Do ARB and ACEI Offer Similar Cardiovascular Protection?

Xuming, Zhang

Aug 25, 2013

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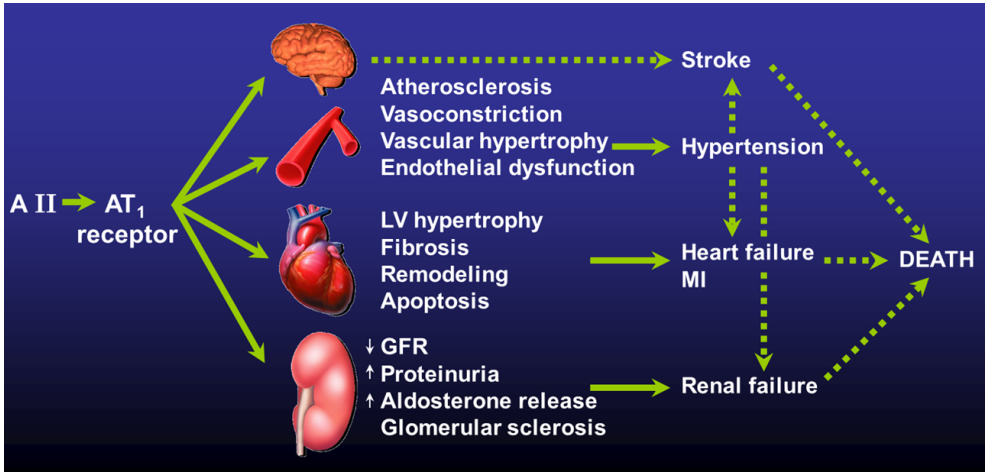
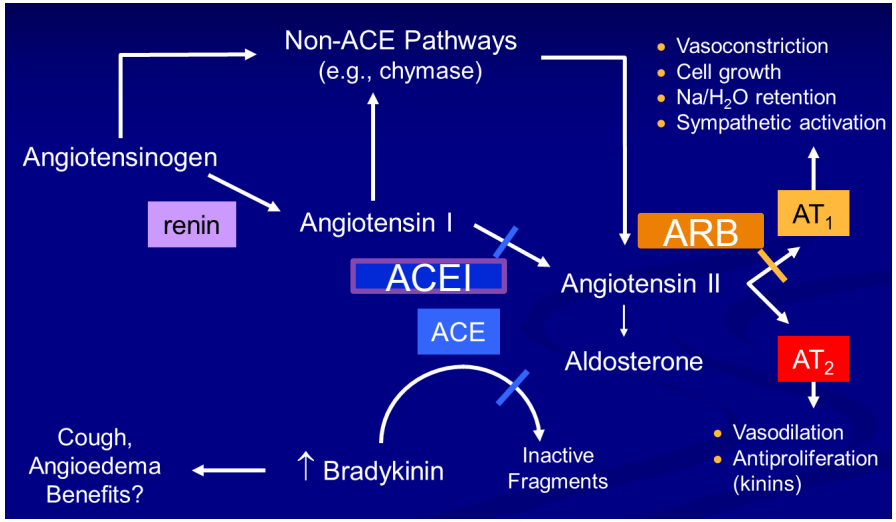
There are no conflicts of interest.

Hypertension Overview

- Number one risk factor for mortality, attributable to 13% of all deaths (worldwide annually 7.5 million deaths, WHO)
- Treatment aim at the reduction of CV morbidity and total mortality and not only of surrogates
- Treatment benefit is due to lowering of BP and independent of the drugs used.
- ACEI and ARB play an important role in prevention of CVD

Angiotensin II Plays a Central Role in End-Organ Damage



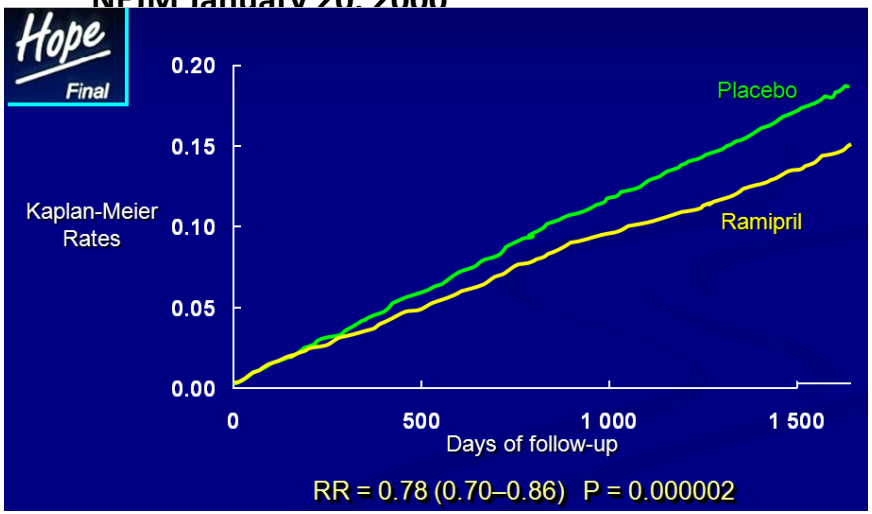


ACEI Reduce CV Events

HOPE

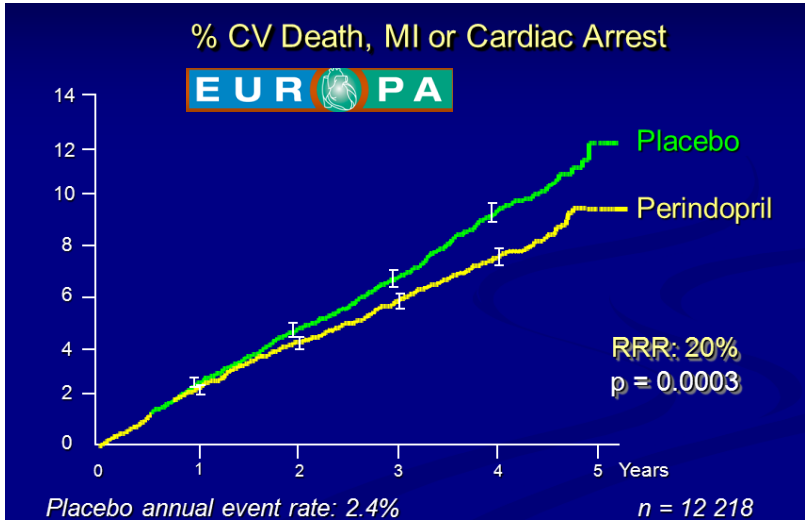
- 9297 high-risk patients, CAD or DM+1 RF, no CHF
- Ramipril vs. placebo(SBP-3mmHg)
- Ramipril yields a 22% risk reduction of death, MI, and stroke

NEJM January 20, 2000

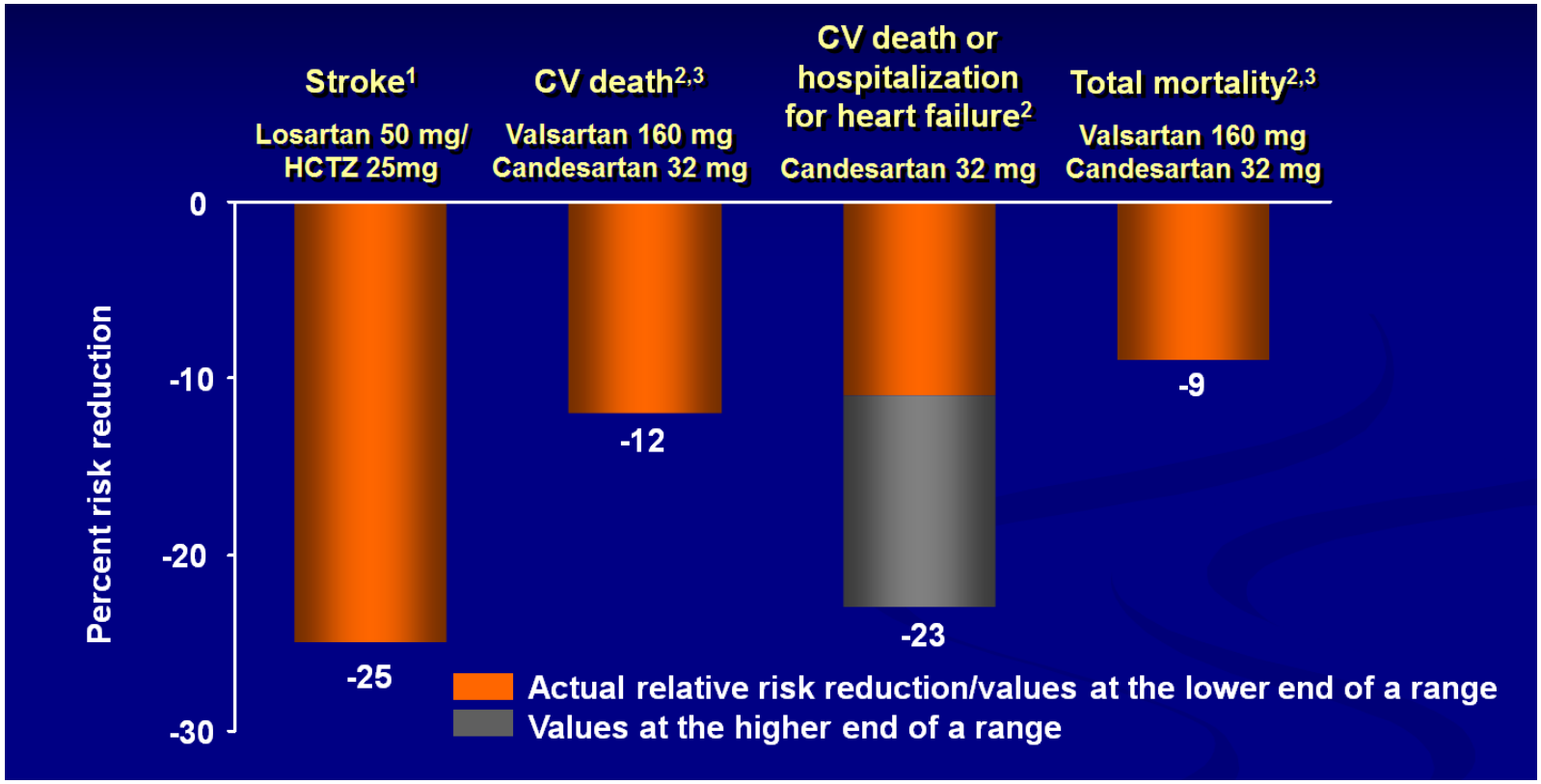


EUROPA

- 12 218 low-risk patients with stable CHD and no HF
- Perindopril vs. placebo(SBP-4.6mmHg)
- A 20% risk reduction of MI or cardiac arrest with perindopril



ARB Reduce CV Events



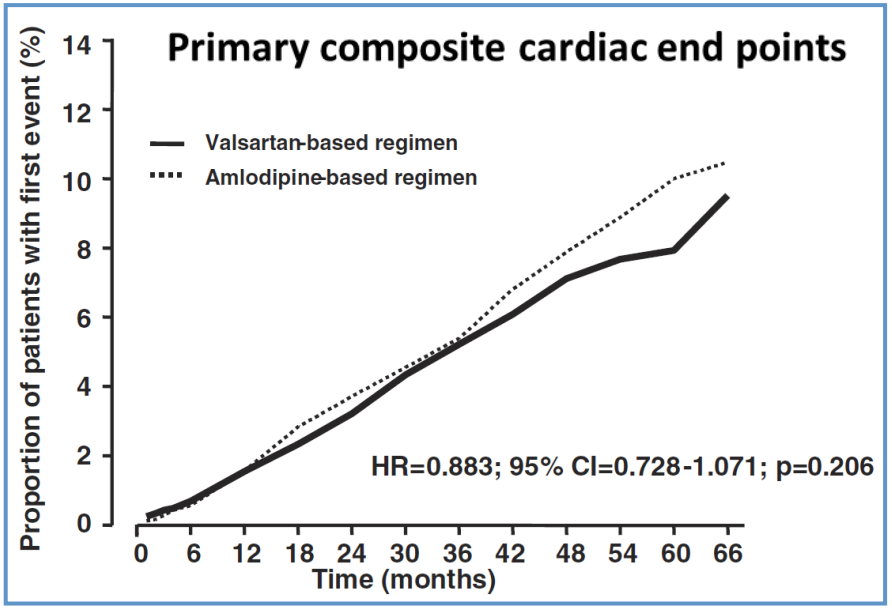
*Risk reductions are relative to placebo, with the exception of stroke, which is relative to atenolol.
CV=cardiovascular.

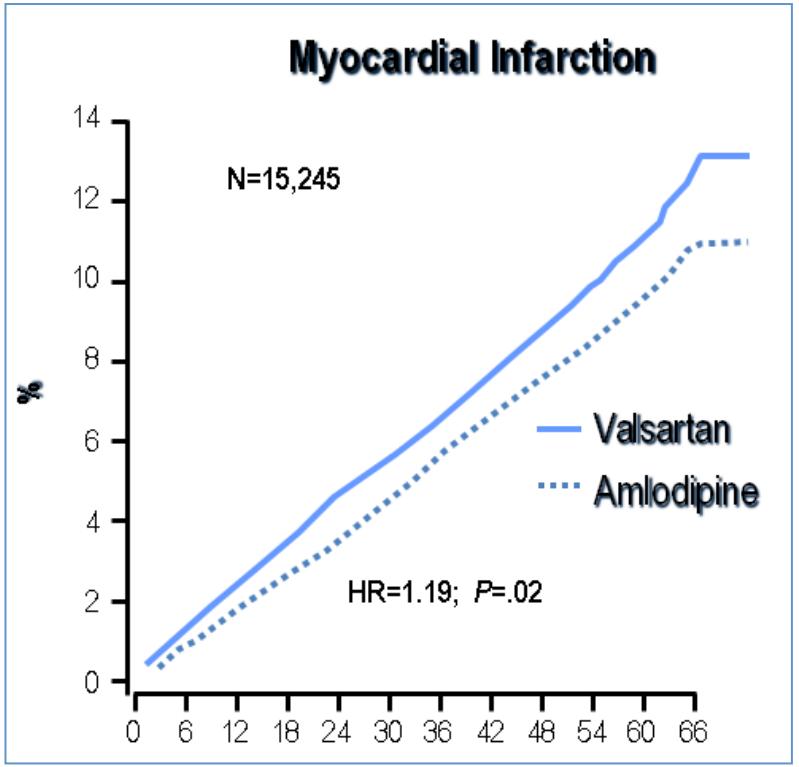
1. Dahlof B et al. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomized trial against atenolol. *Lancet*. 2002;359(9311):995-1003.
2. Cohn JN et al. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *N Engl J Med*. 2001;345(23):1667-1675.
3. Yusuf S et al. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. *Lancet*. 2003;362(9386):777-781.

VALUE

Stevo Julius, Hypertension. 2006;48:385-391.

- 15 245 high-risk HTN subjects , valsartan vs. amlodipine
- No difference found in primary cardiac end points (strokes, MI, and all-cause deaths)
- MI increase in 19%(p = 0.02) and stroke increase in 15% (p = 0.08) with valsartan treatment (lower 1.8/1.5 mmHg in amlodipine arm)





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BMJ. 2004 November 27; 329(7477): 1248–1249. PMCID: PMC534428

doi: 10.1136/bmj.329.7477.1248

Angiotensin receptor blockers and myocardial infarction

These drugs may increase myocardial infarction—and patients may need to be told

Subodh Verma, scientist

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(Email: subodh.verma@sympatico.ca)

Marty Strauss, consultant cardiologist

Key Questions

1. Do ARB increase the risk of MI and CV death ?

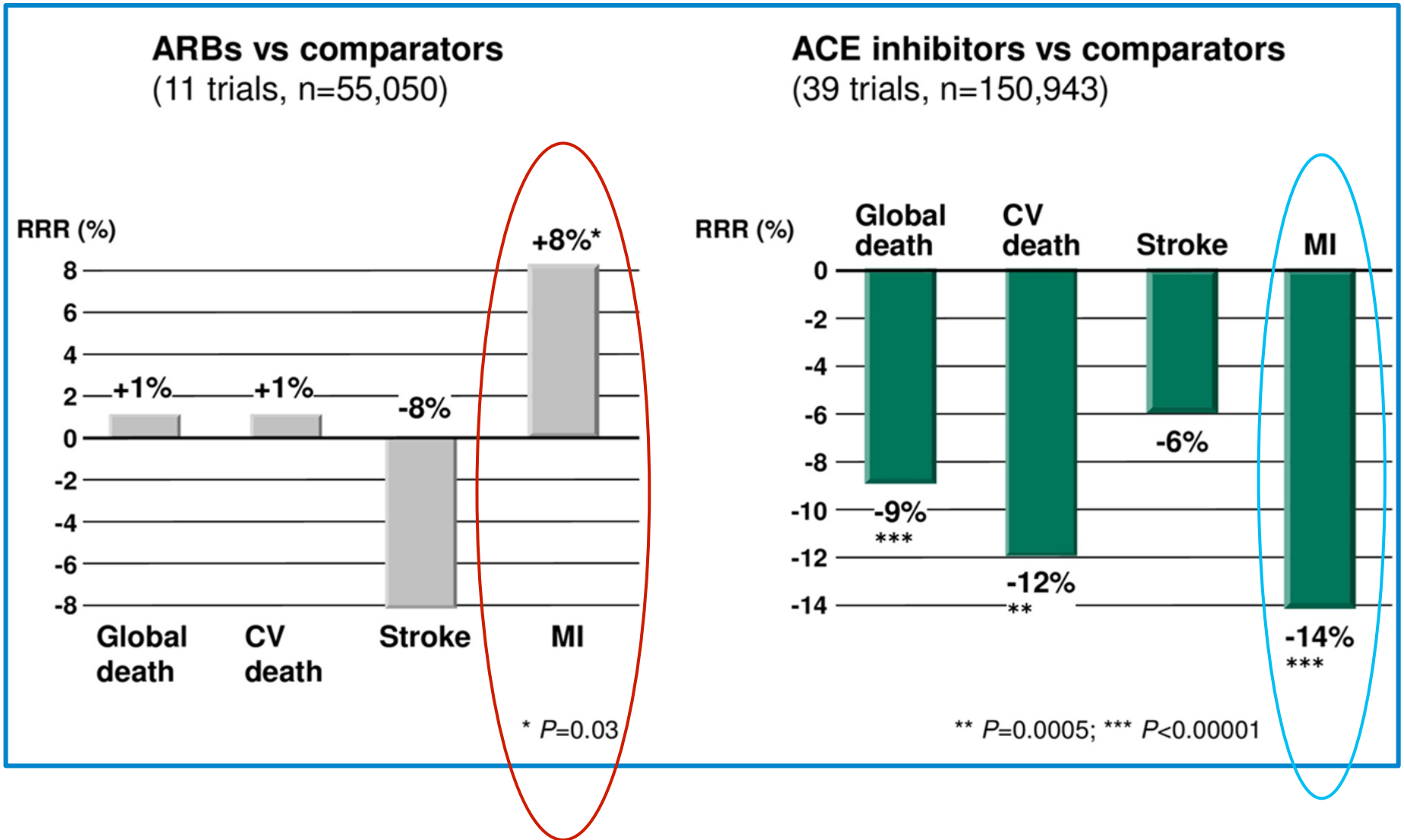
2. For HTN patients, how do ACEI and ARB differ in BP control, CV risk reduction, CV events, and other outcomes?

3. Are ACEI and ARB interchangeable and equivalent?

ARB is ACEI without cough?

Do ARB Increase Risk of MI ?

Meta-analysis by Strauss (Circulation. 2006;114:838-854)



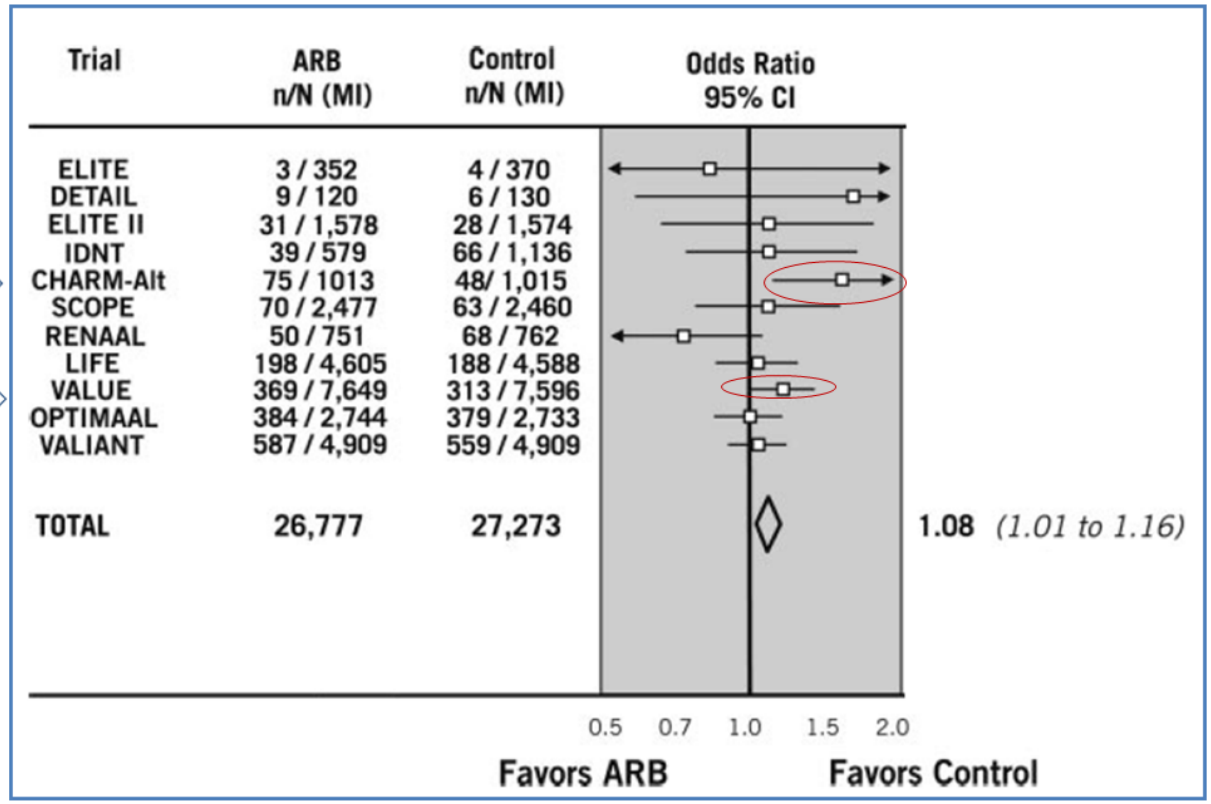
Do ARB Increase Risk of MI ?

Meta-analysis by Strauss (Circulation. 2006;114:838-854)

- 9 of 11 trials reported an excess of MI (ARB vs. placebo/ non-ACEI comparators/or ACEI)
- 2 trails with statistical significance (VALUE and CHARM-Alt)

Candesatan vs Placebo

Valsatan vs Amlodipine



-4.4/-3.9 +36% MI

Do ARB Increase Risk of MI ?

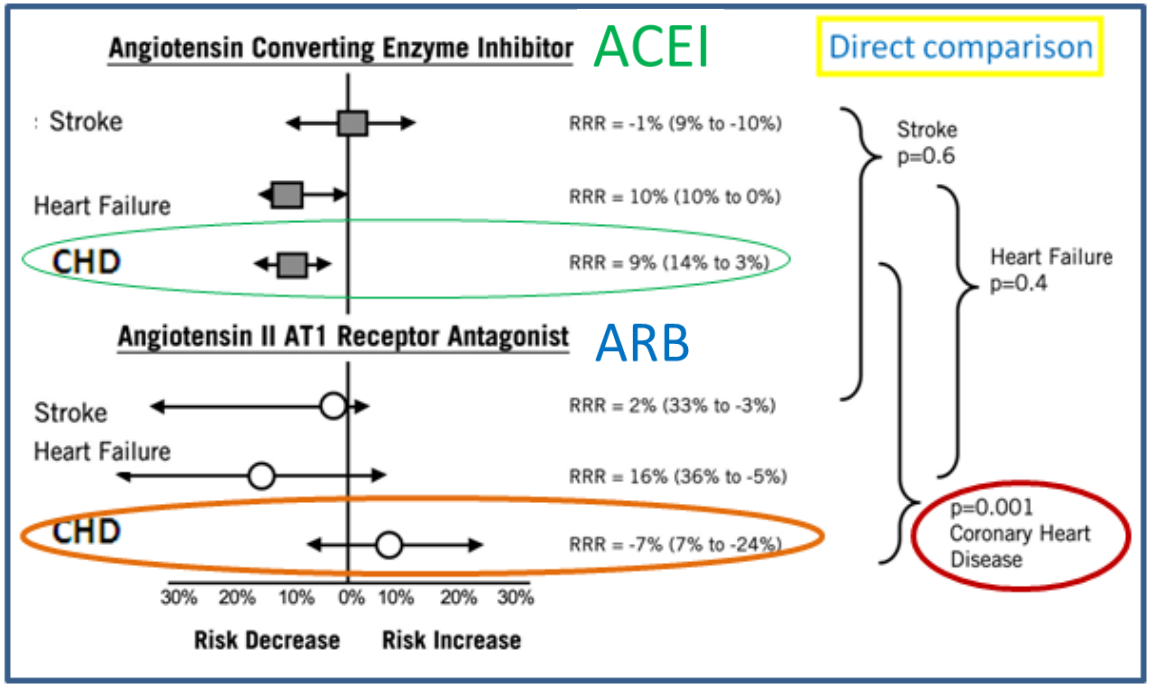
Meta-analysis by Strauss (Circulation. 2006;114:838-854)

- Both ACEI and ARB :
  - BP lowering
  - improvement of CHF symptoms
  - inhibition of diabetic renal disease
  - reduction in stroke rates
  - prevention of new onset-DM
- Different pharmacological properties
- ACEI produce marked reduction of MI and CV death in diverse patient populations, the same cannot be found in ARB

Strauss MH, Circulation 2006;114:838-854

BPLTTC 2005
ACEI vs. ARB

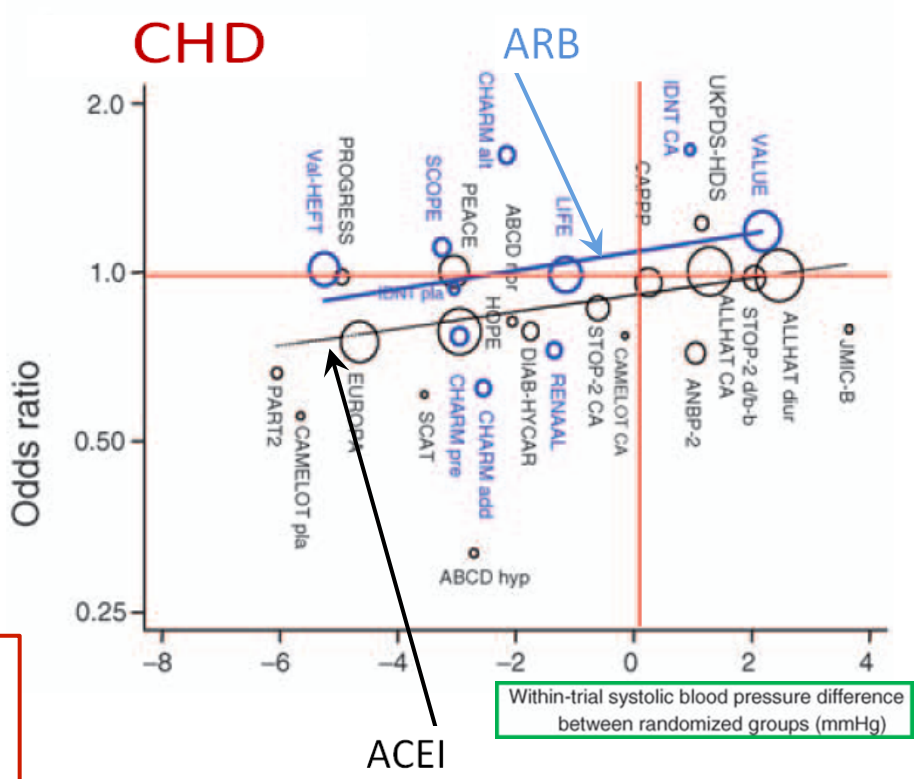
- 21 trails, N=137,356
- ACEI / comparator or ARB / comparator
- ACEI and ARB show no differences on stroke and HF
- Significant benefit of ACEI relative to ARB on MI and CV death (15% RR reduction; P=0.001)



from the 15th European Meeting on Hypertension; 2005

BPLTTC 2007
Indirect Comparisons : ACEI vs. ARB

- 26 trials ; N=146 838 patients with HTN or high risk of CVD
- ACEI / ARB vs. placebo or another class
- Similar BP-dependent effects of both for stroke, CHD and HF
- ACEI shows additional 9% risk reduction beyond the BP differences (=the effect of an additional -3 mmHg SBP)
- No such effect was observed for ARB



Journal of Hypertension 2007, 25:951–958

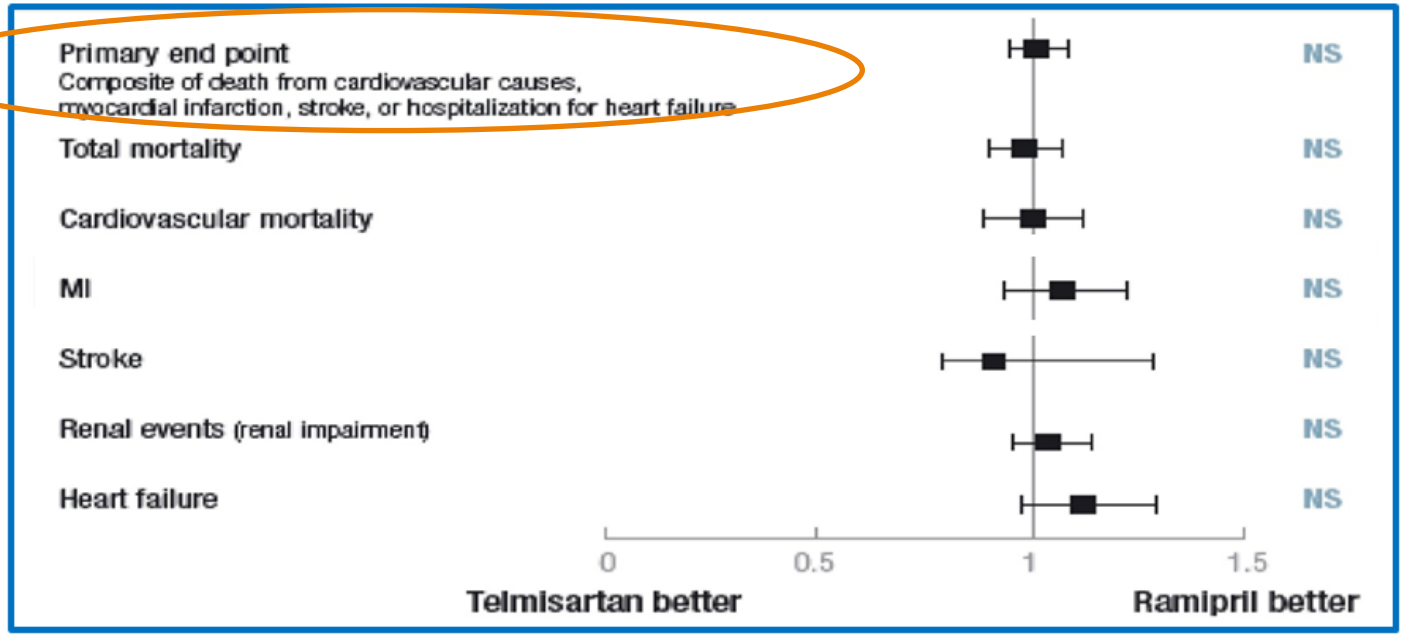
Conclusion

- There are similar BP-dependent effects of ACEI and ARB for the risks of stroke, CHD and HF.
- For ACEI, but not ARB, there is evidence of BP-independent effects on the risk of major CHD events.

ONTARGET

(N Engl JMed 2008;358:1547-59)

- The largest ARB trial , n= 25,000 patients, >55 y , with vascular disease or DM but not HF;
- Ramipril vs telmisartan or in combination
- Telmisartan showed non-inferior to ramipiril in primary outcome
- The combination resulted in no additional benefit and with more adverse effects



- (N Engl JMed 2008;358:1547-59)

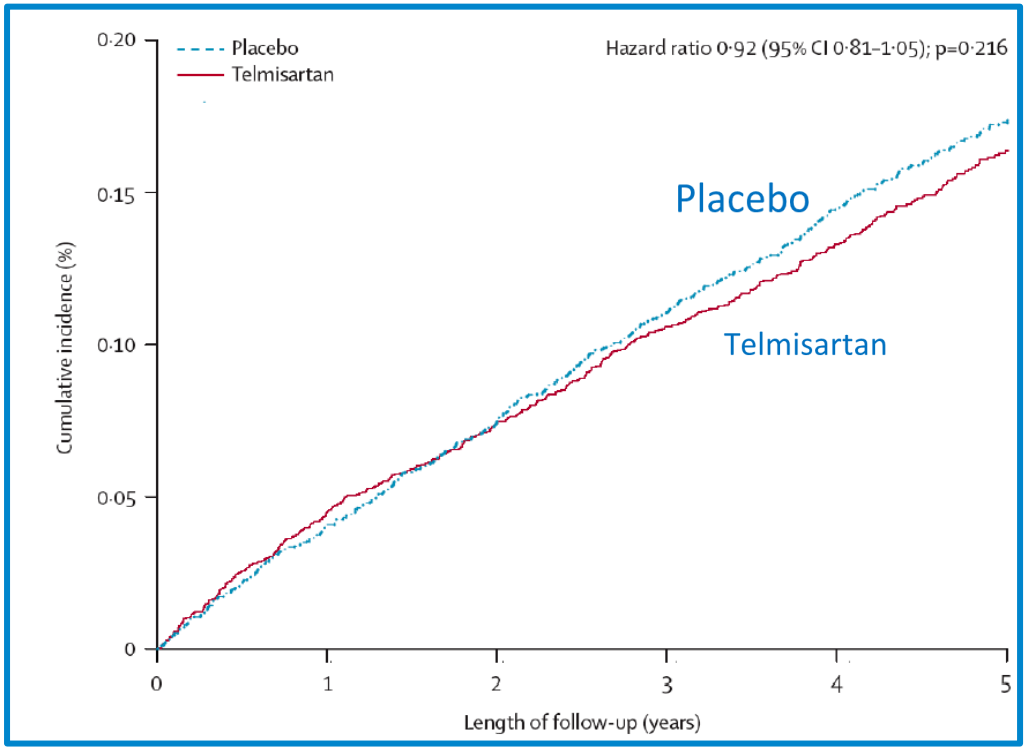
-95% ram no +adverse other? power mi/death, Comb Rx

TRENSCEND

The Lancet, Volume 372, Pages 1174 - 1183, 2008

- Similar patients as in ONTARGET, but intolerant to ACEI . N=5,926
- Telmisartan vs placebo

- BP was lower in telmisartan group by 4.0/2.2 mmHg
- No benefit in the 1st end point with telmisartan vs placebo(CV death, MI, stroke, or HF hospitalization)



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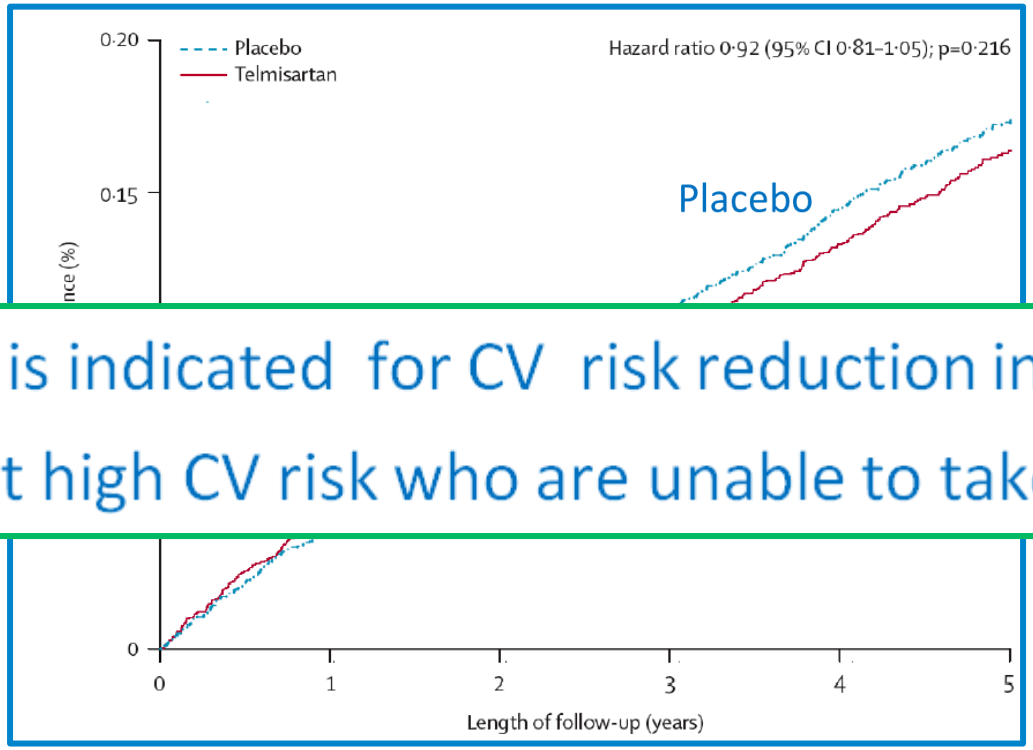
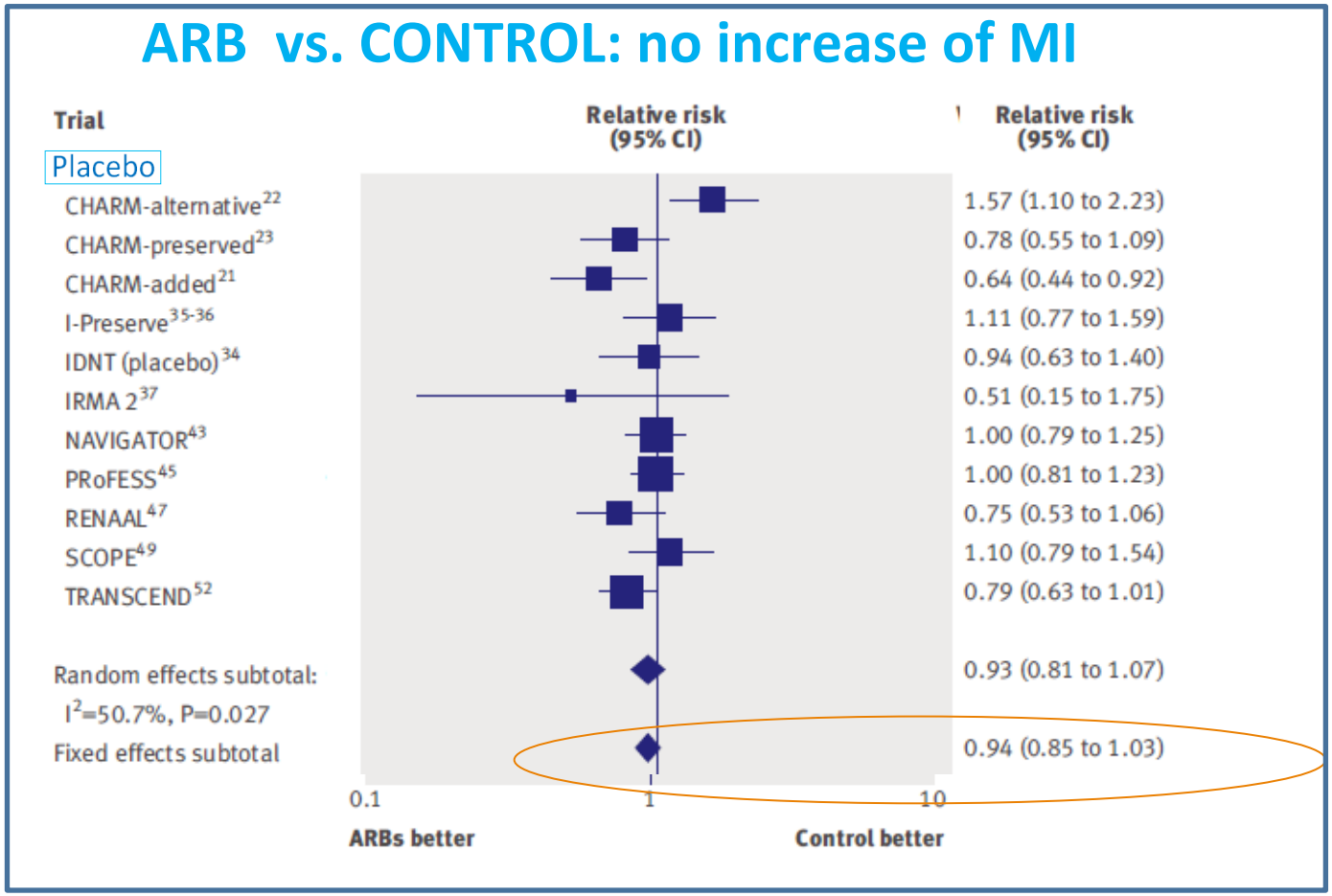


Micardis is indicated for CV risk reduction in patients ≥55 yrs at high CV risk who are unable to take ACEI

ARB and MI

Meta-analyses by Sripal Bangalore BMJ 2011;342:d2234

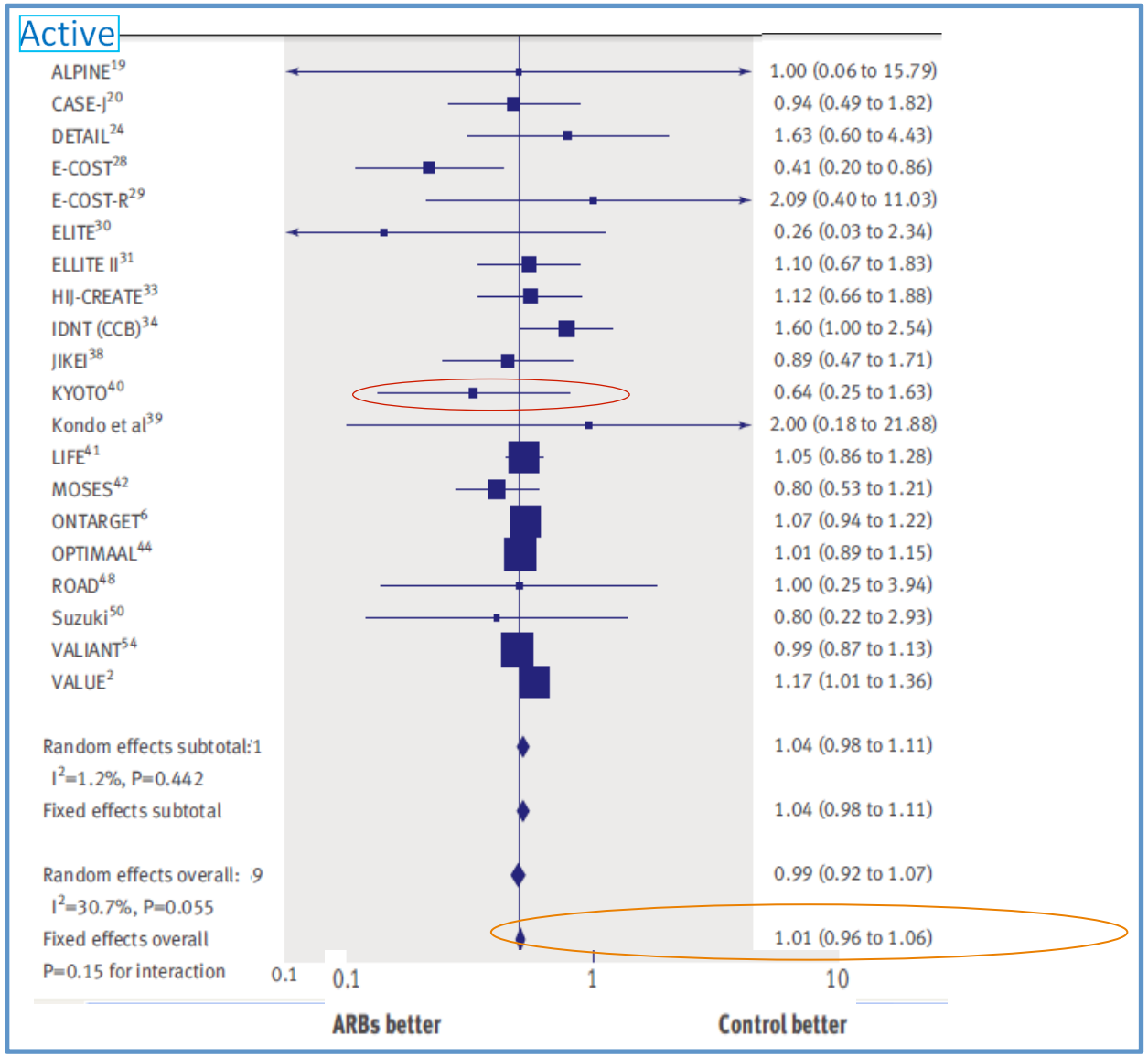
- 37 RCT, N=147 020 objects
- ARB vs. placebo/active treatment



ARB vs Active Rx: no increase of MI

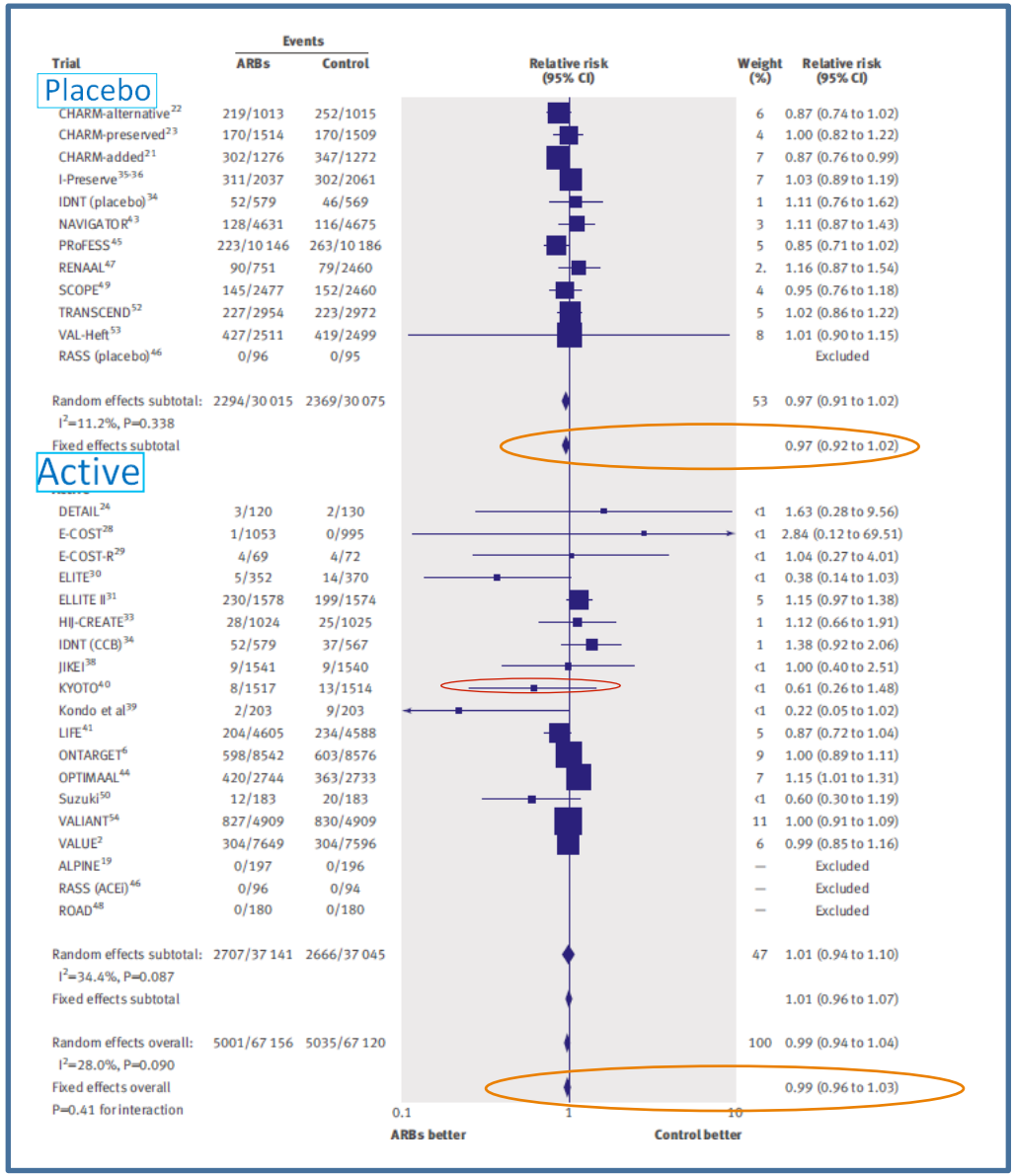
-45% stroke/angina scandal

KYOTO HEART STUDY

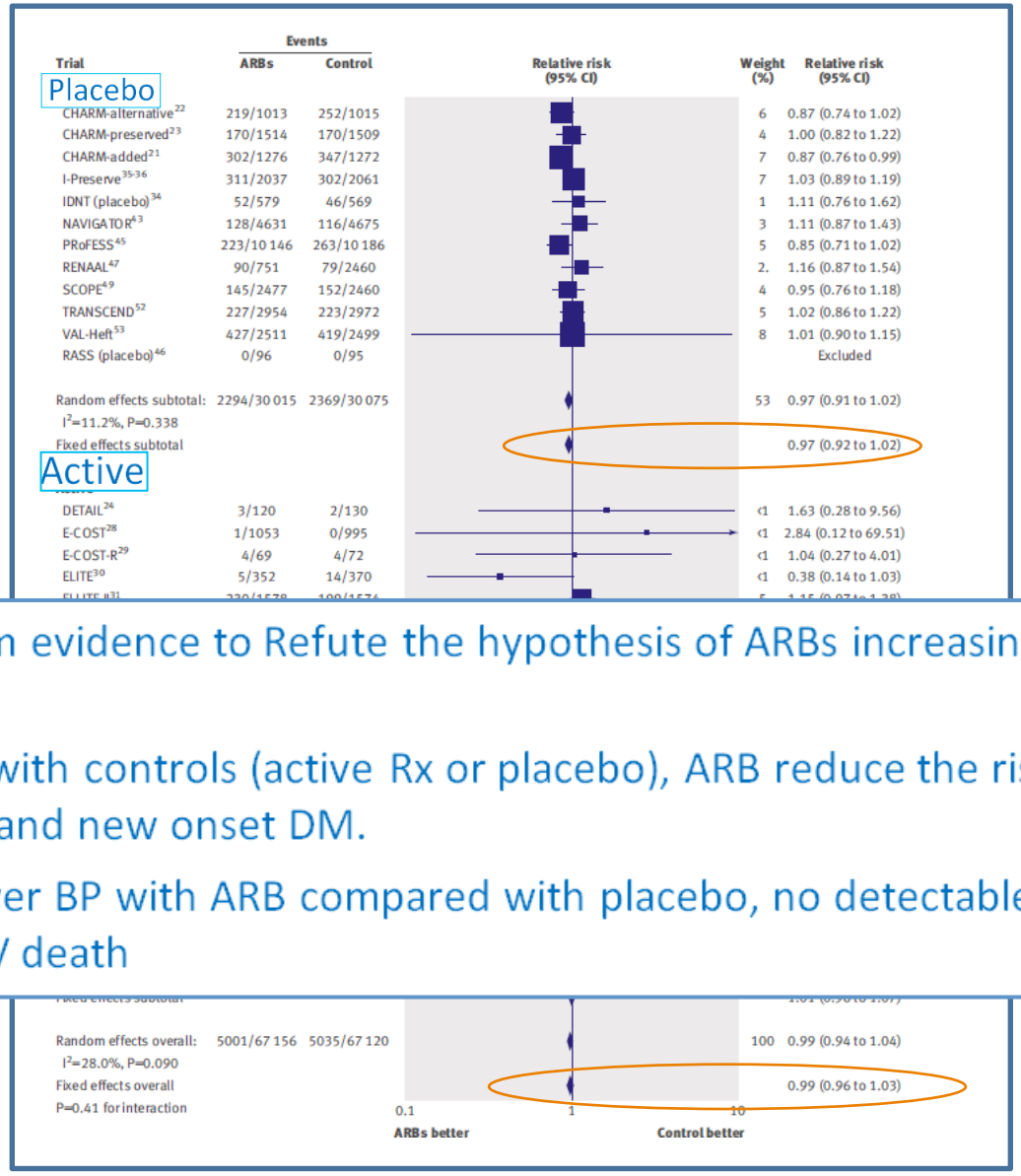


ARB vs. Placebo/ active Rx: no increase of CV dead

KYOTO HEART STUDY



ARB vs. Placebo/ active Rx: no increase of CV dead



There is firm evidence to Refute the hypothesis of ARBs increasing the risk of MI

Compared with controls (active Rx or placebo), ARB reduce the risk of stroke, HF, and new onset DM.

Despite lower BP with ARB compared with placebo, no detectable benefit for MI or CV death

Mortality Outcomes in HTN

Meta-analysis by van Vark ,L.C.

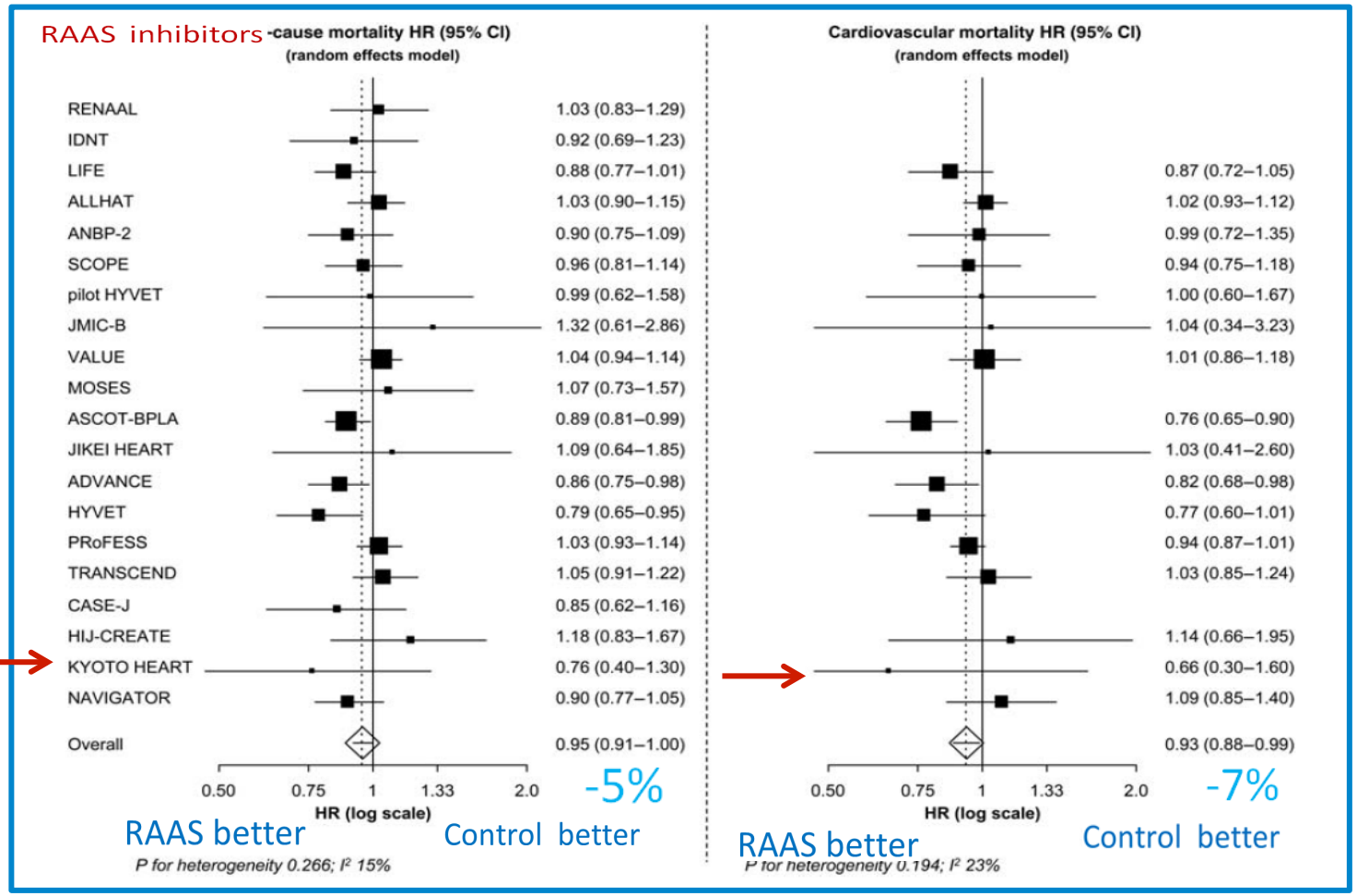
2012 EHJ doi:10.1093/eurheartj/ehs075

- The first meta-analysis of RAAS inhibitors on all cause and CV mortality in HTN
- 20 trials; N=158 998 patients
- The benefits of ACEI /ARB treatment was a 5% reduction in all-cause mortality and a 7% reduction in CV mortality
- The effect resulted entirely from ACEI (significant 10% reduction in all-cause mortality)
- No mortality benefit with treatment in ARB

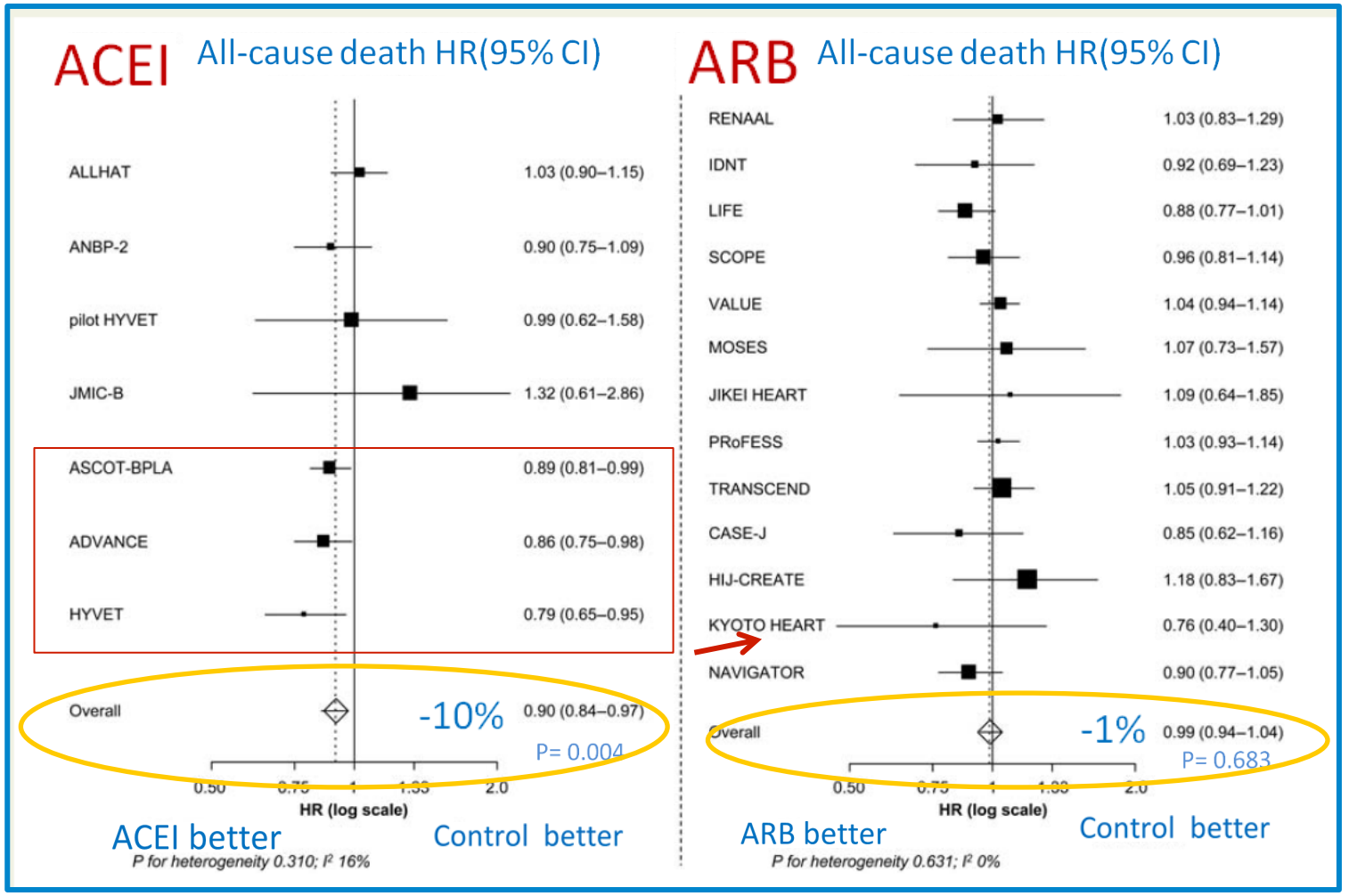
RAAS Inhibitors on Mortality in HTN

All-cause death HR(95% CI)

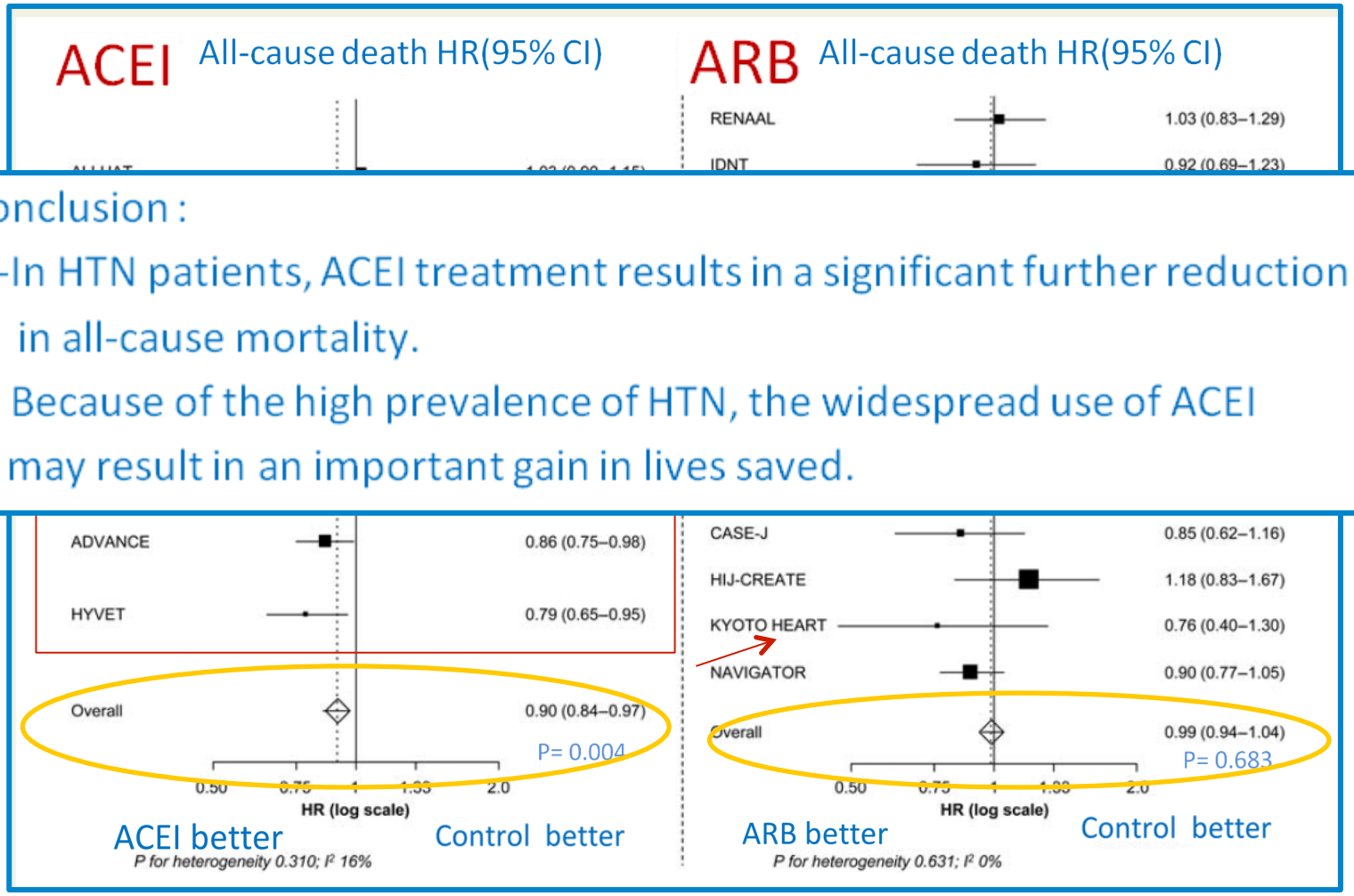
CV death HR(95% CI)



All-course Mortality in HTN: ACEI/ARB vs. control



All-course Mortality in HTN: ACEI/ARB vs. control



Conclusion :

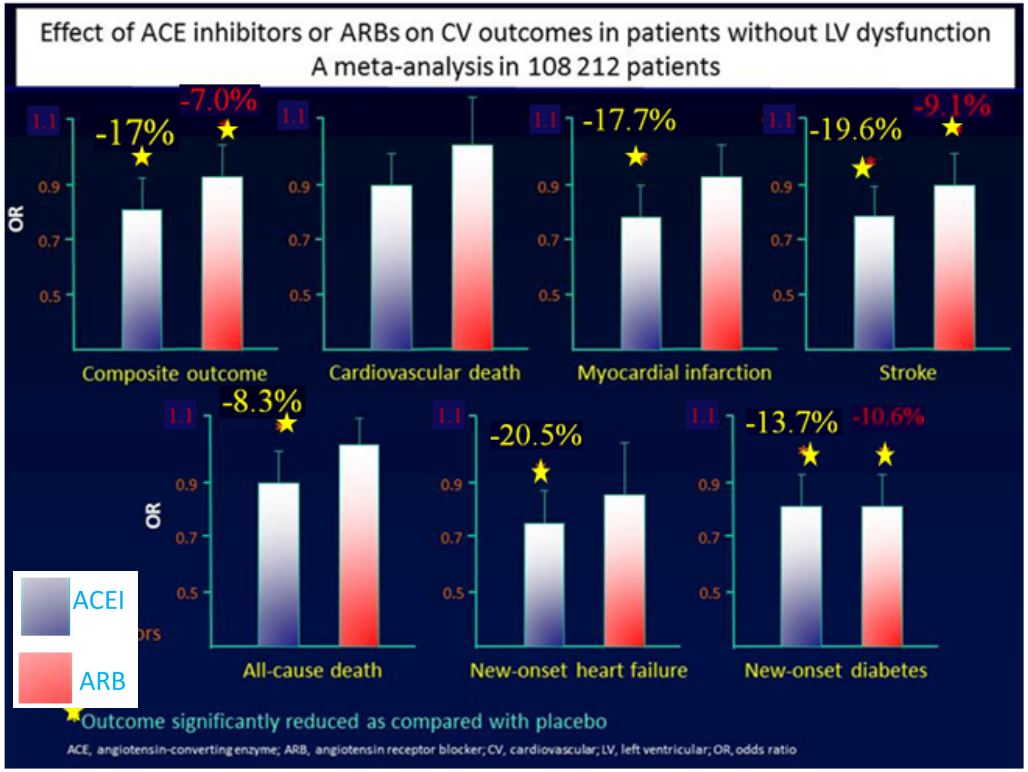
-In HTN patients, ACEI treatment results in a significant further reduction in all-cause mortality.

- Because of the high prevalence of HTN, the widespread use of ACEI may result in an important gain in lives saved.

ACEI vs ARB:
in high-risk patients without HF

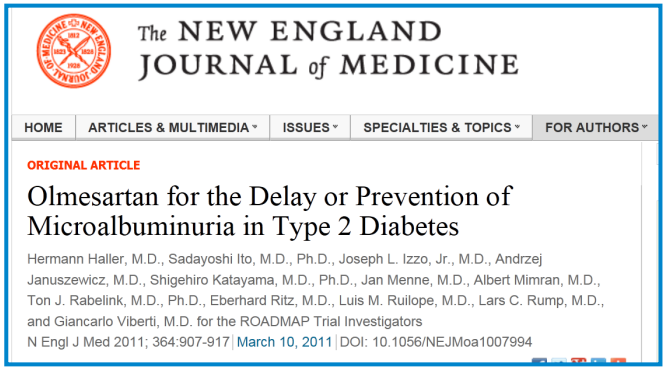
Meta-analyses by Savarese G (J Am Coll Cardiol 2013;61:131–42)

- N=108,212 patients
- ARBs / ACEI vs placebo
- Conclusions :
  - both reduced the composite outcome of CV death, MI, and stroke
  - ACEI reduced all cause death, new-onset HF, and new-onset DM
  - No effects of ARB on all-cause death, MI, and new-onset HF
  - ARB is a valuable option to reduce CV death and morbidity if ACEI cannot be used.



Recent trails in high CV risk patients: Roadmap trail NEJM 2011; 364:907-917

- 4447 DM patients with no HTN. Olmesartan vs. placebo
- Olmesartan delay the onset of albuminuria, but significantly increase CV mortality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ORIGINAL ARTICLE

Olmesartan for the Delay or Prevention of Microalbuminuria in Type 2 Diabetes

Hermann Haller, M.D., Sadayoshi Ito, M.D., Ph.D., Joseph L. Izzo, Jr., M.D., Andrzej Januszewicz, M.D., Shigehiro Katayama, M.D., Ph.D., Jan Menne, M.D., Albert Mimran, M.D., Ton J. Rabelink, M.D., Ph.D., Eberhard Ritz, M.D., Luis M. Ruilope, M.D., Lars C. Rump, M.D., and Giancarlo Viberti, M.D. for the ROADMAP Trial Investigators

N Engl J Med 2011; 364:907-917 | March 10, 2011 | DOI: 10.1056/NEJMoa1007994

Death from cardiovascular causes	15 (0.7)	3 (0.1)	4.94 (1.43-17.06)	0.01

Death from CV causes

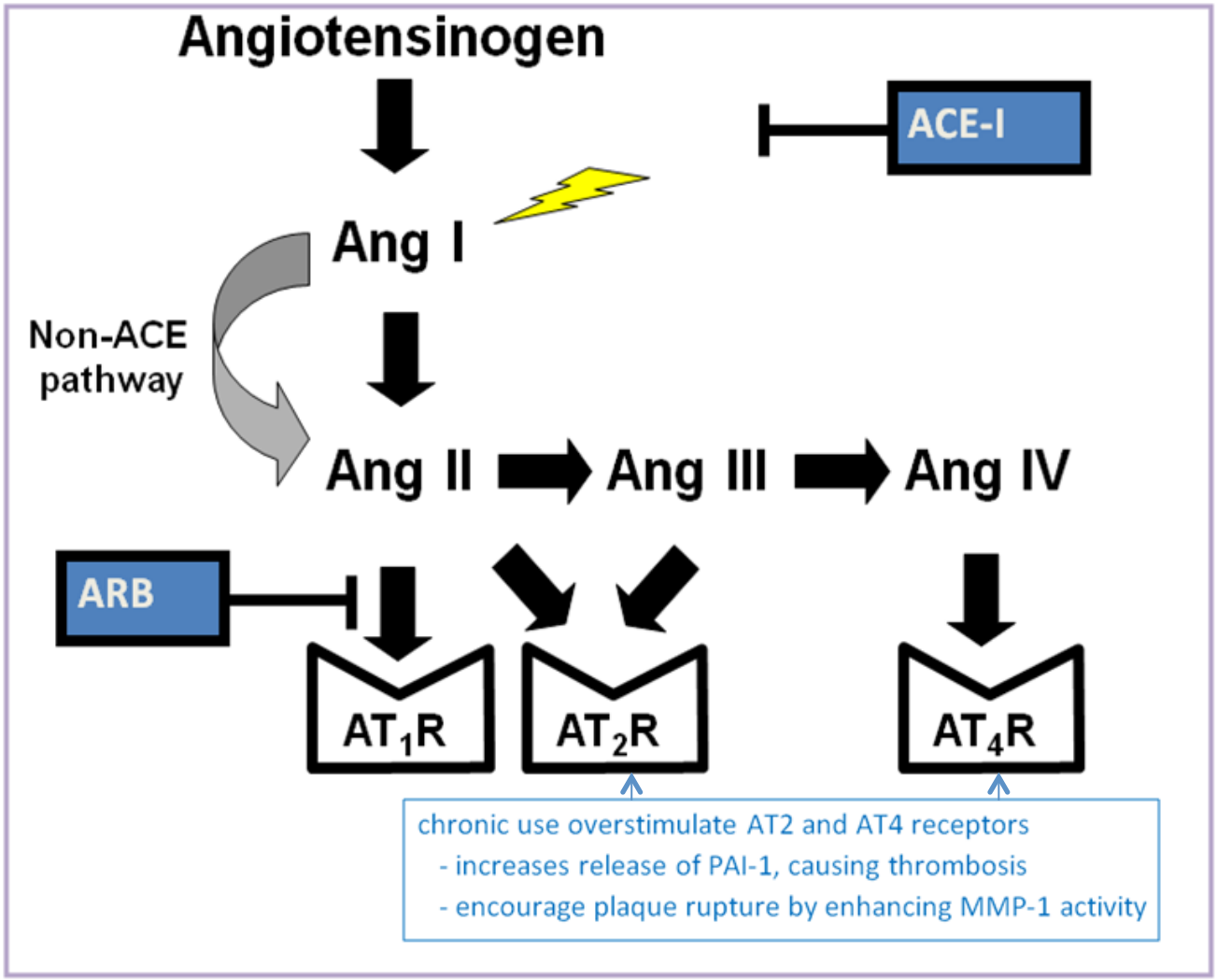
End point	Olmesartan (n=2232) Patients with events (%)	Placebo (n=2215) Patients with events (%)	Hazard ratio (95% CI)	*P* value
Primary end point				
Time to onset of microalbuminuria	178 (8.2)	210 (9.8)	0.77 (0.63-0.94)	0.01
Secondary end points				
Composite of cardiovascular complications or death from cardiovascular causes	96 (4.3)	94 (4.2)	1.00 (0.75-1.33)	0.99
Death from any cause	26 (1.2)	15 (0.7)	1.70 (0.90-3.22)	0.10
Death from cardiovascular causes	15 (0.7)	3 (0.1)	4.94 (1.43-17.06)	0.01
Composite of cardiovascular complications, excluding new-onset atrial fibrillation and transient ischemic attack	63 (2.8)	71 (3.2)	0.87 (0.62-1.22)	0.42
Composite of new-onset atrial fibrillation or transiet ischemic attack	19 (0.9)	28 (1.3)	0.67 (0.37-1.19)	0.17
Composite of all cardiovascular complications	81 (3.6)	91 (4.1)	0.87 (.65-1.18)	0.37

1.Haller H, et al. **Olmesartan for delay or prevention of microalbuminuria in type 2 diabetes.** *N Engl J Med.* 2011;364:9

Conclusions

Olmesartan was associated with a delayed onset of microalbuminuria, even though blood-pressure control in both groups was excellent according to current standards. The higher rate of fatal cardiovascular events with olmesartan among patients with preexisting coronary heart disease is of concern.

Proposed Mechanisms



Safety and Tolerability

- Both ACEI and ARB are generally well tolerated and have a relatively low incidence of adverse effects (hypotension, angioedema, worsening of renal function, hyperkalemia)
- There is no good evidence that ARB is safer than ACEI for any indication
- Both drug contraindicated in pregnancy, not recommended for breastfeeding mothers
- ACEI may cause persistent dry cough
  - In ONTARGET, 4.2% of patients taking an ACEI discontinued because of cough *vs.* 1.1% of patients taking an ARB

2013 ESH/ESC HTN Guideline

Journal of Hypertension 2013, 31:1281–1357

- "Benefits of antihypertensive treatment are due to lowering of BP per se and are largely independent of the drugs employed."
- "….Meta-analyses claiming superiority of one class of agents over another for some outcomes [391–393] , largely depends on the selection bias , has been undermined by ONTARGET trail "
- "…the largest meta-analyses do not show clinically relevant differences between drug classes [284,394,395]. "
- "Diuretics ,BB,CCB, ACEI and ARB are all suitable for the initiation and maintenance of antihypertensive treatment "

References

393. van Vark LC, Eur Heart J 2012; 33:2088–2097

394. BPLTTC. Arch Intern Med 2005; 165:1410–1419.

395. BPLTTC. Lancet 2003; 362:1527–1535.

.

Summary

- The primary goal of antihypertensive treatment is to achieve maximum reduction in total risk of CVD
- ARB does not increase MI and CV mortality
- There is no cogent evidence to support the equivalence of ARB and ACEI
- BP-independent effects of ACEI might account for the differences seen in CV death and Ml reduction between ACEI and ARB
- If CV death and Ml are a major concern in HTN , ACEI should be considered ahead of ARB, and ARB should be reserved to treat patients intolerant of ACEI

*Take home message

" If one regimen proved even slightly better than another, then preferential use of the more effective regimen might prevent tens of thousands of major CV events every year "

(from BPLTTC 2005)

Thank you