Importance of BP lowering to reduce CVD risk

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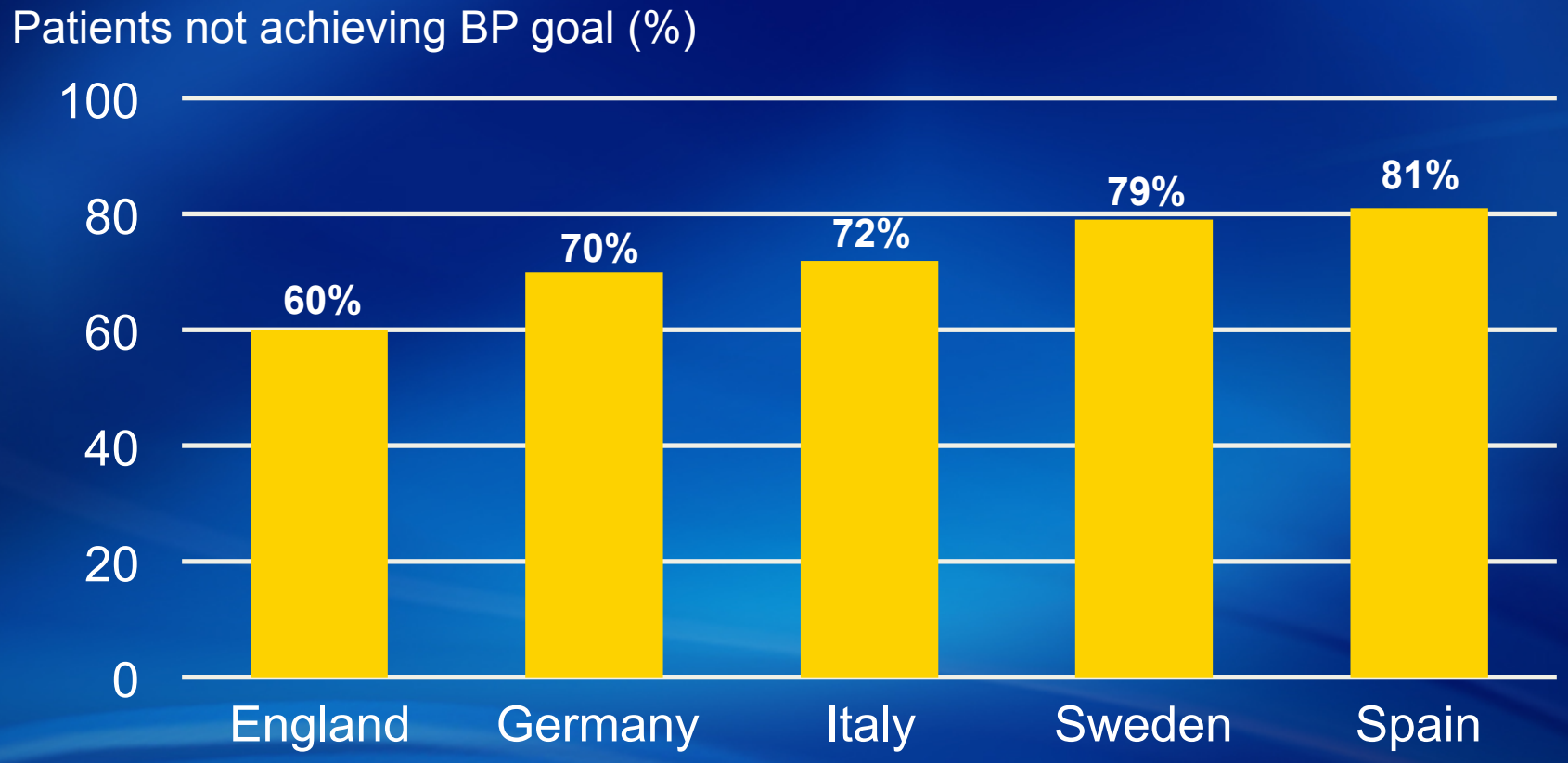
Cardiovascular Disease in Asia

Suboptimal Treatment of Hypertension in Asia

Approximately 70% of Patients who receive treatment do not reach BP goal

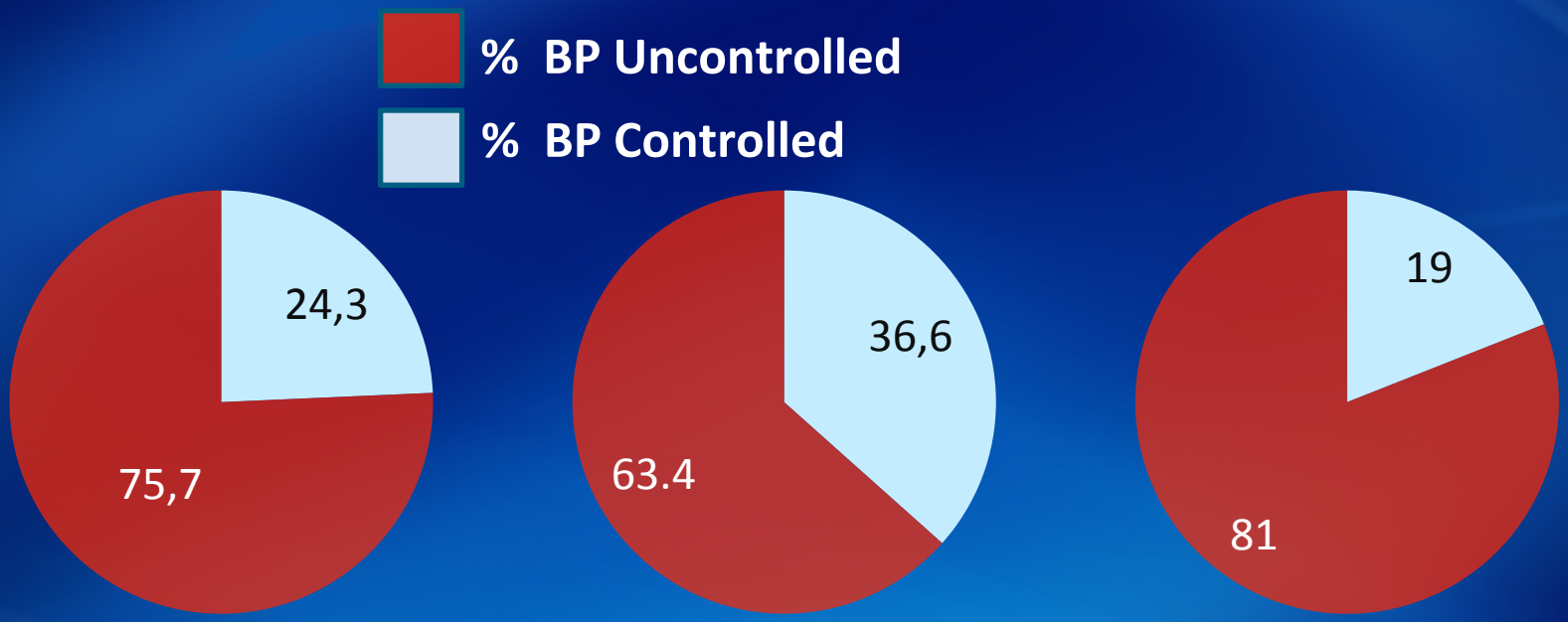
Data from Europe



*Treated for hypertension
#BP goal <140/90 mmHg

Wolf-Maier et al. Hypertension 2004;43:10–17

Blood Pressure Control Rates in Asia



Turkey[1]
(Treated population)

Thailand[2]
(Treated population)

China[3]
(Treated population aware of hypertension)

1Erem et al. J Public Health 2009;31:47–58
2Aekplakorn et al. J Hypertens 2008;26:191–8
3Wu et al. Circulation 2008;118:2679–86

NICE Guidelines 2011
Antihypertensive Drug Treatment

	Aged <55yrs	Aged ≥55yrs
Step 1	A	C*
Step 2	A + C*	
Step 3	A + C + D	
Step 4 Resistant Hypertension	A + C + D + Further Diuretic[+] Consider specialist Advice	

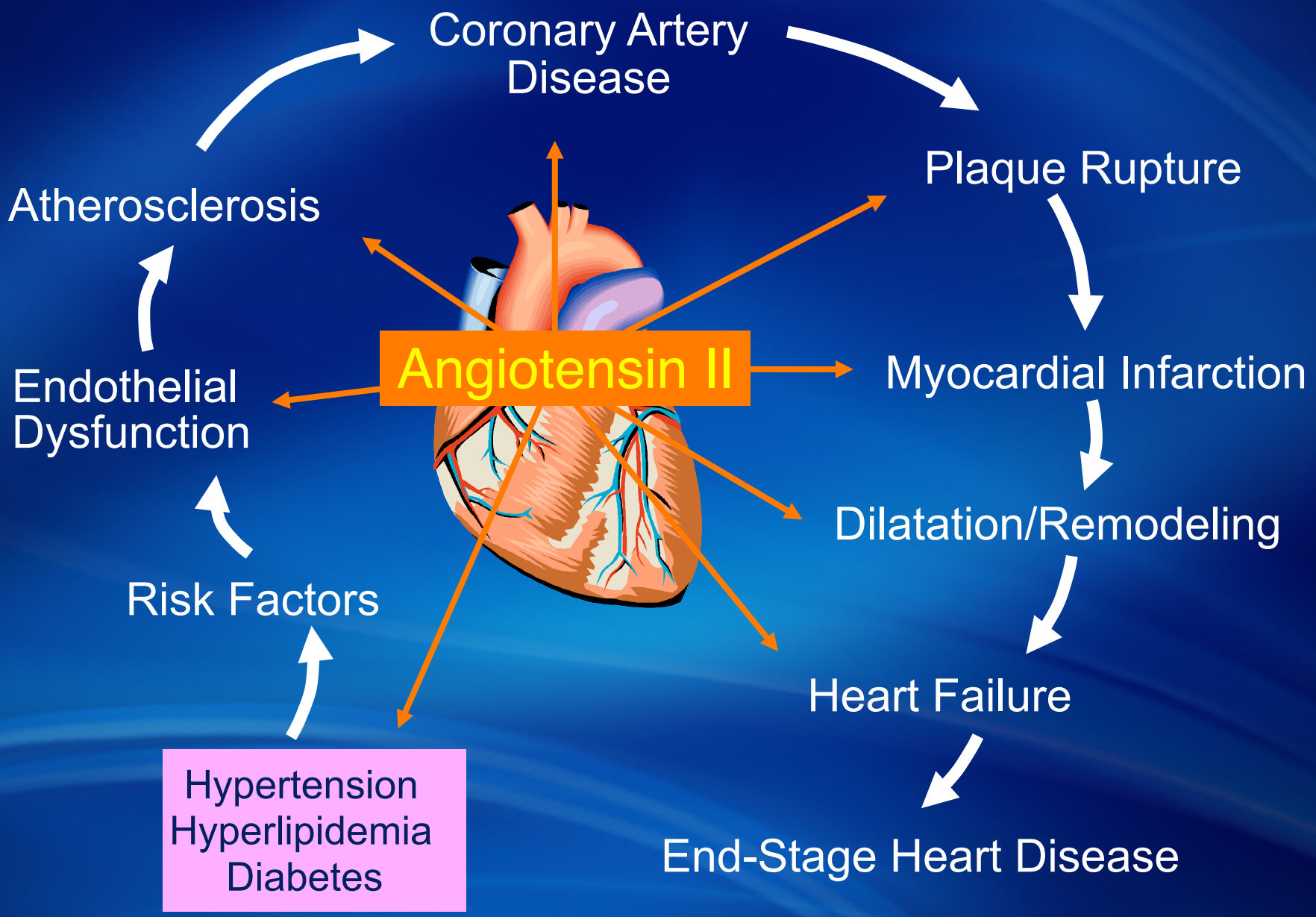
A = ACEi or ARB
C = CCB
D = Thiazide-like diuretic

C* = CCB preferred but D is an alternative in people intolerant of C or at high risk of heart failure

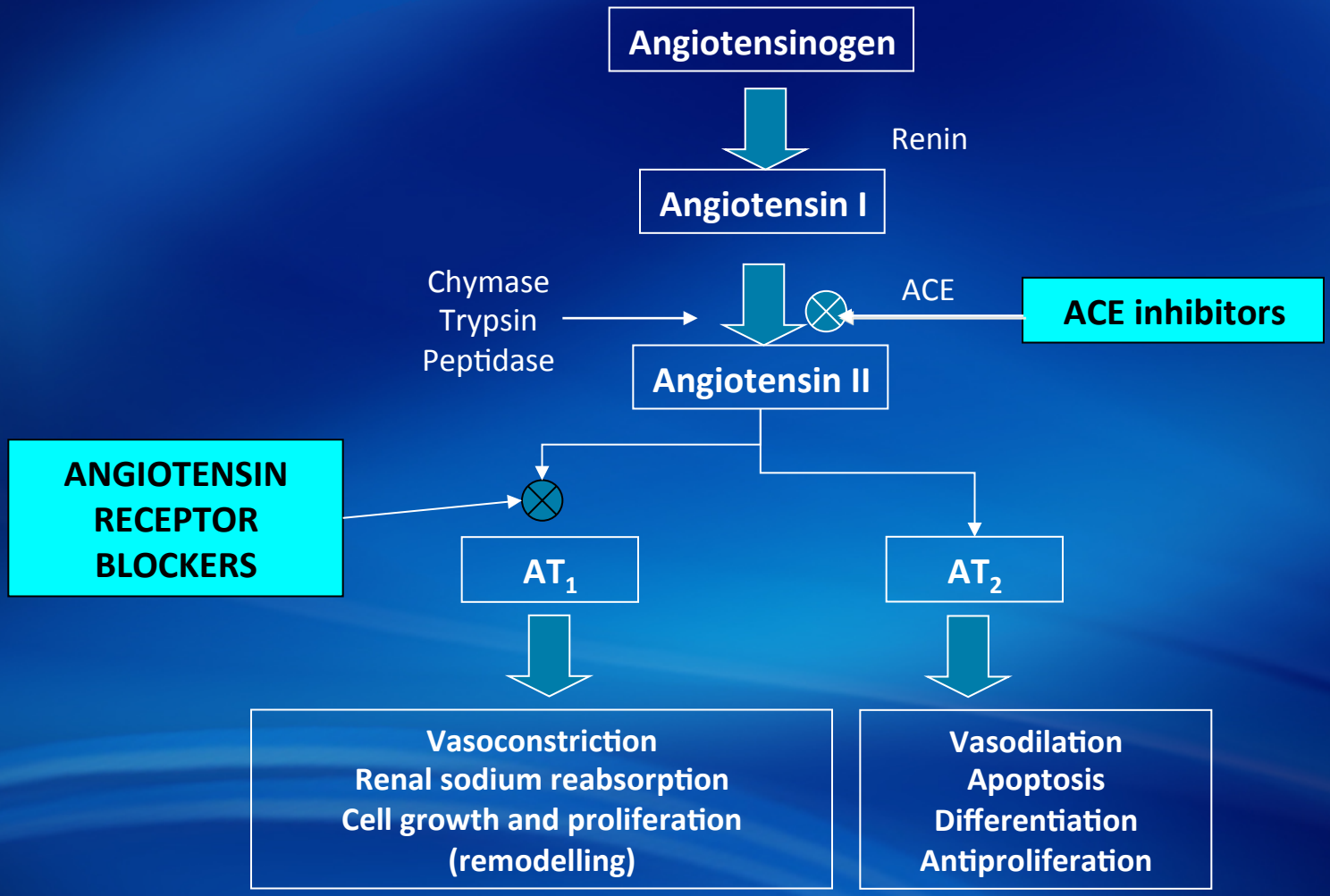
Further Diuretic: Consider low dose spironolactine or higher dose thiazide

The Renin Angiotensin System

The Cardiovascular Continuum



The renin–angiotensin system



Easthope SE, Jarvis B. *Drugs* 2002; **62**:1253–1287.

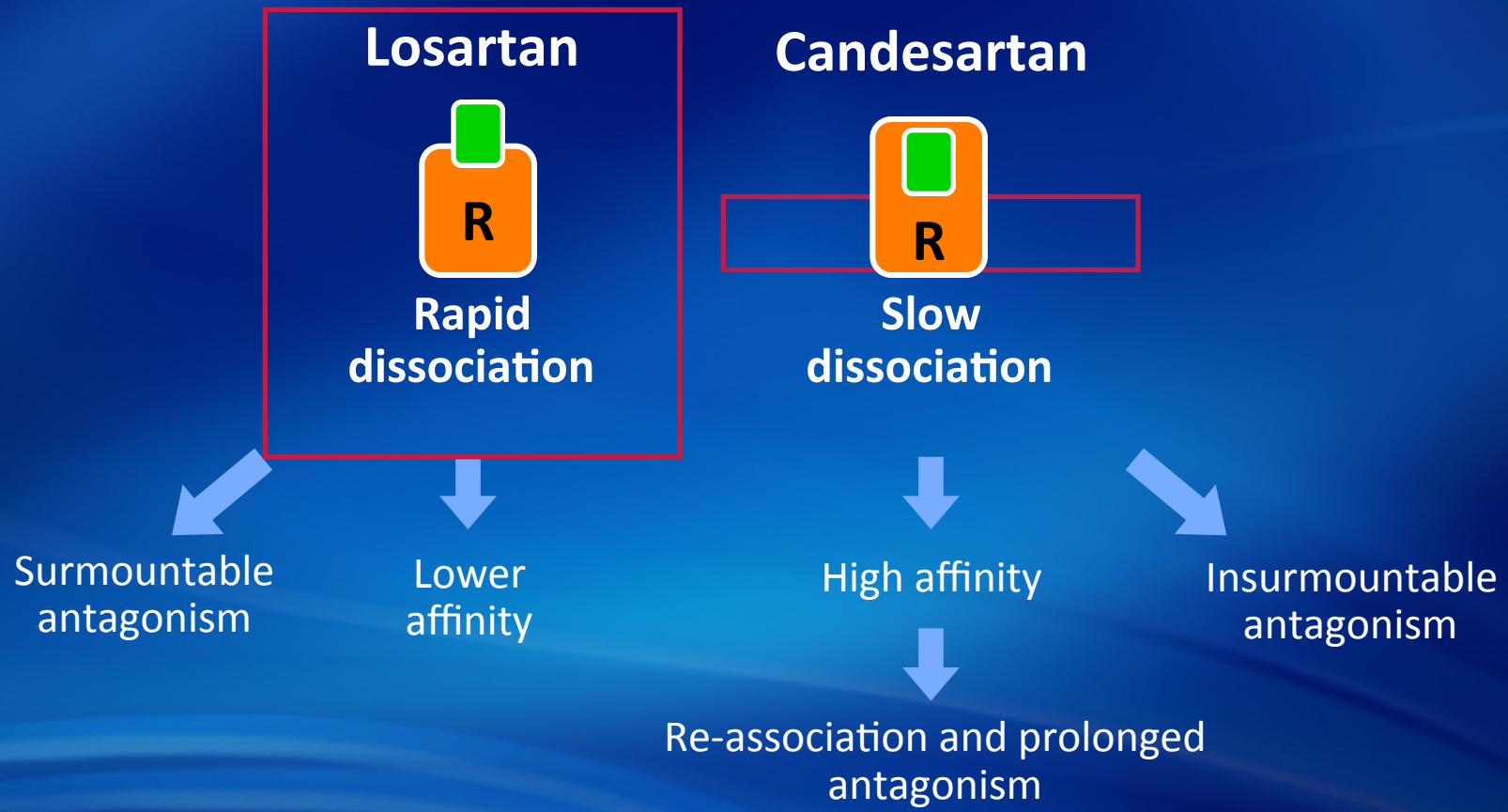
Benefits of ARBs over ACE inhibitors

- ARBs provide a more specific and selective blockade of the effects of angiotensin II than ACE inhibitors
- ARBs tend to have more favourable tolerability than ACE inhibitors
- Unlike ACE inhibitors, ARBs do not disrupt bradykinin and tachykinin degradation, leading to a much lower incidence of treatment-related cough

McClellan KJ, Goa KL. *Drugs* 1998; **56**: 847–869.

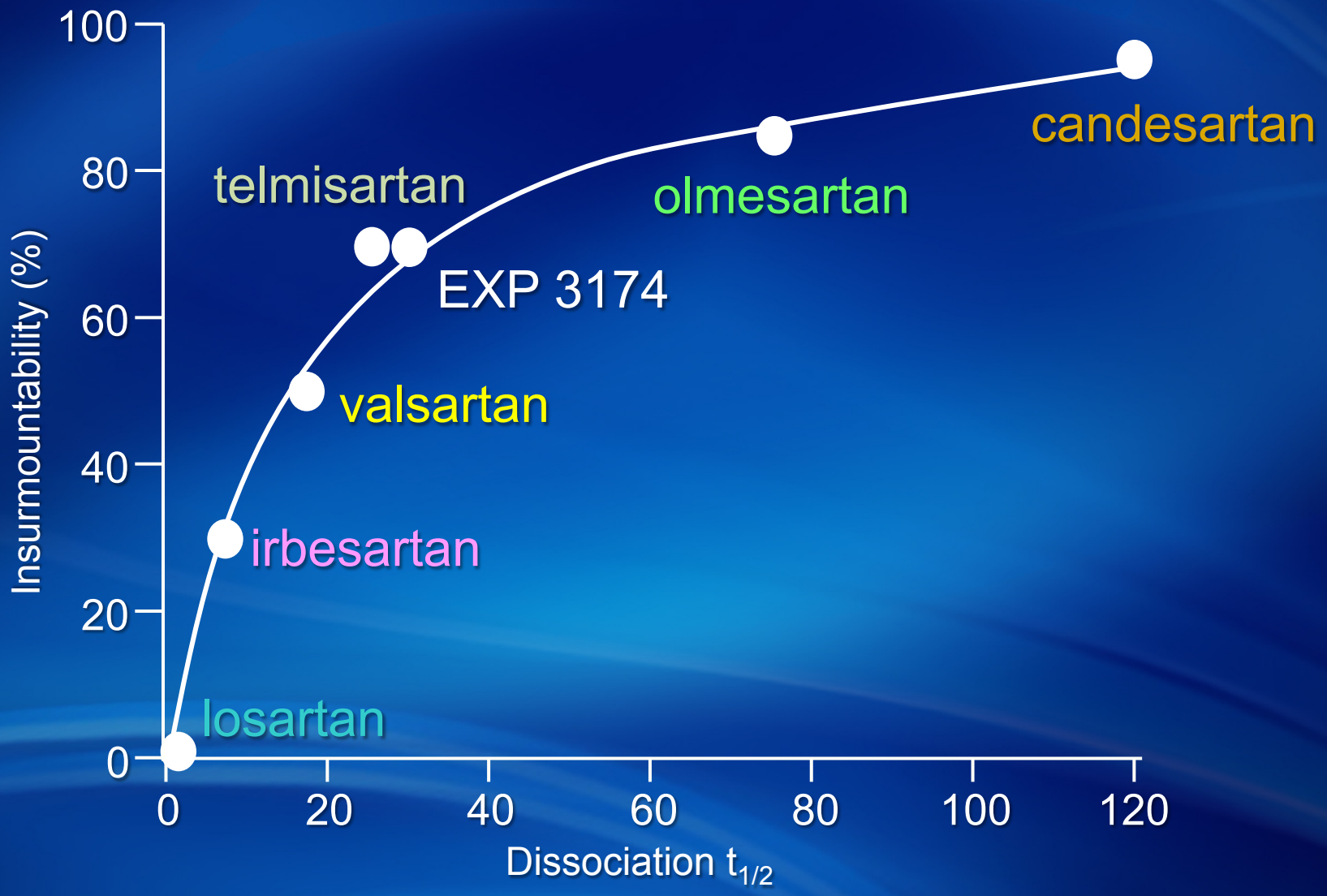
Role of Candesartan

Antagonist: AT_1 receptor interaction



Morsing P, Vauquelin G. *Cell Biochem Biophys* 2001; **35**(1): 89–102.

Insurmountable and Surmountable Antagonism: Relation to Duration of Binding



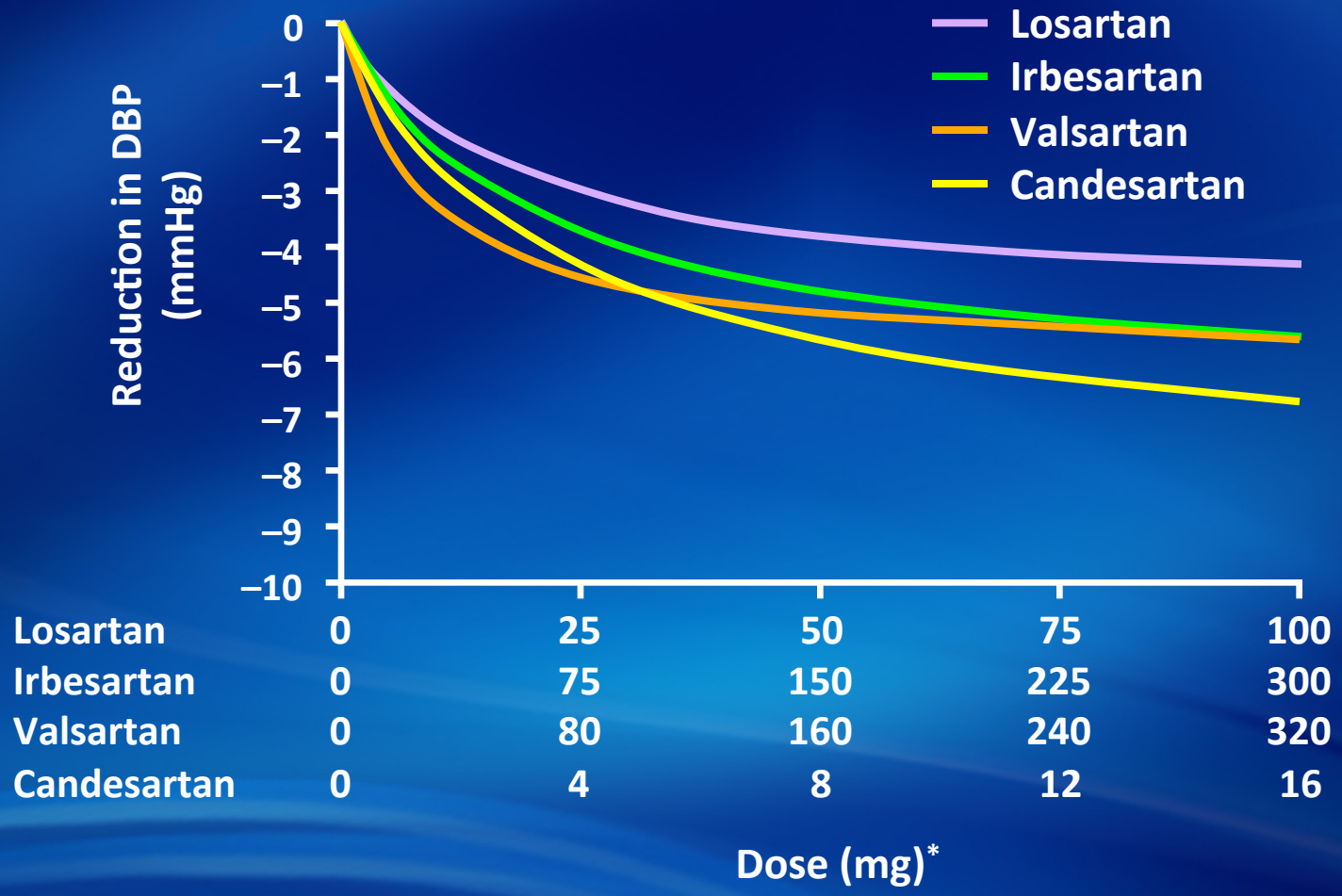
Van Liefde et al 2009

Candesartan: selected properties

- Specific blockade of the effects of angiotensin II through selective AT_1 receptor blockade
- Induces dose-dependent reduction in DBP response to exogenous angiotensin II
- The antihypertensive effect persists for more than 24 hours; this long duration of action appears to be related to a slow dissociation rate from the AT_1 receptor
- Has placebo-like tolerability in hypertension clinical trials

Easthope SE, Jarvis B. *Drugs* 2002; **62**: 1253–1287.

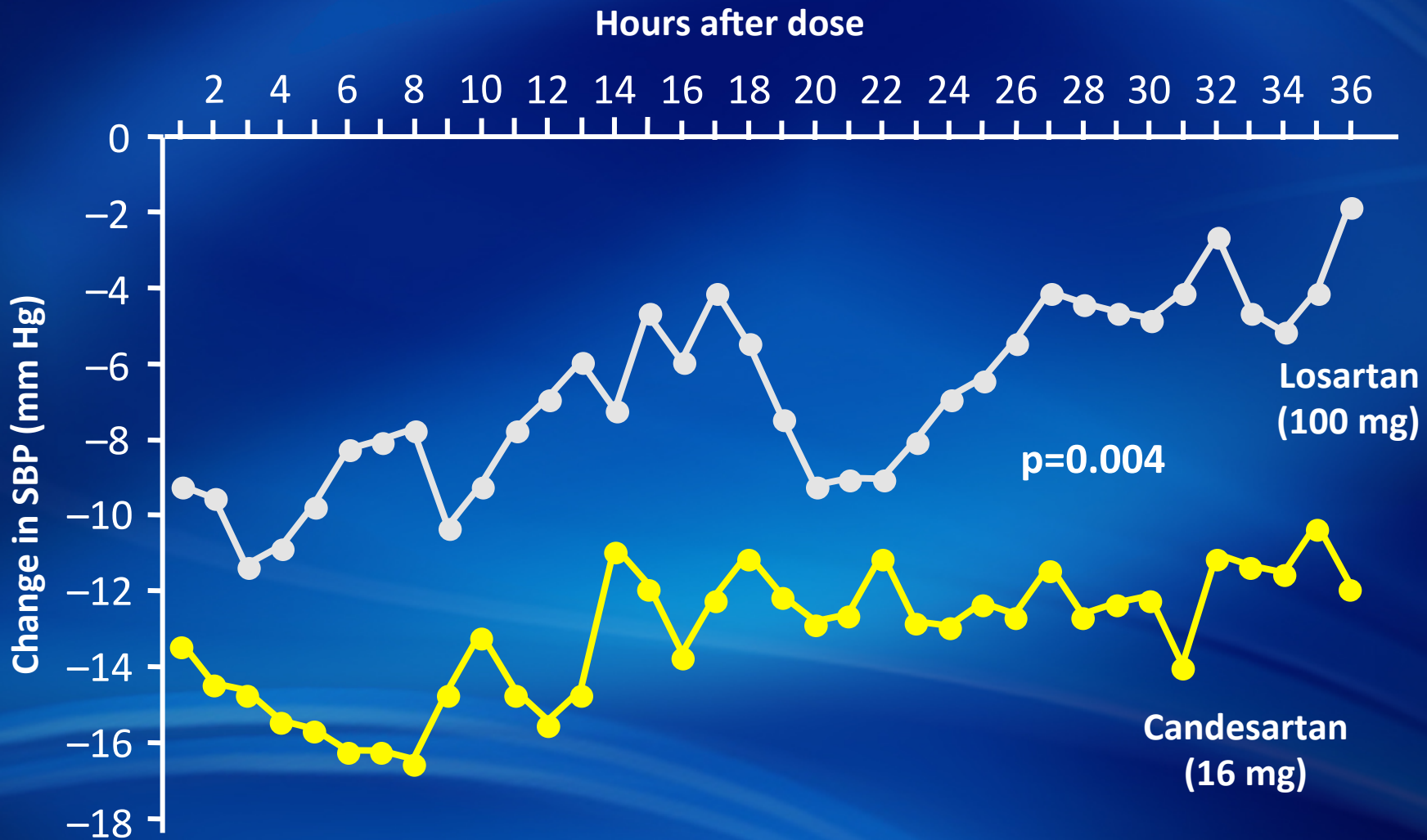
Meta-analysis based on USA New Drug Application evaluation reports



* x-axis is extended to the highest recommended dose in the EU at the time of meta-analysis

Elmfeldt D, *et al*. *Blood Press* 2002; **11**: 293–301.

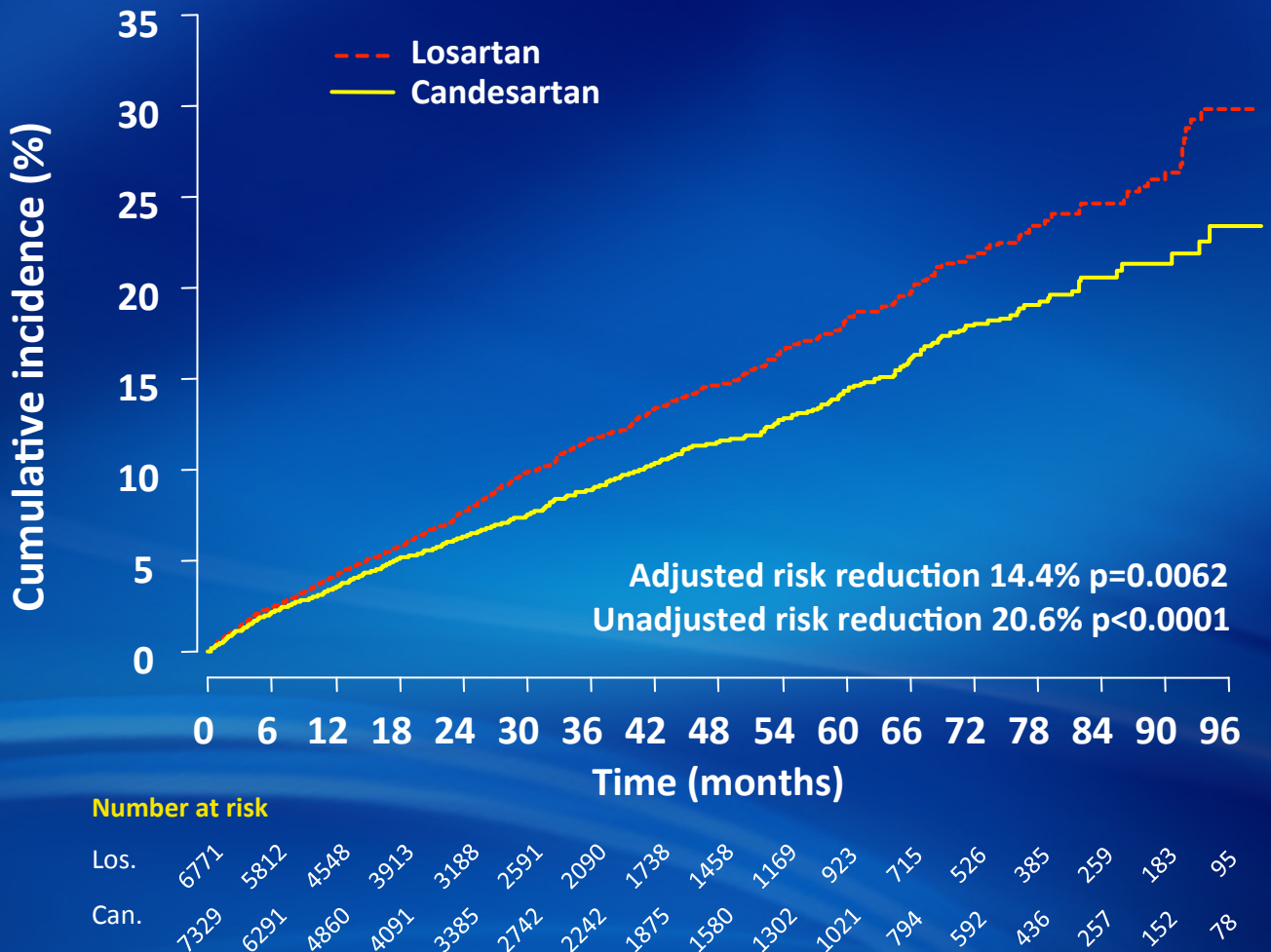
Mean change from baseline to week 8 in SBP



Lacourciere Y, Asmar R. *Am J Hyper* 1999; **12**: 1181–1187.

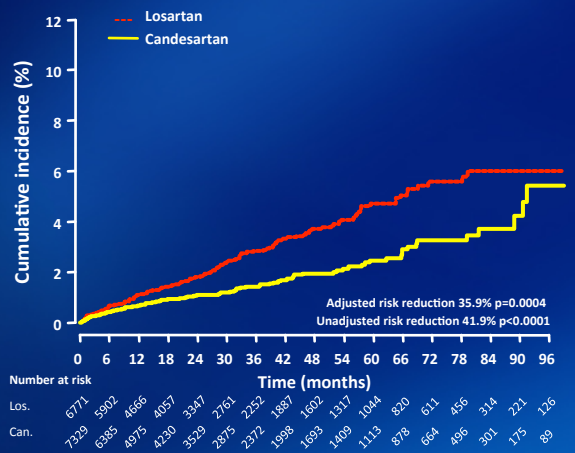
Real Life study: CVD Risk

Primary composite endpoint

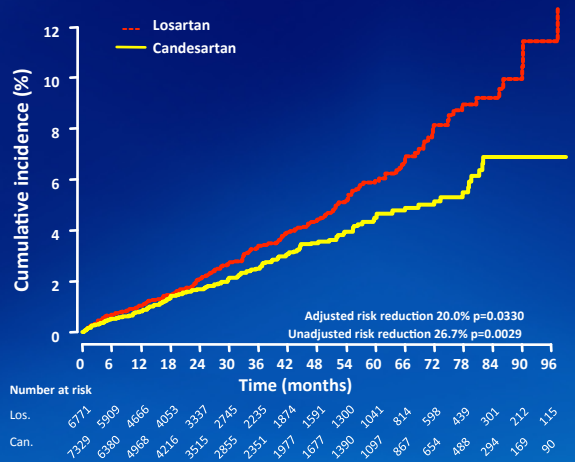


Real Lifestudy: Risk of Separate Endpoints

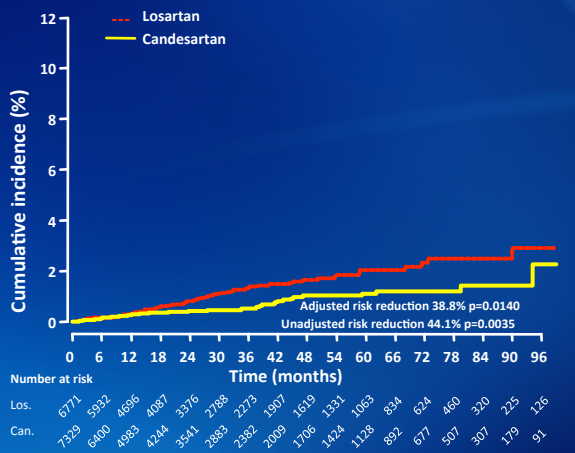
A Heart failure



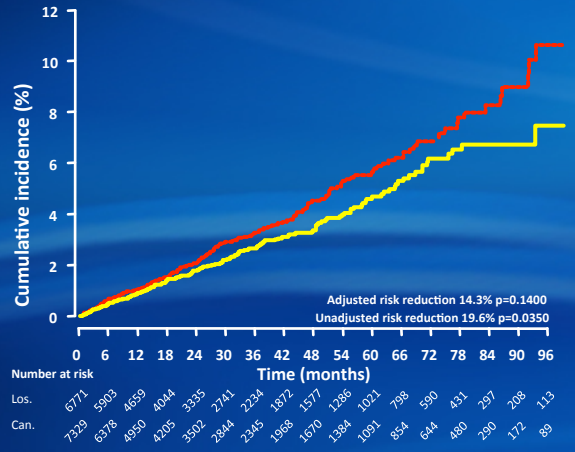
B Arrhythmias



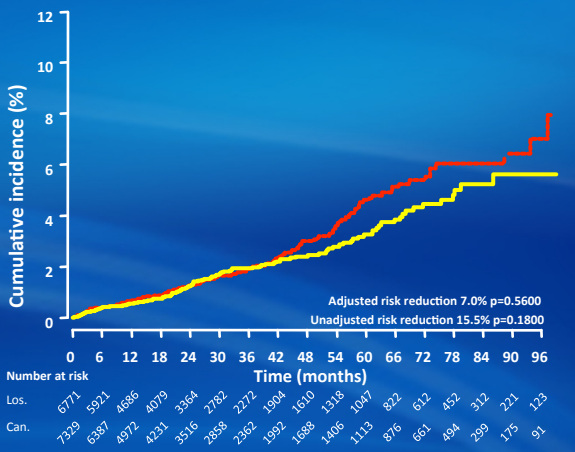
C Peripheral artery disease



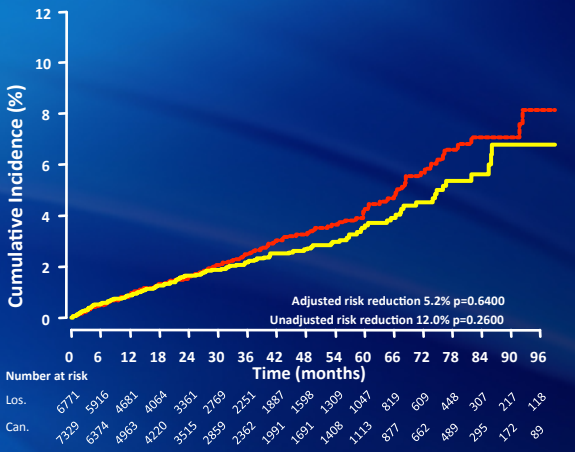
D Chronic ischemic heart disease



E Myocardial infarction

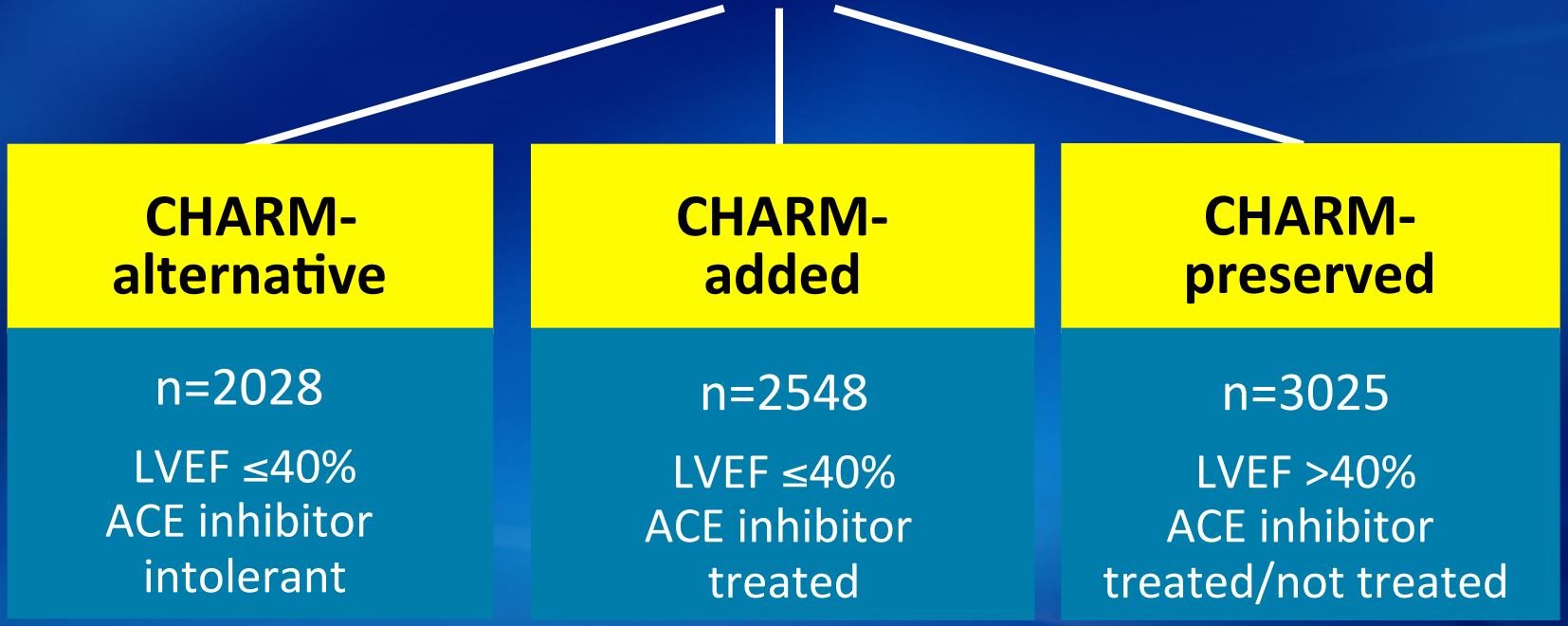


F Stroke



CHARM study programme

Three component trials comparing candesartan with placebo in patients with symptomatic heart failure

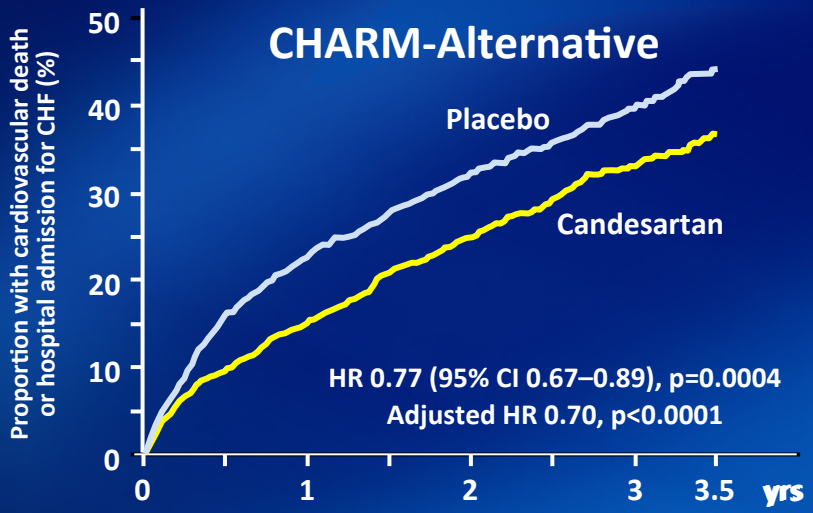


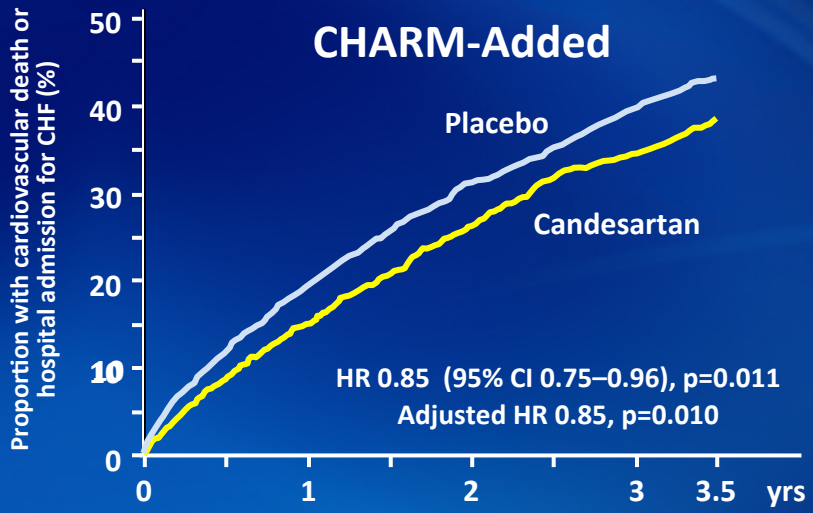
Primary outcome for each trial: CV death or CHF hospitalisation

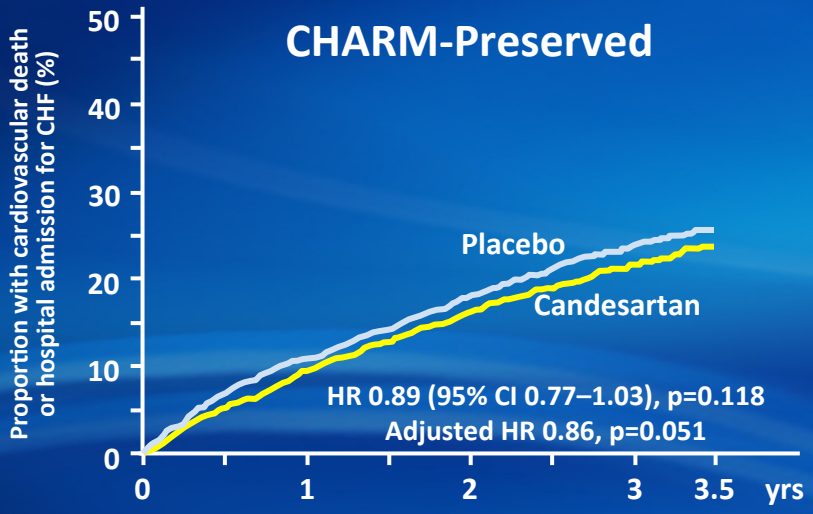
Primary outcome for overall programme: all-cause death

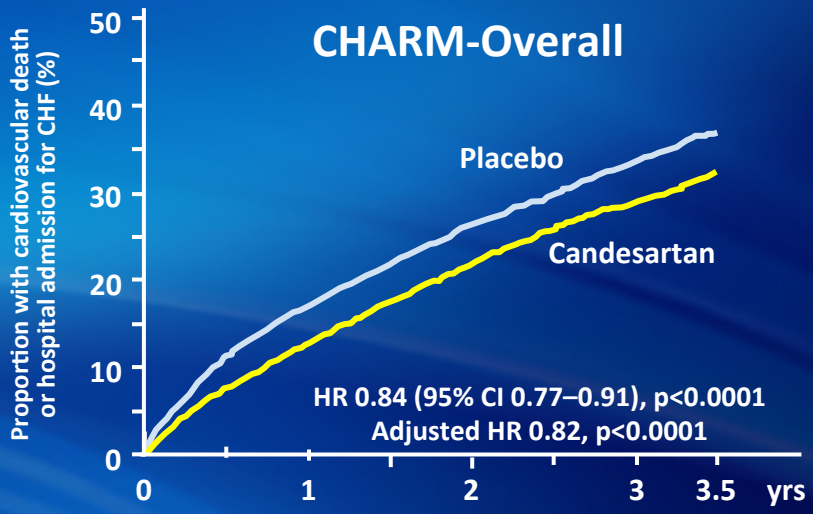
Pfeffer MA, *et al*. *Lancet* 2003; **362**(9386): 759–766.

CV death and CHF hospitalisation in the CHARM studies



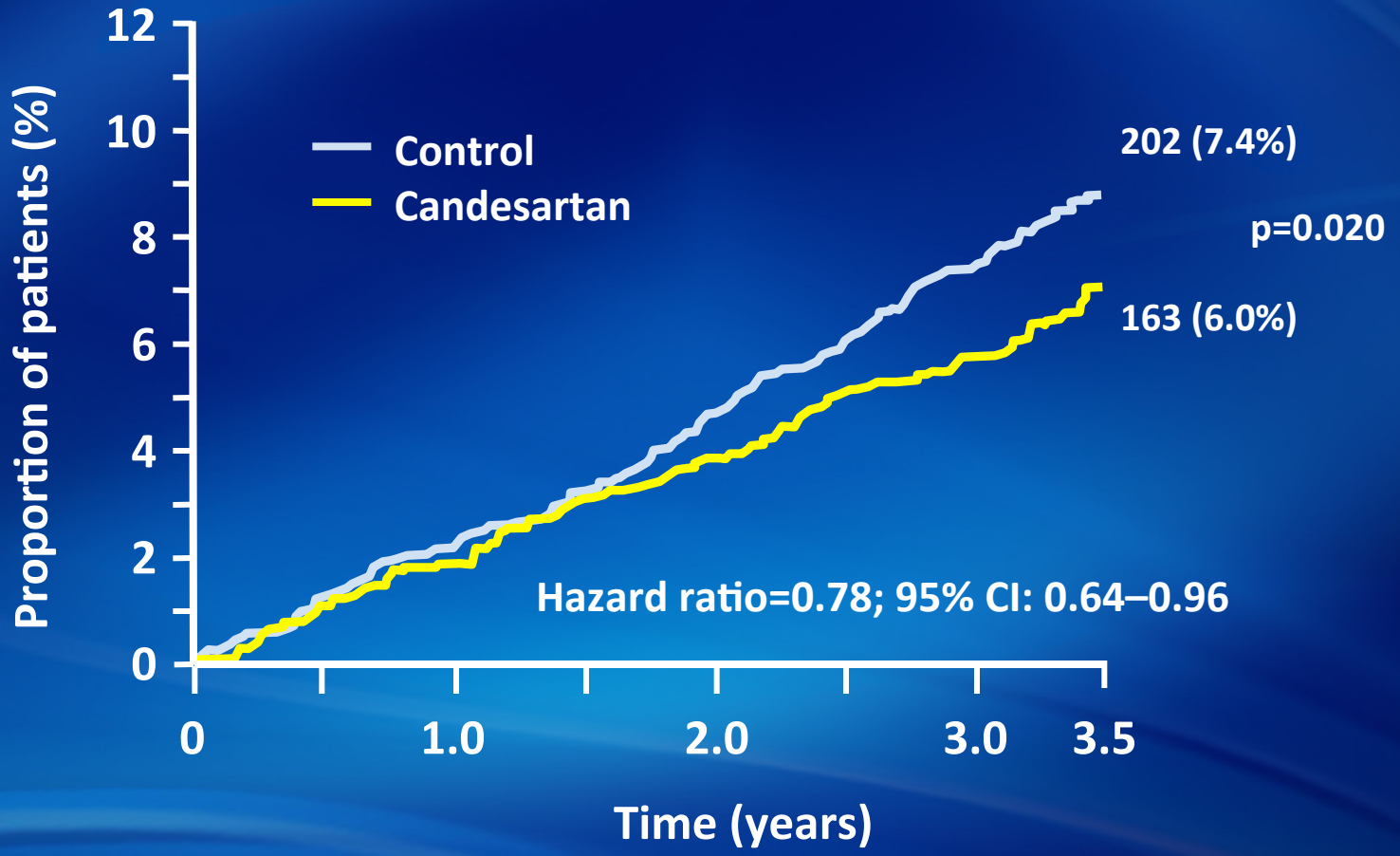






1. Yusuf S, Pfeffer MA, Swedberg K, *et al*. *Lancet* 2003; **362**(9386): 777–781.
2. Granger CB, McMurray JJ, Yusuf S, *et al. Lancet* 2003; **362**(9386): 772–776.
3. McMurray JJ *et al, Lancet* 2003; **362**(9386): 767–771
4. Pfeffer MA *et al; Lancet* 2003; **362**(9386): 759–766.

CHARM-Overall: new diagnosis of diabetes



Candesartan	2715	2565	2395	1662
Placebo	2721	2501	2304	1622

Yusuf S, *et al. Circulation* 2005; **112**(1): 48–53.

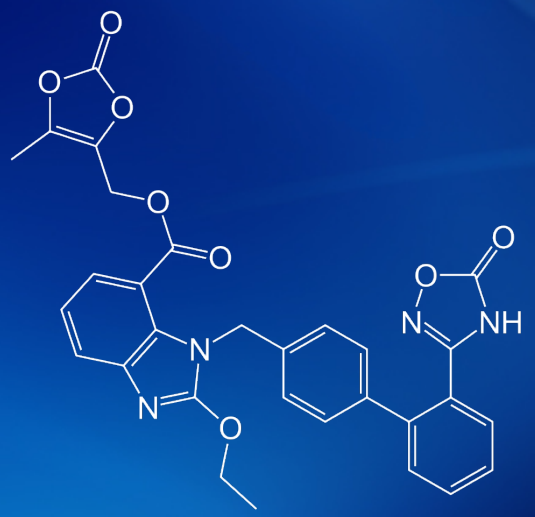
Do we need a new ARB?

Role of

- Azilsartan
- Azilsartan/chlorthalidone

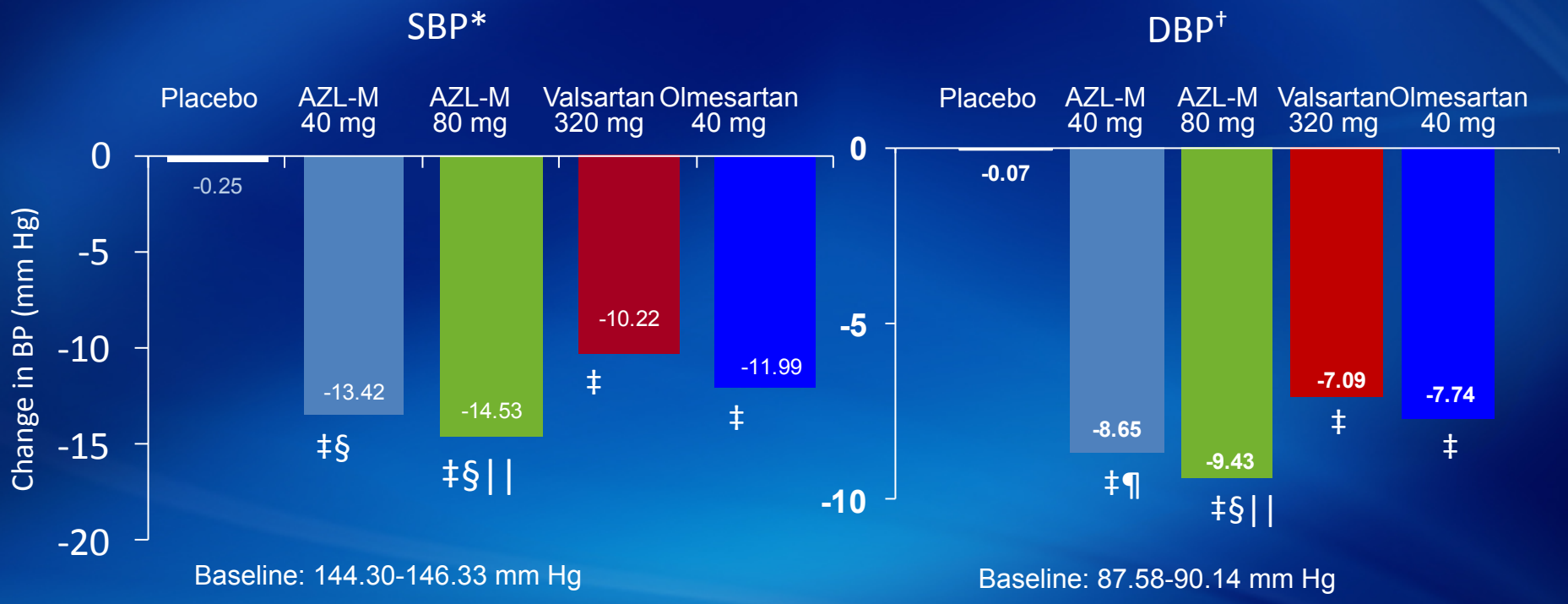
Azilsartan

- Azilsartan Medoximil (AZL-M) is the prodrug of a potent and selective Angiotensin Receptor blocker (ARB)
- Indication: HTN
- Formulation:
  - Approved dosages (US): 40 mg, 80 mg tablets
  - Approved dosage (EU): 80 mg tablet
- Posology: Once daily dosing



Azilsartan efficacy vs. Valsartan and Olmesartan

Change From Baseline in 24-h Mean BP at Week 6

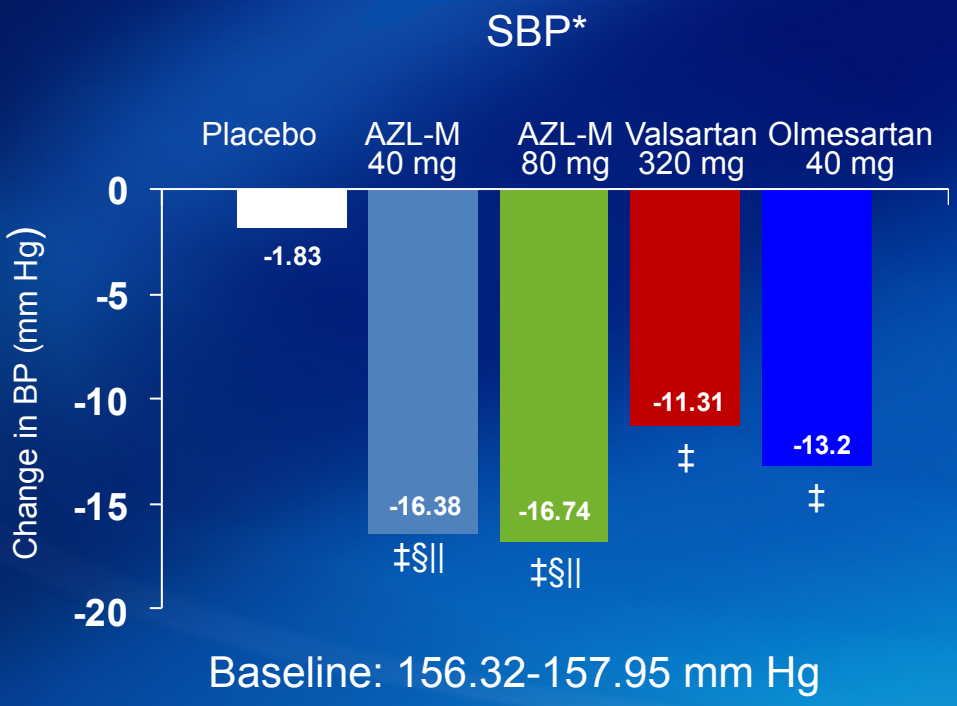


*Primary endpoint
†Secondary endpoint
‡*P*<0.001 vs placebo
§*P*≤0.001 vs valsartan 320 mg
||*P*≤0.011 vs olmesartan 40 mg
¶*P*=0.020 vs valsartan 320 mg

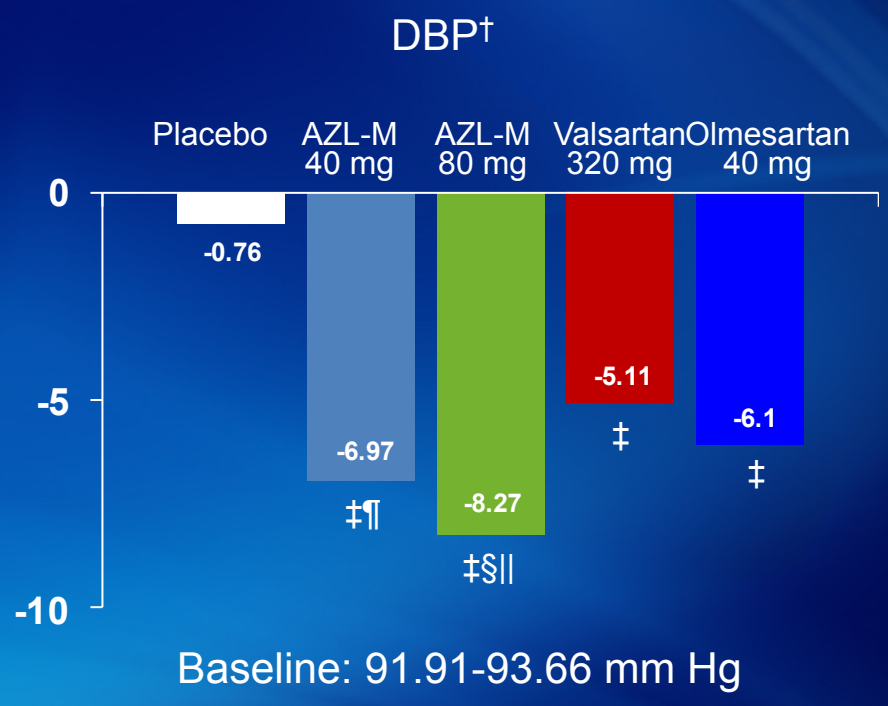
White WB, et al. *Hypertension*. 2011;57(3):413-20

Azilsartan efficacy vs. Valsartan and Olmesartan

Change From Baseline in Clinic BP at Week 6



Baseline: 156.32-157.95 mm Hg

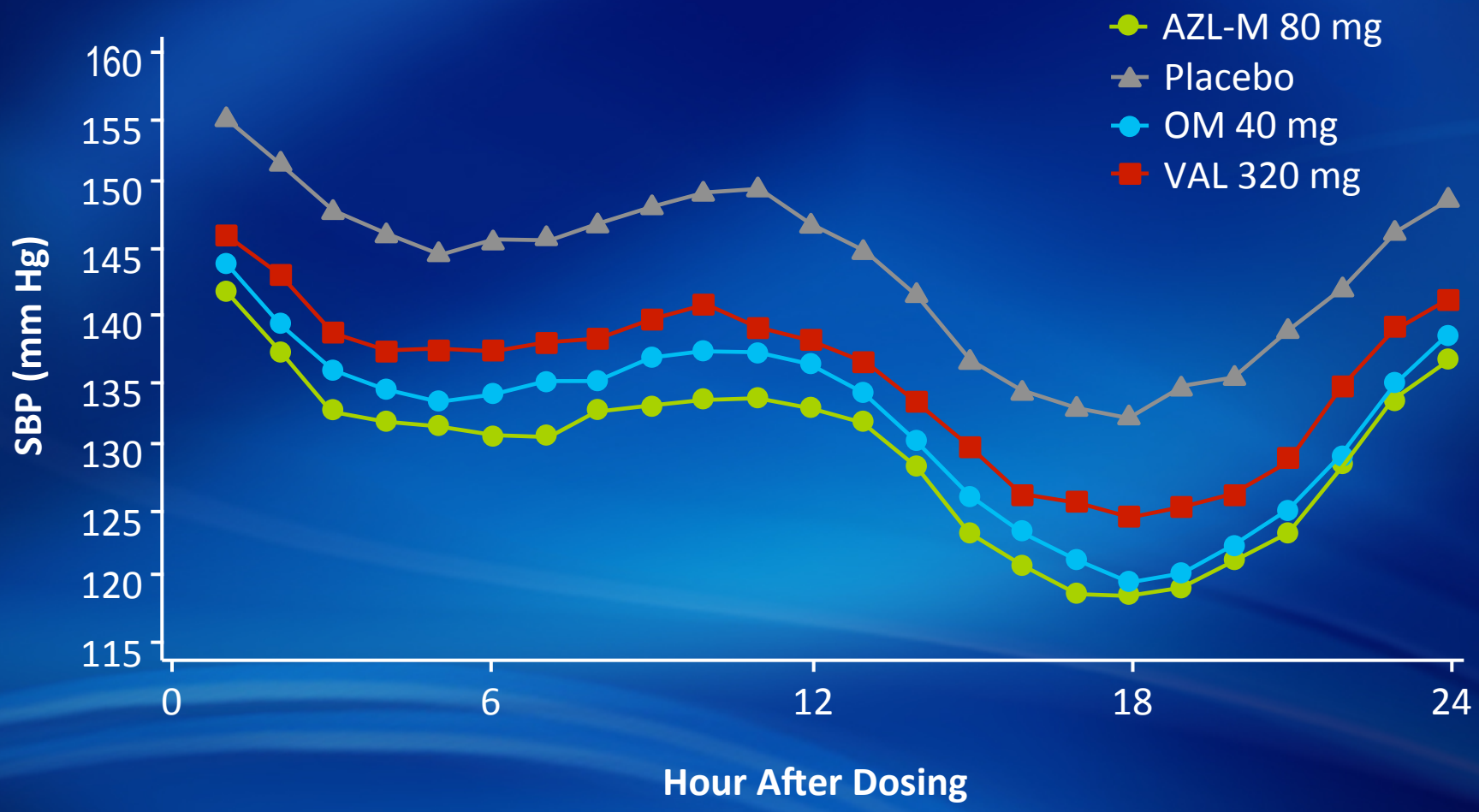


Baseline: 91.91-93.66 mm Hg

*Key secondary endpoint
† Secondary endpoint
‡*P*<0.001 vs placebo
§*P*<0.020 vs olmesartan 40 mg
||*P*<0.001 vs valsartan 320 mg
¶*P*=0.017 vs valsartan 320 mg

White WB, et al. *Hypertension*. 2011;57(3):413-20

Pooled Analysis: Change in SBP by ABPM During 24-h Interval Post-Dose at Week 6



Edarbi® (azilsartan medoxomil tablets). Full Prescribing Information, Deerfield, IL, Takeda Pharmaceuticals America, Inc., 2011

Conclusion

- Hypertension remains the main cause of death around the world.
- 60-80% of patients treated for hypertension in Asia & Europe do not attain target blood pressure (BP) goals of <140/90 mmHg.
- ARBs remain a valuable treatment options with their specificity for ATR.
- In particularly for candesartan, with its insurmountable binding to AT1 receptors, it offers a substantially more powerful blood-pressure lowering effect.

Thank you very much!