalbuminuria and adequate blood pressure-lowering therapy including the use of ACE-inhibitors and angiotensin receptor II blockers improves micro-and macrovascular morbidity in type 1 and type 2 diabetes.	I	A

Blood pressure control needs to be meticulous in diabetic patients as indicated in Table 1. Such treatment strategy is associated with a lower incidence of cardiovascular complications. Life style changes are usually insufficient and most patients need a combination of blood pressure lowering drugs. The beneficial effects of diuretics are as well documented as those of beta-blockers, calcium channel blockers and ACE-inhibitors and angiotensin II receptor blockers. Blockade of the renin–angiotensin–aldosterone system is of particular value in the diabetic patient. ACE-inhibitors and angiotensin II receptor blockers are the preferred therapies for delaying microalbuminuria/proteinuria and renal impairment.

7. Management of cardiovascular disease

Coronary artery disease

Recommendation	Class	Level
Early risk stratification should be part of the evaluation of the diabetic patient after ACS.	IIa	C
Treatment targets, as listed in Table 1, should be outlined and applied in each diabetic patient following an ACS.	IIa	C
Patients with acute MI and diabetes should be considered for thrombolytic therapy on the same grounds as their non-diabetic counterparts.	IIa	A
Whenever possible, patients with diabetes and ACS should be offered early angiography and mechanical revascularization.	IIa	B
Beta-blockers reduce morbidity and mortality in patients with diabetes and ACS.	IIa	B
Aspirin should be given for the same indications and in similar dosages to diabetic and non-diabetic patients.	IIa	B
Adenosine diphosphate (ADP) receptor dependent platelet aggregation inhibitor (clopidogrel) may be considered in diabetic patients with ACS in addition to aspirin.	IIa	C
The addition of an ACE-inhibitor to other therapies reduces the risk for cardiovascular events in patients with diabetes and established CVD.	I	A
Diabetic patients with acute MI benefit from tight glucometabolic control. This may be accomplished by different treatment strategies.	IIa	B

Patients with acute coronary syndromes (ACS) and concomitant diabetes mellitus are at high risk for complications. Their absolute mortality is high, 7-18% at 30 days and 15-34% after one year, and the adjusted relative risk for mortality ranging from 1.3 to 5.4, is somewhat higher in women than men underlining the profound role of the glucometabolic derangement. Registry studies reveal that diabetic patients are not as well treated as non-diabetic patients with regard to evidence-based therapy and coronary interventions. One reason may be that, due to autonomic neuropathy, silent

ischaemia or atypical symptoms are common in the diabetic patient. Another reason is that diabetes is experienced as a relative contra-indication to some treatment modalities. Nevertheless, evidence-based coronary care treatment, including early coronary angiography and, if possible, revascularization, is at least as effective in the diabetic patient as in the non-diabetic patient without indications for increased numbers of side-effects. Thus, they should be given meticulous attention according to existing management guidelines for patients with acute coronary syndromes.

Available treatment options meant to preserve and optimize myocardial function, achieve stabilisation of vulnerable plaques, prevent recurrent events by controlling prothrombotic activity and counteract progression of atherosclerotic lesions are summarised in Table 9.

Table 9. Treatment options based on accumulated evidence

- Revascularization
- Anti-ischaemic medication
- Anti-platelet agents
- Anti-thrombin agents
- Secondary prevention by means of
  - Lifestyle habits including food and physical activity
  - Smoking cessation
  - Blocking the renin–angiotensin system
  - Blood pressure control
  - Lipid-lowering medication
- Blood glucose control
  - Acute if needed by means of insulin infusion
  - Long term as demanded

Specific treatment

Thrombolytic drugs and coronary interventions are as efficient in patients with as those without diabetes. Due to a significantly higher absolute risk the relative benefits are substantially larger in diabetic than in non diabetic patients.

Oral *beta-blockers* are, in the absence of contra-indications, recommended for all diabetic patients with acute coronary syndromes.

Acetylsalicylic acid (ASA) reduces mortality and morbidity in patients with CAD. It has been claimed, but not verified, that ASA is less efficient in diabetic patients and that they need particularly high doses of ASA.

Clopidogrel may be considered in addition to ASA.

ACE-inhibitors protect diabetic patients from future events and should be considered in particular if the patient is hypertensive or has sign of renal impairment.

Glucose control by means of insulin should be immediately initiated in diabetic patients admitted for acute myocardial infarctions with significantly elevated blood glucose levels in order to reach normoglycaemia as soon as possible. Patients admitted with relatively normal glucose levels may be handled with oral glucose lowering agents. Strict glucose control should be continued based on life style counseling and supplemented with oral glucose lowering agents and/or insulin. Importantly long-term control has to be followed closely with glucose levels targeted as normal as possible (see also elsewhere in these guidelines).

Risk assessment and secondary prevention

A comprehensive risk assessment (Table 10) will help identify specific threats and outline goals for long-term management aiming at the prevention of further events and progression to irreversible myocardial damage in patients with acute coronary events.

Table 10. Risk assessment of patients with diabetes and acute coronary syndromes

Variable	Examination tools
Peripheral, renal and cerebrovascular disease	Case history, clinical examination
Traditional risk factors	
Eating and exercise habit	Case history
Smoking	Case history
Blood lipids	Blood chemistry
Blood pressure	Record (including ankle)
Previous or ongoing diseases	Case history and clinical examination supplemented by special examinations as indicated (exercise testing, holter monitoring, echo-doppler examination, magnetic resonance imaging, myocardial scintigraphy, ST-segment monitoring, stress echo)
Autonomic dysfunction	
Hypotension	
Heart failure	
Arrhythmias	
Ischaemic heart disease	

Recommendations for secondary prevention are the same for patients with as those without diabetes. For an equal treatment induced proportionate risk reduction, the number of patients needed to treat to save one life or prevent one defined end-point, is lower among diabetic patients due to their higher absolute risk.

Important treatment targets are usually more ambitious for those with than those without diabetes, as outlined in Table 1.

In general it seems that many diabetic patients presently are less well controlled than they deserve and great efforts should be made to improve the situation for this group of patients at a high cardiovascular risk.

Diabetes and coronary revascularization

Recommendation	Class	Level
Treatment decisions regarding revascularization in patients with diabetes should favour coronary artery bypass surgery over percutaneous intervention.	IIa	A
Glycoprotein IIb/IIIa inhibitors are indicated in elective PCI in a diabetic patient.	I	B
When PCI with stent implantation is performed in a diabetic patient, drug-eluting stents (DES) should be used.	IIa	B
Mechanical reperfusion by means of primary PCI is the revascularization mode of choice in a diabetic patient with acute MI.	I	A

Patients with diabetes have a higher mortality and morbidity after bypass surgery (CABG) compared with non-diabetics. This is also seen in patients undergoing percutaneous coronary interventions (PCI). The influence of glucometabolic control on the outcome after revascularisation is still unclear. Patients who require insulin have more adverse events, but this may be related to longer diabetes duration or more advanced diabetes affecting the morbidity or perhaps by so far unknown variables.

Surgery vs. percutaneous intervention

The effectiveness of PCI and CABG has been compared in randomised controlled trials. Originally major concerns were raised when a post-hoc subgroup analysis of patients with diabetes and multivessel disease, demonstrated a less favourable prognosis after PCI than after CABG. Other studies (Table 11), including those applying coronary stenting (Table 12) could, however, not confirm the negative outcome with PCI. In BARI the survival difference was linked to diabetic patients who received at least one arterial internal mammary graft.

Table 11. Trials addressing diabetes and revascularization for multivessel disease

Trial	Patients (n)	Follow-up (years)	Mortality (%) CABG	Mortality (%) PCI	p-value
BARI	353	7	23.6	44.3	<0.001
CABRI	124	4	12.5	22.6	ns
EAST	59	8	24.5	39.9	ns
BARI registry	339	5	14.9	14.4	ns

Drug Eluting Stents have been hailed to improve the outcome of PCI in the diabetic patient. A recent meta-analysis comparing drug eluting stents to bare metal stents in diabetic subpopulations revealed that drug eluting stents were associated with a 80% relative risk reduction for restenosis during the first year of follow-up. However, trials comparing drug eluting stents with CABG are still needed to determine the optimal revascularization strategy.

Table 12. Revascularization in diabetes patients with multivessel disease in the stent-era

Trial	Patients (n)	Follow up (years)	Mortality (%) CABG	Mortality (%) PCI	Repeat revascularization (%) CABG	Repeat revascularization (%) PCI	Mortality p value
ARTS	208	3	4.2	7.1	8.4	41.1	0.39
SoS	150	1	0.8	2.5			ns
AWESOME	144	5	34	26			0.27

Adjunctive therapy

Glycoprotein IIb/IIIa inhibitors improve the outcome after PCI when administered during the procedure in diabetic patients. Moreover adenosine diphosphate receptor antagonists like clopidogrel prevent early as well as late thrombotic complications after stent implantation, particularly in patients with diabetes.

Revascularization and reperfusion in MI

An analysis of diabetic patients included in randomized trials demonstrated a survival benefit for those treated with primary percutaneous coronary interventions over those with thrombolytic treatment.

8. Heart failure and diabetes

Recommendation	Class	Level
ACE-inhibitors are recommended as first-line therapy in diabetic patients with reduced left ventricular dysfunction with or without symptoms of heart failure.	I	C
Angiotensin-II receptor blockers have similar effects in heart failure as ACE-inhibitors and can be used as an alternative or even as added treatment to ACE-inhibitors.	I	C
BBs in the form of metoprolol, bisoprolol, and carvedilol are recommended as first-line therapy in diabetic patients with heart failure.	I	C
Diuretics, in particular loop diuretics, are important for symptomatic treatment of diabetic patients with fluid overload owing to heart failure.	IIa	C
Aldosterone antagonists may be added to ACE-inhibitors, BBs, and diuretics in diabetic patients with severe heart failure.	IIb	C

There is a strong association between diabetes and heart failure and this combination has a deleterious prognosis. Few if any clinical trials on heart failure treatment have specifically addressed diabetic patients. Thus, information on treatment efficacy of various drugs is based on diabetic subgroups in various heart failure trials. Most data favour a similar efficacy in patients with and without diabetes, which means that the relative benefit is higher in the latter patient category who have a higher absolute risk. As outlined in European guidelines for heart failure (2) management should be based on diuretics, ACE-inhibitors and beta-blockers. Moreover it has been assumed that meticulous metabolic control should be beneficial in heart failure patients with diabetes.

9. Arrhythmias, atrial fibrillation and sudden cardiac death

Atrial fibrillation

Recommendation	Class	Level
Aspirin and anticoagulant use as recommended for patients with atrial fibrillation should be rigorously applied in diabetic patients with atrial fibrillation to prevent stroke.	I	C
Chronic oral anticoagulant therapy in a dose adjusted to achieve a target international normalized ratio (INR) of 2–3 should be considered in all patients with atrial fibrillation and diabetes, unless contra-indicated.	IIa	C
Control of glycaemia even in the pre-diabetic stage is important to prevent the development of the alterations that predispose to sudden cardiac death.	I	C
Microvascular disease and nephropathy are indicators of increased risk of sudden cardiac death in diabetic patients.	IIa	B

Diabetes seems to favour the occurrence of atrial fibrillation although the underlying mechanisms remain to be elucidated. In the guidelines on atrial fibrillation from the American College of Cardiology/American Heart Association/European Society of Cardiology (3), diabetes is classified as a moderate risk factor together with age > 75 years, hypertension, heart failure and a left ventricular ejection fraction < 35%. In patients with permanent or paroxysmal atrial fibrillation, who already had a stroke or a transient ischaemic attack, anticoagulant therapy with an INR between 2.0 and 3.0 is indicated. Also patients with more than one moderate risk factor for thrombo-embolism, whereof diabetes is one, should receive anticoagulant therapy. Recommendation for antithrombotic therapy in the presence of only one moderate risk factor is aspirin 81-325 mg daily or anticoagulant therapy. Aspirin in a dose of 325 mg is indicated as an alternative in patients with contra-indications to oral anticoagulation.

Sudden Cardiac Death

The incidence of cardiac arrhythmias, including ventricular fibrillation and sudden death is enhanced in the diabetic patient. Ischaemic heart disease, direct metabolic

alterations, ion channel abnormalities and autonomic dysfunction may all contribute to create the substrate for sudden cardiac death. Recent evidence favours the concept that the risk relates to the glucose level, present already at the stage of impaired glucose tolerance. The identification of independent predictors of sudden cardiac death in diabetic patients has not yet progressed to a stage where it is possible to devise a risk stratification scheme for the prevention of such deaths. Microvascular disease and nephropathy may, however, be indicators of an increased risk.

10. Peripheral and cerebrovascular disease

Peripheral vascular disease

Recommendation	Class	Level
All patients with type 2 diabetes and CVD are recommended treatment with low-dose aspirin.	IIa	B
In diabetic patients with peripheral vascular disease, treatment with clopidogrel or low molecular weight heparin may be considered in certain cases.	IIb	B
Patients with critical limb ischaemia should, if possible, undergo revascularization procedures.	I	B
An alternative treatment for patients with critical limb ischaemia, not suited for revascularization, is prostacyclin infusion.	I	A

Subjects with diabetes have a two to four-fold increase in the incidence of peripheral vascular disease and an abnormal ankle-brachial blood pressure index is present in approximately 15% of such patients.

Diagnosis

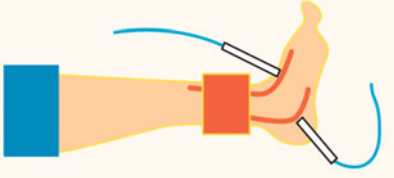
Symptoms of leg ischaemia in diabetic patients may be atypical and vague due to peripheral neuropathy. Rather than experience typical pain in the legs the patient may suffer from leg fatigue or only inability to walk at a normal pace. Physical examination is of critical importance for the diagnosis (Table 13).

A valuable tool for early detection of peripheral artery disease is to measure the ankle-brachial blood pressure index. This is defined as the ratio between the arterial pressure at the ankle level and in the brachial artery with the highest pressure (Figure 5). Measurement is made in the supine position after 5 minutes of rest. The ankle-brachial blood pressure index should normally be above 0.9.

Table 13. Investigations of the peripheral circulation in diabetic patients

At the physician's office (regularly)	
Inspection	Dependent rubor Pallor with elevation Absence of hair growth Dystrophic toenails Ulcers or gangrenes
Palpation	Decreased pulses Dry and cool skin Impaired sensibility
Pressure measurement	Ankle and arm blood pressure
At the vascular laboratory (if appropriate)	
Distal and/or segmental pressure measurements Oscillography Treadmill testing (with or without distal pressure after exercise) Duplex sonography *For evaluation of the microcirculation* Transcutaneous oxygen pressure Vital capillaroscopy	
At the radiology department (if appropriate)	
Magnetic resonance imaging Angiography	

Figure 5. Measurement of ankle blood pressure. A Doppler device is used to detect pulses in the posterior tibial artery and the dorsal pedal artery while slowly deflating the cuff around the ankle. The highest pressure is the ankle pressure.



An ankle-brachial blood pressure index below 0.5 or an ankle pressure below 50 mm Hg indicates severely impaired circulation of the foot.

An ankle-brachial blood pressure index above 1.3 indicates poorly compressible vessels as a result of stiff arterial walls, which usually in diabetic patients are due to atherosclerosis in the media layer of the arterial wall. An arterial angiography should only be performed when this

makes it likely that an invasive intervention to restore arterial circulation may be possible.

Treatment

Platelet inhibition with low-dose *aspirin* is indicated in all patients with type 2 diabetes who do not have contra-indication and for patients with severe peripheral vascular disease further inhibition of platelet aggregation by *clopidogrel or dipyridamole* may be indicated.

In patients with non-ischaemic neuropathic ulcers it is of utmost importance to remove any external pressure from the ulcer area sometimes necessitating immobilization of the patient. Amputations have been performed where a careful treatment would have saved the extremity.

The only pharmacological agent so far convincingly shown to have a positive influence on the prognosis of patients with critical limb ischaemia is a synthetic *prostacyclin*. If anatomically possible a *revascularization* procedure, with angioplasty or surgery, should be attempted in all such patients.

Stroke

Recommendation	Class	Level
For stroke prevention, blood pressure lowering is more important than the choice of drug. Inhibition of the renin–angiotensin–aldosterone system may have additional benefits beyond blood pressure lowering *per se*.	IIa	B
Patients with acute stroke and diabetes should be treated according to the same principles as stroke patients without diabetes.	IIa	C

Diabetes is a strong independent risk factor for stroke. The relationship between hyperglycaemia *per se* and stroke is, however, less clear than the relationship between hyperglycaemia and myocardial infarction. Microvascular complications further increase the risk for stroke. In diabetic patients the type of stroke is usually ischaemic.

Prevention of stroke

Measures to prevent stroke should include a multifactorial strategy aimed at treatment of hypertension, hyperlipidaemia, microalbuminuria, hyperglycaemia and the use of antiplatelet medication as outlined elsewhere in these guidelines.

Treatment of acute stroke

The treatment in the acute phase follows similar principles as for the treatment of stroke in the general population. Thrombolysis is an effective treatment for ischaemic stroke if instituted within 3-4 hours. Conservative treatment includes close surveillance in a stroke ward and includes optimisation of circulatory and metabolic conditions, including glycaemic control. Currently it is recommended to acutely reduce high blood pressures, above 220 mm Hg systolic and/or 120 mm Hg diastolic, but with great caution not lowering blood pressure to levels which may enhance ischaemia.

11. Intensive care

Recommendation	Class	Level
Strict blood glucose control with intensive insulin therapy improves mortality and morbidity of adult cardiac surgery patients.	I	B
Strict blood glucose control with intensive insulin therapy improves mortality and morbidity of adult critically ill patients.	I	A

Hyperglycaemia and outcome of critical illness

Stress imposed by critical illness leads to metabolic and endocrine abnormalities. Due to insulin resistance and accelerated glucose production patients usually become hyperglycaemic. In contrast to previous beliefs it is nowadays clearly established that even a modest hyperglycaemia is an important risk factor in terms of mortality and morbidity.

Blood glucose control with intensive insulin therapy in critical illness

Intensive insulin therapy aiming at maintaining blood glucose at a normal level decreases mortality and prevents several critical illness-associated complications as presented in Table 14. Further analyses revealed that it is blood glucose control, and/or other metabolic effects of insulin, that accompany tight blood glucose control, and not the insulin dose *per se* that contributed to improved survival.

Table 14. Published trials on intensive insulin therapy in critical illness

Patient population[a]	Surgical	Medical	Surgical and medical	Surgical	Heart surgery in diabetes
Number of patients	1548	1200/767[b]	1600	61	4864
Randomized study	Yes	Yes	No	Yes	No
Target glucose (mmol/L)	< 6.1	< 6.1	< 7.8	< 6.7	< 8.3
Mortality	↓	↓	↓		↓
Critical illness polyneuropathy	↓				
Bacteraemia/severe infections	↓	-	-	↓	
Acute renal failure	↓	↓	↓		
Red blood cell transfusions	↓		↓		
Duration of mechanical ventilation	↓	↓			
Length of stay	↓	↓	↓		↓
Deep sternal wound infections					↓

a: See full text document for detailed information

b: Morbidity in all intention-to-treat patients (n = 1200); morbidity and mortality in the patients who required ≥ third day in ICU (n = 767).

12. Health economics and diabetes

Recommendation	Class	Level
Lipid-lowering provides a cost-effective way of preventing complications.	I	A
Tight control of hypertension is cost-effective.	I	A

The total costs for patients with type 2 diabetes have been analysed in eight European countries (Table 15). Due to the strong impact of co-morbidity in type 2 diabetes patients it is not possible to separate which resource use is due to diabetes and which are due to other diseases.

The main cost-driver is not diabetes in itself or its treatment, but the complications. Costs are 1.7, 2.0 and 3.5 times higher if the patient has microvascular, macrovascular or both types of complications respectively. The key driver is the cost for hospitalization. Since complications are the most important cost driver the effective prevention of complications is essential and cost-effective.

Table 15. Direct medical costs for patients with type 2 diabetes in eight European countries and percentage of healthcare expenditure in the respective countries (1998)

Country	Total costs (million €)	Cost per patient (€)	Cost of healthcare expenditure (%)
Belgium	1094	3295	6.7
France	3983	3064	3.2
Germany	12438	3576	6.3
Italy	5783	3346	7.4
The Netherlands	444	1889	1.6
Spain	1958	1305	4.4
Sweden	736	2630	4.5
UK	2608	2214	3.4
All countries	29000	2895	5.0

13. References

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Section IV:
Coronary Heart Disease

1. Non-ST-segment Elevation Acute Coronary Syndromes

2. Acute Myocardial Infarction in Patients Presenting with Persistent ST-Segment Elevation

3. Stable Angina Pectoris

4. Percutaneous Coronary Interventions (PCI)

Chapter 1
Non-ST-segment Elevation Acute Coronary Syndromes*
2007

The Task Force for the Diagnosis and Treatment of Non-ST-Segment Elevation Acute Coronary Syndromes of the European Society of Cardiology

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1. Introduction

These guidelines aim to present management recommendations based on all of the relevant evidence on a particular subject in order to help physicians to select the best possible management strategy for the individual patient. The strength of evidence for or against particular procedures or treatments is weighted, according to predefined scales for grading recommendations and levels of evidence, as outlined below. However, the ultimate judgment regarding the care of an individual patient must be made by the physician in charge of his/her care.

Classes of Recommendations

Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful and effective
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a given treatment or procedure.
Class IIa	Weight of evidence/opinion is in favour of usefulness/efficacy.
Class IIb	Usefulness/efficacy is less well established by evidence/opinion
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective and in some cases may be harmful

Levels of Evidence

Level of Evidence A	Data derived from multiple randomized clinical trials or meta-analyses
Level of Evidence B	Data derived from a single randomized clinical trial or large non-randomized studies
Level of Evidence C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries

2. Definitions

The different presentations of acute coronary syndromes (ACS) share a common pathophysiological substrate. The leading symptom that initiates the diagnosis and

*Adapted from the ESC Guidelines on the Diagnosis and Treatment of Non-ST Segment Elevation Acute Coronary Syndromes (European Heart Journal 2007; 28 (13) 1598-1660). An updated version of these pocket guidelines on Non-ST-segment Elevation Acute Coronary Syndromes is now available. The full text of these ESC Guidelines is available on www.escardio.org/guidelines.

J. Bax et al., *Compendium of Abridged ESC Guidelines 2001*

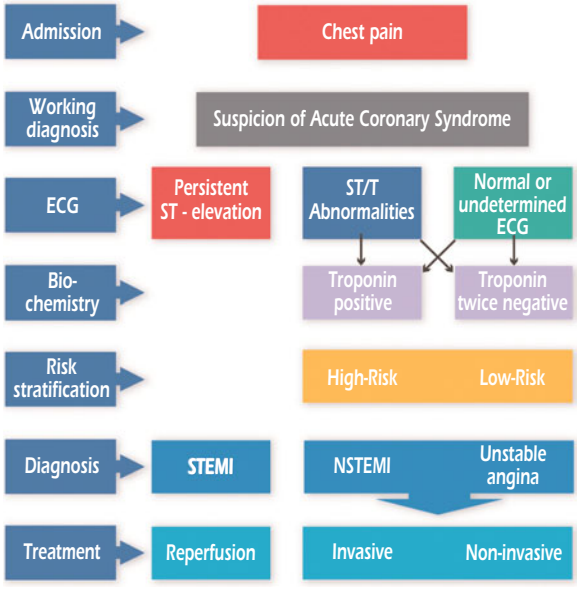
therapeutic decision making process is chest pain, but the classification of patients is based on the electrocardiogram (ECG). Two categories of patients may be encountered:

1. **Patients with typical acute chest pain and persistent (> 20 minutes) ST-segment elevation:** This is termed ST-elevation ACS (STE-ACS) and generally reflects an acute total coronary occlusion. Most of these patients will ultimately develop an ST-elevation MI (STEMI). The therapeutic objective is to achieve rapid, complete, and sustained reperfusion by primary angioplasty or fibrinolytic therapy.

2. **Patients with acute chest pain but without persistent ST-segment elevation.** They have rather persistent or transient ST-segment depression or T-wave inversion, flat T-waves, pseudo-normalisation of T-waves, or no ECG changes at presentation.

The initial working diagnosis of non-ST-elevation acute coronary syndrome (NSTE-ACS), based on the measurement of troponins, will subsequently be further qualified as non-ST-elevation MI (NSTEMI) or unstable angina; (Figure 1). In a certain number of patients, coronary artery disease (CAD) will be excluded as the cause of symptoms. The therapeutic management is guided by the final diagnosis.

Figure 1: The spectrum of acute coronary syndromes



3. Epidemiology and natural history

Data from registries consistently show that NSTE-ACS have become more frequent than ST-elevation ACS. Hospital mortality is higher in patients with STEMI than among those with NSTE-ACS (7% vs 5% respectively), but at 6 months, the mortality rates are very similar in both conditions (12% vs 13% respectively). Long-term follow-up showed that death rates were higher among those with NSTE-ACS than STEMI, with a two fold difference at four years. This difference in mid- and long-term evolution may be due to different patient profiles, since NSTE-ACS patients tend to be older, with more co-morbidities, especially diabetes and renal failure. The difference could also be due to the greater extent of coronary artery and vascular disease, or persistent triggering factors such as inflammation. The implications for therapy are as follows:

- NSTE-ACS is more frequent than STEMI.
- In contrast to STEMI, where most events occur before or shortly after presentation, in NSTE-ACS these events continue over days and weeks.
- Mortality of STEMI and NSTE-ACS after 6 months are comparable.

This implies that treatment strategies for NSTE-ACS need to address the requirements of the acute phase as well as longer-term treatment.

4. Pathophysiology

ACS represent a life-threatening manifestation of atherosclerosis usually precipitated by acute thrombosis, induced by a ruptured or eroded atherosclerotic plaque, with or without concomitant vasoconstriction, causing a sudden and critical reduction in blood flow. In the complex process of plaque disruption, inflammation was revealed as a key pathophysiologic element. In rare cases, ACS may have a non-atherosclerotic aetiology such as arteritis, trauma, dissection, thrombo-embolism, congenital anomalies, cocaine abuse, and complications of cardiac catheterization. Some key pathophysiologic elements are described in more detail in the main document because they are important to understand the therapeutic strategies, particularly the notions of vulnerable plaque, coronary thrombosis, vulnerable patient, endothelial vasodilatory dysfunction, accelerated atherothrombosis, secondary mechanisms of non-ST-elevation ACS and myocardial injury.

5. Diagnosis and risk assessment

The clinical presentation of NSTE-ACS encompasses a wide variety of symptoms. Traditionally, several clinical presentations have been distinguished:

- Prolonged (> 20 minutes) anginal pain at rest,
- New onset (*de novo*) severe angina Class III of the Classification of the Canadian Cardiovascular Society (CCS),
- Recent destabilisation of previously stable angina with at least CCS III angina characteristics (crescendo angina), or
- Post MI angina.

Prolonged pain is observed in 80% of patients, while *de novo* or accelerated angina are observed in only 20%. It is important to note that a reliable distinction between ACS with or without ST-elevation cannot be based on symptoms.

Clinical symptoms: Retro-sternal pressure or heaviness ("angina") radiating to the left arm, neck or jaw is the most common symptom. This may be accompanied by other symptoms such as diaphoresis, nausea, abdominal pain, dyspnoea, and syncope. Atypical presentations are not uncommon. These include epigastric pain, recent onset indigestion, stabbing chest pain, chest pain with some pleuritic features, or increasing dyspnoea. Atypical complaints are often observed in younger (25-40 years) and older (> 75 years) patients, in women, and in patients with diabetes, chronic renal failure or dementia.

Diagnostic tools: These include:

- physical examination
- electrocardiogram
- biochemical markers
- echocardiography
- imaging of the coronary anatomy.

Clinical history, ECG findings and biomarkers (particularly troponin T or I sampling) are essential for diagnostic (and prognostic) purposes.

Physical examination: Frequently normal. Signs of heart failure or haemodynamic instability must prompt the physician to expedite the diagnosis and treatment of patients. An important goal of the physical examination is to exclude non-cardiac causes.

ECG: ST-segment shifts and T-wave changes are the ECG indicators of unstable coronary artery disease. The number of leads showing ST depression and the magnitude of ST-depression are indicative of extent and severity of ischaemia and correlate with prognosis. ST-segment depression ≥ 0.5 mm (0.05 mV) in two or more contiguous leads, in the appropriate clinical context, is suggestive of NSTE-ACS and linked to prognosis. Minor (0.5 mm) ST-depression may be difficult to measure in clinical practice. More relevant is ST-depression of ≥ 1 mm (0.1 mV), which is associated with an 11% rate of death and MI at 1 year. ST-depression of ≥ 2 mm carries about a 6 fold increased mortality risk. ST-depression combined with transient ST-elevation also identifies a high risk subgroup. Deep symmetrical inversion of the T-waves in the anterior chest leads is often related to a significant stenosis of the proximal left anterior descending coronary artery or main stem.

- A normal ECG does not exclude the possibility of NSTE-ACS.

Biomarkers

Troponins: In patients with MI an initial rise in troponins in peripheral blood occurs after 3 to 4 hours. Troponin levels may persist elevated for up to 2 weeks after myocardial infarction. In NSTE-ACS, minor elevation of troponins may be measurable only over 48 to 72 hours. The high sensitivity of troponin tests allows the detection of myocardial damage undetected by CK-MB in up to one third of patients presenting with NSTE-ACS. Minor or moderate elevations of troponins appear to carry the highest early risk in patients with NSTE-ACS.

It should be noted that troponin elevation can be encountered in many conditions that do not constitute acute coronary syndromes (Table 1). Other life threatening conditions presenting with chest pain may also result in elevated troponins and should always be considered as a differential diagnosis.

- The diagnosis of NSTE-ACS should never be made only on the basis of cardiac biomarkers whose elevation should be interpreted in the context of other clinical findings.

Other biomarkers are helpful for differential diagnoses: D-dimer (pulmonary embolism), BNP/NT-proBNP (dyspnoea, heart failure), haemoglobin (anaemia), leucocytes (inflammatory disease), markers of renal function.

Echocardiography: Routine use is recommended to detect wall motion abnormalities and to rule out differential diagnoses.

Differential diagnoses: Other conditions that may mimic NSTE-ACS are summarised in Table 2.

Table 1: Non-coronary conditions with troponin elevations

• Severe congestive heart failure - acute and chronic
• Aortic dissection, aortic valve disease or hypertrophic cardiomyopathy
• Cardiac contusion, ablation, pacing, cardioversion, or endomyocardial biopsy
• Inflammatory diseases, e.g., myocarditis, or myocardial extension of endo-/pericarditis
• Hypertensive crisis
• Tachy- or bradyarrhythmias
• Pulmonary embolism, severe pulmonary hypertension
• Hypothyroidism
• Apical ballooning syndrome
• Chronic or acute renal dysfunction
• Acute neurological disease, including stroke, or subarachnoid haemorrhage
• Infiltrative diseases, e.g., amyloidosis, haemochromatosis, sarcoidosis, scleroderma
• Drug toxicity, e.g., adriamycin, 5-fluorouracil, herceptin, snake venoms
• Burns, if affecting > 30% of body surface area
• Rhabdomyolysis
• Critically ill patients, especially with respiratory failure, or sepsis

Risk Stratification

Several risk stratification scores have been developed and validated in large patient populations. The GRACE risk score is based on a large unselected population of an international registry with a full spectrum of ACS patients. The risk factors were derived with independent predictive power for in-hospital deaths and post-discharge deaths at 6 months. GRACE risk score makes it possible to assess risk of in-hospital and 6-month death (Table 3). Further details are available at:
http://www.outcomes-umassmed.org/grace/

Table 2: Cardiac and non-cardiac conditions that can mimic NSTE-ACS

Cardiac	Pulmonary	Haematological
Myocarditis Pericarditis Myopericarditis Cardiomyopathy Valvular disease Apical ballooning (Tako-Tsubo syndrome)	Pulmonary embolism Pulmonary infarction Pneunonia Pleuritis Pneumothorax	Sickle cell anaemia
Vascular	**Gastro-intestinal**	**Orthopaedic**
Aortic dissection Aortic aneurysm Aortic coarctation Cerebrovascular disease	Oesophageal spasm Oesophagitis Peptic ulcer Pancreatitis Cholescystitis	Cervical discopathy Rib fracture Muscle injury/ inflammation Costochondritis

Table 3: Mortality in hospital and at 6 months in low, intermediate and high risk categories in registry populations according to the GRACE Risk Score

Risk category (tertiles)	GRACE Risk Score	In-hospital deaths (%)
Low	≤ 108	< 1
Intermediate	109-140	1-3
High	> 140	> 3
Risk category (tertiles)	**GRACE Risk Score**	**Post-discharge to 6 months deaths (%)**
Low	≤ 88	< 3
Intermediate	89-118	3-8
High	> 118	> 8

Recommendations for diagnosis and risk stratification

- Diagnosis and short-term risk stratification of NSTE-ACS should be based on a combination of clinical history, symptoms, ECG, biomarkers and risk score results **(I-B)**.

- The evaluation of the individual risk is a dynamic process that is to be updated as the clinical situation evolves.

  - A 12-lead ECG should be obtained within 10 minutes of first medical contact and immediately read by an experienced physician **(I-C)**. Additional leads (V_3R and V_4R, V_7-V_9) should be recorded. ECG should be repeated in case of recurrence of symptoms, and at 6, 24 hours and before hospital discharge **(I-C)**.

  - Blood must be drawn promptly for troponin (cTnT or cTnI) measurement. The result should be available within 60 minutes **(I-C)**. The test should be repeated after 6-12 hours if the initial test is negative **(I-A)**.

  - Established risk scores (such as GRACE) should be implemented for initial and subsequent risk assessment **(I-B)**.

  - An echocardiogram is recommended to rule in/out differential diagnoses **(I-C)**.

  - In patients without recurrence of pain, normal ECG findings, and negative troponins tests, a non-invasive stress test for inducible ischaemia is recommended before discharge **(I-A)**.

- The following predictors of *long-term* death or MI should be considered in risk stratification **(I-B)**:

  - Clinical indicators: age, heart rate, blood pressure, Killip class, diabetes, previous MI/CAD.

  - ECG markers: ST-segment depression.

  - Laboratory markers: troponins, GFR/CrCl/ Cystatin C, BNP/NT-proBNP, hsCRP.

  - Imaging findings: low ejection fraction, main stem lesion, 3-vessel disease.

  - Risk score result.

6. Treatment

The management of NSTE-ACS includes five therapeutic tools:

- Anti-ischaemic agents
- Anticoagulants
- Antiplatelet agents
- Coronary revascularization
- Long-term management

6.1. Anti-ischaemic agents

These drugs decrease myocardial oxygen consumption (decreasing heart rate, lowering blood pressure or depressing LV contractility) and/or induce vasodilatation.

Recommendations for anti-ischaemic drugs:

- Beta-blockers are recommended in the absence of contraindications, particularly in patients with hypertension or tachycardia **(I-B)**.

- Intravenous or oral nitrates are effective for symptom relief in the acute management of anginal episodes **(I-C)**.

- Calcium channel blockers provide symptom relief in patients already receiving nitrates and beta-blockers; they are useful in patients with contraindications to beta-blockade, and in the subgroup of patients with vasospastic angina **(I-B)**.

- Nifedipine, or other dihydropyridines, should not be used unless combined with beta-blockers **(III-B)**.

6.2. Anticoagulants

Several anticoagulants, which act at different levels of the coagulation cascade, have been investigated in NSTE-ACS:

- Unfractionated heparin (UFH) as intravenous infusion;
- Low molecular weight heparin (LMWH) as subcutaneous injection;
- Fondaparinux as subcutaneous injection;
- Direct thrombin inhibitors (DTIs) as intravenous infusion;
- Vitamin-K antagonists (VKAs) as oral medication.

Most anticoagulants have been shown to be capable of reducing the risk of death and/or MI at the cost of bleeding complications. The recommendations for the use of anticoagulants have mostly been based on the safety-efficacy profile of each drug (balance between risk reduction for ischaemic events, and risk of bleeding).

Recommendations for anticoagulation:

- Anticoagulation is recommended for all patients in addition to antiplatelet therapy **(I-A)**.
- Anticoagulation should be selected according to the risk of ischaemic and bleeding events **(I-B)**.
- Several anticoagulants are available, namely UFH, LMWH, fondaparinux, bivalirudin. The choice depends on the initial strategy (see section 9 Management strategies) urgent invasive, early invasive, or conservative strategies **(I-B)**.
- In an urgent invasive strategy UFH **(I-C)**, or enoxaparin **(IIa-B)** or bivalirudin **(I-B)** should be immediately started. (See section 9 Management strategies).
- In non-urgent situations, when the decision whether to follow early invasive or conservative strategy is pending (see Section 9 Management strategies):
  - Fondaparinux is recommended on the basis of the most favourable efficacy/safety profile **(I-A)**.
  - Enoxaparin with a less favourable efficacy/safety profile than fondaparinux should be used only if the bleeding risk is low **(IIa-B)**.
  - As efficacy/safety profile of LMWH (other than enoxaparin) or UFH relative to fondaparinux is unknown, these anticoagulants cannot be recommended over fondaparinux **(IIa-B)**.
- At PCI procedures the initial anti-coagulant should be maintained also during the procedure regardless whether this treatment is UFH **(I-C)**, enoxaparin **(IIa-B)** or bivalirudin **(I-B)**, while addititional UFH in standard dose (50-100 IU/kg bolus) is necessary in case of fondaparinux **(IIa-C)**.
- Anticoagulation can be stopped within 24 hours of the invasive procedure **(IIa-C)**. In a conservative strategy, fondaparinux, enoxaparin or other LMWH may be maintained up to hospital discharge **(I-B)**.

6.3. Antiplatelet agents

Antiplatelet therapy is necessary for the acute event, and subsequent maintenance therapy. Three related, but complementary strategies provide effective antiplatelet therapy: cyclooxygenase-1 inhibition (aspirin), inhibition of ADP mediated platelet aggregation with thienopyridines (ticlopidine and clopidogrel) and GP IIb/IIIa inhibition (tirofiban, eptifibatide, abciximab).

Premature withdrawal of antiplatelet agents, particularly dual antiplatelet therapy prescribed for the long-term, may lead to recurrence of events, particularly in patients with recent stent implantation. Interruption of dual antiplatelet therapy may become mandatory in certain situations, such as need for urgent surgery or major bleeding that cannot be controlled by local treatment. In this case, different alternative treatments have been proposed, depending on the clinical setting, type of stent and date of implantation, or type of surgery. However, none has formally been proven efficacious. All are based on experts' consensus opinion. LMWH have been advocated without tangible proof of efficacy.

Recommendations for oral antiplatelet drugs

- Aspirin is recommended for all patients presenting with NSTE-ACS without contra-indication at an initial loading dose of 160-325 mg (non-enteric) **(I-A)**, and at a maintenance dose of 75 to 100 mg long-term **(I-A)**.
- For all patients, immediate 300 mg loading dose of clopidogrel is recommended, followed by 75 mg clopidogrel daily **(I-A)**. Clopidogrel should be maintained for 12 months unless there is an excessive risk of bleeding **(I-A)**.
- For all patients with contra-indication to aspirin, clopidogrel should be given instead **(I-B)**.
- In patients considered for an invasive procedure/PCI, a loading dose of 600 mg of clopidogrel may be used to achieve more rapid inhibition of platelet function **(IIa-B)**.
- In patients pre-treated with clopidogrel who need to undergo CABG, surgery should be postponed for 5 days for clopidogrel withdrawal if clinically feasible **(IIa-C)**.

Recommendations for GP IIb/IIIa inhibitors

- In patients at intermediate to high risk, particularly patients with elevated troponins, ST-depression, or diabetes, either eptifibatide or tirofiban for initial early treatment are recommended in addition to oral antiplatelet agents **(IIa-A)**.

Table 4: Summary of antiplatelet and anticoagulant therapies available for the treatment of non-ST-segment elevation ACS

Oral Antiplatelet Therapy
• Aspirin initial dose: 160-325 mg non-enteric formulation, followed by 75-100 mg daily
• Clopidogrel 75 mg/day after a loading dose of 300 mg (600 mg loading dose when rapid onset of action is wanted)
Anticoagulants
• Fondaparinux 2.5 mg subcutaneously daily
• Enoxaparin 1 mg/kg subcutaneously every 12 h
• Dalteparin 120 IU/kg every 12 h
• Nadroparin 86 IU/kg every 12 h
• UFH intravenous bolus 60-70 IU/kg (maximum 5000 IU) followed by infusion of 12-15 IU/kg/h (maximum 1000 IU/h) titrated to aPTT 1.5-2.5 times control
• Bivalirudin intravenous bolus of 0.1 mg/kg and infusion of 0.25 mg/kg/hr. Additional intravenous bolus 0.5 mg/kg and infusion increased to 1.75 mg/kg/hour before PCI
GP IIb/IIIa inhibition
• Abciximab 0.25 mg/kg intravenous bolus followed by infusion of 0.125 μg/kg/min (maximum 10 μg/min) for 12 to 24 h
• Eptifibatide 180 μg/kg intravenous bolus (second bolus after 10 min for PCI) followed by infusion of 2.0 μg/kg/min for 72 to 96 h
• Tirofiban 0.4 μg/kg/min intravenously for 30 minutes followed by infusion of 0.10 μg/kg/min for 48 to 96 h. A high dose regimen (bolus 25 μg/kg + 0.15 μg/kg/min infusion for 18 hours) is tested in clinical trials.

- The choice of combination of antiplatelet agents and anticoagulants should be made in relation to risk of ischaemic and bleeding events **(I-B)**.
- Patients who received initial treatment with eptifibatide or tirofiban prior to angiography, should be maintained on the same drug during and after PCI **(IIa-B)**.
- In high risk patients not pretreated with GP IIb/IIIa inhibitors and proceeding to PCI, abciximab is recommended immediately following angiography **(I-A)**. The use of eptifibatide or tirofiban in this setting is less well established **(IIa-B)**.
- GP IIb/IIIa inhibitors must be combined with an anticoagulant **(I-A)**.
- Bivalirudin may be used as an alternative to GP IIb/IIIa inhibitors plus UFH/LMWH **(IIa-B)**.
- When the anatomy is known and PCI is planned to be performed within 24 hours and using GP IIb/IIIa inhibitors, most secure evidence is for abciximab **(IIa-B)**.

Recommendations for withdrawal of antiplatelet treatment

- Temporary interruption of dual antiplatelet therapy (aspirin and clopidogrel) within the first 12 months after the initial episode is discouraged **(I-C)**.
- Temporary interruption for major or life-threatening bleeding or for surgical procedures where even minor bleeding may result in severe

consequences (e.g. brain or spinal surgery) is mandatory **(IIa-C)**.

- Prolonged or permanent withdrawal of aspirin, clopidogrel or both is discouraged unless clinically indicated. Consideration should be given to the risk of recurrence of ischaemic events which depends (among other factors), on initial risk, on presence and type of stent implanted, and on time window between proposed withdrawal and index event and/or revascularization **(I-C)**.

6.4. Coronary revascularization

Revascularization for NSTE-ACS is performed to relieve angina and ongoing myocardial ischaemia, and to prevent progression to MI or death. The indications for myocardial revascularization and the preferred approach (PCI or CABG) depend on the extent and severity of the lesions as identified by coronary angiography, the patient's condition and co-morbidity.

Recommendations for invasive evaluation and revascularization (see also section 9 Management strategies)

- Urgent coronary angiography is recommended in patients with refractory or recurrent angina associated with dynamic ST deviation, heart failure, life threatening arrhythmias or haemodynamic instability **(I-C)**.

- Early (< 72 hours) coronary angiography followed by revascularization (PCI or CABG) in patients with intermediate to high-risk features is recommended **(I-A)**.

- Routine invasive evaluation of patients without intermediate to high risk features is not recommended **(III-C)**, but non-invasive assessment of inducible ischaemia is advised **(I-C)**.

- PCI of non-significant lesions by angiography is not recommended **(III-C)**.

- After critical evaluation of the risk to benefit ratio, and depending on known co-morbidities and potential need for non-cardiac surgery in the short/medium term (e.g. planned intervention or other conditions) requiring temporary withdrawal of dual antiplatelet therapy, consideration should be given to the type of stent to be implanted bare metal stent (BMS) or drug eluting stent (DES) **(I-C)**.

6.5. Long-term management

Long term management implies lifestyle measures and drug treatment in order to keep under control every risk factor impacting on long-term outcome after ACS, but also long-term treatment necessitated by complications of ACS.

Recommendations for lipid lowering therapy

- Statins are recommended for all NSTE-ACS patients (in the absence of contraindications), irrespective of cholesterol levels, initiated early (within 1-4 days) after admission, in the aim of achieving LDLc levels < 100 mg/dL (< 2.6 mmol/L) **(I-B)**.

- Intensive lipid-lowering therapy with target LDLc levels < 70 mg/dL (< 1.81 mmol/L) initiated within 10 days after admission, is advisable **(IIa-B)**.

Recommendations for use of beta-blockers

- Beta-blockers should be given to all patients with reduced LV function **(I-A)**.

Recommendations for use of ACE-Inhibitors

- ACE-inhibitors are indicated long-term in all patients with LVEF ≤ 40% and in patients with diabetes, hypertension or chronic kidney disease, unless contraindicated **(I-A)**.

- ACE-inhibitors should be considered for all other patients to prevent recurrence of ischaemic events **(IIa-B)**. Agents and doses of proven efficacy are recommended **(IIa-C)**.

Recommendations for use of Angiotensin-Receptor Blockers

- Angiotensin-Receptor Blockers should be considered in patients who are intolerant to ACE-inhibitors and/or who have heart failure or MI with LVEF < 40% **(I-B)**.

Recommendations for aldosterone receptor antagonists

- Aldosterone blockade should be considered in patients after MI who are already treated with ACE-inhibitors and beta-blockers, and who have a LVEF < 40% and either diabetes or heart failure, without significant renal dysfunction or hyperkalaemia **(I-B)**.

6.6. Rehabilitation and return to physical activity

Recommendations for rehabilitation and return to physical activity

- After NSTE-ACS, assessment of functional capacity is recommended **(I-C)**.
- Every patient after NSTE-ACS should undergo an ECG-guided exercise test (if technically feasible), or an equivalent non-invasive test for ischaemia, within 4-7 weeks after discharge **(IIa-C)**.
- Based on cardiovascular status and on the results of functional physical capacity assessment, patients should be informed about the timing of resumption and the recommended level of physical activity, including leisure, work and sexual activities **(I-C)**.

7. Complications and their management

Bleeding complications

Bleeding complications have been shown to have a strong impact on the risk of death, myocardial infarction and stroke at 30 days and long-term, with a four- to five-fold increase in the risk of death, myocardial infarction and stroke. Prevention of bleeding has become an important component of the treatment of non-ST-elevation ACS.

The risk factors for the occurrence of bleeding are listed in Table 5. Many of the factors that lead to bleeding complications are also predictive of the risk of ischaemic events (death, myocardial infarction, stroke).

Several reports have recently suggested that transfusion may add to the risk of bleeding, and should be used with a restrictive policy.

Recommendations for bleeding complications

- Assessment of bleeding risk is an important component of the decision-making process. Bleeding risk is increased with higher or excessive doses of anti-thrombotic agents, length of treatment, combinations of several anti-thrombotic drugs, switch between different anticoagulant drugs, as well as with older age, reduced renal function, low body weight, female gender, baseline haemoglobin and invasive procedures **(I-B)**.
- Bleeding risk should be taken into account when deciding on a treatment strategy. Drugs, combination of drugs and non-pharmacological procedures (vascular access) known to carry a reduced risk of bleeding should be preferred in patients at high risk of bleeding **(I-B)**.
- Minor bleeding should preferably be managed without interruption of active treatments **(I-C)**.
- Major bleeding requires interruption and/or neutralisation of both anticoagulant and antiplatelet therapy, unless bleeding can be adequately controlled by specific haemostatic intervention **(I-C)**.
- Blood transfusion may have deleterious effects on outcome, and should therefore be considered individually, but withheld in haemodynamically

Table 5: Multivariate model for major bleeding in patients with non-ST-elevation MI

Variable	Adjusted OR	95% CI	*P*-value
Age (per 10 year increase)	1.22	1.10-1.35	0.0002
Female sex	1.36	1.07-1.73	0.0116
History of renal insufficiency	1.53	1.13-2.08	0.0062
History of bleeding	2.18	1.14-4.08	0.014
Mean arterial pressure (per 20 mm Hg decrease)	1.14	1.02-1.27	0.019
Diuretics	1.91	1.46-2.49	< 0.0001
LMWH only	0.68	0.50-0.92	0.012
GP IIb/IIIa inhibitors only	1.86	1.43-2.43	< 0.0001
IV inotropic agents	1.88	1.35-2.62	0.0002
Right-heart catheterization	2.01	1.38-2.91	0.0003

stable patients with haematocrit > 25% or haemoglobin level > 8 g/L **(I-C)**.

Thrombocytopenia

Thrombocytopenia can occur in the course of the treatment of non-ST-elevation ACS. It could be related to drug treatment, particularly use of heparin or GP IIb/IIIa inhibitors. It requires specific measures.

Recommendations for management of thrombocytopenia

- Significant thrombocytopenia (< 100,000/μL^{-1} or > 50% drop in platelet count) occurring during treatment with GP IIb/IIIa inhibitors and/or heparin (LMWH or UFH) requires the immediate interruption of these drugs **(I-C)**.
- Severe thrombocytopenia (< 10,000/μL^{-1}) induced by GP IIb/IIIa inhibitors requires platelet transfusion with or without fibrinogen supplementation with fresh frozen plasma or cryoprecipitate in case of bleeding **(I-C)**.
- Interruption of heparin (UFH or LMWH) is warranted in case of documented or suspected heparin-induced thrombocytopenia (HIT). In case of thrombotic complications, anticoagulation can be achieved with direct thrombin inhibitor (DTI) **(I-C)**.
- Prevention of HIT can be achieved with use of anticoagulants devoid of risk of HIT, such as fondaparinux or bivalirudin, or by brief prescription of heparin (UFH or LMWH) in case these compounds are chosen as anticoagulant **(I-B)**.

8. Special populations and conditions

These include the elderly, female gender, patients with diabetes mellitus, chronic kidney disease or anaemia at baseline, and all may require specific management strategies.

Recommendations for elderly

- Elderly patients (> 75 years) often have atypical symptoms. Active screening for NSTE-ACS should be initiated at lower levels of suspicion than among younger (< 75 years) patients **(I-C)**.
- Treatment decisions in the elderly should be tailored according to estimated life expectancy, patient wishes and co-morbidities to minimize risk and improve morbidity and mortality outcomes in this frail but high-risk population **(I-C)**.
- Elderly patients should be considered for routine early invasive strategy, after careful evaluation of their inherent raised risk of procedure-related complications, especially during CABG **(I-B)**.

Recommendations for women

- Women should be evaluated and treated in the same way as men, with special attention to co-morbidities **(I-B)**.

Recommendations for diabetes

- Tight glycaemic control to achieve normoglycaemia as soon as possible is recommended in all diabetic patients with NSTE-ACS in the acute phase **(I-C)**.
- Insulin infusion may be needed to achieve normoglycaemia in selected NSTE-ACS patients with high blood glucose levels at admission **(IIa-C)**.
- Early invasive strategy is recommended for diabetic patients with NSTE-ACS **(I-A)**.
- Diabetic patients with NSTE-ACS should receive intravenous GP IIb/IIIa inhibitors as part of the initial medical management which should be continued through the completion of PCI **(IIa-B)**.

Recommendations for patients with chronic kidney disease (CKD)

- CrCl and/or GFR should be calculated for every patient hospitalised for NSTE-ACS **(I-B)**. Elderly people, women and low body weight patients merit special attention as near normal serum creatinine levels may be associated with lower than expected CrCl and GFR levels **(I-B)**.
- Patients with CKD should receive the same first-line treatment as any other patient, in the absence of contra-indications **(I-B)**.
- Anticoagulants should be carefully dosed. In patients with CrCl < 30 mL/min or GFR < 30 mL/min/1.73m^2, a careful approach to the use of anticoagulants is recommended, since dose adjustment is necessary with some, while others are contraindicated **(I-C)**.
- UFH infusion adjusted according to aPTT is recommended when CrCl < 30 mL/min or GFR < 30 mL/min/1.73 m^2 **(I-C)**.
- GP IIb/IIIa inhibitors can be used in case of renal failure. Dose adaptation is needed with eptifibatide and tirofiban. Careful evaluation of

Table 6: Recommendations for the use of drugs in case of CKD

Drug	Recommendations in case of CKD
Simvastatin*	Low renal elimination. In patients with severe renal failure (CrCl < 30 mL/min), careful with doses > 10 mg
Ramipril*	Dose adaptation required if CrCl < 30 mL/min (initial dose 1.25 mg daily). Dose must not exceed 5 mg per day.
Losartan*	Recommended for the treatment of hypertension or renal failure in diabetes type 2 with microalbuminuria 50-100 mg per day. Regular monitoring of electrolyte balance and serum creatinine is recommended.
Clopidogrel	No information in patients with renal failure
Enoxaparin*	In case of severe renal failure (CrCl<30 mL/min), either contraindicated or dose adjustment required, according to country-specific labelling
Fondaparinux	Contraindicated in severe renal failure (CrCl < 30 mL/min). However, as much lower risk of bleeding complications was observed in Oasis-5 with fondaparinux as compared with enoxaparin, even in patients with severe renal failure, this drug might be the anticoagulant of choice in this situation.
Bivalirudin	If the CrCl < 30 mL/min, reduction of the infusion rate to 1.0 mg/kg/h should be considered. If a patient is on haemodialysis, the infusion should be reduced to 0.25 mg/kg/h. No reduction in the bolus dose is needed.
Tirofiban	Dose adaptation required in patients with renal failure. 50% of the dose only if CrCl < 30 mL/min.
Eptifibatide	As 50% of eptifibatide is cleared through the kidney in patients with renal failure, precautions must be taken in patients with impaired renal function (CrCl < 50 mL/min). The infusion dose should be reduced to 1 μg/kg/min in such patients. The dose of the bolus remains unchanged at 180 μg/kg. Eptifibatide is contra-indicated in patients with creatinine clearance < 30 mL/min.
Abciximab	No specific recommendations for the use of abciximab, or for dose adjustment in case of renal failure. Careful evaluation of haemorrhagic risk is needed before using the drug in case of renal failure.
Atenolol	Half dose recommended for patients with CrCl between 15 and 35 mL/min (50 mg/day). Quarter dose (25 mg/day) recommended if CrCl < 15 mL/min.

*Recommendations are indicated where applicable. It is assumed that the same recommendations are valid for other drugs of the same pharmacological class, but this needs to be assessed on a case by case basis (other LMWH, other statins, ACE-inhibitors, angiotensin receptor inhibitors), since, within the same pharmacological class, the route of elimination may vary. Recommendations for the use of drugs listed in this table may vary depending on the exact labelling of each drug in the country where it is used. Some differences in labelling can appear between countries.

the bleeding risk is recommended for abciximab **(I-B)**.

- Patients with CKD with CrCl < 60 mL/min are at high risk of further ischaemic events and therefore should be submitted to invasive evaluation and revascularization whenever possible **(IIa-B)**.
- Appropriate measures are advised to reduce the risk of contrast induced nephropathy **(I-B)**.

Recommendations for anaemia

- Low baseline haemoglobin is an independent marker of the risk of ischaemic and bleeding events at 30 days. It should be taken into consideration in assessing initial risk **(I-B)**.
- All necessary measures should be taken during the course of initial management to avoid worsening of anaemia by bleeding **(I-B)**.

- Well tolerated anaemia at baseline in patients with NSTE-ACS should not lead to systematic blood transfusion, which should be considered only in case of compromised haemodynamic status **(I-C)**.

9. Management strategies

A stepwise strategy should be applicable to most patients admitted with suspected NSTE-ACS (Figure 2). It must be appreciated, however, that specific findings in individual patients may result in appropriate deviations from the proposed strategy. For every patient, the physician must make an individual decision taking into account the patient's history (co-morbid illnesses, age etc), his/her clinical condition, findings during the initial assessment on first contact, and the available pharmacological and non-pharmacological treatment options.

First step: initial strategy

Chest pain or discomfort will be the symptom that leads to the patient seeking medical attention or hospitalisation. A patient with suspected NSTE-ACS must be evaluated in a hospital and immediately seen by a qualified physician. Specialised chest pain units provide the best and expeditious care.

The initial step is to assign the patient without delay to a working diagnosis on which the treatment strategy will be based. The criteria are:

- Quality of chest pain and a symptom-oriented physical examination;
- Assessment of the likelihood of CAD (e.g. age, risk factors, previous MI, CABG, PCI);
- ECG (ST deviation or other ECG abnormalities).

Based on these findings, which should be available within 10 minutes of first medical contact, the patient can be assigned to one of the 3 major working diagnoses:

- STEMI requiring immediate reperfusion;
- NSTE-ACS;
- ACS (highly) unlikely.

Second step: diagnostic validation and risk assessment

After the patient is assigned to the group NSTE-ACS intravenous and oral treatments will be started according to Table 7.

Table 7: Primary therapeutic measures

Oxygen	Insufflation (4 to 8 L/min) if oxygen saturation is < 90%
Nitrates	Sublingually or intravenously (caution if systolic blood pressure < 90 mmHg)
Aspirin	Initial dose of 160-325 mg non-enteric formulation followed by 75-100 mg/d (intravenous administration is acceptable)
Clopidogrel	Loading dose of 300 mg (or 600 mg for rapid onset of action) followed by 75 mg daily
Anticoagulation	Choice between different options depends on strategy: • UFH intravenous bolus 60-70 IU/kg (maximum 5000 IU) followed by infusion of 12-15 IU/kg/h (maximum 1000 IU/h) titrated to aPTT 1.5-2.5 times control • Fondaparinux 2.5 mg-daily subcutaneously • Enoxaparin 1 mg/kg twice-daily subcutaneously • Dalteparin 120 IU/kg twice-daily subcutaneously • Nadroparin 86 IU/kg twice-daily subcutaneously • Bivalirudin 0.1 mg/kg bolus followed by 0.25 mg/kg/h
Morphine	3 to 5 mg intravenous or subcutaneous, depending on pain severity
Oral beta-blocker	Particularly, if tachycardia or hypertension without sign of heart failure
Atropine	0.5-1 mg intravenously, if bradycardia or vagal reaction

The further management will be based on additional information/data:

- Routine clinical chemistry, particularly troponins (on presentation and after 6 to 12 hours) and other markers according to working diagnosis (e.g. D-dimers, BNP, NT-proBNP);
- Repeat, preferably continuous ST segment monitoring (when available);
- Echocardiogram, MRI, CT or nuclear imaging for differential diagnoses (e.g. aortic dissection, pulmonary embolism);
- Responsiveness to antianginal treatment;
- Risk score assessment;
- Bleeding risk assessment.

Risk assessment is an important component of the decision-making process and is subject to constant re-evaluation. It encompasses assessment of both ischaemic and bleeding risk. The risk factors for bleeding and ischaemic events overlap considerably, with the result that patients at high risk of ischaemic events are also at high risk of bleeding complications. Therefore, the choice of the pharmacological environment (dual or triple antiplatelet therapy, anticoagulants) has become critical, as has the dosage of the drugs. In addition, in case invasive strategy is needed, the choice of the vascular approach is very important, since the radial approach has been shown to reduce the risk of bleeding as compared to the femoral approach. In this context, particular attention has to be paid to renal dysfunction, shown to be particularly frequent in elderly patients and among diabetics.

During this step the decision has to be made whether the patient should go on to cardiac catheterization or not.

During this step other diagnoses must be confirmed or excluded, like acute anaemia, pulmonary embolism, aortic aneurysm.

Third step: invasive strategy

Cardiac catheterization is advised to prevent early complications and/or to improve long-term outcome. Accordingly, the need for and timing of invasive strategy has to be tailored according to the acuteness of risk into three categories:

- conservative,
- urgent invasive or
- early invasive.

Conservative strategy: Recommended in patients that fulfil all of the following criteria:

- No recurrence of chest pain;
- No signs of heart failure;
- No abnormalities in the initial ECG or a second ECG (6 to 12 hours);
- No elevation of troponins (arrival and at 6-12 hours).

Low risk, as assessed by a risk score, can support the decision making process for a conservative strategy. The further management in these patients is similar to the evaluation of stable CAD. Before discharge a stress test for inducible ischaemia is useful for further decision making.

Patients who cannot be excluded by the above criteria should go on to cardiac catheterization.

Urgent invasive strategy: Should be undertaken within 2 hours for patients who are early in the process of developing major myocardial necrosis escaping the ECG (e.g. occlusion of the circumflex artery) or are estimated to be at high risk of rapid progression to vessel occlusion. These patients are characterised by:

- Refractory angina (e.g. evolving MI without ST abnormalties);
- Recurrent angina despite intense antianginal treatment associated with ST depression (≥ 2 mm) or deep negative T-waves;
- Clinical symptoms of heart failure or haemodynamic instability ("shock");
- Life threatening arrhythmias (ventricular fibrillation or ventricular tachycardia).

In addition to the medication in Table 7, a GP IIb/IIIa inhibitor (tirofiban, eptifibatide) should be added in symptomatic patients bridging the time to catheterization.

Early invasive strategy: Should be performed within 72 hours in moderate- to high-risk patients.

The following features indicate patients that should undergo routine early angiography:

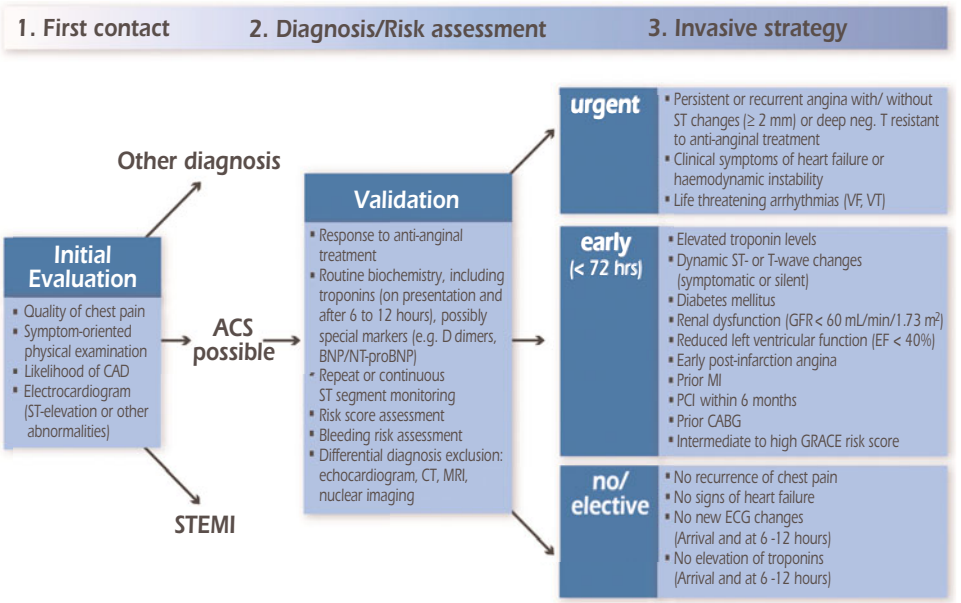
- Elevated troponin levels;
- Dynamic ST- or T-wave changes (symptomatic or silent) (≥ 0.5 mm);

- Diabetes mellitus;
- Reduced renal function (GFR < 60 mL/min/1.73 m^2);
- Depressed LVEF < 40%;
- Prior MI;
- Early post MI angina;
- PCI within 6 months;
- Prior CABG;
- Intermediate to high risk according to a risk score (Table 3).

A GP IIb/IIIa inhibitor (tirofiban, eptifibatide) should be added to the standard treatment prior to catheterization in case of elevated troponins, dynamic ST/T changes, or diabetes provided there is no overt excessive bleeding risk.

The decision about the timing of catheterization must be re-evaluated continuously and modified according to clinical evolution and occurrence of new clinical findings.

Figure 2: Decision-making algorithm for the management of patients with NSTE-ACS



Chapter 2
AMI in Patients Presenting with Persistent ST-Segment Elevation*
2008

The Task Force on the Management of ST-Segment Elevation Acute Myocardial Infarction of the European Society of Cardiology

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Introduction

Acute myocardial infarction can be defined from a number of different perspectives related to clinical, electrocardiographic (ECG), biochemical and pathologic characteristics. The present guidelines pertain to patients presenting with ischaemic symptoms and persistent ST-segment elevation on the ECG, i.e. ST-segment elevation myocardial infarction (STEMI). The great majority of these patients will show a typical rise of biomarkers of myocardial necrosis and progress to Q-wave myocardial infarction. Separate guidelines have been developed by another Task Force of the ESC for patients presenting with ischaemic symptoms but without persistent ST-segment elevation.

When compared with the 2003 guidelines the most significant changes are related to the selection of the most appropriate reperfusion strategy, the performance of angiography after fibrinolytic therapy and the use of antithrombotic co-therapies. As in other guidelines the strength of the recommendation and the level of evidence are graded according to predefined scales (see Tables 1 and 2).

Although somewhat arbitrarily, the management of a STEMI can be divided into four phases:

1) first medical contact and emergency care/triage

2) pre-hospital or early in-hospital care (initiation of reperfusion therapy as soon as possible)

3) later in-hospital care in which the complications that usually ensue are addressed

4) initiation of secondary prevention measures before discharge.

These pocket guidelines are based on the tables included in the full document. No recommendations for rare complications are provided in these pocket guidelines.

* Adapted from the ESC Guidelines on the Management of Acute Myocardial Infarction in Patients Presenting with Persistent ST-Segment Elevation (European Heart Journal 2008;29:2909-2945)

Table 1: ESC Classes of Recommendations

Recommendations	Definition
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful and effective
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure
Class IIa	Weight of evidence/opinion is in favour of usefulness/efficacy
Class IIb	Usefulness/efficacy is less well established by evidence/opinion
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful

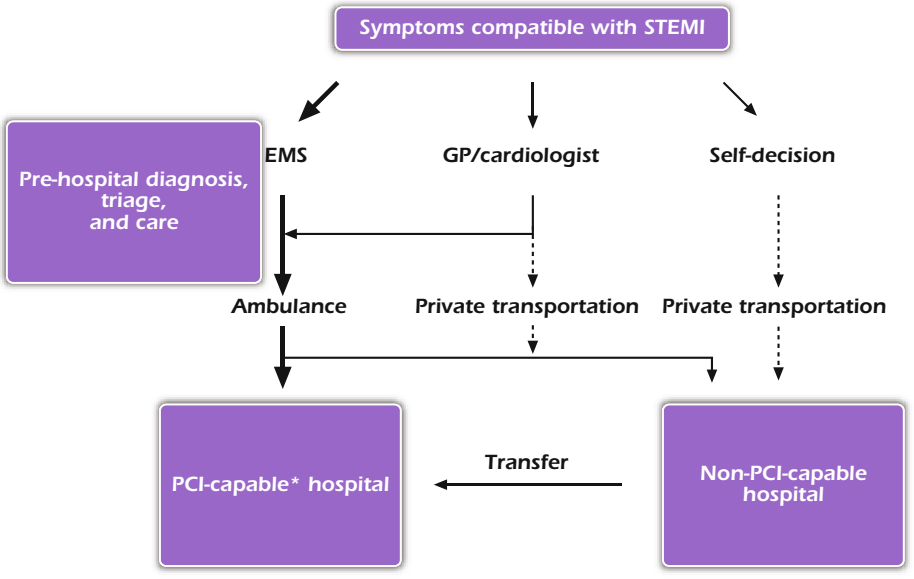
Table 2: Levels of Evidence

Level of evidence A	Data derived from multiple randomized clinical trials or meta-analyses
Level of evidence B	Data derived from a single randomized clinical trial or large non-randomized studies
Level of evidence C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries

1. First medical contact and emergency care flow

Optimal treatment of STEMI should be based on the implementation of an emergency medical system (EMS) supervising a network between hospitals with various levels of technology, connected by an efficient ambulance (or helicopter) service.

Figure 1: Pre-hospital management



*PCI-capable hospital = 24 /7 service; EMS = Emergency Medical System; STEMI = ST-segment elevation myocardial infarction;

GP = general practitioner; PCI = percutaneous coronary intervention; Thick arrows = preferred patient flow; Dotted line = to be avoided.

For selection of reperfusion strategy see Figure 2

Table 3: Initial diagnosis and early risk stratification

• History of chest pain/discomfort.
• Persistent ST-segment elevation or (presumed) new left bundle-branch block. Repeated ECG recordings often needed.
• Elevated markers of myocardial necrosis (CK-MB, troponins). One should not wait for the results to initiate reperfusion treatment.
• 2-D echocardiography to rule out major acute myocardial ischaemia or other causes of chest pain/discomfort.

CK-MB = creatine kinase MB form

Table 4: Relief of pain, breathlessness and anxiety

Recommendations	Class[a]	Level[b]
• I.v. opioids (4 to 8 mg morphine) with additional doses of 2 mg at 5 to 15 min intervals	I	C
• O_2 (2-4 L/min) if breathlessness or other signs of heart failure	I	C
• Tranquillizer - in very anxious patients	IIa	C

a = Class of recommendation

b = Level of evidence

2. Pre-hospital or early in-hospital care

Restoring coronary flow and myocardial tissue reperfusion

For patients with the clinical presentation of STEMI within 12 h after symptom onset and with persistent ST-segment elevation or new or presumed new left bundle-branch block, mechanical (PCI) or pharmacological reperfusion should be performed as soon as possible.

Primary PCI (balloon inflation) should be performed within 2 h after first medical contact (FMC) in all cases. In patients presenting early with a large amount of myocardium at risk, the delay should be shorter (< 90 min).

Figure 2: Reperfusion strategies

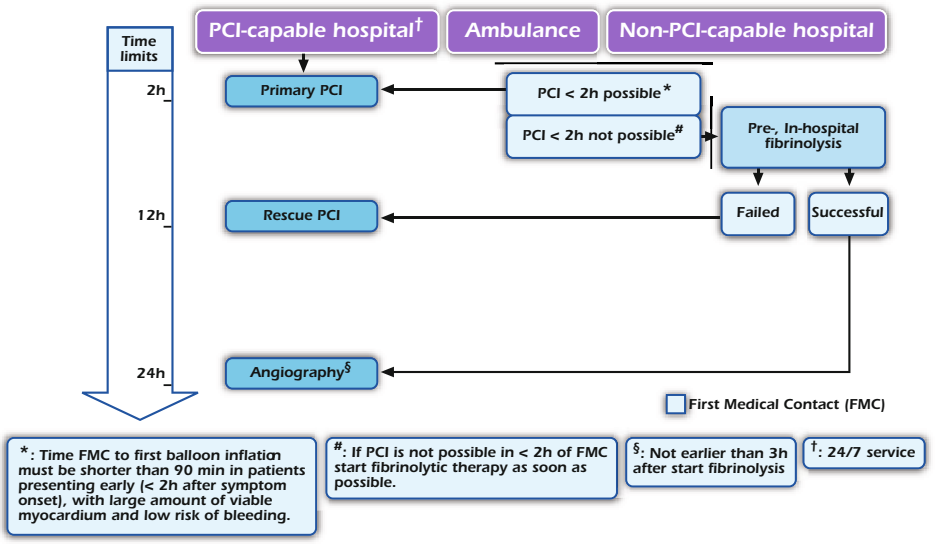


Table 5: Reperfusion therapies

Recommendations	Class[a]	Level[b]
• Reperfusion therapy is indicated in all patients with history of chest pain/discomfort of < 12 h and with persistent ST-segment elevation or (presumed) new left bundle-branch block	I	A
• Reperfusion therapy should be considered if there is clinical and/or ECG evidence of ongoing ischaemia even if, according to patient, symptoms started > 12 h before	IIa	C
• Reperfusion using PCI may be considered in stable patients presenting > 12 to 24 h after symptom onset	IIB	C
• PCI of a totally occluded infarct artery > 24 h after symptom onset in stable patients without signs of ischaemia	III	B
Primary PCI		
• Preferred treatment if performed by an experienced team as soon as possible after FMC	I	A
• Time from FMC to balloon inflation should be < 2 h in any case and < 90 min in patients presenting early (e.g. < 2 h) with large infarct and low bleeding risk	I	B
• Indicated for patients in shock and those with contra-indications to fibrinolytic therapy irrespective of time delay	I	B
• Antiplatelet co-therapy* o Aspirin o NSAID and COX-2 selective inhibitors o Clopidogrel loading dose o GPIIb/IIIa antagonist • Abciximab • Tirofiban • Eptifibatide	 I III I IIa IIb IIb	 B B C A B C
• Antithrombin therapy* o Heparin o Bivalirudin o Fondaparinux	 I IIa III	 C B B
• Adjunctive devices o Thrombus aspiration	 IIb	 B
Rescue PCI		
• After failed fibrinolysis in patients with large infarcts if performed within 12 h of onset	IIa	A
Fibrinolytic therapy*		
• In the absence of contra-indications (see Table 9) and if primary PCI cannot be performed within the recommended time (see above and Figure 2).	I	A
• A fibrin-specific agent should be given	I	B
• Pre-hospital initiation of fibrinolytic therapy	IIa	A
• Antiplatelet co-therapy*: - if not already on aspirin oral (soluble or chewable/nonenteric-coated) or i.v. dose of aspirin plus - clopidogrel oral loading dose if age ≤ 75 years - if age > 75 years start with maintenance dose	 I I IIa	 B B B

a = Class of recommendation

b = Level of evidence

* = for doses see Tables 6, 7 and 8

COX = cyclo-oxygenase; ECG = electrocardiographic/electrocardiogram; FMC = first medical contact; NSAID = non-steroidal antiinflammatory drugs; PCI = percutaneous coronary intervention

Table 5: Reperfusion therapies (cont.)

Recommendations	Class[a]	Level[b]
Fibrinolytic therapy* (cont.)		
• Antithrombin co-therapy*:		
o With alteplase, reteplase and tenecteplase:		
• enoxaparin i.v. bolus followed 15 min later by first s.c. dose; if age > 75 years no i.v. bolus and start with reduced first s.c. dose	I	A
• if enoxaparin is not available: a weight-adjusted bolus of i.v. heparin followed by a weight-adjusted i.v. infusion with first aPTT control after 3 h	I	A
o With streptokinase:		
• an i.v. bolus of fondaparinux followed by a s.c. dose 24 h later or	IIa	B
• enoxaparin i.v. bolus followed 15 min later by first s.c. dose; if age > 75 years no i.v. bolus and start with reduced first s.c. dose	IIa	B
• or a weight-adjusted dose of i.v. heparin followed by a weight–adjusted infusion	IIa	C

a = Class of recommendation

b = Level of evidence

* = for doses see Tables 6, 7 and 8

aPTT = activated partial prothrombin time; PCI = percutaneous coronary intervention

Table 6: Doses of fibrinolytic agents

	Initial treatment	Specific contra-indications
• Streptokinase (SK)	1.5 million units over 30-60 min i.v.	Prior SK or anistreplase
• Alteplase (t-PA)	15 mg i.v. bolus 0.75 mg/kg over 30 min then 0.5 mg/kg over 60 min i.v. Total dosage not to exceed 100 mg	
• Reteplase (r-PA)	10 U + 10 U i.v. bolus given 30 min apart	
• Tenecteplase (TNK-tPA)	single i.v. bolus 30 mg if < 60 kg 35 mg if 60 to < 70 kg 40 mg if 70 to < 80 kg 45 mg if 80 to < 90 kg 50 mg if ≥ 90 kg	

Table 7: Doses of antiplatelet co-therapies

With primary PCI	
• Aspirin	Oral dose of 150-325 mg or i.v. dose of 250-500 mg if oral ingestion is not possible
• Clopidogrel	Oral loading dose of at least 300 mg, preferably 600 mg
• GPIIb/IIIa inhibitors	Abciximab: i.v. bolus of 0.25 mg/kg bolus followed by 0.125 µg/kg per min infusion (maximum 10 µg/min for 12 h)
With fibrinolytic treatment	
• Aspirin	Oral dose of 150-325 mg or i.v. dose of 250 mg if oral ingestion is not possible
• Clopidogrel	Loading dose of 300 mg if age ≤ 75 years; 75 mg if age > 75
Without reperfusion therapy	
• Aspirin	Oral dose of 150-325 mg
• Clopidogrel	Oral dose of 75 mg

Table 8: Doses of antithrombin co-therapies

With primary PCI	
• Heparin	I.v. bolus at a usual starting dose of 100 U/kg weight (60 U/kg if GPIIb/IIIa antagonists are used). If the procedure is being performed under activated clotting time (ACT) guidance, heparin is given at a dose able to maintain an ACT of 250-350 s (200-250 s if GPIIb/IIIa antagonists are used). Infusion should be stopped at the end of the procedure
• Bivalirudin	I.v. bolus of 0.75 mg/kg followed by an infusion of 1.75 mg/kg/h not titrated to ACT and usually terminated at the end of the procedure
With fibrinolytic treatment	
• Enoxaparin	In patients < 75 years and creatinine levels ≤ 2.5 mg/mL or 221 μmol/L (men) or ≤ 2 mg/mL or 177 μmol/L (women): i.v. bolus of 30 mg followed 15 min later by s.c. dose of 1 mg/kg every 12 h until hospital discharge for a maximum of 8 days. The first two s.c. doses should not exceed 100 mg. In patients > 75 years: no i.v. bolus; start with first s.c. dose of 0.75 mg/kg with a maximum of 75 mg for the first two s.c. doses. In patients with creatinine clearance of < 30 mL/min, regardless of age, the s.c. doses are repeated every 24 h
• Heparin	I.v. bolus of 60 U/kg with a maximum of 4000 U followed by an i.v. infusion of 12 U/kg with a maximum of 1000 U/h for 24-48 h. Target aPTT: 50-70 s to be monitored at 3, 6,12 and 24 h
• Fondaparinux	2.5 mg i.v. bolus followed by a s.c. dose of 2.5 mg once daily up to 8 days or hospital discharge if creatinine ≤ 3 mg/mL or 265 μmol/L
Without reperfusion therapy	
• Fondaparinux	Same dose as with fibrinolytics
• Enoxaparin	Same dose as with fibrinolytics
• Heparin	Same dose as with fibrinolytics

Table 9: Contra-indications to fibrinolytic therapy

Absolute contra-indications
• Haemorrhagic stroke or stroke of unknown origin at any time • Ischaemic stroke in preceding 6 months • Central nervous system trauma or neoplasms • Recent major trauma/surgery/head injury (within preceding 3 weeks) • Gastrointestinal bleeding within the last month • Known bleeding disorder • Aortic dissection • Non-compressible punctures (e.g. liver biopsy, lumbar puncture)

Relative contra-indications
• Transient ischaemic attack in preceding 6 months • Oral anticoagulant therapy • Pregnancy or within 1 week post-partum • Refractory hypertension (systolic blood pressure > 180 mmHg and/or diastolic blood pressure > 110 mmHg) • Advanced liver disease • Infective endocarditis • Active peptic ulcer • Refractory resuscitation

Table 10: Antithrombotic treatment without reperfusion therapy

Recommendations	Class[a]	Level[b]
Antiplatelet co-therapy*		
• If not already on aspirin oral (soluble or chewable/non-enteric-coated) or i.v. dose of aspirin if oral ingestion is not feasible	I	A
• Oral dose of clopidogrel	I	B
Antithrombin co-therapy*		
• I.v. bolus of fondaparinux followed 24 h later by a s.c. dose	I	B
• If fondaparinux is not available: enoxaparin i.v. bolus followed 15 min later by first s.c. dose; if age > 75 years no i.v. bolus and start with reduced s.c. dose or	I	B
• I.v. heparin followed by a weight-adjusted i.v. infusion with first aPTT control after 3 h	IIb	C

a = Class of recommendation

b = Level of evidence

* = for doses see Tables 7 and 8

Table 11: Angiography during hospital stay after fibrinolytic therapy and in patients who did not receive reperfusion therapy

Recommendations	Class[a]	Level[b]
• Evidence of failed fibrinolysis or uncertainty about success: immediate	IIa	B
• Recurrent ischaemia, reocclusion after initial successful fibrinolysis: immediate	I	B
• Evidence of successful fibrinolysis: within 3-24 h after start of fibrinolytic therapy*	IIa	A
• In unstable patients who did not receive reperfusion therapy: immediate	I	C
• In stable patients who did not receive reperfusion therapy: before discharge	IIb	C

a = Class of recommendation

b = Level of evidence

* = In order to avoid an early PCI during the prothrombotic period following fibrinolysis, on the one hand, and to minimize the risk of reocclusion, on the other hand, a time window of 3-24 h following successful fibrinolysis is recommended.

3. Later in-hospital care

Recommendations for routine prophylactic therapies and management of frequent complications (pump failure and shock, arrhythmias and conduction disturbances) are presented here.

a. Pump failure and shock

Table 12: Haemodynamic states

Normal	Normal blood pressure, heart and respiration rates, good peripheral circulation
Hyperdynamic state	Tachycardia, loud heart sounds, good peripheral circulation
Hypotension • Bradycardia	'Warm hypotension', bradycardia, venodilatation, normal jugular venous pressure, decreased tissue perfusion. Usually in inferior infarction, but may be provoked by opiates. Responds to atropine or pacing
• Right ventricular infarction	High jugular venous pressure, poor tissue perfusion or shock, bradycardia, hypotension
• Hypovolaemia	Venoconstriction, low jugular venous pressure, poor tissue perfusion. Responds to fluid infusion
Pump failure • Pulmonary congestion	Tachycardia, tachypnoea, basal rales
• Pulmonary oedema	Tachycardia, tachypnoea, rales over 50% of lung fields
Cardiogenic shock	Clinical signs of poor tissue perfusion (oliguria, decreased mentation), hypotension, small pulse pressure, tachycardia, pulmonary oedema

Table 13: Treatment of pump failure and cardiogenic shock

Recommendations	Class[a]	Level[b]
Treatment of mild heart failure (Killip class II)		
• O_2	I	C
• Loop diuretics: i.e. furosemide: 20-40 mg i.v. repeated at 1-4 hourly intervals if necessary	I	C
• Nitrates if no hypotension	I	C
• ACE-inhibitor in the absence of hypotension, hypovolaemia or renal failure	I	A
• ARB (valsartan) if ACE-inhibitor is not tolerated	I	B

Table 13: Treatment of pump failure and cardiogenic shock (cont.)

Recommendations	Class[a]	Level[b]
Treatment of severe heart failure (Killip class III)		
• O_2	I	C
• Ventilatory support according to blood gasses	I	C
• Furosemide: see above	I	C
• Nitrates if no hypotension	I	C
• Inotropic agents: dopamine and/or dobutamine	IIb IIa	C B
• Haemodynamic assessment with balloon floating catheter	IIb	B
• Early revascularization	I	C
Treatment of shock (Killip class IV)		
• O_2	I	C
• Mechanical ventilatory support according to blood gases	I	C
• Haemodynamic assessment with balloon floating catheter	IIb	C
• Inotropic agents: dopamine and dobutamine	IIb IIa	B C
• Intra-aortic balloon pump	I	C
• LV assist devices	IIa	C
• Early revascularization	I	B

a = Class of recommendation; b = Level of evidence

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; LV = left ventricular

b. Arrhythmias and conduction disturbances

Table 14: Management of arrhythmias and conduction disturbances in the acute phase

Recommendations	Class[a]	Level[b]
Haemodynamically unstable VT and VF:		
• DC cardioversion	I	C
Haemodynamically unstable, sustained monomorphic VT refractory to DC cardioversion		
• I.v. amiodarone	IIa	B
• I.v. lidocaine or sotalol*	IIa	C

Table 14: Management of arrhythmias and conduction disturbances in the acute phase (cont.)

Recommendations	Class[a]	Level[b]
Haemodynamically unstable, sustained monomorphic VT refractory to DC cardioversion		
• Transvenous catheter pace termination if refractory to cardioversion or frequently recurrent despite antiarrhythmic medication	IIa	C
Repetitive symptomatic salvoes of non-sustained monomorphic VT		
• I.v. amiodarone, sotalol* or other β-blocker*	IIa	C
Polymorphic VT		
• If baseline QT is normal - i.v. sotalol* or other β-blocker*, amiodarone, or lidocaine	I	C
• If baseline QT is prolonged - correct electrolytes, consider magnesium, overdrive pacing, isoproterenol, or lidocaine - urgent angiography should be considered	I I	C C
Rate control of atrial fibrillation		
• I.v. β-blockers or non-dihydropyridine, calcium antagonists (e.g. diltiazem, verapamil)#. If no clinical signs of heart failure, bronchospasm (only for β-blockers), or AV block	I	C
• I.v. amiodarone to slow a rapid ventricular response and improve LV function	I	C
• I.v. digitalis if severe LV dysfunction and/or heart failure	IIb	C
• Electrical cardioversion if severe haemodynamic compromise or intractable ischaemia, or when adequate rate control cannot be achieved with pharmacological agents	I	C
Anticoagulation for atrial fibrillation		
• I.v. administration of a therapeutic dose of heparin or a LMWH	I	C
Sinus bradycardia associated with hypotension		
• I.v. atropine	I	C
• Temporary pacing if failed response to atropine	I	C

Table 14: Management of arrhythmias and conduction disturbances in the acute phase (cont.)

Recommendations	Class[a]	Level[b]
AV block II (Mobitz 2) or AV block III with bradycardia that causes hypotension or heart failure		
• I.v. atropine	I	C
• Temporary pacing if atropine fails	I	C

a = Class of recommendation

b = Level of evidence

Recommended doses of anti-arrhythmic agents are given in Table 15.

* = i.v. sotalol or other β-blockers should not be given if EF is low.

= These calcium antagonists should be used cautiously or avoided in patients with heart failure because of their negative inotropic effects.

AV = atrio-ventricular; DC = direct current; i.v. = intravenous; LMWH = low-molecular-weight heparin; LV = left ventricular; VT = ventricular tachycardia

Table 15: Intravenous doses of recommended antiarrhythmic/antibradycardiac medications

Drug	Bolus	Maintenance infusion
Amiodarone	150 mg over 10 min. Supplemental boluses of 150 mg may be given over 10-30 min for recurrent arrhythmias, but limited to 6-8 supplemental boluses in any 24-h period	1 mg/min for 6 h and then 0.5 mg/min may be necessary after initial bolus dose
Esmolol	500 μg/kg over 1 min, followed by 50 μg/kg/min over 4 min	60 to 200 μg/kg/min
Metoprolol	2.5-5 mg over 2 min; up to 3 doses	
Atenolol	5-10 mg (1 mg/min)	
Propranolol	0.15 mg/kg	
Digoxin	0.25 mg each 2 h, up to 1.5 mg	
Lidocaine	0.5-0.75 mg/kg	
Sotalol	20 -120 mg over 10 min (0.5-1.5 mg/kg). May be repeated after 6 h (maximum 640 mg/24h)	
Verapamil	0.075-0.15 mg/kg over 2 min	
Diltiazem	0.25 mg/kg over 2 min	
Atropine	Rapid bolus of at least 0.5 mg, repeated up to a total dose of 1.5-2.0 mg (0.04 mg/kg)	
Isoproterenol	0.05-0.1 μg/kg/min, up to 2 μg/kg/min. Dosage adjusted to heart rate and rhythm	

c. Routine prophylactic therapies in acute phase

Table 16: Routine prophylactic therapies in acute phase

Recommendations	Class[a]	Level[b]
• Aspirin: maintenance dose of 75-100 mg	I	A
• Clopidogrel: maintenance dose of 75 mg	I	A
• Nonselective and selective COX-2 agents	III	C
• I.v. β-blocker	IIb	A
• Oral β-blocker	I	A
• ACE-inhibitor: oral formulation on first day - for all patients in whom it is not contraindicated - for high-risk patients	 IIa I	 A A

Recommendations	Class[a]	Level[b]
• Nitrates	IIb	A
• Calcium antagonists	III	B
• Magnesium	III	A
• Lidocaine	III	B
• Glucose-insulin-potassium infusion	III	B

a = Class of recommendation

b = Level of evidence

Table 17: Dosages of inhibitors of the renin–angiotensin–aldosterone system

Drug	Initial dosage	Target dosage
GISSI-3 lisinopril	5 mg initially	up to 10 mg daily
ISIS-4 captopril	6.25 mg initially, 12.5 mg in 2 h, 25 mg at 10-12 h	up to 50 mg b.i.d.
CHINESE captopril	6.25 mg initially, 12.5 mg 2 h later if tolerated	up to 12.5 mg t.i.d.
SMILE zofenopril	7.5 mg initially, repeated after 12 h and repeatedly doubled if tolerated	up to 30 mg b.i.d.
AIRE ramipril	2.5 mg b.i.d. increased to 5 mg b.i.d. if tolerated	up to 5 mg b.i.d.
SAVE captopril	Test of 6.25 mg, increased if tolerated to 25 mg t.i.d.	up to 50 mg t.i.d.
TRACE trandolapril	Test of 0.5 mg	up to 4 mg daily
VALIANT valsartan	20 mg initially uptitrated in 4 steps	up to 160 mg b.i.d.
OPTIMAAL losartan	12.5 mg	up to 50 mg daily
EPHESUS eplerone	25 mg initially	up to 50 mg daily

b.i.d. = twice daily; t.i.d. = three times daily

4. Secondary prevention

Several evidence-based interventions can improve prognosis after STEMI. Even though long-term management of this large group of patients will be the responsibility of the general practitioner, these interventions will have a higher chance of being implemented if initiated during hospital stay. In addition, lifestyle changes should be explained and proposed to the patient before discharge.

Table 18: Long-term medical treatment after STEMI

Recommendations	Class[a]	Level[b]
Antiplatelets/anticoagulants		
• Aspirin for ever (75 to 100 mg daily) in all patients without allergy	I	A
• Clopidogrel (75 mg daily) for 12 months in all patients irrespective of the acute treatment	IIa	C
• Clopidogrel (75 mg daily) in all patients with contraindication to aspirin	I	B
• Oral anticoagulant at INR 2-3 in patients who do not tolerate aspirin and clopidogrel	IIa	B
• Oral anticoagulant at recommended INR when clinically indicated (e.g. atrial fibrillation, LV thrombus, mechanical valve)	I	A
• Oral anticoagulant (at INR 2-3) in addition to low-dose aspirin (75-100 mg) in patients at high risk of thromboembolic events	IIa	B
• Oral anticoagulant in addition to aspirin and clopidogrel (recent stent placement plus indication for oral anticoagulation)*	IIb	C
• Oral anticoagulant in addition to clopidogrel or aspirin (recent stent placement plus indication for oral anticoagulation and increased risk of bleeding)*	IIb	C
β-blockers		
• Oral β-blockers in all patients who tolerate these medications and without contra-indications, regardless of blood pressure or LV function	I	A

Table 18: Long-term medical treatment after STEMI (cont.)

Recommendations	Class[a]	Level[b]
ACE-inhibitor and ARB		
• ACE-inhibitor should be considered in all patients without contra-indications, regardless of blood pressure or LV function	IIa	A
• ARB in all patients without contra-indications who do not tolerate ACE-inhibitors, regardless of blood pressure or LV function	IIa	C
Statins		
• Statins in all patients, in the absence of contra-indications, irrespective of cholesterol levels, initiated as soon as possible to achieve LDL cholesterol < 100 mg/dL (2.5 mmol/L) (see also Table 19)	I	A
Influenza immunization		
• In all patients	I	B

a = Class of recommendation

b = Level of evidence

*** = If long-term oral anticoagulation is required, use of a bare metal stent rather than a drug-eluting stent will expose the patient to a shorter duration of triple therapy and hence a lower bleeding risk.**

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; INR = international normalized ratio; LDL = low-density lipoprotein; LV = left ventricular

Table 19: Long-term management of specific coronary risk factors and LV dysfunction

Recommendations	Class[a]	Level[b]
Smoking cessation		
• Assess smoking status and advise to quit and to avoid passive smoking at each visit	I	B
• Bupropion and nicotine treatment in patients who keep smoking at follow-up	I	B
• Antidepressants	IIa	C
Physical activity		
• Exercise test-guided moderate intensity aerobic exercise at least 5 times per week	I	B
• Medically supervised rehabilitation programmes for high-risk patients	I	B
Diabetes management		
• Lifestyle changes and pharmacotherapy to achieve HbA1C < 6.5 %	I	B
• Intensive modification of other risk factors (hypertension, obesity, dyslipidaemia)	I	B
• Coordination with a physician specialized in diabetes	I	C
Diet and weight reduction		
• Weight reduction is recommended when BMI is ≥ 30 kg/m^2 and when waist circumference is > 102/88 cm (men/women)	I	B
• Diet based on low intake of salt and saturated fats and regular intake of fruit, vegetables and fish	I	B
• Increased consumption of omega-3 fatty acid (oily fish)	IIb	B
• Supplementation with 1 g of fish oil in patients with a low intake of oily fish	IIa	B
• Moderate alcohol consumption should not be discouraged	I	B

a = Class of recommendation; b = Level of evidence; BMI = body mass index

Table 19: Long-term management of specific coronary risk factors and LV dysfunction (cont.)

Recommendations	Class[a]	Level[b]
Blood pressure control		
• Lifestyle changes and pharmacotherapy to achieve BP < 130/80 mmHg	I	A
Lipid management		
• Statins in all patients, in the absence of contra-indications, irrespective of cholesterol levels, initiated as soon as possible to achieve LDLc < 100 mg/dL (2.5 mmol/L)	I	A
• Further reduction of LDL cholesterol to achieve < 80 mg/dL (2.0 mmol/L) should be considered in high-risk patients	IIa	A
• Lifestyle change emphasized if TG > 150 mg/dL (1.7 mmol/L) and/or HDL cholesterol < 40 mg/dL (1.0 mmol/L)	I	B
• Fibrates and omega-3 supplements should be considered in patients who do not tolerate statins, especially if TG > 150 mg/dL (1.7 mmol/L) and/or HDL cholesterol < 40 mg/dL (1.0 mmol/L)	IIa	B
Management of heart failure or LV dysfunction		
• Oral β-blockers in all patients without contra-indications	I	A
• ACE-inhibitors in all patients without contra-indications	I	A
• ARB (valsartan) in all patients without contra-indications who do not tolerate ACE-inhibitors	I	B
• Aldosterone antagonists if EF ≤ 40% and signs of heart failure or diabetes if creatinine is < 2.5 mg/dL in men and < 2.0 mg/dL in women and potassium < 5.0 mmol/L	I	B
• CRT in patients with EF < 35% and QRS duration of ≥ 120 ms who remain in NYHA class III-VI in spite of optimal medical therapy if stunning can be excluded	I	A
Prevention of sudden death		
• ICD if EF ≤ 30-40 % and NYHA ≥ II or III at least 40 days after STEMI	I	A
• ICD if EF ≤ 30-35 % and NYHA I at least 40 days after STEMI	IIa	B

a = Class of recommendation; b = Level of evidence;

ACE = angiotensin-converting enzyme; ACT = activated clotting time; CRT = cardiac resynchronization therapy; EF = ejection fraction; HDL = highdensity lipoprotein; ICD = implantable cardioverter-defibrillator; LDL = low-density lipoprotein; LV = left ventricular; NYHA = New York Heart Association; QRS = electrocardiographic wave (complex or interval); STEMI = ST-segment elevation myocardial infarction; TG = triglyceride

Chapter 3
Stable Angina Pectoris*
2006

The Task Force on the Management of Stable Angina Pectoris of the European Society of Cardiology

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1. Introduction

These guidelines aim to present management recommendations based on all of the relevant evidence on a particular subject in order to help physicians to select the best possible management strategy for the individual patient. The strength of evidence for or against particular procedures or treatments is weighed, according to predefined scales for grading recommendations and levels of evidence, as outlined below. However, the ultimate judgement regarding the care of an individual patient must be made by the physician in charge of his/her care.

Classes of Recommendations

Class I	Evidence and/or general agreement that a given treatment is beneficial, useful and effective;
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the treatment or procedure;
Class IIa	Weight of evidence/opinion is in favour of usefulness/efficacy;
Class IIb	Usefulness/efficacy is less well established by evidence/opinion;
Class III	Evidence or general agreement that the treatment is not useful/effective and in some cases may be harmful.

Levels of Evidence

Level of Evidence A	Data derived from multiple randomized clinical trials or meta-analyses;
Level of Evidence B	Data derived from a single randomized trial or large non-randomized studies;
Level of Evidence C	Consensus opinion of the experts and/or small studies, retrospective studies, registries.

Recommendations for ESC Guidelines Production at www.escardio.org

*Adapted from the ESC Guidelines for the Management of Stable Angina Pectoris Executive Summary (European Heart Journal 2006; 27(11):1341-1381), and Full Text (www.escardio.org)

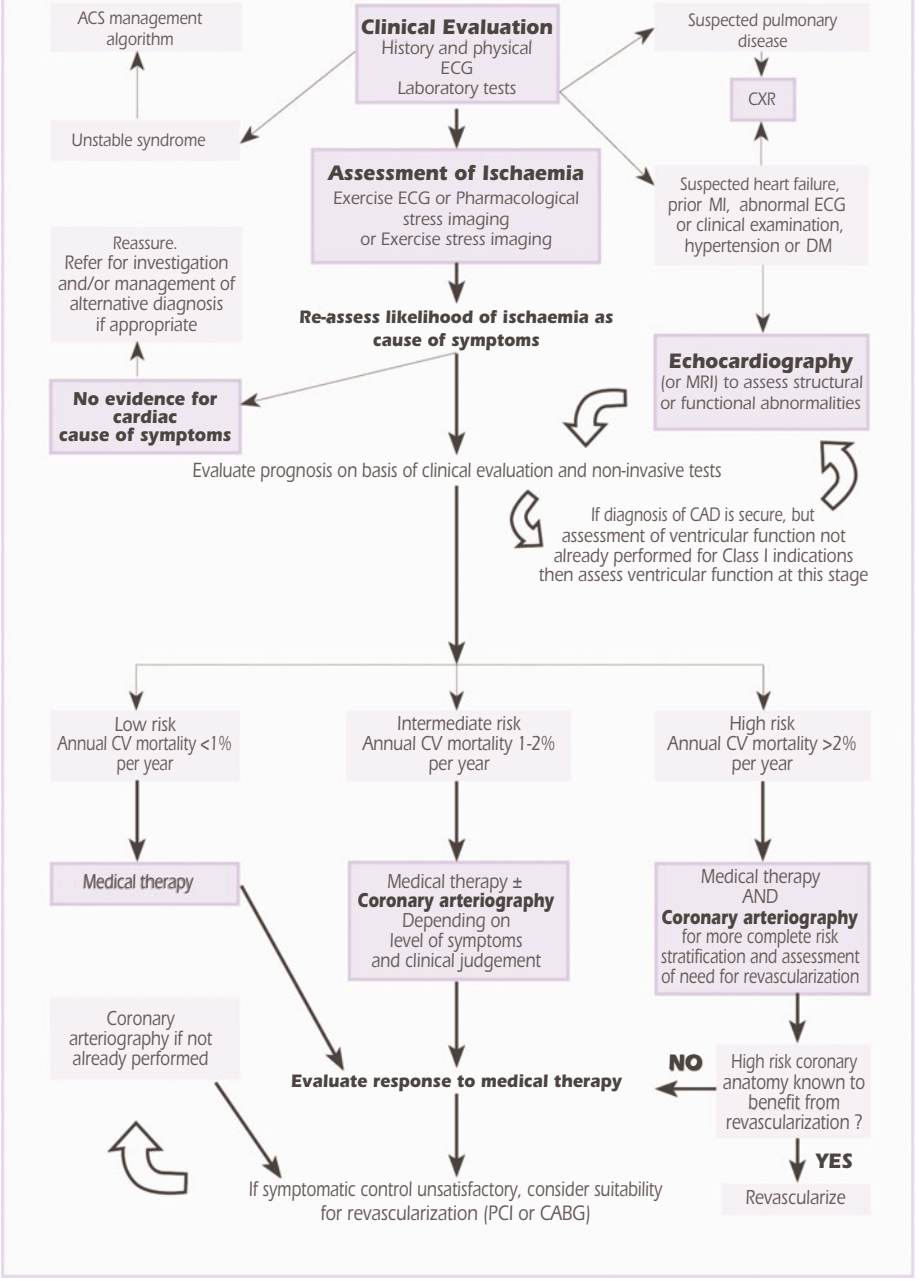
J. Bax et al., *Compendium of Abridged ESC Guidelines 2001*

2. Diagnosis and Assessment

Stable angina is a clinical syndrome characterized by discomfort in the chest, jaw, shoulder, back or arms, typically elicited by exertion or emotional stress and relieved by rest or nitroglycerin. Less typically, discomfort may occur in the epigastric area. It is usual to confine the term to cases in which the syndrome can be attributed to myocardial ischaemia.

Diagnosis and assessment of angina involves clinical assessment, laboratory tests, and specific cardiac investigations. The purpose of investigation can be summarized as follows:

Figure 1. Algorithm for the initial evaluation of patients with clinical symptoms of angina



1. Confirmation of the presence of ischaemia in patients with suspected stable angina.
2. Identification or exclusion of associated conditions or precipitating factors.
3. Risk stratification.
4. To plan treatment options.
5. Evaluation of the efficacy of treatment.

An algorithm for the initial evaluation of patients presenting with clinical symptoms suggestive of angina is depicted in Figure 1. Investigations are summarized in Table 2.

2.1 Symptoms and signs

The history is a vital component in the diagnosis of stable angina. The characteristics of discomfort related to myocardial ischaemia (angina pectoris) may be divided into four categories, location, character, duration and relation to exertion and other exacerbating or relieving factors.

It is important to distinguish patients with unstable angina, which may present as:

(i) Rest angina.

(ii) Rapidly increasing or crescendo angina, i.e. previously stable angina, with rapid progressive increase in severity.

(iii) New onset angina, i.e. recent onset of severe angina with marked limitation of ordinary activity within 2 months of initial presentation.

For patients with stable angina it is also useful to classify the severity of symptoms using a grading system such as that of the Canadian Cardiovascular Society Classification (Table 1), Duke Specific Activity Index or Seattle angina questionnaire.

Features of the history important in risk stratification include current smoking, increasing age, prior MI, symptoms of heart failure, and the pattern of occurrence (recent onset or progressive), and severity of angina, particularly if unresponsive to therapy. The pattern of angina occurrence, angina frequency and resting ECG abnormalities are independent predictors of survival and survival free of MI particularly in the first year after assessment.

Physical examination of a patient with (suspected) angina pectoris should be focused on identification or exclusion of causal or associated conditions or precipitating factors and on risk stratification. Key findings to look for are:

- Signs of valvular heart disease or hypertrophic obstructive cardiomyopathy.
- Hypertension.
- Evidence of non-coronary vascular disease.
- Significant comorbid conditions, particularly respiratory pathology.
- Signs of heart failure.
- Assessment of body mass index and waist circumference to assist in identification of metabolic syndrome.

Table 1. Classification of angina severity according to the Canadian Cardiovascular Society

Class	Level of symptoms
Class I	"Ordinary activity does not cause angina". Angina with strenuous or rapid or prolonged exertion only.
Class II	"Slight limitation of ordinary activity". Angina on walking or climbing stairs rapidly, walking uphill or exertion after meals, in cold weather, when under emotional stress, or only during the first few hours after awakening.
Class III	"Marked limitation of ordinary physical activity". Angina on walking one or two blocks* on the level or one flight of stairs at a normal pace under normal conditions.
Class IV	"Inability to carry out any physical activity without discomfort" or "angina at rest".

* Equivalent to 100-200 m

2.2 Laboratory tests

Fasting plasma glucose and fasting lipid profile including total cholesterol (TC), high density lipoprotein (HDL) and low density lipoprotein (LDL) cholesterol, and triglycerides, should be evaluated in all patients with stable angina, to establish the patient's risk profile and ascertain the need for treatment. Elevated TC, LDL and glucose levels are also indicative of prognosis. Lipid profile and glycaemic status should be reassessed periodically to determine efficacy of treatment and to detect new development of diabetes. A full blood count and serum creatinine are also indicated in all patients.

Further laboratory testing, including oral glucose tolerance testing, cholesterol subfractions (ApoA, ApoB), homocysteine, lipoprotein (a) (Lpa), NT-BNP, haemostatic abnormalities and markers of inflammation such as hs CRP, may have a role in selected patients.

Measurement of markers of myocardial damage such as troponins, should be measured if evaluation suggests clinical instability or acute coronary syndrome. Thyroid function should be tested if dysfunction is suspected clinically.

2.3 Chest X-ray

A chest X-ray (CXR) should be requested only in patients with suspected heart failure, valvular disease or pulmonary disease. The presence of cardiomegaly, pulmonary congestion, atrial enlargement and cardiac calcifications have been related to prognosis.

2.4 Resting electrocardiogram (ECG)

All patients with suspected angina pectoris based upon symptoms should have a resting 12-lead electrocardiogram (ECG) recorded, although it should be emphasised that a normal resting ECG is not uncommon even in patients with severe angina and does not exclude the diagnosis of ischaemia. Resting ECG abnormalities, ST depression, Q waves, left anterior hemiblock and left bundle-branch block (LBBB), are associated with an adverse prognosis in stable angina.

2.5 ECG stress testing

In the majority of patients the exercise ECG is the initial test of choice to diagnose coronary disease and risk stratify.

Diagnosis of CAD

ST-segment depression during exercise is used to define a positive test. The reported sensitivity and specificity of the test for the detection of significant coronary disease are 68% and 77% respectively. Exercise ECG testing is not of diagnostic value in presence of LBBB, paced rhythm and Wolff Parkinson White syndrome (WPW). Additionally, results are less reliable in patients with an abnormal resting ECG in the presence of left ventricular hypertrophy, electrolyte imbalance, intraventricular conduction abnormalities and during use of digitalis. For patients with an abnormal resting ECG, an alternative functional test should be employed for diagnostic and prognostic assessment. Exercise ECG testing is also less sensitive and specific in women.

Risk stratification

The exercise ECG has been extensively validated as an important tool in risk stratification in symptomatic patients with known or suspected coronary disease. Prognostic indicators include exercise capacity and exercise-induced ischaemia (clinical and electrocardiographic). Maximum exercise capacity is a consistent prognostic marker and may be measured by maximum exercise duration, maximum MET level achieved, maximum workload achieved in Watts, maximum heart rate and double (rate–pressure) product. The specific variable used to measure exercise capacity is less important than the inclusion of this marker in the assessment.

The clinical value of stress testing is improved considerably by multivariate analysis including several exercise variables in a given patient such as the combination of heart rate at peak exercise, ST-segment depression, the presence or absence of angina during the test, peak workload and ST-segment slope. The combination of exercise and clinical parameters, with or without the use of scores such as the Duke Treadmill Score (DTS), has been shown to be an effective method of discriminating between high and low risk groups.

2.6 Stress testing in combination with imaging

The most well established stress imaging techniques are echocardiography and perfusion scintigraphy. Both may be used in combination with either exercise stress or pharmacological stress, and many studies have been conducted evaluating their use in both prognostic and diagnostic assessment.

Stress imaging techniques are often preferred in patients with previous percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) because of its superior ability to localize ischaemia. Novel stress imaging techniques also include stress MRI.

Advantages of stress imaging over conventional exercise ECG testing include:

(i) Superior diagnostic and prognostic performance.

(ii) The ability to quantify and localise areas of ischaemia.

(iii) Ability to provide diagnostic information in the presence of resting ECG abnormalities or inability of the patient to exercise.

Exercise testing with echocardiography

Exercise echocardiography is more sensitive and specific than exercise testing for the detection of coronary disease. Technological advances include the use of contrast agents to enhance endocardial border definition, the use of injectable agents to image myocardial perfusion and advances in detection of ischaemia with tissue Doppler and strain rate imaging.

Stress echocardiography may also be used effectively to risk stratify patients. The risk of future events is influenced by the following:

- number of resting regional wall motion abnormalities;
- number of inducible wall motion abnormalities on stress echocardiography.

Exercise testing with myocardial perfusion scintigraphy

Single photon emission computed tomography (SPECT) may be performed in conjunction with a symptom limited exercise test or pharmacological stress to produce images of regional radionuclide tracer uptake that reflect relative regional myocardial blood flow during stress. These images may then be compared with resting images. Thallium-201 and technetium-99m radiopharmaceuticals are the most commonly used tracers.

SPECT perfusion provides a more sensitive and specific prediction of the presence of coronary artery disease than exercise electrocardiography, and is more sensitive but less specific than stress echocardiography. Stress perfusion imaging has also been extensively validated as a prognostic tool. High risk features include:

- Profound extensive ischaemia.
- Transient ischaemic dilation.
- Pulmonary uptake of tracer.

Pharmacological stress testing with imaging techniques

Exercise imaging is preferable where possible, as it allows for more physiological reproduction of ischaemia and assessment of symptoms. When exercise stress is not possible pharmacological stress may also be employed; either:

(i) Short-acting sympatho-mimetic drugs such as dobutamine.

(ii) Coronary vasodilators (e.g. adenosine and dipyridamole).

On the whole stress echo and stress perfusion scintigraphy, whether using exercise or pharmacological stress, have very similar applications. The choice as to which is employed will depend on local facilities and expertise.

Stress imaging has an important role to play in evaluating patients with a low pre-test probability of disease, particularly women, when exercise testing is inconclusive, in selecting lesions for revascularization, and in assessing ischaemia after revascularization.

Stress Cardiac Magnetic Resonance (CMR)

CMR stress testing in conjunction with a dobutamine infusion can be used to detect wall motion abnormalities induced by ischaemia, or perfusion abnormalities, but is not widely used for this purpose.

2.7 Echocardiography at rest

Resting echocardiography is useful to detect or rule out disorders such as valvular heart disease or hypertrophic cardiomyopathy as a cause of symptoms, and to evaluate ventricular function.

For purely diagnostic purposes echocardiography is useful in patients with clinically detected murmurs, history and ECG changes compatible with hypertrophic cardiomyopathy or previous myocardial infarction, and symptoms or signs of heart failure. However, echocardiography may also contribute useful prognostic information.

In stable angina, the strongest predictor of long-term survival is left ventricular function, with mortality increasing with progressive decreases in function. Left ventricular hypertrophy is also an important prognostic finding. Echocardiography may be used to assess ventricular function in patients who have not had ventricular function assessed by another modality.

Cardiac magnetic resonance may also be used to define structural cardiac abnormalities and evaluate ventricular function, but routine use for such purposes is limited by availability.

Computed Tomography (CT)

Electron beam CT and multi-detector or multi-slice CT have been validated as effective in detection of coronary calcium and quantification of the extent of coronary calcification. CT coronary arteriography can also be performed by injection of intravenous contrast agents. The negative predictive power of CT angiography used with multi-detector CT is high. Until further data is available to support its wider application CT angiography may be used in patients with a low pre-test probability of disease with an equivocal functional test (exercise ECG or stress imaging).

Magnetic Resonance (MR) Arteriography

Advances in magnetic resonance technology permit non-invasive MR contrast coronary arteriography but remains a research tool rather than part of routine clinical practice.

Non-invasive risk stratification

For the purposes of these guidelines, if an individual with angina is determined, on the basis of a well validated risk prediction model, to have annual cardiovascular mortality of >2%, that individual is deemed high risk, while an annual cardiovascular mortality of <1% is considered low risk, and 1-2% intermediate risk.

Coronary arteriography

Non-invasive testing can establish the likelihood of the presence of obstructive coronary disease with an acceptable degree of certainty, and through appropriate risk stratification may be used to determine the need for coronary arteriography. However, coronary arteriography retains a fundamental position in the investigation of patients with stable angina, providing reliable anatomical information to identify the presence or absence of coronary lumen stenosis, define therapeutic options (suitability of medical treatment or myocardial revascularization) and determine prognosis.

Two vessel and three vessel disease have more severe prognostic implications than single vessel disease. High risk anatomical disease includes left main disease, or multi vessel disease involving the proximal left anterior descending coronary artery (LAD).

When appropriately used, non-invasive tests have an acceptable predictive value for adverse events. When the estimated annual cardiovascular mortality rate is less than or equal to 1%, the use of coronary arteriography to identify patients whose prognosis can be improved is likely to be inappropriate; in contrast it is appropriate for patients whose cardiovascular mortality risk is greater than 2% per annum.

Decisions regarding the need to proceed to arteriography in the intermediate risk group, those with an annual cardiovascular mortality of 1-2% should be guided by a variety of factors including the patient's symptoms, functional status, lifestyle, occupation, comorbidity, and response to initial therapy.

Coronary angiography is also warranted in the following circumstances:

- Serious ventricular arrhythmias or post cardiac arrest (without identifiable non-cardiac cause).
- Early recurrence of moderate or severe symptoms post revascularization.
- High risk of restenosis after PCI if PCI has been performed in a prognostically important site.
- Symptoms require consideration of revascularization.

3. Treatment

3.1 Aims of Treatment

1) To improve prognosis by preventing myocardial infarction and death.

2) To minimize or abolish symptoms.

3.2 General management including non-pharmacological considerations

- Patients and their close associates should be informed of the nature of angina pectoris, and the implications of the diagnosis and the treatments that may be recommended.
- Advice should be given for the management of an acute attack, i.e. to rest, at least briefly, from the activity that provoked the angina and the use of sublingual nitrate for acute relief of symptoms.
- The patient should be informed of potential side-effects of nitrates and appropriate prophylactic use of nitrate.
- Patients should be informed of the need to seek medical advice if angina symptoms persist for >10-20 minutes after rest and/or is not relieved by sublingual nitrate.
- Cigarette smoking should be strongly discouraged.
- Patients should be advised to adopt a "Mediterranean" diet, with vegetables, fruit, fish and poultry being the mainstays. A weight reducing diet should be recommended if the patient is overweight.
- Alcohol in moderation may be beneficial, but excessive consumption is harmful.
- Fish oils rich in omega-3 fatty acids (n-3 polyunsaturated fatty acids) are recommended at least once weekly.
- Physical activity within the patient's limitations should be encouraged.

Table 2. Summary of recommendations for routine non-invasive investigations in evaluation of stable angina

Test	For Diagnosis		For Prognosis	
	Class of Indication	Level of Evidence	Class of Indication	Level of Evidence
Laboratory tests				
Full blood count, creatinine	I	C	I	B
Fasting glucose	I	B	I	B
Fasting lipid profile	I	B	I	B
hs CRP, homocysteine, lp(a), apoA, apoB	IIb	B	IIb	B
ECG				
Initial evaluation	I	C	I	B
During episode of angina	I	B		
Routine periodic ECG on successive visits	IIb	C	IIb	C
Ambulatory ECG monitoring				
Suspected arrhythmia	I	B		
Suspected vasospastic angina	IIa	C		
In suspected angina with normal exercise test	IIa	C		
Chest X-ray				
Suspected heart failure, or abnormal cardiac auscultation	I	B	I	B
Suspected significant pulmonary disease	I	B		
Echocardiogram				
Suspected heart failure, abnormal auscultation, abnormal ECG, Q waves, BBB, marked ST changes	I	B	I	B
Previous MI			I	B
Hypertension or Diabetes Mellitus	I	C	I	B/C
Intermediate or low risk patient not due to have alternative assessment of LV function			IIa	C
Exercise ECG				
First line for initial evaluation, unless unable to exercise/ECG not evaluable	I	B	I	B
Patients with known CAD and significant deterioration in symptoms			I	B
Routine periodic testing once angina controlled	IIb	C	IIb	C
Exercise imaging technique (echo or radionuclide)				
Initial evaluation in patients with uninterpretable ECG	I	B	I	B
Patients with non-conclusive exercise test (but adequate exercise tolerance)	I	B	I	B
For Angina post revascularization	IIa	B	IIa	B
To identify location of ischaemia in planning revascularization	IIa	B		
Assessment of functional severity of intermediate lesions on arteriography	IIa	C		
Pharmacological stress imaging technique				
Patients unable to exercise	I	B	I	B
Patients with non-conclusive exercise test due to poor exercise tolerance	I	B	I	B
To evaluate myocardial viability	IIa	B		
Other indications as for exercise imaging where local facilities favour pharmacological rather than exercise stress	IIa	B	IIa	B
Non-invasive CT arteriography				
Patients with low probability of disease and non-conclusive or positive stress test	IIb	C		

- Concomitant disorders such as diabetes and hypertension should be managed appropriately. Patients with concomitant diabetes and/or renal disease should be treated with a blood pressure goal of <130/80 mmHg. Multifactorial intervention in diabetic patients may reduce both cardiovascular and other diabetic complications markedly.

- Anaemia or hyperthyroidism, if present, should be corrected.

- Sexual intercourse may trigger angina. Nitroglycerin prior to intercourse may be helpful. Phosphodiesterase inhibitors, such as sildenafil, tadafil or vardenafil, can be safely prescribed to men with coronary artery disease but should not be used in those receiving long acting nitrates.

3.3 Pharmacological therapy to improve prognosis

Antithrombotic drugs

Antiplatelet therapy to prevent coronary thrombosis is indicated, due to a favourable ratio between benefit and risk in patients with stable coronary artery disease. Low-dose aspirin (75-150 mg) is the drug of choice in most cases. The thienopyridine clopidogrel may be considered as an alternative in patients who are aspirin allergic, or in addition to aspirin post-stenting or after an acute coronary syndrome. For patients with a history of gastrointestinal bleeding, aspirin in combination with a proton pump inhibitor may be used rather than clopidogrel.

Anticoagulant drugs (warfarin or thrombin inhibitors), which are combined with aspirin in certain high risk patients, such as post myocardial infarction, are not indicated in the general stable angina population without a separate indication such as atrial fibrillation for example.

Lipid-lowering drugs

Statin treatment reduces the risk of atherosclerotic cardiovascular complications by some 30% in stable angina patients. Subgroup analyses indicate beneficial effects also in diabetic patients with vascular disease and benefits of statin therapy have also been demonstrated in the elderly (>70 years). Similar relative benefits of long-term statin therapy have been observed in patients with different pre-treatment levels of serum cholesterol, even in the "normal" range. Thus, recommendations to treat with statins may be guided as much by the level of cardiovascular risk as by the cholesterol level (within the normal to moderately elevated range).

Statin therapy should always be considered for patients with stable coronary artery disease and stable angina. Therapy should aim at statin dosages documented to reduce morbidity/mortality in clinical trials. The daily statin dosages with solid documentation of mortality benefit are simvastatin 40 mg, pravastatin 40 mg and atorvastatin 10 mg. If this dose is not sufficient to achieve the target total cholesterol and LDL levels mentioned above the dose of statin therapy may be increased as tolerated to achieve the targets.

Recently high-dose atorvastatin treatment (80 mg daily) has been shown to reduce the risk of cardiovascular events compared to 10 mg, but high-dose atorvastatin therapy should be reserved for high risk patients.

Other lipid lowering drugs, e.g. fibrates, prolonged release nicotinic acid and their combinations with statins and other hypolipidaemics may be needed to control the lipid levels in patients with severe dyslipidaemia, particularly those with low levels of HDL-cholesterol and high triglycerides. Adjunctive therapy to statin therapy may be considered on an individualised basis in patients who have severe dyslipidaemia and remain at high risk (estimated cardiovascular mortality >2% per annum) after conventional measures.

ACE-inhibitors

Angiotensin-converting enzyme (ACE) inhibitors are well established for the treatment of hypertension, heart failure, and LV dysfunction. In addition ramipril and perindopril have been shown to reduce the risk of cardiovascular morbidity and mortality in patients with stable coronary disease without heart failure in two large scale randomized controlled trials. A third trial, using the ACE-inhibitor trandalopril, failed to show a significant reduction in cardiovascular mortality and myocardial infarction.

ACE-inhibitors are indicated for the treatment of patients with stable angina pectoris and co-existing hypertension, diabetes, heart failure, asymptomatic LV dysfunction and post-MI. In angina patients without coexisting indications for ACE-inhibitor treatment the anticipated benefit of treatment (possible absolute risk reduction) should be weighed against costs and risks for side-effects, and the dose and agent used of proven efficacy for this indication in randomized clinical trials.

Beta-blockers

There is evidence of prognostic benefit from the use of beta-blockade in patients with angina who have suffered prior MI or have heart failure, and extrapolated from these data beta-blockers are suggested as a first line anti-anginal therapy in patients without contraindications.

3.4 Pharmacological treatment of symptoms and ischaemia

Symptoms of angina pectoris and signs of ischaemia (also silent ischaemia) may be reduced by drugs that reduce myocardial oxygen demand and/or increase blood flow to the ischaemic area. Commonly used antianginal drugs are beta-blockers, calcium antagonists and organic nitrates (Table 3); potassium channel openers may also be used. Recently sinus node inhibitors have been made available, and metabolic agents may also be used

General recommendations for pharmacological therapy:

- Anti-anginal drug treatment should be tailored to the needs of the individual patient, and should be monitored individually.
- Short-acting nitrate therapy for all patients for immediate relief of acute symptoms as tolerated.
- Different drug classes may have additive anti-anginal effects in clinical trials.
- Dosing of one drug should be optimized before adding another one.

Table 3: Pharmacological agents to reduce symptoms and ischaemia (recommendations relate to monotherapy, for relief of symptoms, and ischaemia).

Drugs	Action	Comments	Recommendations
Short-acting nitrates	Venodilatation, ↓ diastolic filling - ↓ reduced intracardiac pressure, ↑ subendocardial perfusion.	- Sublingual administration. - Situational prophylaxis.	IC
Long-acting nitrates		- Oral or transdermal formulations. - Care to maintain a nitrate free period.	IC
Beta-blockers	↓ oxygen demand by ↓ heart rate ↓ contractility ↓ blood pressure.	- Less side-effects with B1 receptor selective agents. - Titrate dose to symptoms and HR. - Proven to reduce frequency of symptoms and improve exercise tolerance. - May worsen vasospastic angina.	IA
Calcium channel blockers	- Heterogenous class. - Systemic and coronary vasodilation by inhibition of calcium influx via L-type channels. - Verapamil and diltiazem also reduce myocardial contractility. - HR and A-V conduction Dihydropyridine CCB's (e.g. nifedipine, amlodipine and felodipine) are more vaso-selective.	- Proven to reduce frequency of symptoms and improve exercise tolerance. - Efficacy comparable to beta-blockade. - Particularly effective in vasospastic angina.	IA
Potassium channel opener	- Activates potassium channels. - Also has nitrate like vasodilator effects.	- Nicorandil shown to reduce death. - MI and hospitalization for angina in one large RCT in addition to other treatments. - Not available in all countries.	IC
Sinus node inhibitor	- Reduces heart rate via direct inhibition of if channel in sinus node.	- Ivabradine shown to be as effective as beta-blockade in reducing symptoms in a RCT.	IIaB
Metabolic agents	- Increase glucose utilisation relative to fatty acid metabolism.	- Limited haemodynamic effects. - Trimetazidine not available in all countries. - Ranolazine not yet licensed in Europe.	IIbB

- Advisable to switch drug combinations before attempting a three drug regimen.
- Poor compliance should be considered when drug therapy is unsuccessful.
- Patients with symptoms that are poorly controlled on double therapy should be assessed for suitability for revascularization if not already considered.

The following strategy (see algorithm in Figure 2) is recommended for anti-anginal drug treatment in patients who are considered suitable for medical management after initial evaluation and risk stratification.

3.5 Coronary artery bypass surgery (CABG)

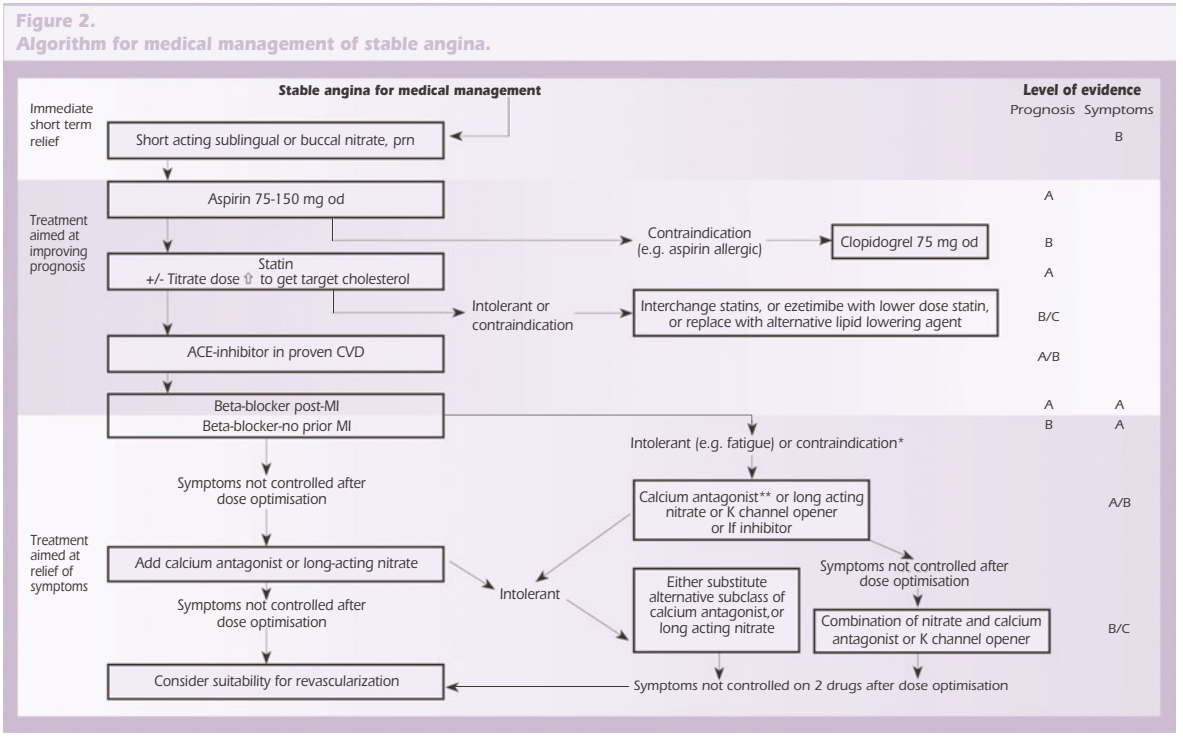
There are two main indications for CABG: prognostic and symptomatic. Prognostic benefit of CABG is mainly due to a reduction in cardiac mortality, as there is less evidence for reduction in myocardial infarction. Evidence of prognostic benefit of CABG compared to medical therapy has been demonstrated for patients at moderate to high risk of death. Specific anatomical groups shown to have a better prognosis with surgery than with medical treatment include:

1. Significant stenosis of the left main stem.
2. Significant proximal stenosis of the three major coronary arteries.
3. Significant stenosis of two major coronary arteries, including high grade stenosis of the proximal left anterior descending coronary artery.
4. Three vessel disease with impaired ventricular function.

CABG has also been shown to effectively reduce symptoms of angina and ischaemia in patients with coronary disease.

The overall operative mortality for CABG is between 1-4%, and there are well-developed risk stratification models available for the assessment of risk in individual patients. The risk of surgery should be weighed against quality of life gains, and potential prognostic benefit in the anatomical subgroups above. The use of the internal

Figure 2.
Algorithm for medical management of stable angina.



High risk candidates for revascularization on prognostic grounds alone should be identified and referred appropriately.

* Relative contraindications to beta-blockade include asthma, symptomatic peripheral vascular disease and first degree heart block

** Avoid short acting dihydropyridine formulations when not combined with beta-blocker.

Evidence for prognosis refers to evidence of reduction CV death or CV death MI. Evidence for symptoms include reduction in need for revascularization and hospitalization for chest pain.

mammary artery graft to LAD improves survival and reduces the incidence of late myocardial infarction, recurrent angina, and the need for further cardiac interventions. The use of other arterial grafts, also improve long-term patency rates.

3.6 Percutaneous coronary intervention (PCI)

In patients with stable angina and suitable coronary anatomy, the use of stents, the advent of drug eluting stents, and adequate adjuvant therapy allows a competent practitioner to perform either single or multivessel PCI with a high likelihood of initial procedural success and acceptable risk. The risk of death associated with the procedure in routine angioplasty is approximately 0.3% to 1%.

PCI may be considered an alternative to CABG for relief of symptoms in almost all cases. On available evidence, PCI compared to medical therapy does not provide survival benefit in stable angina, but PCI is more often effective than medical treatment in reducing events that impair quality of life (angina pectoris, dyspnoea, and need for re-hospitalization or limitation of exercise capacity). Advances in interventional technology have improved both initial and long term success rates of percutaneous revascularization, and are discussed in detail in the guidelines for PCI.

3.7 PCI versus surgery

Randomized trial evidence suggests that, outside of the population with high risk indicators, which have been proven to benefit prognostically from surgery, either PCI or surgery may be considered as an effective option for the treatment of symptoms.

In non-diabetic patients with 1-2 vessel disease without high-grade stenosis of the proximal LAD in whom angioplasty of one or more lesions has a high likelihood of initial success, PCI is generally the preferred initial approach, influenced by factors such as the less invasive nature and lower risk of the procedure, and the absence of survival advantage of CABG in lower risk subgroups. The individual circumstances and preferences of each patient must be considered carefully when planning the treatment strategy.

3.8 Specific patient and lesion subsets

Patients with severely depressed left ventricular function and/or high surgical risk, patients with left main disease, patients with diabetes and multivessel disease and patients with previous bypass surgery warrant particular consideration when selecting revascularization options:

- Patients in whom surgical risk is prohibitively high may benefit from revascularization by PCI, particularly when residual viability can be demonstrated in the dysfunctioning myocardium perfused by the target vessel(s).

- PCI in left main stem disease is feasible, and good results have been achieved in registries comparing drug-eluting and bare metal stents. However surgery should remain the preferred approach until the outcome of further trials are known.

- Subgroup analyses of randomized trials have shown reduced mortality with bypass surgery compared to PCI in diabetic patients with multivessel disease. Trials are underway to address this important issue, but for the present, PCI should be used with reservation in diabetics with multivessel disease until the results of these trials are available.

- There are no randomized controlled trials comparing treatment options in patients with previous bypass surgery. Re-do surgery may be undertaken on symptomatic grounds where the anatomy is suitable. However, the operative risks are high. In such cases PCI provides a useful alternative to re-do surgery for symptomatic relief.

3.9 Revascularization versus medical therapy

Outside the high risk population known to benefit prognostically from revascularization, an initial pharmacological approach to symptom control may be taken. Revascularization may be recommended for patients with suitable anatomy who do not respond adequately to medical therapy, or for the individual patient who, regardless of age, wishes to remain physically active (performing regular physical exercise).

An adequate response to therapy must be judged in consultation with the patient. Optimal secondary preventative medical therapy, including antiplatelet therapy, statin therapy, +/- beta-blockade, +/- ACE-inhibition should be continued in patients after revascularization irrespective of the need for anti-anginal therapy. Recommendations for revascularization are summarized in Table 4.

Table 4. Summary of recommendations for revascularization in stable angina.

Recommendations for revascularization on symptomatic grounds take into account the range of symptomatic grades for which evidence is available and should be construed in this fashion rather than as a directive to perform revascularization across the entire range of symptomatology.

	For Prognosis*		For Symptoms**		
Indication	**Class of Indication**	**Level of Evidence**	**Class of Indication**	**Level of Evidence**	**Studies**
PCI (assuming suitable anatomy for PCI, appropriate risk stratification and discussion with the patient)					
Angina CCS Class I to IV despite medical therapy with single vessel disease			I	A	ACME, MASS
Angina CCS Class I to IV despite medical therapy with multi vessel disease (non diabetic)			I	A	RITA 2, VA-ACME
Stable Angina with minimal (CCS Class I) symptoms on medication and one, two or three vessel disease but objective evidence of large ischaemia	IIb	C			ACIP
CABG (assuming suitable anatomy for surgery, appropriate risk stratification and discussion with the patient)					
Angina and left main stem disease	I	A	I	A	CASS, European Coronary Surgery study, VA Study, Yusef meta-analysis
Angina and three vessel disease with objective large ischaemia	I	A	I	A	
Angina and three vessel disease with poor ventricular function	I	A	I	A	
Angina with two or three vessel disease including severe disease of the proximal LAD	I	A	I	A	
Angina CCS Class I to IV with multivessel disease (diabetic)	IIa	B	I	B	BARI, GABI, ERACI-I, SoS, ARTs, Yusef et al, Hoffman et al.
Angina CCS Class I to IV with multivessel disease (non diabetic)			I	A	
Angina CCS Class I to IV despite medical therapy and single vessel disease including severe disease of the proximal LAD			I	B	MASS
Angina CCS Class I to IV despite medical therapy and single vessel disease not including severe disease of the proximal LAD			IIb	B	
Angina with minimal (CCS Class I) symptoms on medication and one, two or three vessel disease but objective evidence of large ischaemia	IIb	C			ACIP

* Prognosis = relates to effects on mortality, cardiac or cardiovascular mortality or mortality combined with myocardial infarction.

** Symptoms = relates to changes in angina class, exercise duration, time to angina on treadmill testing, repeat hospitalization for angina or other parameters of functional capacity or quality of life.

CCS = Canadian Cardiovascular Society.

Selection of the method of revascularization should be based on:

1. Risk of periprocedural morbidity and mortality.
2. Likelihood of success, including factors such as technical suitability of lesions for angioplasty or surgical bypass.
3. Risk of restenosis or graft occlusion.
4. Completeness of revascularization.
5. Diabetic status.
6. Local hospital experience in cardiac surgery and interventional cardiology.
7. Patient's preference.

4. Special diagnostic considerations: angina with "normal" coronary arteries

A considerable proportion of patients, especially women, who undergo coronary arteriography because of symptoms of chest pain do not have significant coronary artery disease. In these patients the features of chest pain may suggest one of the following three possibilities:

(i) non-cardiac chest pain.

(ii) atypical angina including vasospastic angina.

(iii) cardiac Syndrome X.

It is important to differentiate Syndrome X and vasospastic angina from non-cardiac chest pain. Intra-vascular ultrasound (IVUS), or assessment of coronary flow reserve or fractional flow reserve may be considered to exclude missed obstructive lesions, if angiographic appearances are suggestive of a non-obstructive lesion rather than completely normal, and stress imaging techniques identify an extensive area of ischaemia. Intracoronary acetyl-choline or ergonovine may be administered during coronary arteriography, if the angiogram is visually normal, to assess vasospasm or endothelium dependent coronary flow reserve.

4.1 Syndrome X

The classical description of "Syndrome X" requires the presence of the triad of:

1. Typical exercise induced angina (with or without additional resting angina and dyspnoea).

2. Positive exercise stress ECG or other stress imaging modality.

3. Normal coronary arteries.

A resting echocardiogram should be performed to assess for the presence of LVH and/or diastolic dysfunction. Although the prognosis in terms of survival of patients with Syndrome X appears to be favourable the morbidity is high. Treatment of Syndrome X should focus on symptom relief. Risk factors such as hypertension and hyperlipidaemia that are associated with endothelial dysfunction and may contribute to symptoms should be treated appropriately.

4.2 Vasospastic/Variant Angina

Often referred to as "Prinzmetal angina" it is characterized by typically located pain. It usually occurs at rest, but does not, or only occasionally, occurs with exertion, and is relieved within minutes by nitrates. The pain is classically associated with ST elevation.

Vasospastic angina may coexist with typical exertional angina due to fixed coronary lesions. Vasospasm may occur in response to smoking, electrolyte disturbances (potassium, magnesium), cocaine use, cold stimulation, autoimmune diseases, hyperventilation or insulin resistance. The prognosis of vasospastic angina depends on the extent of underlying coronary artery disease. Ambulatory ST-segment monitoring may be useful. Treatment of vasospastic angina centres on removing the stimulus, and calcium channel blockade or nitrate therapy.

Chapter 4
Myocardial Revascularisation*
2011

Joint Task Force on Myocardial Revascularisation of the European Society of Cardiology (ESC) and the European Association of Cardio-Thoracic Surgery (EACTS). Developed with the special contribution of the European Association for Percutaneous Cardiovascular Interventions (EAPCI)

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1. Introduction

Myocardial revascularisation, either by coronary artery bypass grafting (CABG) or by percutaneous coronary intervention (PCI), has been an established mainstay in the treatment of coronary artery disease (CAD) for almost half a century. While both interventions have witnessed significant technological advances, in particular the use of drug-eluting stent (DES) in PCI and of arterial grafts in CABG, their role for treatment of patients presenting with stable CAD is being challenged by advances in medical treatment, referred to as optimal medical therapy (OMT), including intensive lifestyle and pharmacological management. Furthermore, the differences between the two revascularisation strategies should be recognised. In CABG, bypass grafts are placed to the mid coronary vessel beyond the 'culprit' lesion(s), providing extra sources of nutrient blood flow to the myocardium and offering protection against the consequences of further proximal obstructive disease. In contrast, coronary stents aim at restoring the normal conductance of the native epicardial vessels without offering protection against new disease proximal to the stent.

In addition, myocardial revascularisation provides best results when focusing on the relief of ischaemia. In acute situations, culprit coronary stenoses are usually easily identified by angiography whereas in patients with stable CAD and multivessel disease (MVD), identification of the culprit lesion(s)

* Adapted from the Joint ESC-EACTS Guidelines on Myocardial Revascularisation (European Heart Journal 2010;31:2501-2556 - doi:10.1093/eurheartj/ehq277 & European Journal of Cardio-Thoracic Surgery 2010;38: S1:S1-S52-doi:10.1016/j.ejcts.2010.08.019)

Table 1: Classes of Recommendations	
Classes of Recommendations	**Definition**
Class I	**Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.**
Class II	**Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.**
Class IIa	***Weight of evidence/opinion is in favour of usefulness/efficacy.***
Class IIb	***Usefulness/efficacy is less well established by evidence/opinion.***
Class III	**Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.**

Table 2: Level of Evidence	
Level of Evidence A	**Data derived from multiple randomized clinical trials or meta-analyses.**
Level of Evidence B	**Data derived from a single randomized clinical trial or large non-randomized studies.**
Level of Evidence C	**Consensus of opinion of the experts and/or small studies, retrospective studies, registries.**

requires combined anatomic and functional evaluation. Many conditions, stable or acute, can be treated in different ways, including PCI or surgical revascularisation. The timing of risk and the morbidity encountered after CABG and PCI is different. Thus patients and physicians need to "balance short-term convenience of the less invasive PCI procedure against the durability of the more invasive surgical approach".

2. Scores and risk stratification, impact of comorbidity

Myocardial revascularisation is appropriate when the expected benefits, in terms of survival or health outcomes (symptoms, functional status, and/or quality of life), exceed the expected negative consequences of the procedure at various time points. No risk score can accurately predict events in an individual patient, who may have comorbidities not assessed in the risk model selected. Moreover, limitations exist with all databases used to build risk models, and differences in definitions and variable content can affect the performance of risk scores when they are applied across different populations. Ultimately, risk stratification should be used as a guide, while clinical judgement and multidisciplinary dialogue remain essential.

Limitations to existing databases restrict the ability to recommend one specific risk model; however:

1. The EuroSCORE validated to predict surgical mortality was recently shown to be an independent predictor of major adverse cardiac events (MACE) in studies with both percutaneous and surgical treatment arms. Therefore it can be used to determine the risk of revascularisation irrespective of, and even before, the selection of treatment strategy. It has little role, however, in determining optimal treatment.
2. The SYNTAX score has been shown to be an independent predictor of MACE in patients treated by PCI but not by CABG. Therefore it has a role both in aiding the selection of optimal treatment, and identifying those patients at highest risk of adverse events following PCI.
3. The National Cardiovascular Database Registry (NCDR CathPCI risk score) has been validated in PCI patients and should only be used in this context.
4. The Society of Thoracic Surgeons (STS) score and the age, creatinine, ejection fraction (ACEF) score have been validated in surgical patients, and therefore should only be used to determine surgical risk.

Table 3: Recommended risk stratification scores to be used in candidates for PCI or CABG

Score	Validated outcomes	Class[a]/Level[b]	
		PCI	CABG
EuroSCORE[1]	Short and long-term mortality.	IIb B	I B
SYNTAX score[2]	Quantify coronary artery disease complexity.	IIa B	III B
Mayo Clinic Risk Score	MACE and procedural death.	IIb C	III C
NCDR CathPCI	In-hospital mortality.	IIb B	-
Parsonnet score	30-day mortality.	-	III B
STS score[3]	Operative mortality, stroke, renal failure, prolonged ventilation, deep sternal infection, re-operation, morbidity, length of stay < 6 or > 14 days.	-	I B
ACEF score[4]	Mortality in elective CABG.	-	IIb C

a = class of recommendation; b = level of evidence.
ACEF = age, creatinine, ejection fraction; CABG = coronary artery bypass grafting; MACE = major adverse cardiac event; NCDR = National Cardiovascular Database Registry; PCI = percutaneous coronary intervention; STS = Society of Thoracic Surgeons.

Calculation
1: www.euroscore.org/calc.html
2: www.syntaxscore.com
3: http://209.220.160.181/STSWebRiskCalc261/
4: [Age/Ejection fraction (%)] + 1 (if creatinine > 2 mg/dL)

Table 4: Multidisciplinary decision pathways, patient informed consent and timing of intervention						
		ACS			Stable MVD	Stable with indication for ad hoc PCI*
	Shock	STEMI	NSTE - ACS**	Other ACS***		
Multidisciplinary decision making	Not mandatory.	Not mandatory.	Not required for culprit lesion but required for non-culprit vessel(s).	Required.	Required.	According to predefined protocols.
Informed consent	Oral witnessed informed consent or family consent if possible without delay.	Oral witnessed informed consent may be sufficient unless written consent is legally required.	Written informed consent# (if time permits).	Written informed consent#.	Written informed consent#.	Written informed consent#.
Time to revascularisation	Emergency: No delay.	Emergency: No delay.	Urgency: within 24 hours if possible and no later than 72 hours.	Urgency: Time constraints apply.	Elective: No time constraints.	Elective: No time constraints.
Procedure	Proceed with intervention based on best evidence/ availability.	Proceed with intervention based on best evidence/ availability.	Proceed with intervention based on best evidence/ availability. Non-culprit lesions treated according to institutional protocol.	Proceed with intervention based on best evidence/ availability. Non-culprit lesions treated according to institutional protocol.	Plan most appropriate intervention allowing enough time from diagnostic catheterization to intervention.	Proceed with intervention according to institutional protocol defined by local Heart Team.

* *Ad hoc* PCI indications are listed in Table 5.
** See also Tables 5 and 9.
*** Other ACS refers to unstable angina, with the exception of NSTE-ACS.
# This may not apply to countries that legally do not ask for written informed consent. ESC and EACTS strongly advocate documentation of patient consent for all revascularisation procedures.
ACS = acute coronary syndrome; MVD = multivessel disease; NSTE-ACS = non-ST-segment elevation acute coronary syndrome; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

3. Process for decision making and patient information

3.1 Patient information

Patient information needs to be objective and unbiased, patient-oriented, evidence-based, up-to-date, reliable, understandable, accessible, relevant, and consistent with legal requirements. Informed consent requires transparency especially if there is known controversy about the indication for a particular treatment (PCI versus CABG versus OMT alone).

3.2 Multidisciplinary decision making (Heart Team)

Patients should be adequately informed about the potential benefits and short- and long-term risks of a revascularisation procedure. Enough time should be spared for informed decision making. The appropriate revascularisation strategy in patients with MVD should be discussed by the Heart Team, which involves one of each of the following specialists: a non-invasive/clinical cardiologist, an invasive cardiologist, and a cardiac surgeon.

Ad hoc PCI is defined as a therapeutic interventional procedure performed immediately (with the patient still on the catheterisation table) following the diagnostic procedure as opposed to a staged procedure performed during a different

Table 5: Potential indications for *ad hoc* PCI versus revascularisation at an interval
***Ad hoc* PCI**
Haemodynamically unstable patients (including cardiogenic shock).
Culprit lesion in STEMI and NSTE-ACS.
Stable low-risk patients with single or double vessel disease (proximal LAD excluded) and favourable morphology (RCA, non-ostial LCx, mid or distal LAD).
Non-recurrent restenotic lesions.
Revascularisation at an interval
Lesions with high-risk morphology.
Chronic heart failure.
Renal failure (creatinine clearance < 60 mL/min), if total contrast volume required > 4 mL/kg.
Stable patients with MVD including LAD involvement.
Stable patients with ostial or complex proximal LAD lesion.
Any clinical or angiographic evidence of higher periprocedural risk with *ad hoc* PCI.

LAD = left anterior descending; LCx = left circumflex; MVD = multivessel disease; NSTE-ACS = Non-ST-segment elevation acute coronary syndrome; PCI = percutaneous coronary intervention; RCA = right coronary artery; STEMI = ST-segment elevation myocardial infarction.

Table 6: Indications of different imaging tests for the diagnosis of obstructive CAD and for the assessment of prognosis in subjects without known CAD #

	Asymptomatic (screening)	Symptomatic			Prognostic value of positive result #	Prognostic value of negative result #
		Pretest likelihood* of obstructive disease				
		Low	Intermediate	High		
Anatomical test						
Invasive angiography	III A	III A	IIb A	I A	I A	I A
MDCT angiography	III B §	IIb B	IIa B	III B	IIb B	IIa B
MRI angiography	III B	III B	III B	III B	III C	III C
Functional test						
Stress echo	III A	III A	I A	III A ##	I A	I A
Nuclear imaging	III A	III A	I A	III A ##	I A	I A
Stress MRI	III B	III C	IIa B	III B ##	IIa B	IIa B
PET perfusion	III B	III C	IIa B	III B ##	IIa B	IIa B

*The pretest likelihood of disease is calculated based on symptoms, sex, and risk factors.
§ This refers to MDCT angiography, not calcium scoring.
# For the prognostic assessment of known coronary stenosis, functional imaging is similarly indicated.
In patients with obstructive CAD documented by angiography, functional testing may be useful in guiding the revascularisation strategy based on the extent, severity, and localisation of ischaemia.
CAD = coronary artery disease; MDCT = multidetector computed tomography; MRI = magnetic resonance imaging; PET = positon emission tomography.

session. *Ad hoc* PCI is convenient for the patient, associated with fewer access site complications and is often cost-effective.

4. Strategies for pre-intervention diagnosis and imaging

Exercise testing and cardiac imaging are used to confirm the diagnosis of CAD, to document ischaemia in stable patients, to risk stratify patients with stable and acute coronary syndrome, to help choose treatments options and evaluate their efficacy.

5. Revascularisation for stable coronary artery disease

Depending on its symptomatic, functional and anatomic complexity, stable CAD can be treated by OMT alone or combined with revascularisation using PCI or CABG.

Table 7: Indications for revascularisation in stable angina or silent ischaemia

	Subset of CAD by anatomy	Class[a]	Level[b]
For prognosis	Left main > 50%*	I	A
	Any proximal LAD > 50%*	I	A
	2VD or 3VD with impaired LV function*	I	B
	Proven large area of ischaemia (> 10% LV)	I	B
	Single remaining patent vessel > 50% stenosis*	I	C
	1VD without proximal LAD and without > 10% ischaemia	III	A
For symptoms	Any stenosis > 50% with limiting angina or angina equivalent, unresponsive to OMT	I	A
	Dyspnoea/CHF and > 10% LV ischaemia/viability supplied by > 50% stenotic artery	IIa	B
	No limiting symptoms with OMT	III	C

a = class of recommendation; b = level of evidence.
* with documented ischaemia or FFR < 0.80 for angiographic diameter stenoses 50-90%.
CAD = coronary artery disease; CHF = chronic heart failure; FFR = fractional flow reserve; LAD = left anterior descending; LV = left ventricle; OMT = optimal medical therapy; VD = vessel disease.

Table 8: Indications for CABG versus PCI in stable patients with lesions suitable for both procedures and low predicted surgical mortality

Subset of CAD by anatomy	Favours CABG	Favours PCI
1VD or 2VD - non-proximal LAD	IIb C	I C
1VD or 2VD - proximal LAD	I A	IIa B
3VD simple lesions, full functional revascularisation achievable with PCI, SYNTAX score ≤ 22	I A	IIa B
3VD complex lesions, incomplete revascularisation achievable with PCI, SYNTAX score > 22	I A	III A
Left main (isolated or 1VD, ostium/shaft)	I A	IIa B
Left main (isolated or 1VD, distal bifurcation)	I A	IIb B
Left main + 2VD or 3VD, SYNTAX score ≤ 32	I A	IIb B
Left main + 2VD or 3VD, SYNTAX score ≥ 33	I A	III B

CABG = coronary artery bypass grafting; CAD = coronary artery disease; LAD = left anterior descending; PCI = percutaneous coronary intervention; VD = vessel disease.

6. Revascularisation in non-ST-segment elevation acute coronary syndrome (NSTE-ACS)

Patients with NSTE-ACS constitute a very heterogeneous group of patients with highly variable prognosis. Mortality and morbidity of high-risk NSTE-ACS patients remain high and equivalent to that of patients with ST-segment elevation myocardial (STEMI) after the initial month. Early risk stratification is essential for selection of medical and revascularisation strategies. The ultimate goals of coronary angiography and revascularisation are symptom relief and improvement of prognosis in the short and long term.

Table 9: Recommendations for revascularisation in NSTE-ACS

Specification	Class[a]	Level[b]
An invasive strategy is indicated in patients with: ▪ GRACE score > 140 or at least one high-risk criterion. ▪ recurrent symptoms. ▪ inducible ischaemia at stress test.	I	A
An early invasive strategy (< 24 h) is indicated in patients with GRACE score > 140 or multiple other high-risk criteria.	I	A
A late invasive strategy (within 72 h) is indicated in patients with GRACE score < 140 or absence of multiple other high-risk criteria but with recurrent symptoms or stress-inducible ischaemia.	I	A
Patients at very high ischaemic risk (refractory angina, with associated heart failure, arrhythmias or haemodynamic instability) should be considered for emergent coronary angiography (< 2 h).	IIa	C
An invasive strategy should not be performed in patients: ▪ at low overall risk. ▪ at a particularly high-risk for invasive diagnosis or intervention.	III	A

a = class of recommendation; b = level of evidence.
NSTE-ACS = non-ST-segment elevation acute coronary syndrome.

Table 10: Recommendations for reperfusion strategies in STEMI patients

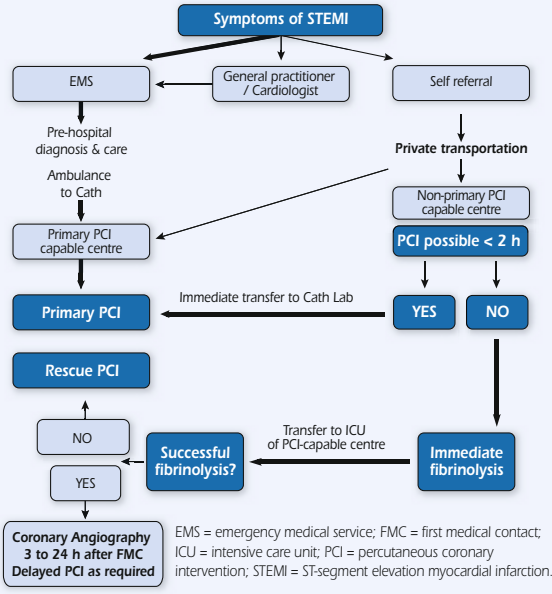
	Class[a]	Level[b]
Implementation of a well functioning network based on pre-hospital diagnosis, and fast transport to the closest available primary PCI capable centre is recommended.	I	A
Primary PCI capable centres should deliver 24 hours per day/7 days per week on call service, be able to start primary PCI as soon as possible and within 60 min from the initial call.	I	B
In case of fibrinolysis, pre-hospital initiation by properly equipped EMS should be considered and full-dose administered.	IIa	A
With the exception of cardiogenic shock, PCI (whether primary, rescue or post-fibrinolysis) should be limited to the culprit stenosis.	IIa	B
In PCI capable centers, unnecessary intermediate admissions to the emergency room or the intensive care unit should be avoided.	III	A
The systematic use of balloon counterpulsation, in the absence of haemodynamic impairment, is not recommended.	III	B

a = class of recommendation; b = level of evidence.
EMS = emergency medical service; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

7. Revascularisation in ST-segment elevation myocardial infarction

Figure 1: Organization of STEMI patient disposal describing pre- and in-hospital management, and reperfusion strategies within 12 h of First Medical Contact (FMC)

Thick lines indicate the preferred patient flow



EMS = emergency medical service; FMC = first medical contact; ICU = intensive care unit; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

Table 11: Recommendations for PCI in STEMI

Indication	Time from FMC	Class[a]	Level[b]
Primary PCI:			
Is recommended in patients with chest pain/discomfort < 12 h + persistent ST-segment elevation or non-previously documented left bundle branch block.	As soon as possible and at any rate < 2 h from FMC*	I	A
Should be considered in patients with ongoing chest pain/ discomfort > 12 h + persistent ST-segment elevation or previously undocumented left bundle branch block.	As soon as possible	IIa	C
May be considered in patients with history of chest pain/discomfort > 12 h and < 24 h + persistent ST-segment elevation or previously undocumented left bundle branch block.	As soon as possible	IIb	B

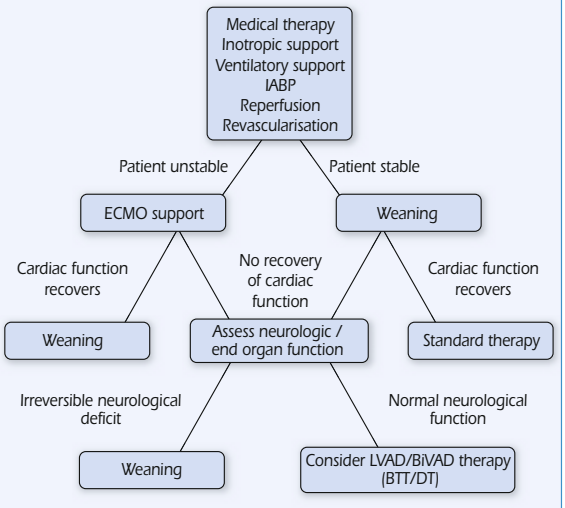
Table 11 (contd)			
Indication	**Time from FMC**	**Class[a]**	**Level[b]**
PCI after fibrinolysis:			
Routine urgent PCI is indicated after successful fibrinolysis (resolved chest pain/discomfort and ST-segment elevation).	Within 24 h**	I	A
Rescue PCI should be considered in patients with failed fibrinolysis.	As soon as possible	IIa	A
Elective PCI/CABG:			
Is indicated after documentation of angina/positive provocative tests.	Evaluation prior to hospital discharge	I	B
Not recommended in patients with fully developed Q wave MI and no further symptoms/signs of ischaemia or evidence of viability in the infarct related territory.	Patient referred > 24 h	III	B

a = class of recommendation; b = level of evidence.
* < 90 min if patient presents less than 2 h from symptoms onset and has large infarct and low bleeding risk.
** In order to reduce delay for patients with no reperfusion, transfer to PCI centre of all post-fibrinolysis patients is recommended.
CABG = coronary artery bypass grafting; FMC = first medical contact; MI = myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

Cardiogenic shock and mechanical complications

After failure of initial therapy including reperfusion and revascularisation to stabilize haemodynamics, temporary mechanical support using an extra-corporeal membrane oxygenator (ECMO) should be considered. If weaning from ECMO fails or heart failure (HF) persists, LVAD/Bi-VAD therapy may be considered if neurological function is not permanently impaired.

Figure 2: Treatment algorithms for AHF and cardiogenic shock



AHF = acute heart failure; BiVAD = biventricular assist device; BTT = bridge to transplantation; DT = destination therapy; ECMO = extracorporeal membrane oxygenator; IABP = intra-aortic balloon pump; LVAD = left ventricular assist device.

Table 12: Recommendations for treatment of patients with AHF in the setting of acute MI		
	Class[a]	**Level[b]**
Patients with NSTE-ACS or STEMI and unstable haemodynamics should immediately be transferred for invasive evaluation and target vessel revascularisation.	I	A
Immediate reperfusion is indicated in AHF with ongoing ischaemia.	I	B
Echocardiography should be performed to assess LV function and exclude mechanical complications.	I	C
Emergency angiography and revascularisation of all critically narrowed arteries by PCI/CABG as appropriate is indicated in patients in cardiogenic shock.	I	B
IABP insertion is recommended in patients with haemodynamic instability (particularly those in cardiogenic shock and with mechanical complications).	I	C
Surgery for mechanical complications of AMI should be performed as soon as possible with persistent haemodynamic deterioration despite IABP.	I	B
Emergent surgery after failure of PCI or of fibrinolysis is only indicated in patients with persistent haemodynamic instability or life threatening ventricular arrhythmia due to extensive ischaemia (LM or severe 3-vessel disease).	I	C
If the patient continues to deteriorate without adequate cardiac output to prevent end-organ failure, temporary mechanical assistance (surgical implantation of LVAD/BiVAD) should be considered.	IIa	C
Routine use of percutaneous centrifugal pumps is not recommended.	III	B

a = class of recommendation; b = level of evidence.
AMI = acute myocardial infarction; BiVAD = bi-ventricular assist device; CABG = coronary artery bypass grafting; HF = heart failure; IABP = intra-aortic balloon pump; LM = left main; LV = left ventricle; LVAD = left ventricular assist device; NSTE-ACS = non-ST-segment elevation acute coronary syndrome; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

8. Special conditions

8.1 Diabetes

Diabetic patients represent an increasing proportion of CAD patients, many of whom are treated with revascularisation procedures. They are at increased risk, including long-term mortality, compared with non-diabetic patients, whatever the mode of therapy used, and they may pose specific problems, such as a higher recurrence rate after PCI and CABG.

Table 13: Specific recommendations for diabetic patients

	Class[a]	Level[b]
In patients presenting with STEMI, primary PCI is preferred over fibrinolysis if it can be performed within recommended time limits.	I	A
In stable patients with extensive CAD, revascularisation is indicated in order to improve MACCE-free survival.	I	A
Use of DES is recommended in order to reduce restenosis and repeat TVR.	I	A
In patients on metformin, renal function should be carefully monitored after coronary angiography/ PCI.	I	C
CABG should be considered, rather than PCI, when the extent of the CAD justifies a surgical approach (especially MVD) and the patient's risk profile is acceptable.	IIa	B
In patients with known renal failure undergoing PCI, metformin may be stopped 48 h before the procedure.	IIb	C
Systematic use of GIK in diabetic patients undergoing revascularisation is not indicated.	III	B

a = class of recommendation; b = level of evidence.
CABG = coronary artery bypass grafting; CAD = coronary artery disease; DES = drug-eluting stent; GIK = glucose insulin potassium; MACCE = major adverse cardiac and cerebral event; MVD = multivessel disease; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction; TVR = target vessel revascularisation.

8.2 Myocardial revascularisation in patients with chronic kidney disease (CKD)

Table 14: Specific recommendations for patients with mild to moderate CKD

	Class[a]	Level[b]
CABG should be considered, rather than PCI, when the extent of the CAD justifies a surgical approach, the patient's risk profile is acceptable and life expectancy is reasonable.	IIa	B
Off-pump CABG may be considered, rather than on-pump CABG.	IIb	B
For PCI, DES may be considered, rather than BMS.	IIb	C

a = class of recommendation; b = level of evidence.
BMS = bare metal stent; CABG = coronary artery bypass grafting; CAD = coronary artery disease; CKD = chronic kidney disease; DES = drug-eluting stent; PCI = percutaneous coronary intervention.

Recommendations are less well established in patients with severe CKD (GFR < 30 mL/min/1.73 m^2) or in end-stage renal disease or on haemodialysis.

Table 15: Recommendations for prevention of CIN

Intervention	Dose	Class[a]	Level[b]
All patients with CKD			
OMT (including statins, ß-blockers, and ACE-inhibitors or sartans) is recommended.	According to clinical indications.	I	A
Hydration with isotonic saline is recommended.	1 mL/kg/h 12 h before and continued for 24 h after the procedure (0.5 mL/kg/h if EF < 35% or NYHA > 2).	I	A
N-Acetylcysteine administration may be considered.	600-1200 mg 24 h before and continued for 24 h after the procedure.	IIb	A
Infusion of sodium bicarbonate 0.84% may be considered.	1 h before: bolus = body weight in kg x 0.462 mEq i.v. infusion for 6 h after the procedure = body weight in kg x 0.154 mEq per hour.	IIb	A
Patients with mild, moderate or severe CKD[$]			
Use of LOCM or IOCM is recommended.	< 350 mL or < 4mL/kg.	I*	A*
Patients with severe CKD[$]			
Prophylactic haemofiltration 6 h before complex PCI should be considered.	Fluid replacement rate 1000 mL/h without weight loss and saline hydration, continued for 24 h after the procedure.	IIa	B
Elective haemodialysis is not recommended as a preventive measure.		III	B

a = class of recommendation; b = level of evidence.
* Recommendation pertains to the type of contrast.
$ mild CKD = 60 ≤ GFR < 90 mL/min/1.73m²; moderate CKD = 30 ≤ GFR < 60 mL/min/1.73m²; severe CKD = GFR < 30 mL/min/1.73m².
ACE = angiotensin-converting enzyme; CIN = contrast-induced nephropathy; CKD = chronic kidney disease; EF = ejection fraction; IOCM: iso-osmolar contrast media; i.v. = intravenous; LOCM: low osmolar contrast media; NYHA = New York Heart Association; OMT = optimal medical therapy; PCI = percutaneous coronary intervention.

8.3 Myocardial revascularisation in patients requiring valve surgery

Table 16: Recommendations for combined valve surgery and CABG

Combined valve surgery and:	Class[a]	Level[b]
CABG is recommended in patients with a primary indication for aortic/mitral valve surgery and coronary artery diameter stenosis ≥ 70%.	I	C
CABG should be considered in patients with a primary indication for aortic/mitral valve surgery and coronary artery diameter stenosis 50-70%.	IIa	C
Combined CABG and:		
Mitral valve surgery is indicated in patients with a primary indication for CABG and severe* ischaemic mitral regurgitation and EF > 30%.	I	C
Mitral valve surgery should be considered in patients with a primary indication for CABG and moderate ischaemic mitral regurgitation provided valve repair is feasible, and performed by experienced operators.	IIa	C
Aortic valve surgery should be considered in patients with a primary indication for CABG and moderate aortic stenosis (mean gradient 30 to 50 mmHg or Doppler velocity 3-4 m/sec or heavily calcified aortic valve even when Doppler velocity 2.5-3 m/sec).	IIa	C

a = class of recommendation; b = level of evidence.
* Definition of severe mitral regurgitation is available in the ESC Guidelines on Valvular Heart Disease; Eur heart J 2007;28(2)230-268 and www.escardio.org/guidelines; CABG = coronary artery bypass grafting; EF = ejection fraction.

8.4 Associated carotid/peripheral arterial disease

Table 17: Carotid artery screening before planned myocardial revascularization

Diagnosis of carotid artery stenosis	Class[a]	Level[b]
Duplex ultrasound scanning is recommended in patients with previous TIA/stroke or carotid bruit on auscultation.	I	C
Duplex ultrasound scanning should be considered in patients with LM disease, severe PAD or ≥ 75 years.	IIa	C
MRI, CT or digital subtraction angiography may be considered if carotid artery stenosis by ultrasound is > 70%* and myocardial revascularisation is contemplated.	IIb	C

a = class of recommendation; b = level of evidence.
* See appendix for methods of carotid artery stenosis measurement (available in the online version of these Guidelines at www.escardio.org/guidelines); CT = computed tomography; LM = left main; MRI = magnetic resonance imaging; PAD = peripheral arterial disease; TIA = transient ischaemic attack.

Table 18: Carotid revascularisation in patients scheduled for CABG

	Class[a]	Level[b]
CEA or CAS should be performed only by teams with demonstrated 30 day combined death-stroke rate: < 3% in patients without previous neurologic symptoms < 6% in patients with previous neurologic symptoms.	I	A
The indication for carotid revascularisation should be individualised after discussion by a multidisciplinary team including a neurologist.	I	C
The timing of the procedures (synchronous or staged) should be dictated by local expertise and clinical presentation targeting the most symptomatic territory first.	I	C
In patients with previous TIA/non-disabling stroke, carotid revascularisation:		
Is recommended in 70-99% carotid stenosis.	I	C
May be considered in 50-69% carotid stenosis in men with symptoms < 6 months.	IIb	C
Is not recommended if carotid stenosis < 50% in men and < 70% in women.	III	C
In patients with no previous TIA/stroke, carotid revascularisation:		
May be considered in men with bilateral 70-99% carotid stenosis or 70-99% carotid stenosis + contralateral occlusion.	IIb	C
Is not recommended in women or patients with a life expectancy < 5 years.	III	C

a = class of recommendation; b = level of evidence.
CABG = coronary artery bypass grafting; CAS = carotid artery stenting; CEA = carotid endarterectomy; TIA = transient ischaemic attack.

Table 19: Carotid revascularisation in patients scheduled for PCI

	Class[a]	Level[b]
The indication for carotid revascularisation should be individualized after discussion by a multidisciplinary team including a neurologist.	I	C
CAS should not be combined with elective PCI during the same endovascular procedure except in the infrequent condition of concomitant severe carotid and acute coronary syndromes.	III	C

a = class of recommendation; b = level of evidence.
CAS = carotid artery stenting; PCI = percutaneous coronary intervention.

Table 20: Recommendations for the method of carotid revascularisation

	Class[a]	Level[b]
CEA remains the procedure of choice but selection of CEA versus CAS depends on multidisciplinary assessment.	I	B
Aspirin is recommended immediately before and after carotid revascularisation.	I	A
Patients who undergo CAS should receive DAPT for at least 1 month after stenting.	I	C
CAS should be considered in patients with: ▪ Post-radiation or post-surgical stenosis ▪ Obesity, hostile neck, tracheostomy, laryngeal palsy ▪ Stenosis at different carotid levels or upper internal carotid artery stenosis ▪ Severe comorbidities contraindicating CEA.	IIa	C
CAS is not recommended in patients with: ▪ Heavily calcified aortic arch or protruding atheroma ▪ Internal carotid artery lumen diameter < 3 mm ▪ Contraindication to DAPT.	III	C

a = class of recommendation; b = level of evidence.
CAS = carotid artery stenting; CEA = carotid endarterectomy; DAPT = dual antiplatelet therapy.

8.5 Associated coronary and peripheral arterial disease

Table 21: Management of patients with associated coronary and peripheral arterial disease

	Class[a]	Level[b]
In patients with unstable CAD, vascular surgery is postponed and CAD treated first, except when vascular surgery cannot be delayed due to a life threatening condition.	I	B
ß-blockers and statins are indicated prior to and continued postoperatively in patients with known CAD who are scheduled for high-risk vascular surgery.	I	B
The choice between CABG and PCI should be individualized and assessed by a Heart Team considering patterns of CAD, PAD, comorbidity and clinical presentation.	I	C
Prophylactic myocardial revascularisation prior to high-risk vascular surgery may be considered in stable patients if they have persistent signs of extensive ischaemia or a high cardiac risk.	IIb	B

a = class of recommendation; b = level of evidence.
CABG = coronary artery bypass grafting; CAD = coronary artery disease; PAD = peripheral arterial disease; PCI = percutaneous coronary intervention.

Table 22: Management of patients with renal artery stenosis		
	Class[a]	Level[b]
Functional assessment of renal artery stenosis severity using pressure gradient measurements may be useful in selecting hypertensive patients who benefit from renal artery stenting.	IIb	B
Routine renal artery stenting to prevent deterioration of renal function is not recommended.	III	B

a = class of recommendation; b = level of evidence.

8.6 Myocardial revascularisation in chronic heart failure

Table 23: In patients with CHF and presenting with angina		
	Class[a]	Level[b]
CABG is recommended for: ▪ Significant LM stenosis ▪ LM equivalent (proximal stenosis of both LAD and LCx) ▪ Proximal LAD stenosis with 2- or 3- vessel disease.	I	B
CABG with SVR may be considered in patients with LVESV index ≥ 60 mL/m² and scarred LAD territory.	IIb	B
PCI may be considered if anatomy is suitable, in the presence of viable myocardium.	IIb	C

a = class of recommendation; b = level of evidence.
CABG = coronary artery bypass grafting; CHF = chronic heart failure; LAD = left anterior descending; LCx = left circumflex; LM = left main; LVESV = left ventricular end-systolic volume; PCI = percutaneous coronary intervention; SVR = surgical ventricular reconstruction.

Table 24: Recommendations for patients with CHF and systolic LV dysfunction (EF ≤ 35%), presenting predominantly with HF symptoms (no or mild angina: CCS 1-2)		
	Class[a]	Level[b]
LV aneurysmectomy during CABG is indicated in patients with a large LV aneurysm.	I	C
CABG should be considered in the presence of viable myocardium, irrespective of LVESV.	IIa	B
CABG with SVR may be considered in patients with a scarred LAD territory.	IIb	B
PCI may be considered if anatomy is suitable, in the presence of viable myocardium.	IIb	C
Revascularisation in the absence of evidence of myocardial viability is not recommended.	III	B

a = class of recommendation; b = level of evidence.
CABG = coronary artery bypass grafting; CCS = Canadian Cardiovascular Society; CHF = chronic heart failure; EF = ejection fraction; HF = heart failure; LAD = left anterior descending; LV = left ventricle; LVESV = left ventricular end-systolic volume; PCI = percutaneous coronary intervention; SVR = surgical ventricular reconstruction.

8.7 Crossed revascularisation procedures

Ischaemia after CABG may be due to new disease, progression beyond the bypass graft anastomosis, or disease in the graft itself.

Repeat revascularisation in patients with graft failure is indicated in the presence of severe symptoms despite anti-anginal medication, and in less or asymptomatic patients depending on risk stratification by non-invasive testing.

Table 25: Crossed revascularisation procedures		
	Class[a]	Level[b]
Following CABG		
In early graft failure:		
Coronary angiography is indicated for highly symptomatic patients, or in the event of postoperative instability, or with abnormal biomarkers/ECG suggestive of perioperative MI.	I	C
Decision of redo CABG or PCI should be made by the Heart Team.	I	C
PCI is a superior alternative to reoperation in patients with early ischaemia after CABG.	I	B
The preferred target for PCI is the native vessel or ITA graft, not the freshly occluded SVG.	I	C
For freshly occluded SVG, redo CABG is recommended rather than PCI if the native artery appears unsuitable for PCI or several important grafts are occluded.	I	C
In late graft failure following CABG:		
PCI or redo CABG is indicated in patients with severe symptoms or extensive ischaemia despite OMT.	I	B
PCI is recommended as a first choice, rather than redo CABG.	I	B
PCI of the bypassed native artery is the preferred approach when stenosed grafts > 3 years old.	I	B
ITA is the conduit of choice for redo CABG.	I	B
Redo CABG should be considered for patients with several diseased grafts, reduced LV function, several CTO or absence of a patent ITA.	IIa	C
PCI should be considered in patients with patent left ITA and amenable anatomy.	IIa	C
Following PCI		
In early failure following PCI:		
Repeat PCI is recommended for early symptomatic restenosis after PCI.	I	B
Immediate CABG is indicated if failed PCI is likely to cause a large MI.	I	C
In late failure following PCI:		
Patients with intolerable angina or ischaemia will eventually require CABG if: a) lesions are unsuitable for PCI. b) there is additional non-discrete disease progression in other vessels. c) restenoses are repetitive and interventional options are not favourable.	 I I I	 C C C

a = class of recommendation; b = level of evidence.
CABG = coronary artery bypass grafting; CTO = chronic total occlusion; ECG = electrocardiogram; ITA = internal thoracic artery; LV = left ventricle; MI = myocardial infarction; OMT = optimal medical therapy; PCI = percutaneous coronary intervention; SVG = saphenous vein graft.

8.8 Arrhythmias in patients with ischaemic heart disease

Table 26: Prevention and treatment of atrial fibrillation with CABG

	Class[a]	Level[b]
ß-blockers are recommended to decrease the incidence of AF after CABG.	I	A
Sotalol should be considered to decrease the incidence of AF after CABG.	IIa	A
Amiodarone should be considered to decrease the incidence of AF after CABG .	IIa	A
Statins should be considered to decrease the incidence of AF after CABG.	IIa	B
Corticosteroids may be considered to decrease the incidence of AF after CABG.	IIb	B
Restoring sinus rhythm in patients having CABG may be considered in order to increase survival.	IIb	B
Performing AF ablation during CABG may be considered an effective strategy.	IIb	C

a = class of recommendation; b = level of evidence.
AF = atrial fibrillation; CABG = coronary artery bypass grafting.

9. Procedural aspects of coronary artery bypass grafting

Patients admitted for surgical revascularisation are usually taking many medications including ß-blockers, angiotensin-converting enzyme inhibitors, statins, and anti-platelet drugs. ß-blockers should not be stopped to avoid acute ischaemia upon discontinuation.

Table 27: Technical recommendations for CABG

	Class[a]	Level[b]
Procedures should be performed in a hospital structure and by a team specialized in cardiac surgery, using written protocols.	I	B
Arterial grafting to the LAD system is indicated.	I	A
Complete revascularisation with arterial grafting to non-LAD coronary systems is indicated in patients with reasonable life-expectancy.	I	A
Minimisation of the aortic manipulation is recommended.	I	C
Graft evaluation is recommended before leaving the operating theatre.	I	C

a = class of recommendation; b = level of evidence.
CABG = coronary artery bypass grafting; LAD = left anterior descending.

10. Procedural aspects of percutaneous coronary intervention

Table 28: Recommendations for specific PCI devices and pharmacotherapy

	Class[a]	Level[b]
FFR-guided PCI is recommended for detection of ischaemia-related lesion(s) when objective evidence of vessel-related ischaemia is not available.	I	A
DES* are recommended for reduction of restenosis/reocclusion, if no contraindication to extended DAPT.	I	A
Distal embolic protection is recommended during PCI of SVG disease to avoid distal embolisation of debris and prevent MI.	I	B
Rotablation is recommended for preparation of heavily calcified or severely fibrotic lesions that cannot be crossed by a balloon or adequately dilated before planned stenting.	I	C
Manual catheter thrombus aspiration should be considered during PCI of the culprit lesion in STEMI.	IIa	A
For PCI of unstable lesions, intravenous abciximab should be considered for pharmacological treatment of no-reflow.	IIa	B
Drug-eluting balloons* should be considered for the treatment of in-stent restenosis after prior BMS.	IIa	B
Proximal embolic protection may be considered for preparation before PCI of SVG disease.	IIb	B
For PCI of unstable lesions, intracoronary or intravenous adenosine may be considered for pharmacological treatment of no-reflow.	IIb	B
Tornus catheter may be used for preparation of heavily calcified or severely fibrotic lesions that cannot be crossed by a balloon or adequately dilated before planned stenting.	IIb	C
Cutting or scoring balloons may be considered for dilatation of in-stent restenosis, to avoid slipping-induced vessel trauma of adjacent segments.	IIb	C
IVUS-guided stent implantation may be considered for unprotected left main PCI.	IIb	C
Mesh-based protection may be considered for PCI of highly thrombotic or SVG lesions.	IIb	C
For PCI of unstable lesions, intracoronary nitroprusside or other vasodilators may be considered for pharmacological treatment of no-reflow.	IIb	C

a = class of recommendation; b = level of evidence.
* Recommendation is only valid for specific devices with proven efficacy/safety profile, according to the respective lesion characteristics of the studies.
BMS = bare metal stent; DAPT = dual antiplatelet therapy; DES = drug-eluting stent; FFR = fractional flow reserve; IVUS = intravascular ultrasound; MI = myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction; SVG = saphenous vein graft.

Table 29: Relative clinical contraindications to the use of DES
▪ Clinical history difficult to obtain, especially in the setting of acute severe clinical conditions (STEMI or cardiogenic shock).
▪ Expected poor compliance with DAPT, including patients with multiple comorbidities and polypharmacy.
▪ Non-elective surgery required in the short-term that would require interruption of DAPT.
▪ Increased risk of bleeding.
▪ Known allergy to ASA or clopidogrel/prasugrel/ticagrelor.
▪ Absolute indication for long-term anticoagulation.

ASA = acetylsalicylic acid; DES = drug-eluting stent; DAPT = dual antiplatelet therapy; STEMI = ST-segment elevation myocardial infarction.

11. Antithrombotic pharmacotherapy

Table 30: Antithrombotic treatment options in myocardial revascularisation			
Elective PCI			
Antiplatelet therapy		**Class[a]**	**Level[b]**
	ASA	I	B
	Clopidogrel	I	A
	Clopidogrel - Pretreatment with 300 mg loading dose > 6 h before PCI (or 600 mg > 2 h before)	I	C
	+ GPIIb-IIIa antagonists (bailout situation only)	IIa	C
Anticoagulation		**Class[a]**	**Level[b]**
	UFH	I	C
	Enoxaparin	IIa	B
NSTE-ACS			
Antiplatelet therapy		**Class[a]**	**Level[b]**
	ASA	I	C
	Clopidogrel (with 600 mg loading dose as soon as possible)	I	C
	Clopidogrel (for 9-12 months after PCI)	I	B
	Prasugrel*	IIa	B
	Ticagrelor*	I	B
	+ GPIIb-IIIa antagonists (in patients with evidence of high intracoronary thrombus burden)		
	Abciximab (with DAPT)	I	B
	Tirofiban, Eptifibatide	IIa	B
	Upstream GPIIb-IIIa antagonists	III	B
Anticoagulation		**Class[a]**	**Level[b]**
very high-risk of ischaemia**	UFH (+ GPIIb-IIIa antagonists)	I	C
	Bivalirudin (monotherapy)	I	B
medium-to-high-risk of ischaemia**	UFH	I	C
	Bivalirudin	I	B
	Fondaparinux	I	B
	Enoxaparin	IIa	B
low-risk of ischaemia**	Fondaparinux	I	B
	Enoxaparin	IIa	B
STEMI			
Antiplatelet therapy		**Class[a]**	**Level[b]**
	ASA	I	B
	Clopidogrel*** (with 600 mg loading dose as soon as possible)	I	C
	Prasugrel*	I	B
	Ticagrelor*	I	B
	+ GPIIb-IIIa antagonists (in patients with evidence of high intracoronary thrombus burden)		
	Abciximab	IIa	A
	Eptifibatide	IIa	B
	Tirofiban	IIb	B
	Upstream GPIIb-IIIa antagonists	III	B
Anticoagulation		**Class[a]**	**Level[b]**
	Bivalirudin (monotherapy)	I	B
	UFH	I	C
	Fondaparinux	III	B

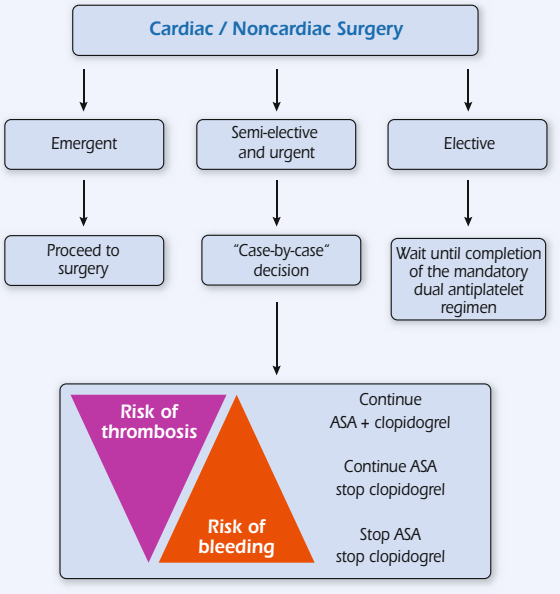
a = class of recommendation; b = level of evidence.
* Depending on approval and availability. Direct comparison between prasugrel and ticagrelor is not available. Long term follow-up is awaited for both drugs.
** See Table 9 for definition of ischaemia risk; *** Primarily if more efficient antiplatelet agents are contraindicated.
ASA = acetylsalicylic acid; DAPT = dual antiplatelet therapy; GPIIb-IIIa = glycoprotein IIb-IIIa; NSTE-ACS = non-ST-segment elevation acute coronary syndrome; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction; UFH = unfractionated heparin.

Table 31: Antithrombotic drug use in CKD	
Antiplatelet therapy	
ASA	No specific recommendations.
Clopidogrel	No information in patients with renal dysfunction.
Prasugrel[a]	No dosage adjustment is necessary for patients with renal impairment, including patients with end stage renal disease.
Ticagrelor[a]	No dose reduction required in patients with GFR < 60 mL/min/1.73 m^2.
GPIIb-IIIa antagonists	
Abciximab	No specific recommendations for the use or dose adjustment in the case of renal failure.
Tirofiban	Dose adaptation required in patients with renal failure: 50% of the dose with GFR of < 30 mL/min/1.73 m^2.

Table 31: Antithrombotic drug use in CKD (contd)	
Antiplatelet therapy	
Eptifibatide	Dose adaptation in moderate renal impairment (GFR < 60 mL/min/1.73 m²). Contraindicated in severe renal dysfunction.
Anticoagulation	
Unfractionated heparin	Dose reduction necessary based on frequent aPTT measurements to control therapeutic range.
Enoxaparin (and other LMWHs)	In case of severe renal failure (GFR < 30 mL/min/1.73 m²) either to be avoided or 50% dose reduction and control of therapeutic levels by factor Xa-activity measurements. In patients with reduced GFR (range 30-60 mL/min/1.73m²) dose reduction to 75% of the recommended full dose.
Fondaparinux	Contraindicated in severe renal failure (< 30 mL/min/1.73 m²); drug of choice in patients with reduced renal function (GFR 30-60 mL/min/1.73 m²) due to lower risk of bleeding complications compared with enoxaparin.
Bivalirudin	Consider reduction of infusion rate to 1.0 mg/kg/h in patients with severe renal dysfunction; consider use in patients with NSTE-ACS and reduced renal function (GFR 30-60 mL/min/1.73 m²) undergoing angiography ± PCI due to lower bleeding risk compared with UFH + GPIIb-IIIa Antagonists.

[a] Depending on approval and availability.
aPTT = activated partial thromboplastin time; ASA = acetylsalicylic acid; CKD = chronic kidney disease; GFR = glomerular filtration rate; GPIIb-IIIa = glycoprotein IIb-IIIa; LMWHs = low molecular weight heparins; NSTE-ACS = non-ST-segment elevation acute coronary syndrome; PCI = percutaneous coronary intervention; UFH = unfractionated heparin.

Figure 3:
Algorithm for pre-operative management of patients considered for/undergoing surgery treated with dual antiplatelet therapy



ASA = acetylsalicylic acid.

12. Secondary prevention

Table 32: Long-term lifestyle and risk factor management after myocardial revascularisation	Class[a]	Level[b]
Long-term management is based on risk stratification that should include:		
▪ full clinical and physical evaluation	I	C
▪ ECG	I	B
▪ laboratory testing	I	B
▪ HbA1c	I	A
▪ physical activity level by history and exercise testing	I	B
▪ echocardiogram prior to and after CABG.	I	C
Echocardiography should be considered pre- or post-PCI.	IIa	C
▪ Counselling on physical activity and exercise training should include a minimum of 30-60 minutes/day of moderately intense aerobic activity	I	A
▪ Medically supervised programmes are advisable for high-risk patients (e.g. recent revascularisation, heart failure).	I	B
Resistance training 2 days/week may be considered.	IIb	C
▪ Diet and weight control management should aim at BMI < 25 kg/m² and waist circumferences < 94 cm in men and < 80 cm in women.	I	B
▪ It is recommended to assess BMI and/or waist circumferences on each visit and consistently encourage weight maintenance/reduction.	I	B
▪ The initial goal of weight-loss therapy is the reduction of body weight by approximately 10% from baseline.	I	B
▪ Healthy food choices are recommended.	I	B
▪ Dietary therapy and lifestyle changes are recommended.	I	B
▪ It is recommended to reach LDL-cholesterol < 100 mg/dL (2.5 mmol/L).	I	A
▪ In high-risk patients, it is recommended to reach LDL-cholesterol < 70 mg/dL (2.0 mmol/L).	I	B
Increased consumption of omega-3 fatty acids in the form of fish oil may be considered.	IIb	B
▪ It is recommended to implement lifestyle changes and pharmacotherapy in order to achieve blood pressure < 130/80 mmHg.	I	A
▪ ß-blockers and/or ACE inhibitors are indicated as first line therapy.	I	A
It is recommended to assess, at each visit, smoking status, to insist on smoking cessation, and to advise avoiding passive smoking.	I	B
In patients with diabetes, the following is recommended:		
▪ lifestyle changes and pharmacotherapy to achieve HbA1c < 6.5%	I	B
▪ vigorous modification of other risk factors	I	B
▪ coordination of diabetic care with a specialised physician.	I	C
Screening for psychological distress is indicated.	I	C
Annual influenza vaccination is indicated.	I	B

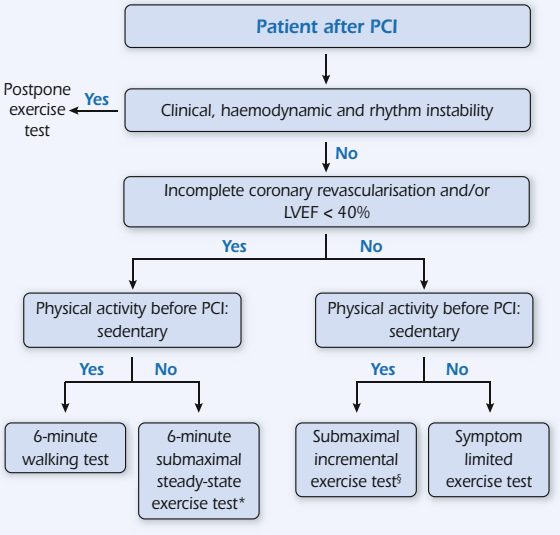
a = class of recommendation; b = level of evidence.
ACE = angiotensin-converting enzyme; BMI = body mass index; CABG = coronary artery bypass grafting; ECG = electrocardiogram; HbA1c = glycated haemoglobin; LDL = low density lipoprotein; PCI = percutaneous coronary intervention.

Table 33: Long-term medical therapy after myocardial revascularisation

	Class[a]	Level[b]
▪ ACE inhibitors should be started and continued indefinitely in all patients with LVEF ≤ 40% and for those with hypertension, diabetes, or CKD, unless contraindicated.	I	A
▪ ACE inhibitors should be considered in all patients, unless contraindicated.	IIa	A
▪ Angiotensin receptor blockers are indicated in patients who are intolerant to ACE inhibitors and have HF or MI with LVEF ≤ 40%.	I	A
▪ Angiotensin receptor blockers should be considered in all ACE-inhibitor intolerant patients.	IIa	A
▪ It is indicated to start and continue ß-blocker therapy in all patients after MI or ACS or LV dysfunction, unless contraindicated.	I	A
▪ High-dose lipid lowering drugs are indicated in all patients regardless of lipid levels, unless contraindicated.	I	A
▪ Fibrates and omega-3 fatty acids (1 g/day) should be considered in combination with statins and in patients intolerant to statins.	IIa	B
▪ Niacin may be considered to increase HDL cholesterol.	IIb	B

a = class of recommendation; b = level of evidence.
ACE = angiotensin-converting enzyme; ACS = acute coronary syndrome; CKD = chronic kidney disease; HDL = high density lipoprotein; HF = heart failure; LV = left ventricle; LVEF = left ventricular ejection fraction; MI = myocardial infarction.

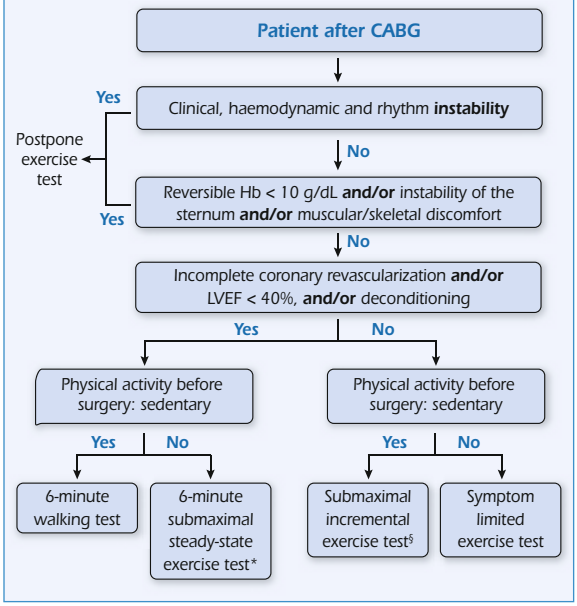
Figure 4: Algorithm for prescription of functional evaluation at the onset of rehabilitation or exercise programme after PCI



The following general criteria should be considered in planning an exercise test for exercise prescription: safety, i.e. stability of clinical, haemodynamic and rhythmic parameters, ischaemic and angina threshold (in case of incomplete revascularisation), degree of LVEF impairment; associated factors (i.e. sedentary habits, orthopaedic limitations, occupational and recreational needs).

*: Upper limit for terminating submaximal 6-min single stage (steady-state) exercise testing: rate of perceived exertion (Borg scale) 11-13 /20 or maximal heart rate = heart rate at standing rest + 20-30 beats /min.
§: Upper limit for terminating submaximal incremental testing: maximal heart rate = 70 % heart rate reserve or 85 % of age-predicted maximal heart rate.
LVEF = left ventricular ejection fraction; PCI = percutaneous coronary intervention.

Figure 5: Algorithm for prescription of functional evaluation at the onset of rehabilitation or exercise programme after CABG



The following general criteria should be considered in planning exercise test for exercise prescription: safety; comorbidities, i.e. haemoglobin values, muscular-skeletal discomfort, healing issues at the incision sites; associated factors, i.e. deconditioning due to prolonged hospitalisation, sedentary habits, orthopaedic limitations, occupational and recreational needs (see also legend to Figure 4).
*: Upper limit for terminating submaximal 6-min single stage (steady-state) exercise testing: rate of perceived exertion (Borg scale) 11-13 /20 or maximal heart rate = heart rate at standing rest + 20-30 beats /min.
§: Upper limit for terminating submaximal incremental testing: maximal heart rate = 70 % heart rate reserve or 85 % of age-predicted maximal heart rate.
CABG = coronary artery bypass grafting; Hb = haemoglobin; LVEF = left ventricular ejection fraction.

13. Strategies for follow-up

Although the need to detect restenosis has diminished in the drug-eluting stent (DES) era, a number of patients are still treated with bare metal stent (BMS) or balloon angioplasty with high recurrence rates. Likewise, the durability of CABG results has increased with the use of arterial grafts and ischaemia stems mainly from saphenous vein graft (SVG) attrition and progression of CAD in native vessels.

Table 34: Strategies for follow-up and management in asymptomatic patients after myocardial revascularisation		
	Class[a]	Level[b]
Stress imaging (stress echo or MPS) should be used rather than stress ECG.	I	A
▪ With low-risk findings (+) at stress testing, the reinforcement of OMT and lifestyle changes should be considered. ▪ With high- to intermediate-risk findings (++) at stress testing, coronary angiography should be considered.	IIa	C
Early imaging testing should be considered in specific patient subsets*.	IIa	C
Routine stress testing may be considered ≥ 2 years after PCI and ≥ 5 years after CABG.	IIb	C

* Specific patient subsets indicated for early stress testing with imaging:
▪ Predischarge, or early post-discharge imaging stress test in STEMI patients treated with primary PCI or emergency CABG.
▪ Patients with safety critical professions (e.g. pilots, drivers, divers) and competitive athletes
▪ Users of 5-phosphodiesterase inhibitors.
▪ Patients who would like to be engaged in recreational activities for which high oxygen consumption is required.
▪ Patients resuscitated from sudden death.
▪ Patients with incomplete or suboptimal revascularisation, even if asymptomatic.
▪ Patients with a complicated course during revascularisation (perioperative MI, extensive dissection during PCI, endarterectomy during CABG, etc.).
▪ Patients with diabetes (especially those requiring insulin).
▪ Patients with MVD and residual intermediate lesions, or with silent ischaemia.

a = class of recommendation; b = level of evidence.
(+) Low-risk findings at stress imaging are ischaemia at high workload, late onset ischaemia, single zone of low grade wall motion abnormality or small reversible perfusion defect, or no evidence of ischaemia.
(++) Intermediate- and high-risk findings at stress imaging are ischaemia at low workload, early onset ischaemia, multiple zones of high grade wall motion abnormality or reversible perfusion defect.
CABG = coronary artery bypass grafting; MI = myocardial infarction; MPS = myocardial perfusion stress; MVD = multivessel disease; OMT = optimal medical therapy; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

Table 35: Strategies for follow-up and management in symptomatic patients after myocardial revascularisation		
	Class[a]	Level[b]
Stress imaging (stress echo or MPS) should be used rather than stress ECG.	I	A
It is recommended to reinforce OMT and life style changes in patients with low-risk findings (+) at stress testing.	I	B
With intermediate- to high-risk findings (++) at stress testing, coronary angiography is recommended.	I	C
Emergent coronary angiography is recommended in patients with STEMI.	I	A
Early invasive strategy is indicated in high-risk NSTE-ACS patients.	I	A
Elective coronary angiography is indicated in low-risk NSTE-ACS patients.	I	C

a = class of recommendation; b = level of evidence.
ECG = electrocardiogram; MPS = myocardial perfusion stress; NSTE-ACS = non-ST-segment elevation acute coronary syndrome; OMT = optimal medical therapy; STEMI = ST-segment elevation myocardial infarction.

(+) Low-risk findings at stress imaging are ischaemia at high workload, late onset ischaemia, single zone of low grade wall motion abnormality or small reversible perfusion defect, or no evidence of ischaemia.
(++) Intermediate- and high-risk findings at stress imaging are ischaemia at low workload, early onset ischaemia, multiple zones of high grade wall motion abnormality or reversible perfusion defect.

Section V: Myocardial Disease

1. Hypertrophic Cardiomyopathy

Chapter 1
Hypertrophic Cardiomyopathy*
2003

The Task Force on Hypertrophic Cardiomyopathy of the American College of Cardiology Foundation and the European Society of Cardiology Committee for Practice Guidelines

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1. Introduction

Hypertrophic Cardiomyopathy (HCM) is a relatively common genetic disorder (1:500) defined by the presence of left ventricular hypertrophy in the absence of a cardiac or systemic cause. It is found in all races and affects men and women equally.

2. Genetics

HCM is inherited as a Mendelian autosomal dominant trait and caused by mutations in any one of 10 genes encoding protein components of the cardiac sarcomere. The most common mutations identified are in the beta-myosin heavy chain, myosin binding protein C and cardiac troponin-T genes. The other genes, which include regulatory and essential myosin light chains, titin, alpha-tropomyosin, alpha-actin, cardiac troponin-I, and alpha-myosin heavy chain, each account for fewer cases. Recently, mutations in the gene encoding the gamma-2-regulatory subunit of the AMP-activated protein kinase have been reported in families with unexplained left ventricular hypertrophy Wolff-Parkinson-White (WPW) syndrome and premature conduction disease. This syndrome is probably more appropriately regarded as a metabolic storage disease distinctive from true HCM.

3. Presentation

HCM can present at any age. Many patients are asymptomatic and are identified incidentally or through screening. When symptoms are present dyspnea, chest pain (which may be anginal or atypical in nature) and impaired consciousness with syncope or presyncope (i.e. dizziness or light-headedness) and palpitation are most common.

4. Diagnosis

4.1 Genetic

Laboratory DNA analysis is the most definitive method for establishing the diagnosis of HCM, however this is not routinely available to most institutions.

4.2 Clinical

ECG: The ECG is abnormal in at least 80% of patients however no specific changes are diagnostic. Left ventricular hypertrophy (LVH) with repolarization abnormalities, pathological Q waves, left and right atrial enlargement are the most common abnormalities detected.

*Adapted from the Clinical Expert Consensus Document on Hypertrophic Cardiomyopathy from the American College of Cardiology and the European Society of Cardiology. (European Heart Journal, 2003, 24 (21): 1965-1991).

Echocardiography: Left ventricular (LV) wall thickening greater than or equal to 15 mm is generally accepted as diagnostic of hypertrophic cardiomyopathy, however, virtually any wall thickness is compatible with the presence of a HCM mutant gene. Hypertrophy is usually associated with a non-dilated and hyperdynamic left ventricle (often with systolic cavity obliteration). Left ventricular outflow tract obstruction, at rest, is seen in approximately one third of patients. Not all patients carrying a HCM causing mutation will express the clinical features (e.g. LVH on echo, abnormal ECG pattern, or disease related symptoms) of the disease. Occasionally mild ECG abnormalities or evidence of diastolic dysfunction assessed by Doppler tissue imaging may precede the development of hypertrophy.

5. Differential diagnosis

Thickening of the LV wall resembling HCM occurs in children (and some adults) with other disease states including Noonan's syndrome, mitochondrial myopathies, Friedreich's ataxia, metabolic disorders, Anderson-Fabry disease, LV non-compaction and cardiac amyloidosis.

6. Pathophysiological features

6.1 Left ventricular outflow tract obstruction (LVOTO)

Obstruction to LV outflow is found in about one third of patients under rest conditions, and may be either subaortic or mid cavity in location. Subaortic obstruction is associated with systolic anterior motion (SAM) of the mitral valve and systolic contact of the anterior or posterior leaflet with the ventricular septum. SAM is usually accompanied by incomplete leaflet apposition with mitral regurgitation (usually mild to moderate in degree). Obstruction in HCM may be fixed (i.e. at rest) or dynamic in which the magnitude of the outflow tract gradient may be labile varying with pharmacological and physiological alterations such as after a heavy meal, ingestion of alcohol or after exercise. Labile gradients are best recorded during and/or immediately following treadmill or bicycle exercise testing.

6.2 Diastolic dysfunction

Diastolic dysfunction with abnormal myocardial relaxation and increased chamber stiffness is common and results in impaired ventricular filling, elevated left atrial and LV end-diastolic pressures (with reduced stroke volume and cardiac output), pulmonary congestion, and impaired exercise performance.

6.3 Myocardial ischaemia

Myocardial ischaemia in HCM is thought to be a consequence of abnormal intramural coronary arterioles with thickened walls (from medial hypertrophy) and narrowed lumen, and/or mismatch between the increased ventricular mass and coronary flow. Ischaemia may lead to myocardial fibrosis and scarring and as a consequence, contribute to systolic and diastolic dysfunction. Ischaemia may also contribute to ventricular arrhythmia and sudden death. The evaluation of ischaemia in HCM however is problematic as non-invasive screening tests such as exercise testing and thallium scintigraphy are difficult to interpret in the presence of ventricular hypertrophy.

Atherosclerotic coronary artery disease is often overlooked and coronary arteriography is indicated in patients with HCM who are over the age of 40 years or who have risk factors for coronary artery disease.

7. Examination

Clinical signs are usually limited to patients with outflow tract obstruction. In these patients there may be a rapid upstroke, arterial pulse, a forceful left ventricular impulse, and a palpable left atrial beat with a prominent "a" wave in the jugular venous pulse. A fourth heart sound is occasionally heard. The murmur of outflow tract obstruction is mid-late systolic and may be increased by physiologic manoeuvres that decrease afterload or venous return (standing or valsalva). The majority of patients with outflow murmurs also have a mitral regurgitation murmur.

8. Treatment

Most patients with HCM have no or only mild symptoms and require no treatment. In patients with symptoms the aim of treatment is to alleviate symptoms and improve exercise capacity.

9. Medical therapy

9.1 Beta-adrenergic blocking agents

Beta-blockers are usually the first line treatment for patients with or without obstruction that have symptoms of exertional dyspnoea or exercise intolerance. The beneficial effects of beta-blockers on symptoms and exercise tolerance appear to be largely due to a decrease in the heart rate with a consequent prolongation of diastole with increased relaxation time and passive ventricular filling. These agents reduce LV contractility, limit latent outflow tract gradient and decrease myocardial oxygen demand and myocardial ischaemia.

9.2 Verapamil

Verapamil in doses up to 480 mg per day has favourable effects on symptoms (particularly chest pain) probably by virtue of improving ventricular relaxation and filling as well as reducing myocardial ischaemia and LV contractility. Occasionally adverse haemodynamic side effects can occur as a result of vasodilatation resulting in augmented outflow tract obstruction, pulmonary oedema and cardiogenic shock. Because of these concerns, caution should be exercised in administrating Verapamil to patients with resting left ventricular outflow tract obstruction (LVOTO).

9.3 Disopyramide

Disopyramide has been shown to reduce SAM, outflow tract obstruction and mitral regurgitation and produce symptomatic benefit in patients with resting obstruction. Anticholinergic side effects such as dry mouth and eyes, constipation, indigestion and difficulty in micturition may be reduced by long acting preparations for which cardioactive benefits are more sustained. Because disopyramide may cause accelerated atrioventricular (A-V) nodal conduction and thus increase ventricular rate during atrial fibrillation/flutter supplementary therapy with beta-blockers in low doses is advised. Disopyramide should not be used together with sotalol or amiodarone because of risk of proarrhythmia.

9.4 Diuretics

Diuretics may be used in patients with hypertrophic cardiomyopathy and heart failure symptoms. However, because many patients have diastolic dysfunction and require relatively high filling pressures to achieve adequate ventricular filling diuretics should be administered cautiously and preferably in the absence of marked outflow obstruction.

10. Treatment options for drug-refractory patients

Patients with marked LVOTO at rest or with provocation (peak gradient usually greater than or equal to 50 mmHg) and severe limiting symptoms of exertional dyspnoea (New York Heart Association [NYHA] III or IV), chest pain and presyncope or syncope, refractory to maximal medical therapy may be considered for non-medical therapies.

10.1 Surgery

The ventricular septal myectomy operation (Morrow procedure) is the gold standard approach to reduce LVOTO in both adults and children. The myectomy operation should be confined to centres experienced with this procedure.

Myectomy is performed through an aortotomy and involves resection of a carefully defined small amount of muscle from the proximal septum extending from near the base of the aortic valve to beyond the distal margins of mitral leaflets, thereby enlarging the left ventricular outflow tract (LVOT), and reducing left ventricular outflow tract obstruction (LVOTO). Other procedures such as mitral valve replacement or repair are occasionally indicated in selected patients with severe mitral regurgitation due to intrinsic abnormalities of the valve apparatus. Muscular mid-cavity obstruction due to anomalous papilliary muscle requires an extended distal myectomy or alternatively mitral valve replacement. Operative mortality in patients at the most experienced centres is around 1-2% or less but may be higher in elderly patients undergoing additional cardiac surgical procedures. Complications such as complete heart block (requiring permanent pacemaker) and iatrogenic ventricular septal perforation are uncommon.

10.2 Percutaneous Alcohol Septal Ablation (ASA)

This involves the introduction of absolute alcohol into a target septal perforator branch of the left interior descending coronary artery (LAD) guided by myocardial contrast echocardiography. Septal ablation mimics the haemodynamic consequences of myectomy by reducing basal septal thickness and excursion (producing akinetic or hypokinetic septal motion), enlarging the left ventricular outflow tract (LVOT) and thereby lessening mitral valve SAM and mitral regurgitation. After ASA there may be rapid reduction in resting left ventricular outflow tract gradient (LVOTG) but more frequently, a progressive decrease in the gradient occurs during the first 6 to 12 months.

Mortality and morbidity associated with ASA in experienced centres is similar to that of surgical myectomy. Permanent PM implantation due to induced high-grade A-V block has been reduced from 30% to 5% with the use of smaller amounts of alcohol. Myocardial infarction from coronary artery dissection, backward extravasation of alcohol producing LAD occlusion or abrupt coronary no-flow are rare complications. There is also concern that extensive wall thinning could lead to arrhythmogenic susceptibility or even end stage disease and the potential long term risk for arrhythmia related cardiac events is unknown. Proper selection of patients for ASA is crucial.

10.3 Dual chamber pacing

Although initial reports suggested that pacing was associated with a substantial decrease in LVOTO and improvements in symptoms, subsequent randomised studies showed no objective improvements after pacing. Despite this pacing may be an option for severely symptomatic older patients with LVOTO refractory to medical therapy for whom other alternatives are undesirable.

11. Drugs for "end stage"

Up to 5% of patients with HCM may develop systolic dysfunction and heart failure, usually associated with left ventricular wall thinning and chamber enlargement. Drug treatment strategies in such patients involve conversion to after load reducing agents such as ACE inhibitors or angiotensin II receptor blockers or diuretics, digitalis, beta-blockers or spironolactone. Ultimately patients with end stage heart failure may become candidates for heart transplantation.

11.1 Atrial fibrillation (AF)

Paroxysmal or established AF develops in 20-25% of HCM patients and is related to advancing age and left atrial enlargement. AF is associated with heart failure related death, occurrence of fatal and non-fatal stroke as well as long-term disease progression with heart failure symptoms. Electrical or pharmacological cardioversion is indicated in patients presenting within 48 hours of onset of AF assuming the presence of atrial thrombi can be excluded or after a suitable period of anticoagulation therapy. Amiodarone is the most effective antiarrhythmic agent for preventing recurrences of AF. In chronic AF, beta-blockers and verapamil are effective in controlling heart rate, although A-V nodal ablation and permanent pacing is occasionally necessary. Anticoagulant therapy (with warfarin) is indicated in patients with either paroxysmal or chronic AF and the threshold for anticoagulation should be low.

12. Infective endocarditis prophylaxis

In HCM there is a small risk of bacterial endocarditis, which appears largely confined to patients with LVOTO or intrinsic valve disease. Therefore patients with evidence of LVOTO at rest or during exercise should be given antibiotic prophylaxis at the time of dental or selected surgical procedures that create a risk for blood borne bacteraemia.

13. Pregnancy

Patients with HCM generally tolerate pregnancy and delivery well. Absolute maternal mortality is very low and appears to be principally confined to women who are severely symptomatic or have high-risk clinical profiles. Such patients should be afforded specialised joint cardiac and obstetric care during pregnancy and delivery.

13.1 Sudden Cardiac Death

Sudden cardiac death is the most common mode of premature demise in HCM and often occurs in asymptomatic or mildly symptomatic young people. Sudden cardiac death most frequently occurs in adolescents and young adults less than 30 to 35 years although risk extends through mid life and beyond. Sudden cardiac death most commonly occurs during mild exertion or sedentary activities (including sleep).

Available data suggests that ventricular tachyarrhythmias (VT) are the most common mechanism by which sudden cardiac death occurs in HCM. Other triggers/contributing factors include supraventricular arrhythmias, ischaemia, inappropriate vasodilation and conduction disease.

13.2 Risk Stratification

HCM patients (particularly those less than 60 years of age) should undergo clinical assessments on an annual basis, for risk stratification as well as evolution of symptoms. It is possible to identify most high risk patients by non-invasive clinical markers. The highest risk of sudden death has been associated with the following:

- Prior cardiac arrest or spontaneously occurring and sustained VT.
- Family history of premature cardiac death particularly if sudden, in a close relative, or if multiple in occurrence.
- Unexplained syncope, particularly when exertional, recurrent or in young patients.
- Non sustained ventricular tachycardia ≥ 3 beats at rate ≥ 120 beats per minute) on 24 hour ambulatory ECG recordings.
- Abnormal BP response during upright exercise which is attenuated or hypotensive particularly in patients less than 50 years.
- Severe LVH with a Maximal Left Ventricular Wall Thickness (MLVWT) of 30 mm or more.

Some disease causing mutations have been associated with adverse prognosis (e.g. troponin-T and Arg403Gln and Arg719Gln in beta-myosin heavy chain).

However, most of the clinical markers of sudden death risk in HCM are limited by relatively low positive predictive values due in part to relatively low event rates. However, the high negative predictive values of these markers suggest that the absence of these markers can be used to develop a profile of patients with lower likelihood for sudden death.

14. Prevention of sudden cardiac death

Patients with prior cardiac arrest (ventricular fibrillation) or sustained and spontaneously occurring VT are at greatest risk and most deserving of an implantable defibrillator for secondary prevention of sudden death. Otherwise, the highest risk for sudden death has been associated with multiple risk factors. Individual patients with a single major risk factor are also often eligible for primary prevention of sudden death with an implantable defibrillator. Management decisions should be based on individual judgement taking into account the overall clinical profile including age, strength of the risk factor and the level of risk acceptable to the patient and family. Although amiodarone has been associated with improved survival in HCM, and may be suitable in highly selected patients, the implantable cardioverter defibrillator (ICD) is the most effective and reliable prophylactic treatment option available.

15. Exercise recommendations

The consensus is that young patients with HCM should be restricted from intense competitive sports to reduce the risk of sudden cardiac death. Intense physical activity involving burst exertion (e.g. sprinting) or systematic isometric exercise (e.g. heavy lifting) should also be discouraged.

16. Screening

Screening of first-degree relatives and other family members should be encouraged. When DNA based diagnosis is not feasible, the recommended clinical strategies for screening family members involves history and physical examination, 12 lead ECG, and two dimensional echocardiography at annual evaluations during adolescence (12 to 18 years of age). Due to the possibility of delayed onset LVH, it is prudent for adult relatives with normal ECG and echocardiograms beyond age 18 to have subsequent clinical studies performed about every 5 years, particularly if there is a history of late onset disease within the family.

17. HCM in the elderly

HCM, due to sarcomere protein mutations may manifest itself later in life and should be distinguished from non-genetic hypertensive heart disease or age-related changes.

Older patients with HCM generally show relatively mild degrees of LVH and mild symptoms. Some elderly patients, however, have large subaortic gradients caused by systolic apposition of the anterior or posterior mitral valve leaflet with the septum in association with accumulation of calcium within the mitral annulus. Definitive clinical diagnosis of HCM in older patients with LVH and systemic hypertension may be difficult; particularly when the LV wall thickness is less than 20 mm and SAM is absent. In the absence of genotyping, marked LVH disproportionate to the level of blood pressure elevation, unusual patterns of LVH unique to HCM, or obstruction to LV outflow at rest represent presumptive evidence for HCM.

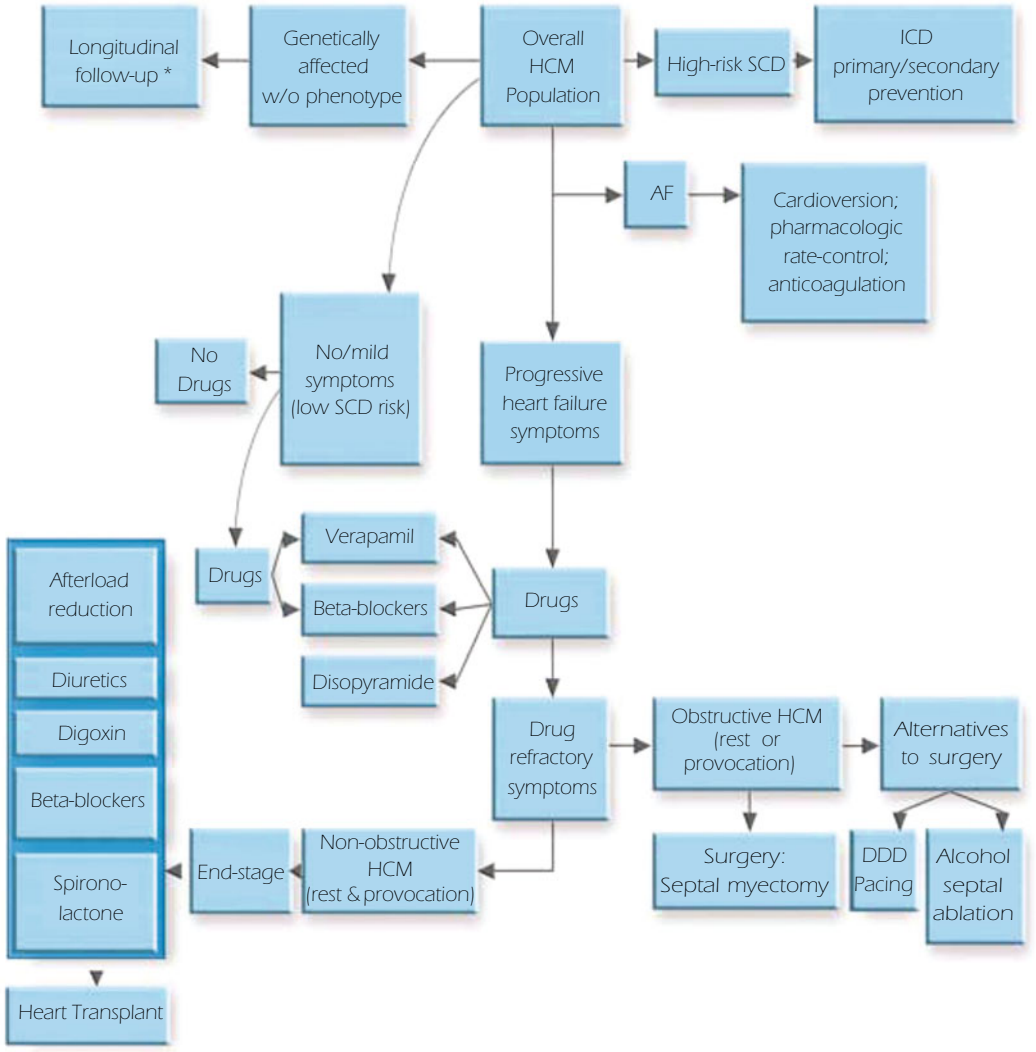

Fig. 1 *Clinical presentation and treatment strategies for patient subgroups within the broad clinical spectrum of hypertrophic cardiomyopathy (HCM). See text for details. AF = atrial fibrillation; DDD = dual-chamber; ICD = implantable cardioverter-defibrillator; SCD = sudden cardiac death; and RX = treatment. Table adapted with permission from "Spirito P, Seidman CE, McKenna WJ, Maron BJ. The management of hypertrophic cardiomyopathy. N Engl J Med 1997; 336:775-85". * No specific treatment or intervention indicated, except under exceptional circumstances.*

Section VI: Pericardial Disease

1. Pericardial Diseases

Chapter 1
Pericardial Diseases*
2004

The Task Force on the Diagnosis and Management of Pericardial Disease of the European Society of Cardiology

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Introduction

These are the first guidelines on the management of pericardial diseases to be published by the European Society of Cardiology (ESC). These are actually the first official guidelines written on the subject worldwide. The main objective of this document is to present cardiologists with guidelines for the Diagnosis and Management of Pericardial Diseases, focusing on the most clinically relevant abnormalities.

Classes of recommendations and levels of evidence

Recommendations for various tests and procedures are ranked in three classes (see opposite).

The level of evidence related to a particular diagnostic or treatment option depends on the available data (see below).

Class I	Evidence and/or general agreement that a given diagnostic procedure/treatment is beneficial, useful and effective;
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the treatment;
Class IIa	Weight of evidence/opinion is in favour of usefulness/efficacy;
Class IIb	Usefulness/efficacy is less well established by evidence/opinion;
Class III*	Evidence or general agreement that the treatment is not useful/effective and in some cases may be harmful.

* Use of Class III is discouraged by the ESC

Level of Evidence A	Data derived from multiple randomized clinical trials or meta-analyses
Level of Evidence B	Data derived from a single randomized clinical trial or large non-randomized studies
Level of Evidence C	Consensus opinion of the experts and/or small studies; retrospective studies and registries

*Adapted from the ESC Guidelines on the Diagnosis and Management of Pericardial Diseases (European Heart Jounal 2004; 25: 587-610).

J. Bax et al., *Compendium of Abridged ESC Guidelines 2001*

Acute pericarditis

Diagnosis

Table 1. Diagnostic pathway and sequence of performance in acute pericarditis (level of evidence B for all procedures)

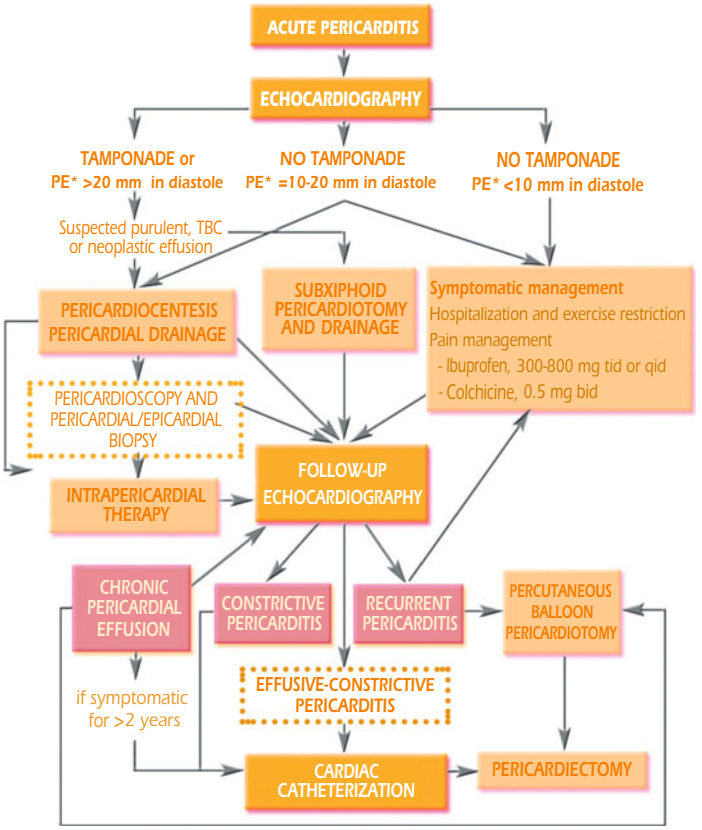
TECHNIQUE	CHARACTERISTIC FINDINGS
Obligatory (class I):	
Auscultation	Pericardial rub (mono-, bi-, or triphasic)
ECG[a]	*Stage I:* anterior and inferior concave ST-segment elevation. PR segment deviations opposite to P polarity. *Early stage II:* ST junctions return to the baseline, PR deviated. *Late stage II:* T waves progressively flatten and invert *Stage III:* generalised T wave inversions *Stage IV:* ECG returns to prepericarditis state.
Echocardiography	Effusion types B-D (Horowitz) Signs of tamponade (Table 2)
Blood analyses	a) ESR, CRP, LDH, leukocytes (inflammation markers) b) cTnI, CK-MB (markers of myocardial lesion)[b]
Chest X-ray	Ranging from normal to "water bottle" heart shadow. Revealing additional pulmonary/mediastinal pathology.
Mandatory in tamponade (class I), optional in large/recurrent effusions or if previous tests inconclusive (class IIa) in small effusions (class IIb):	
Pericardiocentesis and drainage	Pericardial fluid cytology, and cultures, PCRs and histochemistry for determination of infection or neoplasia.
Optional or if previous tests inconclusive (class IIa):	
CT	Effusions, peri-, and epicardium
MRI	Effusions, peri-, and epicardium
Pericardioscopy, pericardial biopsy	Establishing the specific aetiology

[a] Typical lead involvement: I, II, aVL, aVF, and V3-V6. The ST-segment is always depressed in aVR, frequently in V1, and occasionally in V2. Occasionally, stage IV does not occur and there are permanent T wave inversions and flattenings. If ECG is first recorded in stage III, pericarditis cannot be differentiated by ECG from diffuse myocardial injury, "biventricular strain," or myocarditis. ECG in EARLY REPOLARISATION is very similar to stage I. Unlike stage I, this ECG does not acutely evolve and J-point elevations are usually accompanied by a slur, oscillation, or notch at the end of the QRS just before and including the J point (best seen with tall R and T waves - large in early repolarisation pattern). Pericarditis is likely if in lead V6 the J point is >25% of the height of the T wave apex (using the PR segment as a baseline).

[b] cTnI - cardiac troponin I. It is detectable in 32.2-49%, more frequently in younger, male patients, with ST-segment elevation, and pericardial effusion at presentation. An increase beyond 1.5 ng/ml is rare (7.6-22%), and associated with CK-MB elevation. cTnI increase is not a negative prognostic marker regarding the incidence of recurrences, constrictive pericarditis, cardiac tamponade or residual LV dysfunction.

Management

Figure 1. Diagnosis and management of major pericardial syndromes



* PE: Pericardial Effusion

Symptomatic management

- Exercise restriction
- Hospitalization is warranted to determine the aetiology and observe for tamponade as well as the effect of treatment.
- Pain management
  - Nonsteroidal anti-inflammatory drugs (NSAID) are the mainstay (class I, level of evidence B).
  - *Ibuprofen* is preferred for its rare side-effects, favourable impact on the coronary flow, and the large dose range. Depending on severity and response, 300-800 mg every 6-8 hours may be initially required and can be continued for days or weeks, best until the effusion has disappeared.
  - *Aspirin* 300-600 mg every 4-6 hours is an alternative regimen.
  - Indomethacin should be avoided in elderly patients due to its flow reduction in the coronary artery.
  - Gastrointestinal protection must be provided.

Treatment and prevention of recurrences

- *Colchicine* (0.5 mg bid) added to a NSAID or as monotherapy also appears to be effective for the initial attack and the prevention of recurrences (class IIa, level of evidence B). It is well tolerated with fewer side-effects than NSAIDs.
- *Percutaneous balloon pericardiotomy* can be considered in cases resistant to medical treatment (class IIb, level of evidence B).
- *Corticosteroids* should be used only in patients with poor general condition or in frequent crises (class IIa, level of evidence C). A common mistake is to use a dose too low to be effective or to taper the dose too rapidly. The recommended regimen is prednisone 1-1.5 mg/kg, for at least one month. If patients do not respond adequately, *azathioprine* (75-100 mg/day) or *cyclophosphamide* can be added. Corticoids should be tapered over a three-month period.
- *Pericardiectomy* is indicated only in frequent and highly symptomatic recurrences resistant to medical treatment (class IIa, level of evidence B). Before pericardiectomy, the patient should be on a steroid-free regimen for several weeks.

Pericardial effusion and cardiac tamponade

Diagnosis

Table 2. Diagnosis of cardiac tamponade

Clinical presentation:	Elevated systemic venous pressure[a], tachycardia[b], pulsus paradoxus[c], hypotension[d], dyspnoea or tachypnoea with clear lungs.
Precipitating factors:	Drugs (cyclosporine, anticoagulants, thrombolytics, etc.), recent cardiac surgery, indwelling instrumentation, blunt chest trauma, malignancies, connective tissue disease, renal failure, septicaemia[e].
ECG:	Can be normal or non-specifically changed (ST-T wave), electrical alternans (QRS, rarely T), bradycardia (end-stage), Electromechanical dissociation (agonal phase).
Chest X-ray:	Enlarged cardiac silhouette with clear lungs.
M-mode/2D echocardiogram:	Diastolic collapse of the anterior RV free wall[f], RA collapse, LA and very rarely LV collapse, increased LV diastolic wall thickness "pseudohypertrophy", IVC dilatation (no collapse in inspiration), "swinging heart".
Doppler:	1) Tricuspid flow increases and mitral flow decreases during inspiration (reverse in expiration). 2) Systolic and diastolic flows are reduced in systemic veins in expiration and reverse flow with atrial contraction is increased.
M-mode colour Doppler:	Large respiratory fluctuations in mitral/tricuspid flows.
Cardiac catheterization:	1) Confirmation of the diagnosis and quantification of the haemodynamic compromise: • RA pressure is elevated (preserved systolic x descent and absent or diminished diastolic y descent) • Intrapericardial pressure is also elevated and virtually identical to RA pressure (both pressures fall in inspiration) • RV mid-diastolic pressure elevated and equal to the RA and pericardial pressures (no dip-and-plateau configuration) • Pulmonary artery diastolic pressure is slightly elevated and may correspond to the RV pressure. • Pulmonary capillary wedge pressure is also elevated and nearly equal to intrapericardial and right atrial pressure. • LV systolic and aortic pressures may be normal or reduced. 2) Documenting that pericardial aspiration is followed by haemodynamic improvement[g]. 3) Detection of the coexisting haemodynamic abnormalities (LV failure, constriction, pulmonary hypertension). 4) Detection of associated cardiovascular diseases (cardiomyopathy, coronary artery disease).
RV/LV Angiography:	Atrial collapse and small hyperactive ventricular chambers.
Coronary angiography:	Coronary compression in diastole.
Computer tomography:	No visualization of subepicardial fat along both ventricles, which show tube-like configuration and anteriorly drawn atria.

LA = left atrium, LV = left ventricle, RA = right atrium, RV = right ventricle, IVC = inferior vena cava. [a] Jugular venous distension is less notable in hypovolemic patients or in "surgical tamponade". An inspiratory increase or lack of fall of the pressure in the neck veins (Kussmaul sign), when verified with tamponade, or after pericardial drainage, indicates effusive-constrictive disease. [b] Heart rate is usually >100 beats/min, but may be lower in hypothyroidism and in uremic patients. [c] The blood pressure cuff is inflated above the patient's systolic pressure. During slow deflation, the first Korotkoff sound is intermittent. Correlation with the patient's respiratory cycle identifies a point at which the sound is audible during expiration, but disappears when the patient breathes in. As the cuff pressure drops further, another point is reached when the first Korotkoff sound is audible throughout the respiratory cycle. The difference of >10 mmHg in systolic pressure between these two points is accepted as positive pulsus paradoxus. For quick clinical orientation the sign can be also investigated by simply feeling the pulse, which diminishes significantly during inspiration, when the patient is breathing normally. Pulsus paradoxus is absent in tamponade complicating atrial septal defect and in patients with significant aortic regurgitation. Caution: the patient should breathe normally – no deep inspirations. [d] Some patients are hypertensive especially if they have pre-existing hypertension. [e] Febrile tamponade may be misdiagnosed as septic shock. [f] Right ventricular collapse can be absent in elevated right ventricular pressure and right ventricular hypertrophy or in right ventricular infarction. [g] If after drainage of pericardial effusion intrapericardial pressure does not fall below atrial pressure, the effusive-constrictive disease should be considered.

Indications for pericardiocentesis

Class I

- Cardiac tamponade.
- Effusions >20 mm in echocardiography (diastole).
- Suspected purulent or tuberculous pericardial effusion.

Class IIa

- Effusions 10-20 mm in echocardiography in diastole for diagnostic purposes other than purulent pericarditis or tuberculosis (pericardial fluid and tissue analyses, pericardioscopy, and epicardial/pericardial biopsy).
- Suspected neoplastic pericardial effusion.

Class IIb

- Effusions <10 mm in echocardiography in diastole for diagnostic purposes other than purulent; neoplastic or tuberculous pericarditis (pericardial fluid and tissue analyses, pericardioscopy and epicardial/pericardial biopsy). In symptomatic patients diagnostic pericardial puncture should be reserved for dedicated centers.

Contraindications

- Aortic dissection.
- Relative contraindications include uncorrected coagulopathy, anticoagulant therapy, thrombocytopenia <50,000/mm^3, small, posterior and loculated effusions.
- Pericardiocentesis is not necessary when the diagnosis can be made otherwise or the effusions are small and resolving under anti-inflammatory treatment.

How to perform pericardiocentesis

- Obtain recent and reliable echocardiography findings (best immediately before the procedure). The operator performing pericardiocentesis needs to observe the echocardiogram.
- Pericardiocentesis guided by fluoroscopy should be performed in the cardiac catheterization laboratory under local anaesthesia. The subxiphoid approach has been used most commonly, with a 8-17 cm long blunt-tip needle (e.g. Tuohy-17) permitting the passage of the guidewire, directed towards the left shoulder at a 30° angle to the frontal plane.
- Pericardiocentesis guided by echocardiography can be performed in the intensive care unit, or at the bedside. Echocardiography should identify the shortest route to enter the pericardium intercostally (usually in the sixth or seventh rib space in the anterior axillary line). The intercostal arteries should be avoided by puncturing close to the upper margin of the rib.
- It is essential that the needle approaches the pericardium slowly under steady manual aspiration (negative pressure). As soon as the pericardial effusion is aspirated a soft J-tip guidewire should be inserted and after dilatation exchanged for a multi-holed pigtail catheter.
- Strict aseptic conditions, ECG and blood pressure monitoring have to be provided.
- Direct ECG monitoring from the puncturing needle is not an adequate safeguard.
- Right-heart catheterization can be performed simultaneously, allowing the assessment of tamponade, haemodynamic monitoring of pericardiocentesis and exclusion of constriction.
- In large pericardial effusions it is prudent to drain <1 L at the time of initial procedure to avoid the acute right-ventricular dilatation.
- Prolonged pericardial drainage is recommended after pericardiocentesis until the volume of effusion obtained by intermittent pericardial aspiration (every 4-6 h) falls to <25 mL per day.

Analyses of pericardial effusion

Should be carried out according to the clinical presentation.

Class I

- Cytology in suspected **malignant disease**.
- In **suspected tuberculosis** acid-fast bacilli staining, PCR analyses for tuberculosis, mycobacterium culture (preferably with radiometric growth detection e.g., BACTEC-460), adenosine deaminase (ADA), interferon (IFN)-gamma and pericardial lysozyme should be performed.
- In suspected **bacterial infection** cultures of pericardial fluid for aerobes and anaerobes as well as three blood cultures are mandatory. Positive cultures should be followed by sensitivity tests for antibiotics.

Class IIa

- PCR analyses for cardiotropic viruses discriminate viral from auto-reactive pericarditis.
- Tumour markers (carcinoembryonic antigen (CEA), alpha-feto protein (AFP), carbohydrate antigens CA 125, CA 72-4, CA 15-3, CA 19-9, CD-30, CD-25, etc.) should be estimated in suspected neoplastic pericarditis.
- The staining of epithelial membrane antigen, CEA and vimentin can be distinguished between reactive mesothelial and adenocarcinoma cells.

Class IIb

- Analyses of the pericardial fluid specific gravity (>1.015), protein level (>3.0 g/dL; fluid/serum ratio >0.5), LDH (>200mg/dL; serum/fluid >0.6), and glucose (exudates vs. transudates = 77.9±41.9 vs. 96.1±50.7 mg/dL) can separate exudates from transudates but are not directly diagnostic.

Constrictive pericarditis

Diagnosis

Table 3. Diagnostic approach in constrictive pericarditis

Clinical presentation:	Severe chronic systemic venous congestion associated with low cardiac output, including jugular venous distension, hypotension with a low pulse pressure, abdominal distension, oedema and muscle wasting.
ECG:	Can be normal, or reveal low QRS voltage, generalized T wave inversion/flattening, LA abnormalities, atrial fibrillation, atrioventricular block, intraventricular conduction defects, or rarely pseudoinfarction pattern.
Chest X-ray:	Pericardial calcifications, pleural effusions.
M-mode/2D echocardiogram:	Pericardial thickening and calcifications[a] as well as the indirect signs of constriction: - RA & LA enlargement with normal appearance of the ventricles, and normal systolic function. - Early pathological outward and inward movement of the interventricular septum ("dip-plateau phenomenon"). - Flattering waves at the LV posterior wall. - LV diameter is not increasing after the early rapid filling phase. - IVC and the hepatic veins are dilated with restricted respiratory fluctuations.[b]
Doppler:	Restricted filling of both ventricles with respiratory variation >25% over the AV-valves.[c]
TEE:	Measurement of the pericardial thickness.
CT/MRI:	Thickened and/or calcified pericardium, tube-like configuration of one or both ventricles, enlargement of one or both atria, narrowing of one or both atrio-ventricular grooves, congestion of the caval veins.
Cardiac catheterization:	"Dip and plateau" or "square route" sign in the pressure curve of the right and/or left ventricle. Equalisation of LV/RV end-diastolic pressures in the range of 5 mmHg or less.[d]
RV/LV angiography:	The reduction of RV & LV size and increase of RA & LA size. During diastole a rapid early filling with stop of further enlargement ("dip-plateau").
Coronary angiography:	In all patients over 35 years and in patients with a history of mediastinal irradiation, regardless of the age.

LA = left atrium, LV = left ventricle, RA = right atrium, RV = right ventricle, IVC = inferior vena cava, TEE = transoesophageal echocardiography. [a] Thickening of the pericardium is not always equal to constrictive physiology. [b] Diagnosis is difficult in atrial fibrillation. Hepatic diastolic vein flow reversal in expiration is observed even when the flow velocity pattern is inconclusive. [c] Patients with increased atrial pressures or mixed constriction and restriction demonstrate <25% respiratory changes. A provocation test with head-up tilting or sitting position with decrease of preload may unmask the constrictive pericarditis. [d] In the early stage or in the occult form, these signs may not be present and the rapid infusion of 1-2 L of normal saline may be necessary to establish the diagnosis. Constrictive haemodynamics may be masked or complicated by valvular- and coronary artery disease.

Table 4. Differential diagnosis: constrictive pericarditis vs. restrictive cardiomyopathy

METHOD	RESTRICTIVE CARDIOMYOPATHY	CONSTRICTIVE PERICARDITIS
Physical findings	Kussmaul's sign ±, apical impulse +++ S_3 (advanced), S_4 (early disease), regurgitant murmurs ++	Kussmaul's sign +, apical impulse – pericardial knock+, regurgitant murmurs –
ECG	Low voltage, pseudoinfarction, left-axis deviation, AF, conduction disturbances.	Low voltage (<50%)
Chest radiography	No calcifications	Calcifications may be present (low diagnostic accuracy)
2D-echocardiography	Small LV cavity with large atria. Increased wall thickness sometimes present (especially thickened interatrial septum in amyloidosis). Thickened valves and granular sparkling (amyloidosis).	Normal wall thickness Pericardial thickening, prominent early diastolic filling with abrupt displacement of IVS.
Doppler studies		
Mitral inflow	No respiration variation of mitral inflow E wave velocity, IVRT. E/A ratio 2, short DT, diastolic regurgitation.	Inspiration: decreased inflow E wave velocity, prolonged IVRT Expiration: opposite changes, short DT, diastolic regurgitation
Pulmonary vein	Blunted S/D ratio (0.5), prominent and prolonged AR. No respiration variation, D wave.	S/D ratio = 1, Inspiration: decreased PV, S and D waves Expiration: opposite changes
Tricuspid inflow	Mild respiration variation of tricuspid inflow E wave velocity, E/A ratio 2, TR peak velocity, no significant respiration change, Short DT with inspiration, diastolic regurgitation.	Inspiration: increased tricuspid inflow E wave velocity, increased TR peak velocity, Expiration: opposite changes, Short DT, diastolic regurgitation
Hepatic veins	Blunted S/D ratio, increased inspiratory reversals.	Inspiration: minimally increased HV S and D Expiration: decreased diastolic flow / increased reversals
Inferior vena cava	Plethoric	Plethoric
Mitral annular motion	Low-velocity early filling (<8 cm/s)	High-velocity early filling (≥8 cm/s)
Colour M-mode	Slow flow propagation	Rapid flow propagation (≥100 cm/s)
Tissue Doppler echocardiography	Peak early velocity of longitudinal expansion (peak Ea) of ≥ 8.0 cm/s (89% sensitivity and 100% specificity)	Negative
Cardiac catheterization	Dip and plateau LVEDP often >5 mmHg greater than RVEDP, but may be identical, RV systolic pressure >50 mmHg RVEDP < 1/3 RVSP.	Dip and plateau, RVEDP and LVEDP usually equal, Inspiration: Increase in RV systolic pressure. Decrease in LV systolic pressure, with Expiration, opposite
EMB	May reveal specific cause of restrictive cardiomyopathy.	May be normal or show nonspecific hypertrophy or fibrosis.
CT/MRI	Pericardium usually normal.	Pericardium must be thickened or calcified.

Management

- Pericardiectomy is the only treatment for permanent constriction.
- The indications are based upon clinical symptoms, echocardiography findings, CT/MRI, and heart catheterization.
- There are two standard approaches, both aiming at resecting the diseased pericardium as far as possible: 1) The **antero-lateral thoracotomy** (fifth intercostal space) and 2) **median sternotomy** (faster access to the aorta and right atrium for extracorporeal circulation).
- A primary installation of cardiopulmonary bypass is not recommended (diffuse bleeding following systemic heparinization).
- Areas of strong calcification or dense scarring may be left as islands to avoid major bleeding.
- Pericardiectomy for constrictive pericarditis has a mortality rate of 6-12%.
- Major complications include acute perioperative cardiac insufficiency and ventricular wall rupture.
- Cardiac mortality and morbidity at pericardiectomy is mainly caused by the pre-surgically unrecognised presence of **myocardial atrophy or myocardial fibrosis**. Exclusion of patients with extensive myocardial fibrosis and/or atrophy significantly reduces the mortality rate for pericardiectomy.
- Post-operative low cardiac output should be treated by fluid substitution and catecholamines, high doses of digitalis, and intra-aortic balloon pump in most severe cases.
- If indication for surgery was established early, long-term survival after pericardiectomy corresponds to that of the general population.

Viral pericarditis

Diagnosis

- The diagnosis of viral pericarditis is not possible without the evaluation of pericardial effusion and/or pericardial/epicardial tissue, preferably by PCR or in-situ hybridization (class IIa, level of evidence B).
- A four-fold rise in serum antibody levels (two samples within 3-4 weeks) is suggestive but not diagnostic for viral pericarditis (class IIb, level of evidence B).

Management

- In most cases the disease is self-limiting and no specific treatment is necessary.
- Symptomatic treatment for chest pain, eventual rhythm disorders and congestive heart failure is indicated.
- In large effusions and cardiac tamponade pericardiocentesis is necessary.
- In patients with chronic or recurrent symptomatic pericardial effusion and confirmed viral infection, the following specific treatment is under investigation:
  1) CMV pericarditis: hyperimmunoglobulin 4 mL/kg once daily, on days 0, 4 and 8; 2 mL/kg on days 12 and 16;
  2) Coxsackie B pericarditis: Interferon alpha or beta 2.5 million IU/m^2 surface area subcutaneously 3 x per week;
  3) Adenovirus and parvovirus B19 perimyocarditis: immunoglobulin treatment 10 g intravenously on day 1 and 3 for 6-8 hours.

Bacterial pericarditis

Diagnosis

- Percutaneous pericardiocentesis must be promptly performed if bacterial pericarditis is suspected.
- Pericardial fluid should undergo Gram, acid-fast and fungal staining, followed by cultures for aerobes, anaerobes and M. tuberculosis (preferably with radiometric growth detection).
- Drug sensitivity testing is essential for treatment selection.
- PCR analyses, increased levels of adenosine deaminase (>40 IU/L), interferon-gamma (200 pg/L), or pericardial lysozyme (6.5 microg/dL) are highly sensitive and specific for diagnosis of tuberculous effusion.

Management (class I, level of evidence B)

- Urgent pericardial drainage, combined with intravenous antibiotic therapy (e.g. vancomycin 1 g bid, ceftriaxone 1-2 g bid, and ciprofloxacin 400 mg/day) is mandatory in purulent pericarditis.
- In selecting antimicrobial therapy the ability of potential agents to kill the causative organism, as well as the minimum inhibitory concentration (MIC - the lowest concentration that inhibits growth) and

minimum bactericidal concentration (MBC – the lowest concentration that decreases a standard inoculum of organisms 99.9% during 24 hours) need to be considered.

- Irrigation with urokinase or streptokinase, using large catheters, may liquify the purulent exudate, but open surgical drainage is preferable.

- The initial treatment of tuberculous pericarditis should include isoniazid 300 mg/day, rifampicin 600 mg/day, pyrazinamide 15-30 mg/kg/day and ethambutol 15-25 mg/kg/day. After two months most patients can be switched to a two-drug regimen (isoniazid and rifampicin) for the total of six months.

- Prednisone (1-2 mg/kg/day) may be given simultaneously with antituberculous therapy for 5-7 days and progressively reduced to discontinuation in 6-8 weeks.

- Patients with tuberculous pericarditis should be put in respiratory isolation if active pulmonary or laryngeal tuberculosis is also suspected. Determination of the absolute lack of infectiousness requires demonstration that cultures become negative. However, in clinical practice, conversion to negative smear results is used as a surrogate for infectiousness. Patients are considered to be non-infectious if they have a clinical response to anti-tuberculous chemotherapy and three consecutive smear-negative sputum samples that were collected on different days.

- Persons with HIV infection and tuberculosis usually can be treated with standard anti-tuberculous regimens with good results, although in some cases, prolonged therapy may be warranted.

- Since treatment of HIV may require protease inhibitors or non-nucleoside reverse transcriptase inhibitors, use of rifampicin may be precluded. The use of corticoid therapy as an adjunct to tuberculostatic treatment is allowed (class I, level of evidence B).

- Pericardiectomy is reserved for recurrent effusions or continued elevation of central venous pressure after 4-6 weeks of antituberculous and corticosteroid therapy.

Pericarditis in renal failure

Diagnosis

- Chest pain, pericardial friction rub and pericardial effusion in a patient with advanced renal failure (acute or chronic). This can occur before dialysis has been instituted or in patients on maintenance chronic haemodialysis or peritoneal dialysis.

- Due to autonomic impairment in uremic patients, heart rate may remain slow (60–80 beats/min) during tamponade, despite fever and hypotension.

- The ECG does not show the typical diffuse ST/T wave elevations observed with other causes of acute pericarditis due to the lack of the myocardial inflammation.

Management

- Frequent haemo- or peritoneal dialysis.

- To avoid haemopericardium, heparin-free haemodialysis should be used.

- Peritoneal dialysis, which does not require heparinization, may be therapeutic in pericarditis resistant to haemodialysis, or if heparin-free haemodialysis cannot be performed.

- NSAIDs and systemic corticosteroids have limited success when intensive dialysis is ineffective.

- Cardiac tamponade and large chronic effusions resistant to dialysis must be treated with pericardiocentesis (class IIa, level of evidence B).

- Large, non-resolving symptomatic effusions should be treated with intrapericardial instillation of corticosteroids after pericardiocentesis or subxiphoid pericardiotomy (triamcinolone hexacetonide 50 mg every 6 hours for 2 to 3 days).

- Pericardiectomy is indicated only in refractory, severely symptomatic patients.

Autoreactive pericarditis and pericardial involvement in systemic autoimmune diseases

Diagnosis

- Increased number of lymphocytes and mononuclear cells >5,000/mm^3 (autoreactive lymphocytic), or the presence of antibodies against heart muscle tissue (antisarcolemmal) in the pericardial fluid (autoreactive antibody-mediated).

- Inflammation in epicardial/endomyocardial biopsies by 14 cells/mm^2.

- Exclusion of active viral infection both in pericardial effusion and endomyocardial/epimyocardial biopsies (no virus isolation, no IgM-titer against cardiotropic

viruses in pericardial effusion, and negative PCR for major cardiotropic viruses).

- Tuberculosis, *Borrelia burgdorferi, Chlamydia pneumoniae*, and other bacterial infection excluded by PCR and/or cultures.
- Neoplastic infiltration absent in pericardial effusion and biopsy samples.
- Exclusion of systemic, metabolic disorders and uraemia.

Management

- Intrapericardial treatment with triamcinolone plus colchicine per os 0.5 mg bid for six months is highly efficient with rare side-effects. (class IIa, level of evidence B).
- In systemic autoimmune diseases (rheumatoid arthritis, systemic lupus erythematosus, progressive systemic sclerosis, polymyositis/dermatomyositis, mixed connective tissue disease, seronegative spondyloarthropathies, systemic and hypersensitivity vasculitides, Behçet syndrome, Wegener granulomatosis, and sarcoidosis) intensified treatment of the underlying disease and symptomatic management are indicated (class I, level of evidence B). For tapering of prednisone, ibuprofen or colchicine should be introduced early.

The post-cardiac injury syndrome: postpericardiotomy syndrome

Diagnosis

- Chest pain, pericardial friction rub, ECG changes, pericardial effusion within days to months after cardiac, pericardial injury or both.

Management

- Symptomatic treatment is as in acute pericarditis (NSAIDs or colchicine for several weeks or months, even after disappearance of effusion).
- Long term (3-6 months) oral corticoids or preferably pericardiocentesis and intrapericardial instillation of triamcinolone (300 mg/m^2) are therapeutic options in refractory forms.
- Redo surgery and pericardiectomy are very rarely needed.
- Primary prevention of postperiocardiotomy syndrome using short-term perioperative steroid treatment or colchicine is under investigation.
- Warfarin administration in patients with early post-operative pericardial effusion imposes the greatest risk, particularly in those who did not undergo pericardiocentesis and drainage of the effusion.

Post-infarction pericarditis
(pericarditis epistenocardica and Dressler's syndrome)

Diagnosis

- Pericarditis epistenocardica: detection of pericardial effusion 1-5 days after acute myocardial infarction.
- ECG changes may often be overshadowed by myocardial infarction changes.
- Post-infarction pericardial effusion >10 mm is most frequently associated with haemopericardium, and two thirds of these patients may develop tamponade/free wall cardiac rupture.
- Dressler's syndrome occurs from one week to several months after clinical onset of myocardial infarction with symptoms and manifestations similar to the post-cardiac injury syndrome.

Management

- Hospitalization to observe for tamponade, differential diagnosis and adjustments of treatment.
- Ibuprofen, which increases coronary flow, is the agent of choice.
- Aspirin, up to 650 mg every 4 hours for 2 to 5 days has also been successfully applied (other nonsteroidal agents risk thinning the infarction zone).
- Corticosteroid therapy can be used for refractory symptoms only but could delay myocardial infarction healing (class IIa, level of evidence B).
- In cardiac rupture, urgent surgical treatment is life-saving. However, if immediate surgery is not available or contraindicated pericardiocentesis, an intra-pericardial fibrin-glue instillation could be an alternative in subacute tamponade.

Traumatic pericardial effusion

- Urgent echocardiography, trans-esophageal echo-cardiography (TEE) if available.
- Rescue pericardiocentesis
- Autotransfusion

- Urgent thoracotomy and surgical repair.

Haemopericardium in aortic dissection

Diagnosis

- Urgent echocardiography, in unclear cases TEE
- CT or MRI in complex or unclear cases
- Angiography (only in stable patients).

Management

- Pericardiocentesis is contraindicated due to the risk of intensified bleeding and extension of the dissection.
- Surgery should be performed immediately (class I, level of evidence B).

Neoplastic pericarditis

Diagnosis

- Confirmation of the malignant infiltration within the pericardium (cytology, histology, tumour markers if available) (class I, level of evidence B).
- Of note, in almost 2/3 of the patients with documented malignancy, pericardial effusion is caused by non-malignant diseases, e.g. radiation pericarditis or opportunistic infections.

Management

- Systemic antineoplastic treatment as baseline therapy which can prevent recurrences in up to 67% of cases (class I, level of evidence B).
- Pericardiocentesis to relieve symptoms and establish diagnosis (class IIa, level of evidence B).
- Intrapericardial instillation of cytostatic/sclerosing agent (class IIa, level of evidence B). Cisplatin (single instillation of 30 mg/m^2) is preferred for pericardial metastases of lung cancer and intrapericardial instillation of thiotepa (15 mg on days 1, 3 and 5) or cisplatin for breast cancer.
- Pericardial drainage is recommended in all patients with large effusions because of the high recurrence rate (40-70%) (class I, level of evidence B).
- In resistant cases percutaneous balloon pericardiotomy or rarely pericardiectomy may be indicated (patients with very large chronic effusion in whom repeated pericardiocentesis and/or intrapericardial therapy were not successful).
- Radiation therapy is very effective (93%) in controlling malignant pericardial effusion (class IIa, level of evidence B) in patients with radiosensitive tumours such as lymphomas and leukemias. However, radiotherapy of the heart can cause myocarditis and pericarditis by itself.

Pericardial effusion in pregnancy

Diagnosis

- Many pregnant women develop a minimal to moderate clinically silent hydropericardium by the third trimester. Cardiac compression is rare.
- ECG changes of acute pericarditis in pregnancy should be distinguished from the slight ST-segment depressions and T wave changes seen in normal pregnancy.
- Occult constriction becomes manifest in pregnancy due to the increased blood volume.

Management

- Most pericardial disorders are managed as in non-pregnant.
- Caution is necessary while high-dose aspirin may prematurely close the ductus arteriosus.
- Colchicine is contraindicated in pregnancy.
- Pericardiotomy and pericardiectomy can be safely performed if necessary and do not impose a risk for subsequent pregnancies.

Foetal pericardial effusion

- Foetal pericardial fluid can be detected by echocardiography after 20 weeks' gestation and is normally 2 mm or less in depth.
- More fluid should raise questions of hydrops foetalis, Rh disease, hypoalbuminemia, immunopathy or maternally-transmitted mycoplasmal or other infections, and neoplasia.

Drug- and toxin-related pericardial disease

Table 5. Drug- and toxin-related pericardial disease

A. Drug-induced lupus erythematosus		
• Procainamide	• Methyldopa	• Isoniazid
• Tocainide	• Mesalazine	• Hydantoins
• Hydralazine	• Reserpine	
B. Hypersensitivity reaction		
• Penicillins	• Tryptophan	• Cromolyn sodium
C. Idiosyncratic reaction or hypersensitivity		
• Methysergide	• Phenylbutazone	• Sulfa drugs
• Minoxidil	• Amiodarone	• Cyclophosphamide
• Practolol	• Streptokinase	• Cyclosporine
• Bromocriptine	• p-Aminosalicylic acid	• Mesalazine
• Psicofuranine	• Thiazides	• 5-Fluorouracil
• Polymer fume inhalation	• Streptomycin	• Vaccines (Smallpox, Yellow fever)
• Cytarabine	• Thiouracils	• GM-CSF
D. Anthracycline derivatives		
• Doxorubicin	• Daunorubicin	
E. Serum sickness		
• Foreign antisera (e.g., antitetanus)	• Blood products	
F. Venom		
• Scorpion fish sting		
G. Foreign-substance reactions (direct pericardial application)		
• Talc (Mg silicate)	• Tetracycline/other sclerosants	• Iron in beta-thalassaemia
• Silicones	• Asbestos	
H. Secondary pericardial bleeding/haemopericardium		
• Anticoagulants	• Thrombolytic agents	
I. Polymer fume fever – inhalation of burning fumes of polytetrafluoroethylene (Teflon)		

Section VII:
Congenital Heart Disease

1. Grown Up Congenital Heart Disease

2. Neonatal Electrocardiogram

Chapter 1
Grown-up congenital heart disease*
2011

The Task Force on the Management of Grown-up Congenital Heart Disease of the European Society of Cardiology (ESC)
Endorsed by Association for European Paediatric Cardiology (AEPC)

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1. General considerations

1.1 Basic patient assessment

Thorough **clinical evaluation** is of critical importance in the diagnostic work-up of grown-up congenital heart disease (GUCH) patients.

- **Patient history** enables to assess present and past symptoms. Look for intercurrent events and any changes in medication (the patient should be questioned on his/her lifestyle to detect progressive changes in daily activity in order to limit the subjectivity of symptom analysis).
- **Clinical examination** plays a major role and includes, during follow-up,careful evaluation with regard to any changes in auscultation findings, blood pressure or development of signs of heart failure.
- **Electrocardiogram** (ECG) and **pulse oximetry** are routinely carried out alongside clinical examination.
- **Chest x-ray** is no longer performed routinely at each visit but rather on indication. It remains nevertheless helpful for long-term follow-up, providing information on changes in heart size and configuration as well as pulmonary vascularisation.

1.2 Echocardiography

Echocardiography remains the first line investigation and provides, in most instances, information on the basic cardiac anatomy including orientation and position of the heart, venous return, connection of atria and ventricles, and origin

*Adapted from the ESC Guidelines on the Management of Grown-up Congenital Heart Disease (European Heart Journal 2010; doi:10.1093/eurheartj/ehq249)

J. Bax et al., *Compendium of Abridged ESC Guidelines 2001*

of the great arteries. It allows evaluation of the morphology of cardiac chambers, ventricular function and detection and evaluation of shunt lesions as well as the morphology and function of heart valves. Assessment of ventricular volume overload (increase in end-diastolic volume and stroke volume) and pressure overload (hypertrophy, increase in ventricular pressure) are of major importance. Doppler echocardiographic information also includes haemodynamic data such as gradients across obstructions and right ventricle (RV) pressure/pulmonary artery pressure (PAP) (obtained from tricuspid regurgitation [TR] velocity) but also flow calculations.

Limitations: Investigator dependence; assessment of ventricular volumes and function may be complicated by geometry and regional in coordination, particularly in systemic and non-systemic RVs or univentricular hearts; Doppler gradients may sometimes be misleading particularly in right ventricular outflow tract obstruction (RVOTO), coarctation of the aorta (CoA) and stenoses in series; venous return and great arteries may be difficult to image.

1.3 - Cardiac magnetic resonance imaging

Cardiac magnetic resonance (CMR) imaging has become increasingly important in GUCH patients and is an essential facility in the specialist unit. It enables excellent three-dimensional anatomical reconstruction, which is not restricted by body size or acoustic windows.

Indications for CMR:

- Alternative to echocardiography, when both techniques can provide similar information but echocardiography cannot be obtained with sufficient quality (echocardiography is superior in estimating gradients, PAP and detecting small, highly mobile structures such as vegetations).
- Second method when echocardiography measurements are borderline or ambiguous: left ventricle (LV) volumes and left ventricular ejection fraction (LVEF), particularly in the setting of volume overload; quantification of valvular regurgitation.
- Indications where CMR is considered superior to echocardiography and should be regularly used when the information is essential for patient management:
  - quantification of RV volumes and right ventricular ejection fraction (RVEF) (tetralogy of Fallot [ToF], systemic RV)
  - evaluation of the RVOTO and RV-pulmonary artery (PA) conduits
  - quantification of pulmonary regurgitation (PR)
  - evaluation of pulmonary arteries (stenoses, aneurysms) and the aorta (aneurysm, dissection, coarctation)
  - evaluation of systemic and pulmonary veins (anomalous connection, obstruction, etc)
  - collaterals and arteriovenous malformations (computed tomography [CT] is superior)
  - coronary anomalies and coronary artery disease (CAD) (CT is superior)
  - evaluation of intra- and extracardiac masses
  - quantification of myocardial mass (LV and RV)
  - detection and quantification of myocardial fibrosis/scar (gadolinium late enhancement)
  - tissue characterisation (fibrosis, fat, iron, etc).

Currently, patients with implanted pacemakers or defibrillators should in general not be imaged by CMR (CT is indicated).

1.4 Computed tomography

CT plays an increasing role in imaging of GUCH patients, providing excellent spatial resolution and rapid acquisition time. It is particularly good for imaging epicardial coronary arteries and collateral arteries and for parenchymal lung disease. Ventricular size and function can be assessed with inferior temporal resolution compared to CMR. The major drawback of most current CT systems is its high dose of ionising radiation, making serial use unattractive.

1.5 Cardiopulmonary exercise testing

Cardiopulmonary exercise testing (CPET), including assessment of objective exercise capacity (time, maximum oxygen uptake), ventilation efficiency (VE/VCO_2 slope), chronotropic and blood pressure response as well as exercise induced arrhythmia, gives a broader evaluation of function and fitness, and has endpoints which correlate well with morbidity and mortality in GUCH patients. Serial exercise testing should therefore be a part of long-term follow-up protocols and interventional trials. It plays an important role in the timing of interventions and re-interventions.

1.6 Cardiac catheterization (diagnostic and interventional)

Cardiac catheterization is now reserved for resolution of specific anatomical and physiological questions or for intervention.

Indications for diagnostic catheterization include:

- Assessment of PAP and pulmonary vascular resistance (PVR), particularly in shunt lesions when non-invasively estimated PAP exceeds 50% of systemic pressure and in complex congenital heart disease (CHD) (testing of vasoreactivity may be required for the decision to intervene; oxygen has been traditionally used but nitric oxide may be preferable).
- LV and RV diastolic function, pressure gradients and shunt quantification when non-invasive evaluation leaves uncertainty.
- Coronary angiography before surgery in men > 40 years, postmenopausal women, and patients with signs of or risk factors for CAD.
- Evaluation of extracardiac vessels such as aortic pulmonary collateral arteries.

Intervention: There has been a marked increase in the number and range of interventional catheterization procedures in GUCH patients, which in some patients obviates the need for surgery. In others, treatment of congenital cardiac

malformations is best achieved by a collaborative ("hybrid") approach involving interventional catheterization and surgery. Newer techniques include stenting of systemic or pulmonary vessels and percutaneous valve implantation.

1.7 Surgical treatment

Many GUCH patients will have undergone intervention in childhood, but surgery during adulthood may be required in various situations:

1. Patients with prior repair and residual or new haemodynamic complications.
2. Patients with conditions not diagnosed or not considered severe enough to require surgery in childhood.
3. Patients with prior palliation.

Surgery in GUCH patients (including anaesthesia and intensive care) is very different from conventional adult cardiac surgery and this provides a strong case for concentrating resources into specialist units both for treatment and training.
One of the most challenging ongoing issues for surgery in GUCH patients is heart and heart–lung transplantation.

1.8 Heart failure

Heart failure is a frequent problem in the GUCH population. In general current treatment recommendations for heart failure are followed. However, as the pathophysiology of cardiorespiratory dysfunction is often very different from the failing "normal" circulation, extrapolation of results from published studies to GUCH patients may be difficult, particularly in settings such as transposition of the great arteries (TGA) with atrial switch repair (Mustard or Senning operation) or a Fontan circulation. Cardiac resynchronization therapy has gained increasing interest for use in GUCH patients with congestive heart failure. There is, as yet, little evidence on which to define indications and outcomes.

1.9 Arrhythmias and sudden cardiac death

Arrhythmias are the main reason for the hospitalization of GUCH patients and they are an increasingly frequent cause of morbidity and mortality. Risk stratification, investigation and choice of treatment are often different from those applied to the normally formed heart. Furthermore, the onset of arrhythmias may be a signal of haemodynamic decompensation and the risk associated with arrhythmias may be amplified in the presence of the often abnormal underlying circulation. Results of catheter ablation are generally worse in GUCH patients than in other patients but are improving with technical developments and should be considered when symptomatic tachyarrhythmias require action and interventional treatment is feasible. Antiarrhythmic drug therapy is frequently poorly tolerated due to negative inotropic and other side effects. Little data exist on its safety and efficacy.
Sudden cardiac death (SCD) is of particular concern in GUCH patients. The five defects with the greatest known risk of late SCD are ToF, TGA, congenitally corrected TGA (ccTGA), aortic stenosis (AS), and univentricular hearts. Various risk factors have been defined (see sections 2.10 (ToF) and 2.12 (ccTGA). Unexplained syncope is an alarming event. Algorithms for risk assessment of SCD and indications for the implantation of an implantable cardioverter defibrillator (ICD) have so far not been well established.

Recommendations for EP evaluation and ICD implantation	Class[a]	Level[b]
ICD implantation is indicated in survivors of cardiac arrest after exclusion of reversible causes.	I	B
Patients with spontaneous sustained VT should undergo invasive haemodynamic and EP evaluation. Recommended therapy includes catheter ablation or surgical resection to eliminate VT. If that is not successful, ICD implantation is recommended.	I	C
Invasive haemodynamic and EP evaluation is reasonable in patients with unexplained syncope and impaired ventricular function. In the absence of a defined and reversible cause, ICD implantation is reasonable.	IIa	B
EP testing may be considered for patients with ventricular couplets or non-sustained VT to determine the risk of sustained VT.	IIb	C

a = Class of recommendation;
b = Level of evidence.
EP = electrophysiology; ICD = implantable cardioverter defibrillator; VT = ventricular tachycardia.

1.10 Infective endocarditis*

Good oral hygiene and regular dental review have an essential role in reducing the risk of infective endocarditis (IE). Aseptic measures are mandatory during manipulation of venous catheters and during any invasive procedure in order to reduce the rate of health care associated IE. GUCH patients should also be discouraged from getting piercings and tattoos.

It is currently recommended by expert consensus to limit antibiotic prophylaxis to patients with the highest risk of IE undergoing the highest risk procedures (IIaC). This recommendation includes the following patient groups*:

- Patients with a prosthetic valve or prosthetic material used for cardiac valve repair.
- Patients with previous IE.
- Patients with CHD:
  a. cyanotic CHD, without surgical repair, or with residual defects, palliative shunts or conduits.
  b. CHD after repair with prosthetic material whether placed by surgery or by percutaneous technique, up to 6 months after the procedure (until endothelialization).
  c. when a residual defect persists at the site of implantation of a prosthetic device or material by cardiac surgery or percutaneous technique.

The recommendation is limited to dental procedures requiring manipulation of the gingival or periapical region of the teeth or perforation of the oral mucosa.
Antibiotics are not recommended for respiratory tract, gastrointestinal, genitourinary, dermatological or

musculoskeletal procedures unless there is an established infection.

*For more details please read the ESC Guidelines on the prevention, diagnosis and treatment on infective endocarditis 2009 (EHJ 2009;30:2369-2413; www.escardio.org/guidelines)

1.11 Exercise and sports

Recommendations for exercise and sports need to be based on the patient's ability, the impact on underlying haemodynamics, and the risk of acute decompensation and arrhythmias. Counselling should be based on the type of sport and the anticipated effort levels. Formal testing is invaluable and, in general, physicians have been over-conservative in their advice. Participation in regular exercise has a well documented benefit for fitness, psychological well-being and social interaction as well as having a positive effect on the future risk of acquired heart disease. As a general recommendation, dynamic exercise is more suitable than static exercise. In patients with known cardiac conditions, sudden death during exercise is very rare. Detailed recommendations for participation in competitive sports are beyond the scope of this document. Some lesions are not compatible with competitive sports, due to their morphologic severity/complexity and tendency to serious arrhythmias, including Eisenmenger syndrome, pulmonary arterial hypertension (PAH), univentricular heart, coronary artery anomalies, Ebstein's anomaly, ccTGA and TGA repaired by atrial switch or Rastelli procedure.

1.12 Pregnancy, contraception and genetic counselling

The majority of GUCH patients tolerate pregnancy well but specialist care is best provided in a multidisciplinary team setting. This team should have input from GUCH cardiology, obstetrics, anaesthesia, haematology, neonatology, and genetics. Timely counselling should be an essential component of the service provided. The team should be involved early in pregnancy in order to plan antenatal care, including delivery and post-partum follow-up.

High risk patients:

- Severe PAH (Eisenmenger patients and others).
- Severe left heart outflow/inflow obstruction.
- Poor systemic ventricular function (ejection fraction [EF] < 40%).
- Aortic root dilation in Marfan and similar syndromes (Ehlers-Danlos, Loeys Dietz).
- Cyanosis (oxygen saturation < 85%).
- Mechanical valve prosthesis.

Foetal echocardiography should be recommended at 16–18 weeks gestation.

The potential for drugs to affect the foetus should always be considered. In particular, angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor blockers, and amiodarone should not be used.

For contraception, barrier methods are safe, and protect against sexually transmitted diseases. However, they have a high contraceptive efficacy only with compliant couples. Annual failure rates of up to 10% mean that they should be used with an additional, more effective method.

Hormonal contraceptives are highly efficacious, but there are few data on their safety in the GUCH population. The combined oral contraceptive is highly effective (99.9%) but is best avoided in those with a pre-existing thrombotic risk (Fontan circulation, cyanotic patients, poor systemic ventricular function), especially as there are few data to suggest that concomitant oral anticoagulation therapy will negate this risk. Progesterone-only contraceptives on the other hand do not pose such a high thrombosis risk and newer preparations available for oral administration or with intrauterine implants have a high efficacy (> 95%). The risk of endocarditis after insertion of gestagen-coated intrauterine devices is probably low. However, there is a risk of vasovagal reactions (5%) at the time of insertion or removal. Female sterilisation or male partner sterilisation should only be considered after careful discussion, with particular reference to long-term prognosis.

2. Specific problems

2.1 Atrial septal defect

Diagnostic work-up

- ***Echocardiography:*** the key diagnostic technique, providing diagnosis and quantification. RV volume overload characterizes the haemodynamic relevance of the defect best (preferable to shunt ratio). Sinus venous defects require in general transoesophageal echocardiography (TEE) for accurate diagnosis as does the precise evaluation of secundum defects before device closure which should include sizing, exploration of the residual septum's morphology, the rim size and quality, exclusion of additional defects, and confirmation of normal pulmonary venous connection. Other key information to be provided includes PAP and TR.
- ***CMR/CT:*** alternative if echocardiography is insufficient, particularly for assessment of RV volume overload and pulmonary venous connection.
- ***Cardiac catheterization:*** estimation of PVR when echo PAP > 50% of systemic pressure.

In patients of advanced age with atrial septal defects (ASDs) not feasible for device closure, individual surgical risk due to comorbidities must be carefully weighed against the potential benefits of ASD closure.

Follow-up recommendations

Follow-up evaluation should include assessment of a residual shunt, RV size and function, TR and PAP by echocardiography and also assessment of arrhythmias by history, ECG and, only if indicated (not routinely), Holter monitoring.

Late postoperative arrhythmias after surgical repair at age < 40 years are most frequently intra-atrial reentrant tachycardia

Indications for intervention in atrial septal defect	Class[a]	Level[b]
Patients with significant shunt (signs of RV volume overload) and PVR < 5 WU should undergo ASD closure regardless of symptoms.	I	B
Device closure is the method of choice for secundum ASD closure when applicable.	I	C
All ASDs regardless of size in patients with suspicion of paradoxical embolism (exclusion of other causes) should be considered for intervention.	IIa	C
Patients with PVR ≥ 5 WU but < 2/3 SVR or PAP < 2/3 systemic pressure (baseline or when challenged with vasodilators, preferably nitric oxide, or after targeted PAH therapy) and evidence of net L-R shunt (Qp:Qs > 1.5) may be considered for intervention.	IIb	C
ASD closure must be avoided in patients with Eisenmenger physiology.	III	C

a = Class of recommendation.
b = Level of evidence.
ASD = atrial septal defect; L-R shunt = left-to-right shunt; PAH = pulmonary arterial hypertension; PAP = pulmonary artery pressure; PVR = pulmonary vascular resistance; Qp:Qs = pulmonary to systemic flow ratio; SVR = systemic vascular resistance; WU = Wood units.

or atrial flutter which can be successfully treated with radiofrequency ablation. Without repair or with repair after 40 years, atrial fibrillation becomes more common and may require antiarrhythmic therapy (little is known about ablative therapy in this setting). The access to the left atrium may be restricted after device closure. Patients with atrial fibrillation should receive oral anticoagulation.

Patients repaired under age 25 without relevant sequelae or residuae (no residual shunt, normal PAP, normal RV, no arrhythmias) do not require regular follow-up (be aware of late occurrence of tachyarrhythmias).

Patients with residual shunt, elevated PAP or arrhythmias (before or after repair) and those repaired at adult age (particularly > 40 years) should be followed on a regular basis including evaluation in specialized GUCH centres (intervals depending on severity of residual problems). After device closure regular follow-up during the first 2 years, then depending on results every 2-4 years, is recommended.

2.2 Ventricular septal defect

Diagnostic work-up

- ***Echocardiography:*** the key diagnostic technique, in general, providing the diagnosis and assessment of disease severity. Key findings to provide are: location, number and size of defects, severity of LV volume overload, and estimated PAP. Aortic regurgitation (AR) due to prolapse of the right or non-coronary cusp must be checked for, especially in the case of outlet (supracristal) and high perimembranous ventricular septal defects (VSDs). Double chambered right ventricle (DCRV) must be excluded.
- ***CMR:*** alternative if echocardiography is insufficient, particularly for assessment of LV volume overload and shunt quantification.
- ***Cardiac catheterization:*** estimation of PVR when echo PAP > 50% of systemic pressure.

Indications for intervention in ventricular septal defect	Class[a]	Level[b]
Patients with symptoms that can be attributed to L-R shunting through the (residual) VSD and who have no severe pulmonary vascular disease (see below) should undergo surgical VSD closure.	I	C
Asymptomatic patients with evidence of LV volume overload attributable to the VSD should undergo surgical VSD closure.	I	C
Patients with a history of IE should be considered for surgical VSD closure.	IIa	C
Patients with VSD associated prolapse of an aortic valve cusp causing progressive AR should be considered for surgery.	IIa	C
Patients with VSD and PAH should be considered for surgery when there is still net L-R shunt (Qp:Qs > 1.5) present and PAP or PVR are < 2/3 of systemic values (baseline or when challenged with vasodilators, preferably nitric oxide, or after targeted PAH therapy).	IIa	C
Surgery must be avoided in Eisenmenger VSD and when exercise induced desaturation is present.	III	C
If the VSD is small, not subarterial, does not lead to LV volume overload or pulmonary hypertension and if there is no history of IE, surgery should be avoided.	III	C

a = Class of recommendation.
b = Level of evidence.
AR = aortic regurgitation; IE = infective endocarditis; LV = left ventricle; PAH = pulmonary arterial hypertension; L-R shunt = left-to-right shunt; PVR = pulmonary vascular resistance; Qp:Qs = pulmonary to systemic flow ratio; VSD = ventricular septal defect.

Follow-up recommendations

Development of AR or TR, degree of (residual) shunt, LV dysfunction, elevation of PAP, development of DCRV and development of discrete subaortic stenosis (SubAS) should be excluded or assessed if present by echocardiography.

Possible development of complete atrioventricular (AV) block requires attention (patients who develop bifascicular block or transient trifascicular block after VSD closure are at risk in later years for the development of complete AV block).

Patients with LV dysfunction, residual shunt, PAH, AR, RVOTO or left ventricular outflow tract obstruction (LVOTO) obstruction should be seen every year including evaluation in specialized GUCH centres. In patients with a small VSD (native or residual, normal LV, normal PAP, asymptomatic) and no other lesion, 3–5 year intervals may be reasonable. After device closure, regular follow-up during the first 2 years, and then depending on the result every 2-4 years, is recommended. After surgical closure without residual abnormality 5 year intervals may be reasonable.

2.3 Atrioventricular septal defect

Diagnostic work-up

- ***Echocardiography:*** the key diagnostic technique, providing assessment of each anatomic component of

the atrioventricular septal defect (AVSD), of the AV valves and their connections (straddling, overriding) and the severity and exact substrate of AV valve regurgitation, the magnitude and direction of intracardiac shunting, LV and RV function, PAP, and assessment of the presence/absence of SubAS.

- ***CMR:*** indicated when additional quantification of ventricular volumes and function or intracardiac shunting is required for decision making.
- ***Cardiac catheterization:*** estimation of PVR when echo PAP > 50% of systemic pressure.

Indications for intervention in atrioventricular septal defect	Class[a]	Level[b]
Complete AVSD:		
▪ Cardiac surgery must be avoided in patients with Eisenmenger physiology. In case of doubt, PVR testing is recommended ▪ For indication of intervention, see also section 2.2 (VSD).	III	C
Partial AVSD:		
▪ Surgical closure should be performed in case of significant volume overload of the RV. For further details see section 2.1 (ASD).	I	C
AV valve regurgitation:		
▪ Symptomatic patients with moderate to severe AV valve regurgitation should undergo valve surgery, preferably AV valve repair.	I	C
▪ Asymptomatic patients with moderate or severe left-sided valve regurgitation and LVESD > 45 mm and/or impaired LV function (LVEF < 60%) should undergo valve surgery when other causes of LV dysfunction are excluded.	I	B
▪ Surgical repair should be considered in asymptomatic patients with moderate or severe left-sided AV valve regurgitation who have signs of volume overload of the LV and a substrate of regurgitation that is very likely to be amenable for surgical repair.	IIa	C
SubAS:		
▪ section 2.5 (LVOTO).	-	-

a = Class of recommendation.
b = Level of evidence.
ASD = atrial septal defect; AV = atrioventricular; AVSD = atrioventricular septal defect; LV = left ventricle; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic diameter; PVR = pulmonary vascular resistance; RV = right ventricle; SubAS = subaortic stenosis; VSD = ventricular septal defect.

Follow-up recommendations

Particular attention should be paid to residual shunt, AV valve malfunction, LV and RV enlargement and dysfunction, PAP elevation, SubAS, and arrhythmias. Life-long regular follow-up of all patients, operated and unoperated, with an AVSD is recommended, including evaluation in specialized GUCH centres. The frequency of outpatient visits depends on the presence and severity of residual abnormalities. A surgically repaired AVSD without significant residual abnormalities should be seen at least every 2–3 years. In the case of residual abnormalities, the intervals should be shorter.

2.4 Patent ductus arteriosus

Diagnostic work-up

- ***Echocardiography:*** the key diagnostic technique, providing the diagnosis (may be difficult in patients with Eisenmenger physiology), the degree of LV volume overload, PAP, PA size, and right heart changes.
- ***CMR/CT:*** indicated when additional quantification of LV volumes or evaluation of PA anatomy are required.
- ***Cardiac catheterization:*** estimation of PVR when echo PAP > 50% of systemic pressure.

Indications for intervention in patent ductus arteriosus	Class[a]	Level[b]
PDA should be closed in patients with signs of LV volume overload.	I	C
PDA should be closed in patients with PAH but PAP < 2/3 of systemic pressure or PVR < 2/3 of SVR.	I	C
Device closure is the method of choice where technically suitable.	I	C
PDA closure should be considered in patients with PAH and PAP > 2/3 of systemic pressure or PVR > 2/3 of SVR but still net L-R shunt (Qp:Qs > 1.5) or when testing (preferably with nitric oxide) or treatment demonstrates pulmonary vascular reactivity.	IIa	C
Device closure should be considered in small PDAs with continuous murmur (normal LV and PAP).	IIa	C
PDA closure should be avoided in silent duct (very small, no murmur).	III	C
PDA closure must be avoided in PDA Eisenmenger and patients with exercise induced lower limb desaturation.	III	C

a = Class of recommendation.
b = Level of evidence.
L-R shunt = left-to-right shunt; LV = left ventricle; PAH = pulmonary arterial hypertension; PAP = pulmonary artery pressure; PDA = patent ductus arteriosus; PVR = pulmonary vascular resistance; Qp:Qs = pulmonary to systemic flow ratio; SVR = systemic vascular resistance.

Follow-up recommendations

Echocardiographic evaluation should include LV size and function, PAP, residual shunt and associated lesions.
Patients with no residual shunt, normal LV and normal PAP do not require regular follow-up after 6 months.
Patients with LV dysfunction and patients with residual PAH should be followed at intervals of 1–3 years depending on severity, including evaluation in specialized GUCH centres.

2.5 Left ventricular outflow tract obstruction

Diagnostic work-up

- ***Echocardiography:*** the gold standard for diagnosis of AS and for assessing the degree of calcification, LV function, left ventricular hypertrophy (LVH) and associated lesions. With Doppler echocardiography the degree of severity of AS is determined from transvalvular peak velocity (Vmax), mean gradient and continuity equation calculated effective orifice area. TEE may occasionally be helpful to planimeter aortic valve area in noncalcified valves.

- ***Exercise testing:*** recommended in asymptomatic patients, particularly in severe AS to confirm asymptomatic status and evaluate exercise tolerance, blood pressure response and arrhythmias for risk stratification and timing of surgery.
- ***Low dose dobutamine echocardiography:*** helpful in AS with impaired LV function (low flow, low gradient AS).
- ***CMR/CT:*** mainly required to quantify dilation of the aorta.
- ***Cardiac catheterization:*** only required if non-invasive evaluation yields uncertain results.

Indications for intervention in aortic stenosis	Class[a]	Level[b]
Patients with severe AS and any valve related symptoms (angina pectoris, dyspnoea, syncope) should undergo valve replacement.	I	B
Asymptomatic patients with severe AS should undergo surgery when they develop symptoms during exercise testing.	I	C
Regardless of symptoms, surgery should be performed when systolic LV dysfunction is present in severe AS (LVEF < 50%), unless it is due to other causes.	I	C
Regardless of symptoms, surgery should be performed when patients with severe AS undergo surgery of the ascending aorta or of another valve or coronary artery bypass grafting.	I	C
Regardless of symptoms, aortic surgery should be considered if the ascending aorta is greater than 50 mm (27.5 mm/m^2 BSA) and no other indications for cardiac surgery are present.	IIa	C
Asymptomatic patients with severe AS should be considered for surgery when they present with a fall in blood pressure below baseline during exercise testing.	IIa	C
Asymptomatic patients with severe AS and moderate-to-severe calcification and a rate of peak velocity progression of ≥ 0.3 m/sec/year should be considered for surgery.	IIa	C
Patients with moderate AS undergoing coronary artery bypass surgery or surgery of the ascending aorta or another valve should be considered for additional valve replacement.	IIa	C
Severe AS with low gradient (< 40 mmHg) and LV dysfunction with contractile reserve should be considered for surgery.	IIa	C
Severe AS with low gradient (< 40 mmHg) and LV dysfunction without contractile reserve may be considered for surgery.	IIb	C
Asymptomatic patients with severe AS and excessive LVH (≥ 15 mm), unless this is due to hypertension, may be considered for surgery.	IIb	C

a = Class of recommendation.
b = Level of evidence.
AS = aortic stenosis; BSA = body surface area; LV = left ventricle; LVEF = left ventricular ejection fraction; LVH = left ventricular hypertrophy.

Follow-up recommendations

Lifelong and regular follow-up is required, and the intervals depend upon the degree of stenosis severity. It is also necessary after valve intervention at yearly intervals. Echocardiographic imaging of the aortic valve and aortic root to determine progression of valve stenosis and aortic dilation are mandatory.

Supravalvular aortic stenosis

Diagnostic work-up

- ***Echocardiography:*** provides diagnosis and pressure gradients, but these may overestimate the actual pressure drop across the valve.
- For exercise testing see valvular AS.
- ***CMR/CT:*** provide a precise anatomic definition of the lesion itself and identify additional lesions in the aorta and its branches (carotid and renal artery stenosis) and pulmonary arteries.
- ***Cardiac catheterization:*** only when non-invasive quantification remains uncertain.

Indications for intervention in supravalvular aortic stenosis	Class[a]	Level[b]
Patients with symptoms (spontaneous or on exercise test) and mean Doppler gradient ≥ 50 mmHg should undergo surgery.	I	C
Patients with mean Doppler gradient < 50 mmHg should undergo surgery when they have:		
▪ symptoms attributable to obstruction (exertional dyspnoea, angina, syncope) and/or	I	C
▪ LV systolic dysfunction (without other explanation),	I	C
▪ severe LVH, attributable to obstruction (not related to hypertension),	I	C
▪ when surgery for significant CAD is required.	I	C
Patients with mean Doppler gradient ≥ 50 mmHg* but without symptoms, LV systolic dysfunction, LVH or abnormal exercise test may be considered for repair when the surgical risk is low.	IIb	C

a = Class of recommendation.
b = Level of evidence.
*Doppler derived gradients may overestimate the obstruction and may need confirmation by left heart catheterization.
CAD = coronary artery disease; LV = left ventricle; LVH = left ventricular hypertrophy.

Follow-up recommendations

Lifelong and regular follow-up, including echocardiography, is required to determine progression of obstruction (rare), LV size/function and development of symptoms as well as after surgery to detect late restenosis, development of aneurysm (CMR/CT), and the occurrence or progression of CAD. Follow-up should include evaluation in specialized GUCH centres.

Subaortic stenosis

Diagnostic work-up

- ***Echocardiography:*** visualizes left ventricular outflow tract (LVOT) anatomy, associated aortic valve abnormality, amount of AR, LV function, LVH and associated lesions.

With Doppler echocardiography severity of subvalvular obstruction is determined, but Doppler derived gradients may overestimate the obstruction and may require confirmation by cardiac catheterization. Occasionally TEE is necessary to demonstrate the membrane. Three-dimensional TEE can be helpful to characterize the complex LVOT anatomy.

Indications for intervention in subaortic stenosis	Class[a]	Level[b]
Symptomatic patients (spontaneous or on exercise test) with a mean Doppler gradient ≥ 50 mmHg* or severe AR should undergo surgery.	I	C
Asymptomatic patients should be considered for surgery when:		
▪ LVEF is < 50% (gradient may be < 50 mmHg due to low flow).	IIa	C
▪ AR is severe and LVESD > 50 mm (or 25 mm/m² BSA) and/or EF < 50%**).	IIa	C
▪ mean Doppler gradient is ≥ 50 mmHg* and LVH marked	IIa	C
▪ mean Doppler gradient is ≥ 50 mmHg* and blood pressure response is abnormal on exercise testing.	IIa	C
Asymptomatic patients may be considered for surgery when:		
▪ mean Doppler gradient is ≥ 50 mmHg*, LV normal, exercise testing normal and surgical risk low.	IIb	C
▪ progression of AR is documented and AR becomes more than mild (to prevent further progression).	IIb	C

a = Class of recommendation; b = Level of evidence.
*Doppler derived gradients may overestimate the obstruction and may need confirmation by cardiac catheterization. **See ESC guidelines on the management of valvular heart disease; www.escardio.org/guidelines
AR = aortic regurgitation; BSA = body surface area; EF = ejection fraction; LV = left ventricle; LVEF = left ventricular ejection fraction; LVESD = left ventricular end systolic diameter; LVH = left ventricular hypertrophy.

Follow-up recommendations

Lifelong, regular follow-up, including echocardiography is required in the non-operated state to determine progression of obstruction, AR, and LV function and size. Also regular postoperative follow-up is necessary to detect late restenosis (frequent, especially in isolated forms and following surgical treatment in childhood), progressive AR, complications like arrhythmias, heart block and iatrogenic VSD. Follow-up should include evaluation in specialized GUCH centres.

2.6 Coarctation of the aorta

Diagnostic work-up

- ***Echocardiography:*** provides information regarding site, structure, and extent of CoA, LV function and hypertrophy, associated cardiac abnormalities, and aortic and supra-aortic vessel diameters. Doppler gradients are not useful for quantification, neither in native nor in postoperative coarctation. A diastolic "run-off" phenomenon is presumably the most reliable sign of significant coarctation or recoarctation.
- ***CMR/CT:*** the preferred non-invasive techniques to evaluate the entire aorta in adults. Both depict site, extent and degree of the aortic narrowing, the aortic arch, the pre- and post-stenotic aorta, aneurysms and collaterals.
- ***Cardiac catheterization:*** with manometry (a peak-to-peak gradient of > 20 mmHg indicates a haemodynamically significant CoA in the absence of well-developed collaterals) and angiocardiography, it is still the "gold standard" for CoA evaluation at many centres before and after operative or interventional treatment.

Indications for intervention in coarctation of the aorta	Class[a]	Level[b]
All patients with a non-invasive pressure difference > 20 mmHg between upper and lower limbs, regardless of symptoms but with upper limb hypertension (> 140/90 mmHg in adults), pathologic blood pressure response during exercise, or significant LVH should have intervention.	I	C
Independent of the pressure gradient, hypertensive patients with ≥ 50% aortic narrowing relative to the aortic diameter at the diaphragm level (on CMR, CT or invasive angiography) should be considered for intervention.	IIa	C
Independent of the pressure gradient and presence of hypertension, patients with ≥ 50% aortic narrowing relative to the aortic diameter at the diaphragm level (on CMR, CT or invasive angiography) may be considered for intervention.	IIb	C

a = Class of recommendation.
b = Level of evidence.
CMR = cardiac magnetic resonance; CoA = coarctation of the aorta; CT = computed tomography; LVH = left ventricular hypertrophy.

Follow-up recommendations

Residua, sequelae and complications are listed below:

- Arterial hypertension at rest or during exercise (common, even after successful treatment). The significance of isolated, exercise induced hypertension is a matter of debate.
- Recurring or residual CoA may induce or aggravate systemic arterial hypertension and its consequences.
- Aneurysms of the ascending aorta or at the intervention site present a risk of rupture and death.
- Attention is required for bicuspid aortic valve, mitral valve disease, premature CAD, and berry aneurysms of the circle of Willis (currently, most clinicians see no indication for their routine screening in asymptomatic patients).

All coarctation patients require regular follow-up at least every second year, including evaluation in specialized GUCH centres. Imaging of the aorta (preferably with CMR) is required to document the post-repair or post-interventional anatomy and complications (restenosis or aneurysm formation). Imaging intervals depend on baseline pathology.

2.7 Marfan syndrome

Diagnostic work-up

Currently, the diagnosis of Marfan syndrome is primarily based on clinical manifestations and a definite diagnosis requires occurrence of a major manifestation in two different organ systems and involvement of a third organ system (Ghent nosology). These criteria have just been revised and the new nosology will likely replace the old one in future practice. More weight will be given to the two cardinal features of Marfan syndrome: aortic root aneurysm/dissection, and ectopia lentis. In addition, a more prominent role is assigned to molecular genetic testing.

- ***Echocardiography:*** Echocardiographic assessment of the aortic root should include – in addition to determining the maximum diameter – measurements at the ring, sinus, sinotubular junction, and distal ascending aortic levels. It provides evaluation of LV function, aortic valve and AR, mitral valve and/or tricuspid valve prolapse and regurgitation.
- ***CMR/CT:*** should be performed in every patient, providing imaging of the entire aorta including aortic dimensions beyond the root.

Medical therapy

ß-blockers (currently standard of care) might reduce the rate of aortic dilation and might improve survival, at least in adults. Rigorous antihypertensive medical treatment, aiming at a systolic blood pressure less than 120 mmHg, and 110 mmHg in patients with acute aortic dissection (or history of), is important. The angiotensin II receptor 1 blocker losartan is potentially useful because it leads to transforming growth factor ß antagonism. Clinical trials are presently ongoing to evaluate its beneficial effect.

Indications for aortic surgery in Marfan syndrome	Class[a]	Level[b]
Patients should undergo surgery when aortic root maximal diameter is:		
▪ > 50 mm.	I	C*
▪ 46–50 mm with		
- family history of dissection or	I	C
- progressive dilation > 2 mm/year as confirmed by repeated measurement or	I	C
- severe AR or MR or	I	C
- desire of pregnancy.	I	C
▪ Patients should be considered for surgery when other parts of the aorta > 50 mm or dilation is progressive.	IIa	C

a = Class of recommendation.
b = Level of evidence.
*ESC guidelines for valvular heart disease (www.escardio.org/guidelines) are slightly more strict, recommending only one diameter (45 mm) regardless of other findings.
AR = aortic regurgitation; MR = mitral regurgitation.

Women have on average a 5 mm smaller aorta, only partly explained by a smaller body surface area (BSA). In small individuals, the use of an indexed diameter adjusted for BSA of 2.75 cm/m² should probably be used for operative decision making.

Follow-up recommendations

Lifelong and regular follow-up requires involvement of specialists with ample expertise in a specialist centre. Echocardiographic imaging of the aortic root and CMR imaging (or CT if CMR is contraindicated) of the entire aorta is of critical importance, especially if a dissection remains. Valvular regurgitation and ventricular function can be followed by means of echocardiography.

Stable patients need a yearly visit with echocardiography. CMR of the entire aorta should be performed at baseline and repeated at least once in 5 years if the aortic size beyond the root is normal. In the case of aneurysm formation beyond the root, CMR should be repeated at least yearly.

2.8 Right ventricular outflow tract obstruction

Diagnostic work-up

- ***Echocardiography:*** the first line diagnostic technique, providing visualization of the level of RVOTO, pulmonary valve anatomy, right ventricular hypertrophy and co-existing lesions. Doppler echocardiography provides the gradient across the obstruction, the presence and severity of PR and TR, and RV systolic pressure. Doppler gradients may be unreliable(overestimation) in patients with tubular stenosis and in patients with stenoses in series (subvalvular and valvular). In patients with double chambered RV the peak gradient may lead to underestimation of stenosis, because sampling of flow may not be axial. Severity: mild (peak gradient < 36 mmHg, peak velocity < 3 m/sec), moderate (36–64 mmHg; 3–4 m/sec), severe (> 64 mmHg, peak velocity > 4 m/sec). Since Doppler measurements may be unreliable (see above), TR velocity with estimation of RV pressure should always be used in addition when assessing severity.
- ***CMR/CT:*** helpful in identifying the level(s) of obstruction, particularly at the sub-infundibular, conduit or branch PA levels and assessment of the RV. Methods of choice for visualisation of pulmonary dilation and peripheral pulmonary stenosis (PS).
- ***Radionuclide studies:*** may reveal perfusion abnormalities in different lung segments in cases of peripheral PS (can also be measured by CMR).
- ***Cardiac catheterization:*** may be required to confirm the extent, severity and level of obstruction (e.g. DCRV).

Indications for intervention in right ventricular outflow tract obstruction	Class[a]	Level[b]
RVOTO at any level should be repaired regardless of symptoms when Doppler peak gradient is > 64 mmHg (peak velocity > 4 m/s), provided that RV function is normal and no valve substitute is required.	I	C
In valvular PS, balloon valvotomy should be the intervention of choice.	I	C
In asymptomatic patients in whom balloon valvotomy is ineffective and surgical valve replacement is the only option, surgery should be performed in the presence of a systolic RVP > 80 mmHg (TR velocity > 4.3 m/sec).	I	C
Intervention in patients with gradient < 64 mmHg should be considered in the presence of: ▪ symptoms related to PS or, ▪ decreased RV function or, ▪ double chambered RV (which is usually progressive) or, ▪ important arrhythmias or, ▪ right-to-left shunting via an ASD or VSD.	IIa	C
Peripheral PS, regardless of symptoms, should be considered for repair if > 50% diameter narrowing and RV systolic pressure > 50 mmHg and/or lung perfusion abnormalities are present.	IIa	C

a = Class of recommendation.
b = Level of evidence.
ASD = atrial septal defect; PS = pulmonary stenosis; RV = right ventricle; RVOTO = right ventricular outflow tract obstruction; RVP = right ventricular pressure; TR = tricuspid regurgitation; VSD = ventricular septal defect.

For RV-PA conduit see section 2.14 (RV to Pulmonary artery conduit).

Follow-up recommendations

Patients with RVOTO need life-long follow-up with regular echocardiographic imaging. The frequency of follow-up depends on the severity of the lesion, but most patients will need a yearly visit including evaluation in specialized GUCH centres. Patients with mild valvular or mild residual PS need to be seen only once in 5 years.

2.9 Ebstein's anomaly

Diagnostic work-up

- ***Echocardiography:*** the key diagnostic technique, providing information on anatomy and function of the tricuspid valve, apical distal displacement of the septal or posterior leaflet (in adults ≥ 0.8 cm/m^2 BSA), size of the anterior leaflet, "tethering" of the septal or posterior tricuspid valve leaflet on the septum or ventricular wall, size and function of the different cardiac sections (right atrium, atrialised ventricle, remaining functional RV, LV), RVOTO and associated lesions.
- ***CMR:*** has value with regard to evaluation for surgery as it offers unrestricted views for assessment of the dilated right heart, RV function and the tricuspid valve.

Indications for intervention in Ebstein's anomaly	Class[a]	Level[b]
Indications for surgery		
▪ Surgical repair should be performed in patients with more than moderate TR and symptoms (NYHA class > II or arrhythmias) or deteriorating exercise capacity measured by CPET.	I	C
▪ If there is also an indication for tricuspid valve surgery, then ASD/PFO closure should be performed surgically at the time of valve repair.	I	C
▪ Surgical repair should be considered regardless of symptoms in patients with progressive right heart dilation or reduction of RV systolic function and/or progressive cardiomegaly on chest x-ray.	IIa	C
Indications for catheter intervention		
▪ Patients with relevant arrhythmias should undergo electrophysiologic testing, followed by ablation therapy, if feasible, or surgical treatment of the arrhythmias in the case of planned heart surgery.	I	C
▪ In the case of documented systemic embolism likely caused by paradoxical embolism, isolated device closure of ASD/PFO should be considered.	IIa	C
▪ If cyanosis (oxygen saturation at rest < 90%) is the leading problem, isolated device closure of ASD/PFO may be considered but requires careful evaluation before intervention (see text).	IIb	C

a = Class of recommendation.
b = Level of evidence.
ASD = atrial septal defect; CPET = cardiopulmonary exercise testing; NYHA = New York Heart Association; PFO = patent foramen ovale; RV = right ventricle; TR = tricuspid regurgitation; VSD = ventricular septal defect.

Follow-up recommendations

Regular follow-up (at least yearly) is required in all patients in specialized GUCH centres. Typical postoperative residual anomalies to look for are persisting or new TR, the usual complications after valve replacement, failure of RV or LV, residual atrial shunts, arrhythmias and higher grade heart blocks.

2.10 Tetralogy of Fallot

Diagnostic work-up of repaired patients

- ***Echocardiography:*** first line diagnostic technique, providing the assessment of residual RVOTO and PR, residual VSD, RV and LV size and function, TR RVP, aortic root size and AR.
- ***CMR/CT:*** the method of choice for assessment of RV volume and function, PR, size, shape and expansion of the PAs, the ascending aorta and the position of great vessels or conduits in relation to the sternum (resternotomy).
- ***CPET:*** assists timing of re-intervention and provides prognostic information.
- ***Holter monitoring, event recorder:*** required for selected patients (high risk, investigated for suspected or clinical arrhythmia).
- ***Cardiac catheterization:*** restricted to patients undergoing catheter based interventions (i.e. relief of

distal PA stenosis, percutaneous valve implantation) and when non-invasive evaluation is inconclusive.

Indications for intervention after repair of tetralogy of Fallot	Class[a]	Level[b]
Aortic valve replacement should be performed in patients with severe AR with symptoms or signs of LV dysfunction.	I	C
PVRep should be performed in symptomatic patients with severe PR and/or stenosis (RV systolic pressure > 60 mmHg, TR velocity > 3.5 m/s).	I	C
PVRep should be considered in asymptomatic patients with severe PR and/or PS when at least one of the following criteria is present: ▪ Decrease in objective exercise capacity, ▪ Progressive RV dilation, ▪ Progressive RV systolic dysfunction, ▪ Progressive TR (at least moderate), ▪ RVOTO with RV systolic pressure > 80 mmHg (TR velocity > 4.3 m/sec), ▪ Sustained atrial/ventricular arrhythmias.	IIa	C
VSD closure should be considered in patients with residual VSD and significant LV volume overload or if the patient is undergoing pulmonary valve surgery.	IIa	C

a = Class of recommendation; b = Level of evidence.
AR = aortic regurgitation; LV = left ventricle; PR = pulmonary regurgitation; PVRep = pulmonary valve replacement; RV = right ventricle; RVOTO = right ventricular outflow tract obstruction; TR = tricuspid regurgitation; VSD = ventricular septal defect.

Indications for EP testing and ICD

Electrophysiology (EP) testing and/or ablation must be considered for symptomatic patients with suspected or documented clinical arrhythmia, atrial or ventricular.

For ICD see section 1.9 (Arrhythmias and SCD). ICD implantation for primary prevention remains controversial and no ideal risk stratification scheme has so farbeen developed. The following risk markers – although not consistently – have been reported: right and/or left ventricular dysfunction, extensive ventricular fibrosis (on CMR), QRS ≥ 180 msec, significant PR, non-sustained ventricular tachycardia (VT) on Holter monitoring, inducible VT at EP testing, long-lasting palliative shunts, and older age at time of repair.

Follow-up recommendations

All patients with ToF should have periodic cardiac follow-up in a specialized GUCH centre which in most patients should be done annually but can be less frequent in those patients at the best end of the spectrum with minimal/stable haemodynamic disturbance.

Late complications to look for:

- ***PR:*** significant PR is almost always encountered following a transannular patch repair. It may eventually lead to symptomatic RV dilation and dysfunction.
- ***Residual RVOTO:*** can occur at the infundibulum, at the level of the pulmonary valve and main pulmonary trunk, distally, beyond the bifurcation, and occasionally into the branches of the left and right PAs.
- ***RV dilation and dysfunction:*** usually due to residual long standing free PR ± RVOTO. Significant TR may occur as a consequence of RV dilation.
- ***Residual VSD:*** may lead to LV volume overload.
- ***Aortic root dilation with AR:*** commonly leads to AR and rarely to aortic dissection.
- ***LV dysfunction:*** may, among other causes (LV volume overload from longstanding palliativ arterial shunts, residual VSDs, and/or AR), result of an adverse ventricular–ventricular interaction (PR).
- ***Atrial/ventricular tachycardia and SCD:*** related to progressive haemodynamic problems and/or surgical scarring.
- ***Endocarditis*** (rare)

2.11 Transposition of the great arteries

After atrial switch operation (Mustard or Senning)

Diagnostic work-up

- ***Echocardiography:*** the first line diagnostic technique, providing information on systemic and subpulmonary ventricular size and function, subpulmonary outflow tract obstruction, TR, leakage or obstruction of the atrial baffles, and assessment of pulmonary venous return. Superior vena cava stenosis is, however, mostly difficult to assess and may require TEE. Contrast echocardiography is indicated if there is suspicion of baffle leakage or stenosis.
- ***CMR/CT:*** indicated for assessment of systemic RV function and patency of the atrial baffles.
- ***Holter monitoring, event recorder:*** required for selected patients (high risk, investigated for suspected or clinical arrhythmia).
- ***Cardiac catheterization:*** indicated when non-invasive assessment is inconclusive or PAH requires evaluation.

Indications for intervention in transposition of the great arteries after atrial switch	Class[a]	Level[b]
Indications for surgical intervention		
Valve repair or replacement should be performed in patients with severe symptomatic systemic (tricuspid) AV valve regurgitation without significant ventricular dysfunction (RVEF ≥ 45%).	I	C
Significant systemic ventricular dysfunction, with or without TR, should be treated conservatively or eventually with cardiac transplantation.	I	C
LVOTO if symptomatic or if LV function deteriorates should be treated surgically.	I	C
In symptomatic pulmonary venous obstruction surgical repair (catheter intervention rarely possible) should be performed.	I	C
Symptomatic patients with baffle stenosis not amenable for catheter intervention should be treated surgically.	I	C
Symptomatic patients with baffle leaks not amenable for stenting should be treated surgically.	I	C
Valve repair or replacement should be considered for severe asymptomatic systemic (tricuspid) AV valve regurgitation without significant ventricular dysfunction (RVEF ≥ 45%).	IIa	C
Pulmonary artery banding in adult patients, to create septal shift, or as left ventricular training with subsequent arterial switch, is currently experimental and should be avoided.	III	C

Indications for intervention in transposition of the great arteries after atrial switch (contd)	Class[a]	Level[b]
Indications for catheter intervention		
Stenting should be performed in symptomatic patients with baffle stenosis.	I	C
Stenting (covered) or device closure should be performed in symptomatic patients with baffle leaks and substantial cyanosis at rest or during exercise.	I	C
Stenting (covered) or device closure should be performed in patients with baffle leaks and symptoms due to L-R shunt.	I	C
Stenting (covered) or device closure should be considered in asymptomatic patients with baffle leaks with substantial ventricular volume overload due to L-R shunt.	IIa	C
Stenting should be considered in asymptomatic patients with baffle stenosis who require a pacemaker.	IIa	C
Stenting may be considered in other asymptomatic patients with baffle stenosis.	IIb	C

a = Class of recommendation.
b = Level of evidence.
AV = atrioventricular; L-R shunt = left-to-right shunt; LV = left ventricle; LVOTO = left ventricular outflow tract obstruction; RVEF = right ventricular ejection fraction; TR = tricuspid regurgitation.

EP testing, ablation and ICD

These procedures are complicated by the fact that the atria are not normally accessible for catheters and "normal" EP procedures because of the course of the baffles and should only be done in specialized centres with specific expertise. Patients are at increased risk of SCD. Atrial tachyarrhythmias, impaired systemic RV function and QRS duration ≥ 140 msec have been reported to be risk factors. See Arrhythmias and SCD section (1.9).

Follow-up recommendations

All patients should be seen at least annually in a specialized GUCH centre.

Frequent complications to look for:

- Dysfunction of the systemic RV.
- TR: often develops as sign of RV dilation and progresses.
- Tachyarrhythmias: atrial flutter is most typical, but atrial fibrillation and all other types of supraventricular tachycardia can occur. VT and ventricular fibrillation are reported and are associated with SCD.
- Bradyarrhythmias: ongoing loss of sinus node function frequently necessitates pacemaker therapy.
- Baffle (intra-atrial tunnel) leaks may cause left-to-right (L-R) or right-to-left(R-L) shunt
- Obstruction of systemic venous and/or pulmonary venous drainage.
- Subpulmonary outflow tract obstruction: can occur due to leftward bulging of the interventricular septum.

Arterial switch operation

Diagnostic work-up

- ***Echocardiography:*** the key diagnostic technique, providing information on LV function (global and regional), stenosis at the arterial anastomotic sites, most commonly PS, neoaortic valve regurgitation, dimension of the ascending aorta, and the acute angulation of the aortic arch. The pulmonary trunk, the bifurcation and both branches should be evaluated for the presence, localisation and severity of stenoses. RV function should be judged and systolic pressures should be estimated (TR velocity). Stress echocardiography can unmask LV dysfunction and detect provocable myocardial ischaemia.
- ***CMR:*** evaluation of the aorta, pulmonary branch stenosis and flow distribution between left and right lung.
- ***CT:*** might be used for non-invasive imaging of coronary arteries, including the ostia, if stenosis is suspected, and as an alternative to CMR.
- ***Nuclear techniques:*** can be used for evaluation of coronary perfusion when myocardial ischaemia is suspected, and a lung perfusion test is recommended in the case of pulmonary branch stenosis.
- ***Cardiac catheterization:*** including coronary angiography is indicated in the case of LV dysfunction and suspicion of myocardial ischaemia.

Indications for intervention in transposition of the great arteries after arterial switch operation	Class[a]	Level[b]
Stenting or surgery (depending on substrate) should be performed for coronary artery stenosis causing ischaemia.	I	C
Surgical repair of RVOTO should be performed in symptomatic patients with RV systolic pressure > 60 mmHg (TR velocity > 3.5 m/sec).	I	C
Surgical repair of RVOTO should be performed regardless of symptoms when RV dysfunction develops (RVP may then be lower).	I	C
Surgical repair should be considered in asymptomatic patients with RVOTO and systolic RVP > 80 mmHg (TR velocity > 4.3 m/sec).	IIa	C
Aortic root surgery should be considered when the (neo-)aortic root is larger than 55 mm, providing average adult stature (for aortic valve replacement for severe AR see guidelines* for AR).	IIa	C
Stenting or surgery (depending on substrate) should be considered for peripheral PS, regardless of symptoms, if > 50% diameter narrowing and RV systolic pressure > 50 mmHg and/or lung perfusion abnormalities are present.	IIa	C

a = Class of recommendation.
b = Level of evidence.
* ESC Guidelines on valvular heart disease; www.escardio.org/guidelines
AR = aortic regurgitation; AV = atrioventricular; RV = right ventricle; RVP = right ventricular pressure; RVOTO = right ventricular outflow tract obstruction; TR = tricuspid regurgitation.

Follow-up recommendations

All patients should be seen at least annually in a specialized GUCH centre.

Frequent complications to look for:

- LV dysfunction and arrhythmias: both may be related to coronary artery problems (reimplanted ostia).
- Dilation of the proximal part of the ascending aorta, resulting in AR.

- Supravalvular PS, pulmonary branch stenosis (unilaterally or bilaterally).

Rastelli type operation

Diagnostic work-up

- ***Echocardiography:*** the first line diagnostic technique, providing information on LV and RV function. The connection between the posterior positioned LV and the anterior positioned (due to the TGA) aortic valve and the function of the conduit between the RV and pulmonary trunk should be visualized and assessed with Doppler interrogation. Residual VSDs are often difficult to assess, due to the unusual course of the conduit or patch used to connect the LV to the aortic valve. Doppler gradients across the conduit may be difficult to measure and may in addition be unreliable. Therefore, RVP estimation from TR velocity is of particular importance for assessment of conduit stenosis.
- ***CMR:*** indicated when echocardiography information is insufficient (particularly for RV and conduit).
- ***Cardiac catheterization:*** may be required for haemodynamic assessment of conduit stenoses.

Indications for intervention in Rastelli type operation	Class[a]	Level[b]
For indications for treatment of conduit stenosis, see section 2.14 (RV to pulmonary artery conduit).	-	-
If left-to-right shunting through a residual VSD causes symptoms or substantial left sided volume overload, surgical treatment should be performed.	I	C
Stenosis in the connection between LV and aortic valve with a mean gradient > 50 mmHg (less when LV function and cardiac output are reduced) should be considered for surgical repair.	IIa	C

a = Class of recommendation.
b = Level of evidence.
LV = left ventricle; VSD = ventricular septal defect.

Follow-up recommendations

All patients should be seen at least annually in a specialized GUCH centre, with attention given to specific issues described above.

Most common problems are related to the valved conduit between RV and PA and residual VSDs. Arrhythmia – ventricular and supraventricular – can occur as well.

2.12 Congenitally corrected transposition of the great arteries

Diagnostic work-up

- ***Echocardiography:*** the key diagnostic technique, demonstrating double discordance. It is important to identify associated anomalies, particularly AV abnormalities (Ebstein-like malformation) and regurgitation, VSD, LVOTO and PS. Systolic function of the systemic (subaortic) ventricle and severity of AV valve regurgitation can be qualitatively assessed.
- ***CMR:*** provides information on intracardiac and great vessel anatomy and is indicated for quantification of ventricular volumes, mass and EF when required.
- ***Holter monitoring, event recorder:*** required for selected patients (high risk, investigated for suspected or clinical arrhythmia).
- ***Cardiac catheterization:*** indicated when non-invasive assessment is inconclusive.

Indications for intervention in congenitally corrected transposition of the great arteries	Class[a]	Level[b]
Systemic AV valve (tricuspid valve) surgery for severe regurgitation should be considered before systemic (subaortic) ventricular function deteriorates (before RVEF < 45%).	IIa	C
Anatomic repair (atrial switch + arterial switch or Rastelli when feasible in case of non-restrictive VSD) may be considered when LV is functioning at systemic pressure.	IIb	C

a = Class of recommendation.
b = Level of evidence.
AV = atrioventricular; LV = left ventricle; RVEF = right ventricular ejection fraction; VSD = ventricular septal defect.

Follow-up recommendations

Patients with ccTGA need life-long follow-up in a specialized GUCH centre with annual intervals, particularly because of conduction disturbances (AV block), and systemic ventricular and systemic AV valve dysfunction.

2.13 Patients after Fontan operation

Diagnostic work-up

- ***Echocardiography:*** the first line diagnostic tool, providing information on ventricular and valve function. To image the Fontan pathway, TEE or other imaging modalities are generally required.
- ***Annual blood tests:*** should include haematology, serum albumin, liver and renal function. If protein losing enteropathy (PLE) is suspected, α1-antitrypsin clearance must be calculated.
- ***CMR/CT:*** particularly helpful for evaluation of the Fontan pathway, collaterals and pulmonary veins (e.g. right pulmonary vein obstruction by enlarged right atrium) and differential pulmonary flow.
- ***Hepatic evaluation:*** by ultrasound (and CT) is important (fibrosis, cirrhosis, cancer).
- ***Cardiac catheterization:*** should be performed at a low threshold in case of unexplained oedema, exercise deterioration, new onset arrhythmia, cyanosis and haemoptysis. It provides ventricular and valvular function, haemodynamics including PVR, and Fontan obstruction and anomalous vascular connections.

Medical treatment

Anticoagulation: Right atrial blood stasis and disturbed coagulation may predispose to thrombosis. The potential for subclinical, recurrent pulmonary embolism leading to a rise in PVR has led to a recommendation by some for life-long anticoagulation. There is, however, no evidence for benefit and practice varies among centres. Anticoagulation is definitely indicated in the presence of atrial thrombus, atrial arrhythmias or thromboembolic events.

Antiarrhythmic therapy: Loss of sinus rhythm may precipitate rapid haemodynamic decline and sustained arrhythmia should be considered a medical emergency. Electrical cardioversion is the mainstay of treatment as drug therapy is often ineffective. Amiodarone may be effective in preventing recurrence but it has many long-term side effects. Sotalol can be an alternative. There should be a low threshold for radiofrequency ablation although these are difficult arrhythmias to treat in the catheterization laboratory. Anti-tachycardia atrial pacemakers may assist. If AV pacing is required, this will need an epicardial approach. Occurrence of arrhythmias should prompt haemodynamic evaluation.

Medical therapy of PLE: Medical therapy remains challenging and various treatments have been proposed (after exclusion of haemodynamic problems) including salt restriction, high protein diet, diuretics, ACE inhibitors (may be poorly tolerated), steroids, albumin infusion, chronic subcutaneous heparin, creation of a fenestration (by interventional catheter), and eventually consideration of transplantation.

Surgical/interventional treatment

Patients with a "failing Fontan" (with a combination of intractable arrhythmia, right atrial dilation, worsening AV valve regurgitation, deterioration of ventricular function and/or atrial thrombus) should be considered for surgery. Conversion of an atrial–pulmonary connection to a more "energy efficient" total cavopulmonary connection, together with arrhythmia surgery, has provided good early results in a very experienced setting, but is associated with surgical mortality and ongoing morbidity, with the need for both continued drug therapy and pacemaker implantation in the majority of cases. If performed late, conversion may become less likely to result in a good outcome and cardiac transplantation may be required. However, the best timing for a conversion remains a matter of uncertainty. Catheter intervention may be required for closure of a fenestration, in the case of flow obstruction or anomalous vascular connections.

Follow-up recommendations

Fontan patients should be followed in specialized GUCH centres, usually at least annually including echocardiography, ECG, blood and exercise testing. Intervals for CMR and hepatic ultrasound (CT) must be decided on an individual basis. Comprehensive assessment is mandatory for patients with manifestations of the "failing Fontan" complex, with particular care to exclude even minor obstructions to cavopulmonary flow and pulmonary venous return which may have major haemodynamic impact.

2.14 Right ventricular-to-pulmonary artery conduit

Diagnostic work-up

- ***Doppler echocardiography:*** the first line diagnostic tool, providing information on size and function of both ventricles, PR, TR and associated lesions. Gradients across the conduit may be difficult to measure and not reliable. RV pressure derived from TR velocity should be used to assess conduit stenoses.
- ***CMR/CT:*** may be required to image the conduit (level of stenosis), PA and coronary artery anatomy, for the assessment of the RV and severity of PR. Before re-sternotomy, the relationship between the conduit/RV and the inner layer of the sternum must be evaluated.
- ***Catheterization:*** always required if intervention is considered.

Indications for intervention in patients with right ventricular to pulmonary artery conduits	Class[a]	Level[b]
Symptomatic patients with RV systolic pressure > 60 mmHg (TR velocity > 3.5m/sec; may be lower in case of reduced flow) and/or moderate/severe PR should undergo surgery	I	C
Asymptomatic patients with severe RVOTO and/or severe PR should be considered for surgery when at least one of the following criteria is present: ▪ Decrease in exercise capacity (CPET), ▪ Progressive RV dilation, ▪ Progressive RV systolic dysfunction, ▪ Progressive TR (at least moderate), ▪ RV systolic pressure > 80 mmHg (TR velocity > 4.3 m/sec), ▪ Sustained atrial/ventricular arrhythmias.	IIa	C

a = Class of recommendation.
b = Level of evidence.
CPET = cardiopulmonary exercise testing; PR = pulmonary regurgitation; RV = right ventricle; RVOTO = right ventricular outflow tract obstruction; TR = tricuspid regurgitation.

Follow-up recommendations

Regular follow-up in a specialized GUCH centre is recommended at least every 12 months. Special attention should be given to exercise capacity (CPET), RV systolic pressure (conduit gradient), RV function, TR and arrhythmias.

2.15 Eisenmenger syndrome and severe pulmonary arterial hypertension

Recommendations for targeted pulmonary arterial hypertension therapy in congenital heart disease	Class[a]	Level[b]
Targeted PAH therapy in CHD should only be performed in specialized centres.	I	C
The ERA bosentan should be initiated in WHO-FC III* patients with Eisenmenger syndrome.	I	B
Other ERAs, phosphodiesterase type-5 inhibitors and prostanoids should be considered in WHO-FC III* patients with Eisenmenger syndrome.	IIa	C
Combination therapy may be considered in WHO-FC III* patients with Eisenmenger syndrome.	IIb	C
The use of calcium channel blockers should be avoided in patients with Eisenmenger syndrome.	III	C

a = Class of recommendation.
b = Level of evidence.
*Although recent data support the use of ERA such as bosentan also in WHO-FC II in patients with idiopathic PAH and PAH associated with connective tissue diseases such data are currently not available for Eisenmenger patients. Because of marked differences in the natural history between these groups, the results cannot simply be applied to congenital patients and further studies are required before recommendations.
CHD = congenital heart disease; ERA = endothelin receptor antagonist; PAH = pulmonary arterial hypertension; WHO-FC = World Health Organization – functional class.

2.16 Management of cyanotic patients

Late complications:

- ***Hyperviscosity symptoms:*** headache, faintness, dizziness, fatigue, tinnitus, blurred vision, paresthesia of fingers, toes and lips, muscle pain and weakness. Unlikely in an iron-replete patient with haematocrit < 65%.
- ***Bleeding:*** dental bleeding, epistaxis, menorrhagia, haemoptysis (most common major bleeding and external manifestation of an intrapulmonary haemorrhage not reflecting the extent of parenchymal bleeding).
- ***Thrombosis:*** caused by coagulation abnormalities, stasis of blood in dilated chambers and vessels, atherosclerosis and/or endothelial dysfunction, the presence of thrombogenic material (e.g. conduits) and arrhythmias.
- ***Cerebrovascular accidents:*** may be caused by thromboembolic events (paradoxical emboli), rheologic factors (microcytosis), endothelial dysfunction, and "traditional" atherosclerotic risk factors. The severity of secondary erythrocytosis per se is not a risk factor; microcytosis caused by iron deficiency, due to inappropriate phlebotomies, was the strongest independent predictor for cerebrovascular events.
- ***Paradoxical emboli:*** may be caused by supraventricular arrhythmias or transvenous leads or catheters.
- ***Iron deficiency:*** is frequently caused by inappropriate phlebotomies.
- ***Arrhythmias:*** supraventricular and ventricular.
- ***Infectious complications***: endocarditis, cerebral abscess, pneumonia.
- ***Renal dysfunction***: is common and due to functional and structural abnormalities of the kidneys.
- ***Cholelithiasis:*** can be complicated by cholecystitis/choledocholithiasis.
- ***Rheumatologic complications:*** include gouty arthritis, hypertrophic osteoarthropathy, kyphoscoliosis.

Diagnostic work-up

Oxygen saturation must be obtained with pulse oximetry at rest for at least 5 minutes.

Exercise capacity should be assessed on a regular basis preferably with a 6-minute walk test.

Blood work should include cellular blood count, mean corpuscular volume (MCV), serum ferritin (serum iron, transferrin and transferrin saturation may be required for earlier detection of iron deficiency), creatinine, serum uric acid, clotting profile, B-type natriuretic peptide (BNP) or pro-BNP, folic acid and vitamin B12 in the presence of elevated MCV or normal MCV and low serum ferritin.

Laboratory precautions

- Coagulation parameters: plasma volume is reduced due to secondary erythrocytosis; the amount of sodium citrate must be adjusted to haematocrit if haematocrit > 55%.
- Haematocrit determination with automated electronic particle counts (microhaematocrit centrifugation results in falsely high haematocrit due to plasma trapping).
- Glucose level can be reduced (increased in vitro glycolysis which results from the increased number of red blood cells).

Medical therapy

For specific PAH treatment see section 2.15 (Eisenmenger syndrome & severe PAH).

- Arrhythmias: Sinus rhythm should be maintained whenever possible. Drug therapy should be initiated with particular care and generally in hospital. Transvenous leads must be avoided.
- Therapeutic phlebotomy should only be performed in the presence of moderate/severe hyperviscosity symptoms due to secondary erythrocytosis (haematocrit > 65%), in the absence of dehydration and iron deficiency. Isovolumic fluid replacement (750–1000 mL of isotonic saline while removing 400–500 mL of blood) should be undertaken.
- Blood transfusion may be required in the presence of iron replete anaemia (haemoglobin inadequate to oxygen saturation)
- Iron supplementation should be performed in the presence of iron deficiency (MCV < 80 fL) and carefully followed (rebound effect).
- Routine anticoagulation/aspirin: currently available data do not support any benefit in cyanotic patients to prevent thromboembolic complications. There is, however, an increased risk of bleeding.
- Indication for anticoagulation: atrial flutter/fibrillation (target international normalized ratio [INR] 2–2.5; higher target INR in the presence of a mechanical valve).
- Haemoptysis: requires chest x-ray followed by chest CT scan if there is an infiltrate. Bronchoscopy puts the patient at risk and provides seldom useful information. Therapy includes discontinuation of aspirin, non-steroidal anti-inflammatory agents and oral anticoagulants; treatment of hypovolaemia and anaemia; reduction of physical activity and suppression of non-productive cough. Selective embolization of bronchial arteries may be required for refractory intrapulmonary haemorrhage/haemoptysis.
- Hyperuricaemia: No indication to treat asymptomatic hyperuricaemia. Acute gouty arthritis is treated with oral or intravenous colchicine, probenecid and anti-inflammatory drugs with attention to the risk of renal failure and bleeding. Uricosuric (e.g. probenecid) or uricostatic agents (e.g. allopurinol) avoid recurrence.

Follow-up recommendations

All cyanotic patients require life-long evaluation with follow-up visits every 6–12 months in a specialized GUCH centre in close collaboration with the family physician.

Risk reduction strategies in patients with cyanotic congenital heart disease
Prophylactic measures are the mainstay of care to avoid complications. The following exposures/activities should be avoided:
▪ Pregnancy.
▪ Iron deficiency and anaemia (no routine, inappropriate phlebotomies to maintain a predetermined haemoglobin).
▪ Dehydration.
▪ Infectious disease: annual influenza vaccination, pneumovax (every 5 years).
▪ Cigarette smoking, recreational drug abuse including alcohol.
▪ Transvenous pacemaker/ICD leads.
▪ Strenuous exercise.
▪ Acute exposure to heat (sauna, hot tub/shower).
Other risk reduction strategies include:
▪ Use of an air filter in an intravenous line to prevent air embolism.
▪ Consultation of a GUCH cardiologist before administration of any agent and performance of any surgical/interventional procedure.
▪ Prompt therapy of upper respiratory tract infections.
▪ Cautious use or avoidance of agents that impair renal function.
▪ Contraceptive advice.

GUCH = grown-up congenital heart disease; ICD = implantable cardioverter defibrillator.

Chapter 2
Neonatal Electrocardiogram*
2002

The Task Force for the interpretation of the Neonatal Electrocardiogram of the European Society of Cardiology

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Introduction

Most cardiologists who care for adults have no or minimal experience with electrocardiograms (ECGs) recorded in infants. So far, this has had no practical implications because only seldom are they requested to examine a neonatal ECG. This situation, however, may change as some European countries have begun to consider the possibility of introducing in their National Health Services the performance of an ECG during the first month of life in all newborns, as part of a cardiovascular screening programme.

The main objective of the present report is to present adult cardiologists with a consensus document designed to provide guidelines for the interpretation of the neonatal ECG, focusing on the most clinically relevant abnormalities and on the ensuing management and referral options. This document aims also at providing paediatricians and neonatologists with updated information of clinical relevance that can be detected from a neonatal ECG.

Normal electrocardiogram in the newborn

Changes occur in the normal ECG from birth to adult life, mostly in the first year of life with the majority of normal adult values being abnormal in the newborn. Likewise, many normal newborn values and patterns would be abnormal in the adult. Intervals should be hand measured as computerised systems are often inaccurate in the newborn. Intervals in children increase with increasing age, reaching most of the adult normal values by 7-8 years of age. Values are shown in Table 1.

Heart rate

Normal neonates may have rates of 150-230 beats per minute (bpm), especially if they are crying or agitated.

P Wave

The P wave is generally pointed in lead II and aVF and more rounded in other leads. Lead V1 may be diphasic.

QRS complex

Normal axis is between 55° and 200° at birth, but by 1 month, the normal upper limit has fallen to 160° or less. QRS morphology in the newborn may have more notches than in older children or adults. Normally, there is a Q wave in leads V5-V6. Q wave duration >30 ms is abnormal. A secondary r wave (r' or R') in the right chest leads is frequent in normal neonates.

* Adapted from the ESC Guidelines for the Interpretation of the Neonatal Electrocardiogram (European Heart Journal 2002; 23:1329-1344).

J. Bax et al., *Compendium of Abridged ESC Guidelines 2001*

Table 1. Normal Neonatal ECG Standards+

Age Group	Heart Rate (bpm)	Frontal Plane QRS Axis # (degrees)	P Wave Amplitude (mm)	P-R Interval # (sec)	QRS Duration # V_5	Q III ^ (mm)	QV_6 ^ (mm)	RV_1 * (mm)	SV_1 * (mm)	R/S V_1 ^	RV_6 * (mm)	SV_6 * (mm)	R/S V_6 ^	SV_1+ RV_6 ^ (mm)	R + S V_4 ^ (mm)
0-1 day	93-154 (123)	+59 to +192 (135)	2.8	0.08-0.16 (0.11)	0.02-0.08 (0.05)	5.2	1.7	5-26	0-22.5	9.8	0-11	0-9.8	10	28	52
1-3 days	91-159 (123)	+64 to +197 (134)	2.8	0.08-0.14 (0.11)	0.02-0.07 (0.05)	5.2	2.1	5-27	0-21	6	0-12	0-9.5	11	29	52
3-7 days	90-166 (129)	+77 to +187 (132)	2.9	0.08-0.14 (0.10)	0.02-0.07 (0.05)	4.8	2.8	3-24	0-17	9.7	0.5-12	0-9.8	10	25	48
7-30 days	107-182 (149)	+65 to +160 (110)	3.0	0.07-0.14 (0.10)	0.02-0.08 (0.05)	5.6	2.8	3-21.5	0-11	7	2.5-16	0-9.8	12	22	47
1-3 months	121-179 (150)	+31 to +114 (75)	2.6	0.07-0.13 (0.10)	0.02-0.08 (0.05)	5.4	2.7	3-18.5	0-12.5	7.4	5-21	0-7.2	12	29	53

+ From Davignon A, Rautaharju P, Boisselle E, Soumis F, Megelas M, Choquette A. Normal ECG standards for infants and children. Pediatr Cardiol 1979; 1: 123-52.
# 2nd-98th % tile (mean)
* 2nd-98th % tile (1 mm = 100 μV)
^ 98th % tile (1 mm = 100 μV)

QT Interval

The QT interval is the interval between the beginning of the QRS complex and the end of the T wave and should be measured in leads II, V5 and V6 with the longest value being used. The main difficulty lies in identifying correctly the point where the descending limb of the T wave intersects the isoelectric line. Due to the fast heart rate of infants the P wave may be superimposed on the T wave, particularly when the QT interval is prolonged. In this case, the end of the T wave should be extrapolated by drawing a tangent to the downslope of the T wave and considering its intersection with the isoelectric line. The QT interval duration changes with rate and it is usually corrected (QTc) by using Bazett's formula. Correction of the QT interval requires a stable sinus rhythm without sudden changes in the RR interval. QTc is equal to QT interval in seconds divided by the square root of the preceding RR interval in seconds. To avoid time-consuming calculations, a simple chart where the value of QTc is easily obtained by matching QT and RR interval in millimetres (given the paper speed at 25 mm/sec) has been produced (Appendix 1). When heart rate is particularly slow or fast the Bazett's formula may not be accurate in the correction but it remains the standard for clinical use. The mean QTc on the 4th day of life is 400 ± 20 ms and, at variance with the adult, no gender differences are present. Therefore, the upper normal limit of QTc (2 standard deviations above the mean, corresponding to the 97.5 percentile) is 440 ms. By definition, 2.5% of normal newborns are expected to have a QTc greater than 440 ms. In healthy infants there is a physiological prolongation of QTc by the second month (mean 410 ms) followed by a progressive decline, so that by the sixth month QTc returns to the values recorded in the first week. Despite its apparent simplicity the measurement of the QT interval is fraught with errors. An attempt should be made to measure to the nearest 10 ms (1/4 of a mm) while we recognize that this may be within measurement error.

ST Segment and T Wave

In neonates and infants it is better to consider as the isoelectric line the TP segment instead of the PQ segment. After 1 week, the T wave is negative in lead V1 and positive in V5-V6.

Abnormal electrocardiogram in the newborn

Heart rate

Sinus arrhythmia

Sinus arrhythmia should be differentiated from wandering pacemaker which manifests itself with a gradual change of P wave axis and morphology and that is due to a shift of the pacemaker from the sinus node to the atrium and the atrioventricular (AV) junction. Although wandering pacemaker may accompany other types of bradyarrhythmia, it has no pathological meaning.

Work-up

No work-up should be necessary unless significant bradycardia coexists.

Sinus tachycardia

Sinus tachycardia is a sinus rhythm with a heart rate above the normal limit (166 bpm in the first week and 179 bpm at the age of one month) and it may be caused by fever, infection, anaemia, pain, dehydration (hypovolaemia), hyperthyroidism, myocarditis, beta-adrenergic agonists or theophylline.

Work-up

The evaluation should be performed according to the underlying condition. If myocarditis is suspected an echocardiogram should be performed. Appropriate acute treatment of causes of tachycardia may be considered. Persistence of elevated rates should be further evaluated.

Sinus bradycardia

Sinus bradycardia is a sinus rhythm with a heart rate below the normal limit (91 bpm in the first week and 121 bpm at the age of one month) and it may be caused by central nervous system (CNS) abnormalities, hypothermia, hypopituarism, increased intracranial pressure, meningitis, drugs passed from the mother to infant, obstructive jaundice, typhoid fever. Hypothyroidism is another cause of bradycardia and is often associated with the so-called "mosque sign", a dome-shaped symmetric T wave in the absence of an ST segment.

Transient sinus bradycardia has been observed in newborns from anti-Ro/SSA positive mothers. A lower than normal heart rate has been described in patients affected by the Long QT Syndrome (LQTS) and it may sometimes represent the first sign of the disease during the foetal period.

Work-up

24-hour Holter monitoring may be helpful for further evaluation when a heart rate below 80-90 bpm is present on a surface ECG during infancy. Evaluation for underlying conditions should be performed.

Other bradycardias

Sinus pauses in newborns may last from 800 to 1000 ms. Pauses >2 s are abnormal and may be followed by atrial or junctional escape beats. Even a healthy neonate may show periods of junctional rhythm, i.e. a sequence of narrow QRS complexes in the absence of preceding P waves. Infants with augmented vagal tone may have sinus bradycardia, or significant sinus pauses of several seconds, during feeding, sleep, defecation. Apparent life-threatening events (ALTE), described as loss of consciousness, pallor and hypotonia, have been related to vagal overactivity, which may manifest as sinus pauses or abrupt bradycardia. ALTE may be associated with apnoeic episodes, or gastro-oesophageal reflux, that may precede severe bradycardia. Infants with LQTS may also have sinus pauses.

Work-up

24-hour Holter monitoring may be useful for the assessment of significant bradycardia. Long pauses, secondary to excessive vagal tone may be eliminated by the use of atropine, and rarely require pacemakers. Treatment of other underlying diseases should be undertaken.

P Wave

Abnormal P waves may be seen in infants with atrial enlargement or non-sinus origin of the P wave. Right atrial enlargement or/and hypertrophy produces increased P wave amplitude with normal duration, best seen in lead II. Left atrial enlargement and/or hypertrophy produces an increased (>0.1 mV) and prolonged (>40 ms) negative terminal deflection of the P wave in lead V1. Left atrial enlargement also causes exaggerated notching of the P wave in lead II, although this is not a specific sign.

Work up

An echocardiogram should be performed when clinically indicated.

Atrioventricular conduction

Complete (3rd degree) atrioventricular block

Approximately 1 out of every 15 000 to 20 000 live births results in a baby with isolated AV block. Most of them are ascribed to the presence of anti Ro/SSA and La-SSB antibodies in the mothers. 2% to 5% of women with known antibodies will have a first child with AV block. Mortality rate in patients with neonatal AV block is still high, especially during the first 3 months. Acquired complete AV block is rare in neonates. It is mainly caused by infections (viral myocarditis, HIV) or may be related to tumours.

1st and 2nd degree atrioventricular block

Neonates may present with 1st or 2nd degree AV block which may rarely progress to complete AV block. Neonates with LQTS may show 2:1 AV block because they have a fast atrial rate and the P wave falls within the very prolonged T wave. In spite of high doses of beta-blockers and pacing, there is still significant mortality. Heart block associated with prolonged QT interval may be caused by cisapride, diphemanil or doxapram.

Work up

Clinical history of autoimmune disease and plasma titres of maternal antibodies (anti Ro/SSA and antiLa/SSB) should be assessed. In the absence of maternal antibodies, ECG should also be performed on the parents and siblings (see intraventricular abnormalities). Neonates with 1st degree AV block should be followed with additional ECGs in the following months. Neonates and infants with 2nd or 3rd degree AV block need a complete paediatric cardiology work-up, including an echocardiogram. The only effective treatment of congenital complete AV block in neonates with symptoms or a low ventricular escape rhythm is permanent artificial pacing.

Intraventricular conduction

Bundle Branch Block

Congenital isolated complete right bundle branch block (RBBB) and left bundle branch block (LBBB) are very rare in neonates. The classical ECG in Ebstein's anomaly of the tricuspid valve displays a prolonged PR interval and a wide RBBB pattern. Left anterior fascicular block is found in association with atrioventricular canal defects and tricuspid atresia. In severe cardiomyopathy, interruption of the left bundle carries a poor prognosis. Hereditary bundle branch block is an autosomal dominant genetic disease, which induces RBBB, left or right QRS axis deviation or AV block.

Non-specific intraventricular conduction abnormalities

They are very rare in neonates and infants with normal hearts and may be caused by myocarditis or endocarditis.

Work up

Neonates and infants with intraventricular conduction abnormalities need a complete paediatric cardiology work-up. Evaluation of possible underlying causes should be performed. ECG should also be performed on the parents and siblings.

Wolff-Parkinson-White (WPW) syndrome

In newborns and infants preexcitation may be subtle and only be detected in the mid-precordial leads and it is often intermittent. The prevalence of WPW syndrome is high in the presence of 2 of the 4 following characteristics:

- PR interval ≤100 ms,
- QRS duration ≥80 ms,
- lack of a Q wave in V6,
- left axis deviation.

Short PR intervals are also observed in mannosideosis, Fabry's disease, and Pompe's disease. A short PR interval in a normal heart may be caused by a low right atrial pacemaker with a negative P wave in lead aVF and positive or isoelectric in lead I. The prevalence of WPW syndrome in the paediatric population is 0.15-0.3%, with an incidence of 4 per 100 000 persons per year. In children with structural heart disease (Ebstein´s anomaly of the tricuspid valve, l-transposition of the great arteries, hypertrophic cardiomyopathy and cardiac tumours) the prevalence is 0.33-0.5%. The incidence of sudden death in preexcitation syndrome during childhood is 0.5% and cardiac arrest may be the initial presentation.

Work up

Congenital heart disease is more common in infants and young children with preexcitation, with a prevalence as high as 45% for infants with an ECG pattern consistent with a right-sided accessory pathway. Thus, a complete 2-dimensional echocardiography work-up is recommended. Assessment of the conduction properties of the accessory pathway, i.e. the antegrade effective refractory period and the shortest RR-interval with preexcitation, by trans-oesophageal programmed stimulation may be useful in selected patients for risk stratification and mode of therapy.

QRS axis and amplitude

A relative right axis deviation is seen in normal neonates. Left axis deviation is seen in atrioventricular or ventricular septal defect, tricuspid atresia, and WPW syndrome, but occasionally also in normal infants.

Right ventricular hypertrophy

It may be suspected from a QR complex in V1, an upright T wave in V1 (normal in the first week of life), increased R wave amplitude in V1, and increased S wave amplitude in V6 (according to the Davignon criteria). Sensitivity and specificity have not been tested in the neonate. QR patterns are commonly seen with pressure overload congenital lesions, rSR' patterns in volume overload lesions.

Left ventricular hypertrophy

ECG signs in children (not specifically tested in neonates) are T wave abnormalities in leads V5 and V6, increased R wave amplitude in V6, increased S wave amplitude in V1 (according to the Davignon criteria), and a combination of these last two variables. Left to right shunt lesions may result in left ventricular hypertrophy, but this may be in association with right ventricular hypertrophy and manifested as biventricular hypertrophy.

Low QRS voltage

In the limb leads the total amplitude of R+S in each lead ≤0.5 mV may be indicative of myocarditis or cardiomyopathy.

Work-up

Evaluation of the underlying causes should be performed. An echocardiogram should be performed when clinically indicated.

Ventricular repolarisation

QT interval prolongation

Measurements of the QT interval should be performed by hand. QT duration may change over time and it is recommended to repeat the ECG in those infants found to have a prolonged QTc on the first ECG. While exceptions do exist, the more prolonged the QTc interval, the greater the likelihood of its clinical significance. A QTc close to 500 ms implies a clear abnormality even taking into account potential measurement errors.

QT prolongation may be caused by hypocalcaemia with a distinctive lengthening of the ST segment, hypokalaemia and hypomagnesaemia, with a decrease of T wave amplitude and increase of U wave amplitude, CNS abnormalities, with T wave inversion, macrolide antibiotics (spyramycin, erythromycin, clarithromycin), trimethoprim, cisapride. Neonates born from mothers positive for the anti-Ro/SSA antibodies may show transient QT interval prolongation in the first 6 months of life.

Finally, some of the neonates with QT interval prolongation may be affected by the congenital Long QT Syndrome (LQTS), whose prevalence appears to be close to 1/3000-1/5000, and is characterised by the occurrence

of syncopal episodes due to torsades de pointes ventricular tachycardia (VT) and by a high risk of sudden cardiac death among untreated patients. Importantly, in 12% of patients with LQTS sudden death is the first manifestation of the disease and in 4% this happens in the first year of life. This point alone mandates the treatment of all those diagnosed as affected, even if there are no symptoms. LQTS is a genetic disease due to mutations of several genes all encoding ionic (potassium or sodium) currents involved in the control of ventricular repolarisation. In most cases, several members of the same family are gene-carriers. Low penetrance exists in LQTS, which means that gene-carriers may not show the clinical phenotype and may have a normal QT interval. Therefore, a normal QT in the parents does not rule out familial LQTS. In addition, approximately 30% of cases are due to "de novo" mutations which imply unaffected parents and no family history. "De novo" LQTS mutations have been demonstrated in infant victims of cardiac arrest and sudden death diagnosed as Sudden Infant Death Syndrome. Beta-blockers are the first choice therapy in LQTS and if beta-blockers are unable to prevent new cardiac events, additional drug therapy, left cardiac sympathetic denervation, pacemakers or the implantable cardioverter defibrillator should be considered based on evidence, with due consideration for body size.

Work-up

The likelihood of having LQTS increases with increasing QTc; however, since a small percentage of LQTS patients has a QTc < 440 ms, the correlation between QT prolongation and presence of the syndrome is not absolute. Therefore, the following discussion is presented as guidelines based upon experience and current knowledge, and is likely to be updated frequently. Given the life-threatening potential of the disease, once the diagnosis of LQTS becomes probable, it is recommended that these infants are referred to a specialist as soon as possible.

- First ECG: QTc above 440 ms, the upper limit of normal.

Exclude other causes of acquired QT interval prolongation and obtain a detailed family history for the possibility of familial LQTS. In the family, episodes of early sudden death, fainting spells, and seizures-epilepsy should alert to this possibility. The ECG should be repeated after a few days to confirm the abnormal finding. Subsequent management depends on: 1) presence or absence of family history suggestive for LQTS, and 2) the degree of QT interval prolongation. The presence of complex ventricular arrhythmias would have additional importance. The following stepwise approach involves infants with and without family history for LQTS. If family history is positive, then a) as LQTS is an autosomal dominant disease b) the infant has a 50% probability of being affected and complete diagnostic procedures should be performed, as always with LQTS families (Figure 1).

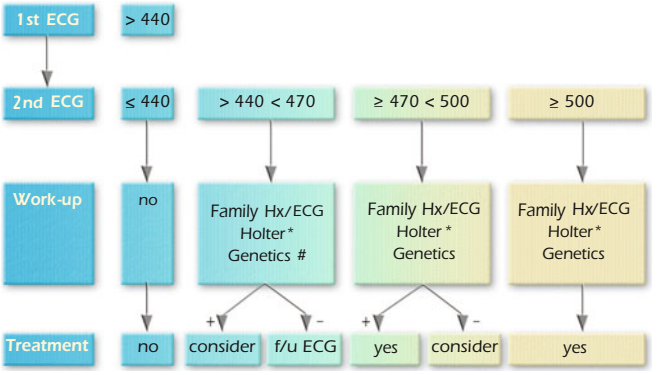
- The 2nd ECG is normal.

If the first QTc was <470 ms, dismiss the case. If the first QTc was ≥470 ms, then plan a 3rd ECG after 1-2 months to remain on the safe side.

- The 2nd ECG shows a QTc between 440 and 470 ms.

In these cases with persistent borderline QT prolongation, electrolytes, including calcium and magnesium, should be checked. Clinical history of autoimmune disease and plasma titres of maternal antibodies (anti Ro/SSA and antiLa/SSB) should be assessed. T wave morphology may be helpful; for example, the presence of notches on the T

Figure 1. QT prolongation management flow-chart



Electrolytes, echocardiogram, intracranial ultrasound are recommended in the appropriate clinical situation. In cases of positive genetics and QTc > 440 ms, therapy is indicated. # In cases of a positive family history (Hx) for LQTS ;* See text on this page.

wave in the precordial leads further suggests the presence of LQTS. Additionally, mild bradycardia can also be found in LQTS. ECGs should be obtained from the parents and siblings of the neonate. In the absence of family history of LQTS, symptoms or arrhythmias, a 24-hour Holter monitoring should be obtained to look for T wave alternans, complex ventricular arrhythmias or marked QTc prolongation, and the ECG should be periodically checked during the first year. No treatment is currently recommended. With a positive family history, the probability of LQTS becomes high. Additional diagnostic procedures (24-hour Holter monitoring, echocardiogram and genetic screening) should be performed and initiation of therapy could be considered.

- The 2nd ECG shows a QTc ≥470 and <500 ms.

All diagnostic procedures listed above should be performed and a 3rd ECG should be planned within a month. In case of a positive family history, therapy should be initiated. Even without family history, therapy should be considered. Even in infants with very prolonged QTc in the first month of life, the ECG may normalised. If subsequent ECGs and diagnostic procedures do not confirm the presence of LQTS, it is logical to progressively withdraw therapy and to return to periodic observations.

- The 2nd ECG shows a QTc ≥500 ms

Infants with a QTc ≥500 ms are very likely to be affected by LQTS and to become symptomatic. All diagnostic procedures listed above should be performed and these infants should be treated.

Highest risk

The presence of QTc close to 600 ms, or of T wave alternans, or of 2:1 AV block secondary to major QT prolongation, or of hearing loss identify infants at extremely high risk.

ST segment elevation

ST segment elevation may be caused by pericarditis (most frequent), hyperkalemia, intracranial haemorrhage, pneumothorax and pneumopericardium, subepicardial injury due to anomalous left coronary artery or to Kawasaki disease with cardiac involvement. ST segment elevation with a RBBB pattern in the right precordial leads (V1 and V2) is the typical finding of the Brugada syndrome, a genetic disorder associated with a high incidence of sudden cardiac death secondary to ventricular fibrillation, in the absence of cardiac structural abnormalities. The ST segment elevation is typically downsloping or "coved" and it is followed by a negative T wave, at variance with the early repolarisation syndrome where ST segment elevation has an upward concavity, it is confined to mid-precordial leads and it is associated with a positive T wave. The diagnosis of the Brugada syndrome is made difficult by the intermittent nature of the ECG abnormalities, as 40% of cases may be normal transiently. Rare cases of Brugada syndrome have been reported during infancy.

Work-up

Whenever the underlying cause has been identified, it should be treated. If the Brugada syndrome is suspected, careful family history should be collected, a 24-hour Holter monitoring should be obtained, and the patient should be referred to a specialist.

Atrial and ventricular arrhythmias

Atrial/junctional

Premature atrial beats

Premature atrial beats (PABs) usually have a different morphology and mean vector from sinus P waves. It is relatively common in the same strip to see PABs conducted normally, aberrantly and blocked.

Work-up

In patients with frequent PABs, a follow-up ECG at one month may be performed. Relatively long periods of blocked atrial bigeminy may simulate sinus bradycardia. The distinction is important since blocked atrial bigeminy is most often benign while severe sinus bradycardia may accompany systemic illness.

Supraventricular tachycardia

Supraventricular tachycardia (SVT) has an extremely regular R-R interval after the first 10–20 beats most often at rates 260–300 bpm. Persistent aberration of SVT in infants is exceedingly rare, implying the diagnosis of VT with a QRS complex different from sinus (Table 2).

Work-up

It is important to document SVT with a 12-lead ECG before attempting conversion of the rhythm unless the infant is critically ill. After sinus rhythm is achieved, the WPW pattern should be sought on a 12-lead ECG. Treatment to prevent further episodes of SVT in infancy is generally recommended. An echocardiogram is indicated to determine ventricular function or the presence of congenital heart disease.

Table 2. Distinguishing Tachyarrhythmias in Infants

	Sinus Tachycardia	**SVT**	**Atrial Flutter**	**VT**
History	Sepsis, fever, hypovolaemia, etc.	Usually normal	Most have a normal heart	Many with abnormal heart
Rate	Almost always <230 bpm	Most often 260 - 300 bpm	Atrial 300 - 500 bpm. Vent. 1:1 to 4:1 conduction	200 - 500 bpm
R-R interval variation	Over several seconds may get faster and slower	After first 10 - 20 beats, extremely regular	May have variable block (1:1, 2:1, 3:1) giving different ventricular rates	Slight variation over several beats
P Wave Axis	Same as sinus almost always visible P waves	60% visible P waves, P waves do not look like sinus P waves	Flutter waves (best seen in LII, LIII, aVF, V1)	May have sinus P waves continuing unrelated to VT (AV dissociation), retrograde P waves, or no visible P waves
QRS	Almost always same as slower sinus rhythm	After first 10 - 20 beats, almost always same as sinus	Usually same as sinus, may have occasional beats different from sinus	Different from sinus (not necessarily "wide")

SVT = Supraventricular tachycardia; VT = Ventricular tachycardia

Atrial flutter

In general, there is variable AV conduction from 1:1 to 4:1 yielding an irregular ventricular rate and the QRS complex is usually the same as in sinus rhythm. Due to the occasional association with WPW, this pattern should be specifically sought. Other types of supraventricular arrhythmias such as atrial fibrillation or multifocal tachycardia are extremely rare in the neonate.

Work-up

Conversion to sinus rhythm should be attempted. An echocardiogram is worthwhile to determine ventricular function and the possible presence of congenital heart disease.

Ventricular arrhythmias

Premature ventricular beats

In infants, the QRS duration of premature ventricular beats (PVBs) may be normal or slightly prolonged, but if the complex has a different morphology from the sinus and it is not preceded by premature P wave, the diagnosis is PVB. It is not possible to distinguish PVBs from PABs with aberrancy on the basis of QRS morphology.

Work-up

The QT interval should be measured (see section on ventricular repolarisation). In complex ventricular arrhythmias, a 24-hour Holter monitoring may be worthwhile. An echocardiogram may be performed to determine ventricular function or structural abnormalities. Occasionally maternal drugs that cause ventricular arrhythmias may be transferred in utero or post-natally in breast milk.

Ventricular tachycardia

SVT in infants with a different QRS beyond the first 10–20 beats is rare and a diagnosis of VT should be strongly considered. The rate of VT may be 200–500 bpm. There may be sinus P waves unrelated to VT (AV dissociation), retrograde P waves or no visible P waves. The diagnosis of VT should be strongly considered if the patient has PVBs during times of sinus rhythm with a similar morphology to the tachyarrhythmia.

Work-up

An underlying cardiac or CNS abnormality may be found in infants with VT. The QT interval should be measured (see section on ventricular repolarisation), a 24-hour Holter monitoring and echocardiogram should be obtained. Treatment is generally indicated.

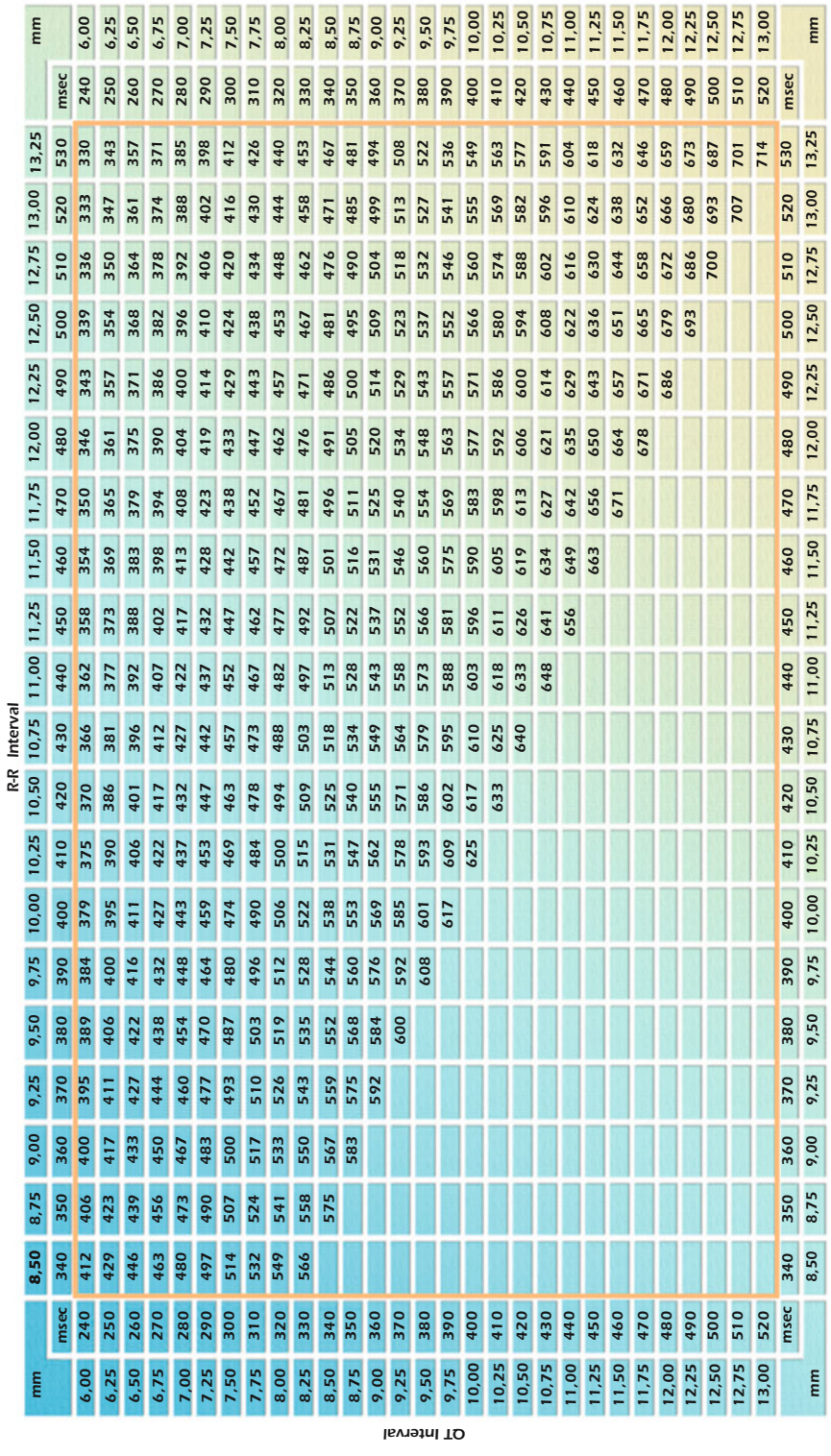
Accelerated ventricular rhythm

It is also known as "slow VT", the rate is approximately the same as the infant's sinus rate (<200 bpm), and the rhythms tend to alternate.

Work-up

While these infants most often have a normal heart, a work-up similar to VT is indicated.

Appendix 1, Part 1. QTc



mm		8,50	8,75	9,00	9,25	9,50	9,75	10,00	10,25	10,50	10,75	11,00	11,25	11,50	11,75	12,00	12,25	12,50	12,75	13,00	13,25		mm
	msec	340	350	360	370	380	390	400	410	420	430	440	450	460	470	480	490	500	510	520	530	msec	
6,00	240	412	406	400	395	389	384	379	375	370	366	362	358	354	350	346	343	339	336	333	330	240	6,00
6,25	250	429	423	417	411	406	400	395	390	386	381	377	373	369	365	361	357	354	350	347	343	250	6,25
6,50	260	446	439	433	427	422	416	411	406	401	396	392	388	383	379	375	371	368	364	361	357	260	6,50
6,75	270	463	456	450	444	438	432	427	422	417	412	407	402	398	394	390	386	382	378	374	371	270	6,75
7,00	280	480	473	467	460	454	448	443	437	432	427	422	417	413	408	404	400	396	392	388	385	280	7,00
7,25	290	497	490	483	477	470	464	459	453	447	442	437	432	428	423	419	414	410	406	402	398	290	7,25
7,50	300	514	507	500	493	487	480	474	469	463	457	452	447	442	438	433	429	424	420	416	412	300	7,50
7,75	310	532	524	517	510	503	496	490	484	478	473	467	462	457	452	447	443	438	434	430	426	310	7,75
8,00	320	549	541	533	526	519	512	506	500	494	488	482	477	472	467	462	457	453	448	444	440	320	8,00
8,25	330	566	558	550	543	535	528	522	515	509	503	497	492	487	481	476	471	467	462	458	453	330	8,25
8,50	340		575	567	559	552	544	538	531	525	518	513	507	501	496	491	486	481	476	471	467	340	8,50
8,75	350			583	575	568	560	553	547	540	534	528	522	516	511	505	500	495	490	485	481	350	8,75
9,00	360				592	584	576	569	562	555	549	543	537	531	525	520	514	509	504	499	494	360	9,00
9,25	370					600	592	585	578	571	564	558	552	546	540	534	529	523	518	513	508	370	9,25
9,50	380						608	601	593	586	579	573	566	560	554	548	543	537	532	527	522	380	9,50
9,75	390							617	609	602	595	588	581	575	569	563	557	552	546	541	536	390	9,75
10,00	400								625	617	610	603	596	590	583	577	571	566	560	555	549	400	10,00
10,25	410									633	625	618	611	605	598	592	586	580	574	569	563	410	10,25
10,50	420										640	633	626	619	613	606	600	594	588	582	577	420	10,50
10,75	430											648	641	634	627	621	614	608	602	596	591	430	10,75
11,00	440												656	649	642	635	629	622	616	610	604	440	11,00
11,25	450													663	656	650	643	636	630	624	618	450	11,25
11,50	460														671	664	657	651	644	638	632	460	11,50
11,75	470															678	671	665	658	652	646	470	11,75
12,00	480																686	679	672	666	659	480	12,00
12,25	490																	693	686	680	673	490	12,25
12,50	500																		700	693	687	500	12,50
12,75	510																			707	701	510	12,75
13,00	520																				714	520	13,00
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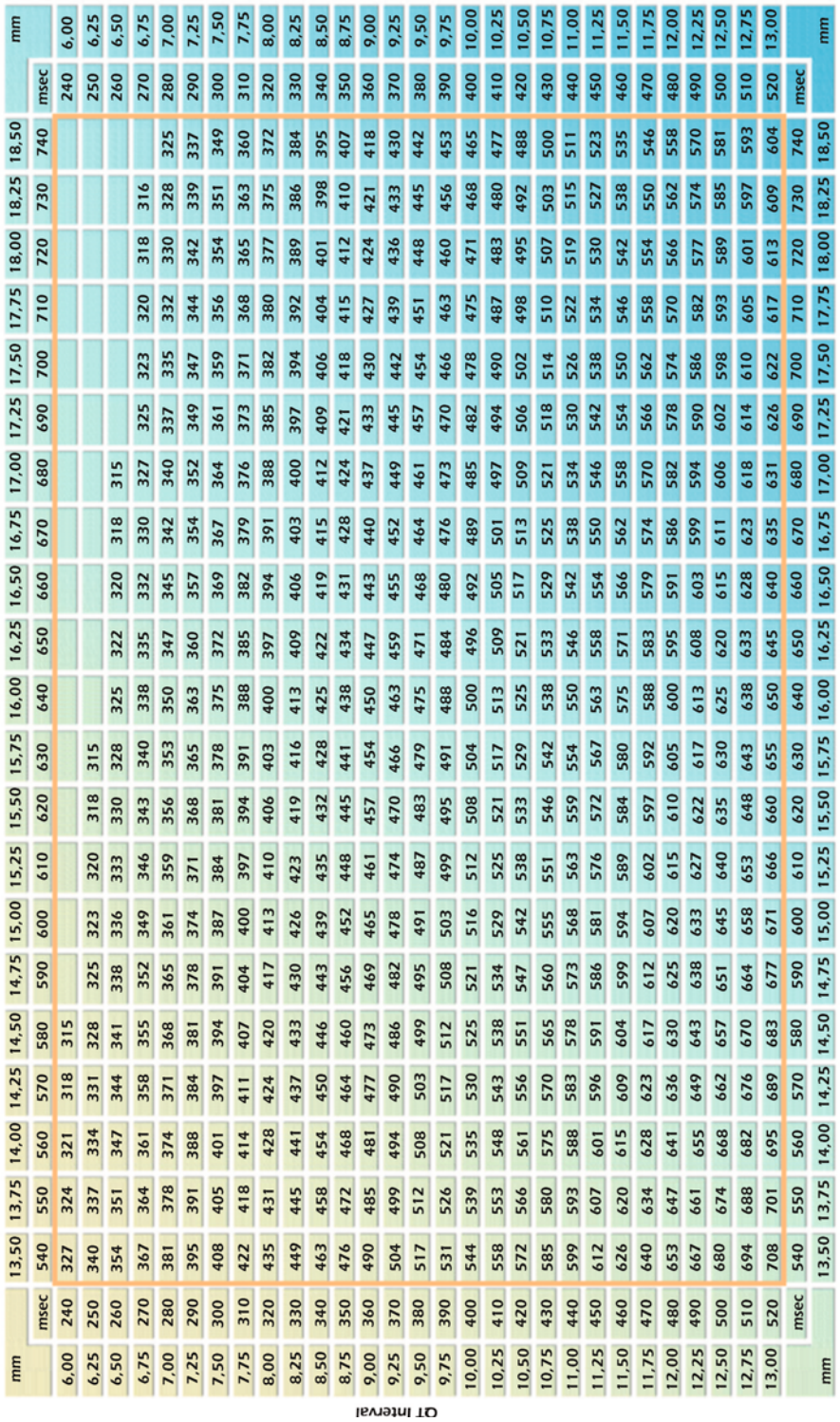
mm		8,50	8,75	9,00	9,25	9,50	9,75	10,00	10,25	10,50	10,75	11,00	11,25	11,50	11,75	12,00	12,25	12,50	12,75	13,00	13,25		mm

Chart for calculation of QTc (for heart rates between 81 and 176 bpm)*. QTc, according to the Bazett's formula, is obtained by matching QT and RR interval inmillimetres, given the paper speed at 25 mm/sec. Corresponding values of RR interval and uncorrected QT interval are also indicated.

Appendix 1, Part 2. QTc



QT Interval mm	msec	R-R Interval mm 13,50	13,75	14,00	14,25	14,50	14,75	15,00	15,25	15,50	15,75	16,00	16,25	16,50	16,75	17,00	17,25	17,50	17,75	18,00	18,25	18,50	msec	mm
6,00	240	327	324	321	318	315																	240	6,00
6,25	250	340	337	334	331	328	325	323	320	318	315												250	6,25
6,50	260	354	351	347	344	341	338	336	333	330	328	325	322	320	318	315							260	6,50
6,75	270	367	364	361	358	355	352	349	346	343	340	338	335	332	330	327	325	323	320	318	316		270	6,75
7,00	280	381	378	374	371	368	365	361	359	356	353	350	347	345	342	340	337	335	332	330	328	325	280	7,00
7,25	290	395	391	388	384	381	378	374	371	368	365	363	360	357	354	352	349	347	344	342	339	337	290	7,25
7,50	300	408	405	401	397	394	391	387	384	381	378	375	372	369	367	364	361	359	356	354	351	349	300	7,50
7,75	310	422	418	414	411	407	404	400	397	394	391	388	385	382	379	376	373	371	368	365	363	360	310	7,75
8,00	320	435	431	428	424	420	417	413	410	406	403	400	397	394	391	388	385	382	380	377	375	372	320	8,00
8,25	330	449	445	441	437	433	430	426	423	419	416	413	409	406	403	400	397	394	392	389	386	384	330	8,25
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8,75	350	476	472	468	464	460	456	452	448	445	441	438	434	431	428	424	421	418	415	412	410	407	350	8,75
9,00	360	490	485	481	477	473	469	465	461	457	454	450	447	443	440	437	433	430	427	424	421	418	360	9,00
9,25	370	504	499	494	490	486	482	478	474	470	466	463	459	455	452	449	445	442	439	436	433	430	370	9,25
9,50	380	517	512	508	503	499	495	491	487	483	479	475	471	468	464	461	457	454	451	448	445	442	380	9,50
9,75	390	531	526	521	517	512	508	503	499	495	491	488	484	480	476	473	470	466	463	460	456	453	390	9,75
10,00	400	544	539	535	530	525	521	516	512	508	504	500	496	492	489	485	482	478	475	471	468	465	400	10,00
10,25	410	558	553	548	543	538	534	529	525	521	517	513	509	505	501	497	494	490	487	483	480	477	410	10,25
10,50	420	572	566	561	556	551	547	542	538	533	529	525	521	517	513	509	506	502	498	495	492	488	420	10,50
10,75	430	585	580	575	570	565	560	555	551	546	542	538	533	529	525	521	518	514	510	507	503	500	430	10,75
11,00	440	599	593	588	583	578	573	568	563	559	554	550	546	542	538	534	530	526	522	519	515	511	440	11,00
11,25	450	612	607	601	596	591	586	581	576	572	567	563	558	554	550	546	542	538	534	530	527	523	450	11,25
11,50	460	626	620	615	609	604	599	594	589	584	580	575	571	566	562	558	554	550	546	542	538	535	460	11,50
11,75	470	640	634	628	623	617	612	607	602	597	592	588	583	579	574	570	566	562	558	554	550	546	470	11,75
12,00	480	653	647	641	636	630	625	620	615	610	605	600	595	591	586	582	578	574	570	566	562	558	480	12,00
12,25	490	667	661	655	649	643	638	633	627	622	617	613	608	603	599	594	590	586	582	577	574	570	490	12,25
12,50	500	680	674	668	662	657	651	645	640	635	630	625	620	615	611	606	602	598	593	589	585	581	500	12,50
12,75	510	694	688	682	676	670	664	658	653	648	643	638	633	628	623	618	614	610	605	601	597	593	510	12,75
13,00	520	708	701	695	689	683	677	671	666	660	655	650	645	640	635	631	626	622	617	613	609	604	520	13,00
	msec	540	550	560	570	580	590	600	610	620	630	640	650	660	670	680	690	700	710	720	730	740	msec	
	mm	13,50	13,75	14,00	14,25	14,50	14,75	15,00	15,25	15,50	15,75	16,00	16,25	16,50	16,75	17,00	17,25	17,50	17,75	18,00	18,25	18,50		mm

Chart for calculation of QTc (for heart rates between 81 and 176 bpm)*. QTc, according to the Bazett's formula, is obtained by matching QT and RR interval inmillimetres, given the paper speed at 25 mm/sec. Corresponding values of RR interval and uncorrected QT interval are also indicated.

Section VIII:
Pregnancy and Heart Disease

1. Cardiovascular Disease during Pregnancy

Chapter 1
Cardiovascular Disease during Pregnancy* 2003

The Task Force on the Management of Cardiovascular Diseases during Pregnancy of the European Society of Cardiology

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1. Introduction

Cardiovascular diseases during pregnancy represent a very heterogeneous group as regards the diseases involved and the risks related to pregnancy. Management is based on haemodynamic principles: full diagnosis of the maternal heart condition plus knowledge of the physiological changes in pregnancy. Likely outcome is determined by these. Good management depends on team work between local physicians and general practitioners, involved cardiologists, obstetricians and anaesthetists and where appropriate, geneticists and neonatologists. Pregnant women do not like to travel and shared care between local doctors and the specialist centre should be practised whenever possible. Most women with heart disease do well but some conditions are dangerous.

2. Physiological changes during pregnancy

An increase in blood volume follows an increase in capacity of the vascular bed caused by hormonal changes which relax smooth muscle. The changes begin as early as the 5th week.

- Both blood volume and cardiac output rise by 30 to 50% (more in multiple pregnancy).
- Stroke volume increases more than heart rate. A resting tachycardia gives warning of inability to raise stroke output and is dangerous when left ventricular filling is slow or coronary flow reserve reduced.
- Diastolic BP falls, is lowest in mid-trimester and rises towards the end with little change in systolic pressure.
- Coagulation factors rise and fibrinolytic activity diminishes. The risk of thromboembolism increases.
- The post-partum period is also not risk-free since haemodynamic conditions do not return to normal for up to one month after the delivery.

*Adapted from the ESC Expert Consensus Document on the Management of Cardiovascular Diseases during Pregnancy. (European Heart Journal 2003; 24(8): 761-781). An updated version of these pocket guidelines on Cardiovascular Disease during Pregnancy is now available. The full text of these ESC Guidelines is available on www.escardio.org/guidelines.

J. Bax et al., *Compendium of Abridged ESC Guidelines 2001*

3. In general

3.1 Pre-existing conditions which may confer high maternal risk

- Pulmonary hypertension of any cause
- Left ventricular inflow or outflow obstruction – mitral or aortic stenosis and some cases of hypertrophic cardiomyopathy
- The fragile aorta e.g. in Marfan syndrome or coarctation
- Valvular prostheses requiring anticoagulant treatment
- Any patients reaching NYHA* class III or IV during pregnancy
- Severe cyanotic congenital heart disease

3.2 Low maternal risk

- Any patient in NYHA* class I to II before pregnancy except for those at high maternal risk (see above)
- Left to right shunts
- Valvular regurgitation
- Modest left ventricular outflow obstruction
- Right ventricular outflow obstruction (unless severe)

3.3 Maternal conditions causing high foetal risk

- Any maternal condition reaching NYHA* class III or IV in pregnancy
- Haemodynamic instability
- Need for warfarin dosage above 5 mg/day
- Pre-eclampsia and eclampsia
- Severe cyanotic congenital heart disease

The presence of functional NYHA* class III and IV during pregnancy requires immediate hospitalization and prompt treatment. Unless haemodynamic improvement is obtained termination of pregnancy or delivery should be considered.

3.4 Heart conditions which may develop in pregnancy or parturition

- Hypertension and pre-eclampsia
- Peripartum cardiomyopathy
- Myocardial infarction (usually due to dissection)
- Aortic dissection
- Pulmonary embolism
- Tachyarrhythmias (all types)

4. Congenital Heart Disease

4.1 High risk patients

- *Eisenmenger syndrome or severe pulmonary hypertension without septal defects*
  These patients face a high mortality and should be strongly advised against pregnancy. If pregnant and if termination is refused they should be admitted to hospital in the second trimester for bed rest, oxygen, oximetry, prophylactic heparin and foetal monitoring. Vasodilators need to be avoided during delivery and good hydration maintained. Most deaths occur suddenly during the post-partum period.
- *Severe left ventricular outflow obstruction*
  Failure of the left ventricular outflow velocity to rise, tachycardia, angina or dyspnoea indicate need for rest, beta-blockers and percutaneous aortic valvotomy or surgery if appropriate. If surgery is needed, the foetus should be delivered by C-section before the intervention.
- *Severe maternal cyanosis*
  Oxygen saturation falls during pregnancy but is maximised by rest and oxygen. Foetal growth is impaired. The risk depends on the severity of cyanosis. The risk is high if O_2 saturation is $< 85\%$. Prophylactic heparin should be given.

4.2 Patients at low or moderate risk

- *Pulmonary stenosis*
  Generally, pulmonary stenosis is better tolerated than aortic stenosis but in the presence of severe stenosis, pregnancy may precipitate right ventricular failure, arrhythmia or tricuspid regurgitation. It only rarely needs intervention by balloon valvotomy during pregnancy.

* NYHA = New York Heart Association

- *Coarctation of the aorta*
  Uncorrected coarctation is only rarely seen. Management of hypertension is never fully successful because of surges on effort despite rest and a beta-blocker. It brings risk of stroke and dissection. Repair reduces but does not remove these risks.

- *Previous surgery with residual defects but good ventricular function*
  After correction of the Tetralogy of Fallot, the risk is low in patients with good repairs. Patients with systemic right ventricle after intra-atrial correction of transposition or univentricular circulations after a Fontan repair can do well provided ventricular function is still sound. Patients with complex congenital defects need careful individual assessment for ventricular function, conduction defects, pulmonary vascular disease, arrhythmic and thromboembolic risk. The risk of foetal defect is low including the 22q11 deletion syndrome.

5. Marfan syndrome and other inherited conditions affecting the aorta

Women with aortic root diameter < 4 cm and no substantial mitral or aortic regurgitation face a 1% risk of aortic dissection or rupture.

Mitral regurgitation is not usually a problem but, if severe, should be repaired before pregnancy.

Patients with aortic root dilatation ≥ 4 cm face about a 10% risk but this risk is reduced after elective aortic root replacement.

Beta-blockers should be continued throughout pregnancy including operated patients.

6. Acquired valvular heart disease

- Rheumatic heart valve disease is still common in developing countries.

- Mitral regurgitation is well tolerated unless atrial fibrillation develops with a fast ventricular rate.

- In aortic regurgitation tachycardia reduces the time for diastolic regurgitation and it is well tolerated even when severe.

6.1 Mitral stenosis

- Left atrial pressure rises due to increased stroke and blood volume and shortened diastole. Tachycardia warns of this. Close follow-up with serial Doppler echocardiography is needed, in particular during the 2nd and 3rd trimesters.

- A mitral valve area < 1.5 cm^2 carries risk. A selective beta-blocker should be started in patients with dyspnoea in a dose sufficient to control sinus rate and a diuretic may be needed.

- Prophylactic balloon valvotomy is not recommended but should be performed in an experienced centre if pulmonary congestion persists or if systolic pulmonary pressure remains > 50 mmHg despite medical therapy.

6.2 Aortic stenosis

Most cases are congenital or are associated with mitral stenosis. The risk is generally low if mean aortic gradient remains ≤ 50 mmHg during pregnancy.

6.3 Heart valve prostheses

Haemodynamic tolerance is generally good. The problem is the absolute need for anticoagulant treatment in patients with mechanical prostheses.

In managing these patients it needs to be remembered that:

- Pregnancy is a hypercoagulable state.

- Vitamin K antagonists cross the placenta and may cause embryopathy.

- The risk of embryopathy is dose related. It is negligible if the dose is 5 mg or less.

- Heparin is less effective.

- Maternal risk of thromboembolism is minimised if warfarin is continued throughout.

- Elective caesarean section at 36 weeks avoids the transfer to heparin which is necessary to avoid neonatal cerebral haemorrhage during vaginal delivery.

- The choice should be made after the patient and her partner have been fully informed.

- The safety and efficacy of low molecular weight heparin has not been established for patients with mechanical heart valves so should not be recommended at the present time.

7. Cardiomyopathies

7.1 Peripartum cardiomyopathy (PPCM)

- This is unexplained left ventricular dysfunction which develops during the last month of pregnancy or within five months of delivery confirmed by echocardiography.
- It presents with heart failure, less often embolism or arrhythmia.
- The worst cases present early post-partum and may need inotropic agents and a ventricular assisting device. As ventricular function usually improves even in the most fulminating cases, every effort should be made to avoid transplantation.
- Early biopsy usually shows myocarditis and immunosuppressives may be helpful.
- Anticoagulants are important. ACE-inhibitors are contra-indicated before delivery.
- The risk of recurrence should lead to discouragement of further pregnancies even after an apparent recovery of left ventricular function.

7.2 Dilated cardiomyopathy (DCM)

Patients with dilated cardiomyopathy should be advised against pregnancy because of a high chance of deterioration.

Termination should be advised if the ejection fraction is < 45% and/or the left ventricular dimensions are definitely above normal.

- Echocardiography should be performed before conception if possible in all patients with a family history of DCM or PPCM.
- Pregnancy is inadvisable if left ventricular function is reduced.
- Patients with a family history of DCM may have a higher risk of PPCM.
- Pregnant patients with DCM are at high risk.

7.3 Hypertrophic cardiomyopathy (HCM)

- Women with HCM usually tolerate pregnancy well but fatalities have been reported. There is no evidence for an increased risk in pregnancy.
- After a diagnosis is first made in pregnancy, an asymptomatic patient can usually be reassured.
- Pulmonary oedema may occur in patients with severe diastolic dysfunction who are very tachycardia sensitive. They are at risk and need rest and a beta-blocker and cautious use of a diuretic.
- If atrial fibrillation develops low molecular weight heparin provides suitable anticoagulation.
- Cardioversion will be needed if atrial fibrillation (AF) persists.
- Normal delivery is advised on a selected date with continued beta-blocker, avoidance of vasodilatation and careful replacement of blood loss.
- The genetic risk needs to be discussed.

8. Arrhythmias

- Both ectopic beats and sustained arrhythmias become more frequent or develop for the first time.
- Treatment is the same as outside pregnancy but as conservative as possible.
- Blood levels of antiarrhythmic drugs need to be checked because of altered pharmacokinetics.
- Cardioversion should be used if tachyarrhythmia is sustained and causing haemodynamic instability. Cardioversion is safe for the foetus.
- Selective beta-1 blocking drugs are preferred for prophylaxis of supraventricular arrhythmias.
- Vagal stimulation and, failing that, intravenous adenosine are first choice for treatment of supraventricular tachycardia.
- Radiofrequency ablation can, if necessary, be performed.
- Ventricular tachycardia is much less common and should be terminated by cardioversion if not well haemodynamically tolerated.

n.b. The reader should consult the ESC Guidelines for the Management of Patients with Supraventricular Arrhythmias for more details.

9. Hypertensive disorders

9.1 Pre-existing hypertension

- Control of pre-existing hypertension should begin before conception and reduces the risk of exacerbation of high BP but has not been shown to reduce super-imposed pre-eclampsia or perinatal mortality.
- Foetal growth should be monitored.
- Methyl dopa remains the first choice and beta-blockers have had extensive and safe use (Atenolol has been reported to reduce foetal growth).
- **ACE-inhibitors and angiotensin receptor inhibitors** are contra-indicated during the second and third trimesters.

9.2 Pre-eclampsia

- There is no specific treatment.
- Pre-eclampsia is completely reversible and usually abates after delivery.
- The aim is to safeguard the mother while securing maturation of the foetus.
- Antihypertensive treatment has not been shown to improve foetal outcome.

9.3 Treatment of acute hypertension

Nifedipine, labetalol and hydralazine are used. Magnesium sulphate is indicated for severe pre-eclampsia and eclampsia but delivery is the only definitive treatment.

Close maternal and foetal surveillance are essential and prompt delivery is indicated if the condition of either worsens.

Section IX:
Valvular Heart Disease

1. Valvular Heart Disease

Chapter 1
Valvular Heart Disease*
2007

The Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology

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1. Introduction

Valvular heart disease (VHD) is common and often requires intervention. Due to the predominance of degenerative valve disease, the two most frequent valve diseases are now calcific aortic stenosis (AS) and mitral regurgitation (MR), while aortic regurgitation (AR) and mitral stenosis (MS) have become less common. The increase in age of patients with valvular heart disease is associated with a higher frequency of comorbidity, which contributes to increased operative risk and renders decision-making for intervention more complex. Another important aspect of contemporary heart valve disease is the growing proportion of previously operated patients who present with further problems.

The guidelines focus on VHD in adults and adolescents, are oriented towards management, and will not deal with endocarditis and congenital valve diseases in adults and adolescents.

The committee emphasises the fact that many factors ultimately determine the most appropriate treatment in individual patients within a given community. Furthermore, due to the lack of evidence-based data in the field of VHD most recommendations are largely the result of expert consensus opinion. Therefore, deviations from these guidelines may be appropriate in certain clinical circumstances.

Table 1: Recommendation classes and levels of evidence

Class I	Evidence and/or general agreement that a given treatment is beneficial, useful and effective
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a given treatment or procedure
Class IIa	Weight of evidence/opinion is in favour of usefulness/efficacy
Class IIb	Usefulness/efficacy is less well established by evidence/opinion

Level of evidence A	Data derived from multiple randomized clinical trials or meta-analyses
Level of evidence B	Data derived from a single randomized trial or non-randomized studies
Level of evidence C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries

*Adapted from the ESC Guidelines on the Management of Valvular Heart Disease (European Heart Journal 2007;28: 230-268).

J. Bax et al., *Compendium of Abridged ESC Guidelines 2001*

2. Patient evaluation

Clinical evaluation is the first step in the diagnosis of VHD and the assessment of its severity.

Echocardiography is the key technique to confirm the diagnosis of VHD as well as to assess its severity and prognosis.

When assessing the severity of VHD it is necessary to check consistency between the different echocardiographic measurements as well as with the anatomy and mechanisms of VHD. It is also necessary to check their consistency with clinical assessment.

The evaluation of the severity of stenotic VHD should combine the assessment of valve area and flow-dependent indices. AS with a valve area <1.0 cm^2 or <0.6 cm^2/m^2 body surface area (BSA) is considered severe. Severe AS is unlikely if cardiac output is normal, and there is a mean pressure gradient <50 mmHg.

In MS, planimetry, when it is feasible, is the method of choice to evaluate valve area. MS usually does not have clinical consequences at rest when valve area is >1.5 cm^2, unless in patients with particularly large body size. No generally accepted grading of tricuspid stenosis severity exists. A mean gradient >5 mmHg is considered indicative of clinically significant tricuspid stenosis. The quantification of severe regurgitation should not rely entirely on one single figure, but requires an integrative approach (Table 2).

Table 2: Criteria for the definition of severe valve regurgitation: An integrative approach

	AR	MR	TR
Specific signs of severe regurgitation	• Central jet width ≥65% of LVOT* • Vena contracta >0.6 cm*	• Vena contracta width ≥0.7 cm with large central MR jet (area >40% of LA) or with a wall impinging jet of any size, swirling in LA* • Large flow convergence*** • Systolic reversal in pulmonary veins • Prominent flail MV or ruptured papillary muscle	• Vena contracta width >0.7 cm in echo • Large flow convergence*** • Systolic reversal in the hepatic veins
Supportive signs	• Pressure half-time <200 ms • Holodiastolic aortic flow reversal in descending aorta • Moderate or greater LV enlargement**	• Dense, triangular CW Doppler MR jet • E-wave dominant mitral inflow (E >1.2 m/s)**** • Enlarged LV and LA size***** (particularly when normal LV function is present)	• Dense, triangular CW TR signal with early peak • Inferior cava dilatation and respiratory diameter variation <<50% • Prominent transtricuspid E-wave, especially if >1 m/s • RA, RV dilatation
Quantitative parameters			
R Vol (ml/beat)	≥60	≥60	
RF (%)	≥50	≥50	
ERO (cm^2)	≥0.30	≥0.40	

AR = aortic regurgitation, CW = continuous wave, ERO = effective regurgitant orifice area, LA = left atrium, LV = left ventricle, LVOT = left ventricular outflow tract, MR = mitral regurgitation, MV = mitral valve, R Vol = regurgitant volume, RA = right atrium, RF = regurgitant fraction, RV = right ventricle, TR = tricuspid regurgitation

** At a Nyquist limit of 50-60 cm/s.*

*** In the absence of other aetiologies of LV dilatation.*

**** Large flow convergence defined as flow convergence radius ≥0.9 cm for central jets, respectively, with a baseline shift at a Nyquist of 40 cm/s; cut-offs for eccentric jets are higher and should be angled correctly.*

***** Usually above 50 years of age or in conditions of impaired relaxation, in the absence of mitral stenosis or other causes of elevated LA pressure.*

****** In the absence of other aetiologies of LV and LA dilatation and acute MR.*

Adapted from Zoghbi WA, Enriquez-Sarano M, Foster E, et al. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. J Am Soc Echocardiogr 2003;16:777-802.

In MR and MS, transthoracic echocardiography (TTE) provides precise assessment of valve morphology, which is important for the selection of candidates for surgical valve repair and percutaneous mitral commissurotomy (PMC). Echocardiography should include a comprehensive evaluation of all valves, the ascending aorta, and indices of left ventricular (LV) enlargement and function, LV dimensions being indexed to BSA. Transoesophageal echocardiography (TEE) should be considered when TTE is of suboptimal quality or to exclude left atrial thrombosis before PMC or if prosthetic dysfunction or endocarditis is suspected. It should be performed intraoperatively to monitor the results of valve repair or complex procedures. TTE also plays an important role in monitoring the results of PMC during the procedure.

Exercise testing is useful to unmask the objective occurrence of symptoms in patients who claim to be asymptomatic. Exercise testing is recommended in truly asymptomatic patients with AS provided it is performed under close monitoring.

Low-dose dobutamine stress echocardiography is useful in AS with impaired LV function to distinguish the rare cases of pseudo-severe AS from truly severe AS. In addition this test may detect the presence of contractile reserve (increase > 20% of stroke volume). The use of stress tests to detect coronary artery disease associated with severe VHD is discouraged because of their low diagnostic value.

In expert centres **multislice computed tomography** can be useful to exclude coronary artery disease in patients who are at low risk of atherosclerosis.

At present, **magnetic resonance imaging** is not indicated in VHD in routine clinical practice; however, it can be used as an alternative technique when echocardiography is not feasible.

Coronary angiography is widely indicated to detect associated coronary artery disease when surgery is planned (Table 3). It can be omitted in patients with acute aortic dissection, large aortic vegetation, or occlusive prosthetic thrombosis leading to an unstable haemodynamic condition.

The performance of **cardiac catheterization** should be restricted to situations where non-invasive evaluation is inconclusive or discordant with clinical findings.

The **assessment of comorbidity** is directed by the clinical evaluation.

Endocarditis prophylaxis should be considered in any patient with VHD, and adapted to the individual patient risk.

The decision to intervene in a patient with VHD relies on an **individual risk-benefit analysis**. Multivariate scores, such as the Euroscore (http://www.euroscore.org/calc.html), are useful in this setting. Decision-making should also take into account the patient's life expectancy, quality of life, as well as local resources and very importantly, the decision of the informed patient. In the elderly, age, *per se*, should not be considered a contra-indication for surgery.

3. Indications for treatment in native valve diseases

3.1 Aortic regurgitation

Indications for surgery

In chronic AR, the goals of the operation are to avoid left ventricular systolic dysfunction and/or aortic complications (Table 4).

Table 3: Indications for coronary angiography in patients with valvular heart disease

	Class
Before valve surgery in patients with severe valvular heart disease and any of the following: • history of coronary artery disease • suspected myocardial ischaemia* • left ventricular systolic dysfunction • in men aged over 40 and post-menopausal women • ≥1 cardiovascular risk factor	IC
When coronary artery disease is suspected to be the cause of severe mitral regurgitation (ischaemic mitral regurgitation)	IC

* Chest pain, abnormal non-invasive testing.

Table 4: Indications for surgery in aortic regurgitation

	Class
Severe AR	
Symptomatic patients (dyspnoea NYHA class II, III, IV or angina)	IB
Asymptomatic patients with resting LVEF ≤50%	IB
Patients undergoing CABG or surgery of ascending aorta, or on another valve	IC
Asymptomatic patients with resting LVEF >50% with severe LV dilatation: End diastolic dimension >70 mm or End systolic dimension >50 mm (or >25 mm/m^2 BSA)*	 IIaC IIaC
Whatever the severity of AR	
Patients who have aortic root disease with maximal aortic diameter**: ≥45 mm for patients with Marfan's syndrome ≥50 mm for patients with bicuspid valves ≥55 mm for other patients	 IC IIaC IIaC

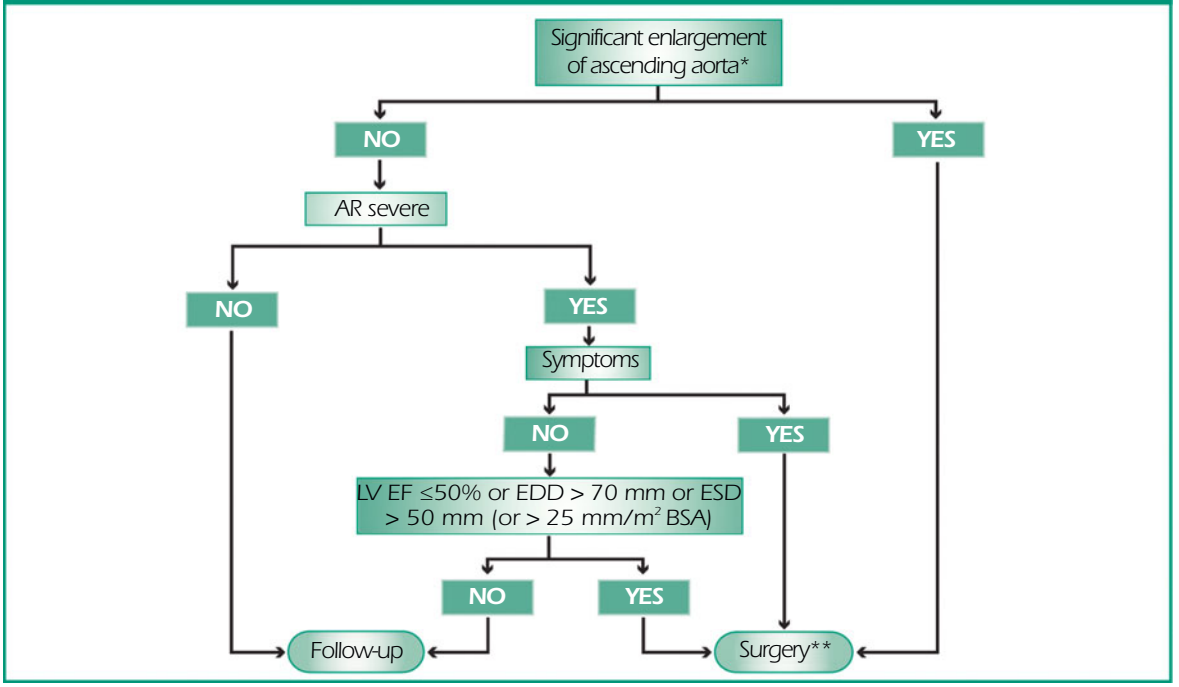
Severity is defined from clinical and echocardiographic assessment.

In asymptomatic patients repeated and high quality measures are necessary before surgery.

** Patient's stature should also be considered. Indexing is helpful. Changes in sequential measurements should be taken into account. ** Decision should take into account the shape and thickness of ascending aorta as well as the shape of the other parts of aorta. For patients who have an indication for surgery on the aortic valve, lower thresholds can be used for combining surgery on the ascending aorta.*

AR = aortic regurgitation, BSA = body surface area, CABG = coronary artery bypass grafting, LV = left ventricular, EF = ejection fraction

Figure 1: Management of aortic regurgitation



AR = aortic regurgitation, LV = left ventricle, EF = ejection fraction, EDD = end-diastolic dimension, ESD = end-systolic dimension, BSA = body surface area

** See Table 4 for definitions.*

*** Surgery must also be considered if significant changes occur during follow-up.*

Medical therapy

The role of vasodilators in asymptomatic patients without hypertension or congestive heart failure is unproven. In patients with Marfan's syndrome beta-blockers should be given before and after the operation.

3.2 Aortic stenosis

Indications for surgery

Early valve replacement should be strongly considered in all symptomatic patients with severe AS who are otherwise candidates for surgery. As long as mean gradient is still >40 mmHg, there is virtually no lower EF limit for surgery. The management of patients with low-flow, low-gradient AS (severely reduced EF and mean gradient <40 mmHg) is more controversial. Surgery is advised in patients with evidence of contractile reserve. Conversely, in patients without contractile reserve surgery can, nonetheless, be performed but decision-making should take into account clinical condition, and feasibility of revascularization.

Balloon valvuloplasty

This can be considered as a bridge to surgery in haemodynamically unstable patients who are at high risk for surgery (*Recommendation class IIb level of fibrillation C*), or in patients with symptomatic severe AS who require urgent major non-cardiac surgery (*Recommendation class IIb level of evidence C*).

Medical therapy

Modification of atherosclerotic risk factors must be strongly recommended following the guidelines of secondary prevention in atherosclerosis.

Serial testing

Patients should be carefully educated about the importance of follow-up and reporting symptoms as soon as they develop.

In cases of moderate to severe calcification of the valve and peak aortic jet velocity >4 m/s at initial evaluation patients should be re-evaluated every 6 months for the occurrence of symptoms, change in exercise tolerance or in echo-parameters. If peak aortic jet velocity has increased since the last visit (>0.3 m/s per year), surgery should be considered. If no change has occurred and the patient remains asymptomatic, 6 monthly clinical and 6-12 monthly clinical and echocardiographic re-evaluations are recommended.

In patients who do not meet these criteria, a clinical yearly follow-up is necessary, follow-up being closer in those with borderline values.

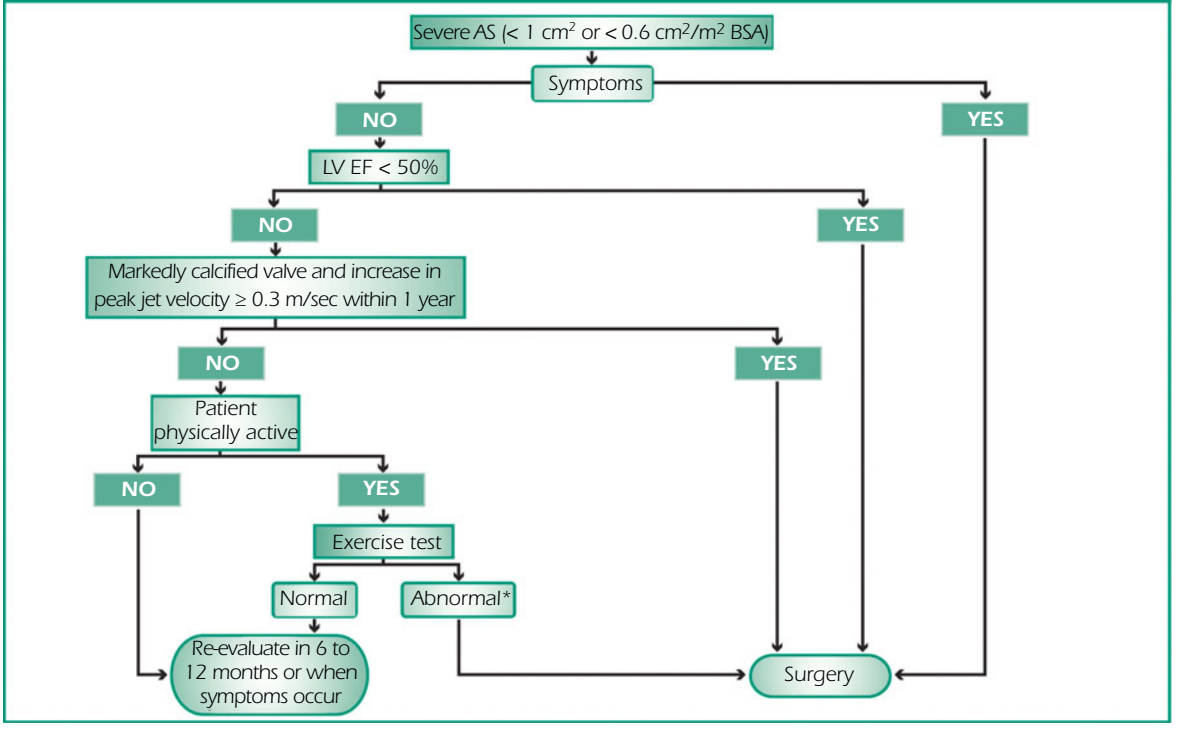
Table 5: Indications for aortic valve replacement in aortic stenosis

	Class
Patients with severe AS and any symptoms	IB
Patients with severe AS undergoing coronary artery bypass surgery, surgery of the ascending aorta, or on another valve	IC
Asymptomatic patients with severe AS and systolic LV dysfunction (LVEF <50%) unless due to other cause	IC
Asymptomatic patients with severe AS and abnormal exercise test showing symptoms on exercise	IC
Asymptomatic patients with severe AS and abnormal exercise test showing fall in blood pressure below baseline	IIaC
Patients with moderate AS* undergoing coronary artery bypass surgery, surgery of the ascending aorta or another valve	IIaC
Asymptomatic patients with severe AS and moderate to severe valve calcification, and a rate of peak velocity progression ≥0.3 m/sec per year	IIaC
AS with low gradient (<40 mmHg) and LV dysfunction with contractile reserve	IIaC
Asymptomatic patients with severe AS and abnormal exercise test showing complex ventricular arrhythmias	IIbC
Asymptomatic patients with severe AS and excessive LV hypertrophy (≥15 mm) unless this is due to hypertension	IIbC
AS with low gradient (<40 mmHg) and LV dysfunction without contractile reserve	IIbC

* Moderate AS is defined as valve area 1.0 to 1.5 cm^2 (0.6 cm^2/m^2 to 0.9 cm^2/m^2 BSA) or mean aortic gradient 30 to 50 mmHg in the presence of normal flow conditions. However, clinical judgment is required.

AS = aortic stenosis, LV = left ventricular, EF = ejection fraction, BSA = body surface area

Figure 2: Management of severe aortic stenosis



AS = aortic stenosis, LV = left ventricle, EF = ejection fraction, BSA = body surface area

* See Table 5 for definitions.

Note: The management of patients with low gradient and low ejection fraction is detailed in the text.

3.3 Mitral regurgitation

Organic mitral regurgitation

Organic MR covers all aetiologies in which leaflet abnormality is the primary cause of the disease, in opposition to ischaemic and functional MR, in which MR is the consequence of LV disease.

Indications for surgery

Valve repair, when feasible and durable results can be expected, is the optimal surgical treatment in patients with severe MR.

Table 6: Indications for surgery in severe chronic organic mitral regurgitation

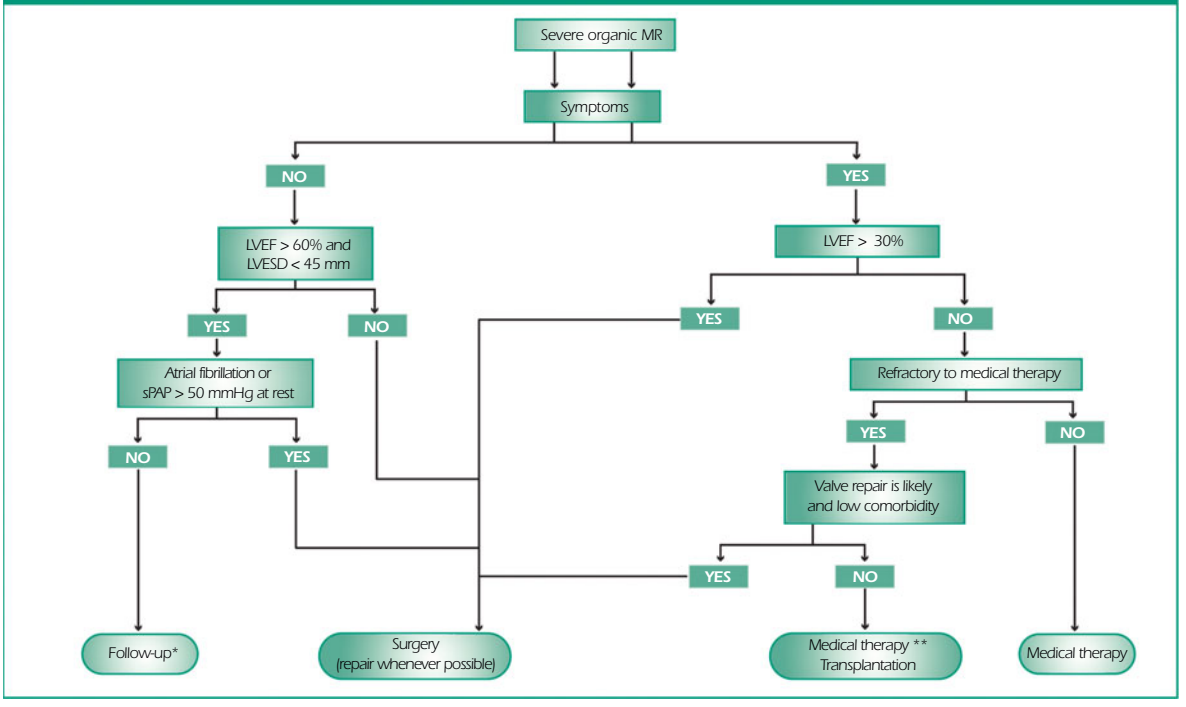
	Class
Symptomatic patients with LVEF >30% and ESD <55 mm*	IB
Asymptomatic patients with LV dysfunction (ESD >45 mm* and/or LVEF ≤60%)	IC
Asymptomatic patients with preserved LV function and atrial fibrillation or pulmonary hypertension (systolic pulmonary artery pressure >50 mmHg at rest)	IIaC
Patients with severe LV dysfunction (LVEF <30% and/or ESD >55 mm*) refractory to medical therapy with high likelihood of durable repair and low comorbidity	IIaC
Asymptomatic patients with preserved LV function, high likelihood of durable repair, and low risk for surgery	IIbB
Patients with severe LV dysfunction (LVEF <30% and/or ESD >55 mm*) refractory to medical therapy with low likelihood of repair and low comorbidity	IIbC

Severity is based on clinical and echocardiographic assessment.

* Lower values can be considered for patients of small stature.

ESD = end systolic dimension, EF = ejection fraction, LV = left ventricular

Figure 3 : Management of severe chronic organic mitral regurgitation



LV = left ventricle, EF = ejection fraction, sPAP = systolic pulmonary artery pressure, ESD = end-systolic dimension

* Valve repair can be considered when there is a high likelihood of durable valve repair at a low risk.

** Valve replacement can be considered in selected patients with low comorbidity.

The management of asymptomatic patients is an area of controversy where the indications for surgery depend on risk stratification, the possibility of valve repair, and the preference of the informed patient.

Medical therapy

Anticoagulant therapy, with a target International Normalised Ratio (INR) range between 2 and 3, should be given in patients with MR and permanent or paroxysmal atrial fibrillation or whenever there is a history of systemic embolism or evidence of left atrial thrombus, and during the first 3 months following mitral valve repair. Vaso-dilators, including ACE-inhibitors, are not recommended in patients with chronic MR without heart failure or hypertension.

Serial testing

Asymptomatic patients with moderate MR and preserved LV function can be clinically followed-up on a yearly basis and echocardiography should be performed every 2 years.

Asymptomatic patients with severe MR and preserved LV function should be seen every 6 months and echocardiography performed every year, the follow-up being closer if no previous evaluation is available, and in patients with borderline values, or significant changes since the last visit.

Ischaemic mitral regurgitation

Ischaemic MR is common, however, it is frequently overlooked in the setting of acute or chronic coronary disease.

Indications for surgery

The limited data in the field of ischaemic MR results in less evidence-based management.

Functional mitral regurgitation

This includes MR observed in cardiomyopathy and in ischaemic disease with severe LV dysfunction. Isolated mitral valve surgery in combination with LV reconstruction techniques, may be considered in selected patients with severe functional MR and severely depressed LV function, including those with coronary disease where bypass surgery is not indicated, who remain symptomatic despite optimal medical therapy, and if comorbidity is low, the aim being to avoid, or postpone transplantation.

Table 7: Indications for surgery in chronic ischaemic mitral regurgitation

	Class
Patients with severe MR, LVEF >30%, undergoing CABG	IC
Patients with moderate MR undergoing CABG if repair is feasible	IIaC
Symptomatic patients with severe MR, LVEF <30% and option for revascularization	IIaC
Patients with severe MR, LVEF >30%, no option for revascularization, refractory to medical therapy, and low comorbidity	IIbC

CABG = coronary artery bypass grafting, MR = mitral regurgitation, EF = ejection fraction, LV = left ventricular

Medical therapy is the preferred treatment which should be used before considering surgical correction of functional MR. ACE-inhibitors and beta-blockers are indicated. Nitrates and diuretics are also useful.

Resynchronization therapy and implantable cardioverter defibrillators should be used according to the appropriate recommendations.

3.4 Mitral stenosis

Indications for intervention

Intervention should be performed in symptomatic patients. In the PMC era, most symptomatic patients with favourable valve anatomy undergo PMC. Indications are a matter of debate for patients with unfavourable anatomy

Table 8: Indications for percutaneous mitral commissurotomy in mitral stenosis with valve area < 1.5 cm^2

	Class
Symptomatic patients with favourable characteristics* for PMC	IB
Symptomatic patients with contra-indications or high risk for surgery	IC
As initial treatment in symptomatic patients with unfavourable anatomy but otherwise favourable clinical characteristics*	IIaC
Asymptomatic patients with favourable characteristics* and high thromboembolic risk or high risk of haemodynamic decompensation:	
• previous history of embolism	IIaC
• dense spontaneous contrast in the left atrium	IIaC
• recent or paroxysmal atrial fibrillation	IIaC
• systolic pulmonary pressure >50 mmHg at rest	IIaC
• need for major non-cardiac surgery	IIaC
• desire of pregnancy	IIaC

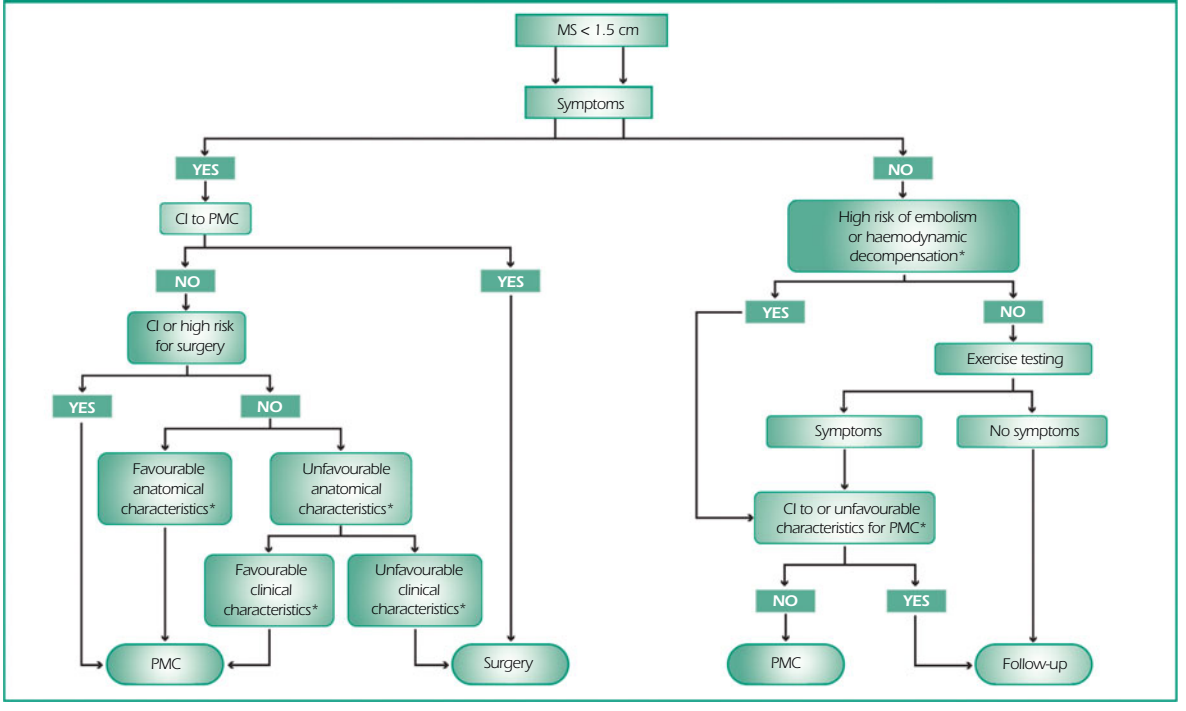
PMC = percutaneous mitral commissurotomy

* Favourable characteristics for PMC can be defined by the absence of several of the following unfavourable characteristics:
• Clinical characteristics: old age, history of commissurotomy, NYHA class IV, atrial fibrillation, severe pulmonary hypertension.
• Anatomic characteristics: echo score > 8, Cormier score 3 (Calcification of mitral valve of any extent, as assessed by fluoroscopy), very small mitral valve area, severe tricuspid regurgitation.

Table 9: Contra-indications to percutaneous mitral commissurotomy

• Mitral valve area >1.5 cm^2
• Left atrial thrombus
• More than mild mitral regurgitation
• Severe or bicommissural calcification
• Absence of commissural fusion
• Severe concomitant aortic valve disease, or severe combined tricuspid stenosis and regurgitation
• Concomitant coronary artery disease requiring bypass surgery

Figure 4: Management of severe mitral stenosis



MS = mitral stenosis, CI = contra-indication, PMC = percutaneous mitral commissurotomy

* See Table 8 for definitions.

where decision-making must take into account the multifactorial nature of result prediction of PMC and the relative experience in PMC and surgery of the treating centre.

Because of the small but definite risk inherent in PMC, truly asymptomatic patients are not usually candidates for the procedure, except in the cases where there is increased risk of thromboembolism, or of haemodynamic decompensation such as severe pulmonary hypertension or a desire of pregnancy. In such patients, PMC should only be performed if they have favourable characteristics and by experienced operators. In asymptomatic patients with MS, surgery is very seldom considered and is limited to the rare patients at high risk of complication and with contra-indications for PMC.

Medical therapy

Diuretics, beta-blockers or heart-rate regulating calcium channel blockers are useful. Anticoagulant therapy with a target INR in the upper half of the range 2 to 3 is indicated in patients with either permanent or paroxysmal atrial fibrillation. In patients in sinus rhythm anti-coagulation is mandatory when there has been prior embolism or a thrombus is present in the left atrium (*Recommendation class I level of evidence C*), and recommended when TEE shows dense spontaneous echo contrast or in patients who have an enlarged left atrium (diameter >50 mm) (*Recommendation class IIa level of evidence C*).

Cardioversion is not indicated before intervention in patients with severe MS as it does not usually restore sinus rhythm in the medium- or long-term. If atrial fibrillation is of recent onset and the left atrium only moderately enlarged, cardioversion should be performed soon after successful intervention.

Serial testing

Asymptomatic patients with clinically significant MS who have not undergone intervention should be followed up yearly, by means of clinical and echocardiographic examinations and at longer intervals in cases with stenosis of a lesser degree.

Special patient populations

When PMC is not successful and symptoms persist, surgery should be considered early unless there are definite contra-indications. When re-stenosis with symptoms occurs after surgical commissurotomy PMC can be considered if the patient has favourable characteristics and no contra-indications and if the predominant mechanism of re-stenosis is commissural re-fusion. Similarly, repeat PMC can be proposed in selected

Table 10: Indications for intervention in tricuspid valve disease

	Class
Severe TR in a patient undergoing left-sided valve surgery	IC
Severe primary TR and symptoms despite medical therapy without severe right ventricular dysfunction	IC
Severe TS (± TR), with symptoms despite medical therapy*	IC
Severe TS (± TR) in a patient undergoing left-sided valve intervention*	IC
Moderate organic TR in a patient undergoing left-sided valve surgery	IIaC
Moderate secondary TR with dilated annulus (>40 mm) in a patient undergoing left-sided valve surgery	IIaC
Severe TR and symptoms, after left-sided valve surgery, in the absence of left-sided myocardial, valve, or right ventricular dysfunction and without severe pulmonary hypertension (systolic pulmonary artery pressure > 60 mmHg)	IIaC
Severe isolated TR with mild or no symptoms and progessive dilation or deterioration of right ventricular function	IIbC

* Percutaneous technique can be attempted as a first approach if TS is isolated.

TR = tricuspid regurgitation, TS = tricuspid stenosis

patients with the same characteristics as above if re-stenosis occurs several years after an initially successful PMC. In patients with MS combined with moderate aortic valve disease PMC can be performed as a means of postponing the surgical treatment of both valves.

3.5 Tricuspid valve diseases

Detection requires careful evaluation, as it is almost always associated with left-sided valve lesions that dominate the presentation.

Indications for surgery

If technically possible, conservative surgery is preferable to valve replacement, for which bioprostheses are preferred. Surgery should be carried out early enough to avoid irreversible right ventricular dysfunction.

4. Prosthetic valves

4.1 Choice of prosthetic valve

There is no perfect valve substitute. All involve some compromise and all introduce new disease processes, whether they are mechanical or biological. The decision should be based on the integration of several factors (Table 11).

4.2 Management after valve replacement

Baseline assessment and modalities of follow-up

A complete baseline assessment should ideally be performed 6 to 12 weeks after surgery, or failing that at the end of the postoperative stay. This will include clinical assessment, chest X-ray, ECG, TTE, and blood testing.

Table 11: Choice of the prosthesis: In favour of mechanical prosthesis

	Class
Desire of the informed patient and absence of contra-indication for long-term anti-coagulation	IC
Patients at risk of accelerated structural valve deterioration*	IC
Patients already on anti-coagulation because of other mechanical prosthesis	IC
Patients already on anti-coagulation because at high risk for thromboembolism**	IIaC
Age <65-70 and long life expectancy***	IIaC
Patients for whom future redo valve surgery would be at high risk (due to left ventricular dysfunction, previous CABG, multiple valve prosthesis)	IIaC

* Young age, hyperparathyroidism.

** Risk factors for thromboembolism: severe left ventricular dysfunction, atial fibrillation, previous thrombo embolism, hypercoagulable state.

*** According to age, gender, the presence of comorbidity, and country-specific life expectancy.

CABG = coronary artery bypass grafting

Table 12: Choice of the prosthesis: In favour of bioprosthesis

	Class
Desire of the informed patient	IC
Unavailability of good quality anti-coagulation (contra-indication or high risk, unwillingness, compliance problems, life style, occupation)	IC
Re-operation for mechanical valve thrombosis in a patient with proven poor anticoagulant control	IC
Patient for whom future redo valve surgery would be at low risk	IIaC
Limited life expectancy*, severe comorbidity, or age >65-70	IIaC
Young woman contemplating pregnancy	IIbC

* According to age, gender, the presence of comorbidity, and country-specific life expectancy.

Clinical assessment should be performed yearly or as soon as possible if new cardiac symptoms occur. TTE should be performed if any new symptoms occur after valve replacement or if complications are suspected. Yearly echocardiographic examination is recommended after the 5th year in patients with bioprosthesis. Transprosthetic gradients during follow-up are best interpreted in comparison to the patient's baseline values, rather than in comparison to theoretical values for a given prosthesis.

TEE should be considered if TTE is of poor quality and in all cases of suspected prosthetic dysfunction or endocarditis. Cinefluoroscopy can provide useful additional information if valve thrombus or pannus is suspected.

Antithrombotic management

Oral anti-coagulation is recommended for the following situations:

- lifelong for all patients with mechanical valves and for patients with bioprostheses who have other indications for anti-coagulation,
- for the first 3 months after insertion in all patients with bioprostheses with a target INR of 2.5.

Target INR

The choice of optimum INR should take into account patient risk factors and the thrombogenicity of the prosthesis (Table 13).

Antiplatelet drugs

Indications for the addition of an antiplatelet agent to anti-coagulation include concomitant arterial disease, in particular coronary disease and other significant atherosclerotic disease. Antiplatelet agents can also be added after recurrent or one definite embolic episode with adequate INR.

Addition of antiplatelet agents should be associated with a full investigation and treatment of identified risk factors and optimisation of anti-coagulation management (*Recommendation class IIa level of evidence C*). The use of drug-eluting stents should be restricted in patients with mechanical prostheses to shorten as much as possible the use of triple antithrombotic therapy. During this period, weekly monitoring of INR is advised.

Table 13: Target International Normalised Ratio (INR) for mechanical prostheses

	Patient-related risk factors**	
Prosthesis thrombogenicity*	**No risk factor**	**≥1 risk factor**
Low	2.5	3.0
Medium	3.0	3.5
High	3.5	4.0

* Prosthesis thrombogenicity: Low = Carbomedics (aortic position), Medtronic Hall, St. Jude Medical (without Silzone); Medium = Bjork-Shiley, other bileaflet valves; High = Lillehei-Kaster, Omniscience, Starr-Edwards

** Patient-related risk factors: • mitral, tricuspid, or pulmonary valve replacement; • previous thromboembolism; • atrial fibrillation; • left atrial diameter >50 mm; • left atrial dense spontaneous contrast; • mitral stenosis of any degree; • left ventricular ejection fraction < 35%; • hypercoagulable state

Interruption of anticoagulant therapy

Anti-coagulation during subsequent non-cardiac surgery requires very careful management based on risk assessment according to prosthesis- and patient-related prothrombotic factors (Table 13). For very high-risk patients, anticoagulation interruption should be avoided, if at all possible. Many minor surgical procedures (including dental extraction) and those where bleeding is easily controlled do not require anti-coagulation interruption. The INR should be lowered to a target of 2 (*Recommendation class I level of evidence B*).

For major surgical procedures, in which anticoagulant interruption is considered essential (INR <1.5), patients should be admitted to hospital in advance and transferred to intravenous unfractionated heparin (*Recommendation class IIa level of evidence C*).

Heparin is stopped 6 hours before surgery and resumed 6-12 hours after. Low molecular weight heparin (LMWH) can be given subcutaneously as an alternative preoperative preparation for surgery (*Recommendation class IIb level of evidence C*).

When LMWHs are used, they should be administered twice-a-day using therapeutic rather than prophylactic doses, adapted to body weight and if possible according to monitoring of anti-Xa activity. Effective anti-coagulation should be resumed as soon as possible after the surgical procedure and maintained until the INR is once again in the therapeutic range.

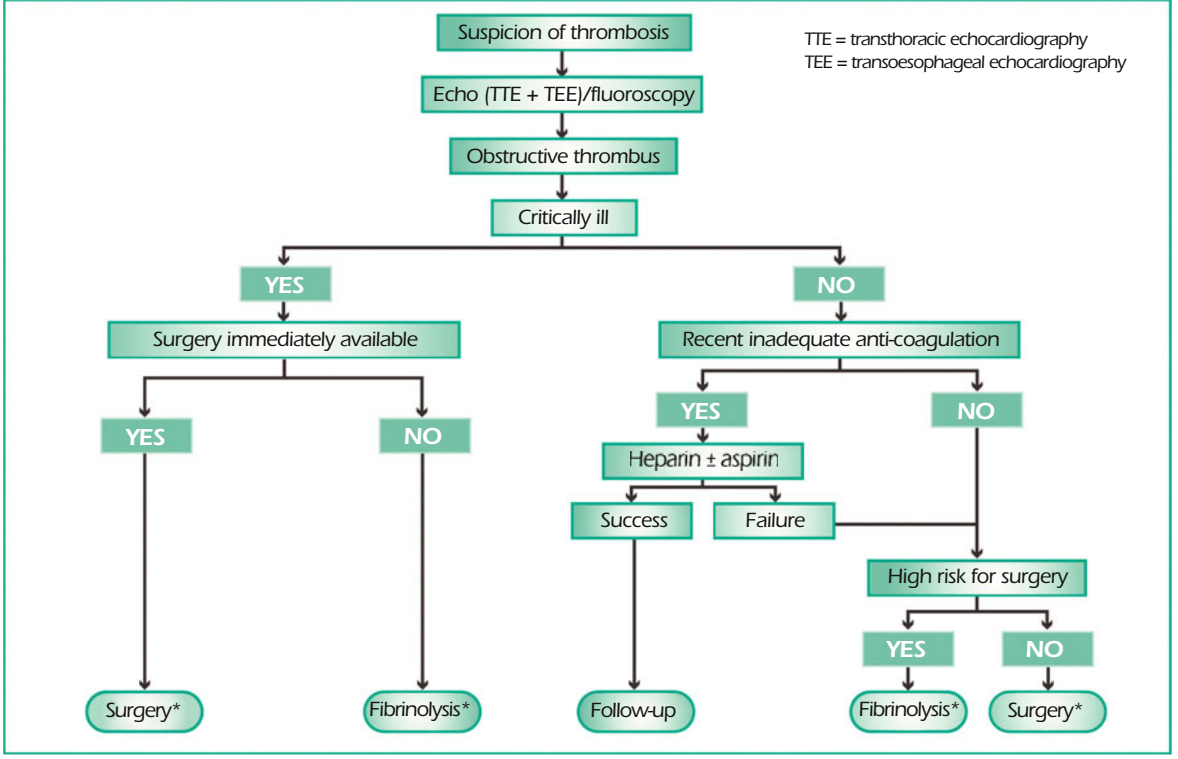
Management of valve thrombosis

Obstructive valve thrombosis should be promptly suspected in any patient with any type of prosthetic valve who presents with a recent increase in shortness of breath or embolic event. The analysis of risk and benefits of fibrinolysis should be adapted to patient characteristics and local resources (Figure 5).

Urgent or emergency valve replacement is the treatment of choice for obstructive thrombosis in critically ill patients without serious comorbidity, (*Recommendation class I level of evidence C*). Fibrinolysis should be considered in:

- critically ill patients unlikely to survive surgery,
- situations in which surgery is not immediately available on site,
- thrombosis of tricuspid or pulmonary valve replacement.

Figure 5: Management of left-sided obstructive prosthetic thrombosis



* Risk and benefits of both treatments should be individualised. The presence of a first-generation prosthesis is an incentive to surgery.

The management of patients with *non-obstructive prosthetic thrombosis* depends mainly on the occurrence of a thromboembolic event and the size of the thrombosis. Close monitoring by echocardiography and/or cinefluoroscopy is mandatory. The prognosis is favourable with medical therapy in most cases of small thrombosis (length <10 mm). A good response with gradual resolution of the thrombus obviates the need for either surgery or fibrinolysis. Conversely, surgery is recommended for large (>10 mm) non-obstructive prosthetic thrombosis complicated by embolism (*Recommendation class IIa level of evidence C*) or which persist despite optimal anti-coagulation. Fibrinolysis may be considered as an alternative if surgery is high risk. However, the use of fibrinolysis for non-obstructive prosthetic thrombosis raises serious concerns regarding the risk of bleeding and thromboembolism and should therefore be very limited.

Thorough investigation of each episode of thromboembolism is essential to allow for appropriate management. Prevention of further thromboembolic events involves: treatment or reversal of remediable risk factors, and optimisation of anticoagulation control, if possible with patient self-management. Aspirin should be added, at a low dose formulation (≥100 mg daily), if not previously prescribed.

Management of haemolysis and paravalvular leak (PVL)

Re-operation is advised if PVL is related to endocarditis or if PVL causes haemolysis needing repeated blood transfusions or leading to severe symptoms (*Recommendation class I level of evidence C*). In patients where surgery is contraindicated, medical therapy includes iron supplementation, beta-blockers and erythropoietin, if haemolysis is severe.

Management of bioprosthetic failure

Re-operation is advised in symptomatic patients with significant prosthetic dysfunction (significant increase in trans-prosthetic gradient or severe regurgitation) (*Recommendation class I level of evidence C*) and in asymptomatic patients with any significant prosthetic dysfunction, if they are at low risk for re-operation (*Recommendation class IIa level of evidence C*).

Prophylactic replacement of a bioprosthesis implanted > 10 years ago, without structural deterioration, could be considered during an intervention on another valve or coronary artery.

Heart failure

Heart failure after valve surgery should lead to a search for prosthetic-related complications, deterioration of repair, LV dysfunction (in particular after correction of regurgitation), or progression of another valve disease. Non-valvular related causes such as coronary disease, hypertension or sustained arrhythmias should also be considered.

5. Management during non-cardiac surgery

Before non-cardiac surgery, severe VHD should be identified and the clinical status of the patient carefully evaluated and agreement reached after a full discussion with cardiologists, anaesthesiologists, ideally with a particular skill in cardiology, and surgeons. The management of patients with *AS* is as indicated in Figure 6.

In asymptomatic patients with significant *MS* and a systolic pulmonary artery pressure <50 mmHg non-cardiac surgery can be performed at low risk. In symptomatic patients or in patients with systolic pulmonary artery pressure >50 mmHg correction of MS, by means of PMC whenever possible, should be attempted before non-cardiac surgery. In asymptomatic patients with severe *MR* or *AR*, and preserved LV function, non-cardiac surgery can be performed at low risk. In symptomatic patients or in patients with depressed LV function (EF < 30%) non-cardiac surgery should only be performed if strictly needed.

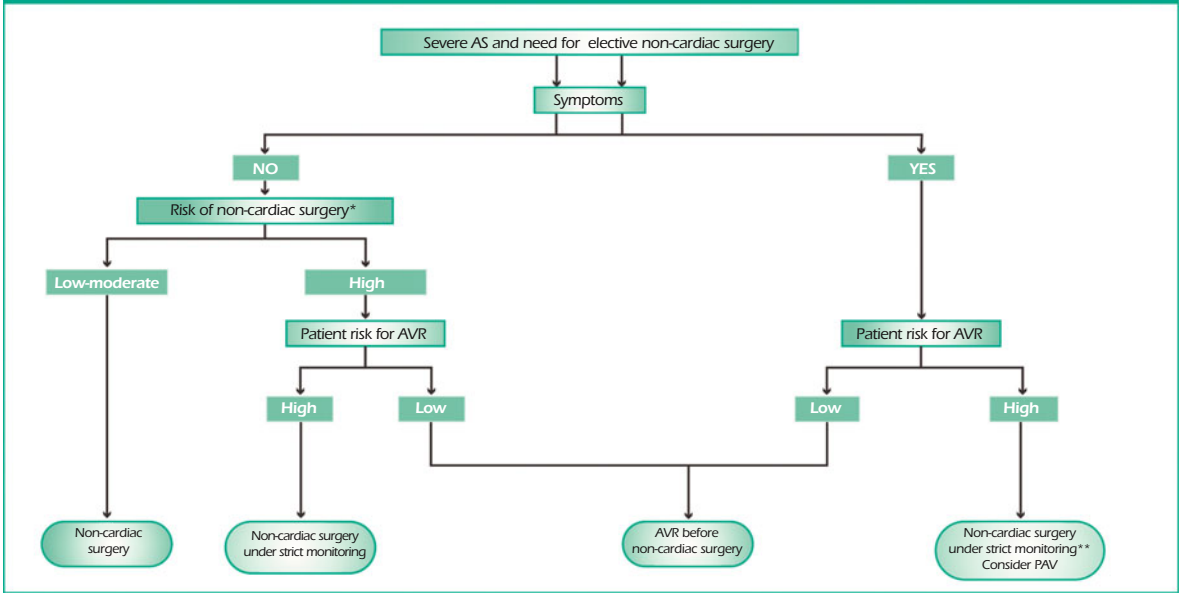
6. Management during pregnancy

Ideally, valve disease should be evaluated before pregnancy and treated if necessary.

Echocardiographic examination should be performed in any pregnant patient presenting with a more than trivial heart murmur, dyspnoea, or who has a prosthetic valve.

When the first visit occurs during pregnancy, early termination may be considered in the following situations: severe LV dysfunction (EF <40%); Marfan's syndrome with aneurysm of ascending aorta >40 mm; or severe symptomatic stenotic valve disease, which cannot be treated using percutaneous procedures. During pregnancy, clinical and echocardiographic follow-up should be performed at 3 and 5 months, and every month thereafter in pregnant patients with severe valve stenosis. Symptomatic *MS* should be treated using bed rest, beta-blockers, possibly associated with diuretics. Beta-agonist agents are contra-indicated. PMC should be considered in patients with severe symptoms or pulmonary artery systolic pressure > 50 mmHg despite medical therapy. In patients with severe *AS* who remain symptomatic despite diuretics, balloon aortic valvuloplasty

Figure 6: Severe aortic stenosis and elective non-cardiac surgery



AS = aortic stenosis, AVR = aortic valve replacement, PAV = percutaneous aortic valvuloplasty

* Assessment of the risk of cardiac complications for non-cardiac surgery (from Eagle KA et al. Guideline Update for Perioperative Cardiovascular Evaluation for Non-cardiac Surgery—Executive Summary: a report of the ACC/AHA. J Am Coll Cardiol 2002;39:542–553).

** Non-cardiac surgery performed only if strictly needed.

• High risk (>5%): Emergent major operations, particularly in the elderly; Aortic and other major vascular surgery; Peripheral vascular surgery; Anticipated prolonged surgical procedures associated with large fluid shifts and /or blood loss

• Intermediate risk (1 to 5%): Carotid endarterectomy; Head and neck surgery; Intraperitoneal and intrathoracic surgery; Orthopedic surgery; Prostate surgery

• Low risk (< 1%): Endoscopic procedures; -Superficial procedure; Cataract surgery; Breast surgery

can be considered during pregnancy. Patients with *AR* or *MR* who become symptomatic should be treated medically using diuretics and vasodilators avoiding ACE-inhibitors and angiotensin receptors blockers. In most cases, surgery can be postponed until the postoperative period. Beta-blockers should be used throughout pregnancy in patients with *Marfan's syndrome* to avoid aortic dissection.

In patients with a *mechanical prosthesis*, vitamin K antagonists are favoured during the second and third trimester until the 36th week when they are replaced by unfractionated heparin. During the first trimester, the choice should take into account patient wishes after information, adherence to treatment, and the possibility to use low-dose warfarin which is the safest regimen for the mother. The use of warfarin throughout pregnancy until the 36th week is recommended when warfarin dose is <5 mg/day during the first trimester. The use of LMWH cannot be recommended based on the information currently available.

Surgery under extracorporeal circulation should be performed during pregnancy only in situations that threaten the mother's life and are not amenable to percutaneous treatment. If valve replacement is necessary during pregnancy a bioprosthesis is the preferred valve substitute.

The mode of delivery should be discussed and planned by cardiologists, obstetricians, anaesthetists and the patient before delivery, even more so for the patients who need to interrupt oral anti-coagulation. Caesarean section is considered in patients who have Marfan's syndrome with an aortic diameter > 40 mm, those in whom haemodynamic conditions are unstable, in particular in the presence of AS, or in case of premature delivery under oral anti-coagulation.

Vaginal delivery is recommended whenever possible in the other cases. Haemodynamic monitoring is recommended in women with severe MS, AS, or LV dysfunction.

When valvular surgery is required during pregnancy, Caesarean section should be performed first if the foetus is viable.

Section X:
Infective Endocarditis

1. Prevention, Diagnosis and Treatment of Infective Endocarditis

Chapter 1
Infective Endocarditis*
2009

The Task Force on the Prevention, Diagnosis and Treatment of Infective Endocarditis of the European Society of Cardiology (ESC), endorsed by the European Society of Clinical Microbiology, Infectious Diseases (ESCMID) and by the International Society of Chemotherapy (ISC) for Infection and Cancer

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1. Introduction

Infective endocarditis (IE) is a severe form of valve disease still associated with a poor prognosis and high mortality, despite major advances in both diagnostic and therapeutic procedures. IE is a rare disease, with reported incidences ranging from 3 to 10 episodes/100,000 people per year.

The epidemiological profile of IE has changed over the past few years. Once a disease affecting young adults with previously well-identified (mostly rheumatic) valve disease, IE is now affecting older patients. Newer predisposing factors have emerged - valve prostheses, degenerative valve sclerosis, intravenous drug abuse (IVDA), associated with the increased use of invasive procedures at risk for bacteraemia, resulting in health care-associated IE, which represents up to 30% cases of IE. This trend is associated with an increased incidence of staphylococci and a decrease in oral streptococci as a cause of IE.

Optimal management of IE requires a multidisciplinary approach including cardiologists, infectious disease specialists, and frequently other specialists, as well as the early involvement of a cardiac surgeon.

*Adapted from the ESC Guidelines on the Prevention, Diagnosis and Treatment of Infective Endocarditis (new version 2009) (European Heart journal 2009;30:2369-2413. doi:10.1093/eurheartj/ehp285).

2. Classification, definitions

Classification and definitions of infective endocarditis
IE according to localisation of infection and presence or absence of intracardiac material • Left-sided native valve IE • Left-sided prosthetic valve IE (PVE) - Early PVE: < 1 year after valve surgery - Late PVE: > 1 year after valve surgery • Right-sided IE • Device-related IE (permanent pacemaker or cardioverter-defibrillator)
IE according to the mode of acquisition • Health care-associated IE - Nosocomial: IE developing in a patient hospitalised > 48 hours prior to the onset of signs / symptoms consistent with IE - Non nosocomial: Signs and / or symptoms of IE starting < 48 hours after admission in a patient with health care contact defined as: 1) home-based nursing or intravenous therapy, haemodialysis or intravenous chemotherapy < 30 days before the onset of IE; or 2) hospitalised in an acute care facility < 90 days before the onset of IE; or 3) resident in a nursing home or long-term care facility • Community-acquired IE: Signs and / or symptoms of IE starting < 48 hours after admission in a patient not fulfilling the criteria for health care-associated infection • Intravenous drug abuse-associated IE: IE in an active injection drug user without alternative source of infection
Active IE • IE with persistent fever and positive blood cultures *or* • Active inflammatory morphology found at surgery *or* • Patient still under antibiotic therapy *or* • Histopathological evidence of active IE
Recurrence • Relapse: Repeat episodes of IE caused by the same microorganism < 6 months after the initial episode • Reinfection: Infection with a different microorganism Repeat episode of IE caused by the same microorganism > 6 months after the initial episode

3. Preventive measures

The indications for antibiotic prophylaxis for IE are reduced in comparison with previous recommendations.

Main changes in IE prevention recommendations
1. The principle of antibiotic prophylaxis when performing procedures at risk of IE in patients with predisposing cardiac conditions is maintained, **but**
2. Antibiotic prophylaxis must be limited to patients with **the highest risk of IE** undergoing **the highest risk dental procedures**.
3. Good oral hygiene and regular dental review are more important than antibiotic prophylaxis to reduce the risk of IE.
4. Aseptic measures are mandatory during venous catheter manipulation and during any invasive procedures in order to reduce the rate of health care-associated IE.
5. Whether the reduced use of prophylaxis is associated with a change in the incidence of IE must be evaluated by prospective epidemiological studies.

Recommended prophylaxis for dental procedures at risk			
		Single dose 30-60 minutes before procedure	
Situation	**Antibiotic**	**Adults**	**Children**
No allergy to Penicillin or Ampicillin	Amoxicillin or Ampicillin (1)	2 g p.o. or i.v.	50 mg/kg p.o. or i.v.
Allergy to Penicillin or Ampicillin	Clindamycin	600 mg p.o. or i.v.	20 mg/kg p.o. or i.v.

Cephalosporins should not be used in patients with anaphylaxis, angio-oedema or urticaria after intake of Penicillin and Ampicillin.

(1) Alternatively Cephalexin 2 g i.v. or 50 mg/kg i.v. for children, Cefazolin or Ceftriaxone: 1 g i.v. for adults or 50 mg/kg i.v. for children

Cardiac conditions at highest risk of infective endocarditis for which prophylaxis is recommended when a high risk procedure is performed

Recommendations: prophylaxis	Class[a]	Level[b]
Antibiotic prophylaxis should only be considered for patients at highest risk of IE 1. Patients with a prosthetic valve or a prosthetic material used for cardiac valve repair 2. Patients with previous IE 3. Patients with congenital heart disease a. cyanotic congenital heart disease, without surgical repair, or with residual defects, palliative shunts or conduits b. congenital heart disease with complete repair with prosthetic material whether placed by surgery or by percutaneous technique, up to 6 months after the procedure c. when a residual defect persists at the site of implantation of a prosthetic material or device by cardiac surgery or percutaneous technique	IIa	C
Antibiotic prophylaxis is no longer recommended in other forms of valvular or congenital heart disease	III	C

a = class of recommendation; b = level of evidence

Recommendations: prophylaxis	Class[a]	Level[b]
A - Dental procedures **Antibiotic prophylaxis should only be considered for** dental procedures requiring manipulation of the gingival or periapical region of the teeth or perforation of the oral mucosa	IIa	C
Antibiotic prophylaxis is not recommended for local anaesthetic injections in non-infected tissue, removal of sutures, dental X-rays, placement or adjustment of removable prosthodontic or orthodontic appliances or braces. Prophylaxis is also not recommended following the shedding of deciduous teeth or trauma to the lips and oral mucosa	III	C
B - Respiratory tract procedures **Antibiotic prophylaxis is not recommended for respiratory tract procedures, including** bronchoscopy or laryngoscopy without biopsy, transnasal or endotracheal intubation	III	C
C - Gastrointestinal or urogenital procedures **Antibiotic prophylaxis is not recommended for** gastroscopy, colonoscopy, cystoscopy or transoesophageal echocardiography	III	C
D - Skin and soft tissue **Antibiotic prophylaxis is not recommended for any procedure**	III	C

a = class of recommendation; b = level of evidence

4. Diagnosis

The clinical history of IE is highly variable according to the causative microorganism, the presence or absence of pre-existing cardiac disease and the mode of presentation. Atypical presentation is common in elderly or immunocompromised patients. Diagnosis may also be more difficult in patients with a prosthetic valve or an intracardiac device and in blood culture negative infective endocarditis (BCNIE).

Echocardiography and blood cultures are the cornerstones of diagnosis of IE.

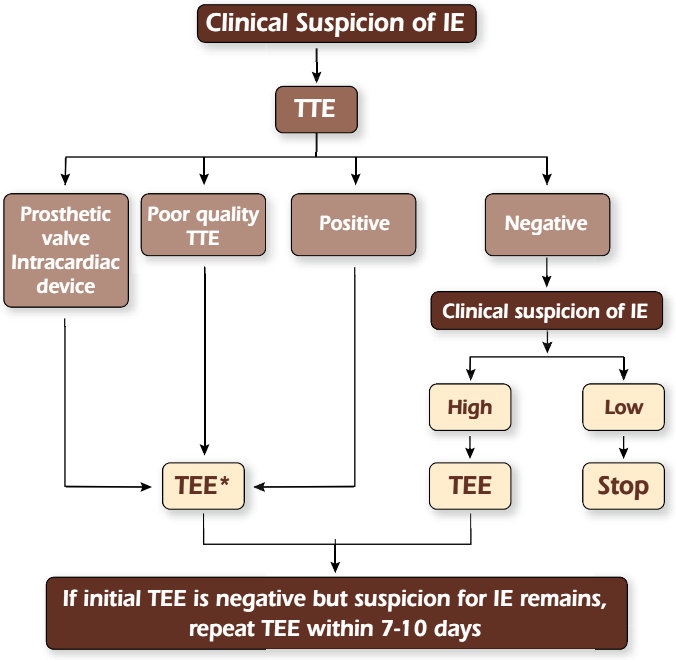
4a. Echocardiography and other imaging techniques

Echocardiography must be performed rapidly, as soon as IE is suspected. Transthoracic echocardiography (TTE) must be performed first, but both TTE and transoesophageal echocardiography (TEE) should ultimately be performed in the majority of cases of suspected or definite IE. Three echocardiographic findings are considered major criteria for IE, including vegetation, abscess and new dehiscence of a prosthetic valve.

Echocardiography is also useful for the assessment of the severity of the disease, the prediction of short and long-term prognosis, and the follow-up of patients under antibiotic therapy.

Other imaging techniques, including MRI, CT scan, and invasive angiography, are of limited value for the diagnosis of IE, but are useful for the diagnosis and management of its complications.

Indications for echocardiography in suspected infective endocarditis



*TEE is not mandatory in isolated right-sided native valve IE with good quality TTE examination and unequivocal echocardiographic findings.

IE = infective endocarditis; TEE = transoesophageal echocardiography; TTE = transthoracic echocardiography

Role of echocardiography in Infective Endocarditis

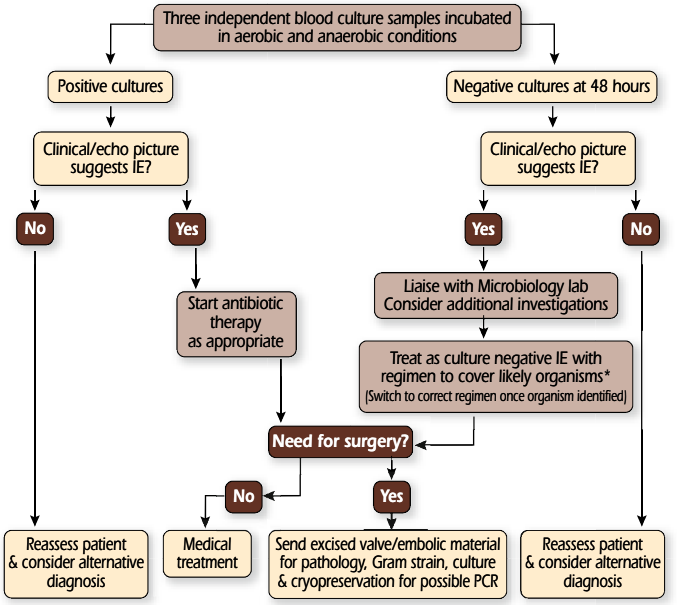
Recommendations: echocardiography	Class[a]	Level[b]
A - Diagnosis		
1. TTE is recommended as the first-line imaging modality in suspected IE	I	B
2. TEE is recommended in patients with high clinical suspicion of IE and a normal TTE	I	B
3. Repeat TTE / TEE within 7-10 days are recommended in the case of an initially negative examination when clinical suspicion of IE remains high	I	B
4. TEE should be considered in the majority of adult patients with suspected IE, even in cases with positive TTE, owing to its better sensitivity and specificity, particularly for the diagnosis of abscesses and measurement of vegetation size.	IIa	C
5. TEE is not indicated in patients with a good-quality negative TTE and low clinical suspicion of IE	III	C
B - Follow-up under medical therapy		
1. Repeat TTE and TEE are recommended as soon as a new complication of IE is suspected (new murmur, embolism, persisting fever, heart failure, abscess, atrioventricular block)	I	B
2. Repeat TTE and TEE should be considered during follow-up of uncomplicated IE, in order to detect new silent complication and monitor vegetation size. The timing and mode (TTE or TEE) of repeat examination depend on the initial findings, type of microorganism, and initial response to therapy	IIa	B
C - Intra-operative echocardiography		
Intraoperative echocardiography is recommended in all cases of IE requiring surgery	I	C
D - Following completion of therapy		
TTE is recommended at completion of antibiotic therapy for evaluation of cardiac and valve morphology and function	I	C

a = class of recommendation; b = level of evidence; TEE = transoesophageal echocardiography; TTE = transthoracic echocardiography

4b. Microbiological diagnosis

Blood cultures are positive in about 85% of all IE. BCNIE is mainly related to prior antibiotic administration, underlining the need for withdrawing antibiotics and repeating blood cultures in this situation, often delaying diagnosis and the initiation of treatment with a profound impact on clinical outcome. BCNIE is also observed in fastidious organisms and intracellular bacteria; its diagnosis relies on serological testing, immunological techniques, molecular biology techniques, or histology.

Microbiological diagnosis in culture-positive and culture-negative infective endocarditis



*If organism remains unidentified and patient is stable, consider antibiotic withdrawal and repeat blood cultures

IE = infective endocarditis; PCR = polymerase chain reaction

4c. Duke criteria

The Duke criteria, based upon clinical, echocardiographic and microbiological findings, provide high sensitivity and specificity (approximately 80% overall) for the diagnosis of IE. The Duke criteria are useful for the classification of IE, but they are of limited value in some subgroups (CRDIE, PVE, BCNIE) and do not replace clinical judgement.

Modified Duke criteria for the diagnosis of infective endocarditis

MAJOR CRITERIA

Blood cultures positive for IE

- Typical microorganisms consistent with IE from 2 separate blood cultures:
  Viridans streptococci, Streptococcus bovis, HACEK group, Staphylococcus aureus; or
  Community-acquired enterococci, in the absence of a primary focus;
  or
- Microorganisms consistent with IE from persistently positive blood cultures:
  At least 2 positive blood cultures of blood samples drawn > 12 h apart; or
  All of 3 or a majority of ≥ 4 separate cultures of blood (with first and last sample drawn at least 1 h apart)
  or
- Single positive blood culture for Coxiella burnetii or phase I IgG antibody titer > 1 : 800

Evidence of endocardial involvement

- Echocardiography positive for IE
  Vegetation - Abscess - New partial dehiscence of prosthetic valve
- New valvular regurgitation

MINOR CRITERIA

- Predisposition: predisposing heart condition, injection drug use
- Fever: temperature > 38°C
- Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial haemorrhages, conjunctival haemorrhages, Janeway lesions
- Immunologic phenomena: glomerulonephritis, Osler's nodes, Roth's spots, rheumatoid factor
- Microbiological evidence: positive blood culture but does not meet a major criterion or serological evidence of active infection with organism consistent with IE

Diagnosis of IE is definite in the presence of	**Diagnosis of IE is possible in the presence of**
2 major criteria, or 1 major and 3 minor criteria, or 5 minor criteria	1 major and 1 minor criteria, or 3 minor criteria

Adapted from : Li JS, Sexton DJ, Mick N, Nettles R, Fowler VG, Jr., Ryan T, Bashore T, Corey GR. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. Clin Infect Dis 2000;30:633-638.

5. Prognostic assessment at admission

The in-hospital mortality rate of patients with IE is still high, ranging from 10 to 26% but this differs considerably from patient to patient.

The quick identification of patients at highest risk of death allows the identification of patients who will benefit from closer follow-up and a more aggressive treatment strategy (e.g. urgent surgery).

Prognostic assessment at admission can be performed using simple clinical, microbiological, and echocardiographic parameters, and should be used to choose the best therapeutic option.

Predictors of poor outcome in patients with IE
Patient characteristics • Older age • Prosthetic valve IE • Insulin-dependent diabetes mellitus • Comorbidity (e.g. frailty, previous cardiovascular, renal or pulmonary disease)
Presence of complications of IE • Heart failure • Renal failure • Stroke • Septic shock • Periannular complications
Microorganism • *S. aureus* • Fungi • Gram-negative bacilli
Echocardiographic findings • Periannular complications • Severe left-sided valve regurgitation • Low left ventricular ejection fraction • Pulmonary hypertension • Large vegetations • Severe prosthetic dysfunction • Premature mitral valve closure and other signs of elevated diastolic pressures

6. Antimicrobial therapy: principles and methods

The treatment of IE relies on the combination of prolonged antimicrobial therapy and - in about half of patients - surgical eradication of the infected tissues.

Prolonged therapy with a combination of bactericidal drugs is the basis of IE treatment. Drug treatment of PVE should last longer (at least 6 weeks) than that of native valve endocarditis (NVE) (2-6 weeks).

In both NVE and PVE, the duration of treatment is based on the first day of effective antibiotic therapy, not on the day of surgery. After surgery, a new full course of treatment should only start if valve cultures are positive, the choice of antibiotic being based on the susceptibility of the latest recovered bacterial isolate.

Antibiotic treatment of infective endocarditis due to oral streptococci and Group D streptococci

Antibiotic	Dosage and Route	Duration (weeks)	Level of Evidence
Strains fully susceptible to Penicillin (MIC < 0.125 mg/L)			
Standard treatment			
Penicillin G	12-18 million U/day i.v. in 6 doses	4	IB
or Amoxicillin	100-200 mg/kg/day i.v. in 4-6 doses	4	IB
or Ceftriaxone	2 g/day i.v. or i.m. in 1 dose	4	IB
Two-week treatment			
Penicillin G	12-18 million U/day i.v. in 6 doses	2	IB
or Amoxicillin	100-200 mg/kg/day i.v. in 4-6 doses	2	IB
or Ceftriaxone	2 g/day i.v. or i.m. in 1 dose	2	IB
with			
Gentamicin	3 mg/kg/day i.v. or i.m. in 1 dose	2	IB
or Netilmicin	4-5 mg/kg/day i.v. in 1 dose	2	IB
In beta-lactam allergic patients			
Vancomycin	30 mg/kg/day i.v. in 2 doses	4	IC
Strains relatively resistant to Penicillin (MIC 0.125 - 2 mg/L)			
Standard treatment			
Penicillin G	24 million U/day i.v. in 6 doses	4	IB
or Amoxicillin	200 mg/kg/day i.v. in 4-6 doses	4	IB
with			
Gentamicin	3 mg/kg/day i.v. or i.m. in 1 dose	2	
In beta-lactam allergic patients			
Vancomycin	30 mg/kg/day i.v. in 2 doses	4	IC
with			
Gentamicin	3 mg/kg/day i.v. or i.m. in 1 dose	2	

Antibiotic treatment of infective endocarditis due to staphylococcus spp.

Antibiotic	Dosage and Route	Duration (weeks)	Level of Evidence
Native valves			
Methicillin-susceptible staphylococci			
(Flu)cloxacillin	12 g /day i.v. in 4-6 doses	4-6	IB
or Oxacillin			
with			
Gentamicin	3 mg/kg/day i.v. or i.m. in 2 or 3 doses	3-5 days	
Penicillin-allergic patients or Methicillin-resistant staphylococci			
Vancomycin	30 mg/kg/day i.v. in 2 doses	4-6	IB
with			
Gentamicin	3 mg/kg/day i.v. or i.m. in 2 or 3 doses	3-5 days	
Prosthetic valves			
Methicillin-susceptible staphylococci			
(Flu)cloxacillin	12 g /day i.v. in 4-6 doses	≥ 6	IB
or Oxacillin			
with	1200 mg/day i.v. or orally in 2 doses	≥ 6	
Rifampin			
and			
Gentamicin	3 mg/kg/day i.v. or i.m. in 2 or 3 doses	2	
Penicillin-allergic patients or Methicillin-resistant staphylococci			
Vancomycin	30 mg/kg/day i.v. in 2 doses	≥ 6	IB
with			
Rifampin	1200 mg/day i.v. or orally in 2 doses	≥ 6	
and			
Gentamicin	3 mg/kg/day i.v. or i.m. in 2 or 3 doses	2	

Antibiotic treatment of infective endocarditis due to Enterococcus spp.

Antibiotic	Dosage and Route	Duration (weeks)	Level of Evidence
Beta-lactam and Gentamicin susceptible strain			
Amoxicillin	200 mg/kg/day i.v. in 4-6 doses	4-6	IB
with			
Gentamicin	3 mg/kg/day i.v. or i.m. in 2 or 3 doses.	4-6	
OR			
Ampicillin	200 mg/kg/day i.v. in 4-6 doses	4-6	IB
with			
Gentamicin	3 mg/kg/day i.v. or i.m. in 2 or 3 doses.	4-6	
OR			
Vancomycin[a]	30 mg/kg/day i.v. in 2 doses	6	IC
with			
Gentamicin	3 mg/kg/day i.v. or i.m. in 2 or 3 doses.	6	

(a) = for patients unable to tolerate beta-lactams

Proposed antibiotic regimens for initial empirical treatment of infective endocarditis

Antibiotic	Dosage and Route	Duration (weeks)	Level of Evidence
Native valves			
Ampicillin-Sulbactam	12 g/day i.v. in 4 doses	4-6	IIb C
or Amoxicillin-Clavulanate	12 g/day i.v. in 4 doses	4-6	IIb C
with			
Gentamicin	3 mg/kg/day i.v. or i.m. in 2 or 3 doses.	4-6	
Vancomycin[a]	30 mg/kg/day i.v. in 2 doses	4-6	IIb C
with			
Gentamicin	3 mg/kg/day i.v. or i.m. in 2 or 3 doses.	4-6	
with			
Ciprofloxacin	1000 mg/day orally in 2 doses or 800 mg/day i.v. in 2 doses	4-6	

(a) = for patients unable to tolerate beta-lactams

Proposed antibiotic regimens for initial empirical treatment of infective endocarditis (cont)

Antibiotic	Dosage and Route	Duration (weeks)	Level of Evidence
Prosthetic valves (early, < 12 months post surgery)			
Vancomycin *with* Gentamicin *with* Rifampin	30 mg/kg/day i.v. in 2 doses 3 mg/kg/day i.v. or i.m. in 2 or 3 doses. 1200 mg/day orally in 2 doses	6 2	IIb C
Prosthetic valves (late, ≥ 12 months post surgery)			
Same as for native valves			

7. Indications for and optimal timing of surgery in left-sided NVE

Surgical treatment is used in approximately half of patients with IE because of severe complications. The 3 main complications and indications for early surgery in the active phase, i.e. while the patient is still receiving antibiotic treatment, are heart failure (HF), uncontrolled infection, and prevention of IE related embolic events.

Indications and timing of surgery in left-sided native valve IE

Recommendations: Indications for surgery	Timing*	Class[a]	Level[b]
A - HEART FAILURE			
Aortic or mitral IE with severe acute regurgitation or valve obstruction causing refractory pulmonary oedema or cardiogenic shock	Emergency	I	B
Aortic or mitral IE with fistula into a cardiac chamber or pericardium causing refractory pulmonary oedema or shock	Emergency	I	B
Aortic or mitral IE with severe acute regurgitation or valve obstruction and persisting heart failure or echocardiographic signs of poor haemodynamic tolerance (early mitral closure or pulmonary hypertension)	Urgent	I	B
Aortic or mitral IE with severe regurgitation and no HF	Elective	IIa	B
B - UNCONTROLLED INFECTION			
Locally uncontrolled infection (abscess, false aneurysm, fistula, enlarging vegetation)	Urgent	I	B
Persisting fever and positive blood cultures > 7-10 days	Urgent	I	B
Infection caused by fungi or multiresistant organisms	Urgent/elective	I	B
C - PREVENTION OF EMBOLISM			
Aortic or mitral IE with large vegetations (>10 mm) following one or more embolic episodes despite appropriate antibiotic therapy	Urgent	I	B
Aortic or mitral IE with large vegetations (> 10 mm) and other predictors of complicated course (heart failure, persistent infection, abscess)	Urgent	I	C
Isolated very large vegetations (> 15 mm)[#]	Urgent	IIb	C

a = class of recommendation; b = level of evidence;

* Emergency surgery: surgery performed within 24 hours, urgent surgery: within a few days, elective surgery: after at least one or 2 weeks of antibiotic therapy

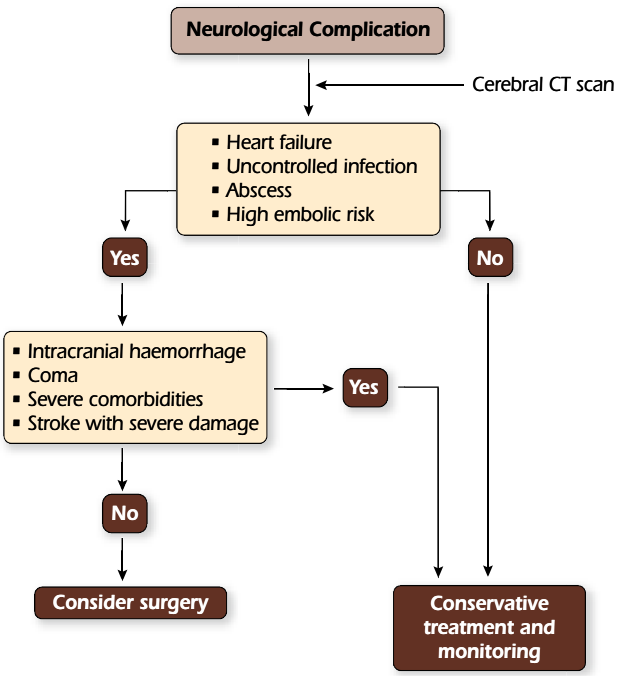
Surgery may be preferred if procedure preserving the native valve is feasible

8. Neurological complications

Neurological events develop in 20-40% of all patients with IE and are mainly the consequence of vegetation embolism. Stroke is associated with excess mortality. Rapid diagnosis and initiation of appropriate antibiotics are of major importance to prevent a first or recurrent neurological complication.

After an ischaemic stroke, cardiac surgery is not contra-indicated unless the neurological prognosis is judged too poor. The optimal time interval between stroke and cardiac surgery is unknown. If cerebral haemorrhage has been excluded by cranial CT and neurological damage is not severe, surgery indicated for HF, uncontrolled infection, or persistent high embolic risk should not be delayed and can be performed with a relatively low neurological risk (3-6%) and good probability of complete neurological recovery. Conversely, in cases with intracranial haemorrhage, neurological prognosis is worse and surgery must be postponed for at least one month.

Therapeutic strategy for patients with infective endocarditis and neurological complications



9. Prosthetic valve infective endocarditis (PVE)

PVE represents 20% of all cases of IE with increasing incidence. Diagnosis is more difficult than in NVE. Complicated PVE, staphylococcal PVE, and early PVE are associated with worse prognosis if treated without surgery and must be managed aggressively. Patients with non complicated, non staphylococcal late PVE can be managed conservatively with close follow-up.

Indications and timing of surgery in Prosthetic valve infective endocarditis (PVE)

Indications for surgery in PVE	Timing*	Class[a]	Level[b]
A - HEART FAILURE			
PVE with severe prosthetic dysfunction (dehiscence or obstruction) causing refractory pulmonary oedema or cardiogenic shock	Emergency	I	B
PVE with fistula into a cardiac chamber or pericardium causing refractory pulmonary oedema or shock	Emergency	I	B
PVE with severe prosthetic dysfunction and persisting heart failure	Urgent	I	B
Severe prosthetic dehiscence without HF	Elective	I	B
B - UNCONTROLLED INFECTION			
Locally uncontrolled infection (abscess, false aneurysm, fistula, enlarging vegetation)	Urgent	I	B
PVE caused by fungi or multiresistant organisms	Urgent/elective	I	B
PVE with persisting fever and positive blood cultures > 7-10 days	Urgent	I	B
PVE caused by staphylococci or gram negative bacteria (most cases of early PVE)	Urgent/elective	IIa	C
C - PREVENTION OF EMBOLISM			
PVE with recurrent emboli despite appropriate antibiotic treatment	Urgent	I	B
PVE with large vegetations (> 10 mm) and other predictors of complicated course (heart failure, persistent infection, abscess)	Urgent	I	C
PVE with isolated very large vegetations (> 15 mm)	Urgent	IIb	C

a = class of recommendation; b = level of evidence;

* Emergency surgery: surgery performed within 24 hours, urgent surgery: within a few days, elective surgery: after at least one or 2 weeks of antibiotic therapy

10. Cardiac device-related infective endocarditis (CDRIE)

CDRIE is one of the most difficult forms of IE to diagnose, and must be suspected in the presence of frequently misleading symptoms, particularly in elderly patients. Prognosis is poor, not least because of its frequent occurrence in elderly patients with associated comorbidity. In the majority of patients, CDRIE must be treated by prolonged antibiotic therapy and device removal.

Recommendations: CDRIE	Class[a]	Level[b]
A - PRINCIPLES OF TREATMENT		
Prolonged antibiotic therapy and device removal are recommended in definite CDRIE	I	B
Device removal should be considered when CDRIE is suspected on the basis of occult infection without other apparent source of infection	IIa	C
In patients with native or prosthetic valve endocarditis and an intracardiac device with no evidence of associated device infection, device extraction may be considered	IIb	c
B - MODE OF DEVICE REMOVAL		
Percutaneous extraction is recommended in most patients with CDRIE, even those with large (> 10 mm) vegetations	I	B
Surgical extraction should be considered if percutaneous extraction is incomplete or impossible or when there is associated severe destructive tricuspid IE	IIa	C
Surgical extraction may be considered in patients with very large (> 25 mm) vegetations	IIb	C
C - REIMPLANTATION		
After device extraction, reassessment of the need for reimplantation is recommended	I	B
When indicated, reimplantation should be postponed if possible to allow a few days or weeks of antibiotic therapy	IIa	B
Temporary pacing is not recommended	III	C
D - PROPHYLAXIS		
Routine antibiotic prophylaxis is recommended before device implantation	I	B

a = class of recommendation; b = level of evidence

11. Right-sided infective endocarditis

Right-sided IE is most frequently observed in IVDA and congenital heart disease (CHD). Diagnostic features include respiratory symptoms and fever. TTE is of major value in these patients. Despite relatively low in-hospital mortality, right-sided IE has a high risk of recurrence in IVDA and a more conservative approach to surgery is recommended in this group.

Indications for surgical treatment of right-sided infective endocarditis

Recommendations: right-sided infective endocarditis	Class[a]	Level[b]
Surgical treatment should be considered in the following scenarios: • Microorganisms difficult to eradicate (e.g. persistent fungi) or bacteraemia for > 7 days (e.g. S. aureus, P. aeruginosa) despite adequate antimicrobial therapy *or* • Persistent tricuspid valve vegetations > 20 mm after recurrent pulmonary emboli with or without concomitant right heart failure *or* • Right HF secondary to severe tricuspid regurgitation with poor response to diuretic therapy	IIa	C

a = class of recommendation; b = level of evidence

Section XI:
Pulmonary Hypertension

1. Pulmonary Hypertension

Chapter 1
Pulmonary Hypertension*
2009

The Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT) and by the Association for European Paediatric Cardiology (AEPC)

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Special thanks to Udo Sechtem for his contribution

1. Introduction:

Pulmonary hypertension (PH) is an haemodynamic and pathophysiological condition defined as an increase in mean pulmonary arterial pressure (PAP)≥ 25 mmHg at rest as assessed by right heart catheterization (RHC) (Table 1). PH may be also estimated by Doppler-echocardiography although this method may give rise to false positive and false negative diagnosis (Table 2).

PH can be found in multiple clinical conditions, which have been classified into six clinical groups with specific characteristics (Table 3).

A diagnostic algorithm is provided to facilitate the identification of the specific clinical group of PH and of the different types of PAH (Figure 1).

The treatment strategy is remarkably different among the six clinical groups. PAH - group 1 is the only clinical group with specific drug therapy and an evidence-based treatment algorithm is provided (Figure 2); definitions for evaluating the severity of the patients' condition, their treatment goals and follow-up strategy have also been included. The particular features of the different types of PAH including in paediatric patients, have been highlighted.

The specific clinical, diagnostic and therapeutic characteristics of the individual clinical groups 2, 3 and 4 are discussed.

* Adapted from the ESC-ERS Guidelines on Diagnosis and Treatment of Pulmonary Hypertension (European Heart Journal 2009;30:2493–2537 doi:10.1093/eurheartj/ehp297).

2. Definitions

Table 1: Haemodynamic definitions of pulmonary hypertension as assessed by RHC*

Definition	Characteristics	Clinical group(s) †
Pulmonary hypertension (PH)	Mean PAP ≥ 25 mmHg	All
Pre-capillary PH	Mean PAP ≥ 25 mmHg PWP ≤ 15 mmHg CO normal or reduced‡	1 - Pulmonary arterial hypertension 3 - PH due to lung diseases 4 - Chronic thromboembolic PH 5 - PH with unclear and/or multifactorial mechanisms
Post-capillary PH	Mean PAP ≥ 25 mmHg PWP > 15 mmHg CO normal or reduced‡	2 - PH due to left heart disease
Passive	TPG ≤ 12 mmHg	
Reactive (out of proportion)	TPG > 12 mmHg	

CO = cardiac output; PAP = Pulmonary arterial pressure; PH = pulmonary hypertension; PWP = pulmonary wedge pressure; TPG = transpulmonary pressure gradient (mean PAP - mean PWP)

* All values measured at rest

† According to Table 3

‡ High cardiac output can be present in cases of hyperkinetic conditions such as systemic-to-pulmonary shunts (only in the pulmonary circulation), anaemia, hyperthyroidism, etc...

Table 2: Arbitrary criteria for the presence of PH based on tricuspid regurgitation peak velocity and Doppler-estimated PA systolic pressure at rest (assuming a normal right atrial pressure of 5 mmHg) and on additional echocardiographic variables suggestive of PH

Echocardiographic diagnosis: PH unlikely
Tricuspid regurgitation velocity ≤ 2.8 m/sec, PA systolic pressure ≤ 36 mmHg and no additional echocardiographic variables suggestive of PH
Echocardiographic diagnosis: PH possible
Tricuspid regurgitation velocity ≤ 2.8 m/sec, PA systolic pressure ≤ 36 mmHg but presence of additional echocardiographic variables suggestive of PH
Tricuspid regurgitation velocity 2.9-3.4 m/sec, PA systolic pressure 37-50 mmHg with/without additional echocardiographic variables suggestive of PH
Echocardiographic diagnosis: PH likely
Tricuspid regurgitation velocity > 3.4 m/sec, PA systolic pressure > 50 mmHg, with/without additional echocardiographic variables suggestive of PH
Exercise Doppler echocardiography is not recommended for screening of PH

The definition of PH on exercise as a mean PAP > 30 mmHg as assessed by RHC is not supported by published data.

Other echocardiographic variables that might raise or reinforce suspicion of PH include an increased velocity of pulmonary valve regurgitation and a short acceleration time of RV ejection into the PA. Increased dimensions of right heart chambers, abnormal shape and movement of interventricular septum, increased RV wall thickness and dilated main PA are also suggestive of PH, but tend to occur later in the course of the disease.

3. Clinical classification of pulmonary hypertension

Clinical conditions with PH are classified into six groups with different pathological, pathophysiological, prognostic and therapeutic features (Table 3).

Table 3: Updated clinical classification of pulmonary hypertension (Dana Point, 2008)

1. Pulmonary arterial hypertension (PAH)
1.1 Idiopathic
1.2 Heritable
1.2.1 BMPR2
1.2.2 ALK1, endoglin (with or without hereditary haemorrhagic telangiectasia)
1.2.3 Unknown.
1.3 Drugs and toxins induced
1.4 Associated with (APAH):
1.4.1 Connective tissue diseases
1.4.2 HIV infection
1.4.3 Portal hypertension
1.4.4 Congenital heart disease
1.4.5 Schistosomiasis
1.4.6 Chronic haemolytic anaemia
1.5 Persistent pulmonary hypertension of the newborn
1′. Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis
2. Pulmonary hypertension due to left heart disease
2.1 Systolic dysfunction
2.2 Diastolic dysfunction
2.3 Valvular disease
3. Pulmonary hypertension due to lung diseases and/or hypoxia
3.1 Chronic obstructive pulmonary disease
3.2 Interstitial lung disease
3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
3.4 Sleep-disordered breathing
3.5 Alveolar hypoventilation disorders
3.6 Chronic exposure to high altitude
3.7 Developmental abnormalities
4. Chronic thromboembolic pulmonary hypertension
5. PH with unclear and/or multifactorial mechanisms
5.1 Haematological disorders: myeloproliferative disorders, splenectomy
5.2 Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis, lymphangioleiomyomatosis, neurofibromatosis, vasculitis
5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
5.4 Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure on dialysis

ALK-1 = activin receptor-like kinase 1 gene; APAH = associated PAH; BMPR2 = bone morphogenetic protein receptor 2; HIV = human immunodeficiency virus; PAH = pulmonary arterial hypertension

The classification of congenital heart disease (CHD) causing PAH requires a clinical (Table 4) and an anatomical-pathophysiological version (provided in the full version of the guidelines) in order to better define each individual patient.

Table 4: Clinical classification of congenital, systemic-to-pulmonary shunts associated with pulmonary arterial hypertension

A) Eisenmenger's syndrome
Includes all systemic-to-pulmonary shunts due to large defects leading to a severe increase in PVR and resulting in a reversed (pulmonary-to-systemic) or bidirectional shunt. Cyanosis, erythrocytosis and multiple organ involvement are present.
B) Pulmonary arterial hypertension associated with systemic-to-pulmonary shunts
In these patients with moderate to large defects, the increase in PVR is mild to moderate, systemic-to-pulmonary shunt is still largely present and no cyanosis is present at rest.
C) Pulmonary arterial hypertension with small* defects
In cases with small defects (usually ventricular septal defects <1 cm and atrial septal defects < 2 cm of effective diameter assessed by echocardiography) the clinical picture is very similar to idiopathic PAH.
D) Pulmonary arterial hypertension after corrective cardiac surgery
In these cases, congenital heart disease has been corrected but PAH is either still present immediately after surgery or has recurred several months or years after surgery in the absence of significant postoperative residual congenital lesions or defects that originate as a sequela to previous surgery.

*The size applies to adult patients; PAH = pulmonary arterial hypertension; PVR = pulmonary vascular resistance

4. Pulmonary arterial hypertension (Group 1)

Pulmonary arterial hypertension (PAH, group 1) is a clinical condition characterised by the presence of precapillary PH in the absence of other causes of precapillary PH such as PH due to lung diseases, chronic thrombo-embolic PH or other rare diseases. PAH includes different forms that share a similar clinical picture and virtually identical pathological changes of the lung microcirculation.

4.1 Diagnosis

PAH should be considered in the differential diagnosis of exertional dyspnoea, syncope, angina and/or progressive

limitation of exercise capacity, particularly in patients without apparent risk factors, symptoms or signs of common cardiovascular and respiratory disorders. Special awareness should be directed towards patients with risk factors (Table 5) and/or conditions listed in the PAH group (Table 3).

Table 5: Updated risk level of drugs and toxins known to induce PAH

Definite	**Possible**
Aminorex	Cocaine
Fenfluramine	Phenylpropanolamine
Dexfenfluramine	St. John's Wort
Toxic rapeseed oil	Chemotherapeutic agents
Benfluorex	Selective serotonin reuptake inhibitors
	Pergolide
Likely	**Unlikely**
Amphetamines	Oral contraceptives
L-tryptophan	Estrogen
Methamphetamines	Cigarette smoking

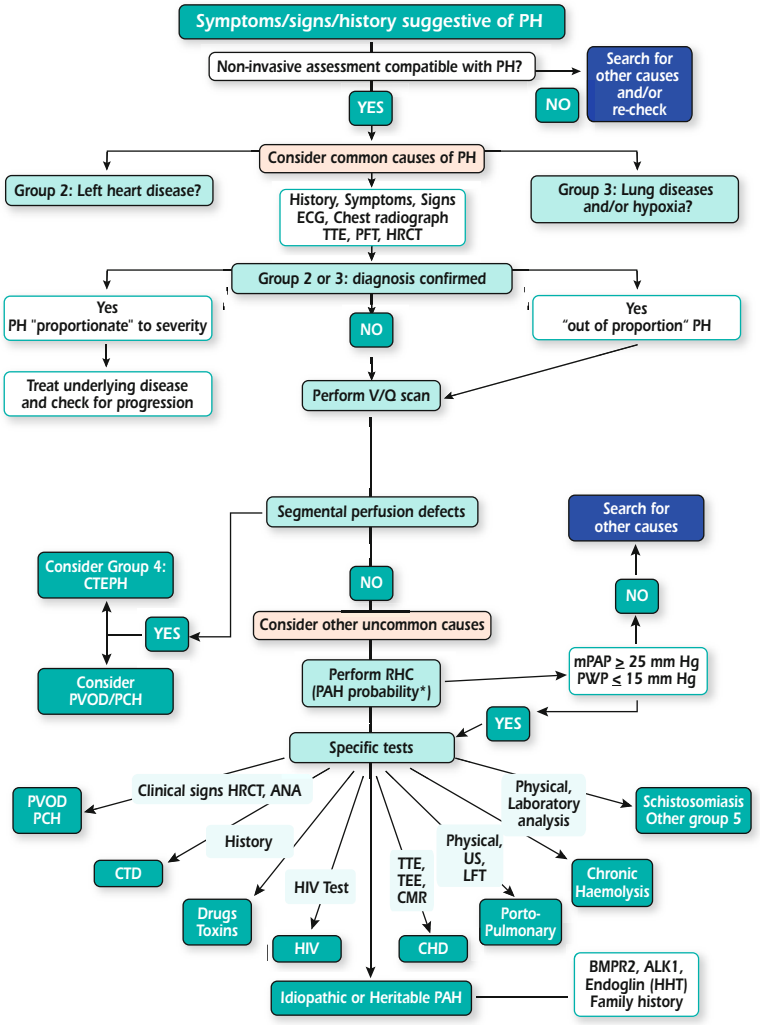
Table 6: Probability of PAH diagnosis and suggested management according to the echocardiographic diagnosis of PH (Table 2), symptoms and additional clinical information

Low probability for PAH diagnosis	**Class[a]**	**Level[b]**
Echocardiographic diagnosis of "PH unlikely", no symptoms: no additional work-up is recommended.	I	C
Echocardiographic diagnosis of "PH unlikely", presence of symptoms and of associated conditions or risk factors for group 1 - PAH: echocardiographic follow-up is recommended.	I	C
Echocardiographic diagnosis of "PH unlikely", presence of symptoms and absence of associated conditions or risk factors for group 1 - PAH: evaluation of other causes for the symptoms is recommended.	I	C
Intermediate probability for PAH	**Class[a]**	**Level[b]**
Echocardiographic diagnosis of "PH possible", no symptoms and absence of associated conditions or risk factors for group 1 - PAH: echocardiographic follow-up is recommended.	I	C
Echocardiographic diagnosis of "PH possible", presence of symptoms and of associated conditions or risk factors for group 1 - PAH: RHC may be considered.	IIb	C
Echocardiographic diagnosis of "PH possible", presence of symptoms and absence of associated conditions or risk factors for group 1 - PAH: alternative diagnosis and echocardiographic follow-up may be considered. If symptoms at least moderate RHC may be considered.	IIb	C
High probability for PAH	**Class[a]**	**Level[b]**
Echocardiographic diagnosis of "PH likely", with symptoms and presence/absence of associated conditions or risk factors for group 1 - PAH: RHC is recommended.	I	C
Echocardiographic diagnosis of "PH likely", without symptoms and presence/absence of associated conditions or risk factors for group 1 - PAH: RHC should be considered.	IIa	C

a = Class of recommendation; b = Level of evidence; PAH = pulmonary arterial hypertension; PH = pulmonary hypertension; RHC = right heart catheterization

In the patient with suspected PH and compatible non-invasive assessment, clinical history, symptoms, signs, ECG, chest radiograph, transthoracic echocardiogram, pulmonary function tests (including nocturnal oximetry if required) and high resolution CT of the chest are requested to identify the presence of group 2 - left heart disease or group 3 - lung diseases. If these are not found or if PH seems "out of proportion" to their severity, less common causes of PH should be looked for. If a ventilation/perfusion scan shows multiple segmental perfusion defects, a diagnosis of group 4 - CTEPH should be suspected. If a ventilation/perfusion scan is normal or shows only subsegmental "patchy" perfusion defects a tentative diagnosis of group 1 - PAH or the rarer conditions of group 5 is made. The further management according to the likelihood of PAH is given in Table 6 including indications for RHC. Additional recommendations for diagnostic tests including RHC and vasoreactivity testing are provided in Table 7 and Table 8.

Figure 1. Diagnostic algorithm



ALK-1 = activin-receptor-like kinase; ANA = antinuclear antibodies; BMPR2 = bone morphogenetic protein receptor 2; CHD = congenital heart disease; CMR = cardiac magnetic resonance; CTD = connective tissue diseases; Group = clinical group (Table 3); HHT = hereditary haemorrhagic telangiectasia; HIV = human immunodeficiency virus; HRCT = high resolution computed tomography; LFT = liver function tests; mPAP = mean pulmonary arterial pressure; PAH = pulmonary arterial hypertension; PCH = pulmonary capillary haemangiomatosis; PFT = pulmonary function test; PH = pulmonary hypertension; PVOD = pulmonary veno-occlusive disease; PWP = pulmonary wedge pressure; RHC = right heart catheterization; TEE = transoesophageal echocardiography; TTE = transthoracic echocardiography; US = ultrasonography; V/Q scan = ventilation/perfusion lung scan; *Refer also to Table 6.

Table 7: Recommendations for diagnostic strategy

Statement	Class[a]	Level[b]
Ventilation/perfusion lung scan is recommended in patients with unexplained PH to exclude CTEPH.	I	C
Contrast CT angiography of the PA is indicated in the work-up of patients with CTEPH.	I	C
Routine biochemistry, haematology, immunology and thyroid function tests are indicated in all patients with PAH, to identify the specific associated condition.	I	C
Abdominal ultrasound is indicated for the screening of portal hypertension.	I	C
High-resolution CT should be considered in all patients with PH.	IIa	C
Conventional pulmonary angiography should be considered in the work-up of patients with CTEPH.	IIa	C
Open or thoracoscopic lung biopsy is not recommended in patients with PAH.	III	C

a = Class of recommendation; b = Level of evidence; CT = computerised tomography; CTEPH = chronic thromboembolic pulmonary hypertension; PA = pulmonary artery; PH = pulmonary hypertension; PAH = pulmonary arterial hypertension

Table 8: Recommendations for right heart catheterization (A) and vasoreactivity testing (B)

Statement	Class[a]	Level[b]
Right heart catheterization (A)		
RHC is indicated in all patients with PAH to confirm the diagnosis, to evaluate the severity and when PAH specific drug therapy is considered.	I	C
RHC should be performed for confirmation of efficacy of PAH specific drug therapy.	IIa	C
RHC should be performed for confirmation of clinical deterioration and as baseline for the evaluation of the effect of treatment escalation and/or combination therapy.	IIa	C
Vasoreactivity testing (B)		
Vasoreactivity testing is indicated in patients with IPAH, heritable PAH and PAH associated with anorexigen use to detect patients who can be treated with high doses of CCB.	I	C
A positive response to vasoreactivity testing is defined as a reduction of mean PAP ≥ 10 mmHg to reach an absolute value of mean PAP ≤ 40 mmHg with an increased or unchanged CO.	I	C
Vasoreactivity testing should be performed only in referral centres.	IIa	C
Vasoreactivity testing should be performed using nitric oxide as vasodilator.	IIa	C
Vasoreactivity testing may be performed in other types of PAH.	IIb	C
Vasoreactivity testing may be performed using i.v. epoprostenol or i.v. adenosine.	IIb	C
The use of oral or i.v. CCB in acute vasoreactivity testing is not recommended.	III	C
Vasoreactivity testing to detect patients who can be safely treated with high doses of CCB is not recommended in patients with other PH groups (Groups 2,3,4,5).	III	C

a = Class of recommendation; b = Level of evidence; CCB = calcium channel blockers; CO = cardiac output; IPAH = idiopathic PAH; PAH = pulmonary arterial hypertension; PAP = pulmonary arterial pressure; PH = pulmonary hypertension; RHC = right heart catheterization

4.2 Evaluation of severity

The evaluation of severity of patients with PAH takes place between the diagnostic process and the therapeutic decision-making (Tables 9, 10, 11, 12 and 13).

Table 9: Functional classification of pulmonary hypertension modified after the NYHA Functional classification according to the WHO 1998

Class I	Patients with pulmonary hypertension but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnoea or fatigue, chest pain or near syncope.
Class II	Patients with pulmonary hypertension resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnoea or fatigue, chest pain or near syncope.
Class III	Patients with pulmonary hypertension resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnoea or fatigue, chest pain or near syncope.
Class IV	Patients with pulmonary hypertension with inability to carry out any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnoea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity.

Table 10: Parameters with established importance for assessing disease severity, stability and prognosis in PAH

Better Prognosis	Determinants of Prognosis	Worse Prognosis
No	Clinical evidence of RV failure	Yes
Slow	Rate of progression of symptoms	Rapid
No	Syncope	Yes
I, II	WHO-FC	IV
Longer (> 500m)*	6MWT	Shorter (< 300 m)
Peak O_2 Consumption > 15 ml/min/kg	Cardio-pulmonary exercise testing	Peak O_2 consumption < 12 ml/min/kg
Normal or near-normal	BNP/NT-proBNP plasma levels	Very elevated and rising
No pericardial effusion TAPSE † > 2.0 cm	Echocardiographic findings†	Pericardial effusion TAPSE † < 1.5 cm
RAP < 8 mmHg and CI ≥2.5 L/min/m²	Haemodynamics	RAP >15 mmHg or CI ≤2.0 L/min/m²

BNP = brain natriuretic peptide; CI = cardiac index; RAP = right atrial pressure; 6MWT = six-minute walking test; TAPSE = tricuspid annular plane systolic excursion; WHO-FC = World Health Organization functional class

* Depending on age

† TAPSE and pericardial effusion have been selected because they can be measured in the majority of the patients

Table 11: Definition of patient status

Stable and satisfactory	Patients in this condition should fulfil the majority of the findings listed in the "better prognosis" column of the prognostic table (see Table 10).
Stable and not satisfactory	This is a patient who although stable has not achieved the status which patient and treating physician would consider desirable. Some of the limits described in the first column of the prognostic table (see Table 10) are not fulfilled. These patients require re-evaluation and consideration for additional or different treatment following full assessment in the expert centre.
Unstable and deteriorating	Patients in this condition fulfil the majority of the findings listed in the "worse prognosis" column of the prognostic table (see Table 10).

Table 12: Suggested assessments and timing for the follow-up of patients with PAH

	At baseline (prior to therapy)	Every 3-6 months*	3-4 months after initiation or changes in therapy	In case of clinical worsening
Clinical assessment WHO-FC ECG	✓	✓	✓	✓
6MWT†	✓	✓	✓	✓
Cardio-pulmonary exercise testing†	✓		✓	✓
BNP/NT-proBNP	✓	✓	✓	✓
Echocardiography	✓		✓	✓
RHC	✓‡		✓§	✓§

* Intervals should to be adjusted to individual patients needs

† usually one of the two exercise tests is performed

‡ is recommended (Table 8A)

§ should be performed (Table 8A)

BNP = brain natriuretic peptide; ECG = electrocardiogram; RHC = right heart catheterization; 6MWT = six-minute walking test; WHO-FC = World Health Organization functional class

Table 13: Recommendations for evaluation of severity and follow-up

Statement
It is recommended to evaluate the severity of PAH patients with a panel of data derived from clinical evaluation, exercise tests, biochemical markers, echocardiographic and haemodynamic assessments.
It is recommended to perform regular follow-up every 3-6 months also in stable patients with PAH.
A goal-oriented treatment strategy is recommended in patients with PAH.

4.3 Therapy

The therapy of PAH patients cannot be considered as a mere prescription of drugs but is characterised by a complex strategy, which includes the evaluation of severity, supportive and general measures, the assessment of vasoreactivity, the estimation of efficacy and combination of different drugs plus interventions. In any of these steps, the experience of the responsible physician is critical to optimize the available resources.

Table 14: Recommendations for general measures

Statement	Class[a]	Level[b]
It is recommended to avoid pregnancy in patients with PAH.	I	C
Immunization of PAH patients against influenza and pneumococcal infection is recommended.	I	C
Physically deconditioned PAH patients should be considered for supervised exercise rehabilitation.	IIa	B
Psycho-social support should be considered in patients with PAH.	IIa	C
In flight O_2 administration should be considered for patients in WHO-FC III and IV and those with arterial blood O_2 pressure consistently less than 8 kPa (60 mmHg).	IIa	C
Epidural anaesthesia instead of general anaesthesia should be utilised, if possible, for elective surgery.	IIa	C
Excessive physical activity that leads to distressing symptoms is not recommended in patients with PAH.	III	C

a = Class of recommendation; b = Level of evidence; PAH = pulmonary arterial hypertension; WHO-FC = World Health Organization functional class

Table 15: Recommendations for supportive therapy

Statement	Class[a]	Level[b]
Diuretic treatment is indicated in PAH patients with signs of RV failure and fluid retention.	I	C
Continuous long-term O_2 therapy is indicated in PAH patients when arterial blood O_2 pressure is consistently less than 8 kPa (60 mmHg)*	I	C
Oral anticoagulant treatment should be considered in patients with IPAH, heritable PAH and PAH due to anorexigens use.	IIa	C
Oral anticoagulant treatment may be considered in patients with APAH.	IIb	C
Digoxin may be considered in patients with PAH who develop atrial tachyarrhythmias to slow ventricular rate.	IIb	C

a = Class of recommendation; b = Level of evidence; APAH = associated PAH; IPAH = idiopathic PAH; PAH = pulmonary arterial hypertension; RV = right ventricle/ventricular

* See also recommendations for PAH associated with congenital cardiac shunts

Specific drug therapy

Drug classes are listed by alphabetical order and single compounds are listed by alphabetical order within each class.

Table 16: Recommendations for efficacy of specific drug therapy, balloon atrial septostomy and lung transplantation for pulmonary arterial hypertension (Group 1) according to WHO functional class

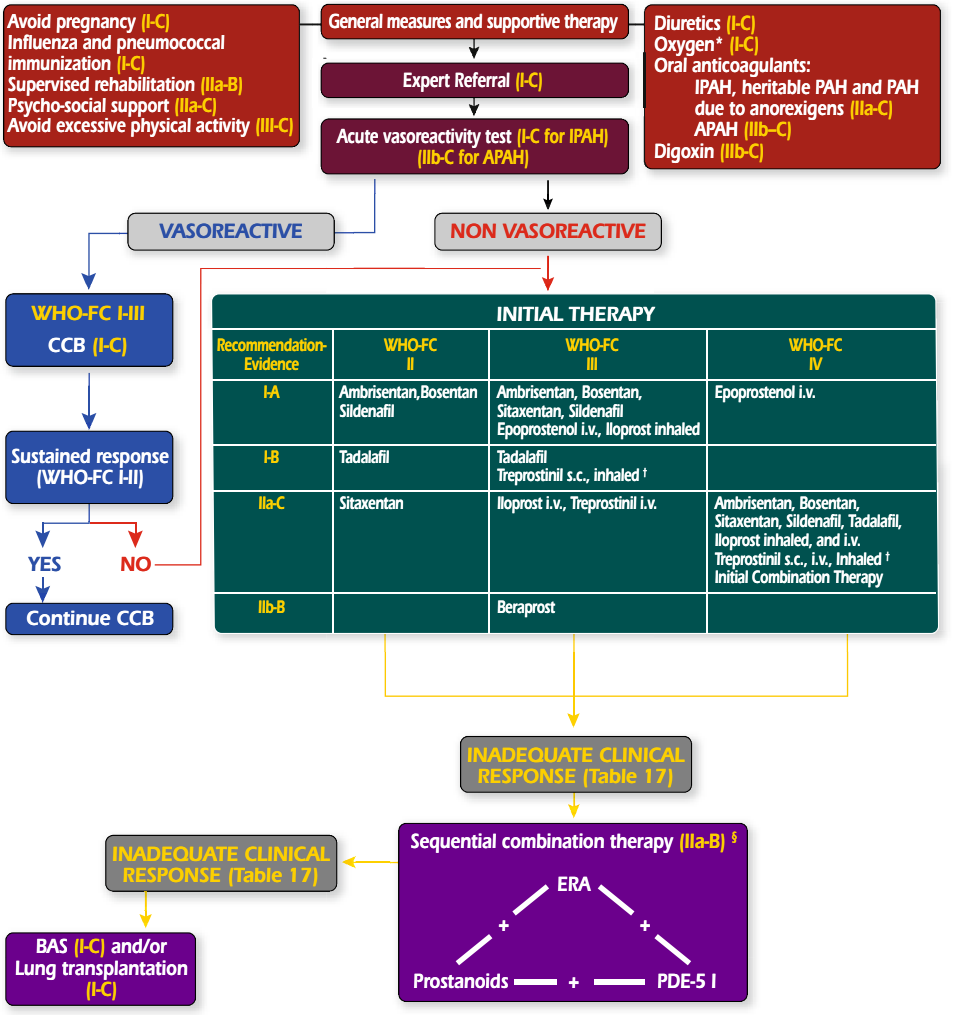
Measure/Treatment		Classes of recommendation - Level of evidence		
		WHO-FC II	WHO-FC III	WHO-FC IV
Calcium channel blockers		I-C *	I-C *	-
Endothelin receptor antagonists	Ambrisentan	I-A	I-A	IIa-C
	Bosentan	I-A	I-A	IIa-C
	Sitaxentan	IIa-C	I-A	IIa-C
Phosphodiesterase type-5 inhibitors	Sildenafil	I-A	I-A	IIa-C
	Tadalafil	I-B	I-B	IIa-C
Prostanoids	Beraprost	-	IIb-B	-
	Epoprostenol (intravenous)	-	I-A	I-A
	Iloprost (inhaled)	-	I-A	IIa-C
	Iloprost (intravenous)	-	IIa-C	IIa-C
	Treprostinil (subcutaneous)	-	I-B	IIa-C
	Treprostinil (intravenous)	-	IIa-C	IIa-C
	Treprostinil (inhaled) †	-	I-B	IIa-C
Initial drugs combination therapy		-	-	IIa-C
Sequential drugs combination therapy		IIa-C	IIa-B	IIa-B
Balloon atrial septostomy		-	I-C	I-C
Lung transplantation		-	I-C	I-C

* Only in responders to acute vasoreactivity tests, I-C for idiopathic PAH, heritable PAH and PAH due to anorexigens; IIa-C for APAH conditions

† Under regulatory review in the European Union

WHO-FC = World Health Organization functional class

Figure 2. Evidence based treatment algorithm for pulmonary arterial hypertension patients (for Group 1 patients only)



*To maintain arterial blood O_2 pressure ≥ 8 kPa (60 mmHg)

† Under regulatory review in the European Union

§ IIa-C for WHO-FC II

APAH = associated pulmonary arterial hypertension; BAS = balloon atrial septostomy; CCB = calcium channel blockers; ERA = endothelin receptor antagonist; IPAH = idiopathic pulmonary arterial hypertension; i.v. = intravenous; PDE5 I = phosphodiesterase type-5 inhibitor; s.c. = subcutaneous; WHO-FC = World Health Organization functional class

The treatment algorithm is specific for PAH and does not apply to patients in other PH clinical groups.

Vasoreactive patients should be treated with high and optimally tolerated doses of CCB; adequate response should be confirmed after 3-4 months of treatment. Patients in WHO-FC II should be treated with an ERA or a phosphodiesterase type-5 inhibitor. Patients in WHO-FC III should be considered candidates for treatment with either an ERA or a phosphodiesterase type-5 inhibitor or a prostanoid. As head-to-head comparisons among different compounds are not available, no evidence-based first-line treatment can be proposed. Continuous i.v. epoprostenol is recommended as first-line therapy for WHO-FC IV PAH patients. In case of inadequate clinical response, sequential combination therapy should be considered. BAS and/or Lung Transplantation are indicated for PAH with inadequate clinical response despite optimal medical therapy, or if medical treatments are unavailable.

Table 17: Definition of inadequate response to PAH treatments

Inadequate clinical response for patients who were initially in WHO-FC II or III:
1. Resulting clinical status defined as stable and not satisfactory* 2. Resulting clinical status defined as unstable and deteriorating*
Inadequate clinical response for patients who were initially in WHO-FC IV:
1. No rapid improvement to WHO-FC III or better 2. Resulting clinical status defined as stable and not satisfactory*

WHO-FC = World Health Organization functional class

* see Table 11

Table 18: Potentially significant drug interactions with PAH targeted therapies

PAH Drug	Mechanism of interaction	Interacting Drug	Interaction
Ambrisentan	?	Cyclosporine Ketoconazole	Caution is required in the co-administration of Ambrisentan with Ketoconazole and cyclosporine.
Bosentan	CYP3A4 inducer	Sildenafil	Sildenafil levels fall 50%; Bosentan levels increase 50%. May not require dose adjustments of either drug.
	CYP3A4 substrate	Cyclosporine	Cyclosporine levels fall 50%; Bosentan levels increase 4-fold. Combination contraindicated.
	CYP3A4 substrate	Erythromycin	Bosentan levels increase. May not require dose adjustment of bosentan during a short course.
	CYP3A4 substrate	Ketoconazole	Bosentan levels increase 2-fold.
	CYP3A4 substrate + bile salt pump inhibitor	Glibenclamide	Increase incidence of elevated aminotransferases. Potential decrease of hypoglycaemic effect of Glibenclamide. Combination contraindicated.
	CYP2C9 and CYP3A4 substrate	Fluconazole, Amiodarone	Bosentan levels considerably increase. Combination potentially contraindicated.
	CYP2C9 and CYP3A4 inducers	Rifampicin, Phenytoin	Bosentan levels decrease by 58%. Need for dose adjustment uncertain.
	CYP2C9 inducer	HMG CoA reductase inhibitors	Simvastatin levels reduce 50%; similar effects likely with Atorvastatin. Cholesterol level should be monitored.
	CYP2C9 inducer	Warfarin	Increases Warfarin metabolism, may need to adjust Warfarin dose. Intensified monitoring of Warfarin recommended following initiation but dose adjustment usually unnecessary.
	CYP2C9 and CYP3A4 inducers	Hormonal contraceptives	Hormone levels decrease. Contraception unreliable.
Sitaxentan	CYP2C9 inhibitor	Warfarin	Inhibits Warfarin metabolism, Warfarin dose needs to be reduced by 80% when initiating Sitaxentan and INR monitoring intensified.
	? inhibition of OATP transporter	Cyclosporine	Increases Sitaxentan levels; combination contraindicated.

This table is adapted from National Pulmonary Hypertension Centres of the UK and Ireland. Consensus Statement on the Management of Pulmonary Hypertension in Clinical Practice in the UK and Ireland. Heart 2008; 94 (Suppl I):i1-i41.

Table 18: Potentially significant drug interactions with PAH targeted therapies (cont.)

PAH Drug	Mechanism of interaction	Interacting Drug	Interaction
Sildenafil	CYP3A4 substrate	Bosentan	Sildenafil levels fall 50%; Bosentan levels increase 50%. May not require dose adjustments of either drug.
	CYP3A4 substrate	HMG CoA reductase inhibitors	May increase Simvastatin/Atorvastatin levels through competition for metabolism. Sildenafil levels may increase. Possible increased risk of rhabdomyolysis.
	CYP3A4 substrate	HIV protease inhibitors	Ritonavir and Saquinovir increase Sildenafil levels markedly. Sildenafil dose adjustments are usually required.
	CYP3A4 inducer	Phenytoin	Sildenafil level may fall.
	CYP3A4 substrate	Erythromycin	Sildenafil levels increase may not require dose adjustment for a short course.
	CYP3A4 substrate	Ketoconazole	Sildenafil levels increase. May not require dose adjustment.
	CYP3A4 substrate	Cimetidine	Sildenafil levels increase. May not require dose adjustment.
	cGMP	Nitrates Nicorandil	Profound systemic hypotension, combination contraindicated.
Tadalafil	CYP3A4 substrate	Bosentan	Tadalafil plasma levels decreases by 42%, no significant changes in Bosentan levels. May not require dose adjustment.
	cGMP	Nitrates Nicorandil	Profound systemic hypotension, combination contraindicated.

cGMP = cyclic guanosine monophosphate; OATP = organic anion transporter proteins

4.4 Specific pulmonary arterial hypertension subsets

Table 19: Recommendations for paediatric PAH

Statement	Class[a]	Level[b]
The PH diagnostic work-up proposed for adults should be considered also in children.	IIa	C
The PAH therapeutic algorithm proposed for adults should be considered also in children.	IIa	C

a = Class of recommendation; b = Level of evidence; PAH = pulmonary arterial hypertension; PH = pulmonary hypertension

Table 20: Recommendations for PAH associated with congenital cardiac shunts

Statement	Class[a]	Level[b]
The ERA bosentan is indicated in WHO-FC III patients with Eisenmenger's syndrome.	I	B
Other ERAs, phosphodiesterase type-5 inhibitors and prostanoids should be considered in patients with Eisenmenger's syndrome.	IIa	C
In the absence of significant haemoptysis, oral anticoagulant treatment should be considered in patients with PA thrombosis or signs of heart failure.	IIa	C
The use of supplemental O_2 therapy should be considered in cases in which it produces a consistent increase in arterial oxygen saturation and reduces symptoms.	IIa	C
If symptoms of hyperviscosity are present, phlebotomy with isovolumic replacement should be considered usually when the haematocrit is > 65%.	IIa	C
Combination therapy may be considered in patients with Eisenmenger's syndrome.	IIb	C
The use of CCBs is not recommended in patients with Eisenmenger's syndrome.	III	C

a = Class of recommendation; b = Level of evidence; CCBs = calcium channel blockers; ERA = endothelin receptor antagonist; WHO-FC = World Health Organization functional class

Table 21: Recommendations for PAH associated with connective tissue disease

Statement	Class[a]	Level[b]
In patients with PAH associated with CTD the same treatment algorithm as in patients with IPAH is recommended.	I	A
Echocardiographic screening for the detection of PH is recommended in symptomatic patients with scleroderma spectrum of diseases.	I	B
Echocardiographic screening for the detection of PH is recommended in symptomatic patients with all other CTD.	I	C
RHC is indicated in all cases of suspected PAH associated with CTD, in particular if specific drug therapy is considered.	I	C
Oral anticoagulation should be considered on an individual basis.	IIa	C
Echocardiographic screening for the detection of PH may be considered in asymptomatic patients with the scleroderma spectrum of disease.	IIb	C

a = Class of recommendation; b = Level of evidence; CTD = connective tissue diseases; PAH = pulmonary arterial hypertension; PH = pulmonary hypertension; RHC = right heart catheterization

Table 22: Recommendations for PAH associated with portal hypertension

Statement	Class[a]	Level[b]
Echocardiographic screening for the detection of PH is recommended in symptomatic patients with liver diseases and/or in candidates for liver transplantation.	I	B
In patients with PAH associated with portal hypertension the same treatment algorithm as in patients with IPAH should be considered, taking into consideration comorbidities.	IIa	C
Anticoagulation is not recommended in patients with increased risk of bleeding.	III	C
Significant PAH is a contra-indication to liver transplantation if mean PAP is ≥ 35 mmHg and/or PVR is ≥ 250 dynes.s.cm-^{5}.	III	C

a = Class of recommendation; b = Level of evidence; IPAH = idiopathic PAH; PAH = pulmonary arterial hypertension; PAP = pulmonary arterial pressure; PH = pulmonary hypertension; PVR = pulmonary vascular resistance

Table 23: Recommendations for PAH associated with HIV infection

Statement	Class[a]	Level[b]
Echocardiography is indicated in patients with unexplained dyspnoea to detect HIV-related cardiovascular complications.	I	C
In patients with PAH associated with HIV infection, the same treatment algorithm as in patients with IPAH should be considered, taking into consideration comorbidities and drug-drug interactions.	IIa	C
Anticoagulation is not recommended in patients with increased risk of bleeding.	III	C

a = Class of recommendation; b = Level of evidence; IPAH = idiopathic PAH; PAH = pulmonary arterial hypertension; HIV = human immunodeficiency virus

5. Pulmonary veno-occlusive disease and pulmonary capillary haemangiomatosis (Group 1')

Table 24: Recommendations for pulmonary veno-occlusive disease

Statement	Class[a]	Level[b]
Referral of patients with PVOD to a transplant centre for evaluation is indicated as soon as the diagnosis is established.	I	C
Patients with PVOD should be managed only in centres with extensive experience in PAH due to the risk of lung oedema after the initiation of PAH specific drug therapy.	IIa	C

a = Class of recommendation; b = Level of evidence; PAH = pulmonary arterial hypertension; PVOD = pulmonary veno-occlusive disease

6. Pulmonary hypertension due to left heart disease (Group 2)

Table 25: Recommendations for pulmonary hypertension due to left heart disease

Statement	Class[a]	Level[b]
The optimal treatment of the underlying left heart disease is recommended in patients with PH due to left heart disease.	I	C
Patients with "out of proportion" PH due to left heart disease should be enrolled in RCTs targeting PH specific drugs.	IIa	C
Increased left-sided filling pressures may be estimated by Doppler echocardiography.	IIb	C
Invasive measurements of PWP or LV end-diastolic pressure may be required to confirm the diagnosis of PH due to left heart disease.	IIb	C
RHC may be considered in patients with echocardiographic signs suggesting severe PH in patients with left heart disease.	IIb	C
The use of PAH specific drug therapy is not recommended in patients with PH due to left heart disease.	III	C

a = Class of recommendation; b = Level of evidence; LV = left ventricle/ventricular; PAH = pulmonary arterial hypertension; PH = pulmonary hypertension; PWP = pulmonary wedge pressure; RCT = randomized controlled trial

7. Pulmonary hypertension due to lung diseases and/or hypoxia (Group 3)

Table 26: Recommendations for pulmonary hypertension due to lung diseases and/or hypoxia

Statement	Class[a]	Level[b]
Echocardiography is recommended as screening tool for the assessment of PH due to lung diseases.	I	C
RHC is recommended for a definite diagnosis of PH due to lung diseases.	I	C
The optimal treatment of the underlying lung disease including long-term O_2 therapy in patients with chronic hypoxaemia is recommended in patients with PH due to lung diseases.	I	C
Patients with "out of proportion" PH due to lung diseases should be enrolled in RCTs targeting PAH specific drugs.	IIa	C
The use of PAH specific drug therapy is not recommended in patients with PH due to lung diseases.	III	C

a = Class of recommendation; b = Level of evidence; PAH = pulmonary arterial hypertension; PH = pulmonary hypertension; RCT = randomized controlled trial; RHC = right heart catheterization

8. Chronic thromboembolic pulmonary hypertension (Group 4)

Table 27: Recommendations for chronic thromboembolic pulmonary hypertension

Statement	Class[a]	Level[b]
The diagnosis of CTEPH is based on the presence of precapillary PH (mean PAP ≥ 25 mmHg, PWP ≤ 15 mmHg, PVR > 2 WU) in patients with multiple chronic/organized occlusive thrombi/emboli in the elastic pulmonary arteries (main, lobar, segmental, sub-segmental).	I	C
In patients with CTEPH lifelong anticoagulation is indicated.	I	C
Surgical pulmonary endarterectomy is the recommended treatment for patients with CTEPH.	I	C
Once perfusion scanning and/or CT angiography show signs compatible with CTEPH, the patient should be referred to a centre with expertise in surgical pulmonary endarterectomy.	IIa	C
The selection of patients for surgery should be based on the extent and location of the organized thrombi, on the degree of PH and on the presence of comorbidities.	IIa	C
PAH specific drug therapy may be indicated in selected CTEPH patients such as patients not candidates for surgery or patients with residual PH after PEA.	IIb	C

a = Class of recommendation; b = Level of evidence; CT = computerised tomography; CTEPH = chronic thromboembolic pulmonary hypertension; PAH = pulmonary arterial hypertension; PAP = pulmonary arterial pressure; PEA = pulmonary endarterectomy; PWP = pulmonary wedge pressure

9. Definition of pulmonary arterial hypertension referral centre

Table 28: Recommendations for pulmonary arterial hypertension referral center

Statement	Class[a]	Level[b]
Referral centres are required to provide care by a multi-professional team (cardiology and respiratory medicine physicians, clinical nurse specialists, radiologists, psychological and social work support, appropriate on-call expertise).	I	C
Referral centres are required to have direct links and quick referral patterns to other services (such as CTD service, family planning service, PEA service, lung transplantation service, adult congenital heart disease service).	I	C
A referral centre should follow at least 50 patients with PAH or CTEPH and should receive at least two new referrals per month with documented PAH or CTEPH.	IIa	C
Referral centres should perform at least 20 vasoreactivity tests in PAH patients per year.	IIa	C
Referral centres should participate in collaborative clinical research in PAH, which includes phase II and phase III clinical trials.	IIa	C

a = Class of recommendation; b = Level of evidence; CTD = connective tissue diseases; CTEPH = chronic thromboembolic pulmonary hypertension; PAH = pulmonary arterial hypertension; PEA = pulmonary endarterectomy

Section XII: Arrhythmias

1. Supraventricular Arrhythmias (SVA)

2. Atrial Fibrillation (AF)

3. Syncope

4. Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death

5. Cardiac Pacing and Cardiac Resynchronization Therapy

Chapter 1
Supraventricular Arrhythmias (SVA)*
2003

A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients with Supraventricular Arrhythmias)

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I. Introduction

Supraventricular arrhythmias (SVAs) include rhythms emanating from or involving the sinus node, atrial tissue (atrial tachycardias (ATs), atrial flutter), and junctional tissue (atrioventricular nodal reciprocating tachycardia (AVNRT)). Accessory pathway-mediated or atrioventricular reciprocating tachycardia (AVRT) are also included. Supraventricular arrhythmia occurs in all age groups and may be associated with minimal symptoms, such as palpitations, or may present with syncope. In some conditions (i.e. those associated with bypass tracts) arrhythmias may be life-threatening. The prevalence of paroxysmal supraventricular tachycardia (PSVT) is 2-3 per 1,000. Over the past decade, impressive advances in curative treatment modes (catheter ablation) have been made.

The purpose of this booklet is to summarize guidelines for use of drug and ablative procedures for patients with supraventricular tachycardia (SVT). Guidelines for treatment of atrial fibrillation were recently published, hence this subject is excluded in the present booklet. In addition, SVT in the paediatric population is excluded. The ACC/AHA/ESC Guidelines for the Management of Patients with Atrial Fibrillation (2) discuss antiarrhythmic drug doses and adverse effects, and therefore, this will not be repeated.

The guidelines outlined come from an expert committee selected by the European Society of Cardiology (ESC), American College of Cardiology (ACC), and American Heart Association (AHA). The ultimate judgment regarding care of a particular patient must be made by the physician and patient in light of all of the circumstances

* Adapted from the ACC/AHA/ESC Guidelines for the Management of Patients with Supraventricular Arrhythmias: Executive Summary (European Heart Journal 2003; 24 (20): 1857-1897) (1)

J. Bax et al., *Compendium of Abridged ESC Guidelines 2001*

presented by that patient. In some circumstances deviations from these guidelines may be appropriate.

Recommendations are provided in tables and use the following classification outline, summarizing both the evidence and expert opinion:

Class I:	Conditions for which there is evidence for and/or general agreement that the procedure or treatment is useful and effective.
Class II:	Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment.
Class IIa:	The weight of evidence or opinion is in favor of the procedure or treatment.
Class IIb:	Usefulness/efficacy is less well established by evidence or opinion.
Class III:	Conditions for which there is evidence and/or general agreement that the procedure or treatment is not useful/effective and in some cases may be harmful.

II. General evaluation and management:

A. Patients without documented arrhythmia (Figure 1)

Clinical History

Distinguish whether palpitations are regular or irregular.

- Pauses or dropped beats followed by a sensation of a strong heartbeat support presence of premature beats.
- Irregular palpitations may be due to premature extra beats, atrial fibrillation or multifocal atrial tachycardia.
- Regular and recurrent palpitations with abrupt onset and termination are designated as paroxysmal (also referred to as PSVT). Termination by vagal manoeuvres suggests a re-entrant tachycardia involving atrioventricular (AV) nodal tissue (e.g. AVNRT, AVRT).
- Sinus tachycardia is non-paroxysmal and accelerates and terminates gradually.

B. Patients with documented arrhythmia

1. Narrow QRS-complex tachycardia

If the ventricular action (QRS) is narrow (less than 120 milliseconds [ms]), then the tachycardia is almost always supraventricular and the differential diagnosis relates to its mechanism (Figure 2). The clinician must determine the relationship of the P waves to the ventricular complex (Figure 3). Responses of narrow QRS-complex tachycardias to adenosine (Figure 4) or carotid massage may aid in the differential diagnosis.

2. Wide QRS-complex tachycardia (Figure 5)

At times, the patient will present with rapid wide QRS-complex tachycardia (greater than 120 ms) and the clinician must decide whether the patient has :

a) SVT with bundle branch block (BBB) (or aberration),

b) SVT with AV conduction over an accessory pathway,

c) ventricular tachycardia (VT).

This categorization depends not only on the relation of P wave to QRS but also on specific morphological findings, especially in the precordial leads (Figure 5).

3. Management

If the diagnosis of SVT cannot be proven, the patient should be treated as if VT were present. Medications for SVT (verapamil or diltiazem) may precipitate haemodynamic collapse in a patient with VT. Special circumstances (i.e., pre-excited tachycardias and VT due to digitalis toxicity) may require alternative therapy. Immediate direct current (DC) cardioversion is the treatment of choice for any haemodynamically unstable tachycardia.

Indications for referral to a cardiac arrhythmia specialist:

- All patients with Wolff-Parkinson-White (WPW) syndrome (pre-excitation + arrhythmias).
- All patients with severe symptoms during palpitations, such as syncope or dyspnea.
- Wide QRS-complex tachycardia of unknown origin.
- Narrow QRS-complex tachycardias with drug resistance, drug intolerance or desire to be free of drug therapy.

Recommendations for acute management of haemodynamically stable and regular tachycardia

ECG	Recommendation*	Class	Level of evidence
Narrow QRS-complex tachycardia (SVT)	Vagal manoeuvres	I	B
	Adenosine	I	A
	Verapamil, diltiazem	I	A
	Beta-blockers	II b	C
	Amiodarone	II b	C
	Digoxin	II b	C
Wide QRS-complex tachycardia	See above		
• SVT and BBB	Flecainide ‡	I	B
• Pre-excited SVT/AF †	Ibutilide ‡	I	B
	Procainamide ‡	I	B
	DC cardioversion	I	C
• Wide QRS-complex tachycardia of unknown origin	Procainamide ‡	I	B
	Sotalol ‡	I	B
	Amiodarone	I	B
	Lidocaine	II b	B
	Adenosine §	II b	C
	Beta-blockers ¶	III	C
	Verapamil**	III	B
	DC cardioversion	I	B
Wide QRS-complex tachycardia of unknown origin in patients with poor LV function	Amiodarone	I	B
	Lidocaine		
	DC cardioversion	I	B

The order in which treatment recommendations appear in this table within each class of recommendation does not necessarily reflect a preferred sequence of administration. Please refer to text for details. For pertinent drug dosing information, please refer to the ACC/AHA/ESC Guidelines for the Management of Patients with Atrial Fibrillation (2). * All listed drugs are administered intravenously. † See Section IIID, specific section in reference 1. ‡ Should not be taken by patients with reduced LV function. § Adenosine should be used with caution in patients with severe coronary artery disease because vasodilation of normal coronary vessels may produce ischaemia in vulnerable territory. It should be used only with full resuscitative equipment available. ¶ Beta-blockers may be used as first-line therapy for those with catecholamine-sensitive tachycardias, such as right ventricular outflow tachycardia. ** Verapamil may be used as first-line therapy for those with LV fascicular VT. AF = atrial fibrillation ; BBB = bundle-branch block; DC = direct current; ECG = electrocardiogram; LV = left ventricular; QRS = ventricular activation on ECG; SVT = supraventricular tachycardia.

III. Specific arrhythmias

A. Inappropriate sinus tachycardia

Inappropriate sinus tachycardia refers to a persistent increase in resting heart rate unrelated to the level of physical, emotional, pathological or pharmacological stress. Approximately 90% are female. The degree of disability can vary from asymptomatic to individuals who are totally incapacitated.

The diagnosis is based on the following criteria:

- Persistent sinus tachycardia (heart rate > 100 bpm) during the day with excessive rate increase in response to activity and nocturnal normalization of rate as confirmed by a 24 hour Holter recording.
- The tachycardia and its symptoms are not paroxysmal.
- P-wave morphology is identical to sinus rhythm.
- Exclusion of a secondary systemic cause (hyperthyroidism, pheochromocytoma, physical deconditioning).

Treatment

The treatment is predominantly symptom driven. The long-term success rate of sinus node modification by catheter ablation has been reported to be around 66%. The diagnosis of Postural Orthostatic Tachycardia Syndrome (POTS) must be excluded before considering ablation.

Recommendations for treatment of inappropriate sinus tachycardia

Treatment	Recommendation	Class	Level of evidence
Medical	Beta-blockers	I	C
	Verapamil, diltiazem	II a	C
Interventional	Catheter ablation - sinus node modification/elimination*	II b	C

The order in which treatment recommendations appear in this table within each class of recommendation does not necessarily reflect a preferred sequence of administration. Please refer to text for details. For pertinent drug dosing information, please refer to the ACC/AHA/ESC Guidelines for the Management of Patients with Atrial Fibrillation (2). *Used as a last resort.

B. Atrioventricular Nodal Reciprocating Tachycardia (AVNRT)

AVNRT is a re-entry tachycardia involving the AV node as well as perinodal atrial tissue. One pathway (fast) is located near the superior portion of the AV node and the other (slow) along the septal margin of the tricuspid annulus. During typical AVNRT (85-90%), antegrade conduction occurs over the slow pathway with a turnaround point in the AV junction, and retrograde conduction occurs over the fast pathway. The converse is found during atypical AVNRT, resulting in a long R-P tachycardia with negative P waves in III and aVF inscribed prior to the QRS.

Treatment

Standard treatment is use of drugs that primarily block AV nodal conduction (beta-blockers, calcium channel blockers, adenosine). Another treatment option that has been shown to be effective and safe involves catheter ablation to destroy the slow pathway. Indications for ablation depend on clinical judgement and are often predicated on patient preference. Factors that contribute to the decision include tachycardia frequency, tolerance of symptoms, and patient inclination relative to chronic drug therapy vs. ablation. The patient must accept the risk, albeit small (< 1%), of AV block and pacemaker insertion.

Recommendations for long-term treatment of patients with recurrent AVNRT

Clinical presentation	Intervention	Class	Level of evidence
Poorly tolerated AVNRT with haemodynamic intolerance	Catheter ablation	I	B
	Verapamil, diltiazem, beta-blockers, sotalol, amiodarone	II a	C
	Flecainide*, propafenone*	II a	C
Recurrent symptomatic AVNRT	Catheter ablation	I	B
	Verapamil	I	B
	Diltiazem, beta-blockers	I	C
	Digoxin †	II b	C
Recurrent AVNRT unresponsive to beta-blockade or calcium-channel blocker and patient not desiring RF ablation	Flecainide*, propafenone*, sotalol	II a	B
	Amiodarone	II b	C
AVNRT with infrequent or single episode in patients who desire complete control of arrhythmia	Catheter ablation	I	B
Documented PSVT with only dual AV-nodal pathways or single echo beats demonstrated during electrophysiological study and no other identified cause of arrhythmia	Verapamil, diltiazem, beta-blockers, flecainide*, propafenone*	I	C
	Catheter ablation ‡	I	B
Infrequent, well-tolerated AVNRT	No therapy	I	C
	Vagal manoeuvres	I	B
	"Pill-in-the-pocket"	I	B
	Verapamil,diltiazem, beta-blockers	I	B
	Catheter ablation	I	B

The order in which treatment recommendations appear in this table within each class of recommendation does not necessarily reflect a preferred sequence of administration. Please refer to text for details. For pertinent drug dosing information, please refer to the ACC/AHA/ESC Guidelines for the Management of Patients with Atrial Fibrillation [2]. * Relatively contraindicated for patients with coronary artery disease, LV dysfunction, or other significant heart disease. † Digoxin is often ineffective because pharmacological effects can be overridden by enhanced sympathetic tone. ‡ Decision depends on symptoms. AV = atrioventricular; AVNRT = atrioventricular nodal reciprocating tachycardia; LV = left ventricular; PSVT = paroxysmal supraventricular tachycardia; RF = radiofrequency.

C. Focal and nonparoxysmal junctional tachycardia

1. Focal junctional tachycardia

The unifying feature of focal junctional tachycardia, also known as automatic or junctional ectopic tachycardia, is their origin from the AV node or His bundle. The ECG features of focal junctional tachycardia include heart rates of 110–250 bpm and a narrow complex or typical BBB conduction pattern with AV dissociation. Occasionally the junctional rhythm is quite erratic, suggesting AF. This is a rare arrhythmia seen in young adults and if persistent, it may produce congestive heart failure. Drug therapy has been associated with only variable success and catheter ablative procedures are associated with a 5–10% risk of AV block.

2. Nonparoxysmal junctional tachycardia

Nonparoxysmal junctional tachycardia is a benign arrhythmia that is characterized by a narrow complex tachycardia with rates of 70–120 bpm. The arrhythmia is thought to be due to abnormal automaticity or triggered rhythms and serves as a marker for underlying problems including digitalis toxicity, postcardiac surgery, hypokalemia, or myocardial ischaemia. Treatment is most often directed at the underlying condition.

Recommendations for treatment of focal and nonparoxysmal junctional tachycardia syndromes

Clinical presentation	Recommendation	Class	Level of evidence
Focal junctional tachycardia	Beta-blockers	II a	C
	Flecainide	II a	C
	Propafenone *	II a	C
	Sotalol *	II a	C
	Amiodarone *	II a	C
	Catheter ablation	II a	C
Nonparoxysmal junctional tachycardia	Reverse digitalis toxicity	I	C
	Correct hypokalemia	I	C
	Treat myocardial ischaemia	I	C
	Beta-blockers, calcium-channel blockers	II a	C

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D. Atrioventricular reciprocating re-entry tachycardia (extranodal accessory pathways)

Typical accessory pathways are extranodal pathways that connect the myocardium of the atrium and the ventricle across the AV groove. Accessory pathways that are capable of only retrograde conduction are referred to as "concealed", whereas those capable of anterograde conduction are "manifest", demonstrating pre-excitation on a standard ECG. The term WPW syndrome is reserved for patients who have both pre-excitation and tachyarrhythmias.

Several forms of tachycardias may occur:

- Orthodromic AVRT (most common, 95%) involves anterograde conduction over the AV node and retrograde conduction over the accessory pathway.
- Antidromic AVRT anterograde conduction over the accessory pathway and retrograde conduction over the AV node (or rarely over a second accessory pathway) resulting in pre-excited QRS-complexes during tachycardia.
- Pre-excited tachycardias in patients with AT or atrial flutter with a bystander (not a critical part of tachycardia circuit) accessory pathway.
- Pre-excited atrial fibrillation, the most feared arrhythmia, occurs in 30% of patients with the WPW syndrome.
- PJRT (permanent form of junctional reciprocating tachycardia) - a rare clinical syndrome with a slowly conducting concealed posteroseptal accessory pathway characterized by an incessant, long RP tachycardia with negative P waves in leads II, III, and aVF.

Sudden Cardiac Death in WPW syndrome and risk stratification

Markers that identify patients at increased risk include: 1) a shortest pre-excited R-R interval < 250 ms during AF, 2) a history of symptomatic tachycardia, 3) multiple accessory pathways, and 4) Ebstein's anomaly. The risk for sudden cardiac death is estimated at between 0.15 - 0.39% of patients with WPW syndrome over 3 to 10 year follow-up.

Asymptomatic patients with accessory pathways

The positive predictive value of invasive electrophysiologic testing is too low to justify routine use in asymptomatic patients. The decision to ablate pathways in individuals with high risk occupations such as school bus drivers, pilots, and athletes, is made on individual clinical considerations.

Treatment

Acute treatment of patients with pre-excited tachycardias

AV nodal blocking agents are not effective and adenosine may produce AF with a rapid ventricular rate. Antiarrhythmic drugs preventing rapid conduction through the pathway (flecainide, procainamide, or ibutilide), are preferable, even if they may not convert the atrial arrhythmia.

Long term therapy

Antiarrhythmic drugs represent one therapeutic option for management of patients with accessory pathway-mediated arrhythmias, but they have been increasingly replaced by catheter ablation. A regimen designed for use of drug(s) at the onset of an episode should only be used for patients with infrequent, well-tolerated episodes.

Some patients with infrequent episodes of tachycardia may be managed with the single-dose "pill-in-the-pocket" approach: taking an antiarrhythmic drug only at the onset of a tachycardia episode. This approach to treatment is reserved for patients without pre-excitation and with uncommon and haemodynamically tolerated tachycardia.

Catheter ablative techniques are successful in approximately 95% of cases and have sufficient efficacy and low risk to be used for symptomatic patients, either as initial therapy or for patients experiencing side effects or arrhythmia recurrence during drug therapy. The type of possible complications varies depending on the site of the pathway. The incidence of inadvertent complete AV block ranges from 0.17 - 1.0%, and relates to septal and posteroseptal accessory pathways. Significant adverse effects range from 1.8 to 4% including 0.08 to 0.13% risk of death.

Recommendations for long-term therapy of accessory pathway-mediated arrhythmias

Arrhythmia	Recommendation	Class	Level of evidence
WPW syndrome (pre-excitation and symptomatic arrhythmias), well tolerated	Catheter ablation	I	B
	Flecainide, propafenone	II a	C
	Sotalol, amiodarone, beta-blockers	II a	C
	Verapamil, diltiazem, digoxin	III	C
WPW syndrome (with AF and rapid-conduction or poorly tolerated AVRT)	Catheter ablation	I	B
AVRT, poorly tolerated (no pre-excitation)	Catheter ablation	I	B
	Flecainide, propafenone	II a	C
	Sotalol, amiodarone	II a	C
	Beta-blockers	II b	C
	Verapamil, diltiazem, digoxin	III	C
Single or infrequent AVRT episode(s) (no pre-excitation)	None	I	C
	Vagal manoeuvres	I	B
	"Pill-in-the-pocket" verapamil, diltiazem, beta-blockers	I	B
	Catheter ablation	II a	B
	Sotalol, amiodarone	II b	B
	Flecainide, propafenone	II b	C
	Digoxin	III	C
Pre-excitation, asymptomatic	None	I	C
	Catheter ablation	II a	B

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E. Focal atrial tachycardia (FAT)

Focal ATs are characterized by radial spread of activation from a focus, with endocardial activation not extending through the entire atrial cycle. They are usually manifest by atrial rates between 100 and 250 bpm (rarely at 300 bpm). The mechanism has been attributed to abnormal or enhanced automaticity, triggered activity (due to delayed after depolarization), or micro-re-entry. A progressive increase in atrial rate with tachycardia onset ("warm-up") and/or progressive decrease before tachycardia termination ("cool-down") suggests an automatic mechanism. Approximately 10% of patients have multiple foci. Focal AT may be incessant leading to tachycardia-induced cardiomyopathy.

Treatment

Therapeutic options include use of drugs for rate control (beta-blockers, calcium-channel blockers, or digoxin) or for suppression of the arrhythmic focus. In addition, class Ia or Ic (flecainide and propafenone) drugs may prove effective.

The available studies suggest use of IV adenosine, beta-blockers or calcium-channel blockers for either acute termination (unusual) or more frequently to achieve rate control. Adenosine will terminate FAT in a significant number of patients. DC cardioversion seldom terminates automatic ATs but may be successful for ATs based on micro-re-entry or triggered automaticity, and should be attempted in patients with drug-resistant arrhythmia.

Chronic control involves initial use of AV nodal blocking drugs since they may prove effective and have minimal side effects. Other more potent agents should be reserved for after failure of an AV nodal blocker. Focal AT is ablated by targeting the site of origin of the AT. Catheter ablation has a success rate of 80% to 90% for right atrial foci and 70% to 80% for left atrial foci. The incidence of significant complications is low (1–2%). Ablation of AT from the atrial septum or Koch's triangle may produce AV block.

F. Multifocal Atrial Tachycardia (MAT)

The tachycardia is characterized by finding three or more different P wave morphologies at different rates. The rhythm is always irregular and frequently confused with AF. It is most commonly associated with underlying pulmonary disease, but may result from metabolic or electrolyte derangements. Therapy includes correction of underlying abnormalities, but often requires use of calcium channel blockers as there is no role for DC cardioversion, antiarrhythmic drugs or ablation.

G. Macro-re-entrant atrial tachycardia

Atrial flutter is defined as an organized rapid (250–350 bpm) macroreentrant atrial rhythm. The most common forms relate to reentrant rhythms that circulate around the tricuspid annulus. Isthmus-dependent flutter refers to circuits in which the arrhythmia involves the cavotricuspid isthmus (CTI). They are most frequently manifest as counterclockwise (negative flutter deflections in inferior leads) but can be clockwise (positive deflections in the inferior leads).

Non-isthmus dependent atrial flutter is less frequent and is often caused by surgical scars that produce a central obstacle for reentry. For patients with non-isthmus dependent flutter, large areas of atrial scar are found (with cardiac mapping) and are often associated with multiple reentrant circuits. Atrial flutter may cause insidious symptoms such as exercise-induced fatigue, worsening heart failure or pulmonary disease. Patients often present with a 2:1 AV conduction which, if left untreated, may promote cardiomyopathy.

Treatment

Acute therapy depends on the clinical status of the patient as well as underlying cardio-respiratory problems. If the arrhythmia is attended by heart failure, shock, or myocardial ischaemia then prompt DC cardioversion is in order. Rapid atrial (or esophageal pacing) as well as low energy DC cardioversion are all very effective in termination of atrial flutter. In most instances, however, patients with flutter are stable and trials of AV-nodal-blocking drugs for rate control are in order.

This is especially important if the subsequent use of antiarrhythmic drugs is planned, since slowing of the flutter rate by antiarrhythmic drugs (especially Class Ic drugs) may result in a paradoxical increase in the ventricular rate. If the atrial flutter persists for longer than 48 hours then either a 3–4 week course of anticoagulant therapy or a negative (Absence of clots) T.E.E. (Trans-esophageal Echocardiogram) is advisable prior to attempting electrical or drug conversion. These recommendations are identical to those used for management of atrial fibrillation. Neither atrioventricular (AV) nodal drugs nor amiodarone are effective for conversion of atrial flutter. Intravenous ibutilide appears to be the most effective agent for acute drug termination of flutter with an efficacy between 38% and 76%, and is more effective than intravenous class Ic agents.

Class III drugs, especially dofetilide appear to be quite effective chronic therapy for patients with flutter (73% response rate). Chronic therapy is usually not required after sinus rhythm is restored if atrial flutter occurs as part of an acute disease process.

Recommendations for treatment of focal atrial tachycardia*

Clinical situation	Recommendation	Class	Level of evidence
Acute treatment †			
A. Conversion			
Haemodynamically unstable patient	DC cardioversion	I	B
Haemodynamically stable patient	Adenosine	II a	C
	Beta-blockers	II a	C
	Verapamil, diltiazem	II a	C
	Procainamide	II a	C
	Flecainide, propafenone	II a	C
	Amiodarone, sotalol	II a	C
B. Rate regulation (in absence of digitalis therapy)	Beta-blockers	I	C
	Verapamil, diltiazem	I	C
	Digoxin	II b	C
Prophylactic therapy			
Recurrent symptomatic AT	Catheter ablation	I	B
	Beta-blockers, calcium-channel blocker	I	C
	Disopyramide ‡	II a	C
	Flecainide, propafenone ‡	II a	C
	Sotalol, amiodarone	II a	C
Asymptomatic or symptomatic incessant ATs	Catheter ablation	I	B
Nonsustained and asymptomatic	No therapy	I	C
	Catheter ablation	III	C

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Catheter ablation of the CTI is a safe and effective cure for patients with CTI dependent flutter. For those patients with non-isthmus dependent flutter referral to a specialized center is in order, since multiple complex circuits are frequently found. Success rates vary from 50 to 88% depending on lesion complexity.

Recommendations for acute management of atrial flutter

Clinical status/Proposed therapy	Recommendation	Class	Level of evidence
Poorly tolerated			
• Conversion	DC cardioversion	I	C
• Rate control	Beta-blockers	II a	C
	Verapamil, diltiazem	II a	C
	Digitalis †	II b	C
	Amiodarone	II b	C
Stable flutter			
• Conversion	Atrial or transesophageal pacing	I	A
	DC cardioversion	I	C
	Ibutilide ‡	II a	A
	Flecainide §	II b	A
	Propafenone §	II b	A
	Sotalol	II b	C
	Procainamide §	II b	A
	Amiodarone	II b	C
• Rate control	Diltiazem or Verapamil	I	A
	Beta-blockers	I	C
	Digitalis †	II b	C
	Amiodarone	II b	C

The order in which treatment recommendations appear in this table within each class of recommendation does not necessarily reflect a preferred sequence of administration. Please refer to text for details. For pertinent drug dosing information, please refer to the ACC/AHA/ESC Guidelines for the Management of Patients with Atrial Fibrillation (2). Cardioversion should be considered only if the patient is anticoagulated (INR equals 2 to 3), the arrhythmia is less than 48 hours in duration, or the TEE shows no atrial clots. All listed drugs are taken intravenously. † Digitalis may be especially useful for rate control in patients with heart failure. ‡ Ibutilide should not be used in patients with reduced LV function. § Flecainide, propafenone, and procainamide should not be used unless they are combined with an AV-nodal-blocking agent. AV = atrioventricular; DC = direct current; INR = international normalized ratio; LV = left ventricular; TEE = transesophageal echocardiography.

Recommendations for long-term management of atrial flutter

Clinical status/Proposed therapy	Recommendation	Class	Level of evidence
First episode and well-tolerated atrial flutter	Cardioversion alone	I	B
	Catheter ablation*	II a	B
Recurrent and well-tolerated atrial flutter	Catheter ablation*	I	B
	Dofetilide	II a	C
	Amiodarone, Sotalol, Flecainide †‡, quinidine †‡, propafenone †‡, procainamide †‡, disopyramide †‡	II b	C
Poorly tolerated atrial flutter	Catheter ablation*	I	B
Atrial flutter appearing after use of class Ic agents or amiodarone for treatment of AF	Catheter ablation*	I	B
	Stop current drug and use another	II a	C
Symptomatic non-CTI-dependent flutter after failed antiarrhythmic drug therapy	Catheter ablation*	II a	B

The order in which treatment recommendations appear in this table within each class of recommendation does not necessarily reflect a preferred sequence of administration. Please refer to text for details. For pertinent drug dosing information, please refer to the ACC/AHA/ESC Guidelines for the Management of Patients with Atrial Fibrillation (2). * Catheter ablation of the AV junction and insertion of a pacemaker should be considered if catheter ablative cure is not possible and the patient fails drug therapy. † These drugs should not be taken by patients with significant structural cardiac disease. Use of anticoagulants is identical to that described for patients with AF. ‡ Flecainide, propafenone, procainamide, quinidine, and disopyramide should not be used unless they are combined with an AV-nodal-blocking agent. AF = atrial fibrillation; AV = atrioventricular; CTI = cavotricuspid isthmus.

H. Special circumstances

1. Pregnancy

SVT occurring during pregnancy may be a particularly difficult problem. There is concern for the haemodynamic effects on the mother and foetus as well as for the possible adverse drug effects on the foetus. Certain principles should be emphasized. 1) Arrhythmias curable by ablation should be seriously considered prior to planned pregnancy. 2) Most arrhythmias consist of isolated atrial or ventricular premature beats and do not require therapy. 3) Acute therapy of arrhythmias should be directed at use of non-pharmacological approaches (i.e. vagal manoeuvres). IV adenosine and DC cardioversion have been shown to be safe. The major concern with antiarrhythmic drug treatment during pregnancy is the potential for adverse effects on the foetus. The first 8 weeks after conception is associated with the greatest teratogenic risk. Adverse effects on foetal growth/development are the major risks during the 2nd and 3rd trimester. Antiarrhythmic drug therapy should only be used if symptoms are intolerable or if the tachycardia causes haemodynamic compromise.

Recommendations for treatment strategies for SVT during pregnancy

Treatment strategy	Recommendation	Class	Level of evidence
Acute conversion of PSVT	Vagal manoeuvres	I	C
	Adenosine	I	C
	DC cardioversion	I	C
	Metoprolol, propranolol	II a	C
	Verapamil	II b	C
Prophylactic therapy	Digoxin	I	C
	Metoprolol *	I	B
	Propranolol *	II a	B
	Sotalol*, flecainide †	II a	C
	Quinidine, propafenone †, Verapamil	II b	C
	Procainamide	II b	B
	Catheter ablation	II b	C
	Atenolol ‡	III	B
	Amiodarone	III	C

The order in which treatment recommendations appear in this table within each class of recommendation does not necessarily reflect a preferred sequence of administration. Please refer to text for details. For pertinent drug dosing information, please refer to the ACC/AHA/ESC Guidelines for the Management of Patients with Atrial Fibrillation (2). * Beta-blocking agents should not be taken in the first trimester, if possible. † Consider AV-nodal-blocking agents in conjunction with flecainide and propafenone for certain tachycardias (see Section V). ‡ Atenolol is categorized in class C (drug classification for use during pregnancy) by legal authorities in some European countries. AV = atrioventricular; DC = direct current; PSVT = paroxysmal supraventricular tachycardia.

2. Adults with congenital heart disease

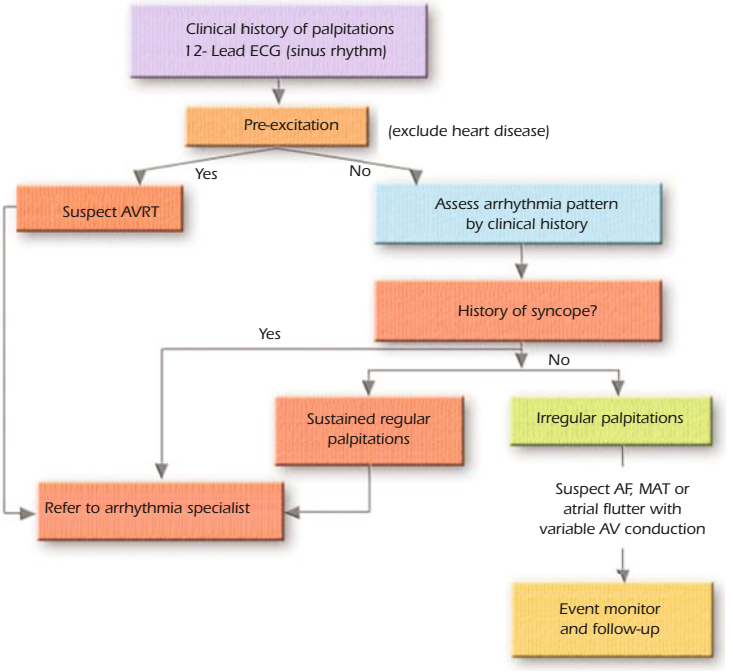
The treatment of SVT in adult patients with repaired or unrepaired congenital heart disease is often complicated and should be managed at experienced centers. Supraventricular arrhythmias are an important cause of morbidity and, in some patients, mortality. These patients often have multiple atrial circuits or mechanisms responsible for arrhythmias. Atrial arrhythmias can indicate deteriorating haemodynamic function, which in some cases warrants specific investigation and operative treatment. Coexistent sinus node dysfunction is common, requiring pacemaker implantation to allow management of SVTs. Cardiac malformations often increase the difficulty of pacemaker implantation and catheter ablation procedures. In addition, arrhythmia therapy by either drugs or catheter ablation must be properly coordinated within the context of surgical repair.

Recommendations for treatment of SVTs in adults with congenital heart disease

Condition	Recommendation	Class	Level of evidence
Failed antiarrhythmic drugs and symptomatic:			
• Repaired ASD:	Catheter ablation in an experienced centre	I	C
• Mustard or Senning repair of transposition of the great vessels:	Catheter ablation in an experienced centre	I	C
Unrepaired haemodynamically significant ASD with atrial flutter*	Closure of the ASD combined with ablation of the flutter isthmus	I	C
PSVT and Ebstein's anomaly with haemodynamic indications for surgical repair	Catheter or surgical ablation of accessory pathways since there may be one or more pathways at the time of operative repair of the malformation at an experienced centre	I	C

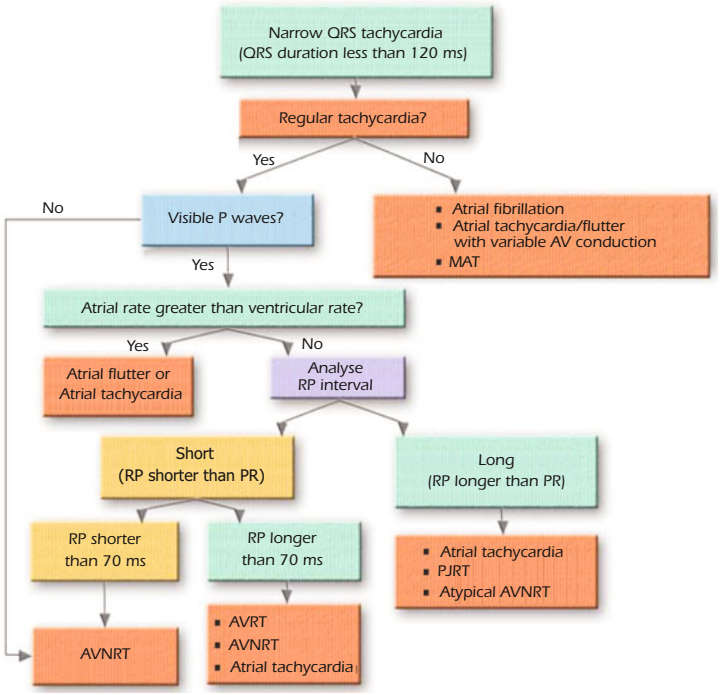
*Conversion and antiarrhythmic drug therapy initial management as described for atrial flutter. ASD = atrial septal defect; PSVT = paroxysmal supraventricular tachycardia.

Figure 1. Initial evaluation of patients with suspected tachycardia



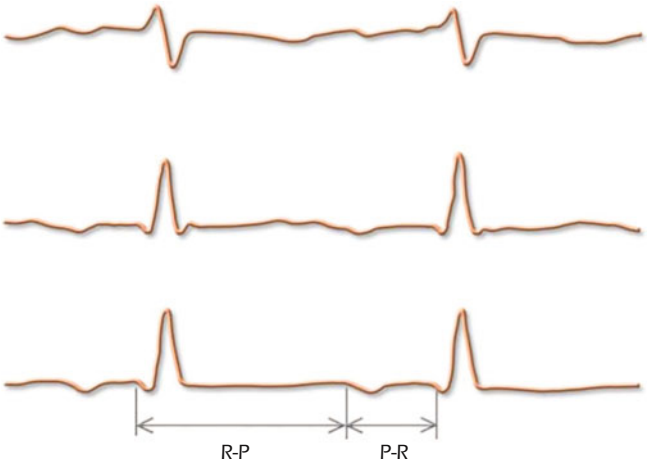
AVRT = atrioventricular reciprocating tachycardia; ECG = electrocardiogram; AF = atrial fibrillation; MAT = multifocal atrial tachycardia; AV = atrioventricular.

Figure 2. Differential diagnosis for narrow QRS tachycardia



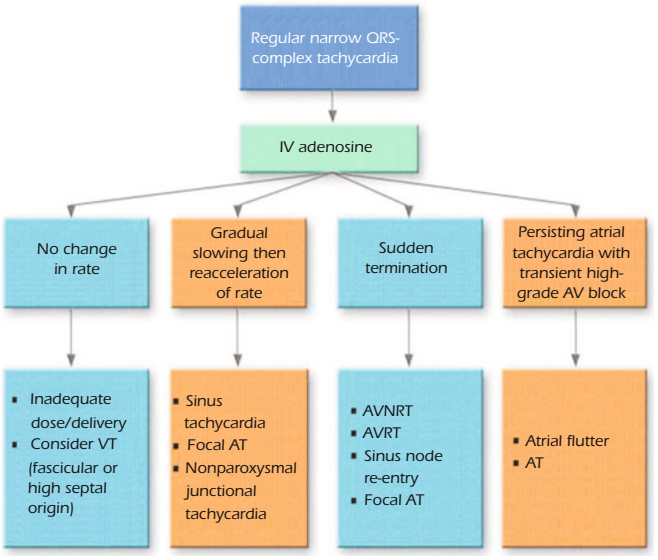
Patients with focal junctional tachycardia may mimic the pattern of slow-fast AVNRT and may show AV dissociation and/or marked irregularity in the junctional rate. AV = atrioventricular; AVNRT = atrioventricular nodal reciprocating tachycardia; AVRT = atrioventricular reciprocating tachycardia; MAT = multifocal atrial tachycardia; ms = milliseconds; PJRT = permanent form of junctional reciprocating tachycardia; QRS = ventricular activation on electrocardiogram.

Figure 3. ECG tracing with limb leads I, II, and III, showing an RP (initial R to initial P) interval longer than the PR interval



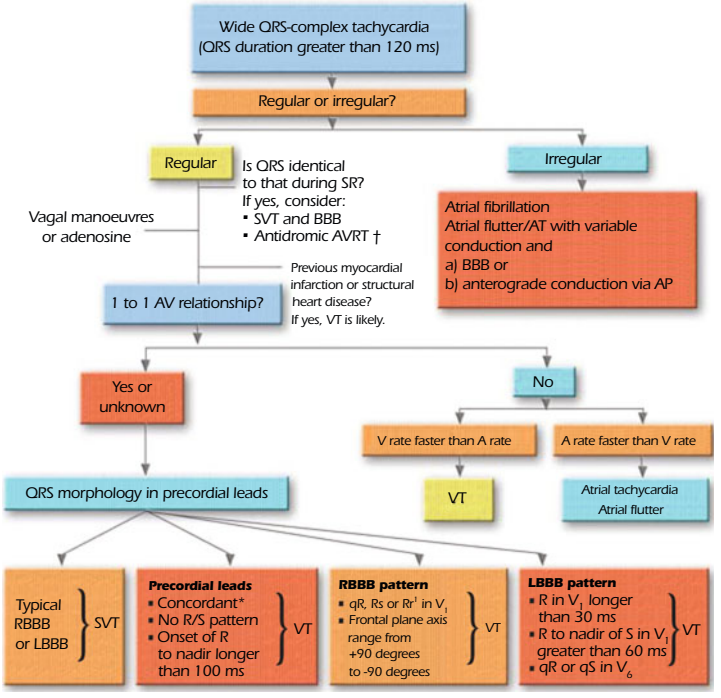
The P wave differs from the sinus P wave. ECG = electrocardiogram.

Figure 4. Responses of narrow complex tachycardias to adenosine



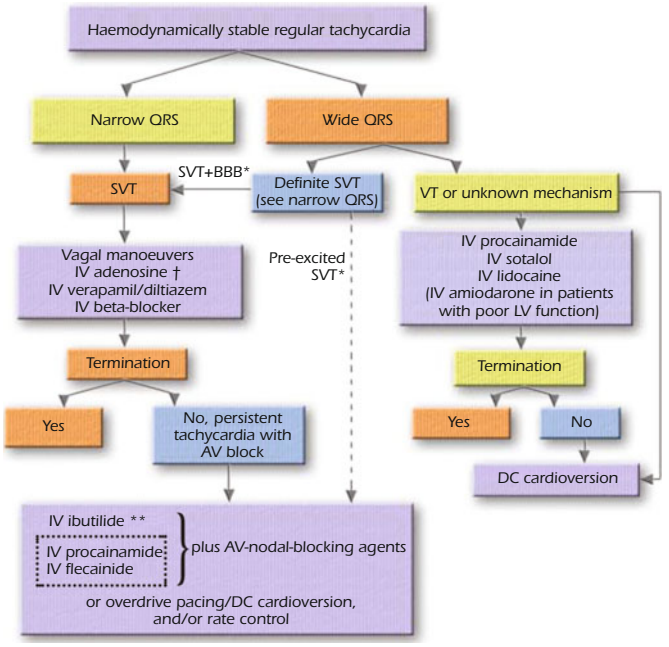
AT = atrial tachycardia; AV = atrioventricular; AVNRT = atrioventricular nodal reciprocating tachycardia; AVRT = atrioventricular reciprocating tachycardia; IV = intravenous; QRS = ventricular activation on electrocardiogram; VT = ventricular tachycardia.

Figure 5. Differential diagnosis for wide QRS-complex tachycardia (greater than 120 ms)



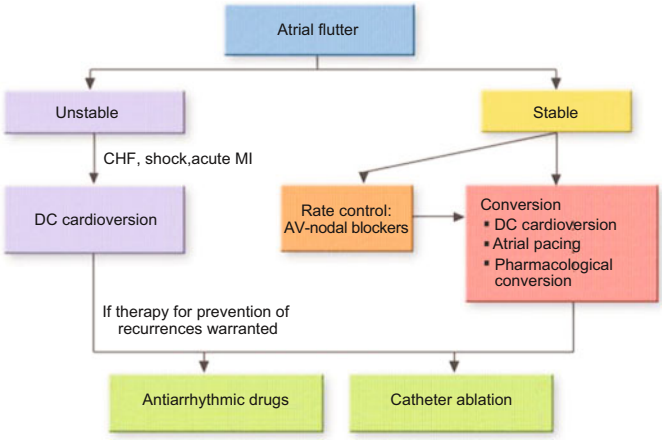
A QRS conduction delay during sinus rhythm, when available for comparison, reduces the value of QRS morphology analysis. Adenosine should be used with caution when the diagnosis is unclear because it may produce VF in patients with coronary artery disease and AF with a rapid ventricular rate in pre-excited tachycardias. Various adenosine responses are shown in Fig. 6. * Concordant indicates that all precordial leads show either positive or negative deflections. Fusion complexes are diagnostic of VT. † In pre-excited tachycardias, the QRS is generally wider (ie, more pre-excited) compared with sinus rhythm. A = atrial; AF = atrial fibrillation; AP = accessory pathway; AT = atrial tachycardia; AV = atrioventricular; AVRT = atrioventricular reciprocating tachycardia; BBB = bundle-branch block; LBBB = left bundlebranch block; ms = milliseconds; QRS = ventricular activation on ECG; RBBB = right bundle-branch block; SR = sinus rhythm; SVT = supraventricular tachycardias; V = ventricular; VF = ventricular fibrillation; VT = ventricular tachycardia.

Figure 6. Acute management of patients with haemodynamically stable and regular tachycardia



*A 12-lead ECG during sinus rhythm must be available for diagnosis. † Adenosine should be used with caution in patients with severe coronary artery disease and may produce AF, which may result in rapid ventricular rates for patients with pre-excitation. **Ibutilide is especially effective for patients with atrial flutter but should not be used in patients with EF less than 30% due to increased risk of polymorphic VT. AF = atrial fibrillation; AV = atrioventricular; BBB = bundle-branch block; DC = direct current; ECG = electrocardiogram; IV = intravenous; LV = left ventricle; QRS = ventricular activation on ECG; SVT = supraventricular tachycardia; VT = ventricular tachycardia.

Figure 7. Management of atrial flutter depending on haemodynamic stability



Attempts to electively revert atrial flutter to sinus rhythm should be preceded and followed by anticoagulant precautions, as per AF. AF = atrial fibrillation; AV = atrioventricular; CHF = congestive heart failure; DC = direct current; MI = myocardial infarction.

IV. References

(1) Adapted from the ACC/AHA/ESC Guidelines for the Management of Patients with Supraventricular Arrhythmias : Executive Summary
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European Heart Journal 2003; 24 (20): 1857-1897.

(2) ACC/AHA/ESC Guidelines for the Management of Patients with Atrial Fibrillation Report from the Joint Task Force of the ESC, ACC and AHA
V. Fuster (Chairperson), L.E. Rydén (Co-Chair), R.W. Asinger, D.S. Cannom, H.J. Crijns, R.L. Frye, J.L. Halperin, G.N. Kay, W.W. Klein, S. Lévy, R.L. McNamara, E.N. Prystowsky, L.S. Wann, D.G. Wyse
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Chapter 2
Atrial Fibrillation*
2010

The Task Force for the Management of Patients with Atrial Fibrillation (2010 Version) of the European Society of Cardiology (ESC)
Developed with the special contribution of the European Heart Rhythm Association
Endorsed by the European Association for Cardio-Thoracic Surgery (EACTS)

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Special thanks to Panos Vardas for his contribution.

1. Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, occurring in 1-2% of the general population. Over 6 million Europeans suffer from this arrhythmia and its prevalence is estimated to increase by at least 2.5-fold in the next 50 years as the population ages.

AF has frequent and severe consequences in affected patients. Their prevention is the main therapeutic goal in the management of AF. Table 1 lists the major consequences (outcomes) of AF in affected patients.

*Adapted from the ESC Guidelines for the Management of Atrial Fibrillation (2010 Version) (European Heart Journal 2010;31:2369-2429; doi:10.1093/eurheartj/ehq278)

Classes of Recommendations	
Classes of Recommendations	**Definition**
Class I	**Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.**
Class II	**Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.**
Class IIa	***Weight of evidence/opinion is in favour of usefulness/efficacy.***
Class IIb	***Usefulness/efficacy is less well established by evidence/opinion.***
Class III	**Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.**

Level of Evidence	
Level of Evidence A	**Data derived from multiple randomized clinical trials or meta-analyses.**
Level of Evidence B	**Data derived from a single randomized clinical trial or large non-randomized studies.**
Level of Evidence C	**Consensus of opinion of the experts and/or small studies, retrospective studies, registries.**

For a complete list of references, please refer to the full guidelines (Guidelines for the Management of Atrial Fibrillation (2010 Version) (European Heart Journal 2010;31:2369-2429; doi:10.1093/eurheartj/ehq278) at www.escardio.org/guidelines.

Table 1: Clinical events (outcomes) affected by AF

Outcome parameter	Relative change in AF patients
1. Death	Death rate doubled.
2. Stroke (includes haemorrhagic stroke and cerebral bleeds)	Stroke risk increased; AF is associated with more severe stroke.
3. Hospitalisations	Hospitalisations are frequent in AF patients and may contribute to reduced quality of life.
4. Quality of life and exercise capacity	Wide variation from no effect to major reduction. AF can cause marked distress through palpitations and other AF-related symptoms.
5. Left ventricular function	Wide variation from no change to tachycardio-myopathy with acute heart failure.

AF = atrial fibrillation

The following concomitant conditions may cause or encourage the progression of AF. They should be recorded and adequately managed in AF patients.

- Hypertension
- Symptomatic heart failure (NYHA classes II - IV) including tachycardiomyopathy
- Valvular heart disease
- Cardiomyopathies including primary electrical cardiac disease
- Atrial septal defect and other congenital heart defects
- Coronary artery disease
- Overt thyroid dysfunction and possibly subclinical thyroid dysfunction
- Obesity
- Diabetes mellitus
- Chronic obstructive pulmonary disease (COPD) and sleep apnoea
- Chronic renal disease

2. Diagnosis and initial management

Documentation (ECG or device-based) of AF is needed to confirm the diagnosis.
AF is defined as a cardiac arrhythmia with the following characteristics:

1. The surface ECG shows 'absolutely' irregular R-R intervals (AF is therefore sometimes known as *arrhythmia absoluta*), i.e., R-R intervals that do not follow a repetitive pattern.

2. There are no distinct P waves on the surface ECG. Apparently regular atrial electrical activity may be seen in some ECG leads, most often in lead V1.

3. The atrial cycle length (when visible), i.e. the interval between two atrial activations, is usually variable and < 200 ms (> 300 beats per minute [bpm]).

In patients with suspected, but not documented AF, intense rhythm monitoring may be necessary. The type of AF should be specified. Asymptomatic ('silent') AF episodes are frequent even in symptomatic patients.

Types of AF

AF is a chronically progressing disease. The five types of AF described here encompass the progression from undiagnosed episodes to first diagnosis, and infrequent paroxysms to long-lasting persistent and eventually permanent AF (Figure 1).
Every patient who presents with AF for the first time is considered a patient with **first diagnosed AF**, irrespective of the duration of the arrhythmia or the presence and severity of AF-related symptoms.

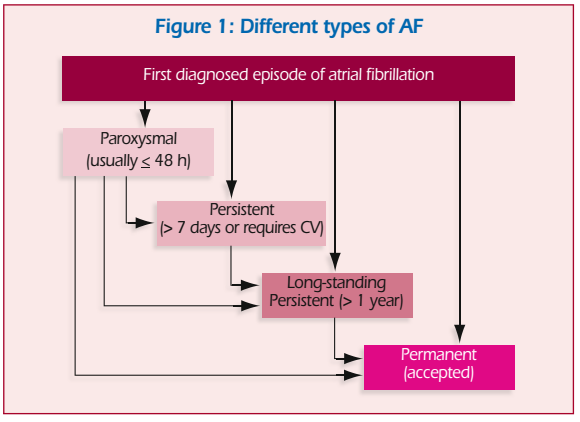
Paroxysmal AF is self-terminating, usually within 48 h. Although AF paroxysms may continue for up to 7 days, the 48 h time point is clinically important. After this period, the likelihood of spontaneous conversion is low and anticoagulation must be considered.

Persistent AF is present when an AF episode either lasts longer than 7 days or requires termination by cardioversion, either with drugs or by direct current cardioversion (DCC).

Long-standing persistent AF has lasted for 1 year or more when it is decided to adopt a rhythm control strategy.

Permanent AF is said to exist when the presence of the arrhythmia is accepted by the patient (and physician). Hence, rhythm control interventions are, by definition, not pursued in patients with permanent AF. Should a rhythm control strategy be adopted the arrhythmia is re-designated as 'long-standing persistent AF'.

Figure 1: Different types of AF



AF = atrial fibrillation; CV = cardioversion

Acute management should concentrate on relief of symptoms and assessment of AF-associated risks. Initial management involves:

- acute ventricular rate control
- immediate assessment of the need for anticoagulation
- first decision to add rhythm control therapy to the management based on symptoms (may be reassessed later)
- treatment of underlying heart disease

To facilitate the follow-up of AF patients, the severity of AF-related symptoms should be quantified. This can be achieved by estimating the EHRA score of AF-related symptoms (Table 2).

Table 2: EHRA score of AF-related symptoms

Classification of AF-related symptoms **(EHRA score)**	
EHRA class	**Explanation**
EHRA I	'No symptoms'
EHRA II	'Mild symptoms'; normal daily activity not affected
EHRA III	'Severe symptoms'; normal daily activity affected
EHRA IV	'Disabling symptoms'; normal daily activity discontinued

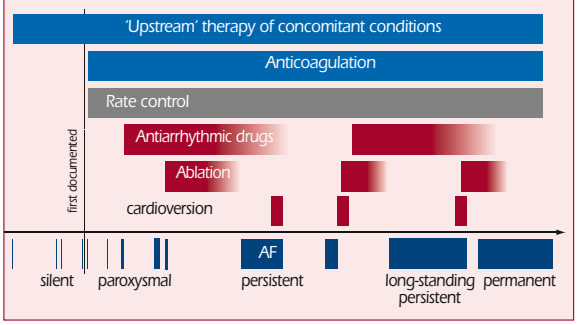
AF = atrial fibrillation; EHRA = European Heart Rhythm Association

Usually AF progresses from short, rare episodes to longer and more frequent episodes, and AF-related risks may change over time (Figure 2).

Thus, after initial diagnosis a structured follow-up plan should be suggested to maintain effective therapy and manage potential therapy-related or AF-related complications.

Important considerations during follow-up of the AF patient are listed below:

Figure 2: 'Natural' time course of AF



AF = atrial fibrillation

The dark blue boxes show a typical sequence of periods in AF against a background of sinus rhythm, and illustrate the progression of AF from silent and undiagnosed to paroxysmal and chronic forms, at times symptomatic. The upper bars indicate therapeutic measures that could be pursued. Light blue boxes indicate therapies that have proven effects on 'hard outcomes' in AF, such as stroke or acute heart failure. Red boxes indicate therapies that are currently used for symptom relief, but may in the future contribute to reduction of AF-related complications. Rate control (grey box) is valuable for symptom relief and may improve cardiovascular outcomes.

- Is anticoagulation now necessary - have new risk factors developed, or has the need for anticoagulation passed, e.g. post-cardioversion in a patient with low thromboembolic risk?
- Have the patient's symptoms improved on therapy? If not, should other therapy be considered?
- Are there signs of proarrhythmia or risk of proarrhythmia; if so, should the dose of an antiarrhythmic drug be reduced or the therapy be changed?
- Has paroxysmal AF progressed into a persistent/permanent form, in spite of antiarrhythmic drugs; in such a case, should another therapy be considered?
- Is the rate control approach working properly as assessed by EHRA score and LV function (e.g. echo)? Has the target for heart rate at rest and during exercise been reached?

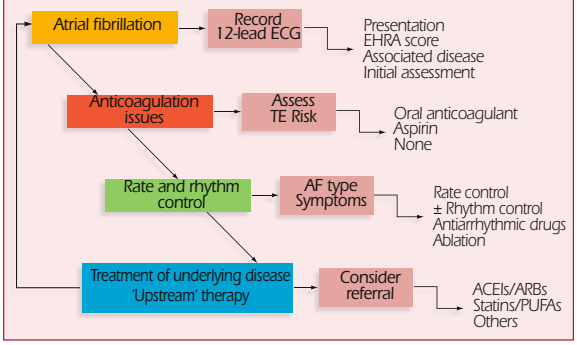
Recommendations for diagnosis and initial management	Class[a]	Level[b]
The diagnosis of AF requires documentation by ECG.	I	B
In patients with suspected AF, an attempt to record an ECG should be made when symptoms suggestive of AF occur.	I	B
A simple symptom score (EHRA score) is recommended to quantify AF-related symptoms.	I	B
All patients with AF should undergo a thorough physical examination and a cardiac and arrhythmia-related history should be taken.	I	C
In patients with severe symptoms, documented or suspected heart disease, or risk factors, an echocardiogram is recommended.	I	B
In patients treated with antiarrhythmic drugs, a 12-lead ECG should be recorded at regular intervals during follow-up.	I	C

Recommendations for diagnosis and initial management (contd)	Class[a]	Level[b]
In patients with suspected symptomatic AF, additional ECG monitoring should be considered in order to document the arrhythmia.	IIa	B
Additional ECG monitoring should be considered for detection of 'silent' AF in patients who may have sustained an AF-related complication.	IIa	B
In patients with AF treated with rate control, Holter ECG monitoring should be considered for assessment of rate control or bradycardia.	IIa	C
In young active patients with AF treated with rate control, exercise testing should be considered in order to assess ventricular rate control.	IIa	C
In patients with documented or suspected AF, an echocardiogram should be considered.	IIa	C
Patients with symptomatic AF or AF-related complications should be considered for referral to a cardiologist.	IIa	C
A structured follow-up plan prepared by a specialist is useful for follow-up by a general or primary care physician.	IIa	C
In patients treated with rhythm control, repeated ECG monitoring may be considered to assess the efficacy of treatment.	IIb	B
Most patients with AF may benefit from specialist follow-up at regular intervals.	IIb	C

a = class of recommendation; b = level of evidence
AF = atrial fibrillation; ECG = electrocardiogram; EHRA = European Heart Rhythm Association

The long-term management of AF requires consideration of antithrombic therapy, rate control, additional rhythm control when necessary, and management of the underlying disease, which promotes AF (upstream therapy) and the consequences of AF upon itself and the cardiovascular system (Figure 3).

Figure 3: The management cascade for patients with AF



ACEI = angiotensin converting enzyme inhibitor; AF = atrial fibrillation; ARB = angiotensin receptor blocker; EHRA = European Heart Rhythm Association; PUFA = polyunsaturated fatty acid; TE = thrombo-embolism

3. Antithrombotic therapy

AF is a major contributor to stroke and thromboembolism. When strokes occur in AF patients, the risk of mortality and disability, as well as recurrent stroke, is higher than with other strokes. However, stroke risk in AF is not homogeneous, and a crucial part of AF management involves stroke risk assessment and the appropriate use of thromboprophylaxis.

In the present guidelines, the use of the 'low', 'moderate' and 'high' risk categorisations has been de-emphasised, given the poor predictive value of such artificial categories, and the use of a risk factor-based approach is encouraged for more detailed stroke risk assessment, recommending the use of antithrombotic therapy on the basis of the presence (or absence) of stroke risk factors.

The simplest risk assessment scheme is the $CHADS_2$ score, as shown in Table 3, which should be used as an initial, rapid and easily remembered means of assessing stroke risk. In patients with a $CHADS_2$ score of ≥ 2, chronic oral anticoagulant therapy, for example with a vitamin K antagonist (VKA), is recommended with an international normalised ratio (INR) in the range of 2.0-3.0, unless contraindicated.

Table 3: $CHADS_2$ score and stroke rate

$CHADS_2$ score	Patients (n = 1733)	Adjusted stroke rate (%/y)* (95% confidence interval)
0	120	1.9 (1.2 – 3.0)
1	463	2.8 (2.0 – 3.8)
2	523	4.0 (3.1 – 5.1)
3	337	5.9 (4.6 – 7.3)
4	220	8.5 (6.3 – 11.1)
5	65	12.5 (8.2 – 17.5)
6	5	18.2 (10.5 – 27.4)

*The adjusted stroke rate was derived from the multivariable analysis assuming no aspirin usage; these stroke rates are based on data from a cohort of hospitalised AF patients, published in 2001, with low numbers in those with a $CHADS_2$ score of 5 and 6 to allow an accurate judgement of the risk in these patients. Given that stroke rates are declining overall, actual stroke rates in contemporary non-hospitalised cohorts may also vary from these estimates. $CHADS_2$ = Cardiac failure, Hypertension, Age, Diabetes, Stroke (Doubled).

In patients with a $CHADS_2$ score of 0 - 1, or where a detailed stroke risk assessment is indicated, use of a more comprehensive risk factor-based approach is recommended, incorporating other risk factors for thromboembolism (Tables 4 and 5; Figure 4).

There is a considerable evidence-base for the use of oral anticoagulation for stroke prevention, while aspirin is inferior to oral anticoagulation and may be no safer, especially in the elderly. The need for thromboprophylaxis should be part of the management evaluation, irrespective of the type of AF (whether paroxysmal, persistent or permanent).

Based on this risk factor-based approach to thromboprophylaxis, those with no risk factors are 'truly low risk' and can be managed with no antithrombotic therapy, while all others with one or more stroke risk factors can be considered for oral anticoagulation.

Table 4

a) Risk factors for stroke and thromboembolism in non-valvular AF

'Major' risk factors	'Clinically relevant non-major' risk factors
Previous stroke, TIA or systemic embolism Age ≥ 75 years	Heart failure or moderate to severe LV systolic dysfunction [e.g. LV EF ≤ 40%] Hypertension - Diabetes mellitus Female sex - Age 65-74 years Vascular disease*

b) Risk factor-based approach expressed as a point-based scoring system, with the acronym CHA_2DS_2-VASc

(Note: maximum score is 9 since age may contribute 0, 1, or 2 points)

Risk factor	Score
Congestive heart failure/LV dysfunction	1
Hypertension	1
Age ≥ 75	2
Diabetes mellitus	1
Stroke/TIA/thrombo-embolism	2
Vascular disease*	1
Age 65-74	1
Sex category [i.e. female sex]	1
Maximum score	**9**

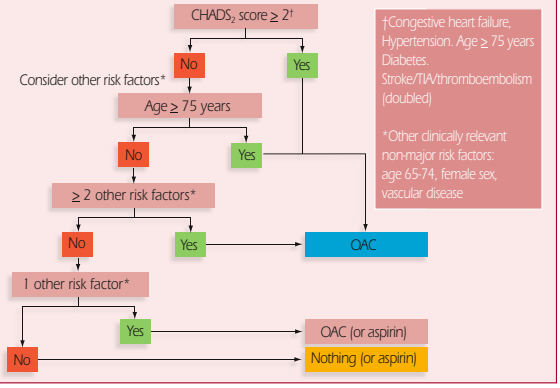
c) Adjusted stroke rate according to CHA_2DS_2-VASc score

CHA_2DS_2-VASc score	Patients (n = 7329)	Adjusted stroke rate (%/y)
0	1	0%
1	422	1.3%
2	1230	2.2%
3	1730	3.2%
4	1718	4.0%
5	1159	6.7%
6	679	9.8%
7	294	9.6%
8	82	6.7%
9	14	15.2%

See text for definitions. *Prior myocardial infarction, peripheral artery disease, aortic plaque. Actual rates of stroke in contemporary cohorts may vary from these estimates.

EF = ejection fraction (as documented by echocardiography, radionuclide ventriculography, cardiac catheterisation, cardiac magnetic resonance imaging, etc.); LV = left ventricular; TIA = transient ischaemic attack.

Figure 4:
Clinical flowchart for the use of oral anticoagulation for stroke prevention in AF



AF = atrial fibrillation; OAC = oral anticoagulant; TIA = transient ischaemic attack. A full description of the $CHADS_2$ can be found on page 12.

Table 5: Approach to thromboprophylaxis in patients with AF

Risk category	CHA_2DS_2-VASc score	Recommended antithrombotic therapy
One 'major' risk factor or ≥ 2 'clinically relevant non-major' risk factors	≥ 2	OAC
One 'clinically relevant non-major' risk factor	1	Either OAC or aspirin 75-325 mg daily. Preferred: OAC rather than aspirin.
No risk factors	0	Either Aspirin 75-325 mg daily or no antithrombotic therapy. Preferred: no antithrombotic therapy rather than aspirin.

CHA_2DS_2-VASc Cardiac failure, Hypertension, Age ≥ 75 [Doubled], Diabetes, Stroke [Doubled] - Vascular disease, Age 65-74 and Sex category [Female]); OAC = oral anticoagulation, such as a vitamin K antagonist (VKA) adjusted to an intensity range of INR 2.0-3.0 (target 2.5). New oral anticoagulants, which may be viable alternatives to a VKA, may ultimately be considered.

Apart from stroke risk assessment, an assessment of bleeding risk should be considered, and a new user-friendly bleeding risk score, HAS-BLED is recommended (see Table 6). The increased risk of thromboembolism following cardioversion is well recognised, and thromboprophylaxis is recommended, whether in a conventional approach or transoesophageal echocardiography (TOE)-guided strategy (Figure 5).

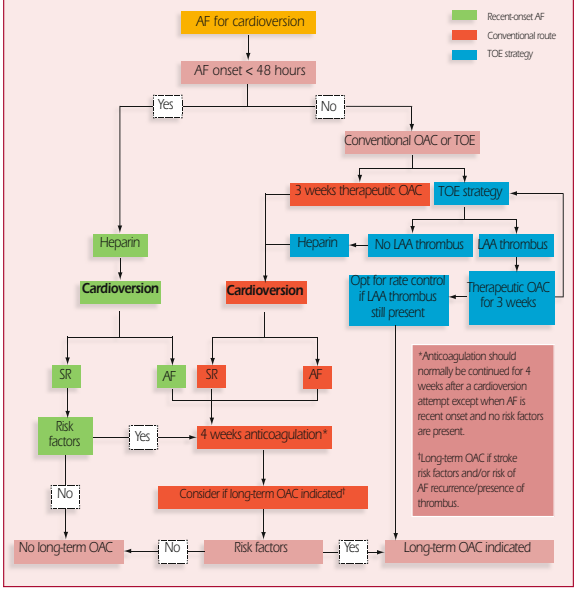
Table 6: Clinical characteristics comprising the HAS-BLED bleeding risk score

Letter	Clinical characteristic*	Points awarded
H	Hypertension	1
A	Abnormal renal and liver function (1 point each)	1 or 2
S	Stroke	1
B	Bleeding	1
L	Labile INRs	1
E	Elderly (e.g. age > 65 years)	1
D	Drugs or alcohol (1 point each)	1 or 2
		Maximum 9 points

* 'Hypertension' is defined as systolic blood pressure > 160 mmHg. 'Abnormal kidney function' is defined as the presence of chronic dialysis or renal transplantation or serum creatinine ≥ 200 µmol/L. 'Abnormal liver function' is defined as chronic hepatic disease (e.g. cirrhosis) or biochemical evidence of significant hepatic derangement (e.g. bilirubin > 2 x upper limit of normal, in association with aspartate aminotransferase/alanine aminotransferase/alkaline phosphatase > 3 x upper limit normal, etc). 'Bleeding' refers to previous bleeding history and/or predisposition to bleeding, e.g. bleeding diathesis, anaemia, etc. 'Labile INRs' refers to unstable/high INRs or poor time in therapeutic range (e.g. < 60%). Drugs/alcohol use refers to concomitant use of drugs, such as antiplatelet agents, non-steroidal anti-inflammatory drugs or alcohol abuse, etc.
INR = international normalized ratio

Cardioversion of AF generally requires effective anticoagulation, often preceding the procedure by 3 weeks, and should be continued for at least 4 weeks post procedure. At that stage the need for long-term anticoagulation should be assessed on the basis of the risk factors described above (Figure 5).

Figure 5: Cardioversion of haemodynamically stable AF, the role of TOE-guided cardioversion and subsequent anticoagulation strategy



AF = atrial fibrillation; DCC = direct current cardioversion; LA = left atrium; LAA = left atrial appendage; OAC = oral anticoagulant; SR = sinus rhythm; TOE = transoesophageal echocardiography.

Recommendations for prevention of thromboembolism	Class[a]	Level[b]
Antithrombotic therapy to prevent thromboembolism is recommended for all patients with AF, except in those at low risk (lone AF, aged < 65 years or with contraindications).	I	A
It is recommended that the selection of the antithrombotic therapy should be based upon the absolute risks of stroke/thromboembolism and bleeding and the relative risk and benefit for a given patient.	I	A
The $CHADS_2$ (Cardiac failure, Hypertension, Age, Diabetes, Stroke [Doubled]) score is recommended as a simple initial (easily remembered) means of assessing stroke risk in non-valvular AF.	I	A
▪ For the patients with a $CHADS_2$ score of ≥ 2, chronic OAC therapy with a VKA is recommended in a dose-adjusted regimen to achieve an INR range of 2.0-3.0 (target 2.5), unless contraindicated.	I	A
For a more detailed or comprehensive stroke risk assessment in AF (e.g. with $CHADS_2$ scores 0-1), a risk factor-based approach is recommended, considering 'major' and 'clinically relevant non-major' stroke risk factors[1].	I	A
▪ Patients with 1 'major' or ≥ 2 'clinically relevant non-major' risk factors are high risk and OAC therapy [for example, with a VKA, dose adjusted to achieve the target intensity INR of 2.0-3.0] is recommended, unless contraindicated.	I	A
▪ Patients with one 'clinically relevant non-major' risk factor are at intermediate risk and antithrombotic therapy is recommended, either as:	I	A B
i. OAC therapy (e.g. VKA), or	I	A
ii. aspirin 75-325 mg daily	I	B
▪ Patients with no risk factors are at low risk (essentially patients aged < 65 years with lone AF, with none of the risk factors) and the use of either aspirin 75-325 mg daily or no antithrombotic therapy is recommended.	I	B
For patients with AF who have mechanical heart valves, it is recommended that the target intensity of anticoagulation with a VKA should be based on the type and position of the prosthesis, maintaining an INR of at least 2.5 in the mitral position and at least 2.0 for an aortic valve.	I	B
Antithrombotic therapy is recommended for patients with atrial flutter as for those with AF.	I	C
The selection of antithrombotic therapy should be considered using the same criteria irrespective of the pattern of AF (i.e. paroxysmal, persistent, or permanent).	IIa	A
Most patients with one 'clinically relevant non-major' risk factor should be considered for OAC therapy (e.g. with a VKA) rather than aspirin, based upon an assessment of the risk of bleeding complications, the ability to safely sustain adjusted chronic anticoagulation, and patient preferences.	IIa	A
In patients with no risk factors who are at low risk (essentially patients aged < 65 years with lone AF, with none of the risk factors), no antithrombotic therapy should be considered, rather than aspirin.	IIa	B
Combination therapy with aspirin 75-100 mg plus clopidogrel 75 mg daily, should be considered for stroke prevention in patients for whom there is patient refusal to take OAC therapy or a clear contraindication to OAC therapy (e.g. inability to cope or continue with anticoagulation monitoring), where there is a low risk of bleeding.	IIa	B
Assessment of the risk of bleeding should be considered when prescribing antithrombotic therapy (whether with VKA or aspirin), and the bleeding risk with aspirin should be considered as being similar to VKA, especially in the elderly.	IIa	A

[1] Major' risk factors are those associated with the highest risk for stroke patients with AF are prior thromboembolism (stroke, transient ischaemic attack [TIA], or systemic embolism), age ≥ 75 years and rheumatic mitral stenosis. 'Clinically relevant non-major' risk factors include hypertension, heart failure or moderate to severe LV dysfunction (ejection fraction 40% or less), and diabetes mellitus (Level of Evidence: A). Other 'clinically relevant non-major' risk factors include female sex, age 65-74 years and vascular disease (myocardial infarction, complex aortic plaque, carotid disease, peripheral artery disease). This risk factor-based approach for non-valvular AF can also be expressed by an acronym, CHA_2DS_2-VASc, (Cardiac failure, Hypertension, Age ≥ 75 years [Doubled], Diabetes, Stroke [Doubled] - Vascular disease, Age 65-74 and Sex category [Female]). This scheme is based on a point system in which 2 points are assigned for a history of stroke or TIA, or age ≥ 75; and 1 point each is assigned for age 65-74 years, a history of hypertension, diabetes, recent cardiac failure, vascular disease (myocardial infarction, peripheral artery disease, complex aortic plaque) and female sex.

Recommendations for prevention of thromboembolism (contd)	Class[a]	Level[b]
The HAS-BLED score (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly (> 65), Drugs/alcohol concomitantly) should be considered as a calculation to assess bleeding risk, whereby a score of ≥ 3 indicates 'high risk' and some caution and regular review is needed, following the initiation of antithrombotic therapy, whether with OAC or aspirin.	IIa	B
In patients with AF who do not have mechanical prosthetic heart valves or those who are not at high risk for thromboembolism who are undergoing surgical or diagnostic procedures that carry a risk of bleeding, the interruption of OAC (with subtherapeutic anticoagulation for up to 48 h) should be considered, without substituting heparin as 'bridging' anticoagulation therapy.	IIa	C
In patients with a mechanical prosthetic heart valve or AF at high risk for thromboembolism who are undergoing surgical or diagnostic procedures, 'bridging' anticoagulation with therapeutic doses of either low molecular weight heparin (LMWH) or unfractionated heparin during the temporary interruption of OAC therapy should be considered.	IIa	C
Following surgical procedures, resumption of OAC therapy should be considered at the 'usual' maintenance dose (without a loading dose) on the evening of (or the next morning after) surgery, assuming there is adequate haemostasis.	IIa	B
Re-evaluation at regular intervals of the benefits, risks and need for antithrombotic therapy should be considered.	IIa	C
In patients with AF presenting with acute stroke or TIA, management of uncontrolled hypertension should be considered before antithrombotic treatment is started, and cerebral imaging (computed tomography or magnetic resonance imaging) performed to exclude haemorrhage.	IIa	C
In the absence of haemorrhage, OAC should be considered approximately 2 weeks after stroke, but in the presence of haemorrhage, anticoagulation should not be given.	IIa	C
In the presence of a large cerebral infarction, delaying the initiation of anticoagulation should be considered, given the risk of haemorrhagic transformation.	IIa	C
In patients with AF and an acute TIA, OAC therapy should be considered as soon as possible in the absence of cerebral infarction or haemorrhage.	IIa	C
In some patients with one 'clinically relevant non-major' risk factor, for example, female patients aged < 65 years with no other risk factors, aspirin may be considered rather than OAC therapy.	IIb	C
When surgical procedures require interruption of OAC therapy for longer than 48 h in high-risk patients, unfractionated heparin or subcutaneous LMWH may be considered.	IIb	C
In patients with AF who sustain ischaemic stroke or systemic embolism during treatment with usual intensity anticoagulation with VKA (INR 2.0-3.0), raising the intensity of the anticoagulation to a maximum target INR of 3.0-3.5 may be considered, rather than adding an antiplatelet agent.	IIb	C

a = class of recommendation; b = level of evidence
AF = atrial fibrillation; $CHADS_2$ = Cardiac failure, Hypertension, Age, Diabetes, Stroke (Doubled); INR = international normalised ratio; LMWH = low molecular weight heparin; OAC = oral anticoagulant; TIA = transient ischaemic attack; VKA = vitamin K antagonist

Recommendations for antithrombotic therapy in AF and ACS/PCI	Class[a]	Level[b]
Following elective PCI in patients with AF with stable coronary artery disease, bare metal stents (BMS) should be considered, and drug eluting stents avoided or strictly limited to those clinical and/or anatomical situations (e.g. long lesions, small vessels, diabetes, etc), where a significant benefit is expected when compared with BMS.	IIa	C
Following elective PCI, triple therapy (VKA, aspirin, clopidogrel) should be considered in the short-term, followed by more long-term therapy (up to 1 year) with VKA plus clopidogrel 75 mg daily (or alternatively, aspirin 75-100 mg daily, plus gastric protection with proton pump inhibitors (PPIs), H2 antagonists or antacids).	IIa	C
Following elective PCI, clopidogrel should be considered in combination with VKA plus aspirin for a minimum of 1 month after implantation of a BMS, but longer with a drug eluting stent (at least 3 months for a sirolimus-eluting stent and at least 6 months for a paclitaxel-eluting stent); following which VKA and clopidogrel 75 mg daily (or alternatively, aspirin 75-100 mg daily, plus gastric protection with either PPIs, H2 antagonists or antacids) should be considered, if required.	IIa	C
Following an ACS with or without PCI in patients with AF, triple therapy (VKA, aspirin, clopidogrel) should be considered in the short-term (3-6 months), or longer in selected patients at low bleeding risk, followed by long-term therapy with VKA plus clopidogrel 75 mg daily (or alternatively, aspirin 75-100 mg daily, plus gastric protection with PPIs, H2 antagonists or antacids).	IIa	C
In anticoagulated patients at very high risk of thromboembolism, uninterrupted therapy with VKA as the preferred strategy and radial access used as the first choice even during therapeutic anticoagulation (INR 2-3).	IIa	C
When VKA is given in combination with clopidogrel or low-dose aspirin, careful regulation of the anticoagulation dose intensity may be considered, with an INR range of 2.0-2.5.	IIb	C
Following revascularisation surgery in patients with AF, VKA plus a single antiplatelet drug may be considered in the initial 12 months, but this strategy has not been evaluated thoroughly and is associated with an increased risk of bleeding.	IIb	C
In patients with stable vascular disease (e.g. > 1 year, with no acute events), VKA monotherapy may be considered, and concomitant antiplatelet therapy should not be prescribed in the absence of a subsequent cardiovascular event.	IIb	C

a = class of recommendation; b = level of evidence
ACS = acute coronary syndrome; AF = atrial fibrillation; BMS = bare metal stent; INR = international normalised ratio; PCI = percutaneous intervention; PPIs = proton pump inhibitors; VKA = vitamin K antagonist

Recommendations for anticoagulation peri-cardioversion	Class[a]	Level[b]
For patients with AF of 48 h duration or longer, or when the duration of AF is unknown, OAC therapy (INR 2.0-3.0) is recommended for at least 3 weeks prior to and for 4 weeks after cardioversion, regardless of the method (electrical or oral/i.v. pharmacological).	I	B
For patients with AF requiring immediate/emergency cardioversion because of haemodynamic instability, heparin (i.v. UFH bolus followed by infusion, or weight-adjusted therapeutic dose LMWH) is recommended.	I	C
▪ After immediate/emergency cardioversion in patients with AF of 48 h duration or longer, or when the duration of AF is unknown, OAC therapy is recommended for at least 4 weeks, similar to patients undergoing elective cardioversion.	I	B
For patients with AF < 48 h and at high risk of stroke, i.v. heparin or weight-adjusted therapeutic dose LMWH is recommended peri-cardioversion, followed by OAC therapy with a VKA (INR 2.0-3.0) long-term.	I	B
If AF is of ≥ 48 h, OAC therapy is recommended for at least 4 weeks after immediate/emergency cardioversion similar to patients undergoing elective cardioversion.	I	B
In patients at high risk of stroke, OAC therapy with a VKA (INR 2.0-3.0) is recommended to be continued long-term.	I	B
As an alternative to anticoagulation prior to cardioversion, TOE-guided cardioversion is recommended to exclude thrombus in the left atrium (LA) or left atrial appendage.	I	B
For patients undergoing TOE-guided cardioversion who have no identifiable thrombus, cardioversion is recommended immediately after anticoagulation with heparin, and heparin should be continued until OAC therapy has been established, which should be maintained for at least 4 weeks after cardioversion.	I	B
For patients undergoing a TOE-guided strategy in whom thrombus is identified, VKA (INR 2.0-3.0) is recommended for at least 3 weeks, followed by a repeat TOE to ensure thrombus resolution.	I	C
For patients with atrial flutter undergoing cardioversion, anticoagulation is recommended as for patients with AF.	I	C
In patients with risk factors for stroke or AF recurrence, OAC therapy should be continued lifelong irrespective of the apparent maintenance of sinus rhythm following cardioversion.	IIa	B
If thrombus resolution is evident on repeat TOE, cardioversion should be performed, and OAC should be considered for 4 weeks or lifelong (if risk factors are present).	IIa	C
If thrombus remains on repeat TOE, an alternative strategy (e.g. rate control) may be considered.	IIb	C
For patients with AF duration that is clearly < 48 h and no thromboembolic risk factors, i.v. heparin or weight-adjusted therapeutic dose LMWH may be considered peri-cardioversion, without the need for post-cardioversion oral anticoagulation.	IIb	C

a = class of recommendation; b = level of evidence
AF = atrial fibrillation; INR = international normalised ratio; LA = left atrium; LMWH = low molecular weight heparin; OAC = oral anticoagulant; TOE = transoesophageal echocardiogram; UFH = unfractionated heparin; VKA = vitamin K antagonist

4. Acute rate and rhythm management

Acute rate control

In stable patients, control of the ventricular rate can be achieved by oral administration of ß-blockers or non-dihydropyridine calcium channel antagonists. In severely compromised patients, i.v. verapamil or metroprolol can rapidly slow atrioventricular (AV) nodal conduction. In the acute setting, the target ventricular rate should usually reach 80-100 bpm. In selected patients, amiodarone may be used acutely (patients with severely depressed left ventricular systolic function).

Pharmacological cardioversion

AF often terminates spontaneously within the first hours or days. The conversion rate with pharmacological cardioversion is lower than with electrical cardioversion (Table 7, Figure 6). Flecainide and propafenone given intravenously in patients with AF of short duration (especially when AF duration is < 24 h) are effective in restoring sinus rhythm. Oral administration of flecainide or propafenone is also effective ('pill in the pocket' approach), after the efficacy and safety of the treatment have been proven in-hospital. Ibutilide and sotalol are more effective for conversion of atrial flutter. A new medication, vernakalant, is also effective and may be used in patients with structural heart disease, but not NYHA III - IV.

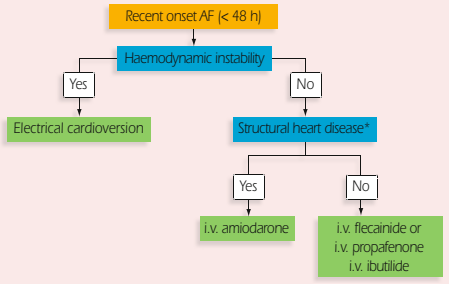
Table 7: Drugs and doses for pharmacological conversion of (recent-onset) AF

Drug	Dose	Follow-up dose	Risks
Amiodarone	5 mg/kg i.v. over 1 h	50 mg/h	Phlebitis, hypotension. Will slow the ventricular rate. Delayed AF conversion to sinus rhythm.
Flecainide	2 mg/kg i.v. over 10 min, or 200-300 mg p.o.	N/A	Not suitable for patients with marked structural heart disease; may prolong QRS duration, and hence the QT interval; and may inadvertently increase the ventricular rate due to conversion to atrial flutter and 1:1 conduction to the ventricles.

Table 7: Drugs and doses for pharmacological conversion of (recent-onset) AF (contd)			
Drug	**Dose**	**Follow-up dose**	**Risks**
Ibutilide	1 mg i.v. over 10 min	1 mg i.v. over 10 min after waiting for 10 min	Can cause prolongation of the QT interval and torsades de pointes; watch for abnormal T-U waves or QT prolongation. Will slow the ventricular rate.
Propafenone	2 mg/kg i.v. over 10 min, or 450-600 mg p.o.		Not suitable for patients with marked structural heart disease; may prolong QRS duration; will slightly slow the ventricular rate, but may inadvertently increase the ventricular rate due to conversion to atrial flutter and 1:1 conduction to the ventricles.
Vernakalant	3 mg/kg i.v. over 10 min	Second infusion of 2 mg/kg i.v. over 10 min after15 min rest	So far only evaluated in clinical trials; recently approved*.

*See footnote in the full text of these guidelines (European Heart Journal 2010;31:2369-2429;doi:10.1093/eurheartj/ehq278) at www.escardio.org/guidelines.
AF = atrial fibrillation; i.v. = intravenous; N/A = not applicable; p.o. = per os; QRS = QRS duration; QT = QT interval; T-U = abnormal repolarisation (T-U) waves

Figure 6: Direct current cardioversion and pharmacological cardioversionof recent-onset of AF in patients considered for pharmacological cardioversion



* Structural heart disease implies pathologies associated with ischaemia, scar, hypertrophy or dilatation.
i.v. = intravenous

Recommendations for pharmacological cardioversion	Class[a]	Level[b]
When pharmacological cardioversion is preferred and there is no structural heart disease, i.v. flecainide or propafenone is recommended for cardioversion of recent-onset AF.	I	A
In patients with recent-onset AF and structural heart disease, i.v. amiodarone is recommended.	I	A
In selected patients with recent-onset AF and no significant structural heart disease, a single high oral dose of flecainide or propafenone (the 'pill-in-the-pocket' approach) should be considered, provided this treatment has proven safe during previous testing in a medically secure environment.	IIa	B
In patients with recent-onset AF, structural heart disease, but without hypotension or manifest congestive heart failure, ibutilide may be considered. Serum electrolytes and the QTc interval must be within the normal range, and the patients must be closely monitored during and for 4 h after the infusion because of risk of proarrhythmia.	IIb	A
Digoxin (LoE A), verapamil, sotalol, metoprolol (LoE B), ajmaline and other ß-blocking agents (LoE C) are ineffective in converting recent-onset AF to sinus rhythm and are not recommended.	III	A B C

a = class of recommendation; b = level of evidence
AF = atrial fibrillation; LoE = level of evidence; i.v. = intravenous

Direct current cardioversion

DCC is an effective method of converting AF to sinus rhythm. Evidence favours the use of biphasic external defibrillators, and anteroposterior electrode placement is more effective than anterolateral placement. The risks and complications of DCC are primarily associated with thromboembolic events, arrhythmias and the risks of general anaesthesia. Pre-treatment with antiarrhythmic drugs increases the likelihood of restoration of sinus rhythm.

Recommendations for direct current cardioversion	Class[a]	Level[b]
Immediate DCC is recommended when a rapid ventricular rate does not respond promptly to pharmacological measures in patients with AF and ongoing myocardial ischaemia, symptomatic hypotension, angina, or heart failure.	I	C
Immediate DCC is recommended for patients with AF involving pre-excitation when rapid tachycardia or haemodynamic instability is present.	I	B
Elective DCC should be considered in order to initiate a long-term rhythm control management strategy for patients with AF.	IIa	B
Pre-treatment with amiodarone, flecainide, propafenone, ibutilide, or sotalol should be considered to enhance success of DCC and prevent recurrent AF.	IIa	B
Repeated DCC may be considered in highly symptomatic patients refractory to other therapy.	IIb	C
Pre-treatment with ß-blockers, diltiazem or verapamil may be considered for rate control, although the efficacy of these agents in enhancing success of DCC or preventing early recurrence of AF is uncertain.	IIb	C
DCC is contraindicated in patients with digitalis toxicity.	III	C

a = class of recommendation; b = level of evidence
AF = atrial fibrillation; DCC = direct current cardioversion

5. Long-term management

General management

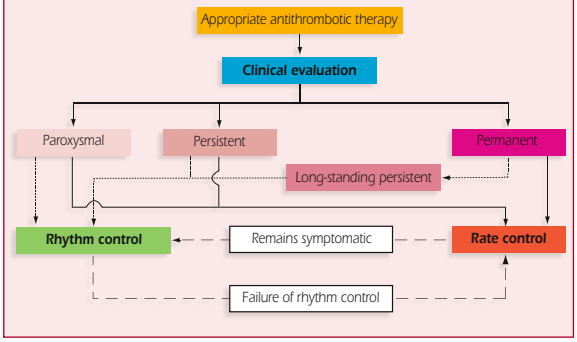
Clinical management of patients with AF involves the following five objectives:

1. Prevention of thromboembolism
2. Optimal management of concomitant cardiovascular disease
3. Symptom relief
4. Rate control
5. Correction of the rhythm disturbance

Rate and rhythm control

Rate control is needed for most patients with AF unless the heart rate during AF is naturally slow. Rhythm control may be added to rate control if the patient is symptomatic despite adequate rate control, or if a rhythm control strategy is selected because of factors such as the degree of symptoms, younger age or higher activity levels. Permanent AF is managed by rate control. Severe AF-related symptoms or worsening of LV function may in selected patients result in attempts to restore and maintain sinus rhythm, thereby designating the AF category as 'long-standing persistent AF'. Paroxysmal AF is more often managed with a rhythm control strategy, especially if symptomatic and there is little or no associated underlying heart disease. The decision to add rhythm control therapy to the management of AF requires an individual decision and should therefore be openly discussed (Figure 7).

Figure 7: Choice of rate and rhythm control strategies



Solid lines indicate the first-line management strategy. Dashed lines represent fall-back objectives and dotted lines indicate alternative approaches which may be used in selected patients.

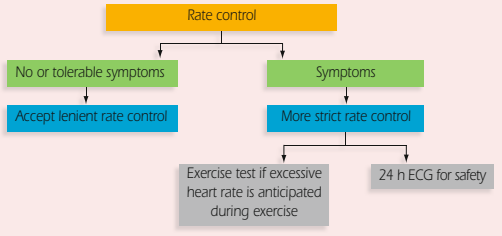
Recommendations for rate and rhythm control of AF	Class[a]	Level[b]
Rate control should be the initial approach in elderly patients with AF and minor symptoms (EHRA score 1).	I	A
Rate control should be continued throughout a rhythm control approach to ensure adequate control of the ventricular rate during recurrences of AF.	I	A
Rhythm control is recommended in patients with symptomatic (EHRA score ≥ 2) AF despite adequate rate control.	I	B
Rhythm control in patients with AF and AF-related heart failure should be considered for improvement of symptoms.	IIa	B
Rhythm control as an initial approach should be considered in young symptomatic patients in whom catheter ablation treatment has not been ruled out.	IIa	C
Rhythm control should be considered in patients with AF secondary to a trigger or substrate that has been corrected (e.g. ischaemia, hyperthyroidism).	IIa	C

a = class of recommendation; b = level of evidence
AF = atrial fibrillation; EHRA = European Heart Rhythm Association

6. Rate control

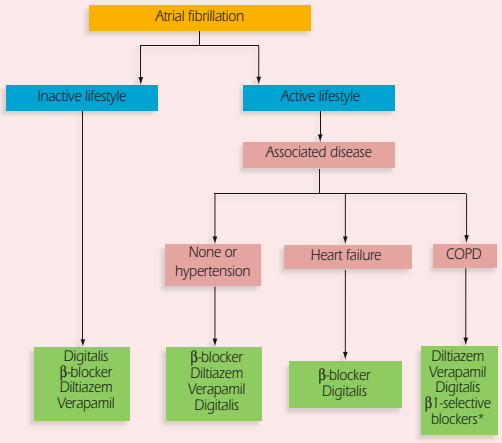
Patients with permanent AF but without severe symptoms due to a high ventricular rate may be treated with lenient rate control (resting heart rate < 110 bpm).Strict rate control (resting heart rate of < 80 bpm and controlled increase in heart rate upon moderate exertion) is necessary only in patients who remain symptomatic (Figure 8).

Figure 8: Optimal level of heart rate control



A range of pharmacological agents may be used for rate control but should be chosen carefully with regard to underlying cardiovascular disease (Figure 9). Dosages for these therapies are given in Table 8.

Figure 9: Rate control
The choice of drugs depends on lifestyle and underlying disease



COPD = chronic obstructive pulmonary disease. * Small doses of β1-selective blockers may be used in COPD if rate control is not adequate with non-dihydropyridine calcium channel antagonists and digoxin. Amiodarone is also used for rate control in patients who do not respond to glycosides, β-blockers or non-dihydropyridine calcium antagonists. Dronedarone may also be used for rate control in patient with recurrent episodes of atrial fibrillation.

Table 8: Drugs for rate control		
	Intravenous administration	**Usual oral maintenance dose**
ß-blockers		
Metoprolol CR/XL	2.5 to 5 mg iv bolus over 2 min; up to 3 doses.	100-200 mg (ER*) o.d.
Bisoprolol	N/A	2.5 - 10 mg o.d.
Atenolol	N/A	25 - 100 mg o.d.
Esmolol	50 to 200 µg/kg/min iv.	N/A
Propranolol	0.15 mg/kg iv over 1 min.	10 - 40 mg t.i.d.
Carvedilol	N/A	3.125 - 25 mg b.i.d.
Non-dihydropyridine calcium channel antagonists		
Verapamil	0.0375 to 0.15 mg/kg iv over 2 min.	40 mg b.i.d. to 360 mg (ER*) o.d.
Diltiazem	N/A	60 mg t.i.d. to 360 mg (ER*) o.d.
Digitalis glycosides		
Digoxin	0.5 - 1 mg	0.125 mg - 0.5 mg o.d.
Digitoxin	0.4 - 0.6 mg	0.05 mg - 0.1 mg o.d.
Others		
Amiodarone	5 mg/kg in 1 h, and 50 mg/h maintenance.	100 mg - 200 mg o.d.
Dronedarone‡	N/A	400 mg b.i.d.

*ER = extended release formulations; ‡only in patients with non-permanent atrial fibrillation
N/A = not applicable

Recommendations for acute rate control	Class[a]	Level[b]
In the acute setting in the absence of pre-excitation, i.v. administration of ß-blockers or non-dihydropyridine calcium channel antagonists is recommended to slow the ventricular response to AF, exercising caution in patients with hypotension or heart failure.	I	A
In the acute setting, i.v. administration of digitalis or amiodarone is recommended to control the heart rate in patients with AF and concomitant heart failure, or in the setting of hypotension.	I	B
In pre-excitation, preferred drugs are class I antiarrhythmic drugs or amiodarone.	I	C
When pre-excited AF is present, ß-blockers, non-dihydropyridine calcium channel antagonists, digoxin and adenosine are contraindicated.	III	C

a = class of recommendation; b = level of evidence
AF = atrial fibrillation

Recommendations for long-term rate control	Class[a]	Level[b]
Rate control using pharmacological agents (ß-blockers, non-dihydropyridine calcium channel antagonists, digitalis, or a combination thereof) is recommended in patients with paroxysmal, persistent or permanent AF. The choice of medication should be individualised and the dose modulated to avoid bradycardia.	I	B
In patients who experience symptoms related to AF during activity, the adequacy of rate control should be assessed during exercise, and therapy should be adjusted to achieve a physiological chronotropic response and to avoid bradycardia.	I	C
In pre-excitation AF, or in patients with a history of AF, preferred drugs for rate control are propafenone or amiodarone.	I	C
It is reasonable to initiate treatment with a lenient rate control protocol aimed at a resting heart rate < 110 bpm.	IIa	B
It is reasonable to adopt a stricter rate control strategy when symptoms persist or tachycardiomyopathy occurs, despite lenient rate control: resting heart rate < 80 bpm and heart rate during moderate exercise < 110 bpm. After achieving the strict heart rate target a 24 h Holter monitor is recommended to assess safety.	IIa	B
It is reasonable to achieve rate control by administration of dronedarone in non-permanent AF except for patients with NYHA class III - IV or unstable heart failure.	IIa	B
Digoxin is indicated in patients with heart failure and LV dysfunction, and in sedentary (inactive) patients.	IIa	C
Rate control may be achieved by administration of oral amiodarone when other measures are unsuccessful or contraindicated.	IIb	C
Digitalis should not be used as the sole agent to control the rate of ventricular response in patients with paroxysmal AF.	III	B

a = class of recommendation; b = level of evidence
AF = atrial fibrillation; bmp = beats per minute; LV = left ventricular; NYHA = New York Heart Association

AV node ablation

Atrioventricular (AV) node ablation provides highly effective control of ventricular rate in patients with AF. Ablation of the AV node is a palliative but irreversible procedure, and is therefore reasonable only in patients in whom rhythm control is not indicated and pharmacological rate control including combination of drugs has failed. Thus, AV node ablation is a valuable but rarely indicated procedure.

Recommendation for AV node ablation in AF patients	Class[a]	Level[b]
Ablation of the AV node to control heart rate should be considered when the rate cannot be controlled with pharmacological agents and when AF cannot be prevented by antiarrhythmic therapy or is associated with intolerable side-effects, and direct catheter-based or surgical ablation of AF is not indicated, has failed or is rejected.	IIa	B
Ablation of the AV node should be considered for patients with permanent AF and an indication for CRT (NYHA functional class III or ambulatory class IV symptoms despite optimal medical therapy, LVEF ≤ 35%, QRS width ≥ 130 ms).	IIa	B
Ablation of the AV node should be considered for CRT non-responders in whom AF prevents effective biventricular stimulation and amiodarone is ineffective or contraindicated.	IIa	C
In patients with any type of AF and severely depressed LV function (LVEF ≤ 35%) and severe heart failure symptoms (NYHA III or IV), biventricular stimulation should be considered after AV node ablation.	IIa	C
Ablation of the AV node to control heart rate may be considered when tachycardia-mediated cardiomyopathy is suspected and the rate cannot be controlled with pharmacological agents, and direct ablation of AF is not indicated, has failed or is rejected.	IIb	C

Recommendation for AV node ablation in AF patients (contd)	Class[a]	Level[b]
Ablation of the AV node with consecutive implantation of a CRT device may be considered in patients with permanent AF, LVEF ≤ 35%, and NYHA functional class I or II symptoms on optimal medical therapy to control heart rate when pharmacological therapy is insufficient or associated with side-effects.	IIb	C
Catheter ablation of the AV node should not be attempted without a prior trial of medication, or catheter ablation for AF, to control the AF and/or ventricular rate in patients with AF.	III	C

a = class of recommendation; b = level of evidence
AF = atrial fibrillation; AV = atrioventricular; CRT = cardiac resynchronisation therapy; LV = left ventricular; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association

Recommendations for pacemakers after AV node ablation	Class[a]	Level[b]
In patients with any type of AF, moderately depressed LV function (LVEF ≤ 45%) and mild heart failure symptoms (NYHA II), implantation of a CRT pacemaker may be considered after AV node ablation.	IIb	C
In patients with paroxysmal AF and normal LV function, implantation of a dual-chamber (DDD) pacemaker with mode-switch function may be considered after AV node ablation.	IIb	C
In patients with persistent or permanent AF and normal LV function, implantation of a single-chamber (VVIR) pacemaker may be considered after AV node ablation.	IIb	C

a = class of recommendation; b = level of evidence
AF = atrial fibrillation; AV = atrioventricular; CRT = cardiac resynchronisation therapy; LV = left ventricular; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association

7. Rhythm control - antiarrhythmic drugs

The following illustrates principles of antiarrhythmic drug therapy to maintain sinus rhythm in AF:

1. Treatment is motivated by attempts to reduce AF-related symptoms
2. Efficacy of antiarrhythmic drugs to maintain sinus rhythm is modest
3. Clinically successful antiarrhythmic drug therapy may reduce rather than eliminate recurrence of AF
4. If one antiarrhythmic drug 'fails' a clinically acceptable response may be achieved with another agent
5. Drug-induced proarrhythmia or extra-cardiac side-effects are frequent
6. Safety rather than efficacy considerations should primarily guide the choice of antiarrhythmic agent

Individual drugs and their main disadvantages are listed in Table 9.

Table 9: Suggested doses and main caveats for commonly used antiarrhythmic drugs

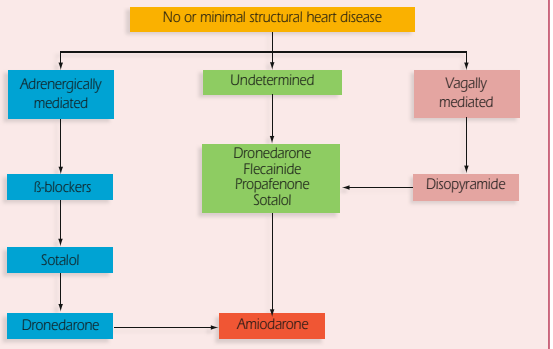
Drug	Dose	Main contraindications and precautions	ECG features prompting lower dose or discontinuation	AV nodal slowing
Disopyramide	100-250 mg t.i.d.	Contraindicated in systolic heart failure. Caution when using concomitant medication with QT-prolonging drugs.	QT interval > 500 ms	None
Flecainide Flecainide XL	100-200 mg b.i.d. 200 mg o.d.	Contraindicated if creatinine clearance < 50 mg/mL, in coronary artery disease, reduced LV ejection fraction. Caution in the presence of conduction system disease.	QRS duration increase > 25% above baseline	None
Propafenone Propafenone SR	150-300 mg t.i.d. 225-425 mg b.i.d.	Contraindicated in coronary artery disease, reduced LV ejection fraction. Caution in the presence of conduction system disease and renal impairment.	QRS duration increase > 25% above baseline	Slight
d,l-Sotalol	80 - 160 mg b.i.d.	Contraindicated in the presence of significant LV hypertrophy, systolic heart failure, pre-existing QT prolongation, hypokalaemia. Creatinine clearance < 50 mg/mL. Moderate renal function requires careful adaptation of dose.	QT interval > 500 ms	Similar to high-dose ß-blockers
Amiodarone	600 mg o.d. for 4 weeks, 400 mg o.d. for 4 weeks, then 200 mg o.d.	Caution when using concomitant medication with QT-prolonging drugs, heart failure. Dose of vitamin K antagonists and of digitoxin/digoxin should be reduced.	QT interval > 500 ms	10 - 12 bpm in AF
Dronedarone	400 mg b.i.d.	Contraindicated in NYHA class III - IV or unstable heart failure, during concomitant medication with QT-prolonging drugs, powerful CYP 3A4 inhibitors, if creatinine clearance < 30 mg/mL. Dose of digitoxin/digoxin should be reduced. Elevations in serum creatinine of 0.1-0.2 mg/dL are common and do not reflect reduced renal function.	QT interval > 500 ms	10 - 12 bpm in AF

AF = atrial fibrillation; AV = atrioventricular; bpm = beats per minute; CYP = cytochrome P; ECG = electrocardiogram; LV = left ventricular; NYHA = New York Heart Association

Choice of antiarrhythmic drugs

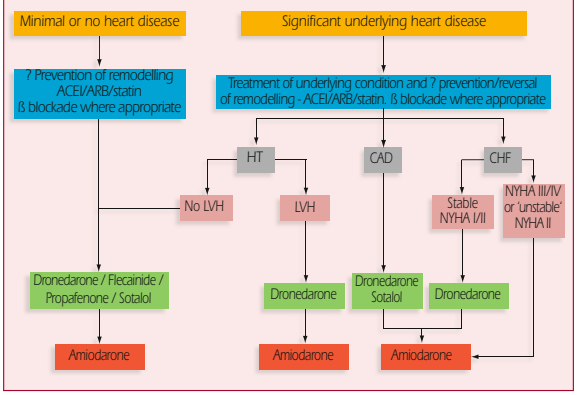
Choices of antiarrhythmic drugs are shown in Figures 10 & 11. In patients with no or only minimal structural heart disease, drugs are selected primarily according to safety, although the clinical pattern of arrhythmia occurrence, vagal versus adrenergic AF, may suggest specific choices. In patients with structural heart disease, the choice of drugs is determined by underlying cardiac pathology. Note that dronedarone is not recommended for patients with heart failure NYHA III/IV.

Figure 10: Choice of antiarrhythmic medication for the patient with AF and no or minimal structural heart disease



Medication may be initially based on the pattern of arrhythmia onset (adrenergic or vagally mediated). Antiarrhythmic agents are listed in alphabetical order within each treatment box.

Figure 11: Choice of antiarrhythmic drug according to underlying pathology



ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; CAD = coronary artery disease;CHF = congestive heart failure; HT = hypertension; LVH = left ventricular hypertrophy; NYHA = New York Heart Association; unstable = cardiac decompensation within the prior 4 weeks. Antiarrhythmic agents are listed in alphabetical order within each treatment box. ? = evidence for 'upstream' therapy for prevention of atrial remodelling still remains controversial.

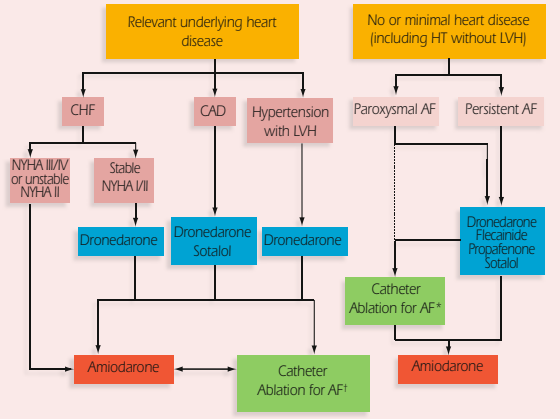
Recommendation for choice of an antiarrhythmic drug for AF control	Class[a]	Level[b]
The following antiarrhythmic drugs are recommended for rhythm control in patients with AF, depending on underlying heart disease:		
▪ amiodarone	I	A
▪ dronedarone	I	A
▪ flecainide	I	A
▪ propafenone	I	A
▪ d,l-sotalol	I	A
Amiodarone is more effective in maintaining sinus rhythm than sotalol, propafenone, flecainide (by analogy) or dronedarone (LoE A), but because of its toxicity profile should generally be used when other agents have failed or are contraindicated (LoE C).	I	A / C
In patients with severe heart failure, NYHA class III and IV or recently unstable (decompensation within the prior month) NYHA class II, amiodarone should be the drug of choice.	I	B
In patients without significant structural heart disease, initial antiarrhythmic therapy should be chosen from dronedarone, flecainide, propafenone, and sotalol.	I	A
ß-blockers are recommended for prevention of adrenergic AF.	I	C
If one antiarrhythmic drug fails to reduce the recurrence of AF to a clinically acceptable level, the use of another antiarrhythmic drug should be considered.	IIa	C
Dronedarone should be considered in order to reduce cardiovascular hospitalisations in patients with non-permanent AF and cardiovascular risk factors.	IIa	B
ß-blockers should be considered for rhythm (plus rate) control in patients with a first episode of AF.	IIa	C
Disopyramide may be considered in patients with vagally mediated AF.	IIb	B
Dronedarone is not recommended for treatment of AF in patients with NYHA class III and IV, or with recently unstable (decompensation within the prior month) NYHA class II heart failure.	III	B
Antiarrhythmic drug therapy is not recommended for maintenance of sinus rhythm in patients with advanced sinus node disease or AV node dysfunction unless they have a functioning permanent pacemaker.	III	C

a = class of recommendation; b = level of evidence
AF = atrial fibrillation; AV = atrioventricular; LoE = level of evidence; NYHA = New York Heart Association

8. Rhythm control - left atrial catheter ablation

Catheter ablation strategies targeting primarily the substrate and/or the initiating triggers for AF have been established in recent years. It is essential to identify the patients with high potential benefit and low expected risk of complications to recommend this rhythm control strategy (Figure 12). Asymptomatic patients should not be considered for catheter ablation.

Figure 12: Choice between ablation and antiarrhythmic drug therapy for patients with and without structural heart disease



Proposed integration of antiarrhythmic drug and catheter ablation for AF in patients with relevant underlying heart disease and for those with no or minimal heart disease, including hypertension (HT) without left ventricular hypertrophy (LVH).

† = more extensive LA ablation may be needed; * = usually PVI is appropriate
AF = atrial fibrillation; CAD = coronary artery disease; CHF = congestive heart failure; HT = hypertension; LVH = left ventricular hypertrophy; NYHA = New York Heart Association; PVI = pulmonary vein isolation.
Antiarrhythmic agents are listed in alphabetical order within each treatment box.
Please note that left atrium (LA) ablation as first-line therapy (dashed line) is a Class IIb recommendation for patients with paroxysmal AF and no or minimal heart disease, who remain highly symptomatic, despite rate control, and who reject antiarrhythmic drug therapy.

Recommendations for left atrial ablation	Class[a]	Level[b]
Ablation of common atrial flutter is recommended as part of an AF ablation procedure if documented prior to the ablation procedure or occurring during the AF ablation.	I	B
Catheter ablation for paroxysmal AF should be considered in symptomatic patients who have previously failed a trial of antiarrhythmic medication.	IIa	A
Ablation of persistent symptomatic AF that is refractory to antiarrhythmic therapy should be considered a treatment option.	IIa	B
In patients post-ablation, LMWH or i.v. UFH should be considered as 'bridging therapy' prior to resumption of systemic OAC, which should be continued for a minimum of 3 months. Thereafter, the individual stroke risk factors of the patient should be considered when determining if OAC therapy should be continued.	IIa	C
Continuation of OAC therapy post ablation is recommended in patients with 1 'major' ('definitive') or ≥ 2 'clinically relevant non-major' risk factors (i.e., CHA_2DS_2-VASc score ≥ 2).	IIa	B
Catheter ablation of AF in patients with heart failure may be considered when antiarrhythmic medication, including amiodarone, fails to control symptoms.	IIb	B
Catheter ablation of AF may be considered prior to antiarrhythmic drug therapy in symptomatic patients despite adequate rate control with paroxysmal symptomatic AF and no significant underlying heart disease.	IIb	B
Catheter ablation of AF may be considered in patients with symptomatic long-standing persistent AF refractory to antiarrhythmic drugs.	IIb	C

a = class of recommendation; b = level of evidence
AF = atrial fibrillation; i.v. = intravenous; LMWH = low molecular weight heparin; OAC = oral anticoagulant; UFH = unfractionated heparin

9. Rhythm control - surgical ablation

Restoration of sinus rhythm improves outcome after cardiac surgery. Surgical ablation is based on creating a pattern of lesions inducing scarring in the atrial wall to block propagation of re-entrant circuits while preserving normal conduction. It can be performed with cut-and-sew techniques or with alternative energy sources.

Recommendation for surgical ablation of AF	Class[a]	Level[b]
Surgical ablation of AF should be considered in patients with symptomatic AF undergoing cardiac surgery.	IIa	A
Surgical ablation of AF may be performed in patients with asymptomatic AF undergoing cardiac surgery if feasible with minimal risk.	IIb	C
Minimally invasive surgical ablation of AF without concomitant cardiac surgery is feasible and may be performed in patients with symptomatic AF after failure of catheter ablation.	IIb	C

a = class of recommendation; b = level of evidence; AF = atrial fibrillation

10. Upstream therapy

Upstream therapy to prevent or delay myocardial remodelling associated with hypertension, heart failure, or inflammation (e.g. after cardiac surgery) may deter the development of new AF (primary prevention) or, once established, its rate of recurrence or progression to permanent AF (secondary prevention). Treatments with angiotensin converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), aldosterone antagonists, statins, and omega-3 polyunsaturated fatty acids (PUFA) usually are referred to as upstream therapies for AF. Despite comprehensive evidence of the antiarrhythmic potential of these agents in animal models of AF, clinical data remain controversial. Best evidence has accumulated for primary prevention of AF in heart failure with ACEIs and ARBs and postoperative AF with statins. At present, there is no robust evidence to make any recommendation for the use of PUFAs for primary or secondary prevention of AF.

Recommendations for primary prevention of AF with 'upstream' therapy	Class[a]	Level[b]
ACEIs and ARBs should be considered for prevention of new-onset AF in patients with heart failure and reduced ejection fraction.	IIa	A
ACEIs and ARBs should be considered for prevention of new-onset AF in patients with hypertension, particularly with left ventricular hypertrophy.	IIa	B
Statins should be considered for prevention of new-onset AF after coronary artery bypass grafting, isolated or in combination with valvular interventions.	IIa	B
Statins may be considered for prevention of new-onset AF in patients with underlying heart disease, particularly heart failure.	IIb	B
Upstream therapies with ACEIs, ARBs, and statins are not recommended for primary prevention of AF in patients without cardiovascular disease.	III	C

a = class of recommendation; b = level of evidence
ACEI = angiotensin converting enzyme inhibitor; AF = atrial fibrillation; ARB = angiotensin receptor blocker

Recommendations for secondary prevention of AF with 'upstream' therapy	Class[a]	Level[b]
Pretreatment with ACEIs and ARBs may be considered in patients with recurrent AF undergoing electrical cardioversion ***and*** receiving antiarrhythmic drug therapy.	IIb	B
ARBs or ACEIs may be useful for prevention of recurrent paroxysmal AF or in patients with persistent AF in the absence of significant structural heart disease if these agents are indicated for other reasons (e.g., hypertension)	IIb	B

a = class of recommendation; b = level of evidence
ACEI = angiotensin converting enzyme inhibitor; AF = atrial fibrillation; ARB = angiotensin receptor blocker

11. Heart failure

The management of AF in patients with heart failure is similar to general management, but certain drugs are restricted, predominantly because of negative inotropic effects. Rate control for patients with heart failure is preferably achieved with a ß-blocker, but digoxin may be needed in addition. The only antiarrhythmic drug forlong-term rhythm control in patients with NYHA III - IV heart failure is amiodarone, whilst dronedarone may be used in patients with NYHA I - II heart failure, provided there was no recent unstable episode requiring hospitalisation.

Recommendations for rate control during AF with heart failure	Class[a]	Level[b]
ß-blockers are recommended as first-line therapy to control the ventricular rate in patients with heart failure and low LVEF.	I	A
▪ Where monotherapy is inadequate for heart rate control, digoxin should be added.	I	B
In haemodynamically unstable patients with acute heart failure and low LVEF, amiodarone is recommended as the initial treatment.	I	B
▪ If an AP is excluded, digoxin is recommended as an alternative to amiodarone to control the heart rate in patients with AF and acute systolic heart failure.	I	C
AV node ablation should be considered to control the heart rate when other measures are unsuccessful or contraindicated in patients with permanent AF and an indication for CRT (NYHA class III - IV, LVEF ≤ 35%, and QRS width ≥ 130 ms).	IIa	B
In patients with heart failure and preserved LVEF, a non-dihydropyridine calcium channel antagonist may be considered.	IIb	C
▪ A ß-blocker may be considered as an alternative to a non-dihydropyridine calcium channel antagonist in heart failure with preserved ejection fraction.	IIb	C
A non-dihydropyridine calcium channel antagonist is not recommended to control the heart rate in patients with systolic heart failure.	III	C

a = class of recommendation; b = level of evidence
AF = atrial fibrillation; AP = accessory pathway; AV = atrioventricular; CRT = cardiac resynchronisation therapy; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association

Recommendations for rhythm control of AF in heart failure	Class[a]	Level[b]
DCC is recommended when a rapid ventricular rate does not respond to pharmacological measures in patients with AF and ongoing myocardial ischaemia, symptomatic hypotension, or symptoms of pulmonary congestion.	I	C
In patients with AF and severe (NYHA class III or IV) or recent (≤ 4 weeks) unstable heart failure, the use of antiarrhythmic therapy to maintain sinus rhythm should be restricted to amiodarone.	I	C
Administration of amiodarone is a reasonable option for pharmacological cardioversion of AF, or to facilitate electrical cardioversion of AF.	IIa	B
In patients with AF and stable heart failure (NYHA class I, II) dronedarone should be considered to reduce cardiovascular hospitalisations.	IIa	C
For patients with heart failure and symptomatic persistent AF despite adequate rate control, electrical cardioversion and rhythm control may be considered.	IIb	B
Catheter ablation (pulmonary vein isolation) may be considered in heart failure patients with refractory symptomatic AF.	IIb	B

a = class of recommendation; b = level of evidence
AF = atrial fibrillation; DCC = direct current cardioversion; NYHA = New York Heart Association

12. Athletes

Endurance activity is associated with a higher prevalence of AF. Adequate rate control in athletes is more difficult (ß-blockers may be prohibited or may not be tolerated), but is important for safe participation in sports. Atrial flutter (spontaneous or induced by flecainide or propafenone) may lead to haemodynamic compromise, which needs to be prevented.

Recommendations for AF in athletes	Class[a]	Level[b]
When a 'pill-in-the-pocket' approach with sodium channel blockers is used, sport cessation should be considered for as long as the arrhythmia persists, and until one to two half-lives of the antiarrhythmic drug used have elapsed.	IIa	C
Isthmus ablation should be considered in competitive or leisure-time athletes with documented atrial flutter, especially when therapy with flecainide or propafenone is intended.	IIa	C
Where appropriate, AF ablation should be considered to prevent recurrent AF in athletes.	IIa	C
When a specific cause for AF is identified in an athlete (such as hyperthyroidism), participation in competitive or leisure time sports should be temporarily suspended until correction of the cause.	III	C
Physical sports activity should not be allowed when symptoms due to haemodynamic impairment (such as dizziness) are present.	III	C

a = class of recommendation; b = level of evidence
AF = atrial fibrillation

13. Valvular heart disease

AF frequently accompanies valvular heart diseases and the presence of paroxysmal or permanent AF is an indication for earlier intervention.
Management follows conventional recommendation, although a rate-control strategy is usually adopted in view of the low likelihood of maintaining sinus rhythm. Principal concerns surround the high risk of thromboembolism, and a low threshold for anticoagulation is recommended. AF frequently accompanies valvular heart disease (VHD).

Recommendations for AF in valvular heart disease	Class[a]	Level[b]
OAC therapy (INR 2.0-3.0) is indicated in patients with mitral stenosis and AF (paroxysmal, persistent, or permanent).	I	C
OAC therapy (INR 2.0-3.0) is recommended in patients with AF and clinically significant mitral regurgitation.	I	C
Percutaneous mitral balloon valvotomy should be considered for asymptomatic patients with moderate or severe mitral stenosis and suitable valve anatomy who have new onset AF in the absence of LA thrombus.	IIa	C
Early mitral valve surgery should be considered in severe mitral regurgitation, preserved LV function, and new onset AF, even in the absence of symptoms, particularly when valve repair is feasible.	IIa	C

a = class of recommendation; b= level of evidence
AF = atrial fibrillation; INR = international normalised ratio; LA = left atrium; LV = left ventricular; OAC = oral anticoagulant

14. Acute coronary syndromes (ACS)

AF occurs in 2-21% of patients with ACS, although the incidence is falling with increased use of PCI and secondary preventive measures. AF is more common in older patients and those with heart failure and is associated with increased mortality and risk of ischaemic stroke.

Recommendations for AF in acute coronary syndromes	Class[a]	Level[b]
DCC is recommended for patients with severe haemodynamic compromise or intractable ischaemia, or when adequate rate control cannot be achieved with pharmacological agents in patients with ACS and AF.	I	C
Intravenous administration of amiodarone is recommended to slow a rapid ventricular response to AF in patients with ACS.	I	C
Intravenous ß-blockers are recommended to slow a rapid ventricular response to AF in patients with ACS.	I	C
Intravenous administration of non-dihydropyridine calcium antagonists (e.g., verapamil) should be considered to slow a rapid ventricular response to AF in patients with ACS and no clinical signs of heart failure.	IIa	C
Intravenous administration of digoxin may be considered to slow a rapid ventricular response in patients with ACS and AF associated with heart failure.	IIb	C
Administration of flecainide or propafenone is not recommended in patients with AF in the setting of ACS.	III	B

a = class of recommendation; b = level of evidence
AF = atrial fibrillation; ACS = acute coronary syndrome; DCC = direct current cardioversion

15. Diabetes mellitus

Diabetes and AF frequently coexist. Community studies demonstrate diabetes in 13% of patients with AF, and longitudinal studies indicate that diabetes is an independent risk factor for the incidence of AF.
Diabetes is an independent risk factor for stroke in patients with AF and rigorous adherence to the use of aspirin or anticoagulation is recommended.

Recommendations for diabetes mellitus	Class[a]	Level[b]
AF patients with diabetes are recommended to undergo full assessment and management of all cardiovascular risk factors, including blood pressure, lipids, etc.	I	C

a = class of recommendation; b = level of evidence
AF = atrial fibrillation

16. The elderly

The prevalence of AF is about 10% at the age of 80 years, and 18% in those aged 85 years and older. Opportunistic screening by the general practitioner is advised to increase the chance of detecting new AF. Elderly patients often have multiple comorbidities, polypharmacy and higher thromboembolic and bleeding risks. Moreover, they may have atypical symptoms and complaints in AF, and may be more sensitive to proarrhythmic effects of drugs.

Recommendations for AF in the elderly	Class[a]	Level[b]
Every patient aged 65 years and older who attends their general practitioner should be screened by checking the pulse, followed by an ECG in case of irregularity.	I	B

a = class of recommendation; b = level of evidence
ECG = electrocardiogram

17. Pregnancy

AF is rare during pregnancy in women without previously detected AF, and is mostly well tolerated in the absence of congenital, valvular or myocardial disease. The cardiac disease associated with AF should be addressed as well, and close cooperation between the obstetrician and the cardiologist is mandatory.

Recommendations for AF in pregnancy	Class[a]	Level[b]
DCC can be performed safely at all stages of pregnancy, and is recommended in patients who are haemodynamically unstable due to AF, and whenever the risk of ongoing AF is considered high, for the mother or for the foetus.	I	C
Protection against thromboembolism is recommended throughout pregnancy in AF patients with a high thromboembolic risk; the choice of agent (heparin or warfarin) should be made according to the stage of pregnancy.	I	C
Administration of an oral VKA is recommended from the second trimester, until 1 month before expected delivery.	I	B
Subcutaneous administration of LMWH in weight adjusted therapeutic doses is recommended during the first trimester and during the last month of pregnancy. Alternatively, UFH may be given, to prolong the activated partial thromboplastin time to 1.5 times the control.	I	B
If rate control is necessary, a ß-blocker or a non-dihydropyridine calcium channel antagonist should be considered. During the first trimester of pregnancy, the use of ß-blockers must be weighed against the potential risk of negative foetal effects.	IIa	C
In haemodynamically stable patients with structurally normal hearts, flecainide or ibutilide given intravenously to terminate recent-onset AF may be considered, if arrhythmia conversion is mandatory and DCC considered inappropriate.	IIb	C
If rate control is indicated, and ß-blockers or non-dihydropyridine calcium channel antagonists are contraindicated, digoxin may be considered.	IIb	C

a = class of recommendation; b = level of evidence
AF = atrial fibrillation; DCC = direct current cardioversion; LMWH = low molecular weight heparin; UFH = unfractionated heparin; VKA = vitamin K antagonist

18. Postoperative AF

AF is the most common arrhythmia after surgery. The peak incidence is between postoperative days 2 and 4, and is associated with a higher risk of stroke, increased costs and hospital stay, and adverse outcomes. Unless haemodynamic instability occurs mandating electrical cardioversion, the goal of management is ventricular rate control, which can be achieved with ß-blockers, sotalol, and amiodarone. Peroperative administration of statins and corticosteroids may be considered to decrease the incidence of AF after surgery.

Recommendations for postoperative AF	Class[a]	Level[b]
Oral ß-blockers are recommended to prevent postoperative AF for patients undergoing cardiac surgery in the absence of contraindications.	I	A
If used, ß-blockers (or other oral antiarrhythmic drugs for AF management) are recommended to be continued until the day of surgery.	I	B
Ventricular rate control is recommended in patients with AF without haemodynamic instability.	I	B
Restoration of sinus rhythm by DCC is recommended in patients who develop postoperative AF and are haemodynamically unstable.	I	C
Preoperative administration of amiodarone should be considered as prophylactic therapy for patients at high risk for postoperative AF.	IIa	A
Unless contraindicated, antithrombotic/anticoagulation medication for postoperative AF should be considered when the duration of AF is ≥ 48 h.	IIa	A
If sinus rhythm is restored successfully, duration of anticoagulation should be for a minimum of 4 weeks but more prolonged in the presence of stroke risk factors.	IIa	B
Antiarrhythmic medications should be considered for recurrent or refractory postoperative AF in an attempt to maintain sinus rhythm.	IIa	C
Sotalol may be considered for prevention of AF after cardiac surgery, but is associated with risk of proarrhythmia.	IIb	A
Biatrial pacing may be considered for prevention of AF after cardiac surgery.	IIb	A
Corticosteroids may be considered in order to reduce the incidence of AF after cardiac surgery, but are associated with risk.	IIb	B

a = class of recommendation; b = level of evidence
AF = atrial fibrillation; DCC = direct current cardioversion

19. Hyperthyroidism

AF is frequent in patients with hyperthyroidism; the treatment is directed primarily towards restoring a euthyroid state, which may be associated with a reversion to sinus rhythm.

Recommendations for AF in hyperthyroidism	Class[a]	Level[b]
In patients with active thyroid disease, antithrombotic therapy is recommended based on the presence of other stroke risk factors.	I	C
Administration of a ß-blocker is recommended to control the rate of ventricular response in patients with AF complicating thyrotoxicosis, unless contraindicated.	I	C
In circumstances when a ß-blocker cannot be used, administration of a non-dihydropyridine calcium channel antagonist (diltiazem or verapamil) is recommended to control the ventricular rate in patients with AF and thyrotoxicosis.	I	C
If a rhythm control strategy is desirable, it is necessary to normalise thyroid function prior to cardioversion, as otherwise the risk of relapse remains high.	I	C
Once a euthyroid state is restored, recommendations for antithrombotic prophylaxis are the same as for patients without hyperthyroidism.	I	C

a = class of recommendation; b = level of evidence
AF = atrial fibrillation

20. Wolff-Parkinson-White syndrome

AF poses a significant risk of potentially life-threatening arrhythmia in patients with antegrade conduction over an accessory pathway (AP), which can be eliminated by catheter ablation.

Recommendations for AF in WPW syndrome	Class[a]	Level[b]
Catheter ablation of an overt AP in patients with AF is recommended to prevent sudden cardiac death (SCD).	I	A
Immediate referral to an experienced ablation centre for catheter ablation is recommended for patients who survived SCD and have evidence of overt AP conduction.	I	C
Catheter ablation is recommended for patients with high risk professions (e.g. pilots, public transport drivers) and overt but asymptomatic AP conduction on the surface ECG.	I	B
Catheter ablation is recommended in patients at high risk of developing AF in the presence of an overt but asymptomatic AP on the surface ECG.	I	B
Asymptomatic patients with evidence of an overt AP may should be considered for catheter ablation of the AP only after a full explanation and careful counselling.	IIa	B

a = class of recommendation; b = level of evidence
AF = atrial fibrillation; AP = accessory pathway; ECG = electrocardiogram; SCD = sudden cardiac death; WPW = Wolff-Parkinson-White

21. Hypertrophic cardiomyopathy

Patients with hypertrophic cardiomyopathy (HCM) are at greater risk of developing AF compared with the general population and around 20-25% develop AF with an annual incidence of 2%. Development of AF is the major determinant of clinical deterioration.

Recommendations for AF in hypertrophic cardiomyopathy	Class[a]	Level[b]
Restoration of sinus rhythm by DCC or pharmacological cardioversion is recommended in patients with HCM presenting with recent-onset AF.	I	B
OAC therapy (INR 2.0-3.0) is recommended in patients with HCM who develop AF unless contraindicated.	I	B
Amiodarone (or alternatively, disopyramide plus ß-blocker) should be considered in order to achieve rhythm control and to maintain sinus rhythm in patients with HCM.	IIa	C
Catheter ablation of AF should be considered in patients with symptomatic AF refractory to pharmacological control.	IIa	C
Ablation procedures (with concomitant septal myectomy if indicated) may be considered in patients with HCM and refractory AF.	IIa	C

a = class of recommendation; b = level of evidence
AF = atrial fibrillation; DCC = direct current cardioversion; HCM = hypertrophic cardiomyopathy; INR = international normalised ratio

22. Pulmonary disease

AF is common in patients with chronic obstructive lung disease and has adverse prognostic implications. Antiarrhythmic therapy and electrical cardioversion are likely to be ineffective until respiratory decompensation has been corrected. Standard recommendations for anticoagulation apply.

Recommendations for AF in pulmonary disease	Class[a]	Level[b]
Correction of hypoxaemia and acidosis is recommended initial management for patients who develop AF during an acute pulmonary illness or exacerbation of chronic pulmonary disease.	I	C
DCC should be attempted in patients with pulmonary disease who become haemodynamically unstable as a consequence of AF.	I	C
A non-dihydropyridine calcium channel antagonist (diltiazem or verapamil) should be considered to control the ventricular rate in patients with obstructive pulmonary disease who develop AF.	IIa	C
ß-1 selective blockers (e.g. bisoprolol) in small doses should be considered as an alternative for ventricular rate control.	IIa	C
Theophylline and ß-adrenergic agonist agents are not recommended in patients with bronchospastic lung disease who develop AF.	III	C
Non-selective ß-blockers, sotalol, propafenone, and adenosine are not recommended in patients with obstructive lung disease who develop AF.	III	C

a = class of recommendation; b = level of evidence
AF = atrial fibrillation; DCC = direct current cardioversion

Chapter 3
Syncope*
2009

The Task Force for the Diagnosis and Treatment of Syncope of the European Society of Cardiology (ESC)

Developed in collaboration with *the European Heart Rhythm Association (EHRA)[1], the Heart Failure Association (HFA)[2] and the Heart Rhythm Society (HRS)[3]*

Endorsed by the following societies: *European Society of Emergency Medicine (EuSEM)[4], European Federation of Internal Medicine (EFIM)[5], European Union Geriatric Medicine Society (EUGMS)[6], American Geriatrics Society (AGS), European Neurological Society (ENS)[7], American Autonomic Society (AAS)[8], European Federation of Autonomic Societies (EFAS)[9]*

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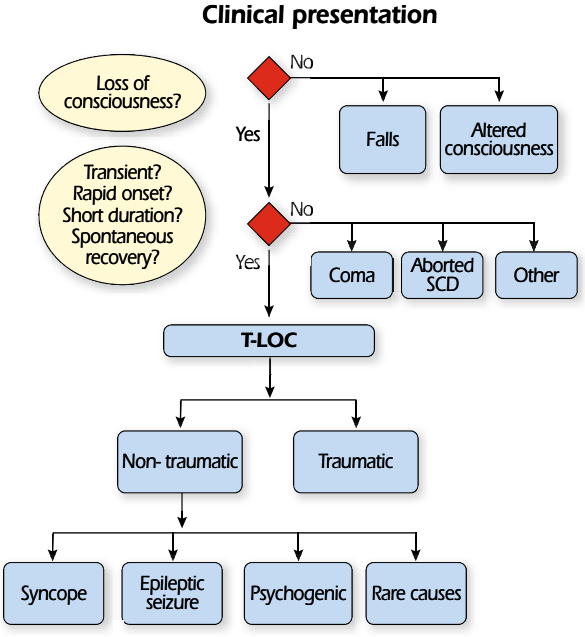
J. Bax et al., *Compendium of Abridged ESC Guidelines 2001*

1. Definition, classification and pathophysiology, epidemiology, prognosis and impact on quality of life

Definition

Syncope is a transient loss of consciousness (T-LOC) due to transient global cerebral hypoperfusion characterized by rapid onset, short duration and spontaneous complete recovery.

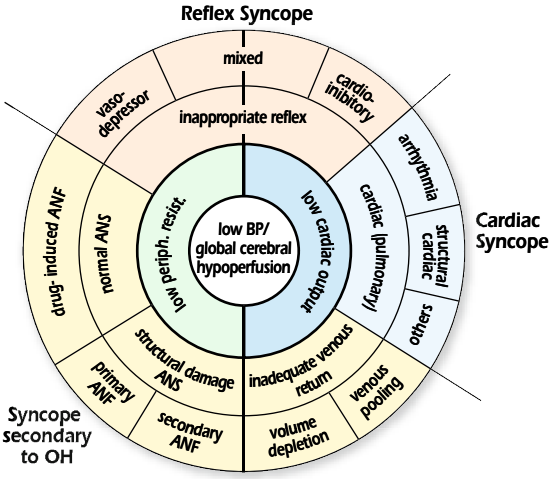
Syncope in the context of T-LOC



T-LOC = transient loss of consciousness; SCD = sudden cardiac death

Classification and pathophysiology
Reflex (neurally-mediated) syncope
Vasovagal
Situational
Carotid sinus syncope
Atypical forms (without apparent triggers and/or atypical presentation)
Syncope due to orthostatic hypotension
Primary autonomic failure
Secondary autonomic failure
Drug-induced orthostatic hypotension
Volume depletion
Cardiac syncope (cardiovascular)
Arrhythmia as primary cause
Structural diseases

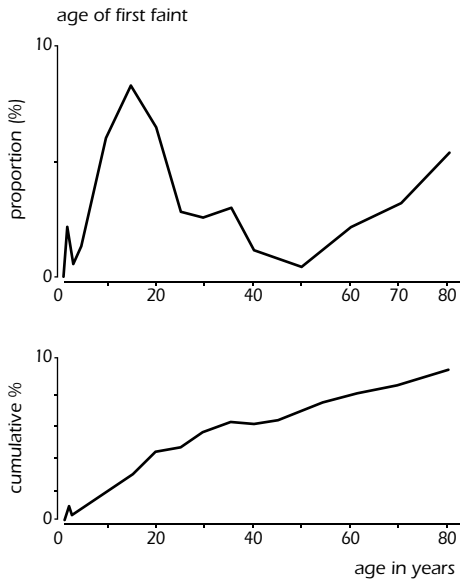
Pathophysiological basis of the classification



ANF = autonomic nervous failure; ANS = autonomic nervous system; BP = blood pressure; low periph. resist. = low peripheral resistance; OH = orthostatic hypotension

Epidemiology

- Syncope is common in the general population,
- Only a small fraction of patients with syncope seek medical attention,
- Reflex syncope is the most frequent aetiology in the general population, especially in the young,
- Syncope secondary to cardiovascular disease is the second most common cause. The number of patients with a cardiovascular cause varies widely between studies; higher frequencies are observed in emergency settings mainly in older subjects, and in settings oriented toward cardiology,
- Syncope secondary to orthostatic hypotension (OH) is rare < 40 years, and frequent in very old patients.



Schematic presentation of the distribution of age and cumulative incidence of first episodes of syncope in the general population from subjects up to 80 years is shown.

Prognosis and impact on quality of life

- Structural heart disease is the major risk factor for sudden cardiac death (SCD) and overall mortality in patients with syncope,
- The number of syncopal episodes during life, and specifically during previous year, is the stronger predictor of recurrence,
- Morbidity is particularly high in the elderly population,
- Recurrent syncope has a serious effect on quality of life.

2. Initial evaluation, risk stratification and diagnosis

Initial evaluation

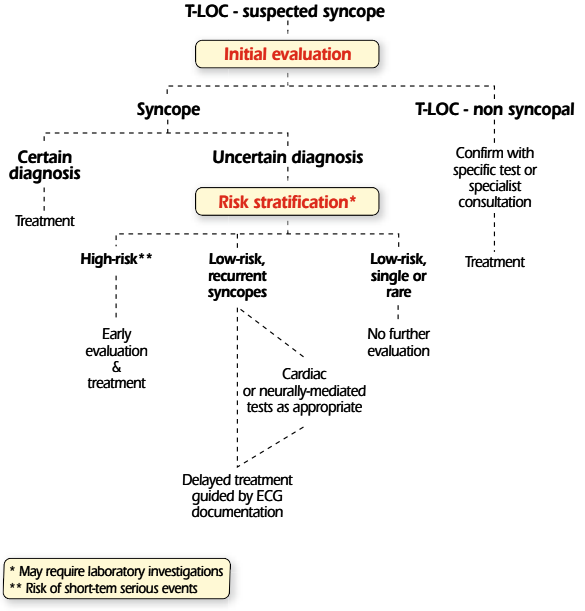
The initial evaluation of a patient presenting with T-LOC consists of careful history, physical examination, including blood pressure (BP) measurement, and standard electrocardiogram (ECG). Based on these findings, additional examinations may be performed:

- Carotid sinus massage (CSM) in patients > 40 years,
- Echocardiogram when there is previous known heart disease or data suggestive of structural heart disease or syncope secondary to cardiovascular cause,
- Immediate ECG monitoring when there is a suspicion of arrhythmic syncope,
- Orthostatic challenge (lying-to-standing orthostatic test and/or head-up tilt testing) when syncope is related to standing position or there is a suspicion of a reflex mechanism,
- Other less specific tests such as neurological evaluation or blood tests are only indicated when there is suspicion of non-syncopal T-LOC.

The initial evaluation should answer 3 key questions:

- Is it a syncopal episode or not?
- Has the aetiological diagnosis been determined?
- Are there data suggestive of a high-risk of cardiovascular events or death?

Diagnostic flowchart in patients with suspected T-LOC



T-LOC = transient loss of consciousness; ECG = electrocardiographic

Risk stratification
Short-term high-risk criteria which require prompt hospitalization or intensive evaluation
Severe structural or coronary artery disease (heart failure, low LVEF or previous myocardial infarction)
Clinical or ECG features suggesting arrhythmic syncope • Syncope during exertion or supine • Palpitations at the time of syncope • Family history of SCD • Non-sustained VT • Bifascicular-block (LBBB or RBBB combined with left anterior or left posterior fascicular block) or other intraventricular conduction abnormalities with QRS duration ≥ 120 ms • Inadequate sinus bradycardia (< 50 bpm) or sino-atrial block in absence of negative chronotropic medications or physical training • Pre-excited QRS complex • Prolonged or short QT interval • RBBB pattern with ST-elevation in leads V1-V3 (Brugada pattern) • Negative T waves in right precordial leads, epsilon waves and ventricular late potentials suggestive of ARVC
Important co-morbidities • Severe anaemia • Electrolyte disturbance

ARVC = arrhythmogenic right ventricular cardiomyopathy; bpm = beats per minute; ECG = electrocardiogram; LBBB = left bundle branch block; LVEF = left ventricular ejection fraction; RBBB = right bundle branch block; SCD = sudden cardiac death; VT = ventricular tachycardia

Recommendations: Diagnostic criteria with initial evaluation	Class[a]	Level[b]
VVS is diagnosed if syncope is precipitated by emotional distress or orthostatic stress and is associated with typical prodrome	I	C
Situational syncope is diagnosed if syncope occurs during or immediately after specific triggers such as coughing, sneezing, gastrointestinal stimulation, micturition, post-exercise, post-prandial, etc…	I	C
Orthostatic syncope is diagnosed when it occurs after standing up and there is documentation of OH	I	C
Arrhythmia related syncope is diagnosed by ECG when there is: • Persistent sinus bradycardia < 40 bpm in awake or repetitive sinoatrial block or sinus pauses ≥ 3 s • Mobitz II 2nd or 3rd degree AV block • Alternating left and right BBB • VT or rapid paroxysmal SVT • Non-sustained episodes of polymorphic VT and long or short QT interval • Pacemaker or ICD malfunction with cardiac pauses	I	C
Cardiac ischaemia related syncope is diagnosed when syncope presents with ECG evidence of acute ischaemia with or without myocardial infarction	I	C
Cardiovascular syncope is diagnosed when syncope presents in patients with prolapsing atrial myxoma, severe aortic stenosis, pulmonary hypertension, pulmonary embolus or acute aortic dissection	I	C

[a] = class of recommendation; [b] = level of evidence; AV = atrioventricular ; BBB = bundle branch block; bpm = beats per minute; ECG = electrocardiogram; ICD = implantable cardioverter defibrillator; OH = orthostatic hypotension; SVT = supraventricular tachycardia; s = seconds; VT = ventricular tachycardia; VVS = vasovagal syncope

Clinical features that can suggest a diagnosis on initial evaluation
Neurally-mediated syncope • Absence of heart disease • Long history of recurrent syncope • After sudden unexpected unpleasant sight, sound, smell or pain • Prolonged standing or crowded, hot places • Nausea, vomiting associated with syncope • During a meal or postprandial • With head rotation or pressure on carotid sinus (as in tumours, shaving, tight collars) • After exertion
Syncope due to orthostatic hypotension: • After standing up • Temporal relationship with start or changes in dosage of vasodepressive drugs leading to hypotension • Prolonged standing especially in crowded, hot places • Presence of autonomic neuropathy or Parkinsonism • Standing after exertion
Cardiovascular syncope • Presence of definite structural heart disease • Family history of unexplained sudden death or channelopathy • During exertion, or supine • Abnormal ECG • Sudden onset palpitation immediately followed by syncope • ECG findings suggesting arrhythmic syncope: - Bifascicular block (defined as either LBBB or RBBB combined with left anterior or left posterior fascicular block) - Other intraventricular conduction abnormalities (QRS duration ≥ 0.12 s) - Mobitz I second degree AV block - Asymptomatic inappropriate sinus bradycardia (< 50 bpm), sinoatrial block or sinus pause ≥ 3 s in the absence of negatively chronotropic medications - Non-sustained VT

Clinical features that can suggest a diagnosis on initial evaluation (cont.)
Cardiovascular syncope (cont.)
• ECG findings suggesting arrhythmic syncope: - Pre-excited QRS complexes - Long or short QT intervals - Early repolarization - Right bundle branch block pattern with ST-elevation in leads V1-V3 (Brugada syndrome) - Negative T waves in right precordial leads, epsilon waves and ventricular late potentials suggestive of ARVC - Q-waves suggesting myocardial infarction

[a] = class of recommendation; [b] = level of evidence; *ARVC* = arrhythmogenic right ventricular cardiomyopathy; *AV* = atrioventricular; LBBB = left bundle branch block; ECG = electrocardiogram; RBBB = right bundle branch block; VT = ventricular tachycardia

Diagnostic tests

Recommendations: Carotid sinus massage	Class[a]	Level[b]
Indications		
• CSM is indicated in patients > 40 years with syncope of unknown aetiology after initial evaluation	I	B
• CSM should be avoided in patients with previous TIA or stroke within the past 3 months and in patients with carotid bruits (except if carotid Doppler studies excluded significant stenosis)	III	C
Diagnostic criteria		
• CSM is diagnostic if syncope is reproduced in presence of asystole longer than 3 s and/or a fall in systolic BP > 50 mm Hg	I	B

[a] = class of recommendation; [b] = level of evidence; BP = blood pressure; CSM = carotid sinus massage; s = seconds; TIA = transient ischaemic attack

Recommendations: Active standing	Class[a]	Level[b]
Indications		
• Manual intermittent determination with sphygmomanometer of BP supine and during active standing for 3 min is indicated as initial evaluation, when OH is suspected	I	B
• Continuous beat-to-beat non-invasive pressure measurement may be helpful in cases of doubt	IIb	C
Diagnostic criteria		
• The test is diagnostic when there is a symptomatic fall in systolic BP from baseline value ≥ 20 mm Hg or diastolic BP ≥ 10 mm Hg or a decrease in systolic BP to < 90 mm Hg	I	C
Diagnostic criteria (cont.)		
• The test should be considered diagnostic when there is an asymptomatic fall in systolic BP from baseline value ≥ 20 mm Hg or diastolic BP ≥ 10 mm Hg or a decrease in systolic BP to < 90 mm Hg	IIa	C

[a] = class of recommendation; [b] = level of evidence; BP = blood pressure; min = minutes; OH = orthostatic hypotension

Recommendations: Tilt testing	Class[a]	Level[b]
Methodology		
• Supine pre-tilt phase of at least 5 min, when no venous cannulation, and of at least 20 min, when cannulation is undertaken, is recommended	I	C
• Tilt angle between 60° to 70° is recommended	I	B
• Passive phase of a minimum of 20 min and a maximum of 45 min is recommended	I	B
• For nitroglycerine, a fixed dose of 300-400 μg sublingually administered in the upright position is recommended	I	B
• For isoproterenol, an incremental infusion rate from 1 up to 3 μg/min in order to increase average heart rate by about 20–25% over baseline is recommended	I	B
Indications		
• Tilt testing is indicated in case of unexplained single syncopal episode in high-risk settings (e.g., occurrence of, or potential risk of physical injury or with occupational implications) or recurrent episodes, in the absence of organic heart disease, or, in the presence of organic heart disease, after cardiac causes of syncope have been excluded	I	B
• Tilt testing is indicated when it is of clinical value to demonstrate susceptibility to reflex syncope to the patient	I	C
• Tilt testing should be considered to discriminate between reflex and OH syncope	IIa	C
• Tilt testing may be considered for differentiating syncope with jerking movements from epilepsy	IIb	C
• Tilt testing may be indicated for evaluating patients with recurrent unexplained falls	IIb	C
• Tilt testing may be indicated for evaluating patients with frequent syncope and psychiatric disease	IIb	C
• Tilt testing is not recommended for assessment of treatment	III	B
• Isoproterenol tilt testing is contraindicated in patients with ischaemic heart disease	III	C

Recommendations: Tilt testing (cont.)	Class[a]	Level[b]
Diagnostic criteria		
• In patients without structural heart disease the induction of reflex hypotension/ bradycardia with reproduction of syncope or progressive OH (with or without symptoms) are diagnostic of reflex syncope and OH respectively	I	B
• In patients without structural heart disease the induction of reflex hypotension/ bradycardia without reproduction of syncope may be diagnostic of reflex syncope	IIa	B
• In patients with structural heart disease, arrhythmia or other cardiovascular cause of syncope should be excluded prior to considering positive tilt test results as diagnostic	IIa	C
• Induction of LOC in absence of hypotension and/or bradycardia should be considered diagnostic of psychogenic pseudosyncope	IIa	C

[a] = class of recommendation; [b] = level of evidence; BP = blood pressure; CSM = carotid sinus massage; HR = heart rate; LOC = loss of consciouness; OH = orthostatic hypotension; µg = micrograms

Recommendations: Electrocardiograhic monitoring	Class[a]	Level[b]
Indications		
• ECG monitoring is indicated in patients who have clinical or ECG features suggesting arrhythmic syncope. The duration (and technology) of monitoring should be selected according to the risk and the predicted recurrence rate of syncope:	I	B
o Immediate in-hospital monitoring (in bed or telemetric) is indicated in high-risk patients defined in the table on "Risk stratification" on page 270	I	C
o Holter monitoring is indicated in patients who have very frequent syncope or presyncope (≥ 1 per week)	I	B
o ILR is indicated in:		
- An early phase of evaluation in patients with recurrent syncope of uncertain origin, absence of high-risk criteria listed in Table on "Risk stratification" and a high likelihood of recurrence within battery longevity of the device	I	B
- High-risk patients in whom a comprehensive evaluation did not demonstrate a cause of syncope or lead to a specific treatment	I	B
o ILR should be considered to assess the contribution of bradycardia before embarking on cardiac pacing in patients with suspected or certain reflex syncope presenting with frequent or traumatic syncopal episodes	IIa	B
o External loop recorders should be considered in patients who have inter-symptom interval ≤ 4 weeks	IIa	B
Diagnostic criteria		
• ECG monitoring is diagnostic when a correlation between syncope and an arrhythmia (brady- or tachyarrhythmia) is detected	I	B
• In the absence of such correlation, ECG monitoring is diagnostic when periods of Mobitz II or III degree AV block or a ventricular pause ≥ 3 s (with possible exception of young trained persons, during sleep, medicated patients or rate-controlled atrial fibrillation), or rapid prolonged paroxysmal SVT or VT are detected. The absence of arrhythmia during syncope excludes arrhythmic syncope	I	C
• The ECG documentation of presyncope without any relevant arrhythmia is not an accurate surrogate for syncope	III	C
• Asymptomatic arrhythmias (other than those listed above) are not an accurate surrogate for syncope	III	C
• Sinus bradycardia (in absence of syncope) is not an accurate surrogate for syncope	III	C

[a] = class of recommendation; [b] = level of evidence; AV = atrioventricular; ECG = electrocardiographic; ILR = implantable loop recorder; s = seconds; SVT = supraventricular tachycardia; VT = ventricular tachycardia

Recommendations: Electrophysiological study	Class[a]	Level[b]
Indications		
• In patients with ischaemic heart disease EPS is indicated when initial evaluation suggests an arrhythmic cause of syncope unless there is already an established indication for ICD	I	B
• In patients with BBB, EPS should be considered when non-invasive tests have failed to make the diagnosis	IIa	B
• In patients with syncope preceded by sudden and brief palpitations, EPS may be performed when other non-invasive tests have failed to make the diagnosis	IIb	B
• In patients with Brugada syndrome, ARVC and hypertrophic cardiomyopathy an EPS may be performed in selected cases	IIb	C
• In patients with high-risk occupations, in whom every effort to exclude a cardiovascular cause of syncope is warranted, an EPS may be performed in selected cases	IIb	C
• EPS is not recommended in patients with normal ECG, no heart disease and no palpitations	III	B
Diagnostic criteria		
• EPS is diagnostic, and no additional tests are required, in the following cases:		
- sinus bradycardia and prolonged CSNRT (> 525 ms)	I	B
- BBB and either a baseline HV interval of ≥ 100ms, or 2nd or 3rd degree His-Purkinje block is demonstrated during incremental atrial pacing, or with pharmacological challenge	I	B
- Induction of sustained monomorphic VT in patients with previous myocardial infarction	I	B
- Induction of rapid SVT, which reproduces hypotensive or spontaneous symptoms	I	B
• An HV interval between 70 and 100 ms should be considered diagnostic	IIa	B
• The induction of polymorphic VT or ventricular fibrillation in patients with Brugada syndrome, ARVC and patients resuscitated from cardiac arrest may be considered diagnostic	IIb	B
• The induction of polymorphic VT or ventricular fibrillation in patients with ischaemic or DCM cannot be considered a diagnostic finding	III	B

[a] = class of recommendation; [b] = level of evidence; ARVC = arrhythmogenic right ventricular cardiomyopathy; BBB = bundle branch block; CSNRT = corrected sinus node recovery time; DCM = dilated cardiomyopathy; EPS = electrophysiological study; ICD = implantable cardioverter defibrillator; HV = His-ventricle; ms = milliseconds; SVT = supraventricular tachycardia; VT = ventricular tachycardia

Recommendations: Adenosine triphosphate test	Class[a]	Level[b]
Indications		
• Owing to lack of correlation with spontaneous syncope, ATP test cannot be used as a diagnostic test to select patients for cardiac pacing	III	B

[a] = class of recommendation; [b] = level of evidence; ATP = adenosine triphosphate test

Recommendations: Echocardiography	Class[a]	Level[b]
Indications		
• Echocardiography is indicated for diagnosis and risk stratification in patients who are suspected of having structural heart disease	I	B
Diagnostic criteria		
• Echocardiography alone is diagnostic of the cause of syncope in severe aortic stenosis, obstructive cardiac tumours or thrombi, pericardial tamponade, aortic dissection and congenital anomalies of coronary arteries	I	B

[a] = class of recommendation; [b] = level of evidence

Recommendations: Exercise testing	Class[a]	Level[b]
Indications		
• Exercise testing is indicated in patients who experience syncope during or shortly after exertion	I	C
Diagnostic criteria		
• Exercise testing is diagnostic when syncope is reproduced during or immediately after exercise in the presence of ECG abnormalities or severe hypotension	I	C
• Exercise testing is diagnostic if Mobitz II 2nd degree or 3rd degree AV block develop during exercise even without syncope	I	C

[a] = class of recommendation; [b] = level of evidence; AV = atrioventricular; ECG = electrocardiogram

Recommendations: Psychiatric evaluation	Class[a]	Level[b]
Indications		
• Psychiatric evaluation is indicated in patients in whom T-LOC is suspected to be psychogenic pseudosyncope	I	C
• Tilt testing, preferably with concurrent EEG recording and video monitoring may be considered for diagnosis of T-LOC mimicking syncope ('pseudosyncope') or epilepsy	IIb	C

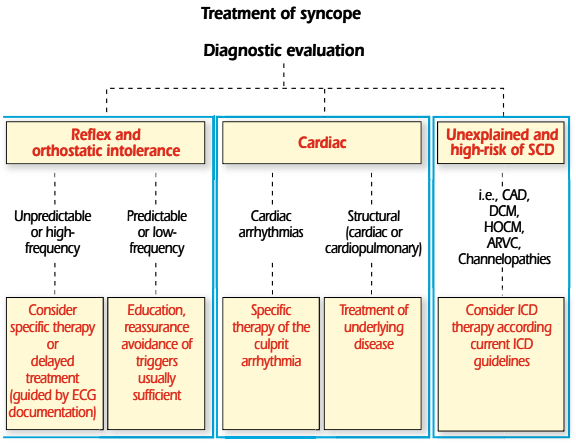
[a] = class of recommendation; [b] = level of evidence; EEG = electroencephalogram; T-LOC = transient loss of consciousness

Recommendations: Neurological evaluation	Class[a]	Level[b]
Indications		
• Neurological evaluation is indicated in patients in whom T-LOC is suspected to be epilepsy	I	C
• Neurological evaluation is indicated when syncope is due to ANF in order to evaluate the underlying disease	I	C
• EEG, ultrasound of neck arteries and computed tomography or magnetic resonance imaging of the brain are not indicated, unless a non-syncopal cause of T-LOC is suspected	III	B

[a] = class of recommendation; [b] = level of evidence; EEG = electroencephalogram; T-LOC = transient loss of consciousness; ANF = autonomic failure

3. Treatment

General principles of treatment



ARVC = arrhythmogenic right ventricular cardiomyopathy; CAD = coronary artery disease; DCM = dilated cardiomyopathy; ECG = electrocardiogram; HOCM = hypertrophic obstructive cardiomyopathy; ICD = implantable cardioverter defibrillator; SCD = sudden cardiac death

Recommendations: Treatment of reflex syncope	Class[a]	Level[b]
• Explanation of the diagnosis, provision of reassurance and explanation of risk of recurrence are indicated in all patients	I	C
• Isometric PCM are indicated in patients with prodrome	I	B
• Cardiac pacing should be considered in patients with dominant cardioinhibitory CSS	IIa	B
• Cardiac pacing should be considered in patients with frequent recurrent reflex syncope, age > 40 years and documented spontaneous cardioinhibitory response during monitoring	IIa	B

Recommendations: Treatment of reflex syncope (cont.)	Class[a]	Level[b]
• Midodrine may be indicated in patients with VVS refractory to lifestyle measures	IIb	B
• Tilt training may be useful for education of patients but long-term benefit depends on compliance	IIb	B
• Cardiac pacing may be indicated in patients with tilt-induced cardioinhibitory response with recurrent frequent unpredictable syncope and age > 40 after alternative therapy has failed	IIb	C
• Cardiac pacing is not indicated in the absence of a documented cardioinhibitory reflex	III	C
• ß-adrenergic blocking drugs are not indicated	III	A

[a] = class of recommendation; [b] = level of evidence; CSS = carotid sinus syndrome; PCM = physical counterpressure manoeuvres; VVS = vasovagal syncope

Recommendations: Treatment of orthostatic hypotension	Class[a]	Level[b]
• Adequate hydration and salt intake must be maintained	I	C
• Midodrine should be administered as adjunctive therapy if needed	IIa	B
• Fludrocortisone should be administered as adjunctive therapy if needed	IIa	C
• PCM may be indicated	IIb	C
• Abdominal binders and/or support stockings to reduce venous pooling may be indicated	IIb	C
• Head-up tilt sleeping (> 10°) to increase fluid volume may be indicated	IIb	C

[a] = class of recommendation; [b] = level of evidence; PCM = physical counterpressure manoeuvres

Recommendations: Treatment of syncope due to cardiac arrhythmias	Class[a]	Level[b]
• Syncope due to cardiac arrhythmias must receive treatment appropriate to the cause	I	B
Cardiac pacing		
• Pacing is indicated in patients with sinus node disease in whom syncope is demonstrated to be due to sinus arrest (symptom-ECG correlation) without a correctable cause	I	C
• Pacing is indicated in sinus node disease patients with syncope and abnormal CSNRT	I	C
• Pacing is indicated in sinus node disease patients with syncope and asymptomatic pauses ≥ 3 s (with possible exceptions of young trained persons, during sleep and in medicated patients)	I	C
• Pacing is indicated in patients with syncope and 2nd degree Mobitz II, advanced or complete AV block	I	B
• Pacing is indicated in patients with syncope, BBB and positive EPS	I	B
• Pacing should be considered in patients with unexplained syncope and BBB	IIa	C
• Pacing may be indicated in patients with unexplained syncope and sinus node disease with persistent sinus bradycardia itself asymptomatic	IIb	C
• Pacing is not indicated in patients with unexplained syncope without evidence of any conduction disturbance	III	C
Catheter ablation		
• Catheter ablation is indicated in patients with symptom/arrhythmia ECG correlation in both SVT and VT in the absence of structural heart disease (with exception of atrial fibrillation)	I	C
• Catheter ablation may be indicated in patients with syncope due to the onset of rapid atrial fibrillation	IIb	C
Antiarrhythmic drug therapy		
• Antiarrhythmic drug therapy, including rate control drugs, is indicated in patients with syncope due to onset of rapid atrial fibrillation	I	C
• Drug therapy should be considered in patients with symptom-arrhythmia ECG correlation in both SVT and VT when catheter ablation cannot be undertaken or has failed	IIa	C
Implantable Cardioverter Defibrillator		
• ICD is indicated in patients with documented VT and structural heart disease	I	B
• ICD is indicated when sustained monomorphic VT is induced at EPS in patients with previous myocardial infarction	I	B
• ICD should be considered in patients with documented VT and inherited cardiomyopathies or channelopathies	IIa	B

[a] = class of recommendation; [b] = level of evidence; AV = atrioventricular; BBB = bundle branch block; CSNRT = corrected sinus node recovery time; ECG = electrocardiogram; EPS = electrophysiological study; ICD = implantable cardioverter defibrillator; s = seconds; SVT = supraventricular tachycardia; VT = ventricular tachycardia

Recommendations: Indications for implantable cardioverter defibrillator in patients with unexplained syncope and a high-risk of sudden cardiac death			
Clinical situation	**Class[a]**	**Level[b]**	**Comments**
• In patients with ischaemic cardiomyopathy with severely depressed LVEF or HF ICD therapy is indicated according to current guidelines for ICD-cardiac resynchronization therapy implantation	I	A	
• In patients with non-ischaemic cardiomyopathy with severely depressed LVEF or HF ICD therapy is indicated according to current guidelines for ICD-cardiac resynchronization therapy implantation	I	A	
• In hypertrophic cardiomyopathy ICD therapy should be considered in patients at high-risk	IIa	C	In non high-risk, consider ILR
• In right ventricular cardiomyopathy ICD therapy should be considered in patients at high-risk	IIa	C	In non high-risk, consider ILR
• In Brugada syndrome ICD therapy should be considered in patients with spontaneous type I ECG	IIa	B	In the absence of spontaneous type I pattern, consider ILR
• In long QT syndrome ICD therapy, in conjunction with ß-blockers, should be considered in patients at risk	IIa	B	In non high-risk, consider ILR
• In patients with ischaemic cardiomyopathy without severely depressed LVEF or HF and negative programmed electrical stimulation ICD therapy may be considered	IIb	C	Consider ILR to help define the nature of unexplained syncope

Recommendations: Indications for implantable cardioverter defibrillator in patients with unexplained syncope and a high-risk of sudden cardiac death (cont.)			
Clinical situation	**Class[a]**	**Level[b]**	**Comments**
• In patients with non-ischaemic cardiomyopathy without severely depressed LVEF or HF ICD therapy may be considered	IIb	C	Consider ILR to help define the nature of unexplained syncope

[a] = class of recommendation; [b] = level of evidence; HF = heart failure; ECG = electrocardiogram; ICD = implantable cardioverter defibrillator; ILR = implantable loop recorder; LVEF = left ventricular ejection fraction; SCD = sudden cardiac death

4. Special issues

Syncope in the elderly

The most common causes of syncope in the elderly are OH, carotid sinus syndrome (CSS), reflex syncope and cardiac arrhythmias. Different forms may often coexist in a patient, making diagnosis difficult.

Key points in the evaluation of syncope in elderly patients

- OH is not always reproducible in older adults (particularly medication and age-related). Therefore, orthostatic BP appraisal should be repeated, preferably in the morning and/or promptly after syncope,
- CSM is particularly useful even if non-specific carotid sinus hypersensitivity is frequent without history of syncope,
- In the evaluation of reflex syncope in older patients tilt testing is well tolerated and safe, with positivity rates similar to those observed in younger patients, particularly after nitroglycerin challenge,
- Twenty-four hour ambulatory BP recordings may be helpful if instability of BP is suspected (e.g., medication or post prandial),
- Due to the high frequency of arrhythmias, ILR may be especially useful in the elderly with unexplained syncope,
- Evaluation of mobile, independent, cognitively normal older adults must be performed as for younger individuals.

Syncope in paediatric patients

Diagnostic evaluation in paediatric patients is similar to that in adults. Reflex syncope represents the vast majority of the aetiology, but in rare cases, syncope is the manifestation of life-threatening cardiac arrhythmia or structural abnormalities. Syncope should also be differentiated from epilepsy and psychogenic pseudo-syncope which are rare but important causes of T-LOC in paediatric patients.

Some aspects of the history can suggest a cardiac origin, and should prompt cardiac evaluation:

- Family history: premature SCD < 30 years; familial heart disease,
- Known or suspected heart disease,
- Event triggers: loud noise, fright, extreme emotional stress,
- Syncope during exercise, including swimming,
- Syncope without prodrome, while supine or sleeping, or preceeded by chest pain or palpitations.

Key points in the evaluation of syncope in the paediatric patients:

- Syncope in childhood is common, the vast majority being of reflex origin, with only a minority having a potentially life-threatening cause,
- Discrimination between benign and serious causes is made primarily by history, physical examination and ECG,
- The cornerstone of therapy for young patients with reflex syncope includes education and reassurance.

Syncope and driving		
Diagnosis	**Group 1 (private drivers)**	**Group 2 (professional drivers)**
Cardiac arrhythmias		
Cardiac arrhythmia, medical treatment	After successful treatment is established	After successful treatment is established
Pacemaker implant	After 1 week	After appropriate function is established
Successful catheter ablation	After successful treatment is established	After long-term success is confirmed
ICD implant	In general low-risk, restriction according to current guidelines	Permanent restriction
Reflex syncope		
Single/mild	No restrictions	No restriction unless it occurred during high-risk activity
Recurrent and severe*	After symptoms controlled	Permanent restriction unless effective treatment has been established
Unexplained syncope		
	No restrictions unless absence of prodrome, occurrence during driving or presence of severe structural heart disease	After diagnosis and appropriate therapy is established

[a] = class of recommendation; [b] = level of evidence; ICD = implantable cardioverter defibrillator

*Neurally mediated syncope is defined as severe if it is very frequent, or occurring during the prosecution of a 'high risk' activity, or recurrent or unpredictable in 'high risk' patients

5. Syncope management unit

Objectives

Any syncope facility is aimed at reaching the following goals:

- Provide state-of-the-art guidelines based assessment of symptomatic patients in order to risk stratify them, then obtain accurate aetiological diagnosis, and assess prognosis,
- Physician(s) in charge of the syncope facility lead the process of comprehensive management from those listed above to therapy, and, if necessary, follow-up. They perform the core laboratory tests and have preferential access to hospitalization, diagnostic tests and therapeutic procedures,
- Reduce hospitalizations. The majority of patients can be investigated as out-patients or day cases,
- Set standards for clinical excellence in adherence to the recommendations on syncope.

Key points for standardized care delivery:

- A cohesive, structured care pathway - either delivered within a single syncope facility or as a more multi-faceted service - is recommended for global assessment of patients with T-LOC (suspected syncope),
- Referral can be directly from: family practitioners, emergency departments and those caring for acutely admitted in-patients and other institutional settings,
- Experience and training in key components of cardiology, neurology, emergency and geriatric medicine are pertinent.

Chapter 4
Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death*
2006

A Report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death)

Developed in Collaboration With the European Heart Rhythm Association and the Heart Rhythm Society

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1. Introduction

The reader should note that the recommendations, text, figures, and tables included in these pocket guidelines represent a succinct summary of the more extensive evidence base, critical evaluation, supporting text, tables, figures, and references that are included in the full text guidelines. Readers are strongly encouraged to refer to the full text guidelines.

Classification of Recommendations and Level of Evidence are expressed in the American College of Cardiology (ACC)/American Heart Association (AHA)/European Society of Cardiology (ESC) format as follows:

Classification of Recommendations

Class I	Conditions for which there is evidence and/or general agreement that a given procedure or treatment is beneficial, useful, and effective.
Class II	Conditions for which there is conflicting evidence and/or divergence of opinion about the usefulness/efficacy of a procedure or treatment.

*Adapted from the ACC/AHA/ESC Guidelines for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death - Executive Summary (European Heart Journal 2006;27:2099-2140) and Full Text (Europace 2006;8:746-837)

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J. Bax et al., *Compendium of Abridged ESC Guidelines 2001*

Class IIa	Weight of evidence/opinion is in favour of usefulness/efficacy.
Class IIb	Usefulness/efficacy is less well established by evidence/opinion.
Class III	Conditions for which there is evidence and/or general agreement that a procedure/treatment is not useful/effective and in some cases may be harmful.

Level of Evidence A	Data derived from multiple randomized clinical trials or meta-analyses.
Level of Evidence B	Data derived from a single randomized trial or large non-randomized studies.
Level of Evidence C	Only consensus opinion of experts, case studies, or standard-of-care.

The schema for classification of recommendations and level of evidence is summarized in Table 1.

Table 1. Applying Classification of Recommendations and Level of Evidence

Estimate of Certainty (Precision) of Treatment Effect	Size of Treatment Effect: **Class I** Benefit >>> Risk Procedure/Treatment should be performed/ administered	**Class IIa** Benefit >> Risk Additional studies with focused objectives needed. It is reasonable to perform procedure/ administer treatment	**Class IIb** Benefit ≥ Risk Additional studies with broad objectives needed; additional registry data would be helpful Procedure/Treatment may be considered	**Class III** Risk ≥ Benefit No additional studies needed Procedure/Treatment should not be performed/administered since it is not helpful and may be harmful
Level A Multiple (3-5) population risk strata evaluated* General consistency of direction and magnitude of effect	- Recommendation that procedure or treatment is useful/effective - Sufficient evidence from multiple randomized trials or meta-analyses	- Recommendation in favour of treatment or procedure being useful/ effective - Some conflicting evidence from multiple randomized trials or meta-analyses	- Recommendation's usefulness/efficacy less well established - Greater conflicting evidence from multiple randomized trials or meta-analyses	- Recommendation that procedure or treatment is not useful/effective and may be harmful - Sufficient evidence from multiple randomized trials or meta-analyses
Level B Limited (2-3) population risk strata evaluated*	- Recommendation that procedure or treatment is useful/effective - Limited evidence from single randomized trial or non-randomized studies	- Recommendation in favour of treatment or procedure being useful/ effective - Some conflicting evidence from single randomized trial or non-randomized studies	- Recommendation's usefulness/efficacy less well established - Greater conflicting evidence from single randomized trial or non-randomized studies	- Recommendation that procedure or treatment is not useful/effective and may be harmful - Limited evidence from single randomized trial or non-randomized studies
Level C Very limited (1-2) population risk strata evaluated*	- Recommendation that procedure or treatment is useful/effective - Only expert opinion, case studies, or standard-of-care	- Recommendation in favour of treatment or procedure being useful/ effective - Only diverging expert opinion, case studies, or standard-of-care	- Recommendation's usefulness/efficacy less well established - Only diverging expert opinion, case studies, or standard-of-care	- Recommendation that procedure or treatment is not useful/effective and may be harmful - Only expert opinion, case studies, or standard-of-care

* Data available from clinical trials or registries about the usefulness/efficacy in different subpopulations, such as gender, age, history of diabetes, history of prior myocardial infarction, history of heart failure, and prior aspirin use.

A recommendation with Level of Evidence B or C does not imply that the recommendation is weak. Many important clinical questions addressed in the guidelines do not lend themselves to clinical trials. Even though randomized trials are not available, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

Table 2. Inconsistencies Between ACC/AHA/ESC Guidelines for the Management of Patients With Ventricular Arrhythmias and the Prevention of SCD and Other Published ACC/AHA and ESC

Group addressed in recommendation	Guideline and Class of Recommendation with Level of Evidence* for Each Group				
	2005 ACC/AHA HF	2005 ESC HF	2004 ACC/AHA	2002 ACC/AHA/NASPE PM and ICD	Comment from the ACC/AHA/ESC VA & SCD Guidelines
LVD d/t MI, LVEF ≤ 30%, NYHA II, III	Class I; LOE: B	Class I; LOE: A	Class IIa; LOE: B	Class IIa; LOE: B	VA & SCD has combined all trials that enrolled patients with LVD d/t MI into one recommendation, Class I; LOE: A
LVD d/t MI, LVEF 30% to 35%, NYHA II, III	Class IIa; LOE: B	Class I; LOE: A	N/A	N/A	
LVD d/t MI, LVEF 30% to 40%, NSVT, positive EP study	N/A	N/A	Class I; LOE: B	Class IIb; LOE: B	
LVD d/t MI, LVEF ≤ 30%, NYHA I	Class IIa; LOE: B	N/A	N/A	N/A	VA & SCD has expanded the range of LVEF to ≤ 30% to 35% for patients with LVD d/t MI and NYHA functional class I into one recommendation, Class IIa; LOE: B.
LVD d/t MI, LVEF ≤ 31% to 35%, NYHA I	N/A	N/A	N/A	N/A	
NICM, LVEF ≤ 30%, NYHA II, III	Class I; LOE: B	Class I; LOE: A	N/A	N/A	VA & SCD has combined all trials of NICM, NYHA II, III into one recommendation, Class I; LOE: B
NICM, LVEF 30% to 35%, NYHA II, III	Class IIa; LOE: B	Class I; LOE: A	N/A	N/A	
NICM, LVEF ≤ 30%, NYHA I	Class IIb; LOE: C	N/A	N/A	N/A	VA & SCD has expanded the range of LVEF to ≤ 30% to 35% for patients with NICM and NYHA functional class I into one recommendation, Class IIb; LOE: B.
NICM, LVEF ≤ 31% to 35%, NYHA I	N/A	N/A	N/A	N/A	

*For an explanation of class of recommendation and level of evidence (LOE), see Table 1.

ACC/AHA HF = ACC/AHA 2005 Guidelines Update for the Diagnosis and Management of Chronic Heart Failure in the Adult; ACC/AHA/NASPE PM and ICD = ACC/AHA/NASPE 2002 Guidelines Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices; ACC/AHA STEMI = ACC/AHA 2004 Guidelines for the Management of Patients with ST-Elevation Myocardial Infarction; EP = electrophysiological; ESC HF = ESC 2005 Guidelines for the Diagnosis and Treatment of Chronic Heart Failure; LOE = level of evidence; LVD d/t MI = left ventricular dysfunction due to prior myocardial infarction; LVEF = left ventricular ejection fraction; N/A = not addressed; NICM = non-ischaemic cardiomyopathy; NSVT = nonsustained ventricular tachycardia; NYHA = New York Heart Association functional class; SCD = sudden cardiac death; VA = ventricular arrhythmias. Guidelines With Respect to ICD Therapy for Primary Prevention to Reduce Total Mortality by a Reduction in SCD

1.1. Prophylactic Implantable Cardioverter Device Recommendations Across Published Guidelines

Please see Table 2 for prophylactic implantable cardioverter defibrillator (ICD) therapy recommendations across published guidelines. A detailed explanation of the rationale used in formulating these recommendations can be found in the full text guidelines.

1.2. Classification of Ventricular Arrhythmias and Sudden Cardiac Death

This classification table is provided for direction and introduction to these pocket guidelines (Table 3).

Table 3. Classification of Ventricular Arrhythmias

Classification by Electrocardiography	
Nonsustained VT	Three or more beats in duration, terminating spontaneously in less than 30 seconds. VT is a cardiac arrhythmia of 3 or more consecutive complexes in duration emanating from the ventricles at a rate of greater than 100 bpm (cycle length less than 600 msec).
Monomorphic	Nonsustained VT with a single QRS morphology.
Polymorphic	Nonsustained VT with a changing QRS morphology at cycle length between 600 and 180 msec.
Sustained VT	VT greater than 30 seconds in duration and/or requiring t ermination due to haemodynamic compromise in less than 30 seconds.
Monomorphic	Sustained VT with a stable single QRS morphology.
Polymorphic	Sustained VT with a changing or multiform QRS morphology at cycle length between 600 and 180 msec.
Bundle branch reentrant tachycardia	VT due to reentry involving the His-Purkinje system,usually with LBBB morphology; this usually occurs in the setting of cardiomyopathy.
Bidirectional VT	VT with a beat-to-beat alternans in the QRS frontal plane axis, often associated with digitalis toxicity.
Torsades de pointes	Characterized by VT associated with a long QT or QTc, and electrocardiographically characterized by twisting of the peaks of the QRS complexes around the isoelectric line during the arrhythmia: - "Typical" initiated following "short long short" coupling intervals. - Short coupled variant initiated by normal short coupling.
Ventricular flutter	A regular (cycle length variability 30 msec or less) ventricular arrhythmia approximately 300 bpm (cycle length 200 msec) with a monomorphic appearance; no isoelectric interval between successive QRS complexes.
Ventricular fibrillation	Rapid, usually more than 300 bpm/200 msec (cycle length 180 msec or less), grossly irregular ventricular rhythm with marked variability in QRS cycle length, morphology, and amplitude.

LBBB = left bundle-branch block; VT = ventricular tachycardia.

2. Incidence of Sudden Cardiac Death

The geographic incidence of sudden cardiac death (SCD) varies as a function of coronary heart disease (CHD) prevalence in different regions. Estimates for the U.S. range from less than 200,000 to more than 450,000 SCDs annually, with the most widely used estimates in the range of 300,000 to 350,000 SCDs annually. The variation is based, in part, on the inclusion criteria used in individual studies. Overall, event rates in Europe are similar to those in the United States, with significant geographic variations reported.

Approximately 50% of all CHD deaths are sudden and unexpected, occurring shortly (within 1 hr) after the onset of a change in clinical status, with some geographical variation in the fraction of coronary deaths that are sudden.

3. Clinical Presentations of Patients With Ventricular Arrhythmias and Sudden Cardiac Death

Ventricular arrhythmias can occur in individuals with or without cardiac disorders. There is a great deal of overlap between clinical presentations (Table 4) and severity and type of heart disease. The prognosis and management are individualized according to symptom burden and severity of underlying heart disease in addition to the clinical presentation.

4. General Evaluation of Patients With Documented or Suspected Ventricular Arrhythmias

4.1. Resting ECG

Recommendations

Class I	Resting 12-lead electrocardiogram (ECG) is indicated in all patients who are evaluated for ventricular arrhythmias (VA). (Level of Evidence: A)

Table 4. Clinical Presentations of Patients With Ventricular Arrhythmias and Sudden Cardiac Death

Clinical Presentations
Asymptomatic individuals with or without electrocardiographic abnormalities
Persons with symptoms potentially attributable to ventricular arrhythmias • Palpitations • Dyspnoea • Chest pain • Syncope and presyncope
Ventricular tachycardia that is haemodynamically stable
Ventricular tachycardia that is not haemodynamically stable
Cardiac arrest • Asystolic (sinus arrest, atrioventricular block) • Ventricular tachycardia • Ventricular fibrillation • Pulseless electrical activity

4.2. Exercise Testing

Recommendations

Class I	1. Exercise testing (ET) is recommended in adult patients with VA who have an intermediate or greater probability of having CHD by age, gender and symptoms* to provoke ischaemic changes or VA.(Level of Evidence: B)
	2. ET is useful in patients regardless of age with known or suspected exercise-induced VA, including catecholaminergic ventricular tachycardia (VT) to provoke the arrhythmia, achieve a diagnosis, and determine the patient's response to tachycardia. (Level of Evidence: B)
Class IIa	ET can be useful in evaluating response to medical or ablation therapy in patients with known exercise-induced VA. (Level of Evidence: B)
Class IIb	1. ET might be useful in patients with VA and a low probability of CHD by age, gender, and symptoms.* (Level of Evidence: C)
	2. ET might be useful in the investigation of isolated premature ventricular complexes (PVCs) in middle-aged or older patients without other evidence of CHD. (Level of Evidence: C)
Class III	See Table 1 in the ACC/AHA 2002 Guideline Update for Exercise Testing for contraindications. (Level of Evidence: B)

*See Table 4 in the ACC/AHA 2002 Guideline Update for Exercise Testing for further explanation of CHD probability.

4.3. Ambulatory Electrocardiography

Recommendations

Class I	1. Ambulatory ECG is indicated when there is a need to clarify the diagnosis by detecting arrhythmias, QT interval changes, T-wave alternans or ST-changes, evaluate risk, or judge therapy. (Level of Evidence: A)
	2.Event monitors are indicated when symptoms are sporadic, to establish whether they are caused by transient arrhythmias. (Level of Evidence: B)
	3.Implantable recorders are useful in patients with sporadic symptoms suspected to be related to arrhythmias such as syncope, when a symptom-rhythm correlation cannot be established by conventional diagnostic techniques. (Level of Evidence: B)

4.4. ECG Techniques and Measurements

Recommendations

Class IIa	It is reasonable to use T-wave alternans for improving the diagnosis and risk stratification of patients with VA or at risk for developing life-threatening VA. (Level of Evidence: A)
Class IIb	ECG techniques such as signal-averaged ECG, heart rate variability, baroflex sensitivity and heart rate turbulence may be useful for improving the diagnosis and risk stratification of patients with ventricular arrhythmias or who are at risk of developing life-threatening ventricular arrhythmias. (Level of Evidence: B)

4.5. Left Ventricular Function and Imaging

Recommendations

Class I	1. Echocardiography is recommended in patients with VA who are suspected of having structural heart disease. (Level of Evidence: B)
	2. Echocardiography is recommended for the subset of patients at high-risk for development of serious VA or SCD, such as those with dilated, hypertrophic, or right ventricular cardiomyopathies, acute myocardial infarction (AMI) survivors, or relatives of patients with inherited disorders associated with SCD. (Level of Evidence: B)
	3. ET with an imaging modality (echocardiography or nuclear perfusion [single-photon emission computed tomography (SPECT)]) is recommended to detect silent ischaemia in patients with VA who have an intermediate probability of having CHD by age, symptoms and gender, and in whom ECG assessment is less reliable because of digoxin use, left ventricular (LV) hypertrophy, greater than 1 mm ST-segment depression at rest, Wolff-Parkinson-White Syndrome or LBBB. (Level of Evidence: B)
	4.Pharmacological stress testing with an imaging modality (echocardiography or myocardial perfusion SPECT) is recommended to detect silent ischaemia in patients with VA who have an intermediate probability of having CHD by age, symptoms, and gender and are physically unable to perform a symptom-limited exercise test. (Level of Evidence: B)
Class IIa	1. Magnetic resonance imaging (MRI), cardiac computed tomography (CT), or radionuclide angiography can be useful in patients with VA when echocardiography does not provide accurate assessment of LV and right ventricular (RV) function, and/or evaluation of structural changes. (Level of Evidence: B)
	2. Coronary angiography can be useful in establishing or excluding the presence of significant obstructive CHD in patients with life-threatening VA or in survivors of SCD, who have an intermediate or greater probability of having CHD by age, symptoms, and gender. (Level of Evidence: C)
	3. LV imaging can be useful in patients undergoing biventricular pacing. (Level of Evidence: C)

4.6. Electrophysiological Testing

Electrophysiological (EP) testing with intracardiac recording and electrical stimulation at baseline and with drugs, has been used for arrhythmia assessment and risk stratification for SCD. EP testing is used to document inducibility of VT, guide ablation, evaluate drug effects, assess the risks of recurrent VT or SCD, evaluate loss of consciousness in selected patients with arrhythmias suspected as a cause and assess the indications for ICD therapy.

I. EP Testing in Patients with CHD

Recommendations

Class I	1. EP testing is recommended for diagnostic evaluation of patients with remote myocardial infarction (MI) with symptoms suggestive of ventricular tachyarrhythmias including palpitations, pre-syncope, and syncope. (Level of Evidence: B)
	2. EP testing is recommended in patients with CHD to guide and assess efficacy of VT ablation. (Level of Evidence: B)
	3. EP testing is useful in patients with CHD for the diagnostic evaluation of wide QRS-complex tachycardias of unclear mechanism. (Level of Evidence: C)
Class IIa	EP testing is reasonable for risk stratification in patients with remote MI, nonsustained (NSVT) and LV ejection fraction (LVEF) ≤40%. (Level of Evidence: B)

2. EP Testing in Patients with Syncope

Recommendations

Class I	EP testing is recommended in patients with syncope of unknown cause with impaired LV function or structural heart disease. (Level of Evidence: B)
	EP testing can be useful in patients with syncope when brady-or tachyarrhythmias are suspected, and in whom non-invasive diagnostic studies are not conclusive. (Level of Evidence: B)

5. Therapies for Ventricular Arrhythmias

Therapies for VA include antiarrhythmic drugs (e.g., beta-blockers, amiodarone, sotalol), devices (e.g., ICDs), ablation, surgery, and revascularization. With the exception of ablation, recommendations for each of these modalities can be found within specific disease based sections (e.g., Heart Failure) of these pocket guidelines. The recommendations for ablation therapy are described below.

5.1. Ablation

Recommendations

Class I	1. Ablation is indicated in patients who are otherwise at low risk for SCD and have sustained predominantly monomorphic VT that is drug resistant, or who are drug intolerant, or who do not wish long-term drug therapy. (Level of Evidence: C)
	2. Ablation is indicated in patients with bundle-branch reentrant VT. (Level of Evidence: C)
	3. Ablation is indicated as adjunctive therapy in patients with an ICD who are receiving multiple shocks as a result of sustained VT that is not manageable by reprogramming or changing drug therapy, or the patient does not wish long term drug-therapy. (Level of Evidence: C)
	4. Ablation is indicated in patients with Wolff-Parkinson-White syndrome resuscitated from sudden cardiac arrest due to atrial fibrillation (AF) and rapid conduction over the accessory pathway causing ventricular fibrillation (VF). (Level of Evidence: B)

Class IIa	1. Ablation can be useful therapy in patients who are otherwise at low risk for SCD and have symptomatic nonsustained monomorphic VT that is drug resistant, or who are drug intolerant, or who do not wish long-term drug therapy. (Level of Evidence: C)
	2. Ablation can be useful therapy in patients who are otherwise at low risk for SCD and have frequent symptomatic predominantly monomorphic PVCs that are drug resistant, or who are drug intolerant, or who do not wish long-term drug therapy. (Level of Evidence: C)
	3. Ablation can be useful in symptomatic patients with Wolff-Parkinson-White syndrome who have accessory pathways with refractory periods less than 240 ms in duration. (Level of Evidence: B)

Class IIb	1. Ablation of Purkinje fiber potentials may be considered in patients with ventricular arrhythmia storm consistently provoked by PVCs of similar morphology.
	2. Ablation of asymptomatic PVCs may be considered when the PVCs are very frequent to avoid or treat tachycardia-induced cardiomyopathy. (Level of Evidence: C)

Class III	Ablation of asymptomatic relatively infrequent PVCs is not indicated. (Level of Evidence: C)

6. Acute Management of Specific Arrhythmias

6.1. Management of Cardiac Arrest

Recommendations

Class I	1. After establishing the presence of definite, suspected, or impending cardiac arrest, the first priority should be activation of a response team capable of identifying the specific mechanism and carrying out prompt intervention. (Level of Evidence: B)
	2. Cardiopulmonary resuscitation (CPR) should be implemented immediately after contacting a response team. (Level of Evidence: A)
	3. In an out of hospital setting, if an automated external defibrillator (AED) is available, it should be applied immediately and shock therapy administered according to the algorithms contained in the documents on CPR developed by either the AHA in association with the International Liaison Committee on Resuscitation (ILCOR) and/or the European Resuscitation Council (ERC). (Level of Evidence: C)
	4. For victims with ventricular tachyarrhythmic mechanisms of cardiac arrest, when recurrences occur after a maximally defibrillating shock (generally 360 Joules for monophasic defibrillators), intravenous amiodarone should be the preferred antiarrhythmic drug for attempting to achieve a stable rhythm after further defibrillations. (Level of Evidence: B)

	5. For recurrent ventricular tachyarrhythmias or nontachyarrhythmic mechanisms of cardiac arrest, it is recommended to follow the algorithms contained in the documents on CPR developed by either the AHA in association with the ILCOR and/or the ERC. (Level of Evidence: C)
	6. Reversible causes and factors contributing to cardiac arrest should be managed during advanced life support, including management of hypoxia, electrolyte disturbances, mechanical factors, and volume depletion. (Level of Evidence: C)

Class IIa	For response times ≥ 5 min, a brief (< 90 to 180 sec) period of CPR is reasonable prior to attempting defibrillation. (Level of Evidence: B)

Class IIb	A single precordial thump may be considered by healthcare professional providers when responding to a witnessed cardiac arrest. (Level of Evidence: C)

6.2. Ventricular Tachycardia Associated With Low Troponin MI

Recommendations

Class I	Patients presenting with sustained VT in whom low level elevations in cardiac biomarkers of myocyte injury/necrosis are documented, should be treated similarly to patients that have sustained VT and in whom no biomarker rise is documented. (Level of Evidence: C)

6.3. Sustained Monomorphic VT

Recommendations

Class I	1. Wide-QRS tachycardia should be presumed to be VT if the diagnosis is unclear. (Level of Evidence: C)
	2. Direct-current (DC) cardioversion with appropriate sedation is recommended at any point in the treatment cascade in patients with suspected sustained monomorphic VT with haemodynamic compromise. (Level of Evidence: C)

Class IIa	1. Intravenous (IV) procainamide (or ajmaline in some European countries) is reasonable for initial treatment of patients with stable sustained monomorphic VT. (Level of Evidence: B)
	2. IV amiodarone is reasonable in patients with sustained monomorphic VT that is haemodynamically unstable, that is refractory to conversion with countershock, or recurrent despite procainamide or other agents. (Level of Evidence: C)
	3. Transvenous catheter pace-termination can be useful to treat patients with sustained monomorphic VT that is refractory to cardioversion or is frequently recurrent despite antiarrhythmic medication. (Level of Evidence: C)

Class IIb	IV lidocaine might be reasonable for the initial treatment of patients with stable sustained monomorphic VT specifically associated with acute myocardial ischaemia or infarction. (Level of Evidence: C)

Class III	Calcium-channel blockers such as verapamil and diltiazem should not be used in patients to terminate wide QRS complex tachycardia of unknown origin, especially in patients with a history of myocardial dysfunction. (Level of Evidence: C)

6.4. Repetitive Monomorphic VT

Recommendations

Class IIa	IV amiodarone, beta-blockers, and IV procainamide (sotalol or ajmaline in Europe) can be useful for treating repetitive monomorphic VT in the context of CHD and idiopathic VT. (Level of Evidence: C)

6.5. Polymorphic VT

Recommendations

Class I	1. DC cardioversion with appropriate sedation as necessary is recommended for patients with sustained polymorphic VT with haemodynamic compromise and is reasonable at any point in the treatment cascade. (Level of Evidence: B)

	2. IV beta-blockers are useful for patients with recurrent polymorphic VT, especially if ischaemia is suspected or cannot be excluded. (Level of Evidence: B)
	3. IV loading with amiodarone is useful for patients with recurrent polymorphic VT in the absence of abnormal repolarization related to congenital or acquired QT syndrome. (Level of Evidence: C)
	4. Urgent angiography with a view to revascularization should be considered for patients with polymorphic VT when myocardial ischaemia cannot be excluded. (Level of Evidence: C)

Class IIb	IV lidocaine may be reasonable for treatment of polymorphic VT specifically associated with acute myocardial ischaemia or infarction. (Level of Evidence: C)

6.6. Torsades de Pointes

Recommendations

Class I	1. Withdrawal of any offending drugs and correction of electrolyte abnormalities are recommended in patients presenting with torsades de pointes. (Level of Evidence: A)
	2. Acute and long-term pacing is recommended for patients presenting with torsades de pointes due to heart block and symptomatic bradycardia. (Level of Evidence: A)

Class IIa	1. Management with IV magnesium sulfate is reasonable for patients who present with long QT syndrome (LQTS) and few episodes of torsades de pointes. Magnesium is not likely to be effective in patients with a normal QT interval. (Level of Evidence: B)
	2. Acute and long-term pacing is reasonable for patients who present with recurrent pause-dependent torsades de pointes. (Level of Evidence: B)
	3. Beta-blockade combined with pacing is reasonable acute therapy for patients who present with torsades de pointes and sinus bradycardia. (Level of Evidence: C)
	4. Isoproterenol is reasonable as temporary treatment in acute patients who present with recurrent pause dependent torsades de pointes who do not have congenital LQTS. (Level of Evidence: B)

Class IIb	1. Potassium repletion to 4.5 to 5 mM/L may be considered for patients who present with torsades de pointes. (Level of Evidence: B)
	2. IV lidocaine or oral mexiletine may be considered in patients who present with LQT3 and torsades de pointes. (Level of Evidence: C)

6.7. Incessant VT

Recommendations

Class I	Revascularization and beta-blockade, followed by antiarrhythmic drugs such as IV procainamide or IV amiodarone are recommended for patients with recurrent or incessant polymorphic VT due to acute myocardial ischaemia. (Level of Evidence: C)

Class IIa	IV amiodarone or procainamide followed by VT ablation can be effective in the management of patients with frequently recurring or incessant monomorphic VT. (Level of Evidence: B)

Class IIb	1. IV amiodarone and IV beta-blockers separately or together may be reasonable in patients with VT storm. (Level of Evidence: C)
	2. Overdrive pacing or general anesthesia may be considered for patients with frequently recurring or incessant VT. (Level of Evidence: C)
	3. Spinal cord modulation may be considered for some patients with frequently recurring or incessant VT. (Level of Evidence: C)

7. Ventricular Arrhythmia and Sudden Cardiac Death Related to Specific Pathology

7.1. Left Ventricular Dysfunction Due to Prior MI

Recommendations

Class I	1. Aggressive attempts should be made to treat heart failure (HF) that may be present in some patients with LV dysfunction (LVD) due to prior MI and ventricular tachyarrhythmias. (Level of Evidence: C)
	2. Aggressive attempts should be made to treat myocardial ischaemia that may be present in some patients with ventricular tachyarrhythmias. (Level of Evidence: C)
	3. Coronary revascularization is indicated to reduce the risk of SCD in patients with VF when direct, clear evidence of acute myocardial ischaemia is documented to immediately precede the onset of VF. (Level of Evidence: B)
	4. If coronary revascularization cannot be carried out, and there is evidence of prior MI and significant LVD, the primary therapy of patients resuscitated from VF should be the ICD in patients who are receiving chronic optimal medical therapy, and who have reasonable expectation of survival with a good functional status for more than 1 year. (Level of Evidence: A)
	5. ICD therapy is recommended for primary prevention to reduce total mortality by a reduction in SCD in patients with LVD due to prior MI who are at least 40 days post-MI, have an LVEF ≤ 30% to 40%, are New York Heart Association (NYHA) functional class II or III, are receiving chronic optimal medical therapy, and who have reasonable expectation of survival with a good functional status for more than 1 year. (Level of Evidence: A)
	6. The ICD is effective therapy to reduce mortality by a reduction in SCD in patients with LVD due to prior MI who present with haemodynamically unstable sustained VT, who are receiving chronic optimal medical therapy, and who have reasonable expectation of survival with a good functional status for more than 1 year. (Level of Evidence: A)
Class IIa	1. Implantation of an ICD is reasonable in patients with LVD due to prior MI who are at least 40 days post-MI, have an LVEF of ≤ 30% to 35%, are NYHA functional class I on chronic optimal medical therapy, and who have reasonable expectation of survival with a good functional status for more than 1 year. (Level of Evidence: B)
	2. Amiodarone, often in combination with beta-blockers, can be useful for patients with LVD due to prior MI and symptoms due to VT unresponsive to beta-adrenergic blocking agents. (Level of Evidence: B)
	3. Sotalol is reasonable therapy to reduce symptoms resulting from VT for patients with LVD due to prior MI unresponsive to beta-blocking agents. (Level of Evidence: C)
	4. Adjunctive therapies to the ICD, including catheter ablation or surgical resection, and pharmacological therapy with agents such as amiodarone or sotalol are reasonable to improve symptoms due to frequent episodes of sustained VT or VF in patients with LVD due to prior MI. (Level of Evidence: C)
	5. Amiodarone is reasonable therapy to reduce symptoms due to recurrent haemodynamically stable VT for patients with LVD due to prior MI who cannot or refuse to have an ICD implanted. (Level of Evidence: C)
	6. ICD implantation is reasonable for treatment of recurrent sustained VT in patients post-MI with normal or near normal ventricular function who are receiving chronic optimal medical therapy, and who have reasonable expectation of survival with a good functional status for more than 1 year. (Level of Evidence: C)
Class IIb	1. Curative catheter ablation or amiodarone may be considered in lieu of ICD therapy to improve symptoms in patients with LVD due to prior MI and recurrent haemodynamically stable VT whose LVEF is > 40%. (Level of Evidence: B)
	2. Amiodarone may be reasonable therapy for patients with LVD due to prior MI with an ICD indication, as defined above, in patients who cannot, or refuse to have an ICD implanted. (Level of Evidence: C)

Class III	1. Prophylactic antiarrhythmic drug therapy is not indicated to reduce mortality in patients with asymptomatic nonsustained VA. (Level of Evidence: B)
	2. Class IC antiarrhythmic drugs in patients with a past history of MI should not be used. (Level of Evidence: A)

7.2. Valvular Heart Disease

Recommendations

Class I	Patients with valvular heart disease and VA should be evaluated and treated following current recommendations for each disorder. (Level of Evidence: C)
Class IIb	The effectiveness of mitral valve repair or replacement to reduce the risk of SCD in patients with mitral valve prolapse, severe mitral regurgitation and serious VA is not well established. (Level of Evidence: C)

7.3. Congenital Heart Disease

Recommendations

Class I	1. ICD implantation is indicated in patients with congenital heart disease who are survivors of cardiac arrest after evaluation to define the cause of the event and exclude any reversible causes. ICD implantation is indicated in patients who are receiving chronic optimal medical therapy, and who have reasonable expectation of survival with a good functional status for more than 1 year. (Level of Evidence: B)
	2. Patients with congenital heart disease and spontaneous sustained VT should undergo invasive haemodynamic and EP evaluation. Recommended therapy includes catheter ablation or surgical resection to eliminate the VT. If that is not successful, ICD implantation is recommended. (Level of Evidence: C)
Class IIa	Invasive haemodynamic and EP evaluation is reasonable in patients with congenital heart disease and unexplained syncope and impaired ventricular function. In the absence of a defined and reversible cause, ICD implantation is reasonable in patients who are receiving chronic optimal medical therapy, and who have reasonable expectation of survival with a good functional status for more than 1 year. (Level of Evidence: B)
Class IIb	EP testing may be considered for patients with congenital heart disease and ventricular couplets or NSVT to determine the risk of a sustained VA. (Level of Evidence: C)
Class III	Prophylactic antiarrhythmic therapy is not indicated for asymptomatic patients with congenital heart disease and isolated PVCs. (Level of Evidence: C)

7.4. Pericardial Diseases

Recommendations

Class I	VA that develop in patients with pericardial disease should be treated in the same manner that such arrhythmias are treated in patients with other diseases, including ICD pacemaker implantation as required. Patients receiving ICD implantation should be receiving chronic optimal medical therapy, and have reasonable expectation of survival with a good functional status for more than 1 year. (Level of Evidence: C)

7.5. Pulmonary Arterial Hypertension

Recommendations

Class III	Prophylactic antiarrhythmic therapy generally is not indicated for primary prevention of SCD in patients with pulmonary arterial hypertension or other pulmonary conditions. (Level of Evidence: C)

7.6. Transient Arrhythmias of Reversible Cause

Recommendations

Class I	1. Myocardial revascularization should be performed, when appropriate, to reduce the risk of SCD in patients experiencing cardiac arrest due to VF or polymorphic VT in the setting of acute ischaemia or myocardial infarction. (Level of Evidence: C)
	2. Unless electrolyte abnormalities are proven to be the cause, survivors of cardiac arrest due to VF or polymorphic VT in whom electrolyte abnormalities are discovered, in general should be evaluated and treated in a similar manner as survivors of cardiac arrest without electrolyte abnormalities. (Level of Evidence: C)
	3. Patients who experience sustained monomorphic VT in the presence of antiarrhythmic drugs or electrolyte abnormalities should be evaluated and treated in a manner similar to that of patients with VT without electrolyte abnormalities or antiarrhythmic drugs present. Antiarrhythmic drugs or electrolyte abnormalities should not be assumed to be the sole cause of sustained monomorphic VT. (Level of Evidence: B)
	4. Patients who experience polymorphic VT in association with prolonged QT interval due to antiarrhythmic medications or other drugs should be advised to avoid exposure to all agents associated with QT prolongation. A list of such drugs can be found on the web sites www.qtdrugs.org and www.torsades.org. (Level of Evidence: B)

8. Ventricular Arrhythmias Associated with Cardiomyopathies

8.1. Dilated Cardiomyopathy (DCM) (Nonischaemic)

Recommendations

Class I	1. EP testing is useful to diagnose bundle branch-reentrant tachycardia, and to guide ablation in patients with nonischaemic DCM. (Level of Evidence: C)
	2. EP testing is useful for diagnostic evaluation in patients with nonischaemic DCM with sustained palpitations, wide QRS-complex tachycardia, syncope or presyncope. (Level of Evidence: C)
	3. An ICD should be implanted in patients with nonischaemic DCM and significant LVD who have sustained VT or VF, who are receiving chronic optimal medical therapy, and who have reasonable expectation of survival with a good functional status for more than 1 year. (Level of Evidence: A)
	4. ICD therapy is recommended for primary prevention to reduce total mortality by a reduction in SCD in patients with nonischaemic DCM who have an LVEF ≤ 30% to 35%, are NYHA functional class II or III receiving chronic optimal medical therapy, and who have reasonable expectation of survival with a good functional status for more than 1 year. (Level of Evidence: B)
Class IIa	1. ICD implantation can be beneficial for patients with unexplained syncope, significant LVD, and nonischaemic DCM who are receiving chronic optimal medical therapy, and who have reasonable expectation of survival with a good functional status for more than 1 year. (Level of Evidence: C)
	2. ICD implantation can be effective for termination of sustained VT in patients with normal or near normal ventricular function and nonischaemic DCM who are receiving chronic optimal medical therapy, and who have reasonable expectation of survival with a good functional status for more than 1 year. (Level of Evidence: C)
Class IIb	1. Amiodarone may be considered for sustained VT or VF in patients with nonischaemic DCM. (Level of Evidence: C)
	2. Placement of an ICD might be considered in patients who have nonischaemic DCM, LVEF ≤ 30% to 35%, are NYHA functional class I receiving chronic optimal medical therapy, and who have reasonable expectation of survival with a good functional status for more than 1 year. (Level of Evidence: C)

8.2. Hypertrophic Cardiomyopathy (HCM)

Recommendations

Class I ICD therapy should be used for treatment in patients with HCM who have sustained VT and/or VF and who are receiving chronic optimal medical therapy, and who have reasonable expectation of survival with a good functional status for more than 1 year. (Level of Evidence: B)

Class IIa 1. ICD implantation can be effective for primary prophylaxis against SCD in patients with HCM who have one or more major risk factor (See Table 5) for SCD and who are receiving chronic optimal medical therapy, and who have reasonable expectation of survival with a good functional status for more than 1 year. (Level of Evidence: C)

2. Amiodarone therapy can be effective for treatment in patients with HCM with a history of sustained VT and/or VF when ICD is not feasible. (Level of Evidence: C)

Class IIb 1. EP testing may be considered for risk assessment for SCD in patients with HCM. (Level of Evidence: C)

2. Amiodarone may be considered for primary prophylaxis against SCD in patients with HCM who have one or more major risk factor for SCD (See Table 5), if ICD implantation is not feasible. (Level of Evidence: C)

Table 5. Risk Factors for SCD in Hypertrophic Cardiomyopathy

Major risk factors	Possible in individual patients
Cardiac arrest (VF)	AF
Spontaneous sustained VT	Myocardial ischaemia
Family history of premature sudden death	LV outflow obstruction
Unexplained syncope	High-risk mutation
LV thickness greater than or equal to 30 mm	Intense (competitive) physical exertion
Abnormal exercise BP	
Nonsustained spontaneous VT	

Modified with permission from Maron BJ, McKenna WJ, Danielson GK, et al. American College of Cardiology/European Society of Cardiology clinical expert consensus document on hypertrophic cardiomyopathy. A report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents and the European Society of Cardiology Committee for Practice Guidelines. Eur Heart J 2003;24: 1965-1991.

AF = atrial fibrillation; BP = blood pressure; LV = left ventricular; SCD = sudden cardiac death; VF = ventricular fibrillation; VT = ventricular tachycardia.

8.3. Arrhythmogenic Right Ventricular Cardiomyopathy

Recommendations

Class I ICD implantation is recommended for prevention of SCD in patients with arrhythmogenic RV cardiomyopathy (ARVC) with documented sustained VT or VF who are receiving chronic optimal medical therapy, and who have reasonable expectation of survival with a good functional status for more than 1 year. (Level of Evidence: B)

Class IIa 1. ICD implantation can be effective for prevention of SCD in patients with ARVC with extensive disease, including those with LV involvement, one or more affected family member with SCD, or undiagnosed syncope when VT/VF has not been excluded as the cause of syncope, who are receiving chronic optimal medical therapy, and who have reasonable expectation of survival with a good functional status for more than 1 year. (Level of Evidence: C)

	2. Amiodarone or sotalol can be effective for treatment of sustained VT/VF in patients with ARVC when ICD implantation is not feasible. (Level of Evidence: C)
	3. Ablation can be useful as adjunctive therapy in management of patients with ARVC with recurrent VT, despite optimal anti-arrhythmic drug therapy. (Level of Evidence: C)
Class IIb	EP testing might be useful for risk assessment of SCD in patients with ARVC. (Level of Evidence: C)

9. Heart Failure

Recommendations

Class I	1. ICD therapy is recommended for secondary prevention of SCD in patients who survived VF or haemodynamically unstable VT, or VT with syncope and have an LVEF ≤ 40%, who are receiving chronic optimal medical therapy and who have a reasonable expectation of survival with a good functional status for more than 1 year. (Level of Evidence: A)
	2. ICD therapy is recommended for primary prevention to reduce total mortality by a reduction in SCD in patients with LVD due to prior MI who are at least 40 days post-MI, have an LVEF ≤ 30% to 40%, are NYHA functional class II or III receiving chronic optimal medical therapy, and who have reasonable expectation of survival with a good functional status for more than 1 year. (Level of Evidence: A)
	3. ICD therapy is recommended for primary prevention to reduce total mortality by a reduction in SCD in patients with nonischaemic heart disease who have an LVEF ≤ 30% to 35%, are NYHA functional class II or III receiving chronic optimal medical therapy, and who have reasonable expectation of survival with a good functional status for more than 1 year. (Level of Evidence: B)
	4. Amiodarone, sotalol and/or other beta-blockers are recommended pharmacological adjuncts to ICD therapy to suppress symptomatic ventricular tachyarrhythmias (both sustained and nonsustained) in otherwise optimally treated patients with heart failure (HF). (Level of Evidence: C)
	5. Amiodarone is indicated for the suppression of acute haemodynamically compromising ventricular or supraventricular tachyarrhythmias when cardioversion and/or correction of reversible causes has failed to terminate the arrhythmia or prevent its early recurrence. (Level of Evidence: B)
Class IIa	1. ICD therapy combined with biventricular pacing can be effective for primary prevention to reduce total mortality by a reduction in SCD, in patients with NYHA functional class III or IV receiving optimal medical therapy, in sinus rhythm with a QRS complex of at least 120ms and who have reasonable expectation of survival with a good functional status for more than 1 year. (Level of Evidence: B)
	2. ICD therapy is reasonable for primary prevention to reduce total mortality by a reduction in SCD in patients with LVD due to prior MI who are at least 40 days post-MI, have an LVEF of ≤ 30% to 35%, are NYHA functional class I receiving chronic optimal medical therapy, and have reasonable expectation of survival with a good functional status for more than 1 year. (Level of Evidence: B)
	3. ICD therapy is reasonable in patients with recurrent stable VT, a normal or near normal LVEF and optimally treated HF, and who have a reasonable expectation of survival with a good functional status for more than 1 year. (Level of Evidence: C)
	4. Biventricular pacing in the absence of ICD therapy is reasonable for the prevention of SCD in patients with NYHA functional class III or IV HF, an LVEF ≤ 35% and a QRS complex ≥ 160ms (or at least 120ms in the presence of other evidence of ventricular dyssynchrony) who are receiving chronic optimal medical therapy and who have reasonable expectation of survival with a good functional status for more than 1 year. (Level of Evidence: B)
Class IIb	1. Amiodarone, sotalol and/or beta-blockers may be considered as pharmacological alternatives to ICD therapy to suppress symptomatic ventricular tachyarrhythmias (both sustained and nonsustained) in optimally treated patients with HF for whom ICD therapy is not feasible. (Level of Evidence: C)

	2. ICD therapy may be considered for primary prevention to reduce total mortality by a reduction in SCD in patients with nonischaemic heart disease who have an LVEF of ≤ 30% to 35%, are NYHA functional class I receiving chronic optimal medical therapy, and who have a reasonable expectation of survival with a good functional status for more than 1 year. (Level of Evidence: B)

10. Genetic Arrhythmia Syndromes

10.1. Long QT Syndrome

Recommendations

Class I	1. Life style modification (see full-text guidelines) is recommended for patients with an LQTS diagnosis (clinical and/or molecular). (Level of Evidence: B)
	2. Beta-blockers are recommended for patients with an LQTS clinical diagnosis (i.e., in the presence of prolonged QT interval). (Level of Evidence: B)
	3. Implantation of an ICD along with use of beta-blockers is recommended for LQTS patients with previous cardiac arrest and who have reasonable expectation of survival with a good functional status for more than 1 year. (Level of Evidence: A)

Class IIa	1. Beta-blockers can be effective to reduce SCD in patients with a molecular LQTS analysis and normal QT interval. (Level of Evidence: B)
	2. Implantation of an ICD with continued use of beta-blockers can be effective to reduce SCD in LQTS patients who are experiencing syncope and/or VT while receiving beta-blockers and who have reasonable expectation of survival with a good functional status for more than 1 year. (Level of Evidence: B)

Class IIb	1. Left cardiac sympathetic neural denervation may be considered for LQTS patients with syncope, torsades de pointes, or cardiac arrest while receiving beta-blockers. (Level of Evidence: B)
	2. Implantation of an ICD with use of beta-blockers may be considered for prophylaxis of SCD for patients who are in categories possibly associated with higher risk of cardiac arrest such as LQT2 and LQT3, and who have reasonable expectation of survival with a good functional status for more than 1 year. (Level of Evidence: B)

10.2. Brugada Syndrome

Recommendations

Class I	An ICD is indicated for Brugada syndrome patients with previous cardiac arrest receiving chronic optimal medical therapy and who have reasonable expectation of survival with a good functional status for more than 1 year. (Level of Evidence: C)

Class IIa	1. An ICD is reasonable for Brugada syndrome patients with spontaneous ST-segment elevation in V1, V2, or V3 who have had syncope with or without mutations demonstrated in the SCN5A gene and who have reasonable expectation of survival with a good functional status for more than 1 year. (Level of Evidence: C)
	2. Clinical monitoring for the development of a spontaneous ST-segment elevation pattern is reasonable for the management of patients with ST-segment elevation induced only with provocative pharmacological challenge with or without symptoms. (Level of Evidence: C)
	3. An ICD is reasonable for Brugada syndrome patients with documented VT that has not resulted in cardiac arrest and who have reasonable expectation of survival with a good functional status for more than 1 year. (Level of Evidence: C)
	4. Isoproterenol can be useful to treat an electrical storm in the Brugada syndrome. (Level of Evidence: C)

Class IIb	1. EP testing may be considered for risk stratification in asymptomatic Brugada syndrome patients with spontaneous ST-segment elevation with or without a mutation in the SCN5A gene. (Level of Evidence: C)
	2. Quinidine might be reasonable for the treatment of electrical storm in patients with Brugada syndrome. (Level of Evidence: C)

10.3. Catecholaminergic Polymorphic Ventricular Tachycardia

Recommendations

Class I	1. Beta-blockers are indicated for patients who are clinically diagnosed with catecholaminergic polymorphic VT (CPVT) based on the presence of spontaneous or documented stress-induced VA. (Level of Evidence: C)
	2. Implantation of an ICD with use of beta-blockers is indicated for patients with CPVT who are survivors of cardiac arrest and who have reasonable expectation of survival with a good functional status for more than 1 year. (Level of Evidence: C)

Class IIa	1. Beta-blockers can be effective in patients without clinical manifestations when the diagnosis of CPVT is established during childhood based on genetic analysis. (Level of Evidence: C)
	2. Implantation of an ICD with use of beta-blockers can be effective for affected patients with CPVT with syncope and/or documented sustained VT who are receiving betablockers and who have reasonable expectation of survival with a good functional status for more than 1 year. (Level of Evidence: C)

Class IIb	Beta-blockers may be considered for patients with CPVT who were genetically diagnosed in adulthood and never manifested clinical symptoms of tachy-arrhythmias. (Level of Evidence: C)

11. Ventricular Arrhythmias and Sudden Cardiac Death Related to Specific Populations

11.1. Athletes

Recommendations

Class I	1. Pre-participation history and physical examination, including family history of premature or sudden death and specific evidence of cardiovascular diseases such as cardiomyopathies and ion channel abnormalities is recommended in athletes. (Level of Evidence: C)
	2. Athletes presenting with rhythm disorders, structural heart disease, or other signs or symptoms suspicious for cardiovascular disorders, should be evaluated as any other patient but recognizing the potential uniqueness of their activity. (Level of Evidence: C)
	3. Athletes presenting with syncope should be carefully evaluated to uncover underlying cardiovascular disease or rhythm disorder. (Level of Evidence: B)
	4. Athletes with serious symptoms should cease competition while cardiovascular abnormalities are being fully evaluated. (Level of Evidence: C)

Class IIb	12-lead ECG and possibly echocardiography may be considered as pre-participation screening for heart disorders in athletes. (Level of Evidence: B)

11.2. Gender & Pregnancy

Recommendations

Class I	1. Pregnant women developing haemodynamically unstable VT or VF should be electrically cardioverted or defibrillated. (Level of Evidence: B)
	2. In pregnant women with LQTS who have had symptoms, it is beneficial to continue beta-blocker medications throughout pregnancy and afterwards, unless there are definite contraindications. (Level of Evidence: C)

11.3. Elderly Patients

Recommendations

Class I	1. Elderly patients with VA should generally be treated in the same manner as younger individuals. (Level of Evidence: A)
	2. The dosing and titration schedule of antiarrhythmic drugs prescribed to elderly patients should be adjusted to the altered pharmacokinetics of such patients. (Level of Evidence: C)

Class III	Elderly patients with projected life expectancy less than 1 year due to major comorbidities should not receive ICD therapy. (Level of Evidence: C)

Despite the demonstrated efficacy in reducing all-cause mortality and SCD, beta-blockers are underused in the elderly. Several randomized prospective trials have demonstrated the efficacy of ICDs in primary and secondary prevention of SCD when compared with antiarrhythmic drug therapy, across all age groups.

11.4. Patients with ICDs

Recommendations

Class I	1. Patients with implanted ICDs should receive regular follow-up and analysis of the device status. (Level of Evidence: C)
	2. Implanted ICDs should be programmed to obtain optimal sensitivity and specificity. (Level of Evidence: C)
	3. Measures should be undertaken to minimize the risk of inappropriate ICD therapies. (Level of Evidence: C)
	4. Patients with implanted ICDs who present with incessant VT should be hospitalized for management. (Level of Evidence: C)

Class IIa	1. Catheter ablation can be useful for patients with implanted ICDs who experience incessant or frequently recurring VT. (Level of Evidence: B)
	2. In patients experiencing inappropriate ICD therapy, electrophysiologic evaluation can be useful for diagnostic and therapeutic purposes. (Level of Evidence: C)

11.5. Drug-Induced Arrhythmias

1. Digitalis Toxicity

Recommendations

Class I	An anti-digitalis antibody is recommended for patients who present with sustained ventricular arrhythmias, advanced AV block, and/or asystole that are considered due to digitalis toxicity. (Level of Evidence: A)

Class IIa	1. Patients taking digitalis who present with mild cardiac toxicity (e.g., isolated ectopic beats only), can be managed effectively with recognition, continuous monitoring of cardiac rhythm, withdrawal of digitalis, restoration of normal electrolyte levels (including serum potassium > 4 mM/L) and oxygenation. (Level of Evidence: C)
	2. Magnesium or pacing is reasonable for patients who take digitalis and present with severe toxicity.* (Level of Evidence: C)

Class IIb	Dialysis for the management of hyperkalemia may be considered for patients who take digitalis and present with severe toxicity.* (Level of Evidence: C)

Class III	Management by lidocaine or phenytoin is not recommended for patients taking digitalis and who present with severe toxicity.* (Level of Evidence: C)

* Sustained VA, advanced AV block, and/or asystole.

2. Drug-Induced LQTS

Recommendations

Class I	In patients with drug-induced LQTS, removal of the offending agent is indicated. (Level of Evidence: A)

Class IIa	1. Management with IV magnesium sulfate is reasonable for patients who take QT-prolonging drugs and present with few episodes of torsades de pointes in which the QT remains long. (Level of Evidence: B)
	2. Atrial or ventricular pacing or isoproterenol is reasonable for patients taking QT-prolonging drugs who present with recurrent torsades de pointes. (Level of Evidence: B)

Class IIb	Potassium ion repletion to 4.5 to 5 mM/L may be reasonable for patients who take QT-prolonging drugs and present with few episodes of torsades de pointes in whom the QT remains long. (Level of Evidence: C)

3. Sodium Channel Blocker-Related Toxicity

Recommendations

Class I	In patients with sodium channel blocker-related toxicity, removal of the offending agent is indicated. (Level of Evidence: A)

Class IIa 1. Stopping the drug, reprogramming the pacemaker or repositioning leads can be useful in patients taking sodium channel blockers who present with elevated defibrillation thresholds or pacing requirement. (Level of Evidence: C)

2. In patients taking sodium-channel blockers who present with atrial flutter with 1:1 AV conduction, withdrawal of the offending agent is reasonable. If the drug needs to be continued, additional A-V nodal blockade with diltiazem, verapamil or beta-blocker or atrial flutter ablation can be effective. (Level of Evidence: C)

Class IIb Administration of a beta-blocker and a sodium bolus may be considered for patients taking sodium-channel blockers if the tachycardia becomes more frequent or more difficult to cardiovert. (Level of Evidence: C)

Arrhythmias caused by sodium channel-blocking drugs and other drugs are included in Table 6.

Table 6. Syndromes of Drug-Induced Arrhythmia and their Management

Drugs	Clinical setting	Management*
Digitalis	Mild cardiac toxicity (isolated arrhythmias only)	
	Severe toxicity: Sustained ventricular arrhythmias; advanced AV block; asystole	Anti-digitalis antibody Pacing Dialysis for hyperkalemia
QT-prolonging drugs	Torsades de pointes: few episodes, QT remains long	IV magnesium sulfate ($MgSO_4$)
		Replete potassium (K+) to 4.5 to 5 mEq/L
	Recurrent torsades de pointes	Ventricular pacing Isoproterenol
Sodium-channel blockers	Elevated defibrillation or pacing requirement	Stop drug; reposition leads
	Atrial flutter with 1:1 AV conduction	Diltiazem, verapamil, beta-blocker (IV)
	Ventricular tachycardia (more frequent; difficult to cardiovert)	Beta-blocker; sodium
	Brugada syndrome	Stop drug; treat arrhythmia

*Always includes recognition, continuous monitoring of cardiac rhythm, withdrawal of offending agents, restoration of normal electrolytes (including serum potassium to greater than 4 mEq/L) and oxygenation. Order of management is not meant to represent the preferred sequence when more than one treatment is listed.

AV = atrioventricular; IV = intravenous.

Chapter 5
Cardiac Pacing and Cardiac Resynchronization Therapy*
2007

ESC Task Force on Cardiac Pacing and Cardiac Resynchronization Therapy
Developed in collaboration with the European Heart Rhythm Association

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Introduction

The guidelines for the appropriate use of pacemaker devices presented in this document, a joint ESC and EHRA initiative, aim to provide for the first time in Europe an up to date specialists' view of the field. The guidelines cover two main areas: the first includes permanent pacing in bradyarrhythmias, syncope, and other specific conditions, while the second refers to ventricular resynchronization as an adjunct therapy in patients with heart failure.

The reader should note that the recommendations, text, figures, and tables included in these pocket guidelines represent a succinct summary of the more extensive evidence base, critical evaluation, supporting text, tables, figures, and references that are included in the full-text guidelines. Readers are strongly encouraged to refer to the full-text guidelines.

Classification of Recommendations and Level of Evidence are expressed in the European Society of Cardiology (ESC) format as follows:

Classes of recommendations

Class I	**Evidence and/or general agreement that a given treatment or procedure is beneficial, useful and effective**
Class II	**Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a given treatment or procedure**
Class IIa	**Weight of evidence/opinion is in favour of usefulness/efficacy**
Class IIb	**Usefulness/efficacy is less well established by evidence/opinion**
Class III	**Evidence or general agreement that the given treatment or procedure is not useful/effective and in some cases may be harmful**

*Adapted from the 2007 Guidelines for Cardiac Pacing and Cardiac Resynchronization Therapy (European Heart Journal 2007;28:2256-2295).

J. Bax et al., *Compendium of Abridged ESC Guidelines 2001*

Levels of evidence

Level of Evidence A	Data derived from multiple randomized clinical trials or meta-analyses
Level of Evidence B	Data derived from a single randomized clinical trial or large non-randomized studies
Level of Evidence C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries

*Recommendations for ESC Guidelines Production at www.escardio.org.

1. Pacing in arrhythmias

1.1. Sinus node disease

Recommendations for cardiac pacing in sinus node disease

Class	Clinical Indication	Level of evidence
Class I	1. Sinus node disease manifests as symptomatic bradycardia with or without bradycardia-dependent tachycardia. Symptom-rhythm correlation must have been: ▪ spontaneously occurring ▪ drug-induced where alternative drug therapy is lacking. 2. Syncope with sinus node disease, either spontaneously occurring or induced at electrophysiological study. 3. Sinus node disease manifests as symptomatic chronotropic incompetence: ▪ spontaneously occurring ▪ drug-induced where alternative drug therapy is lacking.	C
Class IIa	1. Symptomatic sinus node disease, which is either spontaneous or induced by a drug for which there is no alternative but no symptom rhythm correlation has been documented. Heart rate at rest should be < 40 bpm. 2. Syncope for which no other explanation can be made but there are abnormal electrophysiological findings (CSNRT > 800 ms).	C
Class IIb	1. Minimally symptomatic patients with sinus node disease, resting heart rate < 40 bpm while awake and no evidence of chronotropic incompetence.	C
Class III	1. Sinus node disease without symptoms including use of bradycardia-provoking drugs. 2. ECG findings of sinus node dysfunction with symptoms not due directly or indirectly to bradycardia. 3. Symptomatic sinus node dysfunction where symptoms can reliably be attributed to non-essential medication.	C

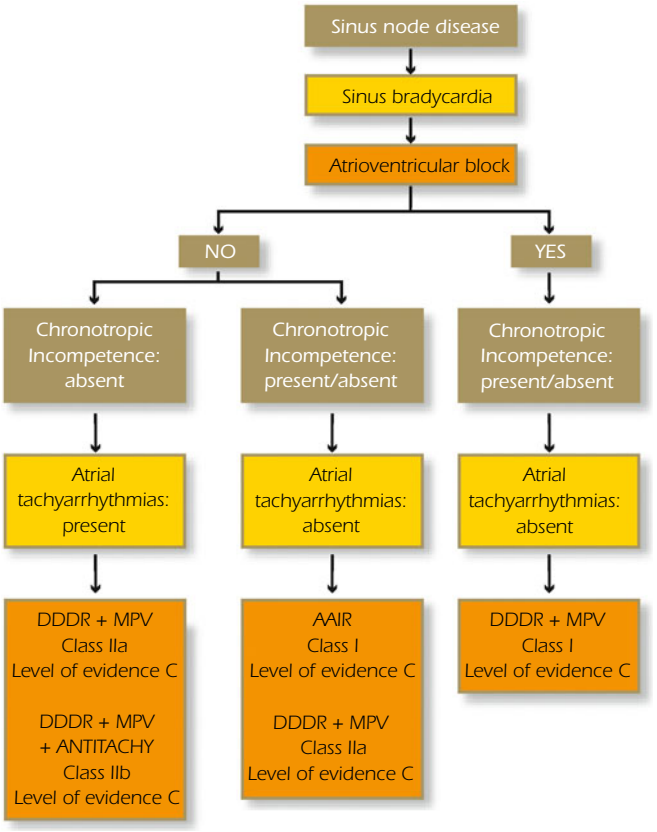
Note: when sinus node disease is diagnosed atrial tachyarrhythmias are likely even if not yet recorded, implying that serious consideration should be given to anticoagulant therapy.

1.2. Atrioventricular and intraventricular conduction disturbances

Recommendations for cardiac pacing in acquired atrioventricular block

Class	Clinical Indication	Level of evidence
Class I	1. Chronic symptomatic third or second degree (Mobitz I or II) atrioventricular block. 2. Neuromuscular diseases (e.g. myotonic muscular dystrophy, Kearns-Sayre syndrome etc.) with third-degree or second-degree atrioventricular block. 3. Third or second degree (Mobitz I or II) atrioventricular block: a) after catheter ablation of the atrioventricular junction b) after valve surgery when the block is not expected to resolve	C B C
Class IIa	1. Asymptomatic third or second degree (Mobitz I or II) atrioventricular block. 2. Symptomatic prolonged first degree atrioventricular block.	C C
Class IIb	1. Neuromuscular diseases (e.g. myotonic muscular dystrophy, Kearns-Sayre syndrome, etc.) with first degree atrioventricular block.	B
Class III	1. Asymptomatic first degree atrioventricular block. 2. Asymptomatic second degree Mobitz I with supra-Hisian conduction block. 3. Atrioventricular block expected to resolve.	C C C

Figure 1. Pacemaker mode selection in sinus node disease



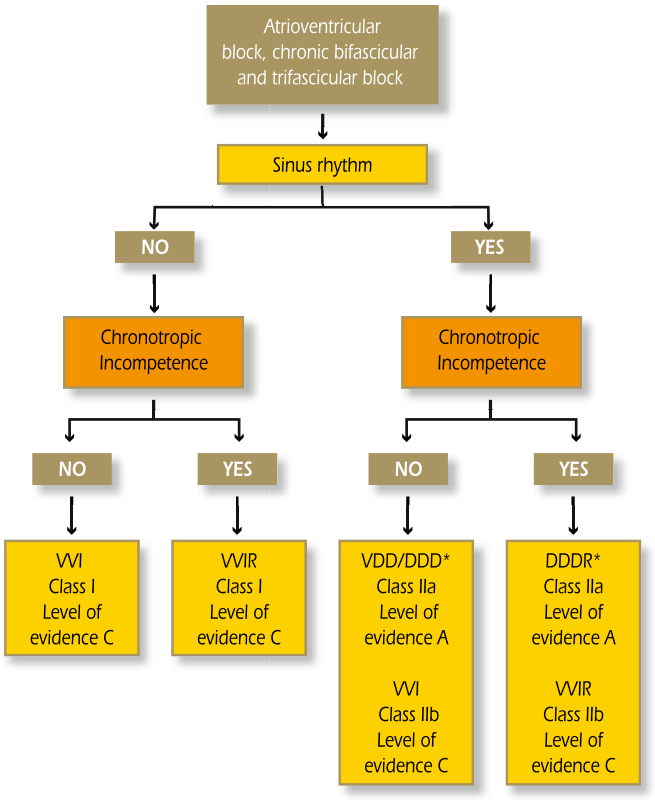
ANTITACHY = antitachycardia algorithms in pacemaker; MPV = minimisation of pacing in the ventricles.

Note: In sinus node disease VVIR and VDDR modes are considered unsuitable and are not recommended. Where atrioventricular block exists AAIR is considered inappropriate.

Recommendations for cardiac pacing in chronic bifascicular and trifascicular block.

Class	Clinical Indication	Level of evidence
Class I	1. Intermittent third degree atrioventricular block. 2. Second degree Mobitz II atrioventricular block. 3. Alternating bundle-branch block. 4. Findings on electrophysiological study of markedly prolonged HV interval (≥ 100 ms) or pacing-induced infra-His block in patients with symptoms.	**C**
Class IIa	1. Syncope not demonstrated to be due to atrioventricular block when other likely causes have been excluded, specifically ventricular tachycardia. 2. Neuromuscular diseases (e.g. myotonic muscular dystrophy, Kearns-Sayre syndrome, etc.) with any degree of fascicular block. 3. Incidental findings on electrophysiological study of markedly prolonged HV interval (≥ 100 ms) or pacing-induced infra-His block in patients without symptoms.	**B** **C** **C**
Class IIb	None.	
Class III	1. Bundle branch block without atrioventricular block or symptoms. 2. Bundle branch block with first-degree atrioventricular block without symptoms.	**B**

Figure 2. Pacemaker mode selection in acquired atrioventricular block, chronic bifascicular and trifascicular block



When atrioventricular block is not permanent, pacemakers with algorithms for preservation of native atrioventricular conduction should be selected.

* VVIR could be an alternative, especially in patients who have a low level of physical activity and in those with a short expected lifespan.

1.3. Recent myocardial infarction

Recommendations for permanent cardiac pacing in conduction disturbances related to acute myocardial infarction

Class	Clinical Indication	Level of evidence
Class I	1. Persistent third degree heart block preceded or not by intraventricular conduction disturbances. 2. Persistent Mobitz type II second degree heart block associated with bundle branch block, with or without PR prolongation. 3. Transient Mobitz type II second or third degree heart block associated with new onset bundle branch block.	**B**
Class IIa	None.	
Class IIb	None.	
Class III	1. Transient second or third degree heart block without bundle branch block. 2. Left anterior hemiblock newly developed or present on admission. 3. Persistent first degree atrioventricular block.	**B**

1.4. Reflex syncope

The main causes of reflex syncope

- Vasovagal syncope (common faint)
- Carotid sinus syncope
- Situational syncope:
  acute haemorrhage (or acute fluid depletion)
  cough, sneeze
  gastrointestinal stimulation (swallowing, defecation, visceral pain)
  micturition (post-micturition)
  post-exercise
  post-prandial
  others (e.g. brass instrument playing, weightlifting)
- Glossopharyngeal neuralgia

Recommendations for cardiac pacing in carotid sinus syndrome

Class	Clinical Indication	Level of evidence
Class I	1. Recurrent syncope caused by inadvertent carotid sinus pressure and reproduced by carotid sinus massage, associated with ventricular asystole of more than three seconds' duration (patient may be syncopal or presyncopal), in the absence of medication known to depress sinus node activity.	**C**
Class IIa	1. Recurrent unexplained syncope, without clear inadvertent carotid sinus pressure, but syncope is reproduced by carotid sinus massage, associated with a ventricular asystole of more than three seconds' duration (patient may be syncopal or presyncopal), in the absence of medication known to depress sinus node activity.	**B**
Class IIb	1. First syncope, with or without clear inadvertent carotid sinus pressure, but syncope (or pre-syncope) is reproduced by carotid sinus massage, associated with a ventricular asystole of more than three seconds' duration, in the absence of medication known to depress sinus node activity.	**C**
Class III	1. Hypersensitive carotid sinus reflex without symptoms.	**C**

Recommendations for cardiac pacing in vasovagal syncope

Class	Clinical Indication	Level of evidence
Class I	None.	
Class IIa	1. Patients over 40 years of age with recurrent severe vasovagal syncope who show prolonged asystole during ECG recording and/or tilt testing, after failure of other therapeutic options and being informed of the conflicting results of trials.	**C**
Class IIb	1. Patients under 40 years of age with recurrent severe vasovagal syncope who show prolonged asystole during ECG recording and/or tilt testing, after failure of other therapeutic options and being informed of the conflicting results of trials.	**C**
Class III	1. Patients without demonstrable bradycardia during reflex syncope.	**C**

1.5. Paediatrics and congenital heart diseases

Recommendations for cardiac pacing in paediatrics and congenital heart disease

Class	Clinical Indication	Level of evidence
Class I	1. Congenital third degree atrioventricular block with any of the following conditions: ▪ symptoms ▪ ventricular rate less than 50-55/min in infants ▪ ventricular rate less than 70/min in congenital heart disease ▪ ventricular dysfunction ▪ wide QRS escape rhythm ▪ complex ventricular ectopy ▪ abrupt ventricular pauses > 2-3x basic cycle length ▪ prolonged QTc, or ▪ presence of maternal antibodies-mediated block.	**B**
	2. Second or third degree atrioventricular block with ▪ symptomatic bradycardia* ▪ ventricular dysfunction	**C**
	3. Postoperative Mobitz type II second- or third-degree block which persists at least 7 days after cardiac surgery.	**C**
	4. Sinus node dysfunction with correlation of symptoms.	**C**
Class IIa	1. Asymptomatic sinus bradycardia in the child with complex congenital heart disease and ▪ resting heart rate less than 40/min, or ▪ pauses in ventricular rate more than 3 s.	**C**
	2. Bradycardia-tachycardia syndrome with the need of antiarrhythmics when other therapeutical options, such as catheter ablation, are not possible.	**C**
	3. Long-QT syndrome with ▪ 2:1 or third-degree atrioventricular block ▪ Symptomatic bradycardia* (spontaneous or due to beta-blocker) ▪ pause dependent ventricular tachycardia.	**B**
	4. Congenital heart disease and impaired haemodynamics due to sinus bradycardia* or loss of atrioventricular synchrony	**C**
Class IIb	1. Congenital third degree atrioventricular blocks without a Class I indication for pacing.	**B**
	2. Transient postoperative third-degree atrioventricular block with residual bifascicular block.	**C**
	3. Asymptomatic sinus bradycardia in the adolescent with congenital heart disease and ▪ resting heart rate less than 40/min or ▪ pauses in ventricular rate more than 3 s.	**C**
	4. Neuromuscular diseases with any degree of atrioventricular block without symptoms.	**C**
Class III	1. Transient postoperative atrioventricular block with return of atrioventricular conduction within 7 days.	**B**
	2. Asymptomatic postoperative bifascicular block with and without first degree atrioventricular block.	**C**
	3. Asymptomatic type I second-degree atrioventricular block.	**C**
	4. Asymptomatic sinus bradycardia in the adolescent with minimum heart rate more than 40/min and maximum pause in ventricular rhythm less than 3 s.	**C**

* Clinical significance of bradycardia is age dependent

1.6. Cardiac transplantation

Recommendations for cardiac pacing after cardiac transplantation

Class	Clinical Indication	Level of evidence
Class I	1. Symptomatic bradyarrhythmias due to sinus node dysfunction or atrioventricular block three weeks after transplantation.	**C**
Class IIa	1. Chronotropic incompetence impeding the quality of life late in the post-transplant period.	**C**
Class IIb	1. Symptomatic bradyarrhythmias between the first and third week after transplantation.	**C**
Class III	1. Asymptomatic bradyarrhythmias and tolerated chronotropic incompetence. 2. Monitoring of cardiac rejection alone. 3. Bradyarrhythmias during the first week of transplantation.	**C**

2. Pacing for specific conditions

2.1. Hypertrophic cardiomyopathy

Recommendations for cardiac pacing in hypertrophic cardiomyopathy

Class	Clinical Indication	Level of evidence
Class I	None.	
Class IIa	Symptomatic bradycardia due to beta blockade when alternative therapies are unacceptable.	**C**
Class IIb	Patients with drug refractory hypertrophic cardiomyopathy with significant resting or provoked LVOT gradient and contra-indications for septal ablation or myectomy.	**A**
Class III	1. Asymptomatic patients. 2. Symptomatic patients who do not have LVOT obstruction.	**C**

LVOT = left ventricular outflow tract

3. Cardiac resynchronization therapy in patients with heart failure

3.1. Introduction

Evidence-based clinical effects of cardiac resynchronization therapy

State-of-the-art management of congestive heart failure (CHF), besides alleviating symptoms, preventing major morbidity, and lowering mortality, increasingly strives to prevent disease progression, in particularly the transition between asymptomatic LV dysfunction and overt CHF. The clinical effects of long-term CRT were firstly evaluated in non-controlled studies, in which a sustained benefit conferred by biventricular pacing was measured. Randomised multi-centre trials with crossover or parallel treatment assignments were subsequently conducted to ascertain the clinical value of CRT in patients with advanced CHF and in sinus rhythm, with or without indications for an implantable cardioverter-defibrillator (ICD). Meta-analyses were also published. The usual study enrolment criteria were: 1) CHF in New York Heart Association (NYHA) functional Class III or IV despite optimal pharmacological treatment; 2) LV ejection fraction (EF) < 35%, LV end-diastolic diameter > 55 mm, and QRS duration ≥ 120 or 150 ms.

3.2. Recommendations

Pacing for heart failure can be applied either by biventricular pacing or, in selected cases, by left ventricular pacing alone. The following recommendations consider cardiac pacing for heart failure delivered through biventricular pacing, since this mode is supported by the greatest body of evidence. This, however, does not preclude other pacing modes, such as LV pacing, to correct ventricular dyssynchrony.

Ventricular conduction delay continues to be defined according to QRS duration (QRS ≥ 120 ms). It is recognised that ventricular conduction delay may not result in mechanical dyssynchrony. Dyssynchrony is defined as an uncoordinated regional contraction-relaxation pattern. Although from the theoretical point of view it may be more appropriate to target mechanical dyssynchrony, rather than electrical conduction delay, no large controlled study has prospectively assessed the value of mechanical dyssynchrony in heart failure patients undergoing pacing for heart failure.

Recommendations for the use of cardiac resynchronization therapy by biventricular pacemaker (CRT-P) or biventricular pacemaker combined with an ICD (CRT-D) in HF patients.

Heart failure patients who remain symptomatic in NYHA Class III-IV despite optimal pharmacological treatment, with low ejection fraction (LVEF ≤ 35%), left ventricular dilatation*, normal sinus rhythm and wide QRS complex (≥ 120 ms)

- Class I - Level of evidence A for CRT-P to reduce morbidity and mortality.
- CRT-D is an acceptable option for patients who have expectancy of survival with a good functional status for more than 1 year, Class I - Level of evidence B.

Recommendations for the use of biventricular pacing in HF patients with a concomitant indication for permanent pacing.

Heart failure patients with NYHA Class III-IV symptoms, low ejection fraction (LVEF ≤ 35%), left ventricular dilatation* and a concomitant indication for permanent pacing (first implant or upgrading of conventional pacemaker).

- Class IIa - Level of evidence C

Recommendations for the use of an ICD combined with biventricular pacemaker (CRT-D) in HF patients with an indication for an ICD.

Heart failure patients with a Class I indication for an ICD (first implant or upgrading at device change) who are symptomatic in NYHA Class III-IV despite optimal pharmacological treatment, with low ejection fraction (LVEF ≤ 35%), left ventricular dilatation*, wide QRS complex (≥ 120 ms).

- Class I - Level of evidence B.

Recommendations for the use of biventricular pacing in HF patients with permanent atrial fibrillation.
Heart failure patients who remain symptomatic in NYHA Class III-IV despite optimal pharmacological treatment, with low ejection fraction (LVEF ≤ 35%), LV dilatation*, permanent atrial fibrillation and indication for AV junction ablation. ▪ Class IIa - Level of evidence C.

* Left ventricular dilatation/Different criteria have been used to define LV dilatation in controlled studies on CRT: LV end diastolic diameter > 55 mm; LV end diastolic diameter > 30 mm/m^2, LV end diastolic diameter > 30 mm/m (height).

Section XIII: Myocardial Infarction

1. Universal Definition of Myocardial Infarction

Chapter 1

Universal Definition of Myocardial Infarction*

2007

The joint ESC–ACCF–AHA–WHF Task Force for the Redefinition of Myocardial Infarction

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*Adapted from the ESC-ACCF-AHA-WHF Expert Consensus Document on the Universal Definition of Myocardial Infarction (European Heart Journal 2007;28:2525-2538).

**Dr. Shanti Mendis of the WHO participated in the task force in her personal capacity but this does not represent WHO approval of this document at the present time.

J. Bax et al., *Compendium of Abridged ESC Guidelines 2001*

Definition of myocardial infarction

Criteria for acute myocardial infarction

The term myocardial infarction should be used when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischaemia. Under these conditions any one of the following criteria meets the diagnosis for myocardial infarction:

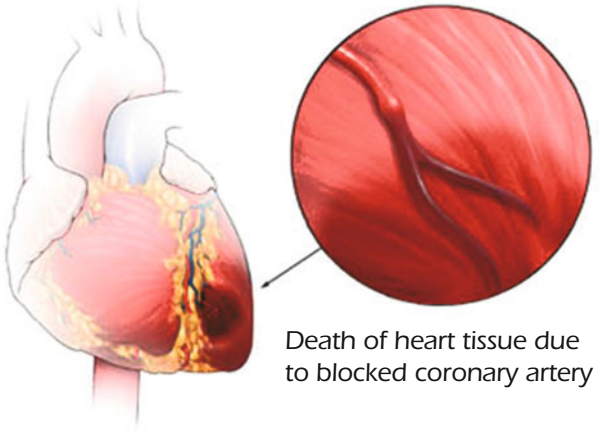
- Detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile of the upper reference limit (URL) together with evidence of myocardial ischaemia with at least one of the following:
  - Symptoms of ischaemia;
  - ECG changes indicative of new ischaemia (new ST-T changes or new left bundle branch block (LBBB));
  - Development of pathological Q waves in the ECG;
  - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.
- Sudden, unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischaemia, and accompanied by presumably new ST-elevation, or new LBBB, and/or evidence of fresh thrombus by coronary angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood.
- For percutaneous coronary interventions (PCI) in patients with normal baseline troponin values, elevations of cardiac biomarkers above the 99th percentile URL are indicative of peri-procedural myocardial necrosis. By convention, increases of biomarkers greater than 3 X 99th percentile URL have been designated as defining PCI-related myocardial infarction. A subtype related to a documented stent thrombosis is recognized.
- For coronary artery bypass grafting (CABG) in patients with normal baseline troponin values, elevations of cardiac biomarkers above the 99th percentile URL are indicative of peri-procedural myocardial necrosis. By convention, increases of biomarkers greater than 5 X 99th percentile URL plus either new pathological Q waves or new LBBB, or angiographically documented new graft or native coronary artery occlusion, or imaging evidence of new loss of viable myocardium have been designated as defining CABG-related myocardial infarction.
- Pathological findings of an acute myocardial infarction.

Criteria for prior myocardial infarction

Any one of the following criteria meets the diagnosis for prior myocardial infarction:

- Development of new pathological Q waves with or without symptoms.
- Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract, in the absence of a non-ischaemic cause.
- Pathological findings of a healed or healing myocardial infarction.

Pathology



Myocardial Infarction is defined as myocardial cell death due to prolonged myocardial ischaemia.

Classification of myocardial infarction

Type 1	**Spontaneous myocardial infarction related to ischaemia due to a primary coronary event such as plaque erosion and/or rupture, fissuring, or dissection.**
Type 2	**Myocardial infarction secondary to ischaemia due to either increased oxygen demand or decreased supply e.g. coronary artery spasm, coronary embolism, anaemia, arrhythmias, hypertension, or hypotension.**
Type 3	**Sudden unexpected cardiac death, including cardiac arrest, often with symptoms suggestive of myocardial ischaemia, accompanied by presumably new ST-elevation, or new LBBB, or presumably new, major obstruction in a coronary artery by angiography and/or pathology, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood.**
Type 4a	**Myocardial infarction associated with PCI.**
Type 4b	**Myocardial infarction associated with stent thrombosis as documented by angiography or autopsy**
Type 5	**Myocardial infarction associated with CABG.**

Cardiac biomarkers for detecting myocardial infarction

Preferably

Detection of rise and/or fall of troponin (I or T) with at least one value above the 99th percentile of a control group measured with a coefficient of variation ≤ 10%.

When Troponin is not available

Detection of rise and/or fall of CKMB mass with at least one value above the 99th percentile of a control group measured with a coefficient of variation ≤ 10%.

Reinfarction

In patients where recurrent myocardial infarction is suspected from clinical signs or symptoms following the initial infarction, an immediate measurement of cardiac troponin is recommended. A second sample should be obtained 3-6 hrs later. Recurrent infarction is diagnosed if there is a 20% or more increase of the value in the second sample. This value should also exceed the 99th percentile for a control group.

Elevations of troponin in the absence of overt ischaemic heart disease

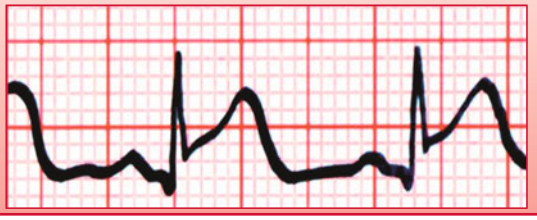
- Cardiac contusion, or other trauma including surgery, ablation, pacing etc
- Congestive heart failure - acute and chronic
- Aortic dissection
- Aortic valve disease
- Hypertrophic cardiomyopathy
- Tachy- or bradyarrhythmias, or heart block
- Apical ballooning syndrome
- Rhabdomyolysis with cardiac injury
- Pulmonary embolism, severe pulmonary hypertension
- Renal failure
- Acute neurological disease, including stroke, or subarachnoid haemorrhage
- Infiltrative diseases, e.g., amyloidosis, haemochromatosis, sarcoidosis, and scleroderma
- Inflammatory diseases, e.g., myocarditis or myocardial extension of endo-/pericarditis
- Drug toxicity or toxins
- Critically ill patients, especially with respiratory failure, or sepsis
- Burns, especially if affecting > 30% of body surface area
- Extreme exertion

Electrocardiographic detection of myocardial infarction

ECG manifestations of acute myocardial ischaemia (in absence of LVH and LBBB)

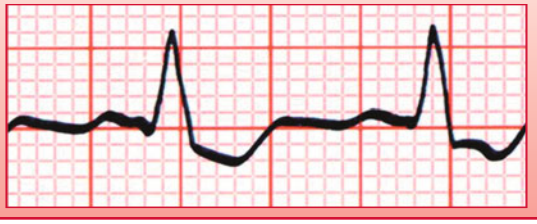
ST-elevation

New ST-elevation at the J point in two contiguous leads with the cut-off points: ≥ 0.2 mV in men or ≥ 0.15 mV in women in leads V_2-V_3 and/or ≥ 0.1 mV in other leads



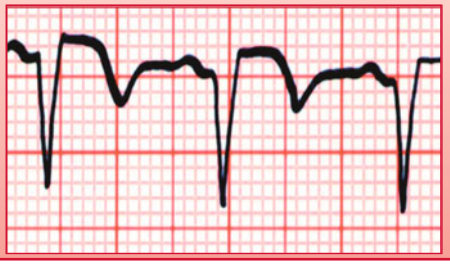
ST-depression and T wave changes

New horizontal or down-sloping ST-depression ≥ 0.05 mV in two contiguous leads; and/or T-inversion ≥ 0.1 mV in two contiguous leads with prominent R wave or R/S ratio > 1



ECG changes associated with prior myocardial infarction

- Any Q wave in leads V_2-V_3 ≥ 0.02 sec or QS complex in leads V_2 and V_3.
- Q-wave ≥ 0.03 sec and ≥ 0.1 mV deep or QS complex in leads I, II, aVL, aVF or V_4-V_6 in any two leads of a contiguous lead grouping (I, aVL, V_6; V_4-V_6; II, III, aVF).
- R-wave ≥ 0.04 sec in V_1-V_2 and R/S ≥ 1 with a concordant positive T-wave in the absence of a conduction defect.



Common ECG pitfalls in diagnosing myocardial infarction

False positives:

- Benign early repolarization
- LBBB
- Pre-excitation
- Brugada syndrome
- Peri-/myocarditis
- Pulmonary embolism
- Subarachnoid haemorrhage
- Metabolic disturbances such as hyperkalemia
- Failure to recognize normal limits for J-point displacement
- Lead transposition or use of modified Mason-Likar configuration
- Cholecystitis

False negatives:

- Prior myocardial infarction with Q waves and/or persistent ST-elevation
- Paced rhythm
- LBBB

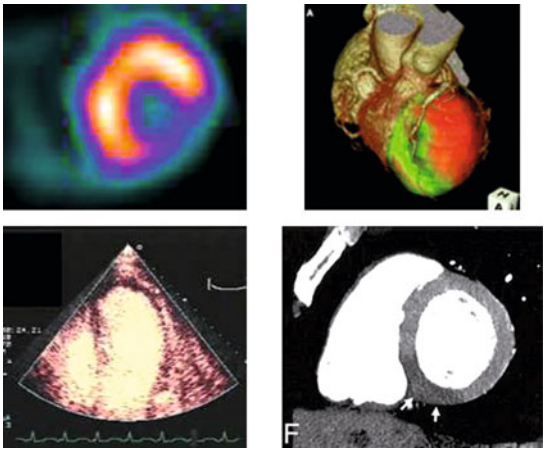
Reinfarction

Reinfarction should be considered when ST-elevation ≥ 0.1 mV reoccurs in a patient having a lesser degree of ST-elevation or new pathognomonic Q waves, particularly when associated with ischaemic symptoms. ST-depression or LBBB on their own should not be considered valid criteria for myocardial infarction.

Imaging techniques for detection of myocardial infarction

Imaging techniques can be useful in the diagnosis of myocardial infarction because of the ability to detect wall motion abnormalities in the presence of elevated cardiac biomarkers. If for some reason biomarkers have not been measured or may have normalized, demonstration of new loss of myocardial viability alone in the absence of non-ischaemic causes meets the criteria for myocardial infarction. However, if biomarkers have been measured at appropriate times and are normal, the determinations of these take precedence over the imaging criteria.

Echocardiography and radionuclide techniques, in conjunction with exercise or pharmacologic stress can identify ischaemia and myocardial viability. Non-invasive imaging techniques can diagnose healing or healed infarction by demonstrating regional wall motion, thinning or scar in the absence of other causes.



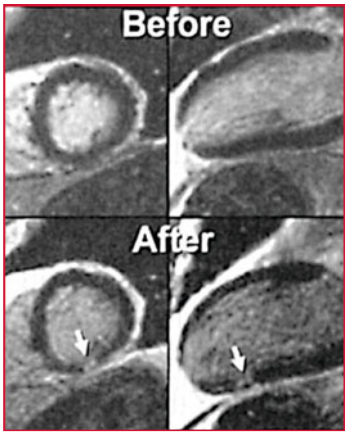
Myocardial infarction associated with interventions

Diagnostic criteria for myocardial infarction with PCI

In the setting of PCI, the occurrence of procedure-related cell necrosis can be detected by measurement of cardiac biomarkers before or immediately after the procedure, and again at 6-12 and 18-24 hours. Elevations of biomarkers above the 99th percentile after PCI, assuming a normal baseline troponin value, are indicative of post-procedural myocardial necrosis. There is currently no solid scientific basis for defining a biomarker threshold for the diagnosis of peri-procedural myocardial infarction.

By arbitrary convention, it is suggested to designate increases greater than 3 X 99th percentile for a control group as PCI-related myocardial infarction (type 4a). If cardiac troponin is elevated before the procedure and not stable for at least two samples 6 hours apart, there are insufficient data to recommend biomarker criteria for the diagnosis of peri-procedural myocardial infarction. If the values are stable, criteria for reinfarction by further measurement of biomarkers together with the features of the ECG or imaging can be applied.

A separate subcategory of myocardial infarction (type 4b) is related to stent thrombosis as documented by angiography and/or autopsy.



Diagnostic criteria for myocardial infarction with CABG

Any increase of cardiac biomarkers after CABG indicates myocyte necrosis, implying that an increasing magnitude of biomarker is likely to be related to an impaired outcome. However, scant literature exists concerning the use of biomarkers for defining myocardial infarction in the setting of CABG. Therefore, biomarkers cannot stand alone in diagnosing myocardial infarction.

In view of the adverse impact on survival observed in patients with significant biomarker elevations, it is suggested, by arbitrary convention, that biomarker values greater than the 5 x 99th percentile for a control group during the first 72 hrs following CABG when associated with the appearance of new pathological Q waves or new LBBB, or angiographically documented new graft or native coronary artery occlusion, or imaging evidence of new loss of viable myocardium should be considered as diagnostic of a CABG related myocardial infarction (type 5).

Clinical investigations involving myocardial infarction

Consistency among investigators and regulatory authorities with regard to the definition of myocardial infarction used in clinical investigations is essential. Furthermore, investigators should ensure that a trial provides comprehensive data for the classification of the different types of myocardial infarction according to multiples of the 99th percentile for a control group of the applied cardiac biomarker.

Classification of the different types of myocardial infarction according to multiples of the 99th percentile URL of the applied cardiac biomarker

Multiples X 99%	MI Type 1 (spontaneous)	MI Type 2 (secondary)	MI Type 3* (sudden death)	MI Type 4a** (PCI)	MI Type 4b (stent thrombosis)	MI Type 5** (CABG)	Total Number
1-2 X							
2-3 X							
3-5 X							
5-10 X							
> 10 X							
Total number							

*Biomarkers are not available for this type of myocardial infarction since the patients expired before biomarker determination could be performed.

**For the sake of completeness, the total distribution of biomarker values should be reported. The hatched areas represent biomarker elevations below the decision limit used for these types of myocardial infarction.

Sample clinical trial tabulation of randomized patients by types of myocardial infarction

Types of MI	Treatment A Number of patients	Treatment B Number of patients
MI Type 1		
MI Type 2		
MI Type 3		
MI Type 4a		
MI Type 4b		
MI Type 5		
Total number		

Section XIV: Pulmonary Embolism

1. Acute Pulmonary Embolism

Chapter 1
Acute Pulmonary Embolism*
2008

The Task Force on Acute Pulmonary Embolism of the European Society of Cardiology

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1. Introduction

Pulmonary embolism (PE) is a major health problem, and may present as a cardiovascular emergency. Occlusion of the pulmonary arterial bed by thrombus may lead to acute life-threatening, but potentially reversible, right ventricular failure in the most severe cases. Alternatively, the clinical presentation of PE may be non-specific, in cases where the pulmonary obstruction is less severe, or moderate.

The diagnosis of PE is difficult to establish, and may often go unrecognised, because of non-specific clinical presentations. However, early diagnosis is critical, since treatment is highly effective. Treatment strategy depends on the clinical presentation. In haemodynamically compromised patients it is primarily aimed at urgent restoration of the flow through occluded pulmonary arteries with potentially life-saving effects. In less severe cases,

*Adapted from the ESC Guidelines on Diagnosis and Management of Acute Pulmonary Embolism (European Heart Journal 2008;29:2276-2315).

J. Bax et al., *Compendium of Abridged ESC Guidelines 2001*

treatment aims at preventing the progression of the thrombotic process, and potentially fatal early recurrences.

In all patients, both initial and long term treatment should be justified by a certified diagnosis of PE using a validated diagnostic strategy.

2. Predisposing factors, symptoms and signs of PE

Predisposing factors for VTE

Strong predisposing factors (OR > 10)
Fracture (hip or leg)
Hip or knee replacement
Major general surgery
Major trauma
Spinal cord injury
Moderate predisposing factors (OR 2-9)
Arthroscopic knee surgery
Central venous lines
Chemotherapy
Chronic heart or respiratory failure
Hormone replacement therapy
Malignancy
Oral contraceptive therapy
Paralytic stroke
Pregnancy/postpartum
Previous VTE
Thrombophilia
Weak predisposing factors (OR < 2)
Bed rest > 3 days
Immobility due to sitting (e.g. prolonged car or air travel)
Increasing age
Laparoscopic surgery (e.g. cholecystectomy)
Obesity
Pregnancy/antepartum
Varicose veins

OR = odds ratio

Adapted from: Anderson FA, Jr., Spencer FA. Risk factors for venous thromboembolism. Circulation 2003; 107(23 Suppl 1):I9-16

Note, that PE occurs in individuals without any predisposing factors (unprovoked or idiopathic PE) in around 30% of cases.

Symptoms and signs reported in confirmed PE

Symptoms	Approximate prevalence
Dyspnoea	80%
Chest pain (pleuritic)	52%
Chest pain (substernal)	12%
Cough	20%
Syncope	19%
Haemoptysis	11%
Signs	**Approximate prevalence**
Tachypnoea (≥ 20/min)	70%
Tachycardia (> 100/min)	26%
Signs of DVT	15%
Cyanosis	11%
Fever (> 38·5 °C)	7%

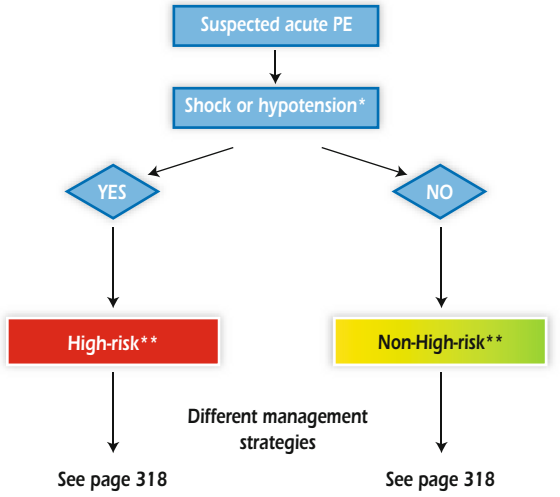
Adapted from Miniati M, Prediletto R, Formichi B, Marini C, Di Ricco G, Tonelli L et al., Am J Respir Crit Care Med 1999; 159(3):864-871 and Stein PD, Saltzman HA, Weg JG., Am J Cardiol 1991; 68(17):1723-1724

Results of routine laboratory tests (chest X-ray, electrocardiogram, arterial blood gas analysis) are often abnormal in PE. Similarly to clinical symptoms and signs, their negative and positive predictive value for diagnosis of PE is low.

Clinical symptoms, signs, predisposing factors and routine laboratory tests do not allow excluding or confirming acute PE, but may serve as components of diagnostic and management algorithms, which should be followed in each suspected case.

3. Initial risk stratification

Immediate bedside clinical assessment for the presence or absence of clinical haemodynamic compromise allows for stratification into "high-risk" and "non-high-risk" PE. This classification should be also applied to patients with suspected PE, helping to choose the optimal diagnostic strategy and initial management. High-risk PE is a life-threatening emergency requiring specific diagnostic and therapeutic strategy (short-term mortality above 15%).



*** Defined as a systolic blood pressure < 90 mmHg or a pressure drop of ≥ 40 mmHg for > 15 minutes**

if not caused by new-onset arrhythmia, hypovolaemia or sepsis

**** Defined as risk of early (in-hospital or 30 day) PE-related mortality**

4. Assessment of clinical probability

In patients with suspected PE, initial clinical assessment is mandatory for concomitant:

- initial risk stratification (see above)
- assessment of clinical probability of PE

Assessment of "clinical probability" is based on predisposing factors, symptoms and signs identified at presentation.

Clinical probability can be estimated either by applying a validated score (e.g. Geneva or Wells score, see tables on this page) or global clinical judgment. In any case it should be done prior to laboratory diagnostic evaluation.

Initial risk stratification is necessary for identifying high-risk patients who should be submitted to a specific diagnostic and management strategy (page 317). Clinical probability assessment is necessary to select the optimal diagnostic strategy and interpret diagnostic test results in patients with non high-risk suspected PE.

Revised Geneva score

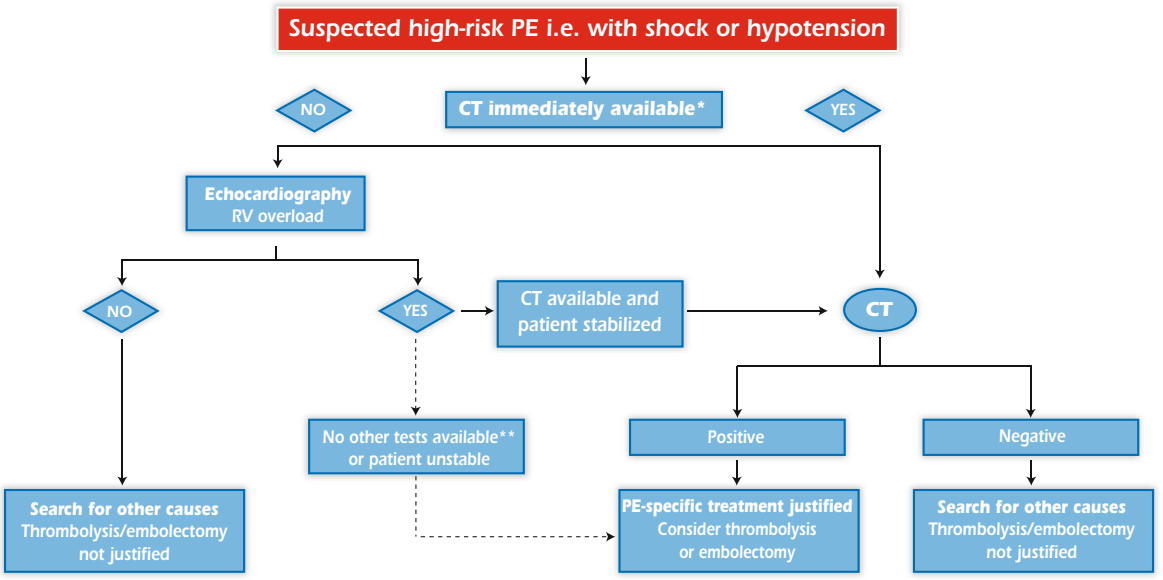
Variables	Points
Predisposing factors	
Age > 65 years	+1
Previous DVT or PE	+3
Surgery or fracture within one month	+2
Active malignancy	+2
Symptoms	
Unilateral lower limb pain	+3
Haemoptysis	+2
Clinical signs	
Heart rate	
75 to 94 beats per minute	+3
≥ 95 beats per minute	+5
Pain on lower limb deep vein at palpation and unilateral oedema	+4
Clinical probability	**Total**
Low	0 to 3
Intermediate	4 to 10
High	≥ 11

Wells score

Variables	Points
Predisposing factors	
Previous DVT or PE	+1.5
Recent surgery or immobilization	+1.5
Cancer	+1
Symptoms	
Haemoptysis	+1
Clinical signs	
Heart rate > 100 beats per minute	+1.5
Clinical sign of DVT	+3
Clinical judgement	
Alternative diagnosis less likely than PE	+3
Clinical probability (3-level)	**Total**
Low	0 to 1
Intermediate	2 to 6
High	≥ 7
Clinical probability (2-level)	**Total**
PE unlikely	0-4
PE likely	> 4

5. Diagnostic assessment

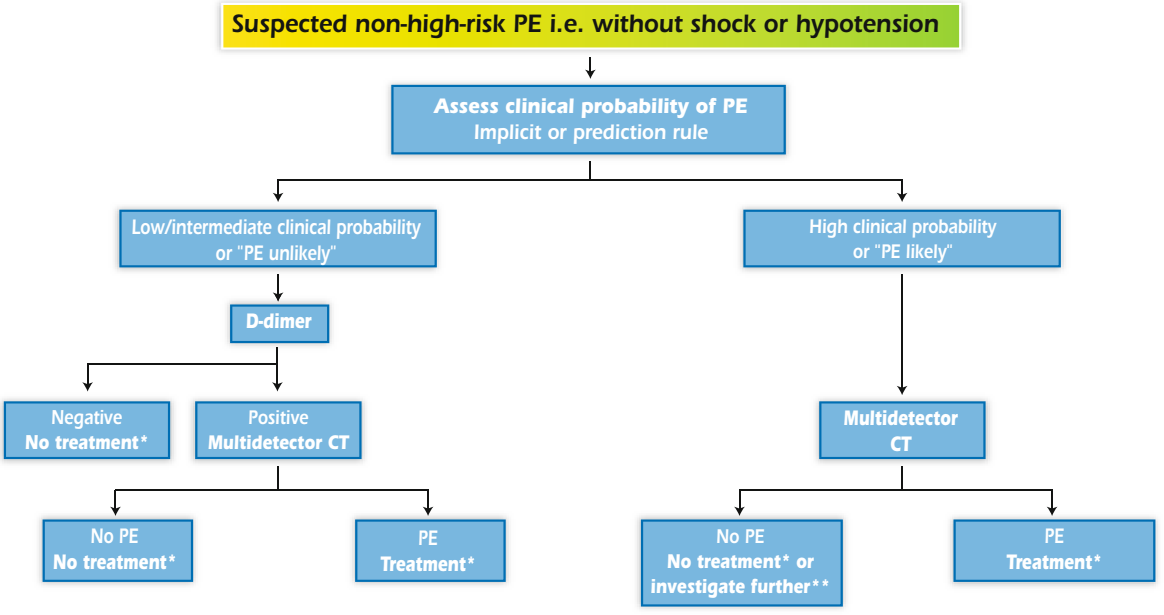
Diagnostic algorithm for patients with suspected high-risk PE



* CT is considered not immediately available also if critical condition of a patient allows only bedside diagnostic tests.

** Note that transesophageal echocardiography may detect thrombi in the pulmonary arteries in a significant proportion of patients with RV overload and PE ultimately confirmed at spiral CT and that confirmation of DVT with bedside CUS might also help in decision making.

Diagnostic algorithm for patients with suspected non-high-risk PE



See page 317 for clinical probability assessment scores.

When using a moderately sensitive assay, decision to withhold anticoagulation based on negative D-dimer test result should be restricted to patients with a low clinical probability or a "PE unlikely" classification.

D-dimer measurement is of limited usefulness in suspected PE occurring in hospitalised patients, due to high number needed to test to obtain a negative result.

* Treatment refers to anticoagulant treatment for PE.

** In case of a negative multi-detector CT in patients with high clinical probability further investigation may be considered before withholding PE-specific treatment.

See page 319 for all validated diagnostic criteria for patients with non-high risk PE, which might be helpful in constructing alternative diagnostic algorithms, whenever needed.

Validated diagnostic criteria for patients without shock and hypotension according to clinical probability

Non-high-risk PE

Exclusion of pulmonary embolism			
Diagnostic criterion	**Clinical probability of PE**		
	Low	**Intermediate**	**High**
Normal pulmonary angiogram	+	+	+
D-dimer			
Negative result, highly sensitive assay	+	+	–
Negative result, moderately sensitive assay	+	–	–
V/Q scan			
Normal lung scan	+	+	+
Non-diagnostic lung scan*	+	–	–
Non-diagnostic lung scan* and negative proximal CUS	+	+	±
Chest CT angiography			
Normal single-detector CT and negative proximal CUS	+	+	±
Normal multi-detector CT alone	+	+	±

Valid criterion (no further testing required): +, color green.

Invalid criterion (further testing mandatory): –, color red.

Controversial criterion (further testing to be considered); ±, color orange.

* Non diagnostic lung scan: low or intermediate probability lung scan according to the PIOPED (Prospective Investigation On Pulmonary Embolism Diagnosis study) classification.

Validated diagnostic criteria for patients without shock and hypotension according to clinical probability

Non-high-risk PE

Confirmation of pulmonary embolism			
Diagnostic criterion	**Clinical probability of PE**		
	Low	**Intermediate**	**High**
Pulmonary angiogram showing PE	+	+	+
High probability V/Q scan	±	+	+
CUS showing a proximal DVT	+	+	+
Chest CT angiography			
Single or multi-detector helical CT scan showing PE (at least segmental)	±	+	+
Single or multi-detector helical CT scan showing sub-segmental PE	±	±	±

Valid criterion (no further testing required): +, color green.

Invalid criterion (further testing mandatory): –, color red.

Controversial criterion (further testing to be considered); ±, color orange.

6. Comprehensive risk stratification

Concurrently with the diagnosis of PE, prognostic assessment is required for risk stratification and therapeutic decision-making. Risk stratification of PE is performed in stages: it starts with clinical assessment of the haemodynamic status and continues with the help of laboratory tests.

Severity of PE should be understood as an individual estimate of PE-related early mortality risk, rather than anatomic burden, shape and distribution of

intrapulmonary emboli. Therefore current guidelines suggest replacing potentially misleading terms such as "massive, sub-massive, non-massive" with the estimated levels of risk of PE-related early death.

Recommendations	Class [a]	Level [b]
• Initial risk stratification of suspected and/or confirmed PE based on the presence of shock and hypotension is recommended to distinguish between patients with high and non-high risk of PE related early mortality	I	B
• In non-high-risk PE patients, further stratification to an intermediate or low-risk PE subgroup based on the presence of imaging or biochemical markers of RV dysfunction and myocardial injury should be considered	IIa	B

[a] Class of recommendation, [b] Level of evidence

Principal markers useful for risk stratification

Clinical markers	Shock Hypotension*
Markers of RV dysfunction	RV dilatation, hypokinesis or pressure overload on echocardiography RV dilatation on spiral computed tomography BNP or NT-proBNP elevation Elevated right heart pressures at right heart catheterization
Markers of myocardial injury	Cardiac troponin T or I positive**

BNP - brain natruretic peptide, NT-proBNP - N-terminal proBNP

* Defined as a systolic blood pressure < 90 mmHg or a pressure drop of ≥ 40 mmHg for > 15 minutes if not caused by new-onset arrhythmia, hypovolaemia or sepsis.

** Heart-type fatty-acids binding protein (H-FABP) is an emerging marker in this category, but still requires confirmation.

Several variables collected during routine clinical and laboratory evaluation also have prognostic significance in PE. Many of them are related to the preexisting condition and comorbidities of the individual patient rather than to the severity of the index PE episode. Consideration of preexisting patient-related factors may be useful for final risk stratification and management decisions.

Risk stratification according to expected PE-related early mortality rate

PE-related early MORTALITY RISK		RISK MARKERS: CLINICAL (Shock or hypotension)	RISK MARKERS: RV Dysfunction	RISK MARKERS: Myocardial injury	Potential treatment implications
HIGH > 15%		+	(+)*	(+)*	Thrombolysis or Embolectomy
NON HIGH	Inter-mediate 3 - 15%	–	+	+	Hospital Admission
			+	–	
			–	+	
	Low <1%	–	–	–	Early discharge or home treatment

* In the presence of shock or hypotension it is not mandatory to confirm RV dysfunction/injury to classify as high risk for PE-related early mortality.

It is likely that patients with intermediate-risk PE in whom markers of dysfunction and injury are both positive have increased risk compared to patients with discordant results.

The currently available data do not allow proposing specific cut-off levels of markers which could be used for therapeutic decision-making in patients with non-high-risk PE.

An ongoing multi-center randomized trial is evaluating the potential benefit of thrombolysis in normotensive patients with predefined echocardiographic signs of RVD and troponin levels.

7. Initial treatment

High-risk PE

Recommendations	Class [a]	Level [b]
• Anticoagulation with UFH should be initiated without delay in patients with high-risk PE	I	A
• Systemic hypotension should be corrected to prevent progression of RV failure and death due to PE	I	C
• Vasopressive drugs are recommended for hypotensive patients with PE	I	C
• Dobutamine and dopamine may be used in patients with PE, low cardiac output and normal blood pressure	IIa	B
• Aggressive fluid challenge is not recommended	III	B
• Oxygen should be administered to patients with hypoxaemia	I	C
• Thrombolytic therapy should be used in patients with high-risk PE presenting with cardiogenic shock and/or persistent arterial hypotension	I	A
• Surgical pulmonary embolectomy is a recommended therapeutic alternative in patients with high-risk PE in whom thrombolysis is absolutely contraindicated or has failed	I	C
• Catheter embolectomy or fragmentation of proximal pulmonary arterial clots may be considered as an alternative to surgical treatment in high-risk patients when thrombolysis is absolutely contraindicated or has failed	IIb	C

[a] Class of recommendation, [b] Level of evidence

Non-high-risk PE

Recommendations	Class [a]	Level [b]
• Anticoagulation should be initiated without delay in patients with high or intermediate clinical probability of PE while diagnostic work-up is still ongoing	I	C
• Use of LMWH or fondaparinux is the recommended form of initial treatment for most patients with non-high-risk PE	I	A
• In patients at high bleeding risk and in those with severe renal dysfunction UFH with an aPTT target range of 1.5 – 2.5 times normal is a recommended form of initial treatment	I	C
• Initial treatment with UFH, LMWH or fondaparinux should be continued for at least 5 days and may be replaced by Vit K antagonists only after achieving target INR levels for at least 2 consecutive days	I I	A C
• Routine use of thrombolysis in non–high-risk PE patients is not recommended, but it may be considered in selected patients with intermediate risk PE	IIb	B
• Thrombolytic therapy should not be used in patients with low-risk PE	III	B

[a] Class of recommendation, [b] Level of evidence

Approved thrombolytic regimens for pulmonary embolism

Streptokinase	250,000 IU as a loading dose over 30 min, followed by 100,000 IU/h over 12-24 h
	Accelerated regimen: 1.5 million IU over 2 h
Urokinase	4,400 IU/kg as a loading dose over 10 min, followed by 4,400 IU/kg/h over 12-24 h
	Accelerated regimen: 3 million IU over 2 h
rtPA	100 mg over 2 h; or 0.6 mg/kg over 15 min (maximum dose 50 mg)

Contra-indications to thrombolytic therapy

Absolute contra-indications*:

- Haemorrhagic stroke or stroke of unknown origin at any time
- Ischaemic stroke in preceding 6 months
- Central nervous system damage or neoplasms
- Recent major trauma/surgery/head injury (within preceding 3 weeks)
- Gastro-intestinal bleeding within the last month
- Known bleeding

Relative contra-indications

- Transient ischaemic attack in preceding 6 months
- Oral anticoagulant therapy
- Pregnancy or within 1 week post partum
- Non-compressible punctures
- Traumatic resuscitation
- Refractory hypertension (systolic blood pressure > 180 mm Hg)
- Advanced liver disease
- Infective endocarditis
- Active peptic ulcer

* Contra-indications to thrombolysis which are considered absolute e.g. in acute myocardial infarction, might become relative in a patient with immediately life-threatening high-risk PE.

Subcutaneous regimens of low molecular-weight heparins and fondaparinux approved for the treatment of PE

	Dosage	Interval
Enoxaparin	1.0 mg/kg or 1.5 mg/kg*	Every 12 h Once daily*
Tinzaparin	175 U/kg	Once daily
Fondaparinux	5 mg (body weight < 50 kg); 7.5 mg (body weight 50-100 kg); 10 mg (body weight > 100 kg)	Once daily

* Once-daily injection of enoxaparin at the dosage of 1.5 mg/kg is approved for inpatient (hospital) treatment of PE in the United States and in some, but not all, European countries.

In patients with cancer Dalteparin is approved for extended treatment of symptomatic VTE (proximal DVT and/or PE), at an initial dose of 200 IU/kg s.c. once daily (see drug labeling for details). Other LMWH approved for the treatment of DVT are sometimes used also in PE.

Adjustment of intravenous unfractionated heparin dosage based on the aPTT

APTT	Change of Dosage
< 35 sec (< 1.2 times control)	80 U/kg bolus, increase infusion rate by 4 U/kg/h
35-45 sec (1.2-1.5 times control)	40 U/kg bolus, increase infusion rate by 2 U/kg/h
46-70 sec (1.5-2.3 times control)	no change
71-90 sec (2.3-3.0 times control)	reduce infusion rate by 2 U/kg/h
> 90 sec (> 3.0 times control)	stop infusion for 1 h, then reduce infusion rate by 3 U/kg/h

aPTT = activated partial thromboplastin time

8. Long term treatment

Recommendations	Class [a]	Level [b]
• For patients with PE secondary to a transient (reversible) risk factor, treatment with a VKA is recommended for 3 months	I	A
• For patients with unprovoked PE, treatment with a VKA is recommended for at least 3 months	I	A
• Patients with a first episode of unprovoked PE and low bleeding risk, and in whom stable anticoagulation can be achieved, may be considered for long-term oral anticoagulation	IIb	B
• For patients with a second episode of unprovoked PE, long-term treatment is recommended	I	A
• In patients who receive long-term anticoagulant treatment, the risk-benefit ratio of continuing such treatment should be reassessed at regular intervals	I	C
• For patients with PE and cancer, LMWH should be considered for the first 3 to 6 months after this period, anticoagulant therapy with VKA or LMWH should be continued indefinitely, or until the cancer is considered cured	IIa I	B C
• In patients with PE, the dose of VKA should be adjusted to maintain a target INR of 2.5 (INR range, 2.0 to 3.0) regardless of treatment duration	I	A

[a] Class of recommendation, [b] Level of evidence

9. Venous filters

Recommendations	Class [a]	Level [b]
• IVC filters may be used when there are absolute contra-indications to anticoagulation and a high risk of VTE recurrence	IIb	B
• The routine use of IVC filters in patients with PE is not recommended	III	B

[a] Class of recommendation, [b] Level of evidence

Permanent inferior vena cava (IVC) filters may provide lifelong protection against PE; however, they are associated with complications and late sequelae including recurrent DVT episodes and development of the post-thrombotic syndrome.

10. Specific situations

PREGNANCY: in pregnant women with a clinical suspicion of PE, an accurate diagnosis is mandatory, as a prolonged course of heparin is required.

The amount of radiation absorbed by the foetus for different diagnostic tests is shown in the appendix (page 324). The upper limit with regard to danger of injury for the foetus is considered to be 50 mSv (50 000 μGy). Therefore, all diagnostic modalities may be used without a significant risk to the foetus. CT radiation dose delivered to the foetus seems lower than that of a perfusion lung scintigraphy in the 1st and 2nd trimester. However, perfusion lung scintigraphy has high diagnostic yield (75%) in pregnant women with less breast tissue radiation compared to CT. Ventilation phase does not appear to add enough information to warrant the additional radiation. In women left undiagnosed by perfusion lung scintigraphy, however, CT should be preferred over pulmonary angiography, which carries a significantly higher X-ray exposure for the foetus (2.2 to 3.7 mSv).

Low-molecular heparins are recommended in confirmed PE, while VKA are not recommended during the first and the third trimesters and may be considered with caution in the second trimester of pregnancy. Thrombolysis carries higher risk of bleeding in pregnant women but - similarly to embolectomy - it should be considered in life-threatening situations.

Anticoagulant treatment should be administered for at least 3 months after the delivery.

MALIGNANCY is a predisposing factor for development and recurrence of VTE. However, routine extensive screening for cancer in patients with first episode of unprovoked PE is not recommended. In cancer patients with confirmed PE, LMWH should be considered for the first 3 to 6 months of treatment and anticoagulant treatment should be continued indefinitely or until definitive cure of the cancer.

RIGHT HEART THROMBI, particularly when mobile, "in-transit" from the systemic veins, are associated with a significantly increased early mortality risk in patients with acute PE. Immediate therapy is mandatory, but optimal treatment is controversial in the absence of controlled trials. Thrombolysis and embolectomy are probably both effective while anticoagulation alone appears less effective.

HEPARIN INDUCED THROMBOCYTOPENIA (HIT) is a life-threatening immunological complication of heparin therapy. Monitoring of platelet counts in patients treated with heparin is important for early detection of HIT.

Treatment consists of discontinuation of heparin and alternative anticoagulant treatment, if still required.

CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION (CTEPH) is a severe though rare consequence of PE. Pulmonary endarteriectomy provides excellent results, and should be considered as a first line treatment, whenever possible. Drugs targeting the pulmonary circulation in patients in whom surgery is not feasible or failed are currently being tested in clinical trials.

NON-THROMBOTIC PE does not represent a distinct clinical syndrome. It may be due to a variety of embolic materials and result in a wide spectrum of clinical presentations making the diagnosis difficult. With the exception of severe air and fat embolism, the haemodynamic consequences of non-thrombotic emboli are usually mild. Treatment is mostly supportive but may differ according to the type of embolic material and clinical severity.

11. Appendix

Estimated radiation absorbed by foetus in procedures for diagnosing PE

Test	Estimated radiation	
	µGy	mSv
Chest radiography	< 10	0.01
Perfusion lung scan with Technetium-99m labelled albumin (1–2 mCi)	60 - 120	0.06 - 0.12
Ventilation lung scan	200	0.2
CT angiography		
1st trimester	3 - 20	0.003 - 0.02
2nd trimester	8 - 77	0.008 - 0.08
3rd trimester	51 - 130	0.051 - 0.13
Pulmonary angiography by femoral access	2210 - 3740	2.2 - 3.7
Pulmonary angiography by brachial access	< 500	< 0.5

Section XV:
Heart Failure

1. Acute and Chronic Heart Failure

Chapter 1
Acute and Chronic Heart Failure*
2008

The Task Force on Heart Failure of the European Society of Cardiology (ESC)
Developed in collaboration with the Heart Failure Association of the ESC (HFA)

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1. Introduction

The aim of this document is to provide practical guidelines for the diagnosis, assessment, and treatment of acute and chronic heart failure (HF). National health policy as well as clinical judgement may dictate the order of priorities in implementation. An evidence-based approach has been used to generate the grade of any recommendation in the guidelines, with an additional assessment of the quality of the evidence. In Table 1 the language used to specify a recommendation is presented.

*Adapted from the ESC Guidelines on Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 (European Heart Journal 2008; 29:2388-2442) and European Journal of Heart Failure 2008:10;933-989

J. Bax et al., *Compendium of Abridged ESC Guidelines 2001*

Table 1: ESC Classes of Recommendations

Classes of Recommendations	Definition	Suggested wording to use
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful and effective	Is recommended/ is indicated
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure	
Class IIa	Weight of evidence/opinion is in favour of usefulness/ efficacy	Should be considered
Class IIb	Usefulness/efficacy is less well established by evidence/opinion	May be considered
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful	Is not recommended

2. Definition & Diagnosis

Definition of heart failure

HF is a complex syndrome in which the patients should have the following features: symptoms of HF, typically shortness of breath at rest or during exertion, and/or fatigue; signs of fluid retention such as pulmonary congestion or ankle swelling; objective evidence of an abnormality of the structure or function of the heart at rest (Table 2).

A clinical response to treatment directed at HF alone is not sufficient for the diagnosis, but is helpful when the diagnosis remains unclear after appropriate diagnostic investigations.

Table 2: Definition of heart failure

HF is a clinical syndrome in which patients have the following features:

- Symptoms typical of HF (breathlessness at rest or on exercise, fatigue, tiredness, ankle swelling)

and

- Signs typical of HF (tachycardia, tachypnoea, pulmonary rales, pleural effusion, raised jugular venous pressure, peripheral oedema, hepatomegaly)

and

- Objective evidence of a structural or functional abnormality of the heart at rest (cardiomegaly, third heart sound, cardiac murmurs, abnormality on the echocardiogram, raised natriuretic peptide concentration)

Table 3: Common clinical manifestations of heart failure

Dominant clinical feature	Symptoms	Signs
Peripheral oedema/ congestion	Breathlessness Tiredness, fatigue Anorexia	Peripheral oedema Raised jugular venous pressure Pulmonary oedema Hepatomegaly, ascites Fluid overload (congestion) Cachexia
Pulmonary oedema	Severe breathlessness at rest	Crackles or rales over lungs, effusion Tachycardia, tachypnoea
Cardiogenic shock (low output syndromes)	Confusion Weakness Cold periphery	Poor peripheral perfusion Systolic BP < 90 mmHg Anuria or oliguria
High blood pressure (hypertensive HF)	Breathlessness	Usually raised BP, LVH and preserved EF
Right HF	Breathlessness Fatigue	Evidence of RV dysfunction Raised JVP, peripheral oedema, hepatomegaly, gut congestion

Acute and chronic heart failure

A useful classification of HF based on the nature of the clinical presentation makes a distinction between new onset HF, transient HF and chronic HF. Transient HF refers to symptomatic HF over a limited time period although long-term treatment may be indicated.

Systolic versus diastolic heart failure

Most patients with HF have evidence of both systolic and diastolic dysfunction at rest or on exercise. Patients with diastolic HF have symptoms and/or signs of HF and a preserved left ventricular ejection fraction above 45-50%. We have elected to use the abbreviation HFPEF in this document.

Table 4: Classification of HF by structural abnormality (ACC/AHA) or by symptoms relating to functional capacity (NYHA)

ACC/AHA Stages of HF Stage of heart failure based on structure and damage to heart muscle		NYHA Functional Classification Severity based on symptoms and physical activity	
Stage A	At high risk for developing HF. No identified structural or functional abnormality; no signs or symptoms.	Class I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnoea.
Stage B	Developed structural heart disease that is strongly associated with the development of HF, but without signs or symptoms.	Class II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnoea.
Stage C	Symptomatic HF associated with underlying structural heart disease.	Class III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity results in fatigue, palpitation, or dyspnoea.
Stage D	Advanced structural heart disease and marked symptoms of HF at rest despite maximal medical therapy.	Class IV	Unable to carry on any physical activity without discomfort. Symptoms at rest. If any physical activity is undertaken, discomfort is increased.
ACC = American College of Cardiology; AHA, American Heart Association. Hunt SA et al. Circulation. 2005;112:1825-1852. NYHA = New York Heart Association.		The Criteria Committee of the New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th Ed. Boston. Mass: Little, Brown & Co; 1994:253-256	

Epidemiology

The prevalence of HF in the overall population is between 2 and 3%. The prevalence of asymptomatic ventricular dysfunction is similar so that HF, or asymptomatic ventricular dysfunction, is evident in about 4% of the population. The prevalence rises sharply around 75 years of age so the prevalence in 70 to 80 year old people is between 10 and 20%.

Overall 50% of patients are dead at four years. Forty percent of patients admitted to hospital with HF are dead or readmitted within one year.

HFPEF (ejection fraction > 45-50%) is present in half the patients with HF. The prognosis in more recent studies has been shown to be essentially similar to systolic HF.

Aetiology of heart failure

The most common causes of functional deterioration of the heart are damage or loss of heart muscle acute or chronic ischaemia, increased vascular resistance with hypertension or the development of a tachyarrhythmia such as atrial fibrillation. Coronary heart disease is by far the commonest cause of myocardial disease being the initiating cause in about 70% of patients with HF. Valve disease accounts for 10% and cardiomyopathies for another 10%.

3. Diagnostic Techniques

Algorithm for the diagnosis of heart failure

An algorithm for the diagnosis of HF or left ventricular dysfunction is shown in Figure 1. The diagnosis of HF is not sufficient alone. Although the general treatment of HF is common to most patients some causes require specific treatments and may be correctable.

Diagnostic tests in heart failure

Diagnostic tests are usually most sensitive for the detection of patients with HF and reduced ejection fraction. Diagnostic findings are often less pronounced in patients with HFPEF. Echocardiography is the most useful method for evaluating systolic and diastolic dysfunction.

Electrocardiogram

An electrocardiogram (ECG) should be performed in every patient with suspected HF (Table 5).

Figure 1: Flow-chart for the diagnosis of HF in untreated patients with symptoms suggestive of HF using natriuretic peptides

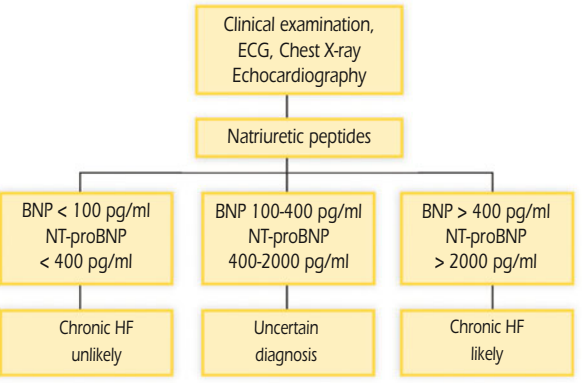


Table 5: Common ECG abnormalities in HF

Abnormality	Causes	Clinical Implications
Sinus tachycardia	Decompensated HF, anaemia, fever, hyperthyroidism	Clinical assessment Laboratory investigation
Sinus bradycardia	Beta-blockade, anti-arrhythmics, hypothyroidism, sick sinus syndrome	Evaluate drug therapy Laboratory investigation
Atrial tachycardia/flutter/ fibrillation	Hyperthyroidism, infection, decompensated HF, infarction	Slow AV conduction, medical conversion, electroversion, catheter ablation, anticoagulation
Ventricular arrhythmias	Ischaemia, infarction, cardiomyopathy, myocarditis hypokalaemia, hypomagnesaemia, digitalis overdose	Laboratory investigation, exercise test, perfusion studies, coronary angiography, electrophysiology testing, ICD
Ischaemia/Infarction	Coronary artery disease	Echo, troponins, coronary angiography, revascularization
Q waves	Infarction, hypertrophic cardiomyopathy, LBBB, pre-excitation	Echo, coronary angiography
LV hypertrophy	Hypertension, aortic valve disease, hypertrophic cardiomyopathy	Echo/Doppler
AV block	Infarction, drug toxicity, myocarditis, sarcoidosis, Lyme disease	Evaluate drug therapy, pacemaker, systemic disease
Microvoltage	Obesity, emphysema, pericardial effusion, amyloidosis	Echo, chest X-ray
QRS length >120 msec of LBBB morphology	Electrical dyssynchrony	Echo, CRT-P, CRT-D

Chest X-ray

Chest X-ray is an essential component of the diagnostic work-up in HF. It permits assessment of pulmonary congestion and may demonstrate important pulmonary or thoracic causes of dyspnoea (Table 6).

Table 6: Common chest X-ray abnormalities in heart failure

Abnormality	Causes	Clinical Implications
Cardiomegaly	Dilated LV, RV, atria Pericardial effusion	Echo/Doppler
Ventricular hypertrophy	Hypertension, aortic stenosis, hypertrophic cardiomyopathy	Echo/Doppler
Normal pulmonary findings	Pulmonary congestion unlikely	Reconsider diagnosis (if untreated) Serious lung disease unlikely
Pulmonary venous congestion	Elevated LV filling pressure	Left heart failure confirmed
Interstitial oedema	Elevated LV filling pressure	Left heart failure confirmed
Pleural effusions	Elevated filling pressures HF likely if bilateral Pulmonary infection, surgery or malignant effusion	Consider non-cardiac aetiology If abundant, consider diagnostic or therapeutic centesis
Kerley B lines	Increased lymphatic pressures	Mitral stenosis or chronic HF
Hyperlucent lung fields	Emphysema or pulmonary embolism	Spiral CT, spirometry, Echo
Pulmonary infection	Pneumonia may be secondary to pulmonary congestion	Treat both infection and HF
Pulmonary infiltration	Systemic disease	Diagnostic work-up

Laboratory tests

Marked haematological or electrolyte abnormalities are uncommon in untreated mild to moderate HF, although mild anaemia, hyponatraemia, hyperkalaemia and reduced renal function are frequently seen, especially in patients treated with a diuretic and/or ACEI, ARB, or an aldosterone antagonist (Table 7).

Table 7: Common laboratory test abnormalities in heart failure

Abnormality	Causes	Clinical Implications
Increased serum creatinine (> 150 μmol/l)	Renal disease, ACEI/ARB, aldosterone blockade	Calculate GFR, consider reducing ACEI/ARB, or aldosterone blockers dose, check potassium and BUN
Anaemia (< 13 g/dl in men, < 12 in women)	Chronic HF, haemodilution, iron loss or poor utilisation, renal failure, chronic disease	Diagnostic work-up, consider treatment
Hyponatraemia (< 135 mmol/l)	Chronic HF, haemodilution, AVP release, diuretics	Consider water restriction, reducing diuretic dosage, ultrafiltration, vasopressin antagonist
Hypernatraemia (> 150 mmol/l)	Hyperglycaemia, dehydratation	Assess water intake, diagnostic work-up
Hypokalaemia (< 3.5 mmol/l)	Diuretics, secondary hyperaldosteronism	Risk of arrhythmia, consider potassium supplements, ACEI/ARB, aldosterone blockers
Hyperkalaemia (> 5.5 mmol/l)	Renal failure, potassium supplement, renin–angiotensin–aldosterone system blockers	Stop potassium sparing treatment (ACEI/ARB, aldosterone blockers), assess renal function and pH, risk of bradycardia
Hyperglycaemia (> 6.5 mmol/l)	Diabetes, insulin resistance	Evaluate hydration, treat glucose intolerance
Hyperuricaemia (> 500 μmol/l)	Diuretic treatment, gout, malignancy	Allopurinol, reduce diuretic dose
BNP > 400 pg/ml, NT proBNP > 2000 pg/ml	Increased ventricular wall stress	HF likely, indication for echo, consider treatment
BNP < 100 pg/ml, NT proBNP < 400 pg/ml	Normal wall stress	Re-evaluate diagnosis, HF unlikely if untreated
Albumin high (> 45 g/l)	Dehydratation, myeloma	Rehydrate
Albumin low (< 30 g/l)	Poor nutrition, renal loss	Diagnostic work-up
Transaminase increase	Liver dysfunction, right HF, drug toxicity	Diagnostic work-up, liver congestion, reconsider therapy
Elevated troponins	Myocyte necrosis, prolonged ischaemia, severe HF, myocarditis, sepsis, renal failure, pulmonary embolism	Evaluate pattern of increase (mild increases common in severe HF), coronary angiography, evaluation for revascularization
Abnormal thyroid tests	Hyper/hypothyroidism, amiodarone	Treat thyroid abnormality
Urinalysis	Proteinuria, glycosuria, bacteria	Diagnostic work-up, rule out infection
INR > 2.5	Anticoagulant overdose, liver congestion	Evaluate anticoagulant dosage, assess liver function, assess anticoagulant dose
CRP > 10 mg/l, neutrophilic leucocytosis	Infection, inflammation	Diagnostic work-up

Natriuretic peptides

Evidence exists supporting the use of plasma concentrations of natriuretic peptides for diagnosing, staging, making hospitalisation/discharge decisions and identifying patients at risk for clinical events. A normal concentration in an untreated patient has a high negative predictive value and makes HF an unlikely cause of symptoms (Figure 1).

Troponin I or T

Troponin should be sampled in suspected HF when the clinical picture suggests an acute coronary syndrome. Mild increases in cardiac troponin are frequently seen in severe HF or during episodes of HF decompensation in patients without evidence of myocardial ischaemia.

Echocardiography*

Confirmation by echocardiography of the diagnosis of HF and/or cardiac dysfunction is mandatory and should be performed shortly following suspicion of the diagnosis of HF. Tables 8 and 9 present the most common echocardiographic and Doppler abnormalities in HF.

* The term echocardiography is used to refer to all cardiac ultrasound imaging techniques, including pulsed and continuous wave Doppler, colour Doppler and Tissue Doppler Imaging (TDI).

Table 8: Common echocardiographic abnormalities in heart failure

Measurement	Abnormality	Clinical Implications
LV ejection fraction	Reduced (< 45-50%)	Systolic dysfunction
Left ventricular function, global and focal	Akinesis, hypokinesis, dyskinesis	Myocardial infarction/ischaemia Cardiomyopathy, myocarditis
End diastolic diameter	Increased (> 55-60 mm)	Volume overload - HF likely
End systolic diameter	Increased (> 45 mm)	Volume overload Systolic dysfunction likely
Fractional shortening	Reduced (< 25%)	Systolic dysfunction
Left atrial size	Increased (> 40 mm)	Increased filling pressures Mitral valve dysfunction Atrial fibrillation
Left ventricular thickness	Hypertrophy (> 11-12 mm)	Hypertension, aortic stenosis, hypertrophic cardiomyopathy
Valvular structure and function	Valvular stenosis or regurgitation (especially aortic stenosis and mitral insufficiency)	May be primary cause of HF or complicating factor Assess gradients and regurgitant fraction - Assess haemodynamic consequences Consider surgery
Mitral diastolic flow profile	Abnormalities of the early and late diastolic filling patterns	Indicates diastolic dysfunction and suggests mechanism
Tricuspid regurgitation peak velocity	Increased (> 3 m/sec)	Increased right ventricular systolic pressure - suspect pulmonary hypertension
Pericardium	Effusion, haemopericardium, thickening	Consider tamponade, uraemia, malignancy, systemic disease, acute or chronic pericarditis, constrictive pericarditis
Aortic outflow velocity time integral	Reduced (< 15 cm)	Reduced low stroke volume
Inferior vena cava	Dilated retrograde flow	Increased right atrial pressures Right ventricular dysfunction Hepatic congestion

Table 9: Doppler-echocardiographic indices and ventricular filling

Doppler indices	Pattern	Consequence
E/A waves ratio	Restrictive (> 2, short deceleration time < 115 to 150 msec)	High filling pressures Volume overload
	Slowed relaxation (< 1)	Normal filling pressures Poor compliance
	Normal (> 1)	Inconclusive as may be pseudo-normal
E/Ea	Increased (> 15)	High filling pressures
	Reduced (< 8)	Low filling pressures
	Intermediate (8 - 15)	Inconclusive
(A mitral - A pulm) duration	> 30 msec	Normal filling pressures
	< 30 msec	High filling pressures
Pulmonary S wave	> D wave	Low filling pressures
Vp	< 45 cm/sec	Slow relaxation
E/Vp	> 2.5	High filling pressures
	< 2	Low filling pressures
Valsalva manoeuver	Change of the pseudonormal to abnormal filling pattern	Unmasks high filling pressure in the setting of systolic and diastolic dysfunction

The diagnosis of HFPEF requires three conditions to be satisfied:

(1) presence of signs or symptoms of CHF,

(2) presence of normal or only mildly abnormal left ventricular systolic function (LVEF ≥ 45-50%),

(3) evidence of diastolic dysfunction (abnormal left ventricular relaxation or diastolic stiffness).

Stress echocardiography

Stress echocardiography (dobutamine or exercise echo) is used to detect ventricular dysfunction caused by ischaemia and to assess myocardial viability in the presence of marked hypokinesis or akinesis.

Further non-invasive imaging may include cardiac magnetic resonance imaging (CMR) or radionuclide imaging.

Cardiac magnetic resonance imaging (CMR)

CMR is a versatile, highly accurate, reproducible, non-invasive imaging technique for the assessment of left and

right ventricular volumes, global function, regional wall motion, myocardial viability, myocardial thickness, thickening, myocardial mass and tumours, cardiac valves, congenital defects, and pericardial disease.

CT Scan

CT angiography may be considered in patients with a low or intermediate pre-test probability of CAD and an equivocal exercise or imaging stress test.

Radionuclide ventriculography

Radionuclide ventriculography is recognised as a relatively accurate method of determining LVEF and is most often performed in the context of a myocardial perfusion scan providing information on viability and ischaemia.

Pulmonary function tests

These tests are useful in demonstrating or excluding respiratory causes of breathlessness and assessing the potential contribution of lung disease to the patient's dyspnoea.

Exercise testing

Exercise testing is useful for the objective evaluation of exercise capacity and exertional symptoms, such as dyspnoea and fatigue. The 6 minute walk test is a simple, reproducible, readily available tool frequently employed to assess submaximal functional capacity and evaluate the response to intervention.

Cardiac catheterisation

Cardiac catheterisation is unnecessary for the routine diagnosis and management of patients with HF but may be indicated to elucidate aetiology, to obtain important prognostic information and if revascularization is being considered.

Coronary angiography

Coronary angiography should be considered in HF patients with a history of exertional angina or suspected ischaemic LV dysfunction. Coronary angiography is also indicated in patients with refractory HF of unknown aetiology and in patients with evidence of severe mitral regurgitation or aortic valve disease potentially correctable by surgery.

Right heart catheterisation

Right heart catheterisation provides valuable haemodynamic information regarding filling pressures, vascular resistance and cardiac output. Monitoring of haemodynamic variables may be considered to monitor treatment in patients with severe HF not responding to appropriate treatment.

Ambulatory ECG monitoring (Holter)

Ambulatory ECG monitoring is valuable in the assessment of patients with symptoms suggestive of an arrhythmia (e.g. palpitations or syncope) and in monitoring ventricular rate control in patients with atrial fibrillation.

Prognosis

Determining prognosis in HF is complex. The variables most consistently cited as independent outcome predictors are reported in Table 10.

Table 10: Conditions associated with a poor prognosis in HF

Demographics	Clinical	Electrophysiological	Functional/ Exertional	Laboratory	Imaging
Advanced age*	**Hypotension***	**Tachycardia**	**Reduced work,**	**Marked elevation of BNP/NT pro-BNP***	**Low LVEF***
Ischaemic aetiology*	**NYHA Functional Class III-IV***	**Q Waves**	**Low peak VO_2***	**Hyponatraemia***	
Resuscitated sudden death*	**Recent HF hospitalization***	**Wide QRS***		**Elevated troponin***	
		LV hypertrophy		**Elevated biomarkers, neurohumoral activation***	
		Complex ventricular arrhythmias*			
Poor compliance Renal dysfunction Diabetes Anaemia COPD Depression	Tachycardia Pulmonary rales Aortic stenosis Low body mass index Sleep related breathing disorders	Low heart rate variability T-wave alternans Atrial fibrillation	Poor 6 min walk distance High VE/VCO_2 slope Periodic breathing	Elevated creatinine/BUN Elevated bilirubin Anaemia Elevated uric acid	Increased LV volumes Low cardiac index High left ventricular filling pressure Restrictive mitral filling pattern, pulmonary hypertension Impaired right ventricular function

* = powerful predictors

4. Non-pharmacological Management

Self-care management

Self-care management is a part of successful HF treatment and can significantly impact on symptoms, functional capacity, well being, morbidity and prognosis.

Self-care can be defined as actions aimed at maintaining physical stability, avoidance of behaviour that can worsen the condition and detection of the early symptoms of deterioration. The essential topics and self-care behaviours are presented in Table 11.

Table 11: Essential topics in patient education with associated skills and appropriate self care behaviours

Educational topics	Skills and Self-care Behaviours
Definition and aetiology of heart failure	Understand the cause of heart failure and why symptoms occur
Symptoms and signs of heart failure	Monitor and recognise signs and symptoms Record daily weight and recognise rapid weight gain Know how and when to notify health care provider Use flexible diuretic therapy if appropriate and recommended
Pharmacological treatment	Understand indications, dosing and effects of drugs Recognise the common side-effects of each drug prescribed
Risk factor modification	Understand the importance of smoking cessation Monitor blood pressure if hypertensive Maintain good glucose control if diabetic Avoid obesity
Diet recommendation	Sodium restriction if prescribed - Avoid excessive fluid intake Modest intake of alcohol - Monitor and prevent malnutrition
Exercise recommendations	Be reassured and comfortable about physical activity Understand the benefits of exercise Perform exercise training regularly
Sexual activity	Be reassured about engaging in sex and discuss problems with health care professionals Understand specific sexual problems and various coping strategies
Immunisation	Receive immunisation against infections such as influenza and pneumococcal disease
Sleep and breathing disorders	Recognise preventive behaviour such as weight loss if obese, smoking cession and abstinence from alcohol Learn about treatment options if appropriate
Adherence	Understand the importance of following treatment recommendations and maintaining motivation to follow treatment plan
Psychosocial aspects	Understand that depressive symptom and cognitive dysfunction are common in patients with heart failure and the importance of social support - Learn about treatment options if appropriate
Prognosis	Understand important prognostic factors and make realistic decisions - Seek psychosocial support if appropriate

The Web Site **heartfailurematters.org** represents an internet tool provided by the Heart Failure Association of the ESC that permits patients, their next of kin and caregivers to obtain useful, practical information in a user-friendly format.

5. Pharmacological Therapy

The objectives of the treatment of HF are summarised in Table 12.

Figure 2 provides a treatment strategy for the use of drugs and devices in patients with symptomatic HF and systolic dysfunction. It is essential to detect and consider treatment of the common cardiovascular and non-cardiovascular comorbidities.

Table 12: Objectives of treatment in chronic heart failure

1. Prognosis	Reduce mortality
2. Morbidity	Relieve symptoms and signs Improve quality of life Eliminate oedema and fluid retention Increase exercise capacity Reduce fatigue and breathlessness Reduce need for hospitalisation Provide for end of life care
3. Prevention	Occurrence of myocardial damage Progression of myocardial damage Remodelling of the myocardium. Reoccurrence of symptoms and fluid accumulation Hospitalisation

Figure 2: Treatment strategy for the use of drugs and devices in patients with symptomatic HF and systolic dysfunction

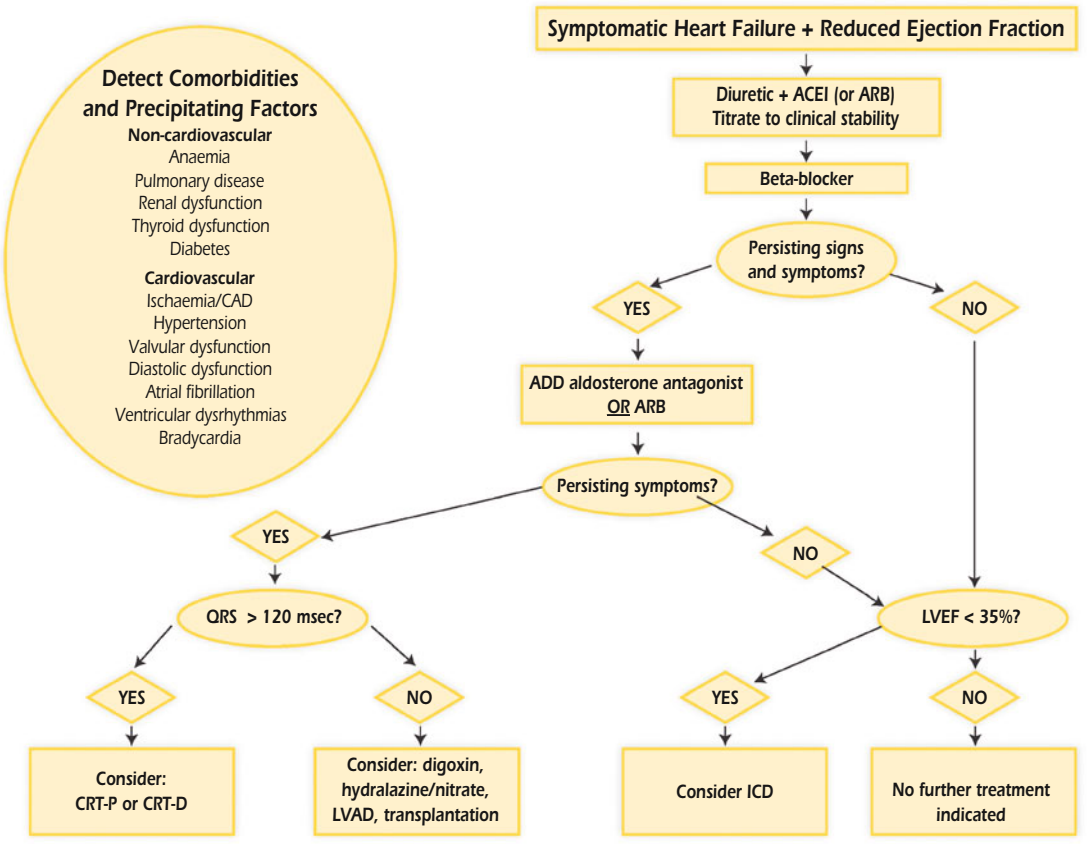


Table 13: Dosages of commonly used drugs in HF

	Starting dose (mg)		Target dose (mg)	
ACEI				
captopril	6.25	t.i.d.	50 - 100	t.i.d.
enalapril	2.5	b.i.d.	10 - 20	b.i.d.
lisinopril	2.5 - 5.0	o.d.	20 - 35	o.d.
ramipril	2.5	o.d.	5	b.i.d.
trandolapril	0.5	o.d.	4	o.d.
ARB				
candesartan	4 or 8	o.d.	32	o.d.
valsartan	40	b.i.d.	160	b.i.d.
Aldosterone antagonist				
eplerenone	25	o.d.	50	o.d.
spironolactone	25	o.d.	25 - 50	o.d.
Beta-blocker				
bisoprolol	1.25	o.d.	10	o.d.
carvedilol	3.125	b.i.d.	25 - 50	b.i.d.
metoprolol succinate	12.5/25	o.d.	200	o.d.
nebivolol	1.25	o.d.	10	o.d.
Hydralazine-ISDN				
Hydralazine-ISDN	37.5/20	t.i.d.	75/40	t.i.d.

Angiotensin converting enzyme inhibitors (ACEI)

Treatment with an ACEI improves ventricular function and patient well-being, reduces hospital admission for worsening HF and increases survival.

Patients who should get an ACEI

- LVEF ≤ 40%, irrespective of symptoms

Initiation of an ACEI:

- Check renal function and serum electrolytes.
- Consider dose up-titration after 2-4 weeks.
- Do not increase dose if worsening renal function or hyperkalaemia.
- It is common to up-titrate slowly but more rapid titration is possible in closely monitored patients.

Angiotensin receptor blockers (ARBs)

Treatment with an ARB improves ventricular function and patient well being and reduces hospital admission for worsening HF. An ARB is recommended as an alternative in patients intolerant of an ACEI.

Patients who should get an an ARB

- LVEF ≤ 40% and either:
- As an alternative in patients with mild to severe symptoms (NYHA functional class II-IV) who are intolerant of an ACEI.
- or in patients with persistent symptoms (NYHA functional class II-IV) despite treatment with an ACEI and beta-blocker.

Initiation of an ARB:

- Check renal function and serum electrolytes.
- Consider dose up-titration after 2-4 weeks.
- Do not increase dose if worsening renal function or hyperkalaemia.
- It is common to up-titrate slowly but more rapid titration is possible in closely monitored patients.

Beta-blockers

Beta-blockade improves ventricular function and patient well-being, reduces hospital admission for worsening HF and increases survival.

Patients who should get a beta-blocker

- LVEF ≤ 40%.
- Mild to severe symptoms (NYHA functional class II-IV).
- Optimal dose level of an ACEI or/and ARB.
- Patients should be clinically stable (e.g. no recent change in dose of diuretic).

Initiation of a beta-blocker:

- Beta-blockers may be initiated prior to hospital discharge in recently decompensated patients with caution.
- Visits every 2-4 weeks to up-titrate the dose of beta-blocker (slower dose up-titration may be needed in some patients). Do not increase dose if signs of worsening HF, symptomatic hypotension (e.g. dizziness) or excessive bradycardia (pulse rate < 50/minute) at each visit.

Diuretics

Diuretics are recommended in patients with HF and clinical signs or symptoms of congestion. Dosages of commonly used diuretics in HF are provided in Table 14.

Table 14: Diuretic dosages

Diuretics	Initial dose (mg)		Usual daily dose (mg)	
Loop diuretics*				
• furosemide	20 - 40		40 - 240	
• bumetanide	0.5 - 1.0		1 - 5	
• torasemide	5 - 10		10 - 20	
Thiazides**				
• bendroflumethiazide	2.5		2.5 - 10	
• hydrochlorothiazide	25		12.5 - 100	
• metolazone	2.5		2.5 - 10	
• indapamide	2.5		2.5 - 5	
Potassium-sparing diuretics***				
	+ ACEI/ ARB	– ACEI/ ARB	+ ACEI/ ARB	– ACEI/ ARB
• spironolactone/ eplerenone	12.5 - 25	50	50	100-200
• amiloride	2.5	5	20	40
• triamterene	25	50	100	200

* Dose might need to be adjusted according to volume status/weight; excessive doses may cause renal impairment and ototoxicity.
** Do not use thiazides if eGFR < 30 mL/min, except when prescribed synergistically with loop diuretics.
*** Aldosterone antagonists should always be preferred to other potassium sparing diuretics.

Volume depletion and hyponatraemia from excessive diuresis may increase the risk of hypotension and renal dysfunction with ACEI/ARB therapy (Table 15).

Table 15: Practical considerations in treatment with loop diuretics:

Problems	Suggested actions
Hypokalaemia/ hypomagnesaemia	• increase ACEI/ARB dosage • add aldosterone antagonist • potassium supplements • magnesium supplements
Hyponatraemia	• water restriction • stop thiazide diuretic or switch to loop diuretic, if possible • reduce dosage/stop loop diuretics if possible • consider AVP antagonist e.g. tolvaptan if available • i.v. inotropic support • consider ultrafiltration
Hyperuricaemia/ gout	• consider allopurinol • for symptomatic gout use colchicine for pain relief • avoid NSAIDs
Hypovolaemia/ dehydration	• assess volume status • consider diuretic dosage reduction
Insufficient response or diuretic resistance	• check compliance and fluid intake • increase dose of diuretic • consider switching from furosemide to bumetanide or torasemide • add aldosterone antagonist • combine loop diuretic and thiazide • administer loop diuretic twice daily or on empty stomach • consider short-term i.v. infusion of loop diuretic
Renal failure (excessive rise in urea/BUN and/or creatinine)	• check for hypovolaemia/dehydration • exclude use of other nephrotoxic agents e.g. NSAIDs, trimethoprim • withhold aldosterone antagonist • if using concomitant loop and thiazide diuretic stop thiazide diuretic • consider reducing dose of ACEI/ARB • consider ultrafiltration

Initiation of diuretic therapy:

- Check renal function and serum electrolytes.
- Most patients are prescribed loop diuretics rather than thiazides due to the higher efficiency of induced diuresis and natriuresis.
- Self-adjustment of diuretic dose based on daily weight-measurements and other clinical signs of fluid retention should be encouraged in HF outpatient care. Patient education is required.

Aldosterone antagonists

Aldosterone antagonists reduce hospital admission for worsening HF and increase survival when added to existing therapy, including an ACEI.

Patients who should get an aldosterone antagonist

- LVEF ≤ 35%
- Moderate to severe symptoms (NYHA functional class III-IV).
- Optimal dose of a beta-blocker and an ACEI or an ARB (but not an ACEI and an ARB).

Initiation of spironolactone (eplerenone):

- Check renal function and serum electrolytes.
- Consider dose up-titration after 4-8 weeks. Do not increase dose if worsening renal function or hyperkalaemia.

Hydralazine and isosorbide dinitrate (H-ISDN)

Treatment with H-ISDN may be considered to reduce the risk of death and hospital admission for worsening HF.

Patients who should get H-ISDN

- An alternative to an ACEI/ARB where both of the latter are not tolerated.
- As add-on, therapy to an ACEI if an ARB or aldosterone antagonist is not tolerated or if significant symptoms persist despite therapy with an ACEI, ARB, beta-blocker, and aldosterone antagonist.

Initiation of H-ISDN:

- Consider dose up-titration after 2-4 weeks. Do not increase dose with symptomatic hypotension.

Digoxin

In patients in sinus rhythm with symptomatic HF and a LVEF ≤ 40%, treatment with digoxin may improve patient well-being and reduce hospital admission for worsening HF, but has no effect on survival.

- Patients in atrial fibrillation with ventricular rate at rest > 80, and at exercise > 110-120 beats/minute should get digoxin.
- In patients with sinus rhythm and left ventricular systolic dysfunction (LVEF ≤ 40%) receiving optimal doses of diuretic, ACEI or/and ARB, beta-blocker and

aldosterone antagonist if indicated, who are still symptomatic, digoxin may be considered.

Anticoagulants (vitamin K antagonists)

- Warfarin (or an alternative oral anticoagulant) is recommended in patients with HF and permanent, persistent or paroxysmal atrial fibrillation without contra-indications.

Pharmacologic management of patients with HF and Coronary Artery Disease

ACEI

- are recommended in patients with atherosclerotic arterial disease and symptoms of HF with impaired LVEF (≤ 40%). Should also be considered in patients with CAD and HFPEF.

ARBs

- are recommended in patients following MI with symptoms of HF or impaired LVEF intolerant to ACEI.

Beta-blockers

- are recommended for CAD patients with symptoms of HF and impaired LVEF (≤ 40%).
- are recommended for all patients following MI with preserved LVEF.

Aldosterone antagonists

- are recommended in patients following MI with impaired LVEF and/or signs and symptoms of HF.

Nitrates

- may be considered to control anginal symptoms.

Calcium channel blockers

- may be considered to control anginal symptoms. In patients with reduced LVEF, amlodipine or felodipine are preferable.

Statins

- may be considered for all patients with HF and CAD. There is no evidence that statins improve survival in these patients, but they may reduce the risk of hospital admissions.

Management of patients with HF and preserved left ventricular ejection fraction (HFPEF)

No treatment has yet been shown, convincingly, to reduce morbidity and mortality in patients with HFPEF. Diuretics are used to control sodium and water retention and relieve breathlessness and oedema. Adequate treatment of hypertension and myocardial ischaemia is also important, as is control of the ventricular rate.

6. Devices & Surgery

Revascularization procedures, valvular and ventricular surgery

- If clinical symptoms of HF are present, surgically correctable conditions should be detected and corrected if indicated.

Revascularization in patients with HF

CABG or PCI should be considered in selected HF patients with CAD. Decisions regarding the choice of the method of revascularization should be based on a careful evaluation of comorbidities, procedural risk, coronary anatomy and evidence of the extent of viable myocardium in the area to be revascularised, LV function and the presence of haemodynamically significant valvular disease.

Valvular surgery

- Valvular heart disease (VHD) may be the underlying aetiology for HF or an important aggravating factor.
- Although impaired LVEF is an important risk factor for higher peri- and postoperative mortality, surgery may be considered in symptomatic patients with poor LV function.
- Optimal medical management of both HF and comorbid conditions prior to surgery is imperative. Emergency surgery should be avoided if possible.

Aortic stenosis (AS)

Surgery:

- is recommended in eligible patients with HF symptoms and severe AS.
- is recommended in asymptomatic patients with severe AS and impaired LVEF (< 50%).
- may be considered in patients with severely reduced valve area and LV dysfunction.

Aortic regurgitation (AR)

Surgery:

- is recommended in all eligible patients with severe AR who have symptoms of HF.
- is recommended in asymptomatic patients with severe AR and moderately impaired LVEF (LVEF ≤ 50%).

Mitral regurgitation (MR)

- Surgery should be considered in patients with severe MR whenever coronary revascularization is an option. Surgical repair of the valve may be an attractive option in carefully selected patients.

Organic MR

Surgery:

- is recommended for patients with LVEF > 30% (valve repair if possible).

Functional MR

Surgery:

- may be considered in selected patients with severe functional MR and severely depressed LV function, who remain symptomatic despite optimal medical therapy.
- Cardiac Resynchronization Therapy should be considered in eligible patients as it may improve LV geometry, papillary muscle dyssynchrony and may reduce MR.

Ischaemic MR

Surgery:

- is recommended in patients with severe MR and LVEF > 30% when CABG is planned.
- should be considered in patients with moderate MR undergoing CABG if repair is feasible.

Tricuspid regurgitation (TR)

- Functional TR is extremely common in HF patients with biventricular dilatation, systolic dysfunction and pulmonary hypertension. Surgery for isolated functional TR is not indicated.

LV aneurysmectomy

- LV aneurysmectomy may be considered in symptomatic patients with large, discrete left ventricular aneurysms.

Pacemakers

- The conventional indications for patients with normal LV function also apply to patients with HF.
- Physiologic pacing to maintain an adequate chronotropic response and maintain atrial-ventricular coordination with a DDD system is preferable to VVI pacing in patients with HF.
- The indications for an ICD, CRT-P or CRT-D device should be detected and evaluated in patients with HF prior to implantation of a pacemaker for an AV conduction defect.
- Right ventricular pacing may induce dyssynchrony and worsen symptoms.
- Pacing, in order to permit initiation or titration of beta-blocker therapy in the absence of conventional indications, is not recommended.

Cardiac Resynchronization Therapy (CRT)

- CRT-P is recommended to reduce morbidity and mortality in patients in NYHA III–IV class who are symptomatic despite optimal medical therapy, and who have a reduced ejection fraction (LVEF ≤ 35%) and QRS prolongation (QRS width ≥ 120 ms).
- CRT with defibrillator function (CRT-D) is recommended to reduce morbidity and mortality in patients in NYHA III–IV class who are symptomatic despite optimal medical therapy, and who have a reduced ejection fraction (LVEF ≤ 35%) and QRS prolongation (QRS width ≥ 120 ms).

Implantable cardioverter defibrillator (ICD)

- ICD therapy for *secondary prevention* is recommended for survivors of VF and also for patients with documented haemodynamically unstable VT and/ or VT with syncope, an LVEF ≤ 40%, on optimal medical therapy and with an expectation of survival with good functional status for more than 1 year.
- ICD therapy for *primary prevention* is recommended to reduce mortality in patients with LV dysfunction due to prior MI who are at least 40 days post-MI, have an LVEF ≤ 35%, in NYHA functional class II or III, receiving optimal medical therapy, and who have a reasonable expectation of survival with good functional status for more than 1 year.
- ICD therapy for *primary prevention* is recommended to reduce mortality in patients with non-ischaemic

cardiomyopathy with a LVEF ≤ 35%, in NYHA functional class II or III, receiving optimal medical therapy, and who have a reasonable expectation of survival with good functional status for more than 1 year.

Heart transplantation, ventricular assist devices, and artificial hearts

Heart transplantation

- Heart transplantation is an accepted treatment for end stage HF. There is consensus that transplantation, provided proper selection criteria are applied, significantly increases survival, exercise capacity, return to work and quality of life compared with conventional treatment.

Left ventricular assist devices (LVAD) and artificial heart

- There has been rapid progress in the development of LVAD technology and artificial hearts. Current indications for LVADs and artificial hearts include bridging to transplantation and managing patients with acute, severe myocarditis. Although experience is limited, these devices may be considered for long-term use when no definitive procedure is planned.

Ultrafiltration

- Ultrafiltration should be considered to reduce fluid overload (pulmonary and/or peripheral oedema) in selected patients and to correct hyponatraemia in symptomatic patients refractory to diuretics.

Remote monitoring

- Remote monitoring can be summarised as the continuous collection of patient information and the capability to review this information without the patient present.
- Continuous analysis of these trends can activate notification mechanisms when clinical relevant changes are detected and therefore facilitate patient management. Remote monitoring may decrease health care utilization through fewer hospital admissions for chronic HF, fewer HF related re-admissions, and more efficient device management.

7. Arrhythmias in Heart Failure

Atrial fibrillation

- A beta-blocker or digoxin is recommended to control the heart rate at rest in patients with HF and LV dysfunction.
- A combination of digoxin and a beta-blocker may be considered to control the heart rate at rest and during exercise.
- In LV systolic dysfunction, digoxin is the recommended initial treatment if the patient is haemodynamically unstable.
- IV administration of digoxin or amiodarone is recommended to control the heart rate in patients with AF and HF, who do not have an accessory pathway.
- Atrio-ventricular node ablation and pacing should be considered to control the heart rate when other measures are unsuccessful or contra-indicated.

Prevention of thromboembolism

- Antithrombotic therapy to prevent thromboembolism is recommended for all patients with AF, unless contra-indicated.
- In patients with AF at highest risk of stroke/thromboembolism, chronic oral anticoagulant therapy with a vitamin K antagonist is recommended, unless contra-indicated.

Rhythm control

- Electrical cardioversion is recommended when the rapid ventricular response does not respond promptly to appropriate pharmacological measures, especially in patients with AF causing myocardial ischaemia, symptomatic hypotension or symptoms of pulmonary congestion. Precipitating factors should be detected and treated. Patients should be anticoagulated.

Ventricular arrhythmias (VA)

- It is essential to detect, and if possible, correct all potential factors precipitating VA. Neurohumoral blockade with optimal doses of beta-blockers, ACEI, ARBs and/or aldosterone blockers is recommended.
- Routine, prophylactic use of antiarrhythmic agents in patients with asymptomatic, non-sustained VA is not recommended. In HF patients, Class Ic agents should not be used.

Patients with HF and symptomatic VA:

- In patients who survived VF or had a history of haemodynamically unstable VT or VT with syncope, with reduced LVEF (< 40%), receiving optimal pharmacological treatment and with a life expectancy of > 1 year, ICD implantation is recommended.

- Amiodarone is recommended in patients with an implanted ICD, otherwise optimally treated, who continue to have symptomatic VA.
- Catheter ablation is recommended as an adjunct therapy in patients with ICD implanted who have recurrent symptomatic VT with frequent shocks that is not curable by device reprogramming and drug therapy.
- Amiodarone may be considered in HF patients with an ICD implanted with frequent ICD shocks despite optimal therapy to prevent discharge.

Bradycardia

The conventional indications for pacing in patients with normal LV function also apply to patients with HF.

8. Comorbidities & Special Populations

Arterial hypertension

- Treatment of hypertension substantially reduces the risk of developing HF (Table 16).

Table 16: Management of arterial hypertension in HF

In hypertensive patients with evidence of LV dysfunction:
• systolic and diastolic blood pressure should be carefully controlled with a therapeutic target of ≤140/90 and ≤130/80 mmHg in diabetics and high risk patients. • anti-hypertensive regimens based on renin–angiotensin system antagonists (ACEI or ARBs) are preferable.
In hypertensive patients with HFPEF:
• aggressive treatment (often with several drugs with complementary mechanisms of action) is recommended. • ACEI and/or ARBs should be considered the first-line agents.

Non-cardiovascular comorbidities

Diabetes mellitus (DM)

- DM is a major risk factor for the development of cardiovascular disease and HF.
- ACEI and ARBs can be useful in patients with DM to decrease the risk of end-organ damage and subsequently the risk of HF.
- All patients should receive life-style recommendations.
- Elevated blood glucose should be treated with tight glycaemic control.
- Oral antidiabetic therapy should be individualised.
- *Metformin* should be considered as a first-line agent in overweight patients with type II DM without significant renal dysfunction.
- *Thiazolidinediones* have been associated with increased peripheral oedema and symptomatic HF. They are contraindicated in HF patients with NYHA functional class III-IV, but may be considered in patients with NYHA functional class I-II with careful monitoring for fluid retention.
- Early initiation of insulin may be considered if glucose target cannot be achieved.
- Agents with documented effects on morbidity and mortality such as ACEI, beta-blockers, ARBs and diuretics confer benefit at least comparable to that demonstrated in non-diabetic HF patients.
- Evaluation of the potential for revascularization may be particularly important in patients with ischaemic cardiomyopathy and DM.

Renal dysfunction

- Renal dysfunction is common in HF and the prevalence increases with HF severity, age, a history of hypertension or diabetes mellitus.
- In HF renal dysfunction is strongly linked to increased morbidity and mortality.
- The cause of renal dysfunction should always be sought in order to detect potentially reversible causes such as hypotension, dehydration, deterioration in renal function due to ACEI, ARBs or other concomitant medications [e.g. NSAIDs] and renal artery stenosis.

Chronic Obstructive Pulmonary Disease (COPD)

- COPD is a frequent comorbidity in HF. Restrictive and obstructive pulmonary abnormalities are common.
- There is a significant overlap in the signs and symptoms with a relatively lower sensitivity of diagnostic tests such as chest X-ray, ECG, echocardiography and spirometry.

- It is essential to detect and treat pulmonary congestion.
- Agents with documented effects on morbidity and mortality such as ACEI, beta-blockers and ARBs are recommended in patients with co-existing pulmonary disease.
- The majority of patients with HF and COPD can safely tolerate beta-blocker therapy. Mild deterioration in pulmonary function and symptoms should not lead to prompt discontinuation.
- A history of asthma should be considered a contra-indication to the use of any beta-blocker.

Anaemia

- The prevalence of anaemia increases with HF severity, advanced age, female gender, renal disease and other coexisting comorbidities.
- Anaemia may aggravate the pathophysiology of HF by adversely affecting myocardial function, activating neurohormonal systems, compromising renal function and contributing to circulatory failure.
- Correction of anaemia has not been established as routine therapy in HF. Simple blood transfusion is not recommended to treat the anaemia of chronic disease in HF.

Cachexia

- Body wasting is a serious complication of HF. This is a generalized process that encompasses loss in all body compartments. Cachexia can be defined as involuntary non-oedematous weight loss of ≥ 6% of total body weight within the last 6-12 months.
  It has not yet been established whether prevention and treatment of cachexia complicating HF should be a treatment goal.

Gout

- Patients with HF are prone to develop hyperuricaemia as a result of loop diuretic therapy use and renal dysfunction. In acute gout, a short course of colchicine to suppress pain and inflammation may be considered. NSAIDs should be avoided if possible in symptomatic patients. Prophylactic therapy with a xanthine oxidase inhibitor (allopurinol) is recommended to prevent recurrence.

Special Populations

Adults with congenital heart disease

- In children, HF is most often related to high-output situations due to intracardiac shunting. This is less frequently observed in adults. Complex lesions associated with cyanosis secondary to impaired pulmonary perfusion may make the diagnosis of HF difficult. Many of these patients benefit from afterload reduction even before significant HF symptoms are clinically manifest.

The Elderly

- HF in the elderly is frequently underdiagnosed, as cardinal symptoms of exercise intolerance are often attributed to ageing, coexisting comorbidities and poor health status. Common comorbidities, may have an impact on management.
- HF with a preserved ejection fraction is more common in the elderly and in females.
- Polypharmacy increases the risk of adverse interactions and side-effects which may reduce compliance. Altered pharmacokinetic and pharmacodynamic properties of drugs must be considered.
- For elderly HF patients suffering from cognitive impairment, individually structured multidisciplinary HF programmes may be particularly useful and improve adherence to therapy and prevent hospitalisation.
- Relative contra-indications to diagnostic procedures and interventions should be carefully evaluated and weighed against the indications.

9. Acute Heart Failure

Definition

Acute HF (AHF) is defined as a rapid onset or change in the signs and symptoms of HF, resulting in the need of urgent therapy. It may present as new HF or worsening HF in the presence of chronic HF. It may be associated with worsening symptoms or signs or as a medical emergency such as acute pulmonary oedema. Multiple cardiovascular and non-cardiovascular morbidities may precipitate AHF (Table 17).

Table 17: Causes and precipitating factors of AHF

Ischaemic heart disease	Circulatory failure
• Acute coronary syndromes • Mechanical complications of acute MI • Right ventricular infarction	• Septicaemia • Thyrotoxicosis • Anaemia • Shunts • Tamponade • Pulmonary embolism
Valvular	**Decompensation of preexisting chronic HF**
• Valve stenosis • Valvular regurgitation • Endocarditis • Aortic dissection	• Lack of adherence • Volume overload • Infections, especially pneumonia • Cerebrovascular insult • Surgery • Renal dysfunction • Asthma, COPD • Drug abuse • Alcohol abuse
Myopathies	
• Postpartum cardiomyopathy • Acute myocarditis	
Hypertension/arrhythmia	
• Hypertension • Acute arrhythmia	

The patient with AHF will usually present in one of 6 clinical categories:

- **Worsening or decompensated chronic HF:** There is usually a history of progressive worsening of known chronic HF on treatment and evidence of systemic and pulmonary congestion.
- **Pulmonary oedema:** patients present with severe respiratory distress, tachypnoea and orthopnoea with rales over the lung fields. Arterial O_2 saturation is usually < 90% on room air prior to treatment with oxygen.
- **Hypertensive HF:** Signs and symptoms of HF accompanied by high blood pressure and usually relatively preserved left ventricular systolic function. There is evidence of increased sympathetic tone with tachycardia and vasoconstriction. The response to appropriate therapy is rapid and hospital mortality is low.
- **Cardiogenic shock:** Cardiogenic shock is defined as evidence of tissue hypoperfusion induced by HF after adequate correction of preload and major arrhythmia. Evidence of organ hypoperfusion and pulmonary congestion develop rapidly.
- **Isolated right HF:** is characterised by a low output syndrome in the absence of pulmonary congestion.
- **ACS and HF:** Many patients with AHF present with a clinical picture and laboratory evidence of an ACS. Approximately 15% of patients with an ACS have signs and symptoms of HF.
  Episodes of acute HF are frequently associated with or precipitated by an arrhythmia (bradycardia, atrial fibrillation, ventricular tachycardia).

Diagnosis of AHF

The assessment of patients with AHF is based on the presenting symptoms and clinical findings (Figure 3). The diagnostic algorithm is similar for AHF developing *de novo* or as an episode as decompensation in chronic HF (Figure 4).

Figure 3: A clinical assessment of patients with AHF

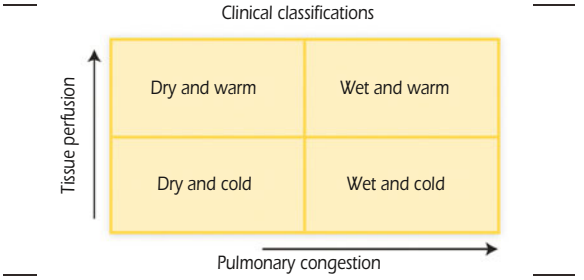
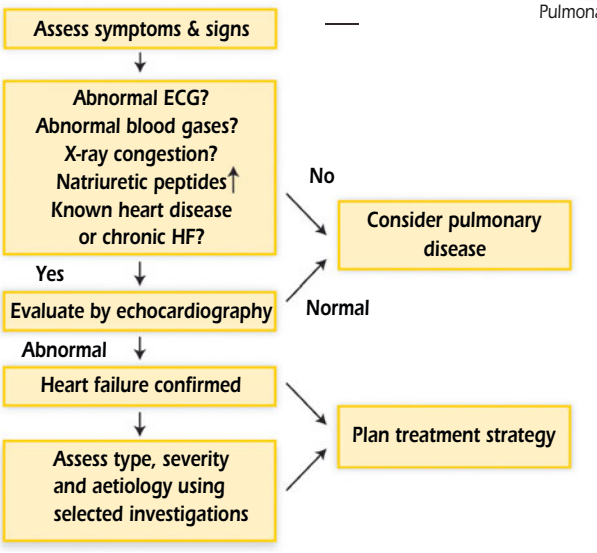


Figure 4: Diagnosis of suspected AHF



The following investigations are considered appropriate in patients with AHF:

Electrocardiogram (ECG)

- The ECG provides essential information regarding heart rate, rhythm, conduction and frequently aetiology. The ECG may indicate ischaemic ST segment changes suggestive of STEMI or non-STEMI.

Chest X-ray

- Chest X-ray should be performed as soon as possible at admission for all patients with AHF to assess the degree of pulmonary congestion and to evaluate other pulmonary or cardiac conditions.

Arterial blood gas analysis

- Arterial blood gas analysis enables assessment of oxygenation (pCO_2), respiratory function (pCO_2) and acid–base balance (pH), and should be assessed in all patients with severe respiratory distress.

Laboratory tests

- Initial diagnostic evaluation of patients with AHF includes full blood count, sodium, potassium, urea, creatinine, glucose, albumin, hepatic enzymes and INR. A small elevation in cardiac troponins may be seen in patients with AHF without ACS.

Natriuretic peptides

- B-type natriuretic peptides (BNP, NT-proBNP) taken in the acute phase have a reasonable negative predictive value for excluding HF. There is no consensus regarding BNP or NT-proBNP reference values in AHF. During 'flash' pulmonary oedema or acute mitral regurgitation, natriuretic peptide levels may remain normal at the time of admission.

Echocardiography

- Echocardiography with Doppler is an essential tool for the evaluation of the functional and structural changes underlying or associated with AHF. The findings will frequently direct treatment strategy.

Instrumentation and monitoring of patients in AHF

- Monitoring of the patient with AHF should be started as soon as possible after the arrival at the emergency unit, concurrent with ongoing diagnostic measures focused on determining the primary aetiology as well as the response to the initial treatment strategy.

Non-invasive monitoring

- In all critically ill patients, monitoring the routine basic observations of temperature, respiratory rate, heart rate, blood pressure, oxygenation, urine output and the electrocardiogram is mandatory. A pulse oximeter should be used continuously in any unstable patient who is being treated with a fraction of inspired oxygen (FiO_2) that is greater than air.

Arterial line

- The indications for the insertion of an arterial catheter are the need for either continuous analysis of arterial blood pressure due to haemodynamic instability, or the requirement for frequent arterial blood samples.

Central venous lines

- Central venous lines provide access to the central circulation and are therefore useful for the delivery of fluids, drugs and monitoring of the CVP and venous oxygen saturation (SVO_2).

Pulmonary artery catheter

- A PAC may be useful in haemodynamically unstable patients who are not responding as expected to traditional treatments. It is critical to have clear objectives prior to insertion of the catheter.

Coronary angiography

- In cases of AHF and evidence of ischaemia such as unstable angina or ACS, coronary angiography is indicated in patients without strong contra-indications.

Organisation of AHF treatment

The immediate goals are to improve symptoms and to stabilize the haemodynamic condition (Figure 5). Treatment of hospitalised patients with AHF requires a well-developed treatment strategy with realistic objectives and a plan for follow-up that should be initiated prior to discharge (Table 18).

Figure 5: Initial treatment algorithm in AHF

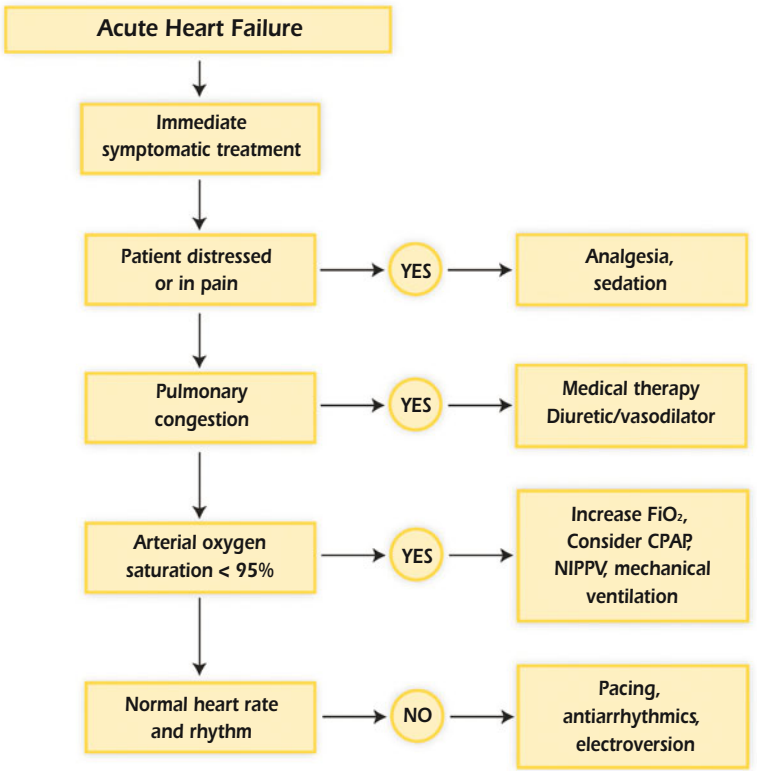


Table 18: Goals of treatment in AHF

• **Immediate (ED/ICU/CCU)**
Improve symptoms Restore oxygenation Improve organ perfusion and haemodynamics Limit cardiac/renal damage Minimize ICU length of stay
• **Intermediate (in hospital)**
Stabilise patient and optimise treatment strategy Initiate appropriate (life-saving) pharmacological therapy Consider device therapy in appropriate patients Minimise hospital length of stay
• **Long-term and predischarge management**
Plan follow-up strategy Educate and initiate appropriate lifestyle adjustments Provide adequate secondary prophylaxis Prevent early readmission Improve quality of life and survival

The following management options are considered appropriate in patients with AHF

Oxygen

- It is recommended to administer oxygen as early as possible in hypoxaemic patients to achieve an arterial oxygen saturation = > 95% (> 90% in COPD patients).

Non-invasive ventilation (NIV)

- Non-invasive ventilation refers to all modalities that assist ventilation without the use of an endotracheal tube but rather with a sealed face-mask.
- Non-invasive ventilation with positive end-expiratory pressure (PEEP) should be considered as early as possible in every patient with acute cardiogenic pulmonary oedema and hypertensive acute HF. NIV should be used with caution in cardiogenic shock and right ventricular failure.

- Intubation and mechanical ventilation should be restricted to patients in whom oxygen delivery is not adequate by oxygen mask or NIV, and in patients with increasing respiratory failure or exhaustion as assessed by hypercapnia.

How to use NIV

- A PEEP of 5-7.5 cm H_2O should be applied first and titrated to clinical response up to 10 cm H_2O; FiO_2 delivery should be ≥ 0.40.

- Usually 30 min/hour until patient's dyspnoea and oxygen saturation remain improved without continuous positive airway pressure (CPAP).

Morphine and its analogues in AHF

Morphine should be considered in the early stage of the treatment of patients admitted with severe AHF especially if they present with restlessness, dyspnoea, anxiety or chest pain. Morphine relieves dyspnoea and other symptoms in patients with AHF and may improve cooperation for the application of NIV.

- IV boluses of morphine 2.5-5 mg may be administered as soon as the IV line is inserted in AHF patients.

- Respiration should be monitored.

- Nausea is common and anti-emetic therapy may be required.

Loop diuretics

Administration of i.v. diuretics is recommended in AHF patients in the presence of symptoms secondary to congestion and volume overload.

- Excessive treatment with diuretics may lead to hypovolaemia and hyponatraemia, and increase the likelihood of hypotension on initiation of ACEI or ARBs. (Table 19).

Table 19: Indications and dosing of diuretics in AHF

Fluid retention	Diuretic	Daily Dose (mg)	Comments
Moderate	furosemide or bumetanide or torasemide	20 - 40 0.5 - 1 10 - 20	Oral or i.v. according to clinical symptoms Titrate dose according to clinical response - Monitor K, Na, creatinine, blood pressure
Severe	furosemide furosemide infusion bumetanide torasemide	40 - 100 (5 - 40 mg/h) 1 - 4 20 - 100	i.v. Increase dose. better than very high bolus doses oral or i.v. oral
Refractory to loop diuretic	add hydrochlorothiazide or metolazone or spironolactone	50 - 100 2.5 - 10 25 - 50	Combination better than very high dose of loop diuretics MTZ more potent if creatinine clr < 30 ml/min Spironolactone best choice if no renal failure and normal or low serum potassium
With alkalosis	acetazolamide	500 mg	i.v.
Refractory to loop diuretics and thiazides	add dopamine (renal vasodilation) or dobutamine		Consider ultrafiltration or haemodialysis if coexisting renal failure Hyponatraemia

Vasodilators

Vasodilators are recommended at an early stage for AHF patients without symptomatic hypotension, systolic BP <90 mmHg or serious obstructive valvular disease. The recommended dosage of vasodilators is presented in Table 20.

- Vasodilators relieve pulmonary congestion usually without compromising stroke volume or increasing myocardial oxygen demand in acute HF, particularly in patients with ACS.

- Hypotension (systolic BP <90 mmHg) should be avoided, especially in patients with renal dysfunction.

Table 20: Indications and dosing of IV vasodilators in AHF

Vasodilator	Indication	Dosing	Main side effects	Other
Nitroglycerine	pulmonary congestion/oedema BP > 90 mmHg	start 10 - 20 μg/min, increase up to 200 μg/min	hypotension, headache	tolerance on continuous use
Isosorbide dinitrate	pulmonary congestion/oedema BP > 90 mmHg	start with 1 mg/h, increase up to 10 mg/h	hypotension, headache	tolerance on continuous use
Nitroprusside	hypertensive HF congestion/oedema BP > 90 mmHg	start with 0.3 μg/kg/min and increase up to 5 μg/kg/min	hypotension, isocyanate toxicity	light sensitive
Nesiritide*	pulmonary congestion/oedema BP > 90 mmHg	bolus 2 μg/kg + infusion 0.015 - 0.03 μg/kg/min	hypotension	

* Not available in many ESC countries

Inotropic agents

The recommended dosage of inotropic agents is reported in Table 21.

- Inotropic agents should be considered in patients with low output states, in the presence of signs of hypoperfusion or congestion despite the use of vasodilators and/or diuretics.

Table 21: Dosing of positive inotropic agents in AHF

	Bolus	Infusion rate
Dobutamine	No	2 to 20 μg/kg/min (β+)
Dopamine	No	< 3 μg/kg/min: renal effect (δ+) 3 - 5 μg/kg/min: inotropic (β+) > 5 μg/kg/min: (β+), vasopressor (α+)
Milrinone	25 - 75 μg/kg over 10 - 20 min	0.375 - 0.75 μg/kg/min
Enoximone	0.25 - 0.75 mg/kg	1.25 - 7.5 μg/kg/min
Levosimendan*	12 μg/kg over 10 min (optional)**	0.1 μg/kg/min which can be decreased to 0.05 or increased to 0.2 μg/kg/min
Norepinephrine	No	0.2 - 1.0 μg/kg/min
Epinephrine	Bolus: 1 mg can be given i.v. during resuscitation, repeated every 3 - 5 min	0.05 - 0.5 μg/kg/min

* This agent also has vasodilator properties.
** In hypotensive patients, (SBP < 100 mmHg) initiation of therapy without a bolus is recommended.

- Infusion of most inotropes is accompanied by an increased incidence of both atrial and ventricular arrhythmias. Continuous clinical monitoring and ECG telemetry is required.

Dobutamine

- Dobutamine, a positive inotropic agent acting through stimulation of β1-receptors to produce dose-dependent positive inotropic and chronotropic effects.

Dopamine

- Dopamine, also stimulate β-adrenergic receptors. Infusion of low doses of dopamine stimulates dopaminergic receptors but has been shown to have limited effects on diuresis.

- Higher doses of dopamine may be used to maintain blood pressure but with an increasing risk of tachycardia, arrhythmia and alpha-adrenergic stimulation with vasoconstriction. Low dose dopamine is frequently combined with higher doses of dobutamine.

Milrinone and enoximone

- Milrinone and enoximone are the two type III phosphodiesterase inhibitors (PDEI) used in clinical practice. The agents have inotropic and peripheral vasodilating effects with an increase in cardiac output and stroke volume, and reductions in systemic and pulmonary vascular resistance.

Levosimendan

- Levosimendan improves cardiac contractility and exerts significant vasodilatation mediated through ATP-sensitive potassium channels. Levosimendan infusion in patients with acutely decompensated HF increases cardiac output and stroke volume and reduces systemic and pulmonary vascular resistance.

- The haemodynamic response to levosimendan is maintained over several days. In that the inotropic effect is independent of beta-adrenergic stimulation, it represents an alternative for patients on beta-blocker therapy.

Vasopressors

- Vasopressors (norepinephrine) are not recommended as first-line agents and are only indicated in cardiogenic shock when the combination of an inotropic agent and fluid challenge fails to restore adequate blood pressure with inadequate organ perfusion. Patients with sepsis complicating AHF may require a vasopressor. Since cardiogenic shock is usually associated with high vascular resistances, all vasopressors should be used with caution and discontinued as soon as possible.

Cardiac glycosides

- In AHF, cardiac glycosides produce a small increase in cardiac output and a reduction of filling pressures. It may be useful to slow ventricular rate in rapid atrial fibrillation.

Algorithm for AHF management

The goal of treatment in the prehospital setting or at the emergency room is to improve tissue oxygenation and optimise haemodynamics in order to improve symptoms and permit interventions.

Figure 6 describes a treatment algorithm based on the level of systolic blood pressure and Figure 7 describes the treatment algorithm based on a clinical assessment of patients' filling pressures and perfusion.

Figure 6: Treatment strategy in AHF according to systolic blood pressure

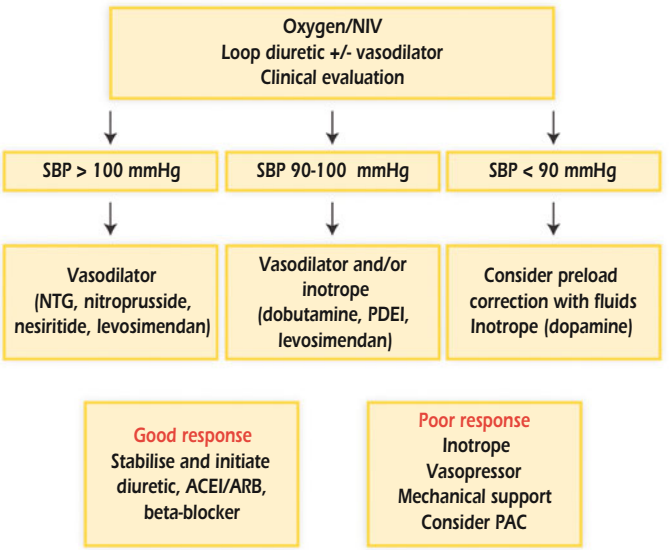
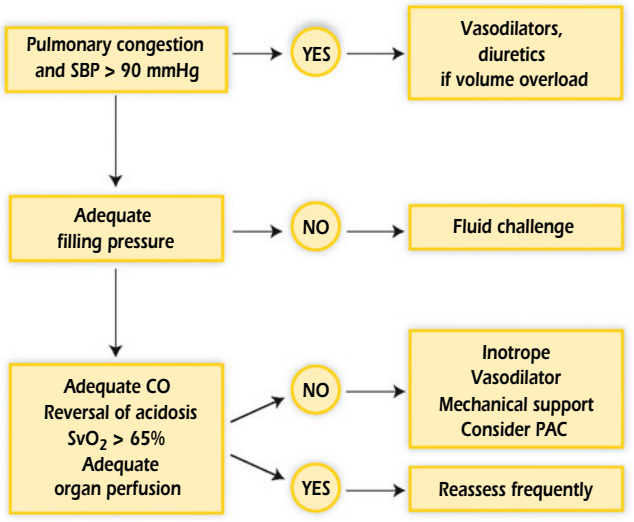


Figure 7: Treatment strategy in AHF according to LV filling pressure



Treatment should be tailored to the clinical presentation:

- **Decompensated chronic HF:** Vasodilators along with loop diuretics are recommended. Inotropic agents are required with hypotension and signs of organ hypoperfusion.

- **Pulmonary oedema:** Morphine is usually indicated especially when dyspnoea is accompanied by pain and anxiety. Vasodilators are recommended when blood pressure is normal or high and diuretics in patients with volume overload or fluid retention. Inotropic agents are required with hypotension and signs of organ hypoperfusion. Intubation and mechanical ventilation may be required to achieve adequate oxygenation.

- **Hypertensive HF:** Vasodilators are recommended with close monitoring and low dose diuretic treatment in patients with volume overload or pulmonary oedema.

- **Cardiogenic shock:** A fluid challenge if clinically indicated followed by an inotrope if SBP remains < 90 mmHg is recommended. An intra-aortic balloon pump (IABP) and intubation should be considered. LVADs may be considered for potentially reversible causes of acute HF as a bridge to treatment response (i.e. surgery or recovery).

- **Right HF:** A fluid challenge is usually ineffective. Inotropic agents are required when there are signs of organ hypoperfusion.

- **AHF and Acute Coronary Syndromes:** In ACS complicated by AHF early reperfusion may improve prognosis. Urgent surgery is indicated in patients with mechanical complications after AMI. In cardiogenic shock caused by ACS, insertion of an intra-aortic balloon pump (IABP), coronary angiography and revascularization should be considered as soon as possible.

Management of patients with acutely decompensated chronic HF treated with beta-blockers and ACEI/ARBs.

- Patients on ACEI/ARBs admitted with worsening HF should be continued on this treatment whenever possible. The dose of beta-blocker may need to be reduced temporarily or omitted. Treatment may be interrupted or reduced in the presence of complications (bradycardia, advanced AV block, severe bronchospasm or cardiogenic shock) or in cases of severe AHF and an inadequate response to initial therapy.

- In patients admitted with AHF, beta-blockers should be considered when the patient has been stabilised on an ACEI or ARB and preferably initiated before hospital discharge.

10. Implementation & Delivery of Care

Management programmes are designed to improve outcomes through structured follow-up with patient education, optimisation of medical treatment, psychosocial support, and access to care. Table 22 summarises the goals and measures involved during potential phases of this transition.

Table 22: Treatment goals and strategies during the course of the patient's journey

Phase	Diagnostic Strategy	Action	Goals	Players
Acute	Assess clinical status Identify cause of symptoms	Treat and stabilise Initiate monitoring Plan required interventions	Stabilise, admit and triage to appropriate department	Primary care services/ Paramedics/ER physicians/ Intensivists Nurses Cardiologists
Subacute	Assess cardiac function Identify aetiology and comorbidities	Initiate chronic medical treatment Perform additional diagnostics Perform indicated procedures	Shorten hospitalisation Plan post-discharge follow-up	Hospital physicians Cardiologists CV nurses HF Management team
Chronic	Target symptoms, adherence and prognosis Identify decompensation early	Optimise pharmacological and device treatment Support self-care behaviour Remote monitoring	Reduced morbidity and mortality	Primary care physicians HF Management team Cardiologists
End of life	Identify patient concerns and symptoms	Symptomatic treatment Plan for long-term care	Palliation Provide support for patients and family	Palliative care team

Heart Failure Management Programmes

- HF management programmes are recommended for patients with HF recently hospitalised and for other high-risk patients.
- Many programmes focus on symptomatic, hospitalised patients with HF since they have a poorer prognosis and are at a higher risk for readmissions. An outpatient visit, early after discharge, is recommended to assess clinical status, identify objectives and design an effective treatment strategy. It is recommended that HF management programmes include the components shown in Table 23.
- Remote management is an emerging field within the broader context of HF management programmes and extends the reach of individualised care to the large group of individuals unable to access traditional programmes of care.

Table 23: Recommended Components of HF Management Programmes

• Multidisciplinary approach frequently led by HF nurses in collaboration with physicians and other related services
• First contact during hospitalisation, early follow-up after discharge through clinic and home-based visits, telephone support and remote monitoring
• Target high-risk, symptomatic patients
• Increased access to health care (telephone, remote monitoring and follow-up)
• Facilitate access during episodes of decompensation
• Optimised medical management
• Access to advanced treatment options
• Adequate patient education with special emphasis on adherence and self-care management
• Patient involvement in symptom monitoring and flexible diuretic use
• Psychosocial support to patients and family and/or caregiver

Palliative care for patients with heart failure

Features that should trigger such consideration and the proposed steps in the process of providing palliative care are presented in Table 24.

- Patients with clinical features of advanced HF who continue to experience symptoms refractory to optimal evidence-based therapy have a poor short-term prognosis and should be considered appropriate for a structured palliative care approach.

Table 24: Steps in the process of providing palliative care

Patient features	> 1 episode of decompensation/6 months Need for frequent or continual i.v. support Chronic poor quality of life with NYHA IV symptoms Signs of cardiac cachexia Clinically judged to be close to the end of life
Confirm diagnosis	Essential to ensure optimal treatment.
Patient education	Principles of self-care maintenance and management of HF.
Establish an advanced care plan	Designed with the patient and a family member. Reviewed regularly and includes the patients' preferences for future treatment options.
Services should be organised	The patients' care within the multidisciplinary team, to ensure optimal pharmacological treatment, self-care management and to facilitate access to supportive services.
Symptom management	Requires frequent assessment of patients' physical, psychological, social and spiritual needs. Patients frequently have multiple co-morbidities that need to be identified.
Identifying end-stage HF	Confirmation of end-stage HF is advisable to ensure that all appropriate treatment options have been explored. A plan for the terminal stage of illness should be agreed upon.
Breaking bad news to the patient and family	Explaining disease progression and a change in treatment emphasis is a sensitive issue and must be approached with care.
Establishing new goals of care	End of life care should include avoidance of circumstances which may detract from a peaceful death. All current pharmacological treatment and device programmes should be considered. Resuscitation orders should be clear.

Chapter 2
Device Therapy in Heart Failure*
2011

The Task Force for an update of the 2008 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure and the 2007 ESC Guidelines for cardiac resynchronization therapy. Developed with the special contribution of the Heart Failure Association (HFA) and the European Heart Rhythm Association (EHRA) of the ESC

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1. Introduction

The Committee for Practice Guidelines (CPG) of the European Society of Cardiology recognizes that new evidence from clinical research trials may impact on current recommendations. The current heart failure (HF) guidelines were published in 2008 and the cardiac pacing guidelines in 2007. In order to keep these guidelines up to date, it would be appropriate to modify the recommendations and levels of evidence according to the most recent clinical trial data. This Focused Update on the use of devices in heart failure 2010 is the first publication of its kind from the CPG.

Practice Guideline recommendations should represent evidence-based medicine. Traditionally, these recommendations are based on the outcomes in the cohort of patients described by the inclusion criteria in the protocols of randomized clinical trials (RCTs). More recently, based on the fact that the characteristics of the patients actually included in a trial may differ substantially from the eligibility criteria, Guideline Task Force members may favour restricting the applicability of these recommendations to the clinical profile and outcomes of the enrolled cohort, representing a more accurate interpretation of the evidence provided by a trial's result.

The text accompanying these recommendations explains and justifies the decisions to diverge from a traditional recommendation based strictly on the protocol inclusion criteria. The Task Force hopes that the users of the Guidelines will appreciate that this adjustment provides a more realistic application of the trial evidence to daily clinical practice.

* Adapted from the 2010 Focused Update of ESC Guidelines on Device Therapy in Heart Failure (European Heart Journal 2010;31:2677-2687:doi:10.1093/eurheartj/ehq337)

Classes of Recommendations	
Classes of Recommendations	**Definition**
Class I	**Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.**
Class II	**Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.**
Class IIa	***Weight of evidence/opinion is in favour of usefulness/efficacy.***
Class IIb	***Usefulness/efficacy is less well established by evidence/opinion.***
Class III	**Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.**

Level of Evidence	
Level of Evidence A	**Data derived from multiple randomized clinical trials or meta-analyses.**
Level of Evidence B	**Data derived from a single randomized clinical trial or large non-randomized studies.**
Level of Evidence C	**Consensus of opinion of the experts and/or small studies, retrospective studies, registries.**

2. Cardiac resynchronization therapy with pacemaker/defibrillator function in patients with heart failure in New York Heart Association function class III/IV

The management of patients with HF represents a substantial economic burden and hospitalization is responsible for > 50% of this expense. The initial expense of device implantation must be weighed against measures of short- and long-term efficacy with regard to survival, morbidity, and quality of life. The effective use of limited health care resources necessitates identification of the characteristics of the patient population most likely to benefit from cardiac resynchronization therapy (CRT) and treatment strategy should target these patients for device implantation. The clinical effects of long-term CRT have been evaluated in a large number of randomized multi-centre trials with crossover or parallel treatment assignment, using CRT pacemakers (CRT-P) or CRT-implantable cardioverter defibrillator (ICD) devices (CRT-D). Practice with regard to the choice of the CRT device varies widely between countries.

All RCTs have confirmed a significant alleviation of symptoms and increase in exercise capacity conferred by CRT. Functional benefits and quality of life improvements were sustained. In CARE-HF, CRT-P lowered the proportion of unplanned hospitalizations for worsening HF by 52%, and the number of unplanned hospitalizations for major cardiovascular events by 39%.

CARE-HF and COMPANION were trials powered to examine the effects of CRT on combined primary endpoints of morbidity and mortality. In COMPANION, CRT-D was associated with a significant decrease in all-cause mortality (relative risk reduction: 36%; P = 0.003). In CARE-HF, where only CRT-P was assessed, a 36% relative reduction in the risk of death (P < 0.002) was observed after a mean follow-up time of 29 months. One large study, MIRACLE ICD and one large meta-analysis support the choice of a CRT-D in patients in NYHA class III/IV, with LVEF of ≤ 35%, QRS width ≥ 120 ms with a conventional indication for an ICD.

A consistent finding in the randomized trials designed with up to 6 months of follow-up has been a reduction in LV end-diastolic diameter and an increase in LVEF following CRT. These observations provide consistent evidence of a substantial, progressive, and sustained reverse remodelling effect conferred by CRT.

Key points

- New: LV dilatation no longer required in the recommendation.
- New: class IV patients should be ambulatory.
- New: reasonable expectation of survival with good functional status for > 1 year for CRT-D.
- Evidence is strongest for patients with typical lower bundle-branch block (LBBB).
- Similar level of evidence for CRT-P and CRT-D.

Recommendation in patients with heart failure in New York Heart Association function class III/IV			
Recommendation	**Patient population**	**Class[a]**	**Level[b]**
CRT-P/CRT-D is recommended to reduce morbidity and mortality†	NYHA function class III/IV LVEF ≤ 35%, QRS ≥ 120 ms, SR Optimal medical therapy Class IV patients should be ambulatory §	I	A

a = Class of recommendation.
b = Level of evidence.
† Reasonable expectation of survival with good functional status for > 1 year for CRT-D. Patients with a secondary prevention indication for an ICD should receive a CRT-D.
§ No admissions for HF during the last month and a reasonable expectation of survival > 6 months.
CRT = cardiac resynchronization therapy; CRT-P = CRT with pacemaker function; CRT-D = CRT with defibrillator function; ICD = implantable cardioverter defibrillator; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; SR = sinus rhythm

3. Cardiac resynchronization therapy with defibrillator function in patients with heart failure in New York Heart Association function class I/II

The role played by CRT in patients presenting with no or only mild manifestations of HF, a depressed LVEF and a wide QRS complex, has been recently addressed in two trials.

The large MADIT-CRT and REVERSE randomized trials evaluated the incremental benefit conferred by CRT in medically optimally treated patients. MADIT CRT enrolled 1820 patients in NYHA function class I (15%) of ischaemic aetiology or II (84%) of any aetiology and SR, whose LVEF was ≤ 30% and QRS duration ≥ 130 ms. REVERSE enrolled 610 patients treated with an optimal medical regimen, in NYHA function class I or II and SR, whose LVEF was ≤ 40%, QRS duration ≥ 120 ms, and LV end-diastolic diameter ≥ 55 mm. Patients were randomly assigned to CRT activated versus CRT off. The time to first hospitalization for management of HF or to death from any cause was significantly delayed.

In MADIT-CRT, the data reveal substantial differences in outcome according to the presence or absence of LBBB. In pre-specified subgroup analyses of data collected in MADIT CRT and REVERSE, the patients whose QRS duration was ≥150 ms derived the greatest benefit from CRT. In MADIT-CRT, women with LBBB demonstrated a particularly favourable response. Considering limited resources, it would be prudent to target the population most likely to respond favourably. In patients with mild symptoms and a QRS width of 120–150 ms, clinicians may wish to assess other criteria associated with a favourable outcome such as dyssynchrony by echocardiography, LV dilatation, LBBB, nonischaemic cardiomyopathy, or recent NYHA class III symptoms.

Paired echocardiographic studies were obtained in nearly all patients in MADIT CRT. Consistent with the echocardiographic studies from CARE-HF and REVERSE, substantial improvements in LV size and function, LVEF, RV function, left atrial size and mitral regurgitation severity were observed in patients treated with CRT compared with ICD only. The improvements in volumes were greatest in patients with a QRS width ≥ 150 ms, patients with LBBB, patients with non-ischaemic aetiology, and in female patients. These findings were strongly concordant with and predictive of the primary outcome of death or a HF event and suggest a compelling cardiac structural and functional mechanism by which CRT therapy improves outcomes. These results suggest that in the long-term, CRT lowers the risk of HF-related adverse clinical events and prevents or reduces the progression of disease by reverse LV remodelling.

MADIT-CRT and REVERSE enrolled a small proportion of asymptomatic patients, only 15% and 18% respectively. MADIT-CRT did not show significant reduction in the all-cause mortality or HF event rate by CRT over ICD. In REVERSE, a trend was observed toward less clinical efficacy conferred by CRT among class I as compared with class II patients. There is no convincing evidence that CRT is indicated in patients presenting with no or transient, mild symptoms and the recommendation is restricted to patients in NYHA II.

There are arguments in favour of a preferential implantation of CRT-D in this less severely ill patient population. The significantly younger age, lower comorbidity and longer life expectancy of patients presenting in NYHA class I or II compared with class III or IV may support the use of CRT-D. The clinical benefit conferred by device therapy in NYHA class I/II patients is probably attributable to cardiac resynchronization through reverse LV remodelling. The benefit was equal for CRT-P and CRT-D, in NYHA class III/IV. Due to the remodelling process, many class I/II patients may see their LVEF increase to > 35% (the threshold value for ICD indication in HF). The relative risk–benefit advantage of CRT-D over CRT-P remains unclear, especially in this population with milder symptoms.

Key points

- Two recent, randomized, prospective, multicentre trials in mild HF (MADIT-CRT and REVERSE) demonstrated reduced morbidity.
- 18% of patients in REVERSE and 15% of patients in MADIT-CRT were in NYHA I class at baseline although most of these patients had been previously symptomatic.
- Improvement was primarily seen in patients with QRS ≥150 ms and/or typical LBBB.
- In MADIT-CRT, women with LBBB demonstrated a particularly favourable response.
- Survival advantage is not established.
- In MADIT-CRT the extent of reverse remodelling was concordant with and predictive of improvement in clinical outcomes.

Recommendation in patients with heart failure in New York Heart Association function class II			
Recommendation	**Patient population**	**Class[a]**	**Level[b]**
CRT preferentially by CRT-D is recommended to reduce morbidity or to prevent disease progression†	NYHA function class II LVEF ≤ 35%, QRS ≥ 150 ms, SR Optimal medical therapy	I	A

a = Class of recommendation.
b = Level of evidence.
† The guideline indication has been restricted to patients with HF in NYHA function class II with a QRS width ≥150 ms, a population with a high likelihood of a favourable response.
CRT = cardiac resynchronization therapy; CRT-D = CRT with defibrillator function; HF = heart failure; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; SR = sinus rhythm

4. Cardiac resynchronization therapy with pacemaker/defibrillator function in patients with heart failure and permanent atrial fibrillation

Randomized studies of CRT to date have been almost exclusively restricted to patients in SR. This contrasts with the high prevalence of CRT use in routine practice as indicated by the recent ESC CRT survey. Approximately one-fifth of patients receiving CRTs in Europe have permanent atrial fibrillation and patients with symptomatic HF, AF, and an LVEF of ≤ 35% may satisfy the criteria for ICD implantation. The presence of QRS prolongation would favour implantation of a CRT-D in these patients.

In that the evidence is limited in AF and most of the patients included in trials had a very wide QRS, we restrict our recommendation for CRT-P/CRT-D to QRS ≥ 130 ms. An adequate trial with pharmacologically induced rate control is advisable. However, there is consensus that essentially complete ventricular capture is mandatory in order to maximize clinical benefit and improve the prognosis of patients with permanent AF.

This often requires creation of complete heart block by ablation of the AV junction given the frequently inadequate efficacy of pharmacological treatment of ventricular rate control at rest and during exercise. Frequent pacing is defined as ≥ 95% pacemaker dependency.

A large, prospective, observational registry showed that, during long-term follow-up, hybrid therapy combining CRT with AV ablation (resulting in 100% effective biventricular stimulation) conferred improvements in LV function and exercise capacity comparable to those achieved in patients with SR.

In the same cohort, evidence was provided that patients with HF and AF treated with CRT received the same survival benefit as those achieved in patients with SR only when AV ablation was performed shortly after CRT implantation. These observational data need to be confirmed in randomized controlled studies in the cohort of patients with HF and permanent AF.

Key points

- Approximately one-fifth of CRT implantations in Europe are in patients with permanent AF.
- NYHA class III/IV symptoms and an LVEF of ≤ 35% are well-established indications for ICD.
- Frequent pacing is defined as ≥ 95% pacemaker dependency.
- AV nodal ablation may be required to assure adequate pacing.
- Evidence is strongest for patients with an LBBB pattern.
- Insufficient evidence for mortality recommendation.

Recommendations in patients with heart failure and permanent atrial fibrillation

Recommendation	Patient population	Class[a]	Level[b]
CRT-P/CRT-D† should be considered to reduce morbidity	NYHA function class III/IV LVEF ≤ 35%, QRS ≥ 130 ms Pacemaker dependency induced by AV nodal ablation	IIa	B
CRT-P/CRT-D† should be considered to reduce morbidity	NYHA function class III/IV LVEF ≤ 35%, QRS ≥ 130 ms Slow ventricular rate and frequent pacing §	IIa	C

a = Class of recommendation.
b = Level of evidence.
† Reasonable expectation of survival with good functional status for >1 year for CRT-D. Patients with a secondary prevention indication for an ICD should receive a CRT-D.
§ Frequent pacing is defined as ≥ 95% pacemaker dependence.
CRT = cardiac resynchronization therapy; CRT-P = CRT with pacemaker function; CRT-D = CRT with defibrillator function; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; SR = sinus rhythm

5. Cardiac resynchronization therapy with pacemaker/defibrillator function in patients with heart failure and a conventional pacemaker indication

There are several retrospective observational series or small prospective trials demonstrating a clinical benefit of upgrading to biventricular pacing with long-standing right ventricular pacing, severe ventricular dysfunction and NYHA function class III symptoms, regardless of QRS duration.

Once severe reduction of functional capacity as well as LV dysfunction have been confirmed, then it is reasonable to consider biventricular pacing for the improvement of symptoms. Conversely, the detrimental effects of right ventricular pacing on symptoms and LV function in patients with HF of ischaemic origin and preserved LVEF have been demonstrated. The underlying rationale of recommending biventricular pacing should therefore aim to avoid chronic right ventricular pacing in HF patients who already have LV dysfunction. Initiation and up-titration of ß-blocker treatment, indicated in patients with symptomatic HF, may reduce heart rate and increase pacemaker dependency. Patients with a CRT-P/CRT-D will better tolerate increased pacing time.

Key points

- In patients with a conventional indication for pacing, NYHA III/IV symptoms, an LVEF of ≤ 35%, and a QRS width ≥ 120 ms, a CRT-P/CRT-D is indicated.
- RV pacing will induce dyssynchrony.
- Chronic RV pacing in patients with LV dysfunction should be avoided.
- CRT may permit adequate up-titration of ß-blocker treatment.

Recommendations in patients with heart failure and a concomitant class I pacemaker indication			
Recommendation	**Patient population**	**Class[a]**	**Level[b]**
CRT-P/CRT-D† is recommended to reduce morbidity	class III/IV LVEF ≤ 35%, QRS ≥ 120 ms	I	B
CRT-P/CRT-D† should be considered to reduce morbidity	NYHA function class III/IV LVEF ≤ 35%, QRS < 120 ms	IIa	C
CRT-P/CRT-D† may be considered to reduce morbidity	NYHA function class II LVEF ≤ 35%, QRS < 120 ms	IIb	C

a = Class of recommendation.
b = Level of evidence.
† Reasonable expectation of survival with good functional status for >1 year for CRT-D. Patients with a secondary prevention indication for an ICD should receive a CRT-D.
CRT = cardiac resynchronization therapy; CRT-P = CRT with pacemaker function; CRT-D = CRT with defibrillator function; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; SR = sinus rhythm.

6. Left ventricular assist device as destination therapy for patients with severe heart failure ineligible for cardiac transplantation

Patients with end-stage HF have a poor quality of life, a very high mortality rate and are potential candidates for implantation of a left ventricular assist device (LVAD). The technical improvements and proven success of implantable LVADs have made it a reasonable treatment option in these patients, either as a bridge to CTX or as destination therapy. Patient selection for LVAD is crucial. Patients with severe renal, pulmonary, or hepatic dysfunction as well as patients with active infection or cardiogenic shock should not be considered as candidates.

One recent study was conducted in 200 patients as destination therapy, who were randomized in a 2:1 ratio to a continuous-flow device (HeartMate II) or a pulsatile device. Patients were in NYHA function class IIIB/IV with an LVEF of ≤ 25%. The primary composite endpoint was, at 2 years, freedom from disabling stroke or reoperation to repair or replace the device. Secondary endpoints included actuarial survival. The primary endpoint was achieved in more patients with the continuous-flow device (46 vs. 11%, P < 0.001) and actuarial survival at 2 years was higher (58 vs. 24%, P = 0.008). The INTERMACS registry, a National Institutes of Health (NIH)-supported initiative, demonstrates that in practice ~10% of patients receiving an LVAD are not considered candidates for CTX at the time of implantation.

Key points

- Data from the NIH-supported INTERMACS registry indicates that ~10% of patients in clinical practice receive an LVAD as destination therapy.
- Patient population consists mainly of patients on inotropic (and/or mechanical) support prior to LVAD implantation.
- Patient selection is crucial and candidates should not have significant renal, pulmonary, or hepatic dysfunction or infection.
- The available evidence suggests that a continuous flow device is superior to a pulsatile flow device.
- No controlled data available as bridge to CTX.

Recommendation in patients with severe heart failure ineligible for transplant			
Recommendation	**Patient population**	**Class[a]**	**Level[b]**
LVAD may be considered as destination treatment to reduce mortality	NYHA function class IIIB/IV LVEF ≤ 25% peak VO2 < 14 mL/kg/min†	IIb	B

a = Class of recommendation.
b = Level of evidence.
† If obtainable.
LVAD = left ventricular assist device; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association

7. Evidence tables

Table 1: Inclusion criteria in randomized clinical trials evaluatingcardiac resynchronization therapy in heart failure

Trial	Patients	NYHA class	LVEF (%)	LVEDD(mm)	SR/AF	QRS (ms)	ICD
MUSTIC-SR	58	III	≤ 35	≥ 60	SR	≥ 150	No
MIRACLE	453	III, IV	≤ 35	≥ 55	SR	≥ 130	No
MUSTIC AF	43	III	≤ 35	≥ 60	AF	≥ 200	No
PATH CHF	41	III, IV	≤ 35	NA	SR	≥ 120	No
MIRACLE ICD	369	III, IV	≤ 35	≥ 55	SR	≥ 130	Yes
CONTAK CD	227	II, IV	≤ 35	NA	SR	≥ 120	Yes
MIRACLE ICD II	186	II	≤ 35	≥ 55	SR	≥ 130	Yes
PATH CHF II	89	III, IV	≤ 35	NA	SR	≥ 120	Yes/no
COMPANION	1520	III, IV	≤ 35	NA	SR	≥ 120	Yes/no
CARE HF	813	III, IV	≤ 35	NA	SR	≥ 120	No
REVERSE	610	I, II	≤ 40	≥ 55	SR	≥ 120	Yes/no
MADIT CRT	1820	I, II	≤ 30	NA	SR	≥ 130	Yes
RAFT	1800	II, III	≤ 30	≥ 60	SR/AF	≥ 130 ≥ 200*	Yes

* Paced QRS

AF = atrial fibrillation; HF = heart failure; ICD = implantable cardioverter defibrillator; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; NA = not applicable; NYHA = New York Heart Association; SR = sinus rhythm

Table 2: Endpoints, design, and main findings of the randomized clinical trials evaluating cardiac resynchronization therapy in heart failure

Trial	Endpoints	Design	Main findings
MUSTIC-SR	6MWT, QoI, pVO_2, Hosp	Single-blinded, controlled, crossover, 6 months	CRT-P improved: 6MWT, QoL, pVO_2; reduced Hosp
MIRACLE	NYHA class, QoL, pVO_2	Double-blinded, controlled, 6 months	CRT-P improved: NYHA, pVO_2, 6MWT
MUSTIC AF	6MWT, QoI, pVO_2, Hosp	Single-blinded, controlled, crossover, 6 months	CRT-P improved all; reduction of Hosp
PATH CHF	6MWT, pVO_2	Single-blinded, controlled, crossover, 12 months	CRT-P improved: 6MWT; pVO_2
MIRACLE ICD	6MWT, QoI, Hosp	Double-blinded, ICD vs. CRT-D 6 months	CRT-D improved all from baseline (not ICD)
CONTAK CD	All-cause death + HF Hosp, pVO_2, 6MWT, NYHA class, QoL, LVEDD, LVEF	Double-blinded, ICD vs. CRT-D 6 months	CRT-D improved: pVO_2, 6MWT; reduced LVEDD and increased LVEF
MIRACLE ICD II	VE/CO_2, pVO_2, NYHA, QoL, 6MWT, LV volumes, LVEF	Double-blinded, ICD vs. CRT-D 6 months	CRT-D improved: NYHA, VE/CO_2; volumes, LVEF
COMPANION	(i) All-cause death or Hosp	Double-blinded, controlled, OMT, CRT-D, CRT-P, ~15 months	CRT-P/CRT-D: reduced (i)
CARE HF	(i) All-cause death or CV event (ii) All-cause death	Double-blinded, controlled, OMT, CRT-P, 29 months	CRT-P reduced (i) and (ii)
REVERSE	(i) % worsened by clinical composite endpoint, (ii) LVESVi, (iii) HF Hosp, (iv) all-cause death	Double-blinded, controlled, OMT, CRT-P ± ICD, 12 months	Primary endpoint NS; CRT-P/CRT-D reduced (ii) and (iii) Hosp but not (iv)
MADIT CRT	(i) HF event or death, (ii) All-cause death, (iii) LVESV	Controlled, CRTP, CRT-D, 2.4 years	CRT-D reduced (i) and (iii) but not (ii)

AF = atrial fibrillation; CRT = cardiac resynchronization therapy; CRT-P = CRT with pacemaker function; CRT-D = CRT with defibrillator function; CV = cardiovascular; HF = heart failure; Hosp = hospitalization; ICD = implantable cardioverter defibrillator; LV = left ventricular; LVEDD = left ventricular end diastolic diameter; LVEF = left ventricular ejection fraction; LVESVi = left ventricular end-systolic volume index; LVESV = left ventricular end-systolic volume; 6MWT = 6 min walk test; NYHA = New York Heart Association; NS = not significant; OMT = optimal medical therapy; pVO_2 = peak oxygen consumption; QoL = quality of life; SR = sinus rhythm; VE/CO_2 = ventilation/carbon dioxide ratio

Summary of indications for devices in patients with heart failure			
Recommendation	**Patient population**	**Class[a]**	**Level[b]**
CRT-P/CRT-D is recommended to reduce morbidity and mortality	NYHA class III/IV symptoms LVEF ≤ 35%, QRS ≥ 120 ms, SR Optimal medical therapy Class IV patients should be ambulatory	I	A
CRT preferentially by CRT-D is recommended to reduce morbidity or to prevent disease progression	NYHA class II symptoms LVEF ≤ 35%, QRS ≥ 150 ms, SR Optimal medical treatment	I	A
CRT-P/CRT-D should be considered to reduce morbidity	Permanent Atrial Fibrillation NYHA class III/IV LVEF ≤ 35%, QRS ≥ 130 ms Pacemaker dependency induced by AV nodal ablation	IIa	B
CRT-P/CRT-D should be considered to reduce morbidity	Permanent Atrial Fibrillation NYHA class III/IV LVEF ≤ 35%, QRS ≥ 130 ms Slow ventricular rate and frequent pacing	IIa	C
CRT-P/CRT-D is recommended to reduce morbidity	Class I indication for pacemaker NYHA class III/IV LVEF ≤ 35%, QRS ≥ 120 ms	I	B
CRT-P/CRT-D should be considered to reduce morbidity	Class I indication for pacemaker NYHA class III/IV LVEF ≤ 35%, QRS < 120 ms	IIa	C
CRT-P/CRT-D may be considered to reduce morbidity	Class I indication for pacemaker NYHA class II LVEF ≤ 35%, QRS < 120 ms	IIb	C
LVAD may be considered as destination treatment to reduce mortality	Ineligible for cardiac transplantation NYHA IIIB/IV symptoms LVEF ≤ 25% Peak VO_2 < 14 mL/kg/min	IIb	B

a = Class of recommendation.
b = Level of evidence.
CRT = cardiac resynchronization therapy; CRT-P = CRT with pacemaker function; CRT-D = CRT with defibrillator function; LVAD = left ventricular assist device; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; SR = sinus rhythm

Section XVI:
Cardiac Consult

1. Preoperative Cardiac Risk Assessment and Perioperative Cardiac Management in Non-Cardiac Surgery

Chapter 1
Preoperative Cardiac Risk Assessment and Perioperative Cardiac Management in Non-Cardiac Surgery* 2009

The Task Force for Preoperative Cardiac Risk Assessment and Perioperative Cardiac Management in Non-Cardiac Surgery of the European Society of Cardiology (ESC), endorsed by the European Society of Anaesthesiology (ESA)

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1. Introduction

The management of patients with pre-existing cardiovascular disease undergoing non-cardiac surgery presents the physician with additional challenges. These guidelines provide recommendations for optimal management strategies for patients presenting with cardiovascular conditions.

The risk of perioperative cardiac complications depends on the condition of the patient prior to surgery, the prevalence of co-morbidities, and the magnitude and duration of the surgical procedure. Cardiac complications can be expected in patients with documented or asymptomatic ischaemic heart disease (IHD), left

* Adapted from the ESC Guidelines on Preoperative Cardiac Risk Assessment and Perioperative Cardiac Management in Non-Cardiac Surgery (European Heart Journal 2009;30:2769-2812;doi:10.1093/eurheartj/ehp285).

ventricular (LV) dysfunction, and valvular heart disease (VHD) undergoing procedures that are associated with prolonged, haemodynamic and cardiac stress.

After major surgery the incidence of cardiac death varies between 0.5% and 1.5%, with non-fatal cardiac complications ranging between 2.0% and 3.5%. When applied to the population in the European Union member states these figures translate into 150,000 to 250,000 life-threatening cardiac complications due to non-cardiac surgical procedures annually.

The guidelines recommend a practical, stepwise evaluation of the patient, integrating cardiac risk factors and test results with the estimated stress of the planned surgical procedure. For each step the class of the recommendations and the strength of evidence is presented. This results in an individualized cardiac risk assessment with the opportunity to initiate medical therapy, coronary interventions, and specific surgical and anaesthetic techniques in order to optimise the patient's perioperative condition. Emphasis is put on a restricted use of prophylactic coronary revascularisation, as this is rarely indicated just to get the patient through surgery. The guidelines focus on non-cardiac surgery, i.e. heart disease as a potential source of complications during surgery instead of the heart as the target of therapy.

In particular, the use of prophylactic coronary revascularization prior to surgery has been evaluated and found to be rarely indicated.

Classes of recommendation

Classes of Recommendation	Definition
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.
Class IIa	Weight of evidence/opinion is in favour of usefulness/efficacy.
Class IIb	Usefulness/efficacy is less well established by evidence/opinion.
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.

Level of evidence

Level of Evidence A	Data derived from multiple randomized clinical trials or meta-analyses.
Level of Evidence B	Data derived from a single randomized clinical tria or large non-randomized studies.
Level of Evidence C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries.

2. Pathophysiology of perioperative myocardial infarction

The perioperative surgical stress response includes a catecholamine surge with associated haemodynamic stress, vasospasm, reduced fibrinolytic activity, platelet activation, and hypercoagulability. Coronary plaque rupture, leading to thrombus formation and subsequent vessel occlusion, is an important cause of acute perioperative coronary syndromes. In patients with significant IHD, myocardial infarction (MI) may thus also be caused by a sustained myocardial supply/demand imbalance due to tachycardia and increased myocardial contractility. Autopsy studies indicate that half of the fatal MIs have direct evidence of plaque disruption defined as plaque fissure or rupture and intra-plaque haemorrhage.

3. Practical preoperative cardiac risk assessment

In order to reduce the risk of perioperative cardiac complications it is essential to perform cardiac evaluation using the patient's medical history prior to the surgical procedure, for two reasons. Firstly, patients with an anticipated low cardiac risk of cardiac death and MI (< 1%) can be operated on safely without further delay. It is unlikely that risk reduction strategies can reduce the perioperative risk further (in these individuals). Secondly, risk reduction by pharmacological treatment is most cost-effective in patients with a suspected increased cardiac risk. Additional non-invasive cardiac imaging techniques are tools to identify patients at higher risk. However, imaging techniques should be reserved only for those patients in whom test results would influence and change management.

Obviously, the intensity of the preoperative cardiac evaluation must be tailored to the patient's clinical condition and the urgency of the circumstances requiring surgery. When emergency surgery is needed, the evaluation must necessarily be limited. However, most clinical circumstances allow the application of a more

extensive, systematic approach, with cardiac risk evaluation that is initially based on clinical characteristics and type of surgery, and then extended - if indicated - to resting electrocardiography (ECG), laboratory measurements, and non-invasive (stress) testing.

Step 1.

The urgency of the surgical procedure should be assessed. In urgent cases, patient or surgical specific factors dictate the strategy, and do not allow further cardiac testing or treatment. In these cases it is recommended that the consultant provides guidance on perioperative medical management, surveillance for cardiac events and continuation of chronic cardiovascular medical therapy.

Step 2.

Does the patient have an unstable cardiac condition?

- Recent (within 30 days) MI and residual ischaemia
- Unstable angina pectoris
- Acute heart failure
- Significant cardiac arrhythmias
- Symptomatic valvular heart disease

If not, proceed to step 3. In patients scheduled for elective surgery, active or unstable cardiac conditions should be clarified and treated appropriately prior to surgery and usually lead to cancellation or delay of the surgical procedure.

Step 3.

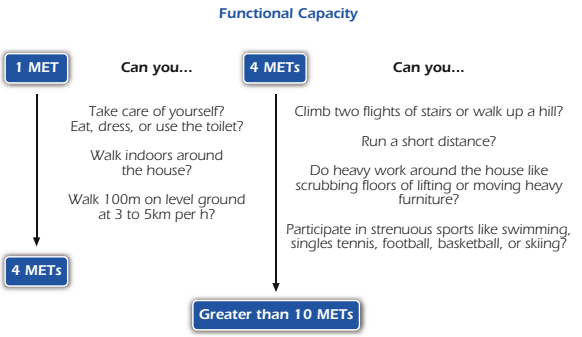
Determine the risk (%) of the surgical procedure for adverse cardiac events within 30 days after surgery (cardiac death and MI).

Low-risk < 1%	Intermediate-risk 1-5%	High-risk > 5%
• Breast • Dental • Endocrine • Eye • Gynaecology • Reconstructive • Orthopaedic - minor (knee surgery) • Urologic - minor	• Abdominal • Carotid • Peripheral arterial angioplasty • Endovascular aneurysm repair • Head and neck surgery • Neurological/ Orthopaedic - major (hip and spine surgery) • Pulmonary Renal / Liver transplant • Urologic - major	• Aortic and major vascular surgery • Peripheral vascular surgery

If the estimated cardiac risk of the procedure in cardiac stable patients is low, < 1%, it is unlikely that test results will change management and is recommended to proceeed with the planned surgical procedure. The consultant can identify risk factors and provide recommendations on life style and medical therapy according to the ESC Guidelines for postoperative care to improve long-term outcome.

Step 4.

Determination of functional capacity is considered a pivotal step in preoperative cardiac risk assessment. Functional capacity is measured in metabolic equivalents (METs). When functional capacity is high, the prognosis is excellent, even in the presence of stable IHD or risk factors. In this case perioperative management will rarely be changed as a result of further cardiac testing, so that the planned surgical procedure can proceed. The inability to climb two flights of stairs or run a short distance (< 4 METs) indicates poor functional capacity and is associated with an increased incidence of post-operative cardiac events. When functional capacity is poor or unknown, the presence and number of risk factors in relation to the risk of surgery will determine preoperative risk stratification and perioperative management.



Step 5.

Discuss the continuation of chronic aspirin therapy with the anaesthesiologist and surgeon. In patients with IHD aspirin non-adherence or withdrawal is associated with a 3-fold higher risk of postoperative cardiac events. Discontinuation of aspirin therapy should be considered only in those patients in whom haemostasis is difficult to control during surgery and the bleeding risk outweighs the potential cardiac benefit.

Step 6.

In patients with a moderate or poor functional capacity consider the risk of the surgical procedure, as outlined. Patients scheduled for intermediate-risk surgery can proceed for surgery; statin therapy and a titrated low-dose beta-blocker regimen should be considered prior to surgery. In patients with systolic LV dysfunction, evidenced

by LV ejection fraction < 40%, angiotensin-converting enzyme (ACE) inhibitors (or angiotensin II receptor blockers (ARBs) in patients intolerant of ACE-inhibitors) are recommended before surgery. In patients with one or more cardiac risk factors a preoperative baseline ECG is recommended to monitor changes during the perioperative period.

In patients scheduled for high-risk surgery, cardiac risk factors are noted. In patients with up to 2 cardiac risk factors statin therapy and a titrated low-dose beta-blocker regimen are recommended prior to surgery. In patients with systolic LV dysfunction, evidenced by LV ejection fraction < 40%, ACE-inhibitors (or ARBs in patients intolerant of ACE-inhibitors) are recommended before surgery. Non-invasive testing in patients with ≥ 3 cardiac risk factors is recommended. Non-invasive testing may also be considered prior to any surgical procedure for patient counselling, change of perioperative management in relation to the type of surgery and anaesthesia technique.

Cardiac risk factors:

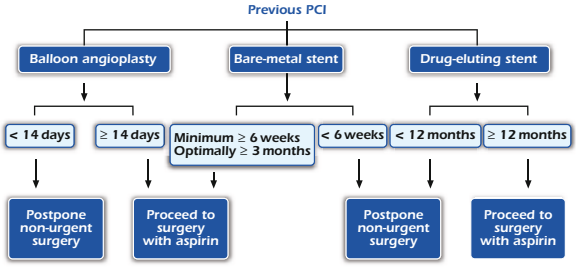
- Angina pectoris
- Prior MI
- Heart failure
- Stroke / Transient ischaemic attack
- Renal dysfunction (serum creatinine > 170 µmol/L or 2 mg/dL or a creatine clearance of < 60 mL/min)
- Diabetes requiring insulin therapy

Step 7.

Interpretation of non-invasive stress test results. Patients without stress-induced ischaemia, or mild to moderate ischaemia suggestive of 1- or 2- vessel disease, can proceed with the planned surgical procedure. It is recommended that statin therapy and a titrated low-dose beta-blocker regimen is initiated.

In patients with extensive stress-induced ischaemia assessed by non-invasive testing, individualized perioperative management is recommended taking into consideration the potential benefit of the proposed surgical procedure compared with the predicted adverse outcome. Also the effect of medical therapy and/or coronary revascularisation must be assessed, not only for the immediate postoperative outcome, but also for the long-term follow-up. In patients referred for percutaneous coronary artery intervention the initiation and duration of antiplatelet therapy will interfere with the planned surgical procedure.

- In patients referred for balloon-only angioplasty non-cardiac surgery can be performed starting from 2 weeks after intervention, with continuation of aspirin treatment.
- In patients with bare-metal stent placement non-cardiac surgery can be performed within 6 weeks to 3 months from the intervention. Dual antiplatelet (aspirin plus clopidogrel) therapy should be continued for at least 6 weeks, preferably up to 3 months. After this period, at least aspirin therapy should be continued.
- In patients with recent drug-eluting stent placement non-cardiac surgery should possibly be avoided within 12 months after intervention, during which time dual antiplatelet therapy is recommended. Surgery could be performed after 12 months keeping the patient at least on aspirin therapy.



4. Preoperative evaluation

Electrocardiography

In IHD patients, the preoperative 12 lead ECG contains important prognostic information and is predictive of long-term outcome independent of clinical findings and perioperative ischaemia.

Recommendations on ECG	Class[a]	Level[b]
Preoperative ECG is recommended for patients who have risk factor(s) and are scheduled for intermediate- or high-risk surgery	I	B
Preoperative ECG should be considered for patients who have risk factor(s) and are scheduled for low-risk surgery	IIa	B
Preoperative ECG may be considered for patients who have no risk factor and are scheduled for intermediate-risk surgery	IIb	B
Preoperative ECG is not recommended for patients who have no risk factor and are scheduled for low-risk surgery	III	B

[a] = class of recommendation; [b] = level of evidence; ECG = electrocardiography

Non-invasive testing

Preoperative non-invasive testing aims at providing information on three cardiac risk markers: LV dysfunction, myocardial ischaemia, and heart valve abnormalities, all major determinants of adverse postoperative outcome. LV function is assessed at rest and various imaging modalities are available. For ischaemia detection, exercise ECG and non-invasive imaging techniques may be used. The underlying principle here is that the diagnostic algorithm of risk stratification of myocardial ischaemia and LV function should be similar to that proposed for patients in the non-surgical setting with known or suspected IHD. Non-invasive testing should not only be considered for coronary artery revascularisation, but also for patient counselling, change of perioperative management in relation to type of surgery, anaesthetic technique, and long-term prognosis.

Recommendations on non-invasive testing	Class[a]	Level[b]
Rest echocardiography		
Rest echocardiography for LV assessment should be considered in patients undergoing high-risk surgery	IIa	C
Rest echocardiography for LV assessment is not recommended in patients undergoing low or intermediate-risk surgery	III	B
Stress testing		
Stress testing is recommended in high-risk surgery patients with ≥ 3 clinical risk factors	I	C
Stress testing may be considered in high-risk surgery patients with ≤ 2 clinical risk factors	IIb	B
Stress testing may be considered in intermediate-risk surgery	IIb	C
Stress testing is not recommended in low-risk surgery	III	C

[a] = class of recommendation; [b] = level of evidence; LV = left ventricular

5. Risk reduction strategies

The occurrence of MI during the intra- or early postoperative period is frequently preceded by prolonged or recurrent myocardial ischaemia. Two mechanisms in the context of perioperative myocardial ischaemia are important; (1) chronic mismatch in the supply-to-demand ratio of the blood flow response to the metabolic demand, which clinically resembles stable IHD due to a flow limiting stenosis in coronary conduit arteries, and (2) coronary plaque rupture presenting as acute coronary syndromes. Besides specific risk reduction strategies, preoperative evaluation is an opportunity to check and optimise the control of all cardiovascular risk factors.

Beta-blockers

Treatment onset and the choice of the optimal dose of beta-blockers are closely linked. Postoperative outcome is improved in patients who have a lower heart rate. On the other hand, bradycardia and hypotension should be avoided. This highlights the importance of preventing overtreatment with fixed high initial doses. The goal for heart rate is the same during the whole perioperative period, using intravenous administration of beta-blockers when oral administration is not possible. Postoperative tachycardia should lead first to the treatment of an underlying cause, for example hypovolaemia, pain, blood loss, or infection, rather than simply increase the beta-blocker dose.

Recommendations on beta-blockers	Class[a]	Level[b]
Dose of beta-blockers should be titrated, which requires treatment initiation optimally 30 days and at least one week before surgery. It is recommended to start with a daily dose of 2.5 mg of bisoprolol or 50 mg of metoprolol succinate and then to adjust the dose before surgery to achieve a resting heart rate between 60 and 70 beats per minute with systolic blood pressure > 100 mmHg	I	B
Beta-blockers are recommended in patients who have known IHD or myocardial ischaemia according to preoperative stress testing	I	B
Beta-blockers are recommended in patients scheduled for high-risk surgery	I	B
Continuation of beta-blockers is recommended in patients previously treated with beta-blockers because of IHD, arrhythmias, or hypertension	I	C
Beta-blockers should be considered for patients scheduled for intermediate-risk surgery	IIa	B
Continuation in patients previously treated with beta-blockers because of chronic heart failure with systolic dysfunction is recommended	IIa	C
Beta-blockers may be considered in patients scheduled for low-risk surgery with risk factor(s)	IIb	B
Beta-blockers are not recommended in patients scheduled for low-risk surgery without risk factors	III	B

[a] = class of recommendation; [b] = level of evidence; IHD = ischaemic heart disease

Statins

Patients with non-coronary atherosclerosis (carotid, peripheral, aortic, renal) should receive statin therapy for secondary prevention, independent of non-cardiac surgery. Statins also induce coronary plaque stabilisation. These so-called non-lipid or pleiotropic effects may prevent plaque rupture and subsequent MI in the perioperative period. Discontinuation of statins may cause a rebound effect and be disadvantageous. A potential limitation of perioperative statin use is the lack of intravenous formulation. Therefore statins with a long half-life time or extended release formulations, such as rosuvastatin, atorvastatin and fluvastatin extended release, are recommended to bridge the period immediately after surgery when oral intake is not feasible.

Recommendations on statins	Class[a]	Level[b]
It is recommended to start statins in high-risk surgery patients, optimally 30 days and at least one week before surgery	I	B
It is recommended to continue statins perioperatively	I	C

[a] = class of recommendation; [b] = level of evidence

Angiotensin-converting enzyme inhibitors

Independent of the blood pressure-lowering effect ACE-inhibitors preserve organ function. The inhibition of ACE may prevent events related to myocardial ischaemia and LV dysfunction. Therefore it seems that perioperative treatment with ACE-inhibitors has beneficial effects on postoperative outcome.

Recommendations on ACE-inhibitors	Class[a]	Level[b]
ACE-inhibitors are recommended in cardiac stable patients with LV systolic dysfunction scheduled for intermediate or high-risk surgery	I	C
ACE-inhibitors should be considered in cardiac stable patients with LV systolic dysfunction scheduled for low-risk surgery	IIa	C
Transient discontinuation of ACE-inhibitors before non-cardiac surgery in hypertensive patients should be considered	IIa	C

[a] = class of recommendation; [b] = level of evidence; LV = left ventricular

Anticoagulant therapy

Anticoagulant therapy is associated with increased bleeding during non-cardiac surgery. In some patients, this risk will be outweighed by the benefit of anticoagulant therapy (e.g. for recent coronary stent implantation, mechanical heart valves, atrial fibrillation), and anticoagulant therapy should be maintained or modified, whereas in other patients with low-risk of thrombosis, therapy should be stopped in order to minimize bleeding complications. Furthermore, the type of surgical procedure should be considered, as the bleeding risk varies considerably and affects the ability to perform haemostatic control. Procedures with a high-risk of serious bleeding complications are those where compression cannot be performed.

Low thromboembolic risk / low bleeding risk
• Continue anticoagulant therapy with INR in therapeutic range.
Low thromboembolic risk / high bleeding risk
• Discontinue anticoagulant therapy 5 days before the procedure.
• Start low-molecular weight heparin (LMWH) prophylaxis once daily or unfractioned heparin (UFH) intravenously 1 day after acenocoumarol interruption, and 2 days after warfarin interruption. Administer the last dose of LMWH at least 12 hours before the procedure or give UFH intravenously up to 4 hours prior to surgery.
• Resume LMWH or UFH at pre-procedural dose 1 to 2 days (at least 12 hours) after the procedure according to haemostatic status. Resume anticoagulant therapy 1 to 2 days after surgery at pre-procedural dose + 50% boost dose for 2 consecutive days according to the haemostatic status.
• LMWH or UFH is continued until the INR has returned to therapeutic levels.
High thromboembolic risk
• Discontinue anticoagulant therapy 5 days before the procedure.
• Start therapeutic LMWH twice daily or UFH intravenously 1 day after acenocoumarol interruption, and 2 days after warfarin interruption. Administer the last dose of LMWH at least 12 hours before the procedure or give UFH intravenously up to 4 hours prior to surgery.
• Resume LMWH or UFH at pre-procedural dose 1 to 2 days (at least 12 hours) after the procedure according to haemostatic status. Resume anticoagulant therapy 1 to 2 days after surgery at pre-procedural dose + 50% boost dose for 2 consecutive days according to haemostatic status.
• LMWH or UFH is continued until the INR has returned to therapeutic levels.

INR = international normalized ratio; LMWH = low molecular weight heparin; UFH = unfractionated heparin

Anticoagulation protocols using LMWH applied according to the patient thromboembolic risk.				
	Patients at high thromboembolic risk		Patients at low thromboembolic risk	
Weight kg	Nadroparin (Twice Daily, SC) (IU)	Enoxaparin (Twice Daily, SC) (IU)	Nadroparin (Once Daily, SC) (IU)	Enoxaparin (Once Daily, SC) (IU)
< 50	2850	2000	2850	4000
50-69	3800	4000	3800	4000
70-89	5700	6000	5700	4000
90-110	7600	8000	5700	4000
> 110	9500	10000	5700	4000

Revascularisation

The main objective of prophylactic myocardial revascularisation is the prevention of potentially lethal perioperative MI. While revascularisation may be particularly effective in treating high-grade stenoses, it cannot prevent rupture of vulnerable plaques during the stress of surgery. The latter mechanism has been advocated in at least half of fatal cases of perioperative MI and may explain the lack of specificity of stress imaging techniques in predicting infarct-related coronary artery lesions.

Recommendations for prophylactic revascularisation in stable/ asymptomatic patients	Class[a]	Level[b]
Prophylactic myocardial revascularisation prior to high-risk surgery may be considered in patients with proven IHD	IIb	B
Prophylactic myocardial revascularisation prior to intermediate-risk surgery in patients with proven IHD is not recommended	III	B
Prophylactic myocardial revascularisation prior to low-risk surgery in patients with proven IHD is not recommended	III	C

[a] = class of recommendation; [b] = level of evidence; IHD = ischaemic heart disease

Recommendations on type of prophylactic revascularisation in stable patients	Class[a]	Level[b]
CABG should be considered to improve prognosis and relieve symptoms in patients with significant left main disease or its equivalent, for significant three vessel disease, in particular in case of depressed LV function	IIa	A
PCI should be considered to improve symptoms in stable symptomatic patients with single or multivessel disease in whom the intervention is technically suitable and in whom the procedural risk does not outweigh potential benefits	IIa	A
Recommendations on prophylactic myocardial revascularisation in patients with unstable IHD	**Class[a]**	**Level[b]**
If non-cardiac surgery can be postponed safely, it is recommended to diagnose and treat patients in line with the guidelines on unstable angina management[1]	I	A
In the unlikely combination of a life-threatening clinical condition requiring urgent non-cardiac surgery and a combination of an acute coronary syndrome, it is recommended to give priority to surgery	I	C
However, on follow-up, aggressive medical treatment and myocardial revascularisation according to the ESC Guidelines on NSTE-ACS[1] and STEMI[2] is recommended	I	B
If PCI is indicated, the use of bare-metal stents or even balloon angioplasty is recommended	I	C

[a] = class of recommendation; [b] = level of evidence; CABG = coronary artery bypass grafting; IHD = ischaemic heart disease; LV = left ventricular; NSTE-ACS = non-ST-segment elevation-acute coronary syndrome; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction

Recommendations on timing of non-cardiac surgery in cardiac stable/asymptomatic patients with prior revascularisation	Class[a]	Level[b]
It is recommended to perform non-cardiac surgery in patients with recent bare-metal stent implantation after a minimum of 6 weeks and optimally 3 months following the intervention	I	B
It is recommended to perform non-cardiac surgery in patients with recent drug-eluting stent implantation after 12 months following the intervention	I	B
It is recommended to send patients with previous CABG in the last 5 years for non-cardiac surgery without further delay	I	C
It should be considered to postpone non-cardiac surgery in patients with recent balloon angioplasty for 2 weeks following the intervention	IIa	B

[a] = class of recommendation; [b] = level of evidence; CABG = coronary artery bypass grafting

6. Specific diseases

Chronic heart failure (CHF)

The prevalence of CHF in the adult population has been estimated between 1.2% and 1.8% and increases to 8% in patients over 75 years. Elderly patients with chronic heart failure scheduled for vascular surgery have higher risks of operative mortality and hospital readmission.

Recommendations on Chronic Heart Failure	Class[a]	Level[b]
It is recommended to continue or to initiate ACE-inhibitors (or ARBs in patients intolerant of ACE-inhibitors) during intermediate or high-risk surgery in stable patients with LV systolic dysfunction	I	C
Diuretics are recommended in heart failure patients with signs or symptoms of congestion	I	A

[a] = class of recommendation; [b] = level of evidence; ARBs = angiotensin receptor blockers; LV = left ventricular

Valvular heart disease (VHD)

Patients with VHD are at higher risk for perioperative cardiovascular complications during non-cardiac surgery. Echocardiography should be performed in patients with known or suspected VHD to assess its severity and consequences.

Recommendations on Valvular Heart Disease	Class[a]	Level[b]
In the presence of severe VHD it is recommended to perform a clinical and echocardiographic evaluation and, if needed, treatment before non-cardiac surgery	I	C

[a] = class of recommendations; [b] = level of evidence; VHD = valvular heart disease

Aortic stenosis (AS) is the most common VHD. Severe AS (defined as aortic valve area < 1cm^2, < 0.6cm^2/m^2 body surface area) constitutes a well-established risk factor for perioperative mortality and MI.

Recommendations on Valvular Heart Disease	Class[a]	Level[b]
In the case of urgent non-cardiac surgery in patients with severe AS, procedures should be performed under haemodynamic monitoring	IIa	C
In symptomatic patients aortic valve replacement should be considered before elective surgery	IIa	A
In patients who are not candidates for valve replacement due to either high-risk associated with serious co-morbidities or to refusal by the patient, balloon aortic valvuloplasty or transcatheter valve implantation may be a reasonable therapeutic option before surgery	IIb	C

[a] = class of recommendation; [b] = level of evidence; AS = aortic stenosis

In asymptomatic patients with significant mitral stenosis (MS) (valve area < 1.5 cm^2) and systolic pulmonary artery pressure > 50 mmHg and in symptomatic patients, the risk related to the non-cardiac procedure is high. Patients may benefit from percutaneous mitral commissurotomy (or open surgical repair) particularly before high-risk surgery.

Non-cardiac surgery can be performed at relatively low-risk in patients with non-significant MS (valve area > 1.5 cm^2) and in asymptomatic patients with significant MS (valve area < 1.5 cm^2) and systolic pulmonary artery pressure < 50 mmHg.

Non-significant *aortic regurgitation* (AR) and *mitral regurgitation* (MR) do not independently increase the risk of cardiovascular complications during non-cardiac surgery. In asymptomatic patients with preserved LV function and severe MR or AR, non-cardiac surgery can be performed at low risk. Symptomatic patients or patients with depressed LV function (EF < 30%) are at high-risk of cardiovascular complications and non-cardiac surgery should be performed only if strictly needed.

Patients who have a prosthetic valve can undergo non-cardiac surgery without additional risk when there is no evidence of valve or ventricular dysfunction. In these patients endocarditis prophylaxis is recommended according to ESC Guidelines[3].

7. Perioperative cardiac monitoring

Blood glucose

Diabetes mellitus is an important risk factor for perioperative cardiac complications and death. This condition promotes atherosclerosis, endothelial dysfunction and activation of platelets and proinflammatory cytokines. Surgical stress is associated with haemodynamic stress and vasospasm and further enhances the prothrombotic state, while inhibiting fibrinolysis. This may lead to instability of pre-existing coronary plaques, thrombus formation, vessel occlusion and MI. Also hyperglycaemia in the absence of established diabetes plays an important role, emphasizing the need for preoperative management of hyperglycaemia where possible.

Recommendations on perioperative glucose control and management	Class[a]	Level[b]
Postoperative prevention of hyperglycaemia (targeting levels at least below 10.0 mmol/L (180 mg/dL) with intensive insulin therapy in adults after high-risk or complicated major surgery requiring admission to ICU is recommended	I	B
Intraoperative and postoperative prevention of hyperglycaemia with insulin therapy may be considered after uncomplicated elective surgery	IIb	C

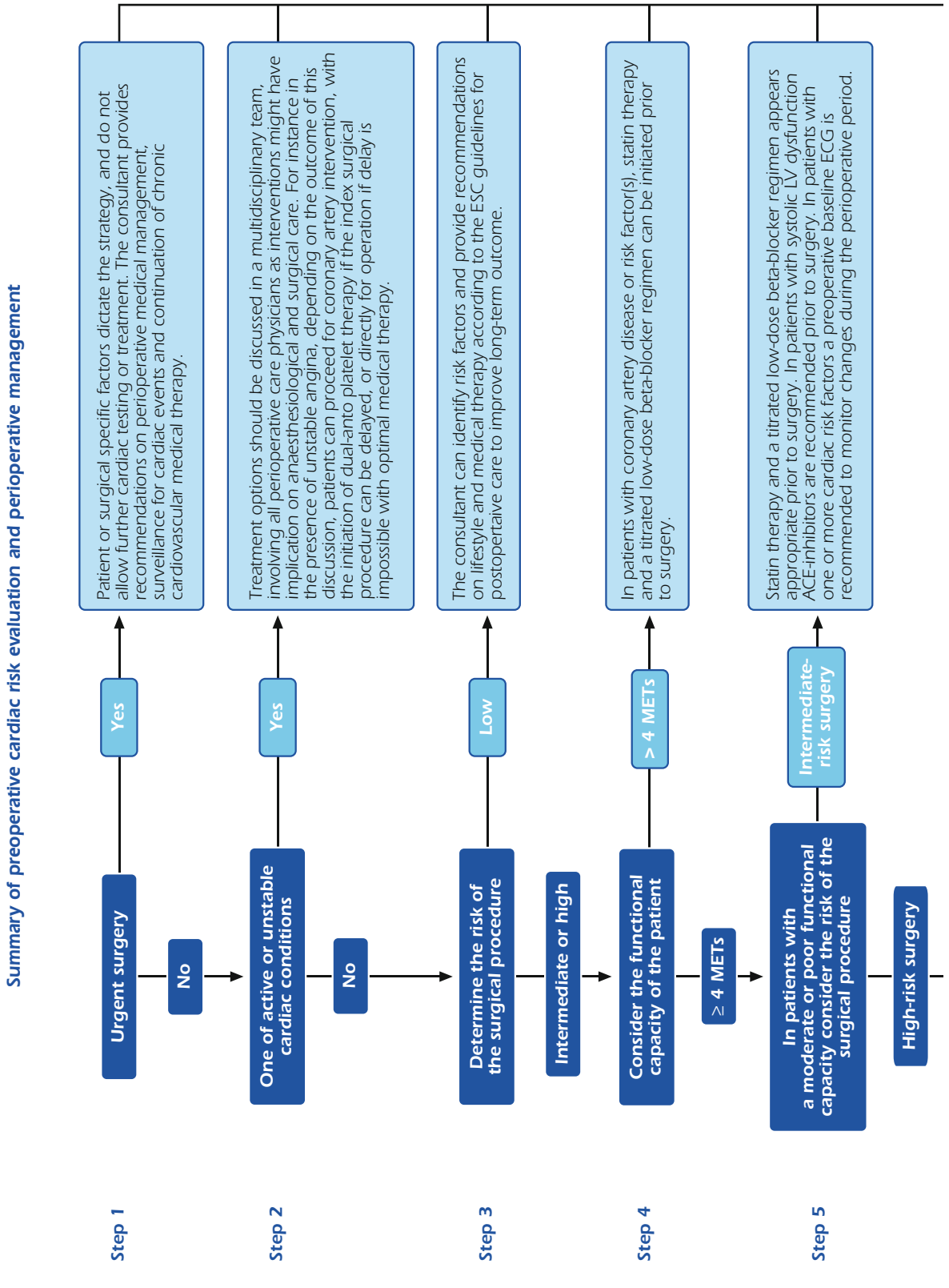
[a] = class of recommendation; [b] = level of evidence; ICU = intensive care unit

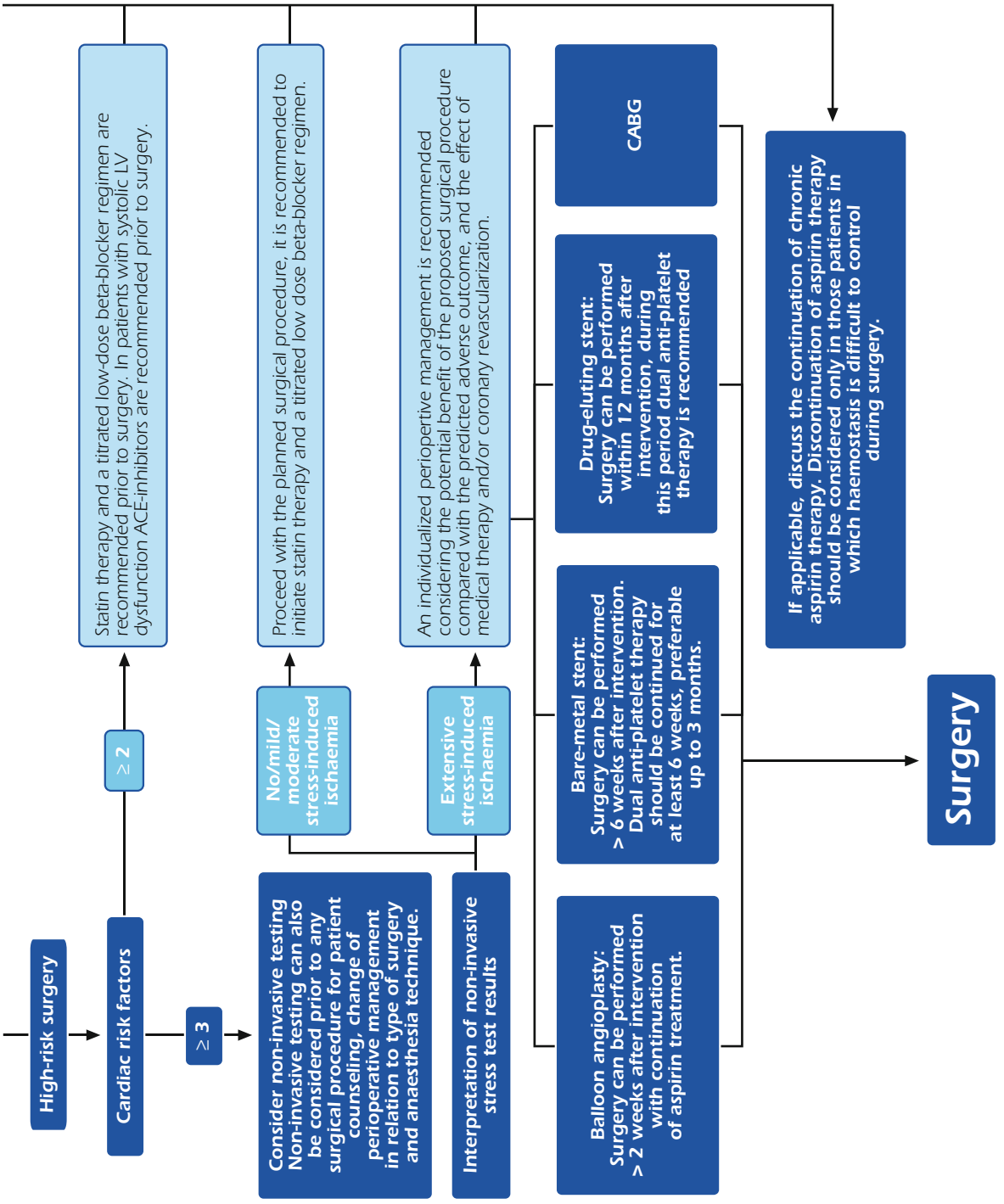
Anaesthesia

An optimal perioperative course stems from a close cooperation between cardiologists, surgeons, pulmonologists, and anaesthesiologists. The choice of the anaesthetic agent has been considered to be of little importance with regard to patients' outcome provided the vital functions are adequately supported. Most anaesthetic techniques reduce sympathetic tone leading to vasodilatation and reduction in systemic blood pressure. Thus, anaesthesiological management must ensure the proper maintenance of organ perfusion pressure.

Recommendation on anaesthesia	Class[a]	Level[b]
It should be considered to perform thoracic epidural anaesthesia in high-risk surgery in patients with cardiac disease	IIa	A

[a] = class of recommendation; [b] = level of evidence


Summary of preoperative cardiac risk evaluation and perioperative management
Step 1
Urgent surgery
Yes
Patient or surgical specific factors dictate the strategy, and do not allow further cardiac testing or treatment. The consultant provides recommendations on perioperative medical management, surveillance for cardiac events and continuation of chronic cardiovascular medical therapy.
No
Step 2
One of active or unstable cardiac conditions
Yes
Treatment options should be discussed in a multidisciplinary team, involving all perioperative care physicians as interventions might have implication on anaesthesiological and surgical care. For instance in the presence of unstable angina, depending on the outcome of this discussion, patients can proceed for coronary artery intervention, with the initiation of dual-anto platelet therapy if the index surgical procedure can be delayed, or directly for operation if delay is impossible with optimal medical therapy.
No
Step 3
Determine the risk of the surgical procedure
Low
The consultant can identify risk factors and provide recommendations on lifestyle and medical therapy according to the ESC guidelines for postopertaive care to improve long-term outcome.
Intermediate or high
Step 4
Consider the functional capacity of the patient
> 4 METs
In patients with coronary artery disease or risk factor(s), statin therapy and a titrated low-dose beta-blocker regimen can be initiated prior to surgery.
≥ 4 METs
Step 5
In patients with a moderate or poor functional capacity consider the risk of the surgical procedure
Intermediate-risk surgery
Statin therapy and a titrated low-dose beta-blocker regimen appears appropriate prior to surgery. In patients with systolic LV dysfunction ACE-inhibitors are recommended prior to surgery. In patients with one or more cardiac risk factors a preoperative baseline ECG is recommended to monitor changes during the perioperative period.
High-risk surgery


High-risk surgery
Cardiac risk factors
≥ 2
Statin therapy and a titrated low-dose beta-blocker regimen are recommended prior to surgery. In patients with systolic LV dysfunction ACE-inhibitors are recommended prior to surgery.
≥ 3
Step 6
Consider non-invasive testing
Non-invasive testing can also be considered prior to any surgical procedure for patient counseling, change of perioperative management in relation to type of surgery and anaesthesia technique.
Step 7
No/mild/ moderate stress-induced ischaemia
Proceed with the planned surgical procedure, it is recommended to initiate statin therapy and a titrated low dose beta-blocker regimen.
Extensive stress-induced ischaemia
An individualized periopertive management is recommended considering the potential benefit of the proposed surgical procedure compared with the predicted adverse outcome, and the effect of medical therapy and/or coronary revascularization.
Interpretation of non-invasive stress test results
Balloon angioplasty: Surgery can be performed > 2 weeks after intervention with continuation of aspirin treatment.
Bare-metal stent: Surgery can be performed > 6 weeks after intervention. Dual anti-platelet therapy should be continued for at least 6 weeks, preferable up to 3 months.
Drug-eluting stent: Surgery can be performed within 12 months after intervention, during this period dual anti-platelet therapy is recommended
CABG
If applicable, discuss the continuation of chronic aspirin therapy. Discontinuation of aspirin therapy should be considered only in those patients in which haemostasis is difficult to control during surgery.
Surgery

Step	Urgency	Cardiac Condition	Type of Surgery	Functional Capacity	Number of Clinical Risk Factors	LV Echo
1	Urgent surgery					III C
2	Elective surgery	Unstable				I C
3	Elective surgery	Stable	Low-risk (< 1%)		None	III B
					> 1	III B
4				Excellent or good		III B
5	Elective surgery		Intermediate risk (1 - 5%)	Moderate or poor	None	III B
					≥ 1	III B
6	Elective surgery		High-risk (> 5%)	Moderate or poor	≤ 2	IIa C
					≥ 3	IIa C

Risk factors: angina pectoris, MI, heart failure, stroke/transient ischaemic attack, renal dysfunction (creatinine > 170 μmol/L or 2 mg/dL or a creatine clearance of < 60 mL/min.), diabetes mellitus. Type of surgery: risk of MI and cardiac death within 30 days after surgery.

* Non-invasive testing not only for revascularization but also for patient counselling, change of perioperative management in relation to type of surgery and anaesthesia technique. ** Initiation of medical therapy, but in case of emergency surgery continuation of current medical therapy. Aspirin should be continued after stent replacement *** In the presence of LV dysfunction (ejection fraction < 40%). **** Class I recommendations for revascularisation are consistent with the 2004 ACC/AHA guidelines: 1. stable angina and significant

ECG	Stress Testing*	Beta-blockers**	ACE-inhibitors**/***	Aspirin**	Statins**	Coronary Revascularisation ****
IIa C	III C	I C	I C	I C	I C	III C
I C	III C					I C
III B	III C	III B	IIa C	IIb C	IIa B	III C
IIa B	III C	IIb B (titration)	IIa C	IIb C	IIa B	III C
IIa B	III C	IIb B (titration)	IIa C	IIb C	IIa B	III C
IIb B	IIb C	IIa B (titration)	I C	IIb C	IIa B	III B
I B	IIb C	IIa B (titration)	I C	IIb C	IIa B	III B
I B	IIb B	I B (titration)	I C	IIb C	I B	IIb B
I B	I C	I B (titration)	I C	IIb C	I B	IIb B

left main disease; 2. stable angina and 3-vessel disease, especially when LV ejection fraction < 50%; 3. stable angina and 2-vessel disease with significant proximal left anterior descending coronary artery stenosis and either LV ejection fraction < 50% or demonstrable ischaemia on non-invasive testing; 4. high risk unstable angina or non-STEMI; 5. acute STEMI

ECG = electrocardiography; LV = left ventricular; MI = myocardial infarction; STEMI = ST-segment elevation myocardial infarction

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European Heart Journal 2008; 29(23): 2909-45.

(3) Habib G, Hoen B, Tornos P, Thuny F, Prendergast B, Vilacosta I, et al. Guidelines on the prevention, diagnosis, and treatment of infective endocarditis (new version 2009).
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Glossary

6MWT	Six Minute Walk Test
A	Atrial
AA	Antiarrhythmic
AAD	Antiarrhythmic Drugs
AAIR	Rate responsive single chamber pacemaker that senses/paces in the atrium and is inhibited by intrinsic rhythm
ACC	American College of Cardiology
ACE	Angiotensin Converting Enzyme
ACEF	age, creatinine, ejection fraction
ACEI or ACE-I	ACE-Inhibitors
ACS	Acute Coronary Syndrome
ACT	Activated Clotting Time
ADA	Adenosine Deaminase
ADH	Antidiuretic Hormone
ADP	Adenosine Diphosphate
AED	Automated External Defibrillator
AF	Atrial Fibrillation
AF CL	Atrial Fibrillation Cycle Length
AFP	Alpha-Feto Protein
AHA	American Heart Association
AHF	Acute Heart Failure
ALS	Advanced Life Support
ALTE	Apparent Life-Threatening Events
AMI	Acute Myocardial Infarction
ANA	Antinuclear Antibodies
ANF	Autonomic Failure
ant.	anterior
ant. RP	anterograde Refractory Period
ANS	Autonomic Nervous System
ANTITACHY	Antitachycardia algorithms in pacemaker
AP	Antero-Posterior
AP	Accessory Pathway
ApoA	Apolipoprotein A
ApoB	Apolipoprotein B
aPTT	activated Partial Thromboplastin Time
APPT	Activated Partial Prothrombin Time
AR	Aortic Regurgitation
ARB	Angiotensin Receptor Blocker
ARR	Absolute Risk Reduction
ARVC	Arrhythmogenic Right Ventricular Cardiomyopathy
AS	Aortic Stenosis
ASA	Acetylsalicyclic Acid
ASA	Alcohol Septal Ablation
ASD	Atrial Septal Defect
ASVD	Arteriosclerotic Vascular Disease
asympt. pts.	symptomatic patients
AT	Atrial Tachycardia
ATP	Adenosine Triphosphate
ATT	Antithrombotic Trialist
AV or A-V	AtrioVentricular
AVB	Atrioventricular Block
AVNRT	AtrioVentricular Nodal Reciprocating Tachycardia
AVP	Arginine Vasopressin
AVR	Aortic Valve Replacement
AVRT	AtrioVentricular Reciprocating Tachycardia
BARI	Bypass Angioplasty Revascularization Investigation
BAS	Balloon Atrial Sepostomy
BB	Beta Blocker
BBB	Bundle Branch Block
BC	Blood Culture
BCNIE	Blood Culture Negative Infective Endocarditis
BE	Bacterial Endocarditis
b.i.d	bis in die – two times a day - twice a day
Bi-VAD	bi-ventricular assist device
BLS	Basic Life Support
BMI	Body Mass Index
BMS	Bare Metal Stent
BNP	Brain Natriuretic Peptide
BNP	B-type Natriuretic Peptide
BP	Blood Pressure
bpm	beat per minute
BRS	Baroreflex Sensitivity
BS	Brugada Syndrome

BSA	Body Surface Area
BTT	bridge to transplantation
BUN	Blood Urea Nitrogen
BV	Biventricular
CA	Calcium Antagonists
CA	Carbohydrate Antigen
CA	Cardiac Arrest
CABG	Coronary Artery Bypass Graft
CAD	Coronary Artery Disease
CAS	carotid artery stenting
cath	Cathether or Catheterization
cAVSD	complete Atrio-Ventricular Septal Defect
CCB	Calcium Channel Blocker
CCD	Congenital Cyanotic Disease
CCS	Canadian Cardiovascular Society
CCU	Coronary Care Unit
CD	Carbohydrate Dehydratase
CDRIE	Cardiac Device Related Infective Endocarditis
CE	Cardiac Event
CEA	carotid endarterectomy
cGMP	cyclic Guanosine 3'- 5' Monophosphate
CHB	Complete Heart Block
CHD	Coronary Heart Disease [congenital heart disease in X-1 & XI-1]
CHF	Congestive Heart Failure
CHF	Chronic Heart Failure
CI	Confidence Interval
CI	Cardiac Index
CIN	Contrast-Induced Nephropathy
CK	Creatinine Kinase
CKD	Chronic Kidney Disease
CK-MB	Creatinine Kinase Myocardial Band
CKMB	Creatinine Kinase Myocardial Band
Class 1c	Vaughan Williams antiarrhythmic classification
Cm	Centimeter
CMR	Cardiac Magnetic Resonance
CMV	Cytomegalovirus
CNE	Culture-Negative Endocarditis
CNS	Central Nervous System
CO	Cardiac Output
CoA	Coarctation of the Aorta
CoNS	Coagulase-Negative Staphylococci
COPD	Chronic Obstructive Pulmonary Disease
COX	Cyclo-Oxygenase
CPAP	Continuous Positive Airway Pressure
CPET	Cardiopulmonary Exercise Testing
CPG	Committee for Practice Guidelines
CPR	Cardiopulmonary Resuscitation
CPVT	Catecholaminergic Polymorphic Ventricular Tachycardia
CrCl	Creatinine Clearance
CRP	C-Reactive Protein
CRT	Cardiac Resynchronisation Therapy
CRT-D	Cardiac Resynchronization Therapy – Defibrillator
CRT-P	Cardiac Resynchronization Therapy – Pacemaker
CSM	Carotid Sinus Massage
CSNRT	Corrected Sinus Node Recovery Time
CSS	Carotid Sinus Syndrome
CT	Computerised Tomography/ Computed Tomography
CTD	Connective Tissue Diseases
CTEPH	Chronic Thromboembolic Pulmonary Hypertension
CTI	Cavotricuspid Isthmus
cTnI	Cardiac Troponin I
cTnT	Cardiac Troponin T
CTO	Chronic Total Occlusion
CTX	cardiac transportation
CUS	Compression Ultrasonography
CV	Cardiovascular
CVA	Cardiovascular Accident
CVD	Cardiovascular Disease
CW	Continuous Wave
CXR	Chest X ray
DAPT	dual antiplatelet therapy
DBP	Diastolic Blood Pressure
DC	Direct Current
DCA	Directional Coronary Atherectomy
DCM	Dilated Cardiomyopathy (Nonischaemic)
DDD	Dual chamber pacemaker that senses/ paces in the atrium/ventricle and is inhibited/triggered by intrinsic rhythm
DDDR	Rate responsive dual chamber pacemaker that senses/paces in the atrium/ventricle and is inhibited/ triggered by intrinsic rhythm
DES	Drug-Eluting Stents
DHA	Docosahexaenoic Acid
dL/dl	decilitre
DLco	Diffusion Capacity for Carbon Monoxide
DM	Diabetes Mellitus
DMF	Diabetes determined by fasting plasma glucose 7.0 mmol/L and 2-h plasma glucose ,<11.1 mmol/L
DMP	Diabetes determined by 2-h plasma glucose 11.1 mmol/L and fasting plasma glucose, <7.0 mmol/L
DNA	Deoxyribonucleic Acid
DPG	Diphosphoglyceric
DT	destination therapy
DTI	Direct Thrombin Inhibitor
DTS	Duke Treadmill Score
DVT	Deep Vein Thrombosis
EASD	European Association for the Study of Diabetes
e.g.	for example

EB-CT	Electron Beam Computer Tomography
ECG	Electrocardiogram
ECHO	Echocardiogram
ECHO	Echocardiography
ECMO	extra-corporeal membrane oxygenator
ED	Emergency Department
EDTA	Ethylenediamine Triacetic Acid
EEG	Electroencephalogram
EF	Ejection Fraction
EGM	Electrogram
EHRA	European Heart Rhythm Association
EMB	Endomyocardial Biopsy
EMS	emergency medical service/system
EP	Electrophysiological
EPA	Eicosaperntaenoic Acid
EPS	Electrophysiologic Study
ER	Emergency Room
ERA	Entothelin Receptor Antagonist
ERO	Effective Regurgitant Orifice Area
ESC	European Society of Cardiology
ESD	End Systolic Dimension
ESR	Erythrocyte Sedimentation Rate
ET	Endothelin
ET	Exercice Testing
f/u	follow-up
Factor-Xa	Activated factor-X
Fam. hist.	Familial history
FAT	Focal Atrial Tachycardia
FDG	Fluorodeoxyglucose
FFR	fractional flow reserve
FiO2	Fraction of Inspired Oxygen
FMC	First Medical Contact
FPG	Fasting Plasma Glucose
g	gram
GFR	Glomerular Filtration Rate
GI	Gastrointestinal
GIK	glucose insulin potassium
GOT	Glutamine-Oxaloacetic Transaminase
GP	General Practitioner
GPI	Glycoprotein Inhibitor
GPIIb/IIIa	Glycoprotein IIb/IIIa inhibitors
GUCH	Grown-up Congenital Heart Disease
h	hour
HB	Heart Block
Hb	haemoglobin
HbA1c	Glycated Haemoglobin
HbCT	Helical Biphasic Contrast Enhanced CT
HCM	Hypertrophic Cardiomyopathy
Hct	Hematocrit
HCTZ	Hydrochlorothiazide
HD	Heart Disease
HDL	High Density Lipoprotein
HDL-C	High Density Lipoprotein Cholesterol
HF	Heart Failure
HFA	Heart Failure Association
HFPEF	Heart Failure with Preserved Ejection Fraction
H-ISDN	Hydralazine and Isosorbide Dinitrate
HIT	Heparin-Induced Thrombocytopenia
HIV	Human Immunodeficiency Virus
HMG-CoA	beta-Hydroxy-Beta-Methylglutaryl-Coenzyme A
HOCM	Hypertrophic Obstructive Cardiomyopathy
Hosp.	Hospitalisation
HR	Hazard Ratio
HR	Heart Rate
HRCT	High Resolution Computerised Tomography
HRT	Heart Rate Turbulence
HRV	Heart Rate Variability
hs	at bed time (Hora Somni)
hsCRP	High sensitive-C-Reactive Protein
HT	Hypertension
HV	Hyperventilation [His-ventricle in XII-3]
Hx	Family History
Hypot. EST	Hypotensive response during Exercise Stress Test
i.e.	that is (id est)
IABP	Intra-Aortic Balloon Pump
ICD	Implantable Cardioverter Defibrillator
ICU	Intensive Care Unit
IDCM	Ischaemic Dilated Cardiomyopathy
IE	Infective Endocarditis
IFG	Impaired Fasting Glucose
IGH	Impaired Glucose Homeostasis
IgM	Immunoglobulin M
IGT	Impaired Glucose Tolerance
IHD	Ischaemic Heart Disease
ILR	Implantable Loop Recorder
IMT	Intima-Media Thickness
Inf. H	Infra-Hissian
INR	International Normalized Ratio
IOCM	iso-osmolar contrast media
IPAH	Idiopathic Pulmonary Arterial Hypertension
IRAF	Immediate Recurrence of Atrial Fibrillation
ISDN	Isosorbide Dinitrate
ISH	Isolated Systolic Hypertension
ITA	internal thoracic artery
IU	International Units
IV or i.v.	intravenous
IVC	Inferior Vena Cava
IVDA	Intravenous Drug Abuser
IVRT	Isovolumic Relaxation Time
IVS	Interventricular Septum
IVUS	Intra-Vascular Ultrasound
JLN	Jervell and Lange Nielsen
JVP	Jugular Venous Pressure
kg	kilogram
L	Litre
LA	Left Atrial
LA	Left Atrium

LAD	Left Anterior Descending (Coronary Artery)
LAO	Left Anterior Oblique
LBBB	Left Bundle-Branch block
LCSD	Left Cardiac Sympathetic Denervation
LCx	left circumflex
LD	Lactate Dehydrogenase
LDH	Lactate Dehydrogenase
LDL	Low Density Lipoprotein
LDL-C	Low Density Lipoprotein Cholesterol
LIPS	Lescol Intervention Prevention Study
LM	Left Main
LMWH	Low Molecular Weight Heparin
LOC	Loss of Consciousness
LOCM	low osmolar contrast media
LOE	Level of Evidence
LP	Late Potentials
Lpa	Lipoprotein a
LQTS	Long QT Syndrome
LV	Left Ventricle
LV	Left Ventricular
LVAD	Left Ventricular Assist Device
LVD d/t	MI Left Ventricular Dysfunction due to prior Myocardial Infarction
LVEDD	Left Ventricular End Diastolic Diameter
LVEDP	Left Ventricular End Diastolic Pressure
LVEF	Left Ventricular Ejection Fraction
LVESVi	Left Ventricular End-Systolic Volume Index
LVESV	Left Ventricular End-Systolic Volume
LVH	Left Ventricular Hypertrophy
LVMI	Left Ventricular Mass Index
LVOT	Left Ventricular Outflow Tract
LVOTG	Left Ventricular Outflow Tract Gradient
LVOTO	Left Ventricular Tract obstruction
LVV	Left Ventricular Volume
MACCE	major adverse cardiac and cerebral event
MACE	Major Adverse Cardiac Event
MAT	Multifocal Atrial Tachycardia
MB	Myocardial Band
MB	Myocardial Bridging
MBC	Minimum Bactericidal Concentration
MDCT	multidetector computed tomography
MDRD	Modification of Diet in Renal Disease
MET	Metabolic Equivalent
Mg	milligram
MI	Myocardial Infarction
MIC	Minimal Inhibitory Concentration min minute
Min	Minute
mL	millilitre
MLVWT	Maximal Left Ventricular Wall Thickness
mm	millimetre
mmHg	Millimetres of Mercury
mmol	millimole
mmol/L or mmol.l	millimole per litre
MODY	Maturity-Onset Diabetes in the Young
MPO	Myeloperoxidase
MPS	myocardial perfusion stress
MPV	Minimisation of Pacing in the Ventricles
MR	Mitral Regurgitation
MRA	Magnetic Resonance Arteriography
MRI	Magnetic Resonance Imaging
MRSA	Methicillin-Resistant *Staphylococcus aureus*
Ms	millisecond
MS	Metabolic Syndrome
MS	Mitral Stenosis
MSSA	Methicillin-Sensitive *Staphylococcus aureus*
MUGA	Multigated Angiogram
mV	millivolt
MV	Mitral Valve
MVA	Malignant Ventricular Arrhythmias
MVD	multivessel disease
MVP	Mitral Valve Prolapse
NA	Not Applicable
NaCl	Sodium Chloride
NCDR	National Cardiovascular Database Registry
NGR	Normal Glucose Regulation
NICM	Non-Ischaemic Cardiomyopathy
NIDCM	Non-Ischaemic Dilated Cardiomyopathy
NIH	National Institutes of Health
NIPPV	Noninvasive Positive Pressure Ventilation
NIV	Non-Invasive Ventilation
NNT	Numbers Needed to Treat
NS	Not Significant
NSAID	Non-Steroidal Anti-Inflammatory Drug
NSTE-ACS	Non-ST-segment Elevation Acute coronary Syndrome
NSTEMI	Non-ST-segment Elevation Myocardial Infarction
NSVT	Nonsustained Ventricular Tachycardia
NTG	Nitroglycerine
NT-proBNP	N-terminal Pro-Hormone Brain Natriuretic Peptide
NVE	Native Valve Endocarditis
NYHA	New York Heart Association
O_2	Oxygen
OB/Gyn	Obstetrician-Gynecologist
o.d.	once a day
OD	Organ Damage
OGTT	Oral Glucose Tolerance Test
OH	orthostatic hypotension
OMT	optimal medical therapy
op.	operative
OPT	Optimal Pharmacological Treatment
OR	Odds Ratio

OTFP	Opinion of the Task Force Panel
PA	Peripheral Artery
PAB	Premature Atrial Beat
PAC	Pulmonary Artery Catheterisation
$PaCO_2$	Arterial Carbon Dioxide Pressure (Tension)
PAD	peripheral arterial disease
PAH	Pulmonary Arterial Hypertension
PaO_2	Arterial Oxygen Pressure (Tension)
PAP	Pulmonary Arterial Pressure
pASVD	partial Atrio-Ventricular Septal Defect
PAV	Percutaneous Aortic Valvuloplasty
PCH	Pulmonary Capillary Haemangiomatosis
PCI	Percutaneous Coronary Intervention
PCM	Physical Counterpressure manoeuvres
PCR	Polymerase Chain Reaction
PCWP	Pulmonary Capillary Wedge Pressure
PDA	Personal Digital Assistant
PDA	Patent Ductus Anteriosus
PDE	Phosphodiesterase
PDEI	Phosphodiesterase Inhibitors
PE	Pulmonary Embolism
PEA	Pulmonary Endarterectomy
PEEP	Positive End-Expiratory Pressure
PES	Programmed Electrical Stimulation
PET	Positron Emission Tomography
PF4	Platelet Factor 4
PFO	Patent Foramen Ovale
PG	Plasma Glucose
PH	Pulmonary Hypertension
PHT	Pulmonary Hypertension
PJRT	Permanent Form of Junctional Reciprocating Tachycardia
PLE	Panlobular Emphysema
PLVEF	Preserved Left Ventricular Ejection Fraction
PM	PaceMaker
PMC	Percutaneous Mitral Commissurotomy
Post-MI	Post Myocardial Infarction
POTS	Postural Orthostatic Tachycardia Syndrome
PPCM	Peripartum Cardiomyopathy
PPH	Primary Pulmonary Hypertension
PS	Pulmonary Stenosis
PSVT	Paroxysmal SupraVentricular Tachycardia
PTFE	Polytetrafluoroethylene
pts.	patients
PUFA	Polyunsaturated Fatty Acids
PVB	Premature Ventricular Beat
PVC	Premature Ventricular Contraction
PVD	Pulmonary Valve Dysplasia
PVE	Prosthetic Valve Endocarditis
PVL	ParaValvular Leak
pVO_2	peak Oxygen Consumption
PVOD	Pulmonary Veno-Occlusive Disease
PVR	Pulmonary Vascular Resistance
PWP	Pulmonary Wedge Pressure
Q-Ao	QRS onset to onset of aortic flow
Q-Mit	QRS onset to onset of mitral annulus systolic wave
QOL	Quality Of Life
Q-Pulm	QRS onset to onset of Pulmonary flow
QRS	Electrocardiographic wave (complex or interval)
QRS	Ventricular Activation on ECG
QT	Electrocardiographic Interval from the beginning of QRS complex to end of the T wave
Q-Tri	QRS onset to onset of tricuspid annulus systolic wave
R vol	Regurgitant volume
RA	Right Atrial
RAAS	Renin Angiotensin Aldosterone System
RAO	Right Anterior Oblique
RA-RV	Right Atrium - Right Ventricle
RBBB	Right Bundle Branch Block
RC	right coronary
RCA	right coronary artery
RCT	randomized clinical trial
rec.	receptor(s)
RF	Radio Frequency
RF	Regurgitant Fraction
RFA	Radio Frequency ablation
RHC	Right Heart Catheterization
R-L	Right-Left
r-PA	Reteplase
RR	Risk Ratio
RRR	Relative Risk Reduction
rtPA	recombinant tissue Plasminogen Activator
RV	Right Ventricle
RVEDP	Right Ventricular Ejection Diastolic Pressure
RVH	Right Ventricular Hypertrophy
RVOT	Right Ventricular Outflow Tract
RVSP	Right Ventricular Systolic Pressure
Rx	Treatment
S	seconds
SC	subcutaneous
S/D	(ratio) Systolic/Diastolic (ratio)
SAM	Systolic Anterior Motion
SAS	Subaortic Stenosis
SBP	Systolic Blood Pressure
SCD	Sudden Cardiac Death
SCN5A	Cardiac Sodium Channel Gene
SD	Sudden Death
SES	Socio-Economic Status
SK	Streptokinase
SPECT	Single Photon Emission Computed Tomography

SpO_2	Oxygen Saturation via Pulse Oxymetry	UFH	Unfractioned Heparin
spp	Plural of "species"	ULN	Upper Limits of Normal
SR	Sinus Rhythm	URL	Upper Reference Limit
SRAF	Subacute Recurrence of Atrial Fibrillation	V	Ventricular
		V/Q	Ventilation/Perfusion
SSR	Stable Sinus Rhythm	VA	Ventricular Arrhythmias
STE-ACS	ST-Elevation Acute Coronary Syndrome	VAD	Ventricular Assist Device
		VD	vessel disease
STEMI	ST-Elevation Acute Myocardial Infarction	VE/CO_2	Minute Ventilation/Carbon Dioxide Production
STS	Society of Thoracic Surgeons	VF	Ventricular Fibrillation
SvO_2	Mixed Venous Oxygen Saturation	VHD	Valvular Heart Disease
SVA	SupraVentricular Arrhythmias	VKA	Vitamin K Antagonist
SVG	saphenous vein graft	VO_2	Oxygen Consumption
SVT	SupraVentricular Tachycardia	vs.	Against
SVR	surgical ventricular reconstruction	VSD	Ventricular Septal Defect
Sympt. VT	Symptomatic Ventricular Tachycardia	VSR	Ventricular Septal Rupture
Synd	Syndactyly	VT	Ventricular Tachyarrhythmias
TC	Total Cholesterol	VT	Ventricular Tachycardia
TCPC	Total Cavo Pulmonary Connection	VTE	Venous Thrombo-Embolism
TdP	Torsades de Pointe	VTns	non sustained Ventricular Tachycardia
TEE	Transoesophageal Echocardiography	VTs	sustained Ventricular Tachycardia
TG	Triglyceride	VVD	Pacemaker that senses in the atrium/ ventricle paces in the ventricle and is inhibited/triggered by intrinsic rhythm
TGA	Transposition of Great Artery		
TIA	Transient Ischaemic Attack		
t.i.d.	three times a day	V/Q	Scan Ventilation/Perfusion Scintigraphy
T-LOC	Transient Loss of Consciousness	VVI	Single chamber pacemaker that senses/paces in the ventricle and is inhibited by intrinsic rhythm.
TNK-tPA	Tenecteplase		
TOE	Tracheoesophageal		
TOF	Tetralogy of Fallot	VVIR	Rate-responsible single chamber pacemaker that senses/paces in the ventricle and is inhibited by intrinsic rhythm.
tPA	Alteplase		
t-PA	Tissue Plasminogen Activator		
TPG	Transpulmonary Pressure Gradient		
TR	Tricuspid Regurgitation	VVS	Vasovagal Syncope
TS	Tricuspid Stenosis	WHF	World Heart Foundation
TTE	TransThoracic Echocardiography	WHO	World Health Organization
TVR	Target Vessel Revascularization	WHO-FC	World Health Organization Functional Class
TWA	T Wave Alternans		
TX	Thromboxane	WPW	Wolff-Parkinson-White Syndrome
U	Unit	µg	microgram
UA	Unstable Angina	µmol	micromole
UAP	Unstable Angina Pectoris		

Index

Indexer: Dr Laurence Errington