Single pill combination therapy: Is there a foundation antihypertensive therapy upon which to base treatment?

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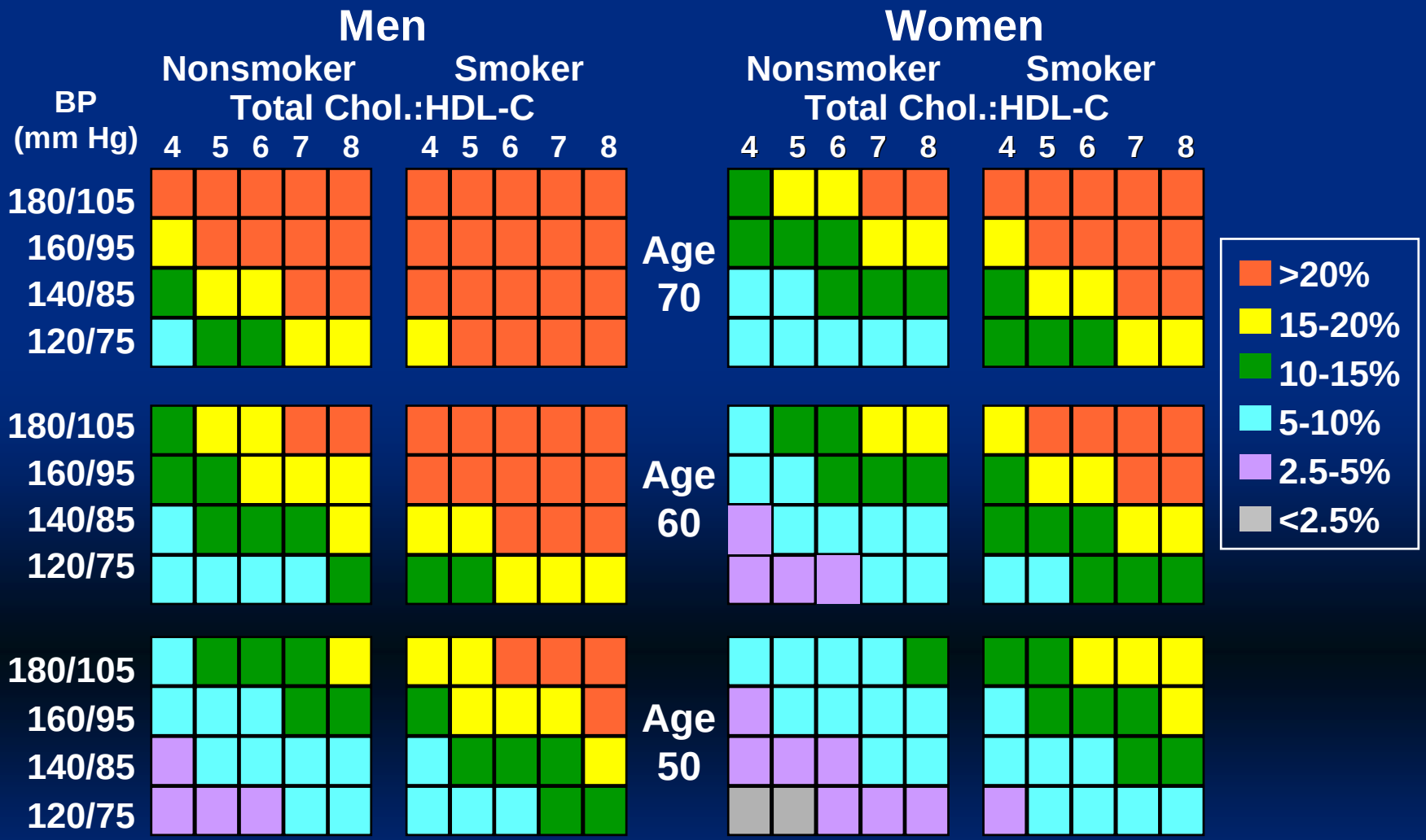
Key Questions

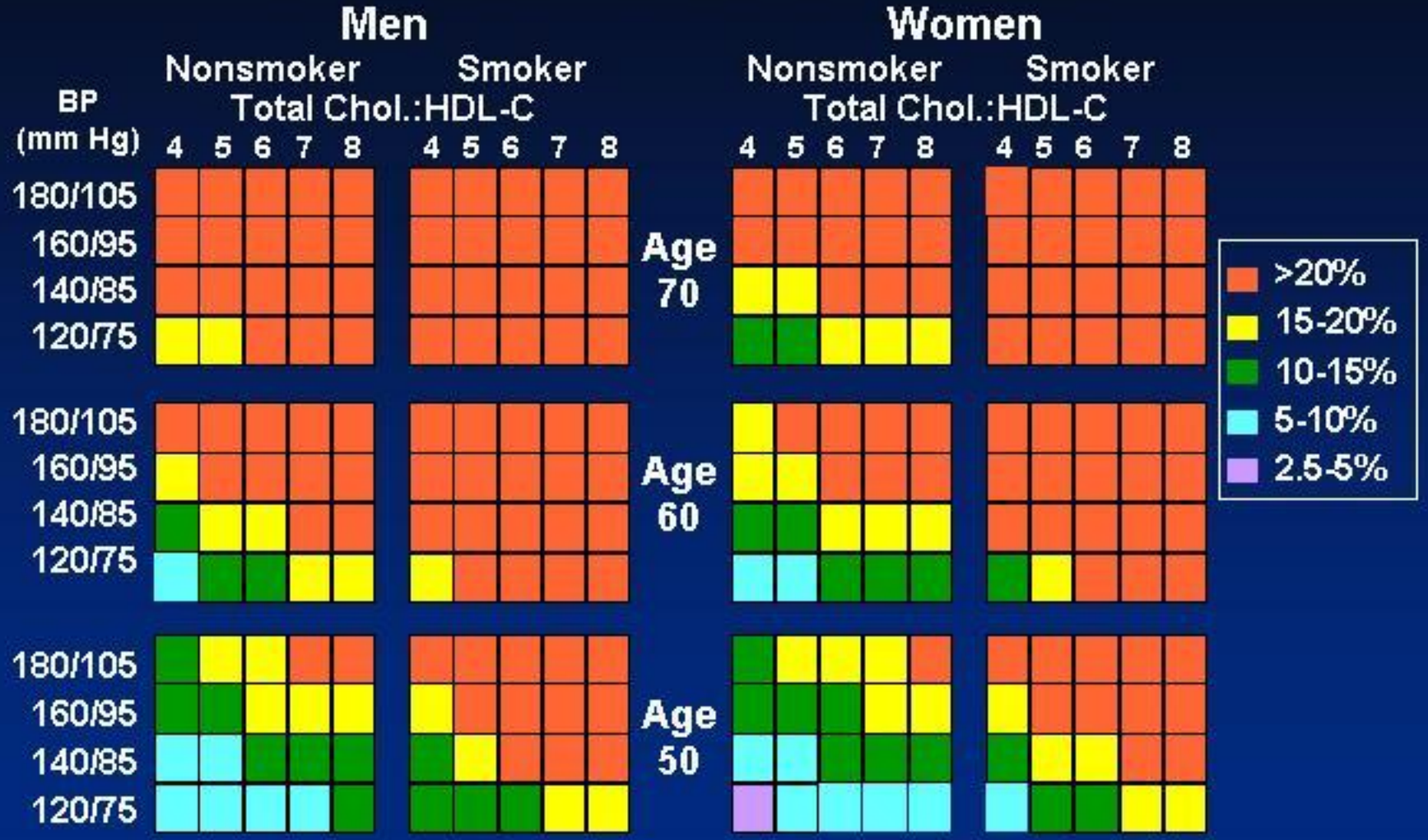
- How early should you start?
- How low should you go?
- What drugs and doses should you use?
- How many medications will you need?

Percent Chance of Cardiovascular Event in 5 Years: No Diabetes



Adapted with permission from Jackson R. *BMJ.* 2000;320:709-710.

Percent Chance of Cardiovascular Event in 5 Years: Diabetes



Adapted with permission from Jackson R. *BMJ*. 2000;320:709-710.

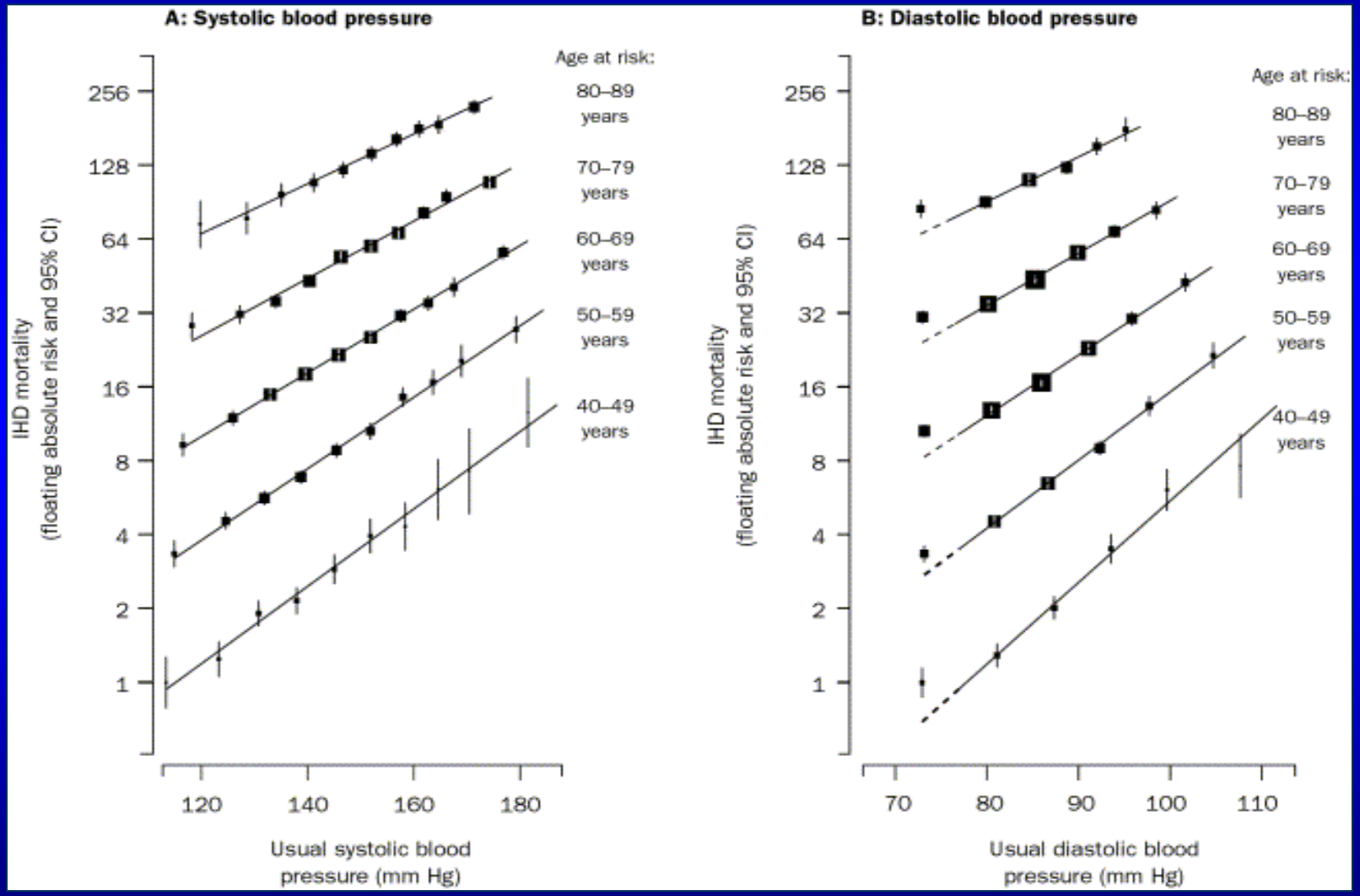
What is Your Definition of “Hypertension”?

- We must delete the word “hypertension”;

  it has no meaning

- The blood pressure goal should be established for each patient

LOWER IS BETTER:
IHD RATES BY SBP, DBP AND AGE



Lewington, et al. Lancet. 2002; 360:1903-1913.

Up to 8 out of 10 patients need multiple medications to help reach blood pressure treatment goals[1,2]

[1]Dahlof et al. Lancet 2005;366:895–906
[2]Pepine et al. JAMA 2003;290:2805–16

Adding an Antihypertensive Agent is More Effective Than Titrating

'The extra blood pressure reduction from combining drugs from 2 different classes is approximately 5 times greater than doubling the dose of 1 drug'

Conclusions from a meta-analysis comparing combination antihypertensive therapy with monotherapy in over 11,000 patients from 42 trials

Wald et al. Am J Med 2009;122:290–300

Multiple-mechanism Therapy: Potential Efficacy Benefits

Multiple-mechanism therapy results in a greater BP reduction than seen with its single-mechanism components[1,2]

- Components with a different mechanism of action interact on complementary pathways of BP control[1]
- Each component can potentially neutralize counter-regulatory mechanisms, e.g.
  - Diuretics reduce plasma volume, which in turn stimulates the renin-angiotensin-aldosterone system (RAAS) and thus increases BP; addition of a RAAS blocker attenuates this effect[1,2]
- Multiple-mechanism therapy may result in BP

BP = blood pressure

[1]Sica. Drugs 2002;62:443–62
[2]Quan et al. Am J Cardiovasc Drugs 2006;6:103–13

Multiple-mechanism Therapy: Potential Tolerability Benefits

Multiple-mechanism therapy may have an improved tolerability profile compared with its single-mechanism components[1,2]

- Components of multiple-mechanism therapy can be given at lower dosages to achieve blood pressure goal than those required as monotherapy → therefore better tolerated[1,2]
- Compound-specific adverse events can be attenuated, e.g.,[1,2]
  - Renin-angiotensin-aldosterone system blockers may attenuate the oedema that is caused by calcium channel blockers

[1]Sica. Drugs 2002;62:443–62
[2]Quan et al. Am J Cardiovasc Drugs 2006;6:103–13

Current Guidelines Recommend Initiating Combination Therapy Early in Patients with Stage 2 Hypertension or High Cardiovascular Risk

- JNC 7 guidelines recommend the consideration of initial therapy with two antihypertensive drugs when BP is more than 20/10 mmHg above goal[1]
- ESH/ESC guidelines state[2]:

'The combination of two antihypertensive drugs may offer advantages also for treatment initiation, particularly in patients at high cardiovascular risk in which early BP control may be desirable.'

BP = blood pressure
ESH = European Society of Hypertension
ESC = European Society of Cardiology
JNC = Joint National Committee

[1]Chobanian et al. Hypertension 2003;42:1206–52
[2]Mancia et al. Blood Press 2009;18:308–47

Overview: single-pill combination (SPC) therapy

- Why?
- When?
- What combination?

Why?

- Most people need more than one drug to achieve appropriate BP targets
  - we start treatment too late
  - many patients have lower recommended SBP goals of less than 130 mmHg (heart disease, kidney disease, diabetes)
  - high dietary salt intake
  - obesity/sleep apnea

BP = blood pressure
SBP = systolic blood pressure

Why?

- Most medications, when appropriately dosed, offer about 10/5 mmHg BP reduction
- The rule of 10’s

When?

- Most guidelines recommend starting two medications, preferably as a SPC, if BP is more than 20/10 mmHg from goal[1,2]

1. Chobanian AV, et al. Hypertension 2003;42:1206–52
2. Mancia G, et al. Eur Heart J 2007;28:1462–586
3. Flack JM, et al. Hypertension 2010;56:801–3

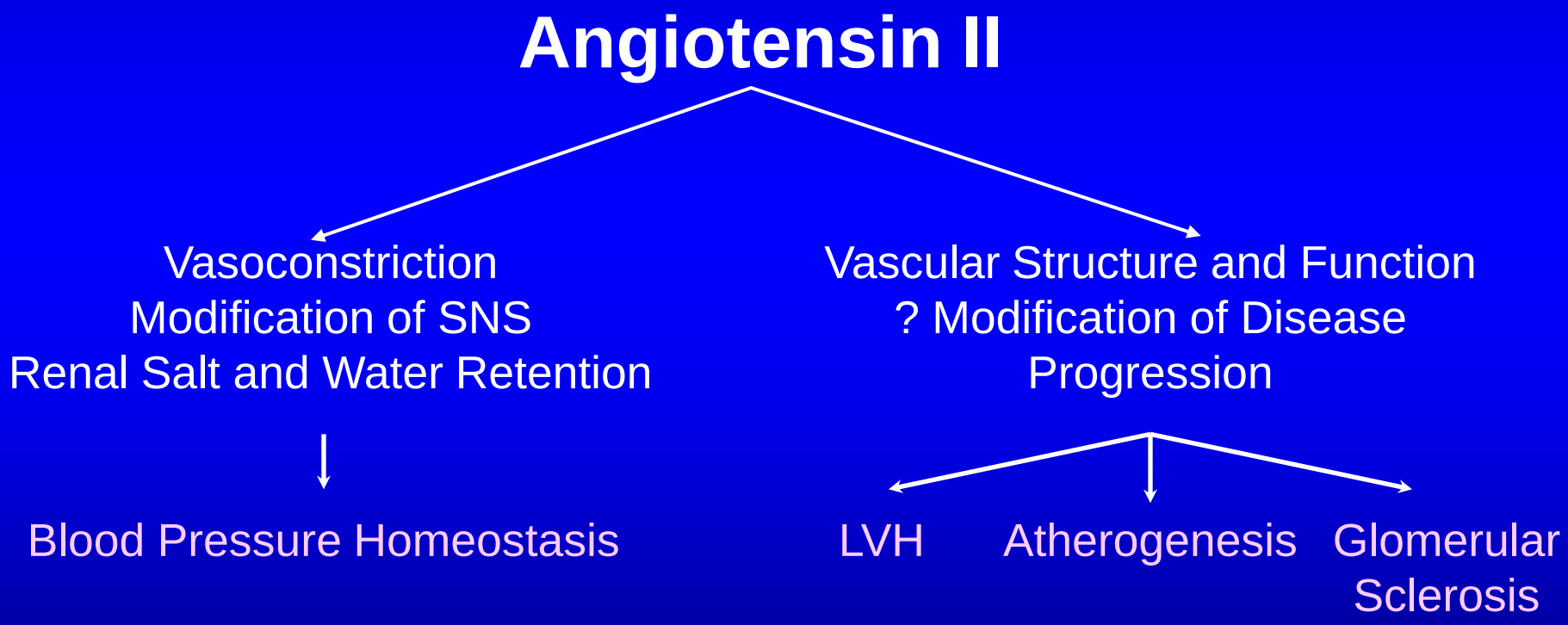
What combination?

- Many different combinations of medications are available
- One part of the SPC should include a RAAS blocker, as this is an important ‘foundation’ therapy

RAAS = renin-angiotensin-aldosterone system

Should RAAS blockade be considered the foundation of antihypertensive therapy?

Angiotensin II Dichotomy



The hypertension damage model

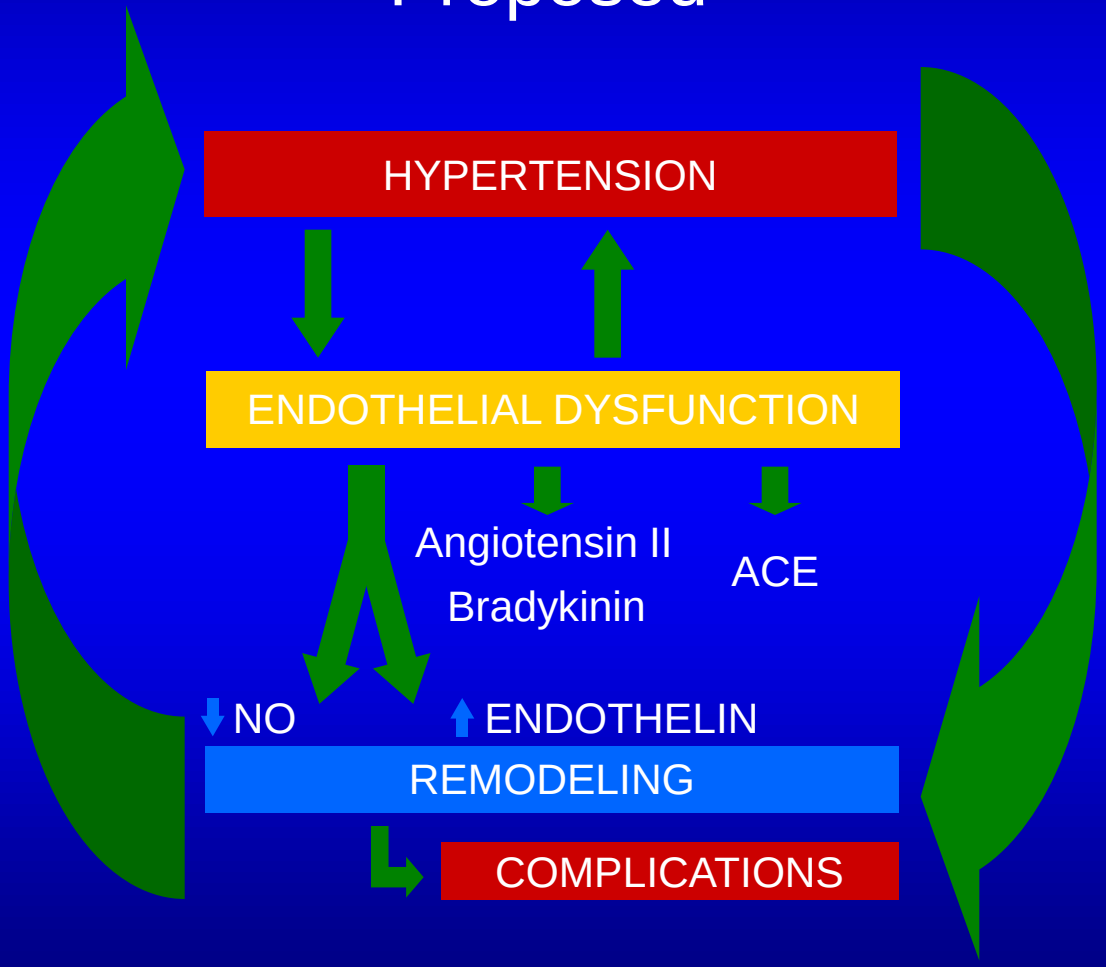
Classic

HYPERTENSION

HEMODYNAMIC OVERLOAD

COMPLICATIONS

Proposed



ACE = angiotensin converting enzyme

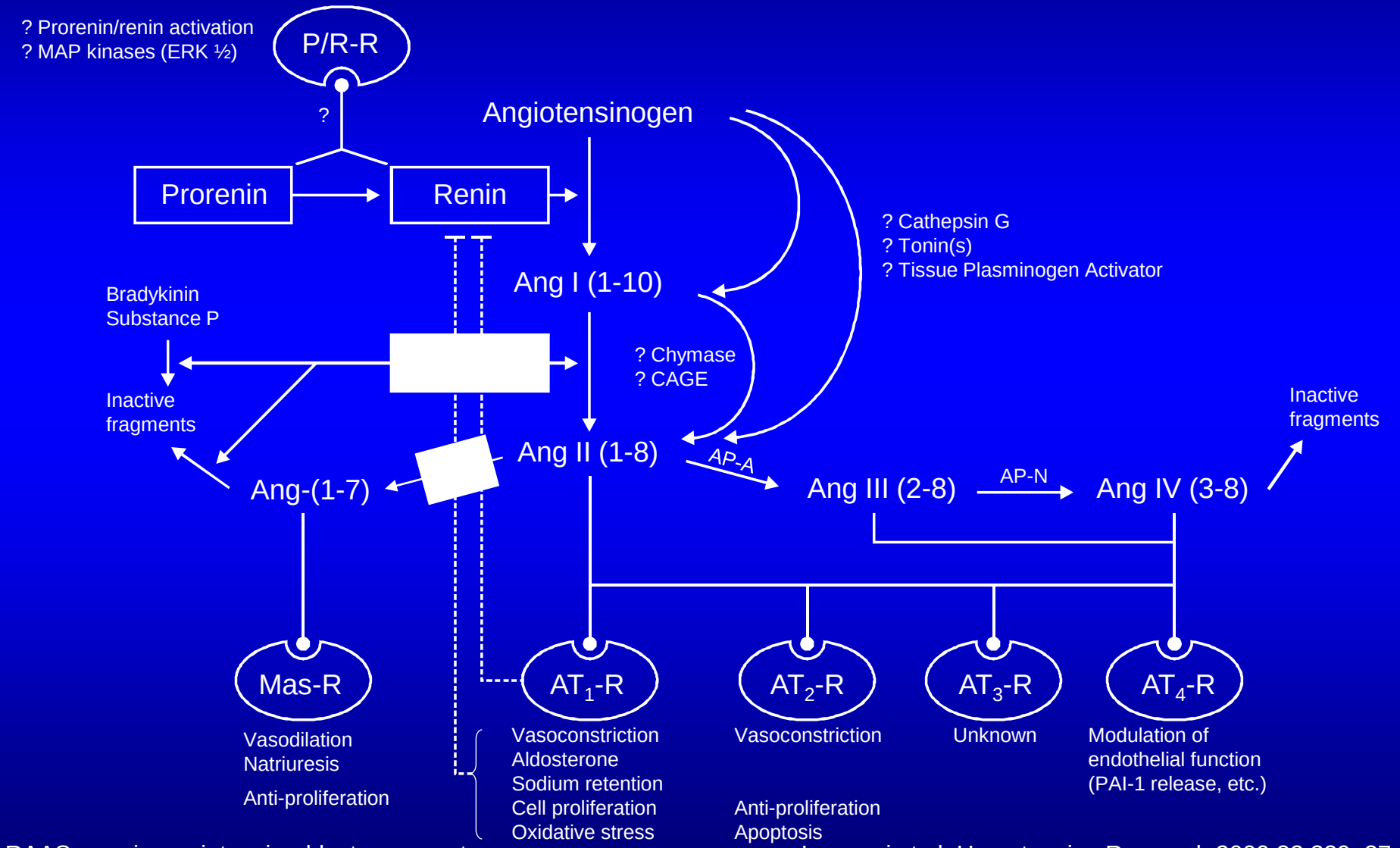
Alcocer L, Cardona EG. Hipertensiòn, SAM, 1998

- What factors might be clinically important with RAAS blockers?
- Is it simply better tolerability?

Vascular Benefits of RAAS Inhibition

- Endothelial Function
- Less Oxidative stress
- Diminished PAI-1
- Diminished TGF-beta

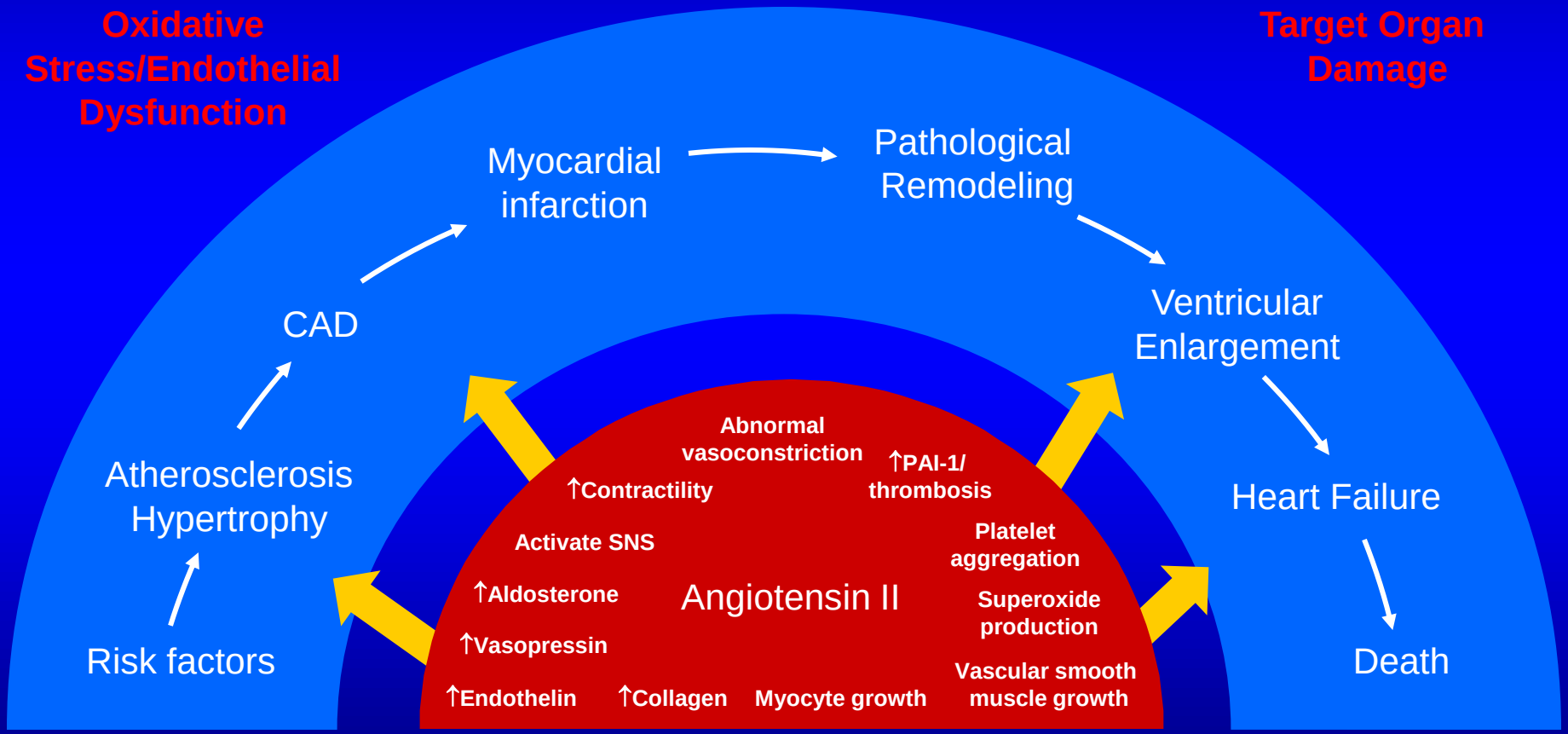
Emerging concept of the RAAS



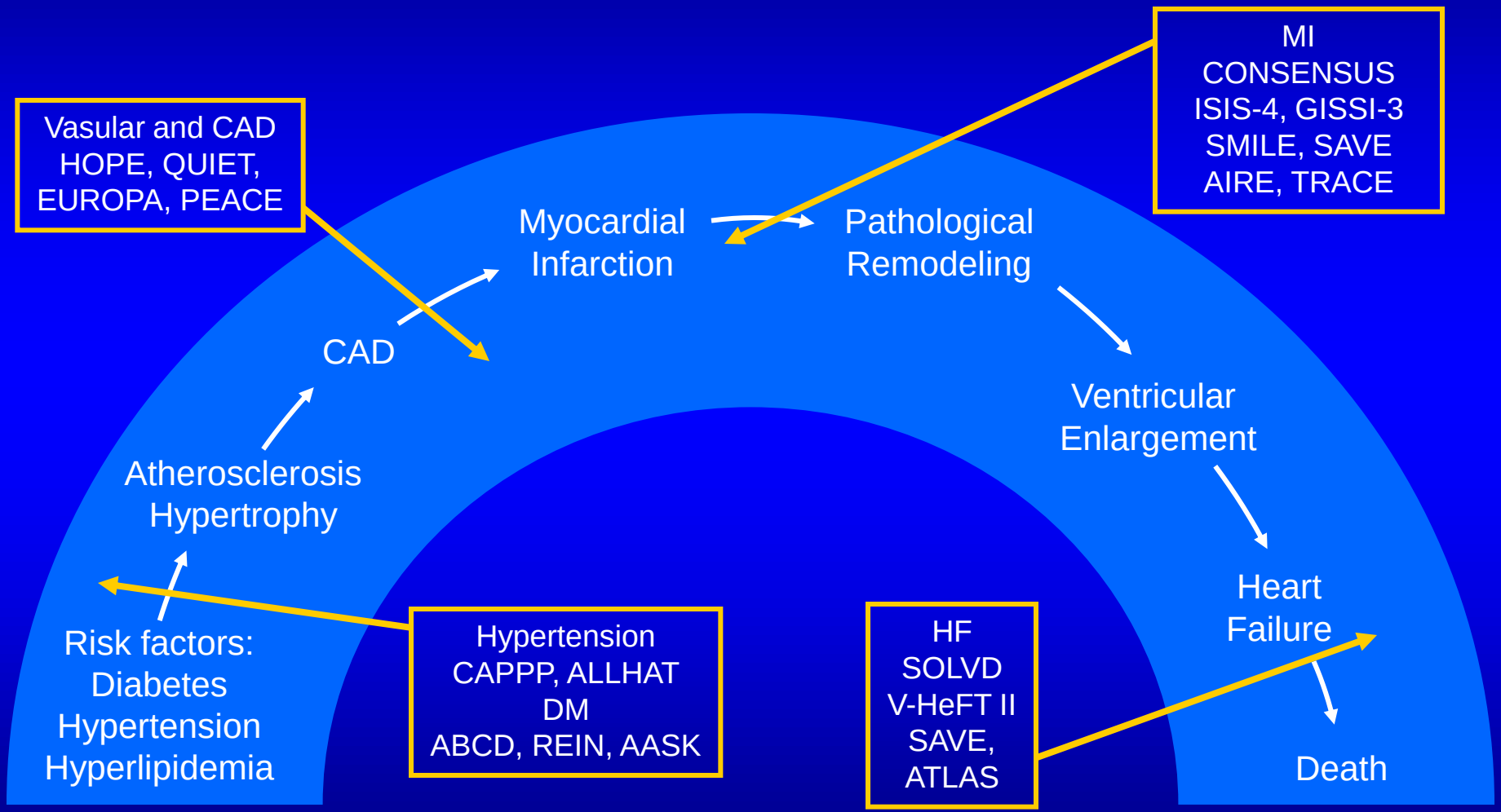
RAAS = renin-angiotensin-aldosterone system

Iwanami et al. Hypertension Research 2009;32:229–37

Angiotensin II and the cardiovascular continuum

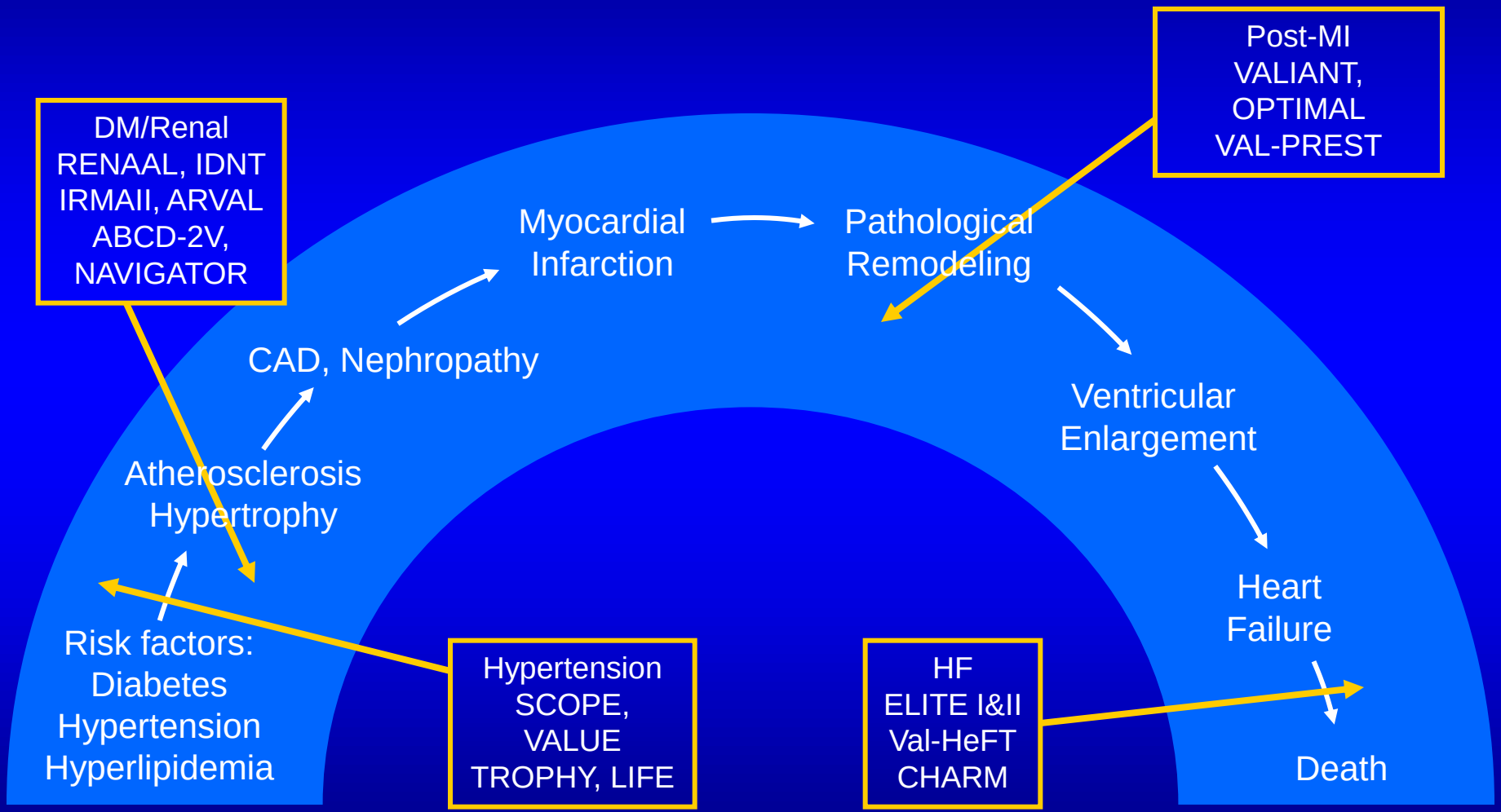


Clinical trials with ACEIs



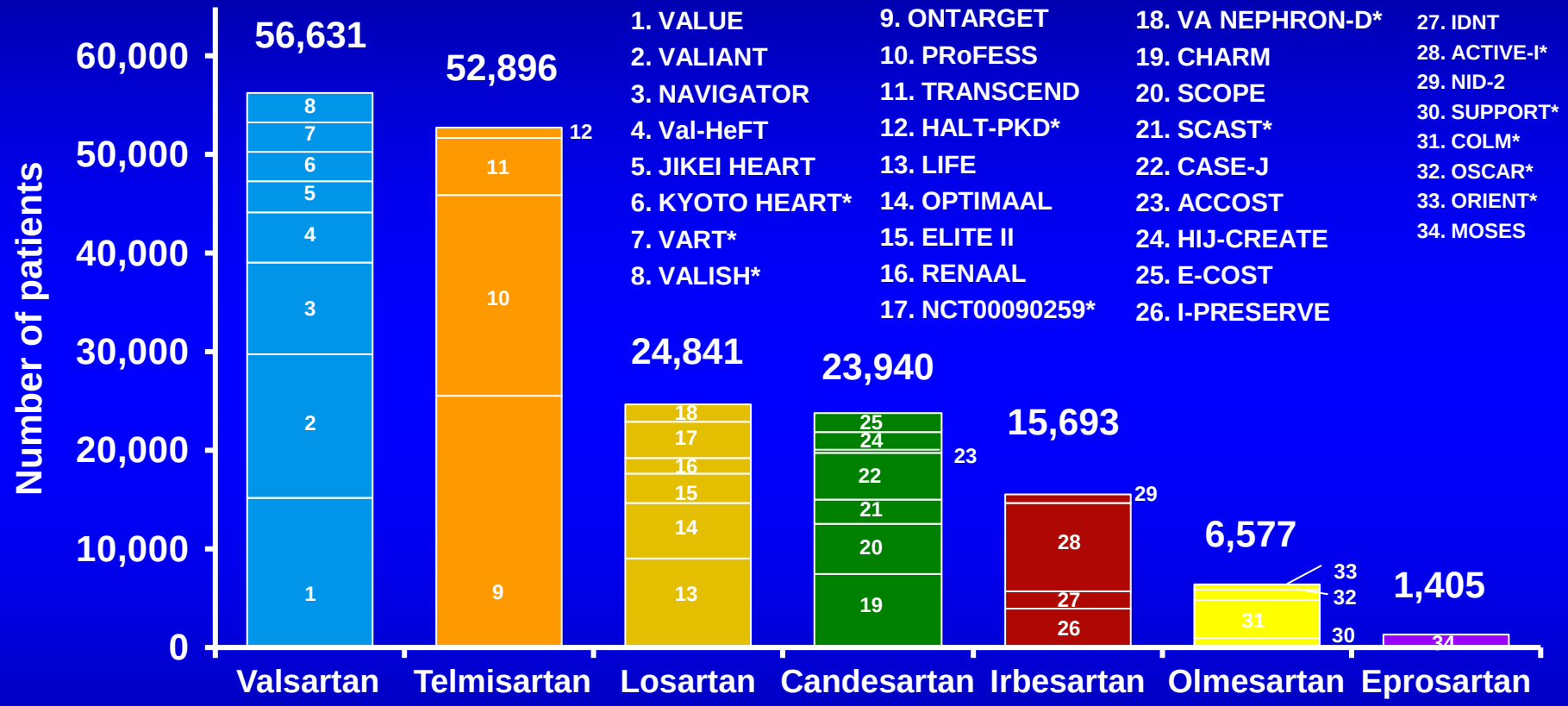
ACEIs = angiotensin-converting enzyme inhibitors

Clinical trials with ARBs



ARBs = angiotensin-receptor blockers

Mortality and Morbidity Endpoint Trials‡¶ with Angiotensin Receptor Blockers



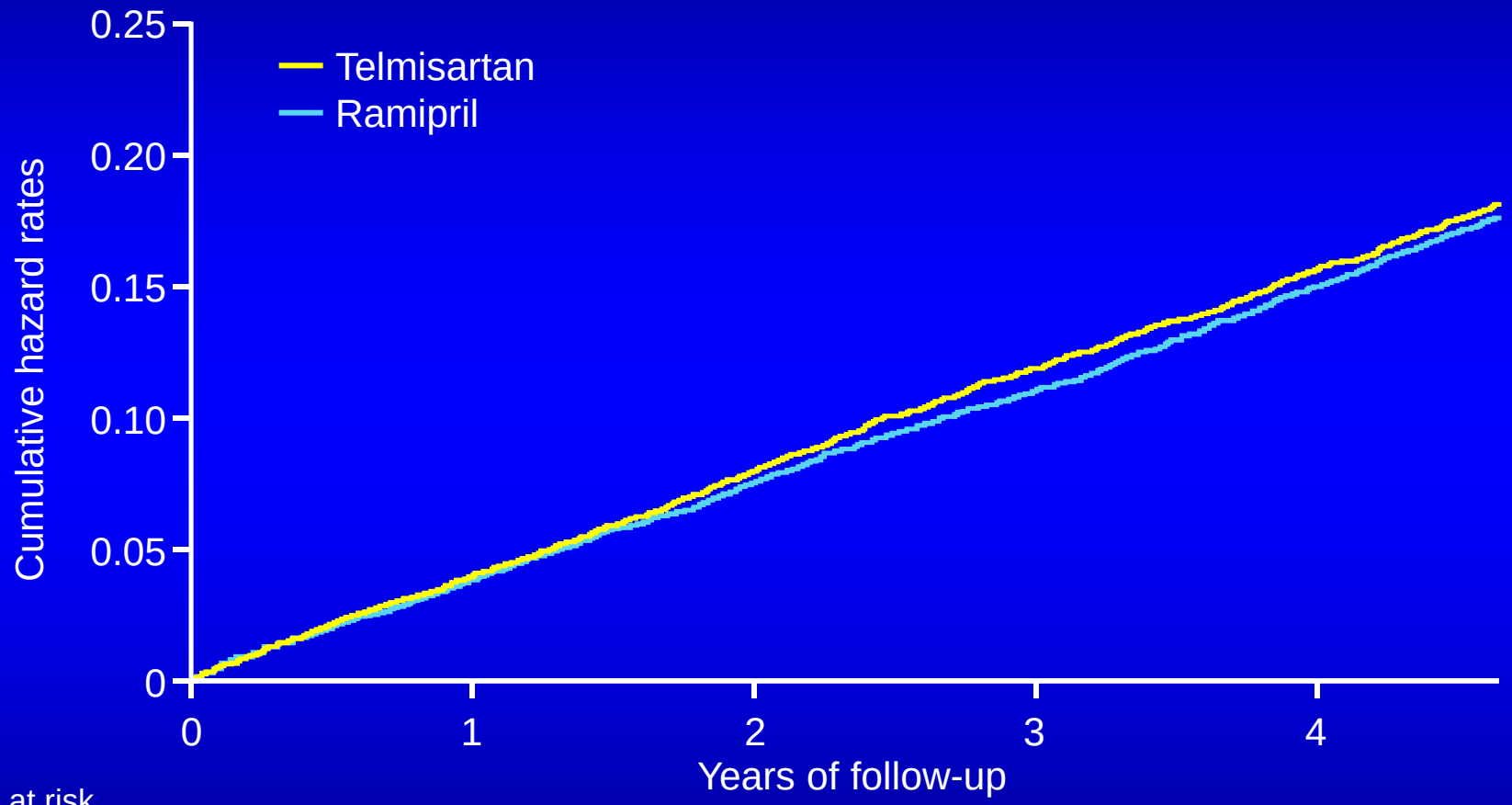
***Expected enrolment**

‡Ongoing and completed randomized controlled trials with death or hard CV events as or part of the primary endpoint

¶Valid as of January 2009

1. Julius et al. 2004; 2. Pfeffer et al. 2003; 3. Califf et al 2008; 4. Cohn et al. 2001; 5. Mochizuki et al. 2007; 6. http://clinicaltrials.gov (NCT00149227); 7. Nakayama et al. 2008; 8. NCT00151229; 9. ONTARGET Investigators 2008; 10. Yusuf et al 2008; 11. TRANSCEND Investigators 2008; 12. http://clinicaltrials.gov (NCT00283686); 13. Dahlöf et al. 2002; 14. Dickstein et al. 2002; 15. Pitt et al. 2000; 16. Brenner et al. 2001; 17. http://clinicaltrials.gov (NCT00090259); 18. http://clinicaltrials.gov (NCT00555217); 19. Pfeffer et al 2003; 20. Papademetriou et al. 2004; 21. http://clinicaltrials.gov (NCT00120003); 22. Ogihara et al. 2008; 23. http://clinicaltrials.gov (NCT00108706); 24. Laufs et al. 2008; 25. Suzuki et al. 2005; 26. Massie et al 2008; 27. Lewis et al. 2001; 28. http://clinicaltrials.gov (NCT00249795); 29. http://clinicaltrials.gov (NCT00535925); 30. http://clinicaltrials.gov (NCT00417222); 31. http://clinicaltrials.gov (NCT00454662); 32. http://clinicaltrials.gov (NCT00134160); 33. http://clinicaltrials.gov (NCT00141453); 34. Schrader et al. 2005

ONTARGET: time to primary outcome*

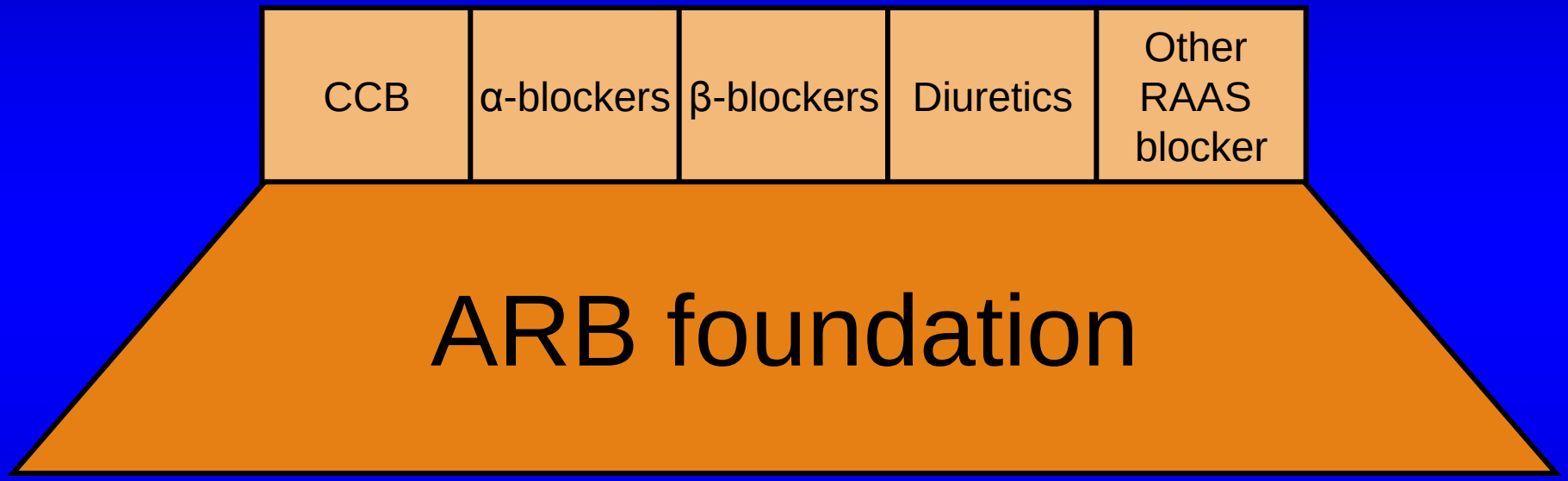


No. at risk					
Telmisartan	8,542	8,176	7,778	7,420	7,051
Ramipril	8,576	8,214	7,832	7,473	7,095

*Composite primary outcome of death from cardiovascular cause, MI, stroke, or hospitalization for HF

Yusuf S, et al. Presented at ACC 2008

RAAS blockade with ARBs can be considered a foundation of antihypertensive therapy



CCB = calcium channel blocker

A RAAS blocker and …?

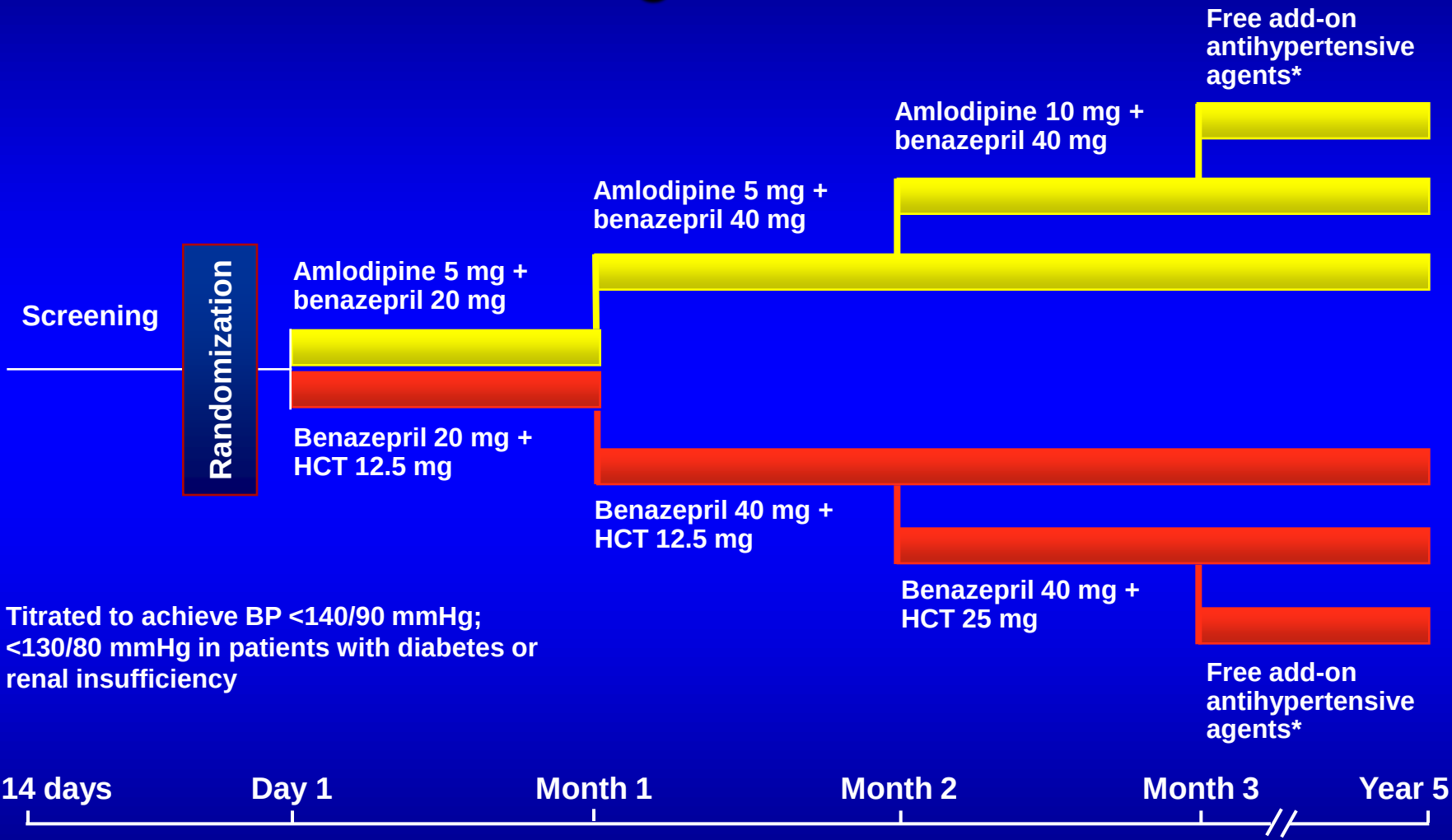
- Most patients need more than one drug
- Get to goal, and block the RAAS!
- Do you live longer if the RAAS blocker is paired with a thiazide diuretic or a CCB?
- Renin inhibitor? Two RAAS blockers?

A RAAS blocker

and

_____?

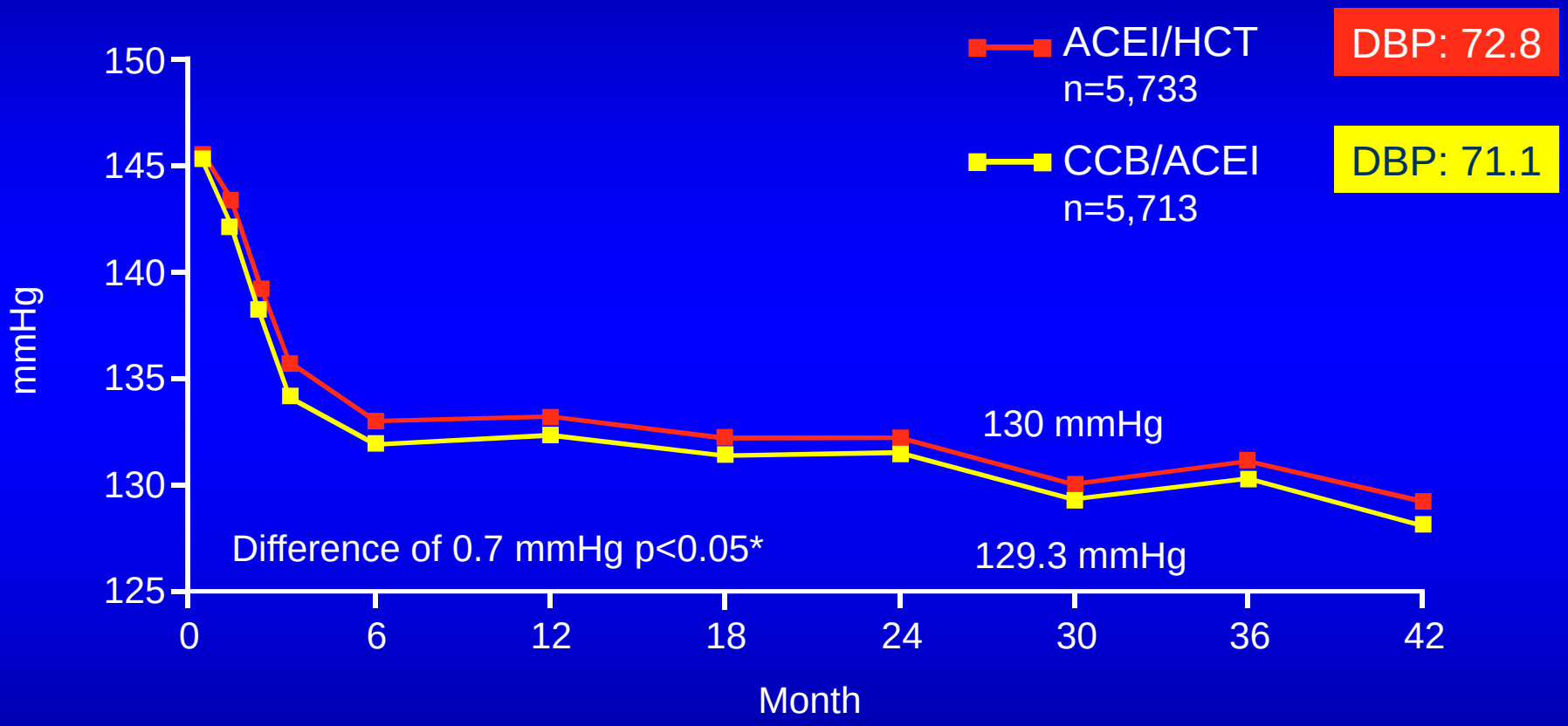
ACCOMPLISH: Design



*Beta blockers; alpha blockers; clonidine; (loop diuretics)
HCT = hydrochlorothiazide

Jamerson KA, et al. Am J Hypertens 2003;16(Pt. 2):193A

SBP over time



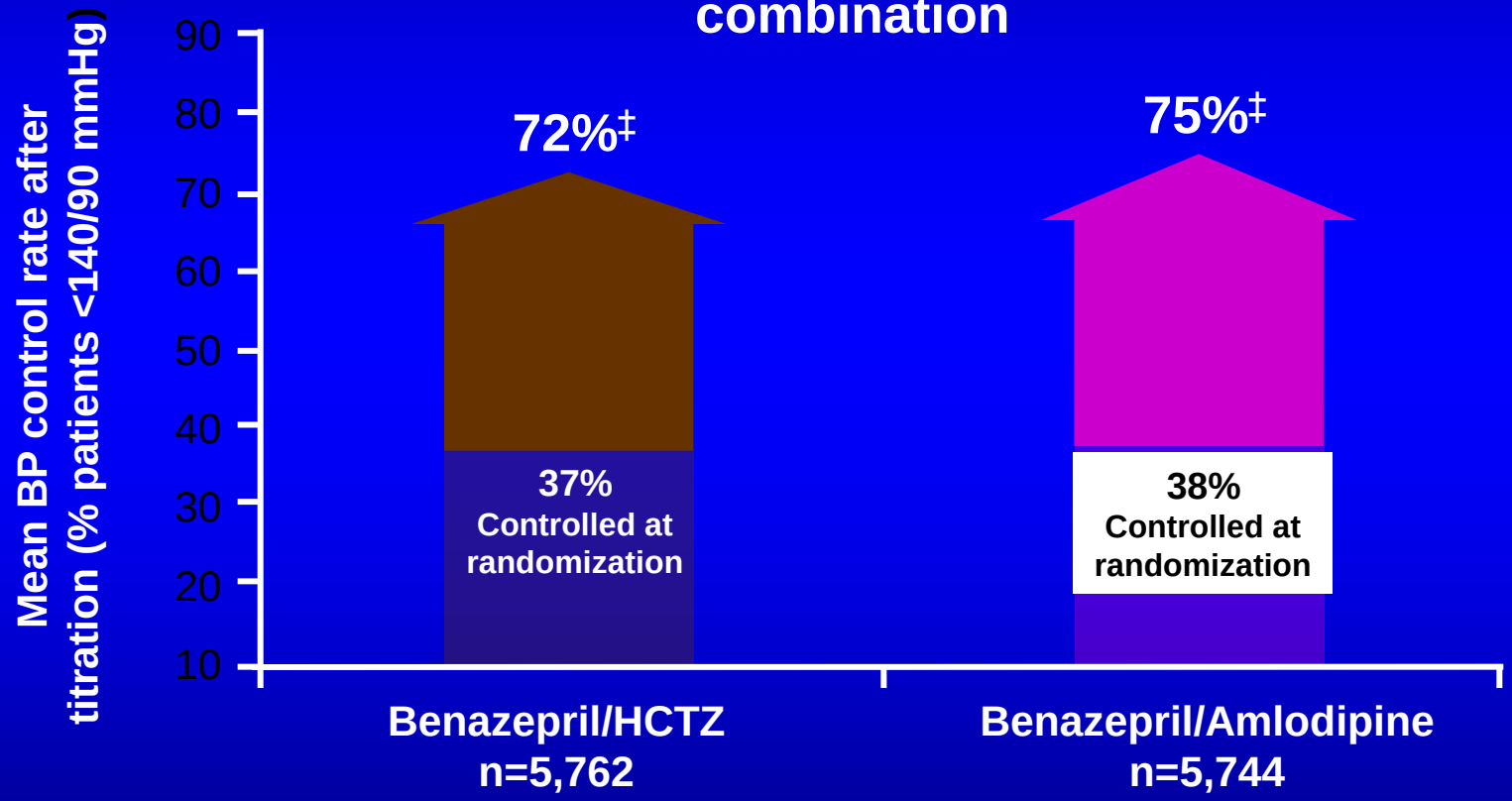
Patients							
5,731	5,387	5,206	4,999	4,804	4,285	2,520	1,045
5,709	5,377	5,154	4,980	4,831	4,286	2,594	1,075

*Mean values are taken at 30 months follow-up visit
DBP = diastolic blood pressure

Jamerson KA, et al. Presented at ACC 2008

ACCOMPLISH: Impressive Blood Pressure (BP) Control* Rates Achieved with Single-pill Combination-based Therapies

Only ~37% of patients had their BP controlled at baseline despite ~74% of patients receiving ≥2 antihypertensive agents as free combination



*Control defined as BP <140/90 mmHg

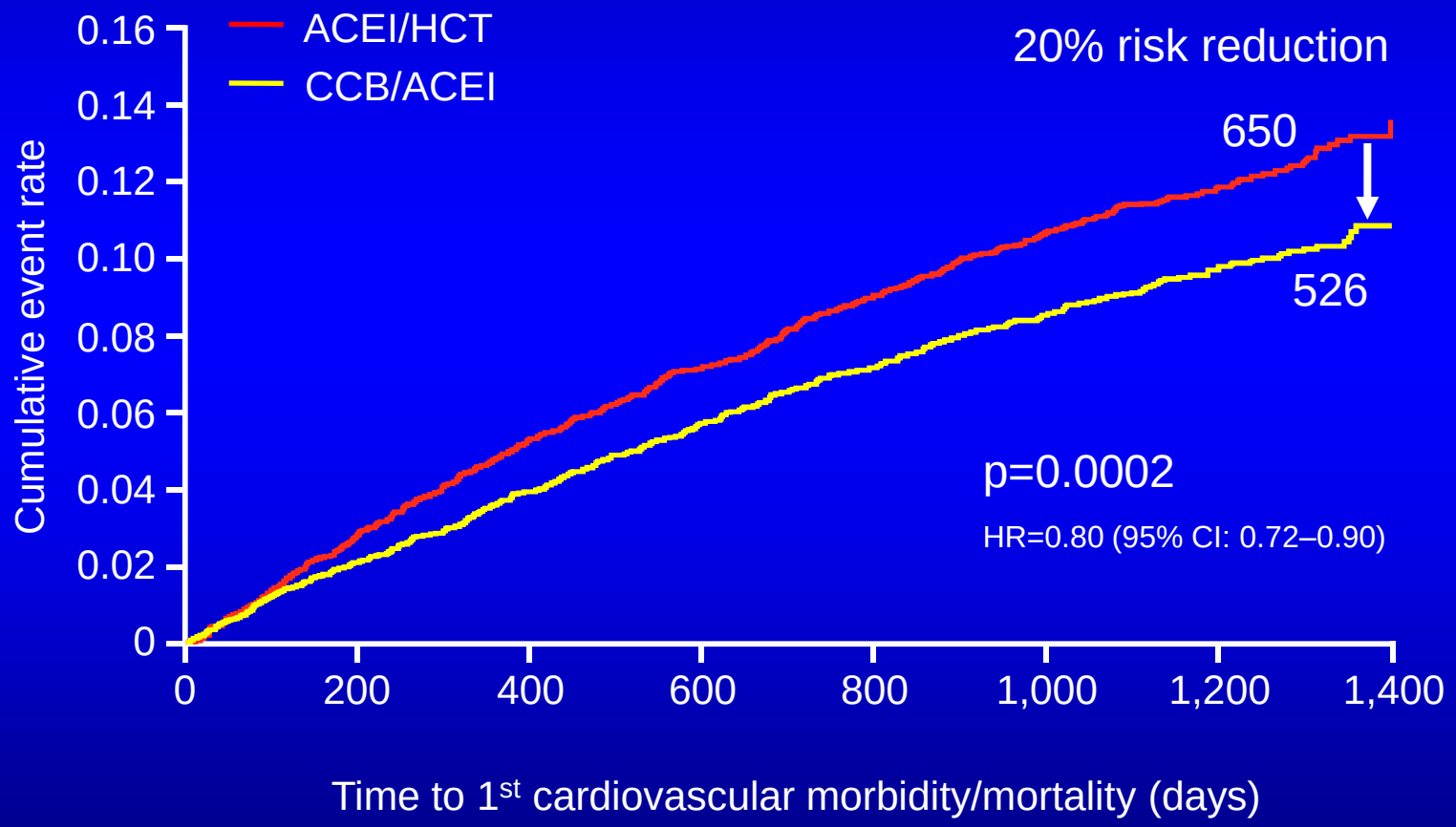
‡Values calculated from mean BP after titration and mean BP control rate over the duration of the study

ACCOMPLISH = Avoiding Cardiovascular events through COMbination therapy in Patients LIving with Systolic Hypertension; HCTZ = hydrochlorothiazide

Jamerson et al. N Engl J Med 2008;359:2417–28

Jamerson et al. Presented at ACC 2008

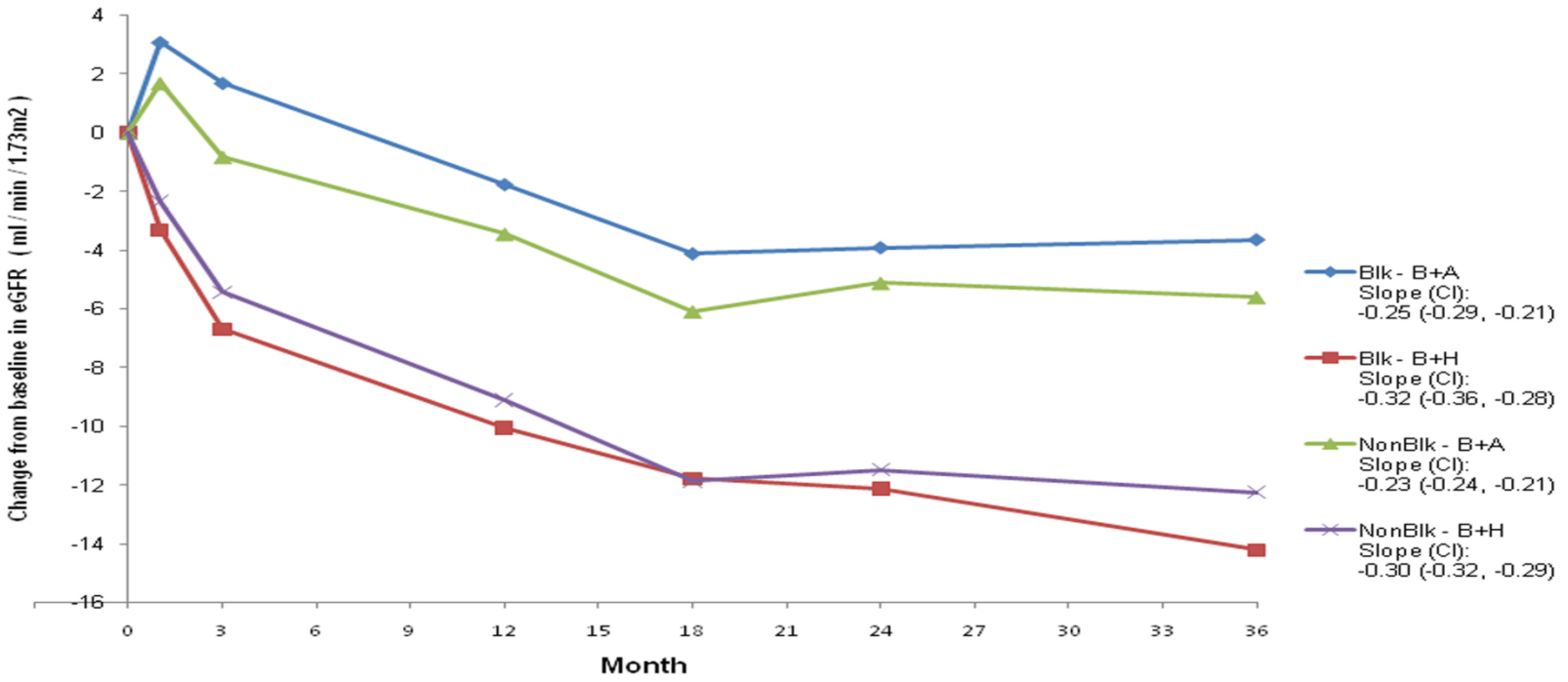
Kaplan-Meier for primary endpoint



INTERIM RESULTS Mar 08
CI = confidence interval; HR = hazard ratio

Jamerson KA, et al. Presented at ACC 2008

Change in Estimated GFR in Hypertensive Treated with B+A or B+H



Number of patients

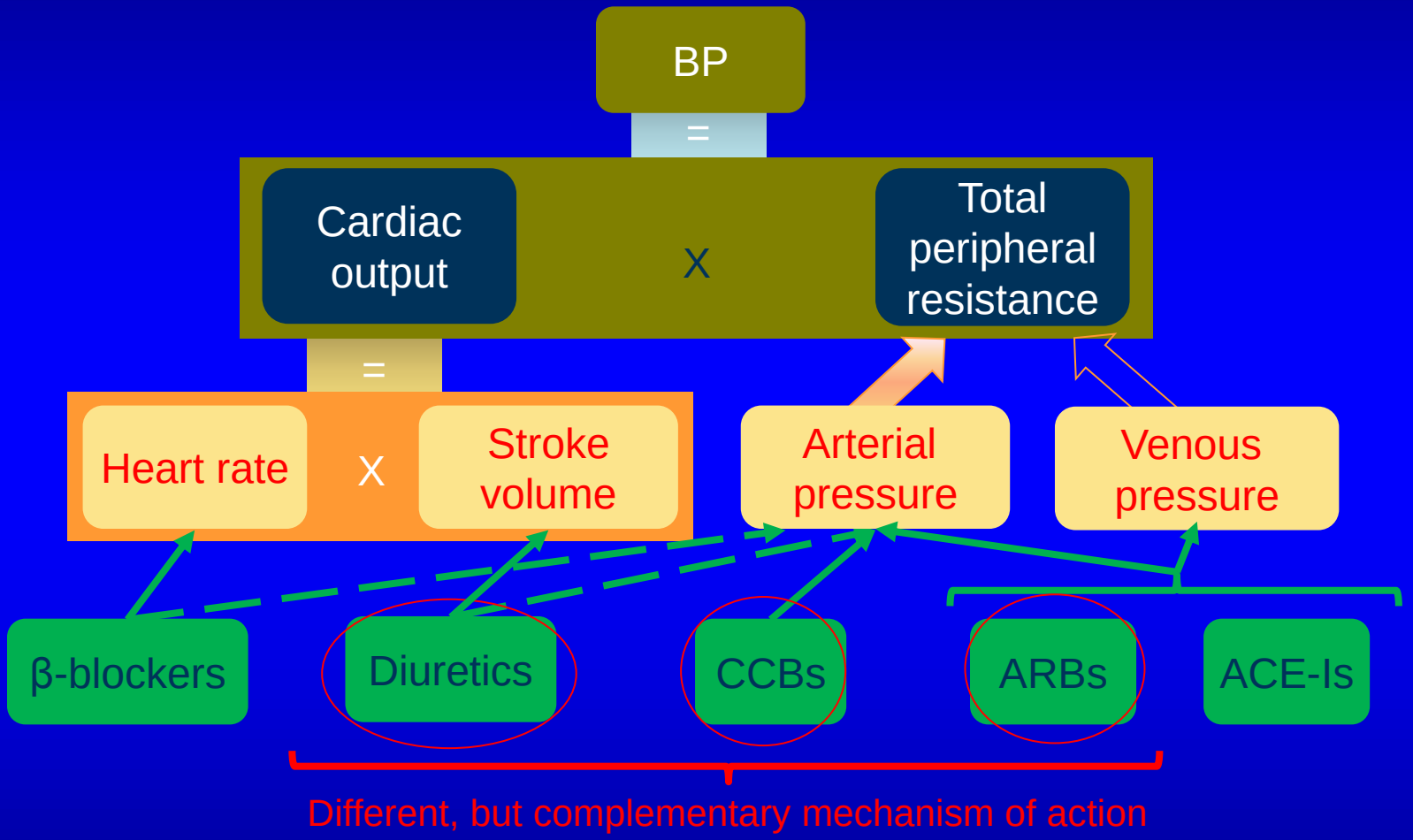
Blk B+A	692	652	614	522	491	462	249
Blk B+H	718	672	650	555	534	489	246
Non-Blk B+A	3363	3250	3167	2910	2786	2705	1654
Non-Blk B+H	3359	3237	3147	2921	2754	2652	1604

eGFR: estimated glomerular filtration rate; B+A: benazepril + amlodipine; B+H: benazepril + hydrochlorothiazide CI: 95% confidence interval
Slope difference between B+A and B+H calculated from baseline: Blacks ($p=0.017$) Non-Blacks ($p<0.0001$)

HCT vs CCB as the add on to the RAAS blocker

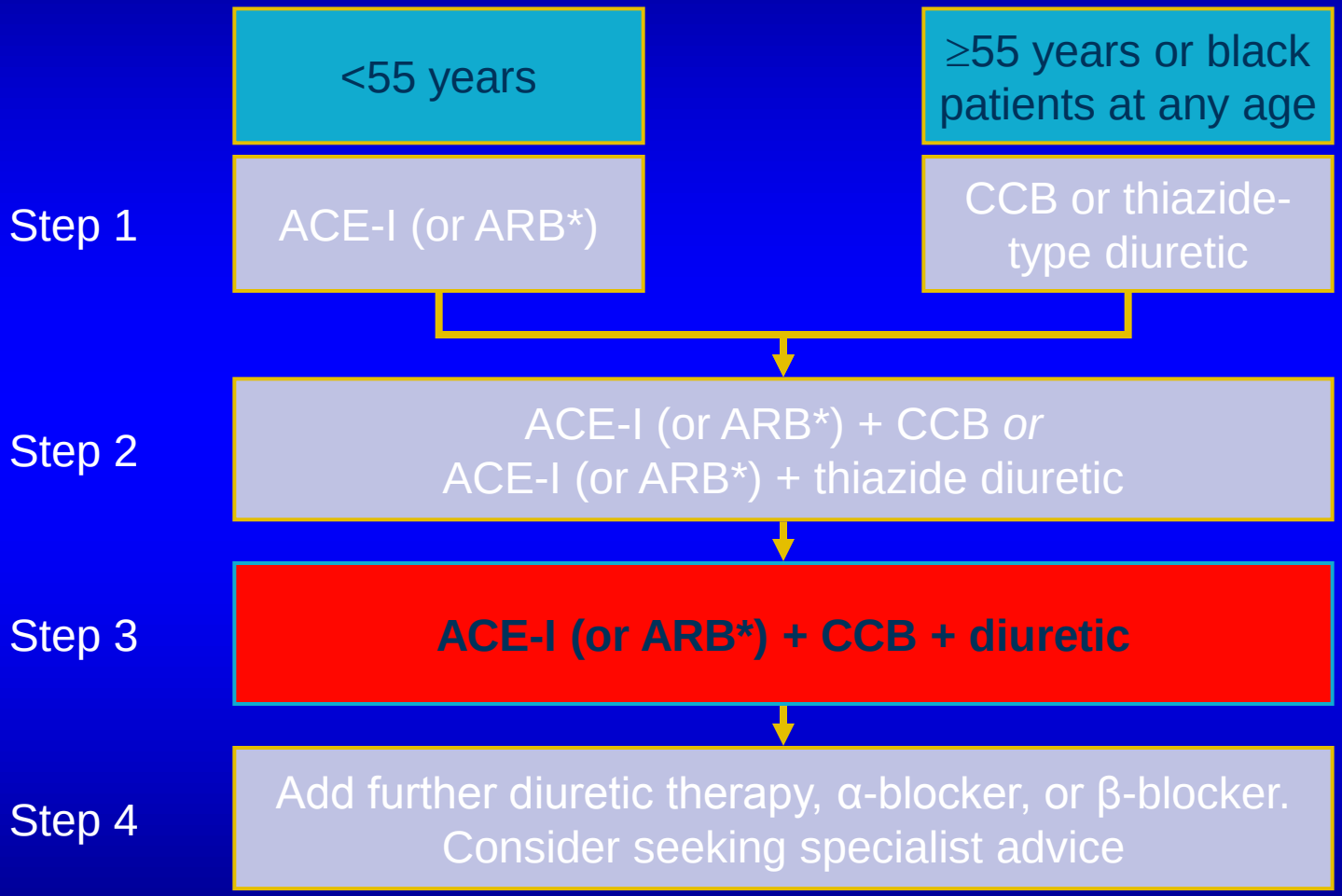
- Efficacy
- Tolerability
  - men, CCB?
  - women, HCT?
- Ability to prevent cardiovascular/renal events

Combining agents with multiple, complementary mechanisms of action



Beevers et al. BMJ 2001;322:912–6; McGhee et al. Crit Care Nurse 2002;22:60–4;
Goodman & Gilman's Pharmacological Basis of Therapeutics. 9th ed. 1995

RAS blocker/CCB/diuretic combinations recognised in UK NICE guidelines for the treatment of hypertension



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*If ACE-I not tolerated

National Institute for Health and Clinical Excellence (NICE) (2006)
Hypertension: management of hypertension in adults in primary care (Quick Reference Guide)
London: NICE. Available from http://www.nice.org.uk/nicemedia/live/10986/30113/30113.pdf. Reproduced with permission

Components supported by a wealth of evidence in CV outcomes trials

Amlodipine	Valsartan	Thiazide diuretics
PREVENT[1]	VALUE[7]	
CAMELOT[2]	VALIANT[8]	HAPPHY[14]
ASCOT[3,4]	Val-HeFT[9-11]	SHEP[15]
ALLHAT[5]	JIKEI HEART[12]	ALLHAT[16]
ACCOMPLISH[6]	KYOTO HEART[13]	

[1]Pitt et al. Circulation 2000;102:1503–10; [2]Nissen et al. JAMA 2004;292:2217–26; [3]Dahlöf et al. Lancet 2005;366:895–906; [4]Williams et al. Circulation 2006;113:1213–25; [5]Leenen et al. Hypertension 2006;48:374–84; [6]Jamerson et al. N Engl J Med 2008;359:2417–28; [7]Julius et al. Lancet 2004;363:2022–31; [8]Pfeffer et al. N Engl J Med 2003;349:1893–906; [9]Maggioni et al. Am Heart J 2005;149:548–57; [10]Wong et al. J Am Coll Cardiol 2002;40:970–5; [11]Cohn et al. N Engl J Med 2001;345:1667–7; [12]Mochizuki et al. Lancet 2007;369:1431–9; [13]Sawada et al. Eur Heart J 2009;30:2461–69; [14]Wilhelmsen et al. J Hypertens 1987;5:561-72; [15]Hulley et al. Am J Cardiol. 1985;56:913-20; [16]The ALLHAT Investigators. JAMA 2002;288:2981–97

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Amlodipine has a wealth of CV outcomes data

PREVENT[1] 825 CAD patients (≥30%): Multicentre, randomised, placebo controlled	Primary outcome: No difference in mean 3 year coronary angiographic changes vs. placebo 35% ↓ hospitalisation for heart failure + angina 43% ↓ revascularisation procedures
CAMELOT[2] 1,991 CAD patients (>20%): Double-blind, randomised study vs. placebo and enalapril 20 mg	Primary outcome: 31% ↓ in CV events vs. placebo 42% ↓ hospitalisation for angina 27% ↓ coronary revascularisation
ASCOT-BPLA/CAFE[3,4] 19,257 hypertension patients: Multicentre, randomised, prospective study vs. atenolol	Primary outcome: 10% ↓ in non-fatal MI & fatal CHD 16% ↓ total CV events and procedures 30% ↓ new-onset diabetes 23% ↓ stroke 11% ↓ all-cause mortality ↓ central aortic pressure by 4.3 mmHg
ALLHAT[5] 18,102 hypertension patients: Randomised, prospective study vs. lisinopril	Primary outcome: No difference in composite of fatal CHD + non-fatal MI vs. lisinopril 6% ↓ combined CVD 23% ↓ stroke
ACCOMPLISH[6] 11,506 hypertension patients: Double-blind, randomised study vs. HCTZ (both in combination with benazepril)	Primary outcome: 20% ↓ in composite of death from CV causes, nonfatal MI/stroke, hospitalisation for angina, resuscitation after sudden cardiac arrest, and coronary revascularisation 21% ↓ death from CV causes + nonfatal MI/stroke 17% ↓ CV events

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[1]Pitt et al. Circulation 2000;102:1503–10; [2]Nissen et al. JAMA 2004;292:2217–26; [3]Dahlöf et al. Lancet 2005;366:895–906; [4]Williams et al. Circulation 2006;113:1213–25; [5]Leenen et al. Hypertension 2006;48:374–84; [6] Jamerson et al. N Engl J Med 2008;359:2417–28

Valsartan has a wealth of CV outcomes data

VALUE[1] 15,245 high-risk hypertension patients: Double-blind, randomised study vs. amlodipine	No difference in composite of cardiac mortality and morbidity (primary) 23% ↓ new-onset diabetes
VALIANT[2] 14,703 MI patients: Double-blind, randomised study vs. captopril and vs. captopril + valsartan	No difference vs. captopril in all-cause mortality (primary) (valsartan is as effective as standard of care)
Val-HeFT[3–5] 5,010 heart failure II–IV patients: Double-blind, randomised study vs. placebo	13% ↓ morbidity and mortality (primary) ↓ left ventricular remodelling 37% ↓ AF occurrence ↓ heart failure signs/symptoms 28% ↓ heart failure hospitalisation
JIKEI HEART[6] 3,081 Japanese patients on conventional treatment for hypertension, CHD, heart failure or combination of these: Multicentre, randomised, controlled trial comparing addition of valsartan vs. non-ARB to conventional treatment	39% ↓ composite CV mortality and morbidity 40% ↓ Stroke/TIA 47% ↓ Hospitalisation for heart failure 65% ↓ Hospitalisation for angina
KYOTO HEART[7] 3,031 Japanese patients on conventional treatment for hypertension and high CV risk; Multicentre PROBE trial comparing addition of valsartan vs. non-ARB to conventional treatment	45% ↓ Composite CV mortality and morbidity 45% ↓ Stroke/TIA 49% ↓ Angina pectoris 33% ↓ New-onset diabetes

[1]Julius et al. Lancet 2004;363:2022–31; [2]Pfeffer et al. N Engl J Med 2003;349:1893–906 [3]Maggioni et al. Am Heart J 2005;149:548–57; [4]Wong et al. J Am Coll Cardiol 2002;40:970–5; [5]Cohn et al. N Engl J Med 2001;345:1667–7; [6]Mochizuki et al. Lancet 2007;369:1431–9; [7] Sawada et al. Eur Heart J 2009;30:2461–69

HCTZ has been studied widely in hypertension

- Thiazide diuretics are the first-line recommendation in patients with uncomplicated hypertension,[1] based on results of several large trials[2-4]
- Diuretics are also widely used for enhancing hypertensive efficacy in multi-drug regimens, including in combination with ARBs and CCBs[1]
- The ALLHAT study provided important evidence supporting the use of thiazide diuretics in patients with hypertension[4]
- HCTZ has been shown to enhance antihypertensive efficacy when combined with Valsartan in numerous controlled clinical trials[5]
  - More than 4,000 patients have been included in the Valsartan/HCTZ groups[5]
  - HCTZ resulted in additive placebo-adjusted decreases in SBP and DBP when combined with Valsartan[5]

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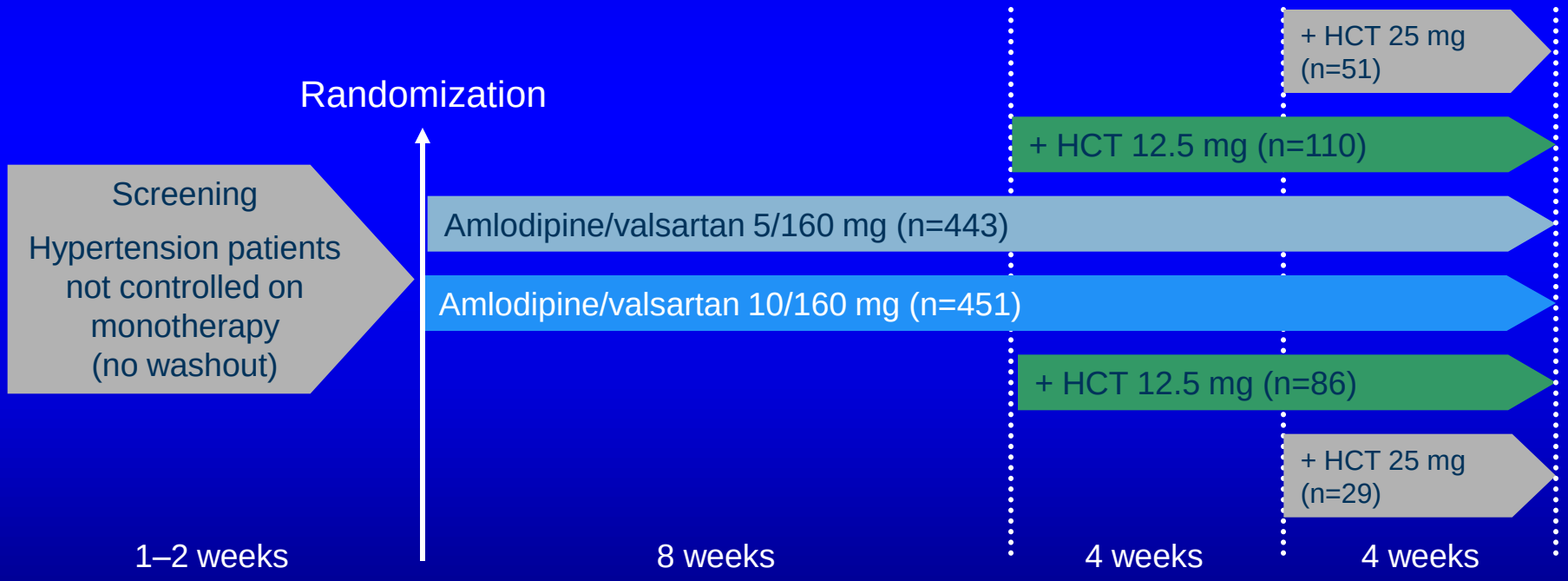
[1]Chobanian et al. Hypertension 2003;42:1206–52; [2]Wilhelmsen et al. J Hypertens. 1987;5:561—72; [3]Hulley et al. Am J Cardiol. 1985;56:913—20; [4]The ALLHAT investigators. JAMA 2002;288:2981–97; [5]DIOVAN-HCT prescribing information. Novartis July 2008

EX-FAST study design

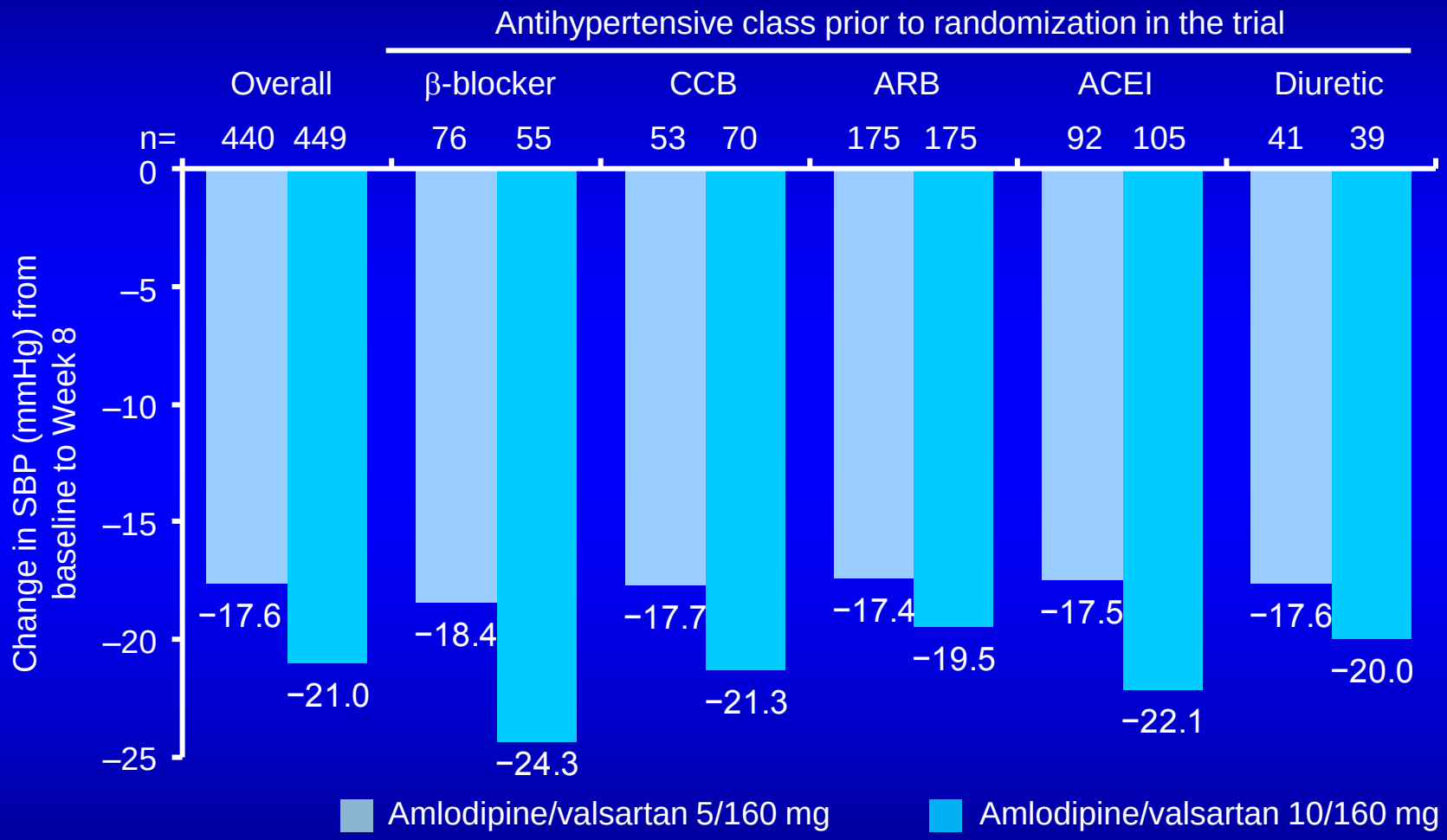
- Primary endpoint: proportion of patients reaching BP control after 16 weeks
  - msSBP <140 mmHg and msDBP <90 mmHg for patients with no diabetes
  - msSBP <130 mmHg and msDBP <80 mmHg for patients with diabetes
- Mean baseline BP: 150/91 mmHg



msDBP = mean sitting DBP; msSBP = mean sitting SBP

Allemann Y, et al. J Clin Hypertens 2008;10:185–94

Incremental BP drops after direct switch to amlodipine/valsartan in patients previously uncontrolled on monotherapy: Week 8



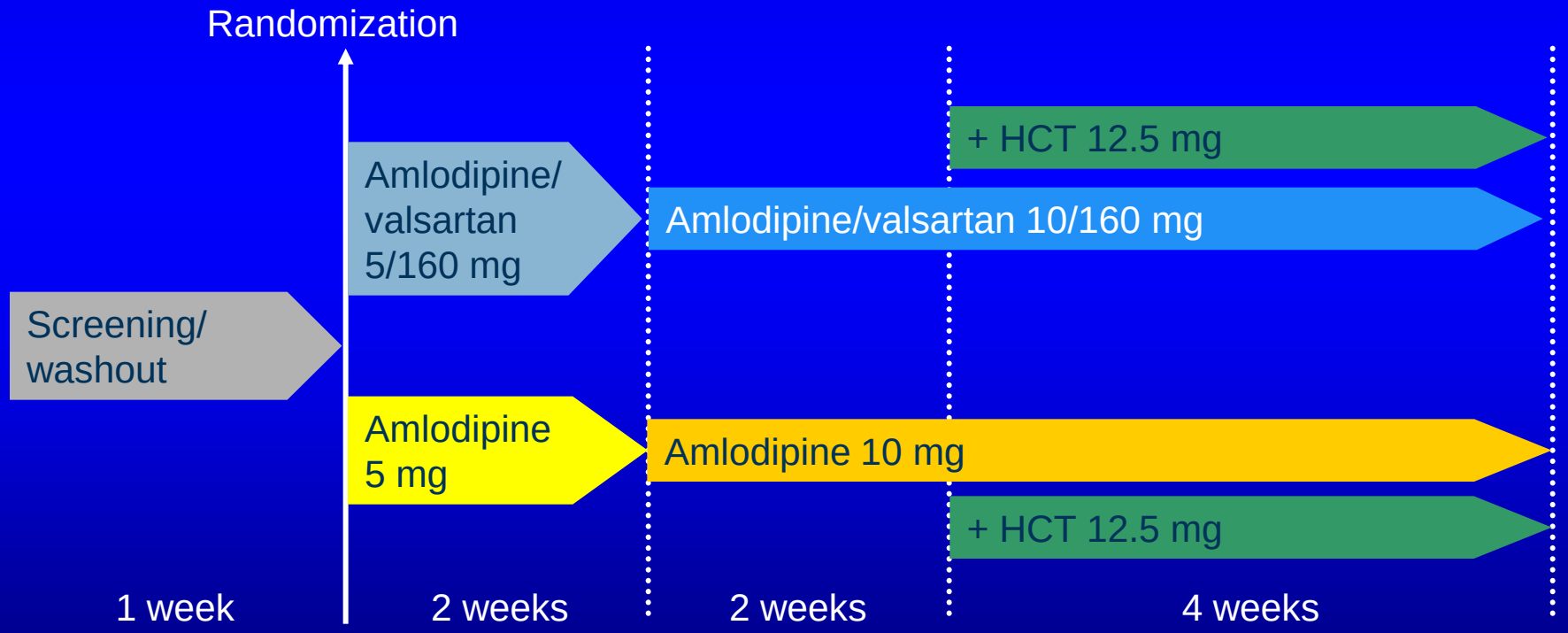
Week 8 msSBP, mmHg	Overall	β-blocker	CCB	ARB	ACEI	Diuretic
	131.9 129.8	130.1 128.8	132.9 131.7	132.8 130.8	131.4 127.1	131.1 130.0

Baseline BP: 150/91 mmHg

Allemann Y, et al. J Clin Hypertens 2008;10:185–94

EX-EFFeCTS study design

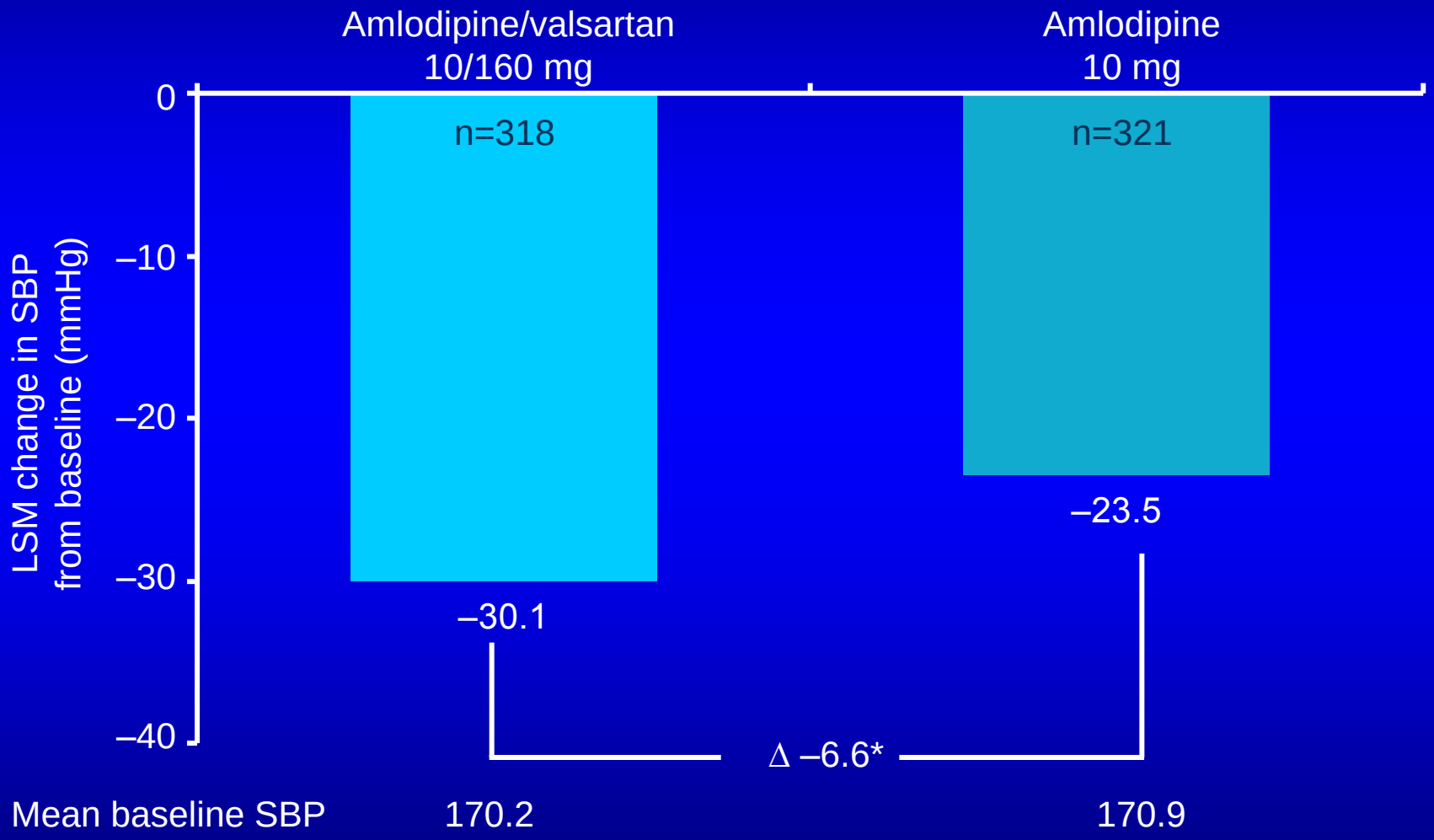
- Primary endpoint: change in SBP from baseline compared with amlodipine 10 mg alone, at Week 4 prior to HCT, in patients with stage 2 hypertension*
- Baseline msSBP: 171 mmHg



*Stage 2 hypertension defined as msSBP ≥160 mmHg

Destro M, et al. J Am Soc Hypertens 2008;2:294–302

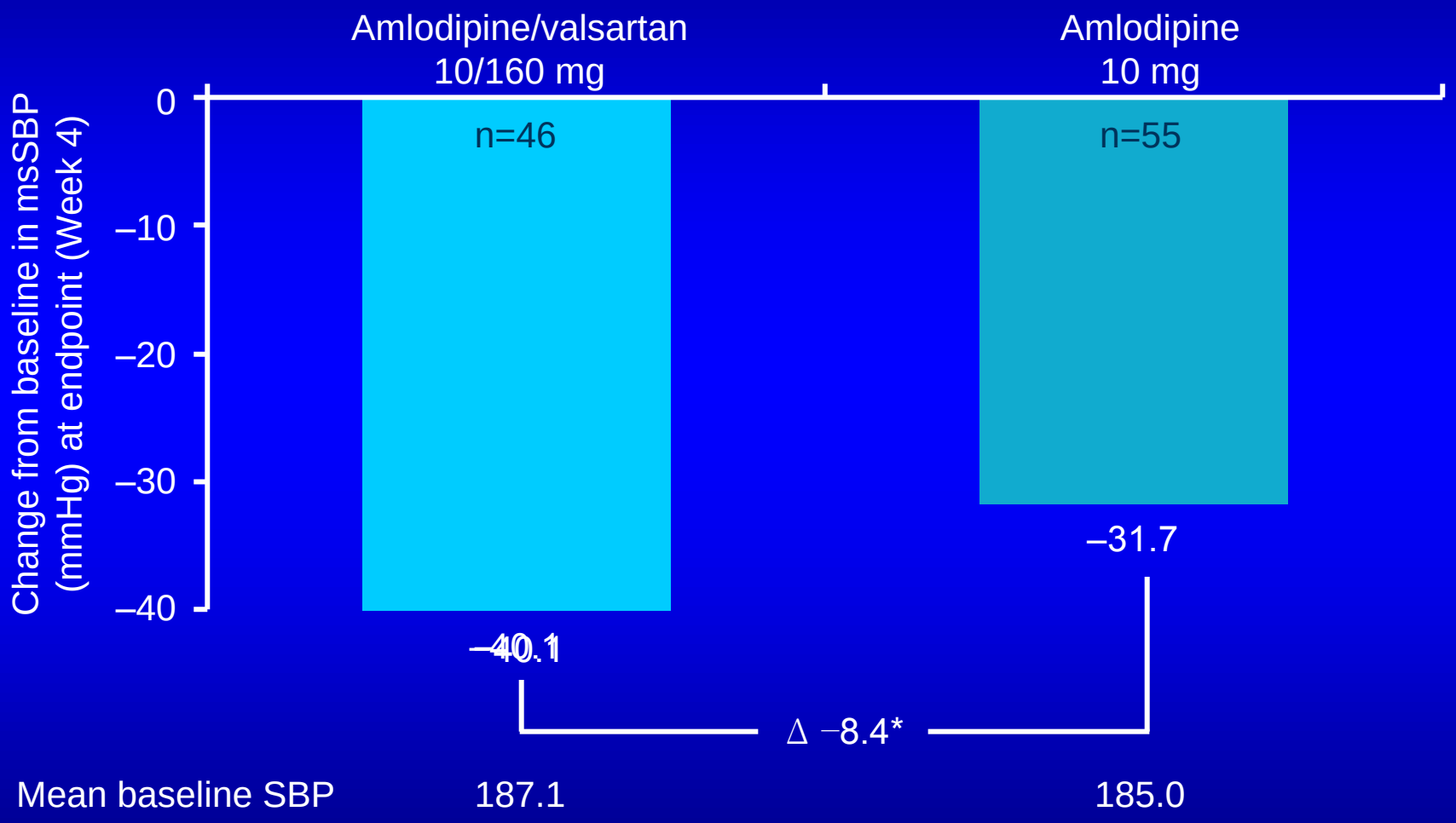
Amlodipine/valsartan provides superior SBP reductions in stage 2 patients at Week 4 (endpoint)



*p<0.0001 vs amlodipine 10 mg
LSM = least squares mean

Destro M, et al. J Am Soc Hypertens 2008;2:294–302

Amlodipine/valsartan SBP reductions in severe† patients at Week 4 (endpoint)

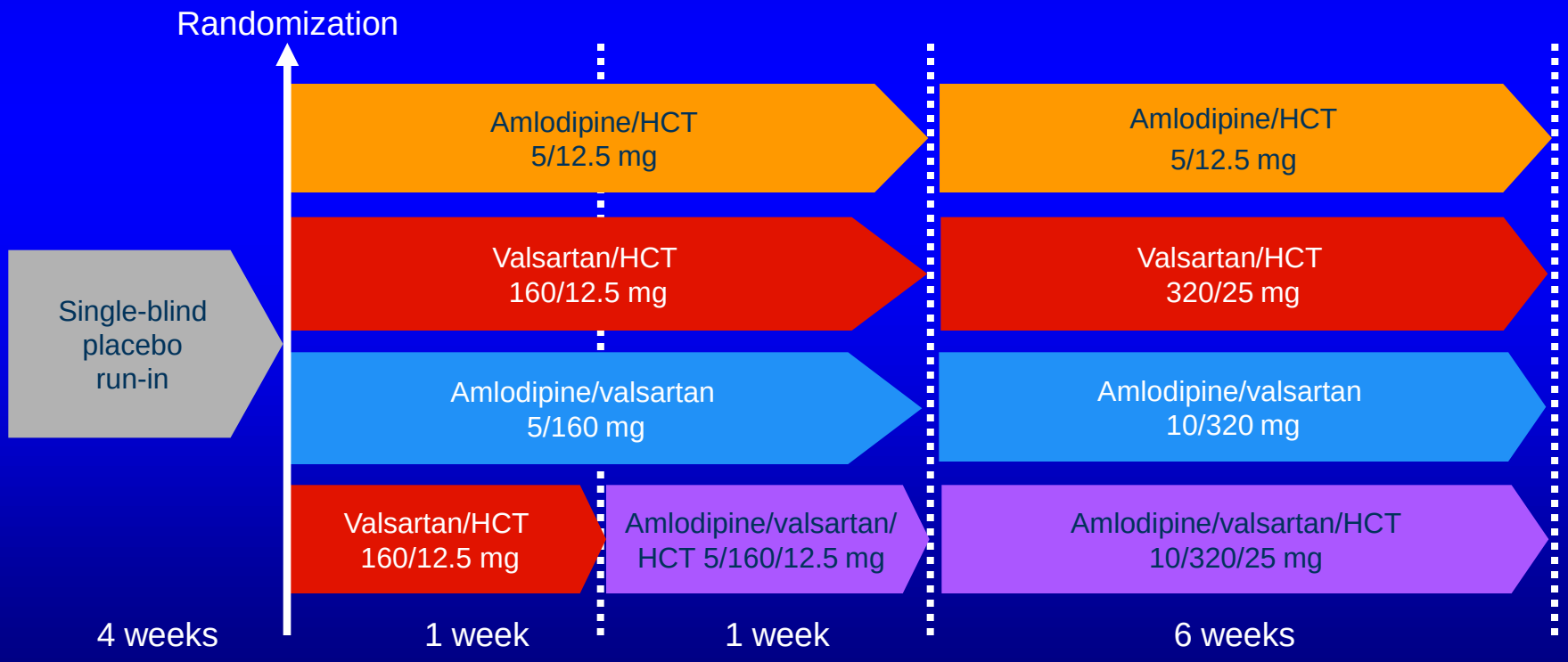


*p=0.0018 vs amlodipine 10 mg
†Severe defined as SBP ≥180 mmHg;
Severe was a pre-specified sub-analysis

Destro M, et al. J Am Soc Hypertens 2008;2:294–302

Amlodipine/valsartan/HCT triple combination therapy in hypertension

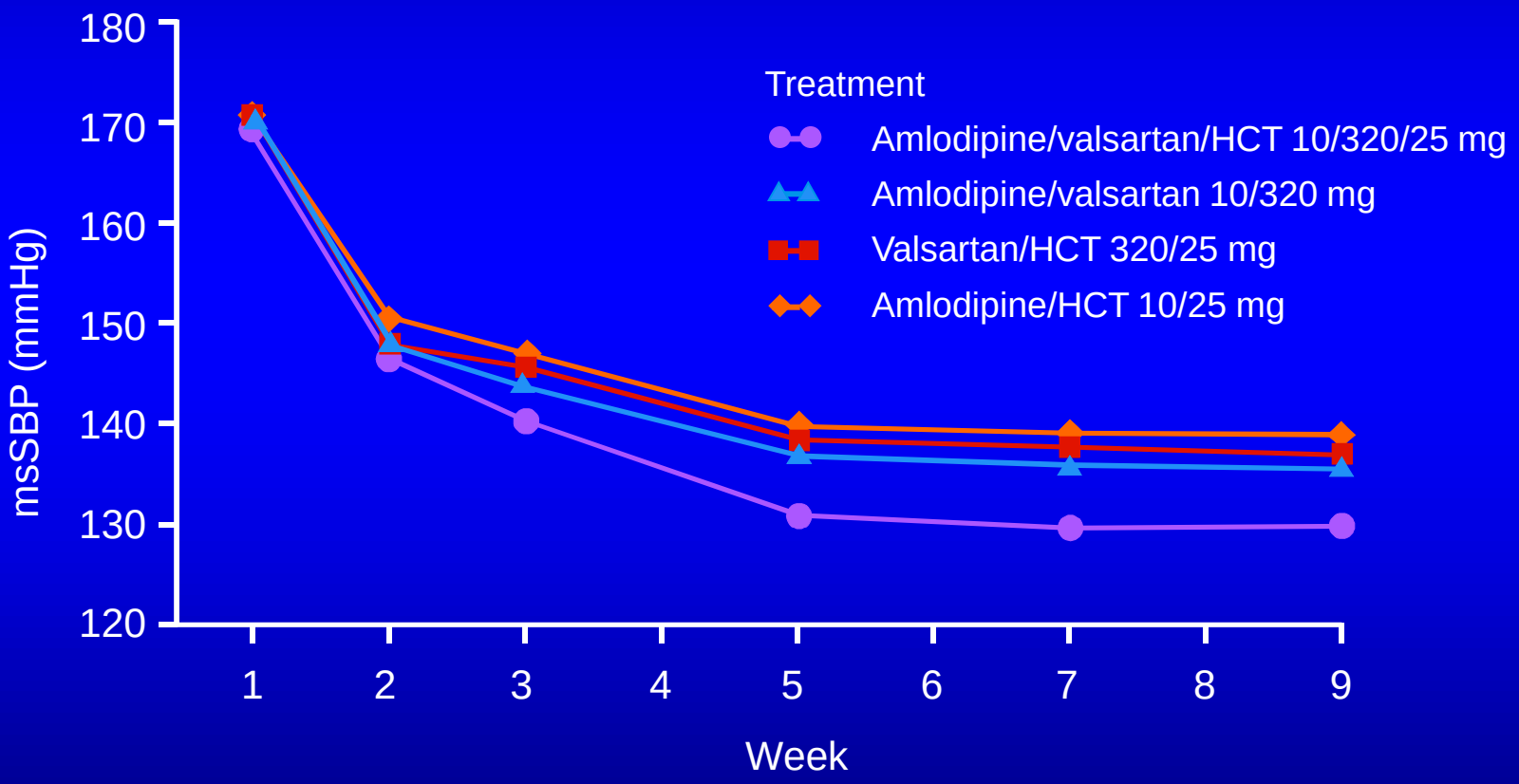
- Study design: 8-week, multicenter, randomized trial in patients with moderate-to-severe hypertension (msDBP ≥100 to <120 mmHg; msSBP ≥145 to <200 mmHg)
- Primary objective: to investigate whether triple combination therapy is superior to respective dual-combinations at lowering either msDBP or msSBP



Calhoun DA, et al. Hypertension 2009;54:32–9

Rapid BP-lowering effect: 30 mmHg drop in msSBP after 2 weeks of therapy

Intent-to-treat population (n=2,271)



Calhoun DA, et al. Hypertension 2009;54:32–9

Clinical perspective

- Hypertension is a:
  - progressive
  - life-long
  - largely asymptomatic

disease process

Clinical perspective

- Therapy needs to be:
  - simple
  - safe
  - effective
  - well-tolerated

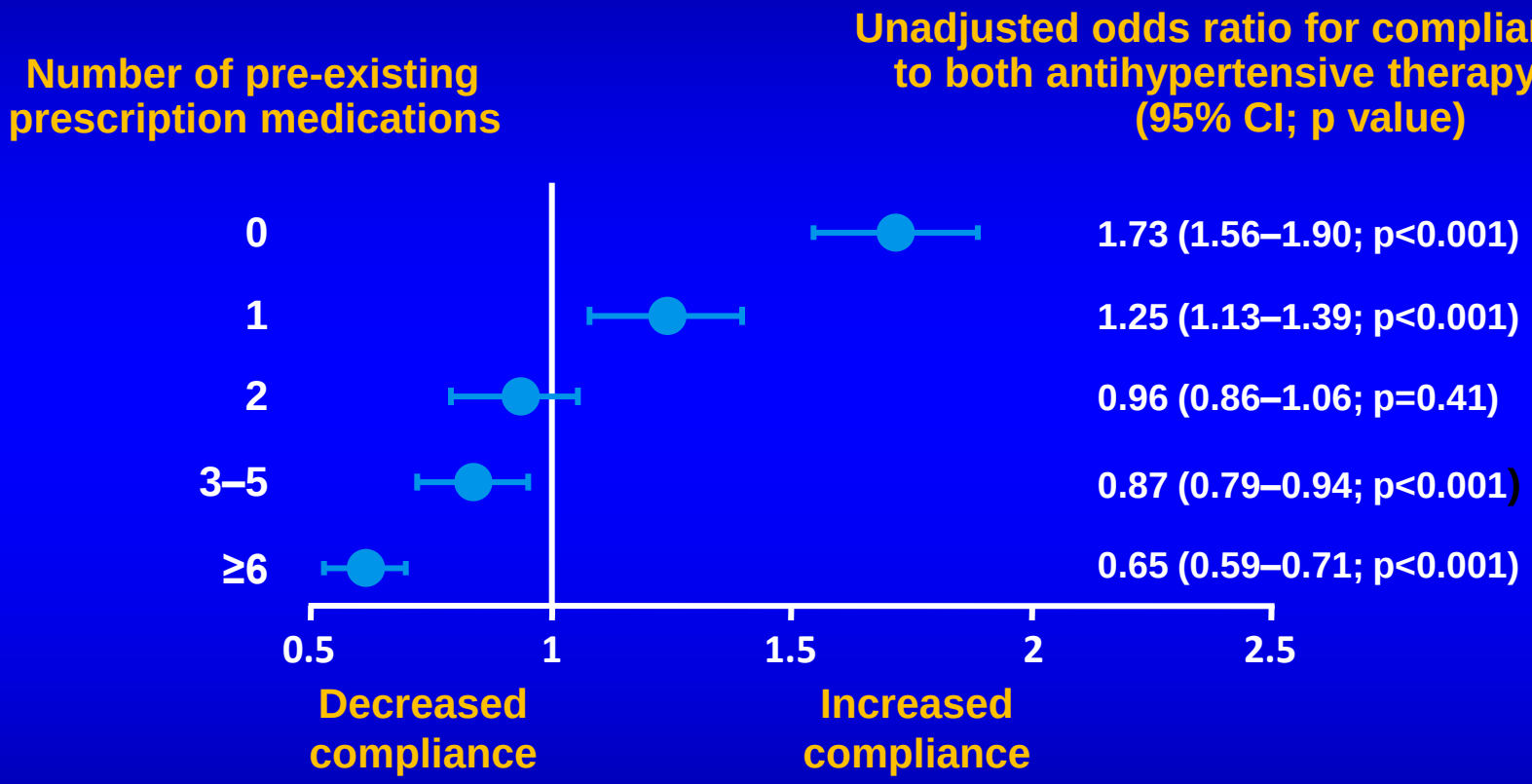
SPCs have several advantages versus free combinations of two or more antihypertensive drugs

	SPC	Free
Simplicity of treatment[1,2]	+	–
Adherence[1,2]	+	–
Efficacy[2]	+	+
Tolerability[2]	+*	–
Price[2]	+	–
Flexibility[2]	+**	++

*Lower doses generally used in SPCs
**An increasing number of SPCs are becoming available with a range of doses
+ = potential advantage

1. Burnier M, et al. Am J Hypertens 2006;19:1190–6
2. Neutel JM. Hypertension. Companion to Brenner & Rector's The Kidney. 2nd ed. Philadelphia: Elsevier Saunders, 2005. p. 522–9

Compliance Decreases as the Number of Medications Increases

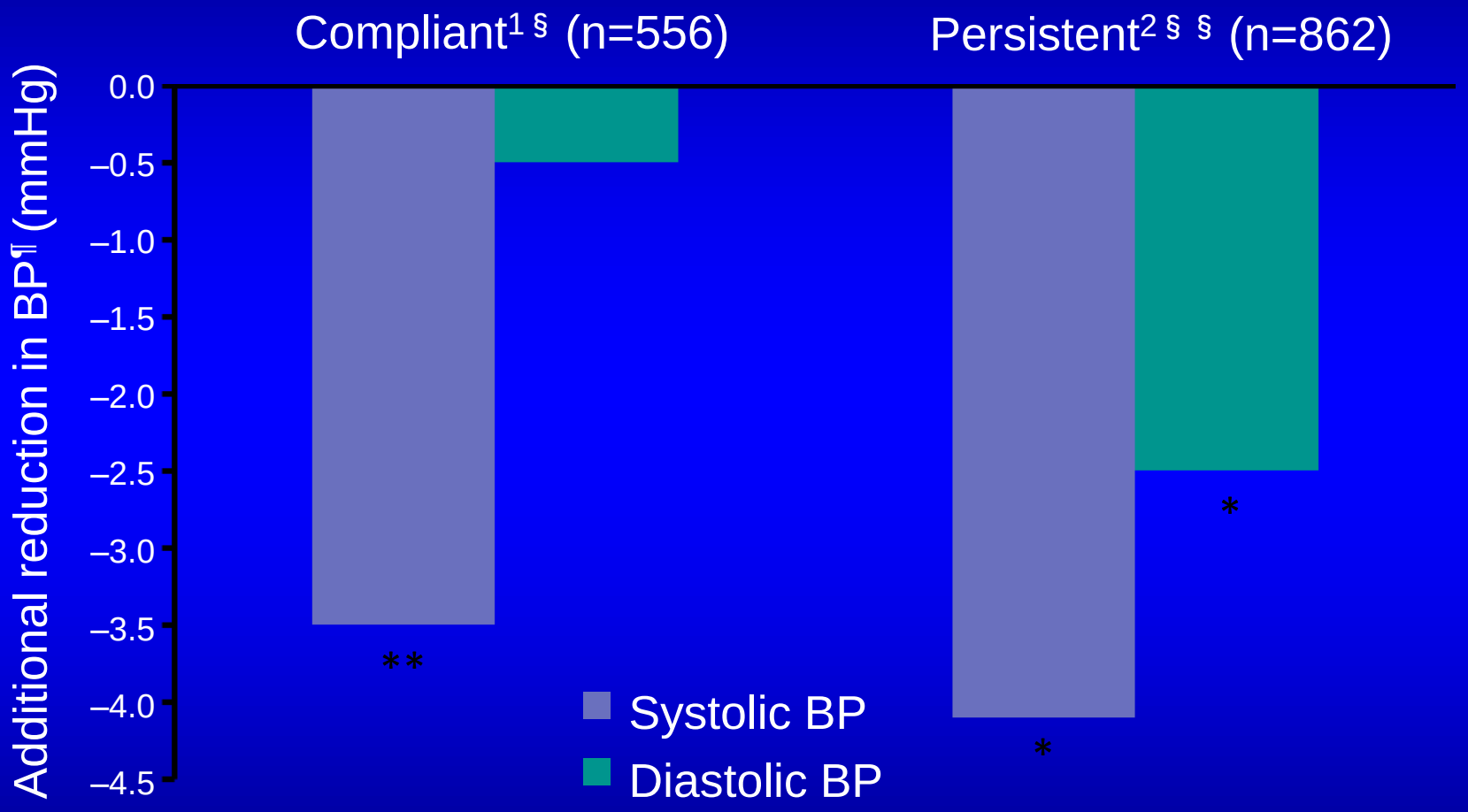


Retrospective cohort study of MCO population. N=8,406 patients with hypertension who added antihypertensive therapy and LLT to existing prescription medications within a 90-day period. Compliance to concomitant therapy: sufficient antihypertensive and LL prescription medications to cover ≥80% of days per 91-day period

CI=confidence interval; LLT = lipid-lowering therapy

Chapman et al. Arch Intern Med 2005;165:1147–52

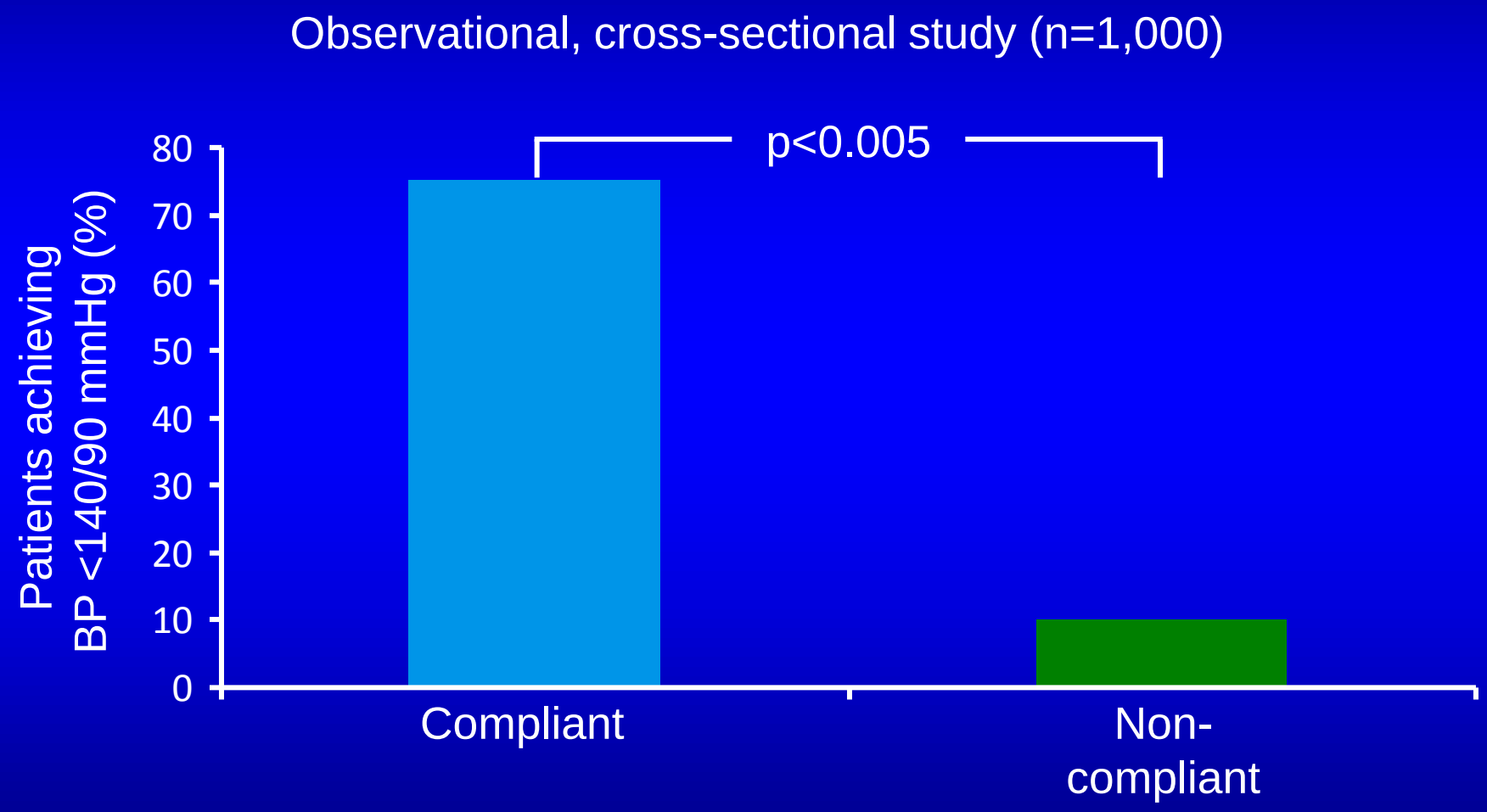
Compliant and Persistent Patients Achieve Superior BP Reductions Compared with Non-compliant/Non-persistent Patients



*p<0.05 vs non-persistent; **p<0.0005 vs non-compliant
§ Medication-possession ratio ≥80%; § § Remaining on therapy for 12 months
¶Vs non-compliant or non-persistent patients, respectively
N=982; BP = blood pressure

[1]Halpern et al. J Hypertens 2006;24(Suppl. 4):S154
[2]Halpern et al. J Hypertens 2006;24(Suppl. 4):S182

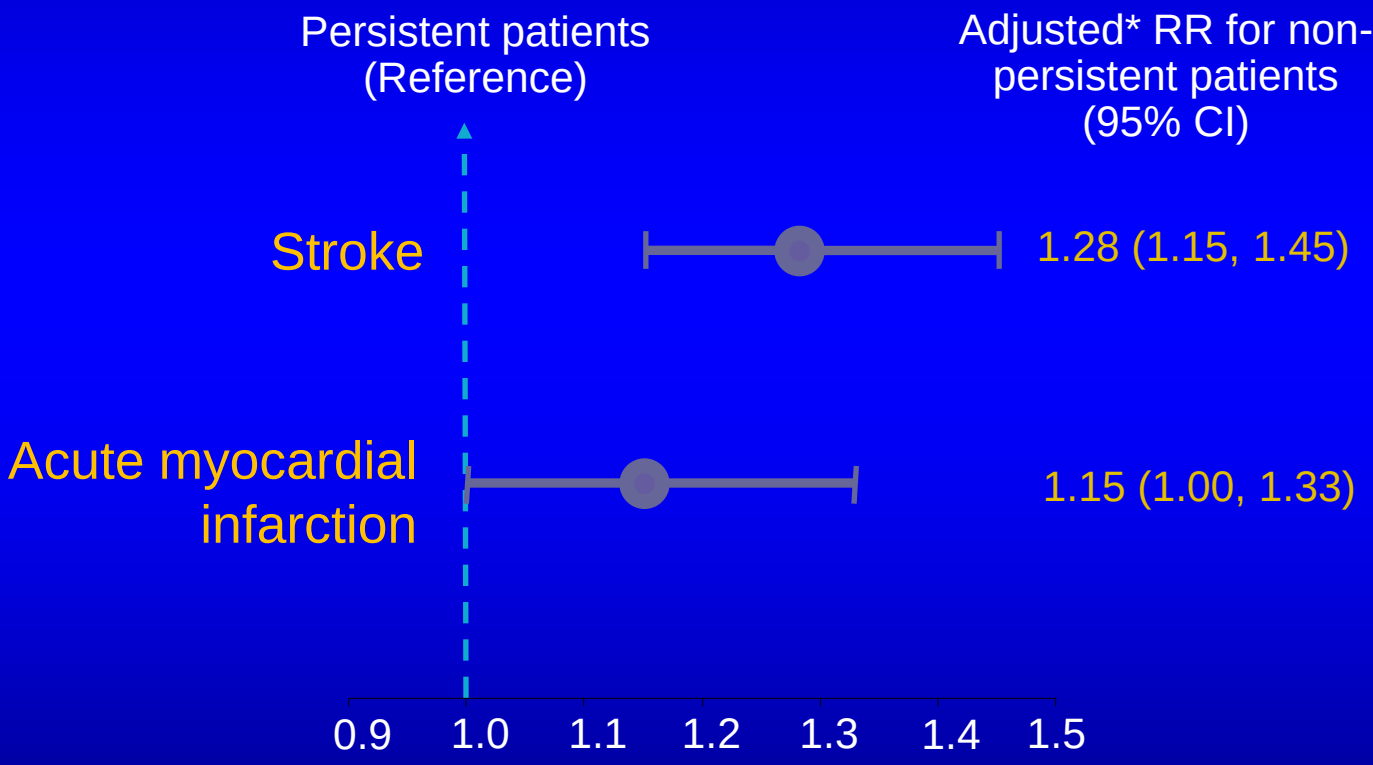
Compliance with Antihypertensive Therapy Results in More Patients Achieving Blood Pressure (BP) Goal (<140/90 mmHg)



Yiannakopoulou et al. Eur J Cardiovasc Prev Rehabil 2005;12:243–9

Non-persistence with Antihypertensive Therapy is Associated with an Increased Risk of Myocardial Infarction and Stroke

Data based on 77,193 new users of antihypertensive treatment identified in the PHARMO record linkage system

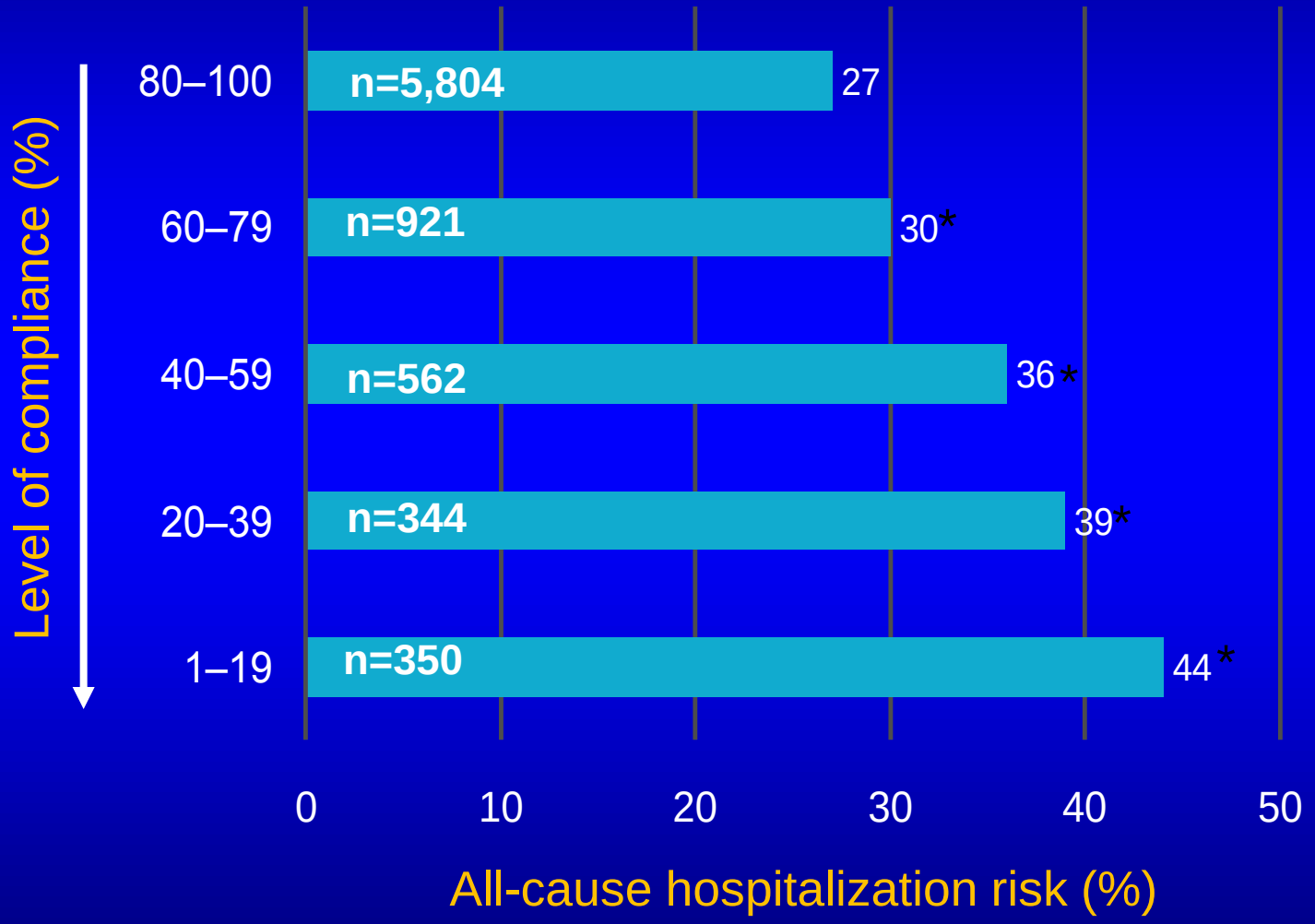


*Adjusted for gender, age, type of prescriber, use of cardiovascular co-medication, initial antihypertensive therapy, number of different antihypertensive classes during the first 2 years of therapy

Breekveldt-Postma, et al. Curr Med Res Opin 2008;24:121–7

Breekveldt-Postma et al. Curr Med Res Opin 2008;24:121–7

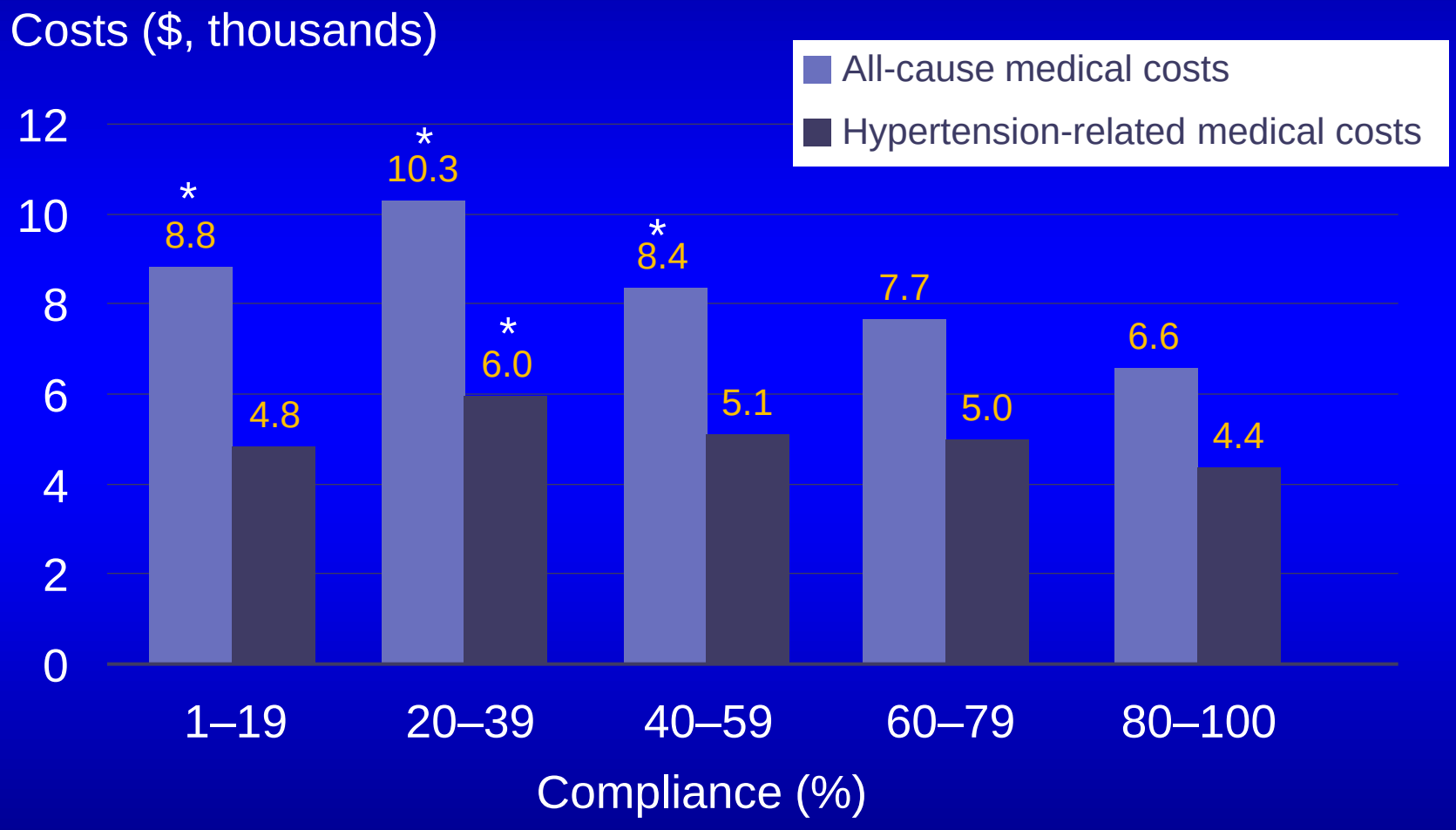
Better Compliance with Antihypertensive Drugs is Associated with a Lower Risk of Hospitalization



*p<0.05 vs 80–100% compliant group

Sokol et al. Med Care 2005;43:521–30

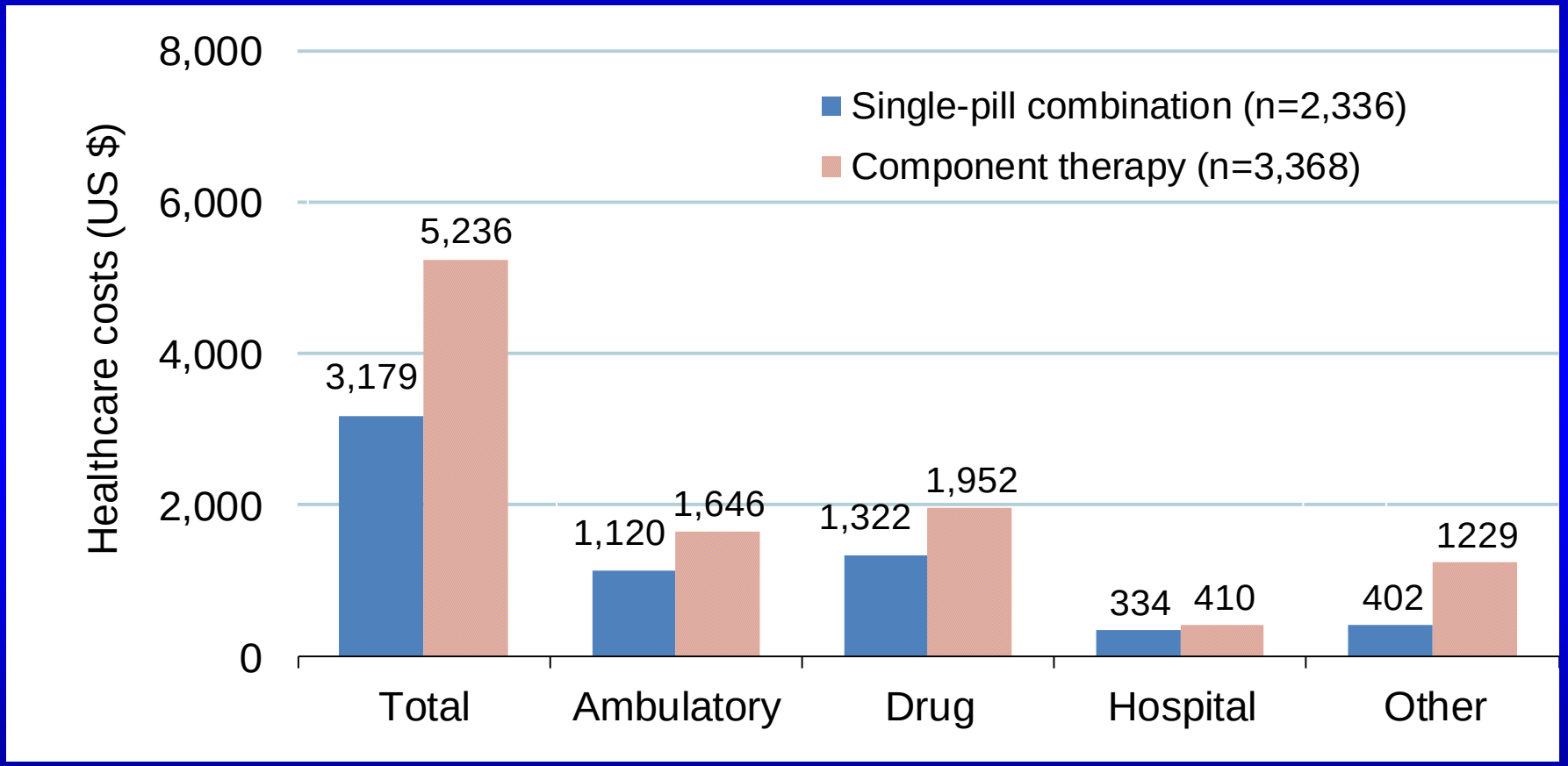
Better Compliance with Antihypertensive Therapy is Associated with a Decrease in Medical Costs



*p<0.05 vs. 80–100% compliant group

Sokol et al. Med Care 2005;43:521–30

Patients Treated with Single-pill Combinations Use Less Resource



NS = not significant

Dickson, Plauschinat. Am J Cardiovasc Drugs 2008;8:45–50

Overview

- How early should you start?
- How low should you go?
- What drugs and doses should you use?
- How many medications will you need?

Answers

- Earlier the better
- Blood Pressure <130/80 mmHg, but likely less in higher risk patients.
- Multi-drug regimen including a full dose of a RAAS blocker
- Start early with effective well tolerated combinations of drugs preferably where you know the appropriate dose to provide both BP and CV risk reduction