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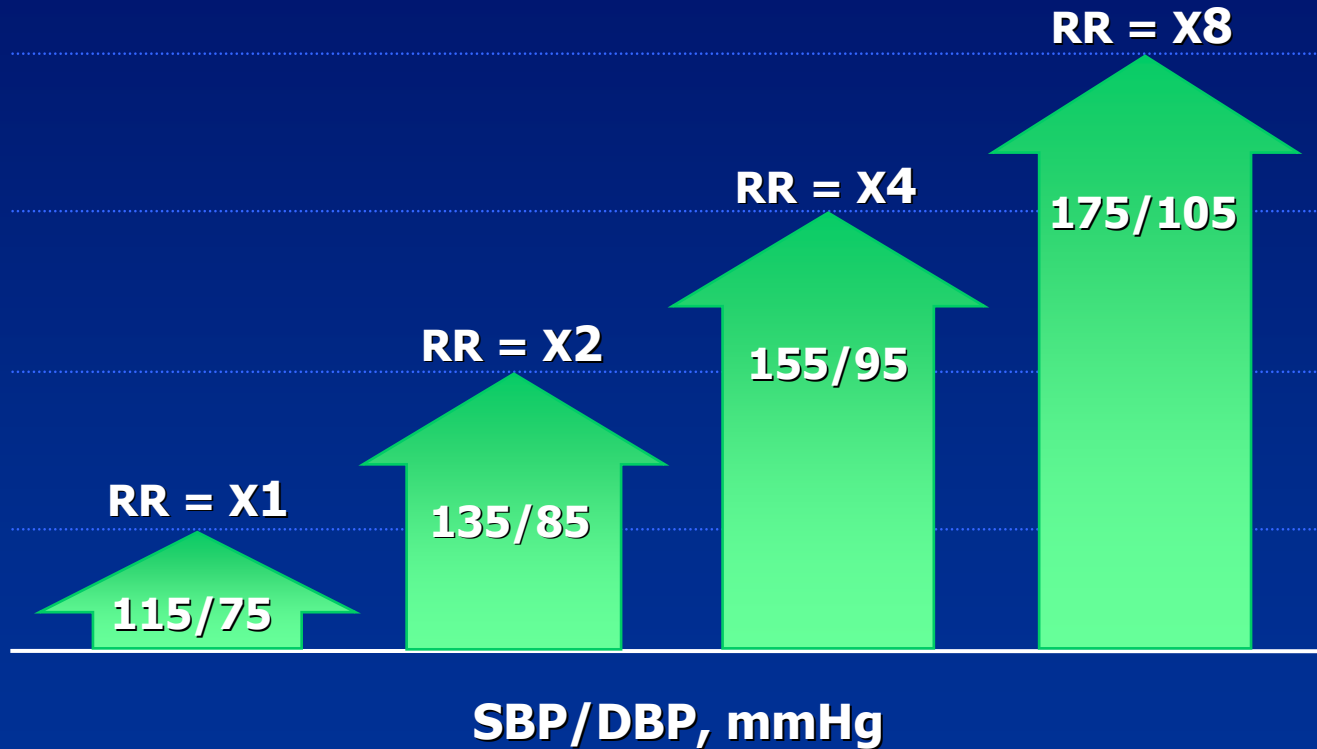
Exploring Optimal Combination in At-Risk Patients

Duk Hyun Kang, M.D.

Asan Medical Center

CV Mortality Risk *Doubles* With Each 20/10 mmHg Increase in BP

INCREASING
CARDIOVASCULAR
RISK*



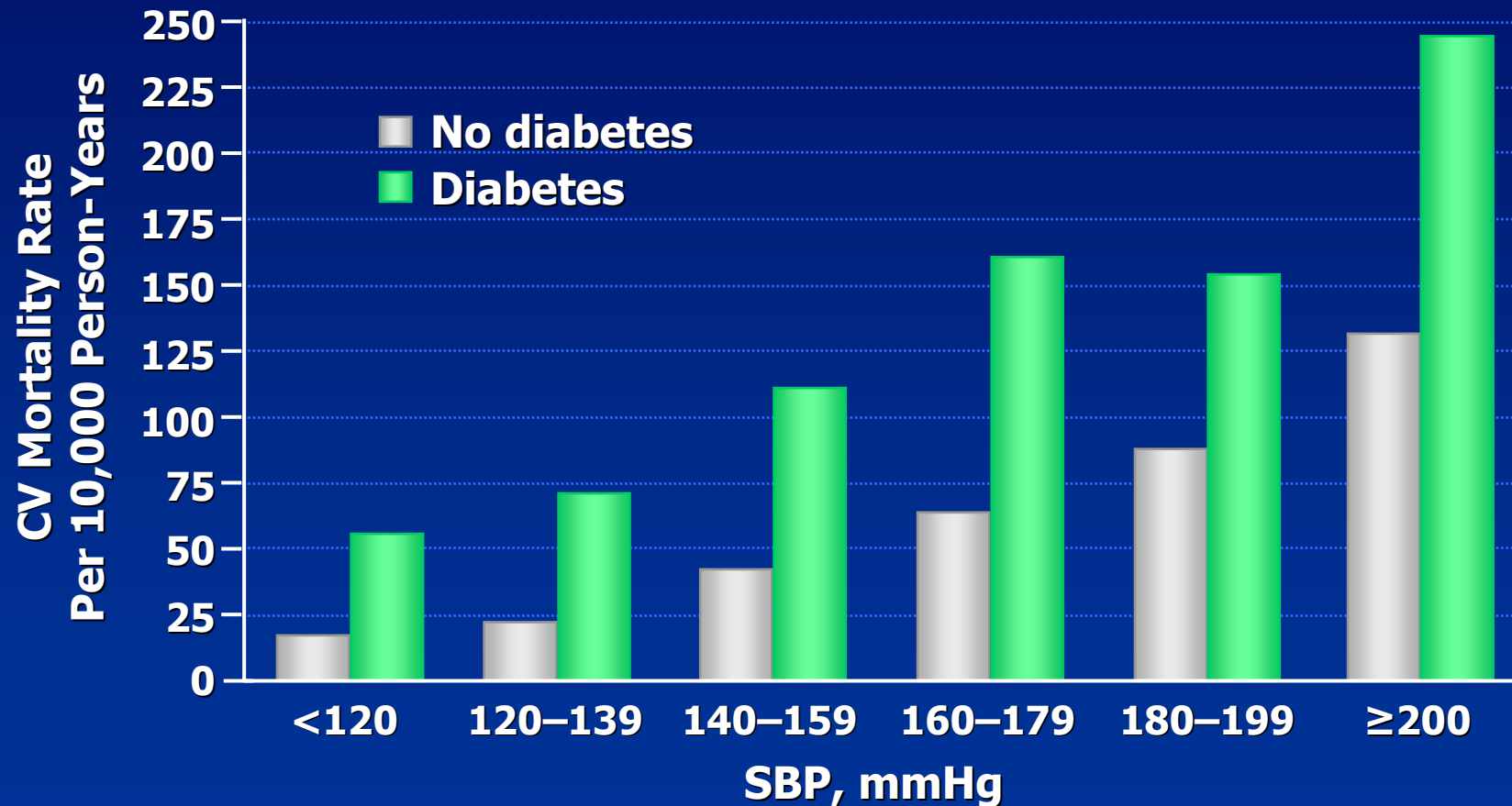
BP=blood pressure.

*Individuals aged 40–69 years (N=1 million).

Lewington S et al. *Lancet*. 2002;60:1903–1913.

Diabetes: Major CV Risk Factor Multiplier in Hypertension

SBP and CV Mortality in Type 2 Diabetes



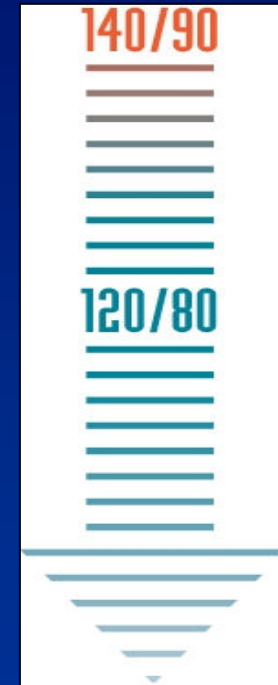
CV=cardiovascular; SBP=systolic blood pressure.

Stamler J et al. *Diabetes Care*. 1993;16:434-444.

Published Guidelines Have Set Clear Treatment Goals

JNC 7 / ADA / NKF / ISHIB Guidelines for Hypertension and Patients at High Risk

Condition	mmHg
Essential hypertension	<140/90
Diabetes mellitus	<130/80
Chronic renal disease	<130/80
High-risk* hypertension	<130/80



ADA=American Diabetes Association.

NKF=National Kidney Foundation.

ISHIB=International Society on Hypertension in Blacks.

*History of CVD event, stroke, transient ischemic attack, evidence of target-organ damage (e.g., left ventricular hypertrophy, microalbuminuria), CHD, or high-risk for CHD (e.g., metabolic syndrome).

Chobanian AV et al. *JAMA*. 2003;289:2560–2572. Arauz-Pacheco C et al. *Diabetes Care*. 2003;26(suppl):S80–S82.

Douglas JG et al. *Arch Intern Med*. 2003;163:525–541. Bakris GL et al. *Am J Kidney Dis*. 2000;36:646–661.

한국인의 고혈압 치료 및 조절율

	남자	여자
치료율	25.2%	39.5%
조절율 (전체 고혈압환자)	7.6%	16.6%
조절율 (항고혈압제복용자)	30.2%	42.0%

- **How are you going to get there?**
- **What drugs should you use?**

Clinical Trials in Hypertension

Should we treat diastolic HBP?

What is the goal of treatment?

Should we treat DBP in older persons?

What is the best way to treat HBP?

Should we treat ISH in older persons?

Can we prevent hypertension?

1960s

1970s

1980s

1990-1995

1996-1999

2000

2001-2003

2004-2008

HDFP

HOT
UKPDS

VA
Cooperative
Studies

EWPHE
MRC-1
ANHBP-1

SHEP

Syst-Eur
Syst-China

SCOPE
CONVINCE
ALLHAT
ANBP2
LIFE

CAMELOT
VALUE
ASCOT
ACCOMPLISH

MRC-2

CAPP
STOP-2

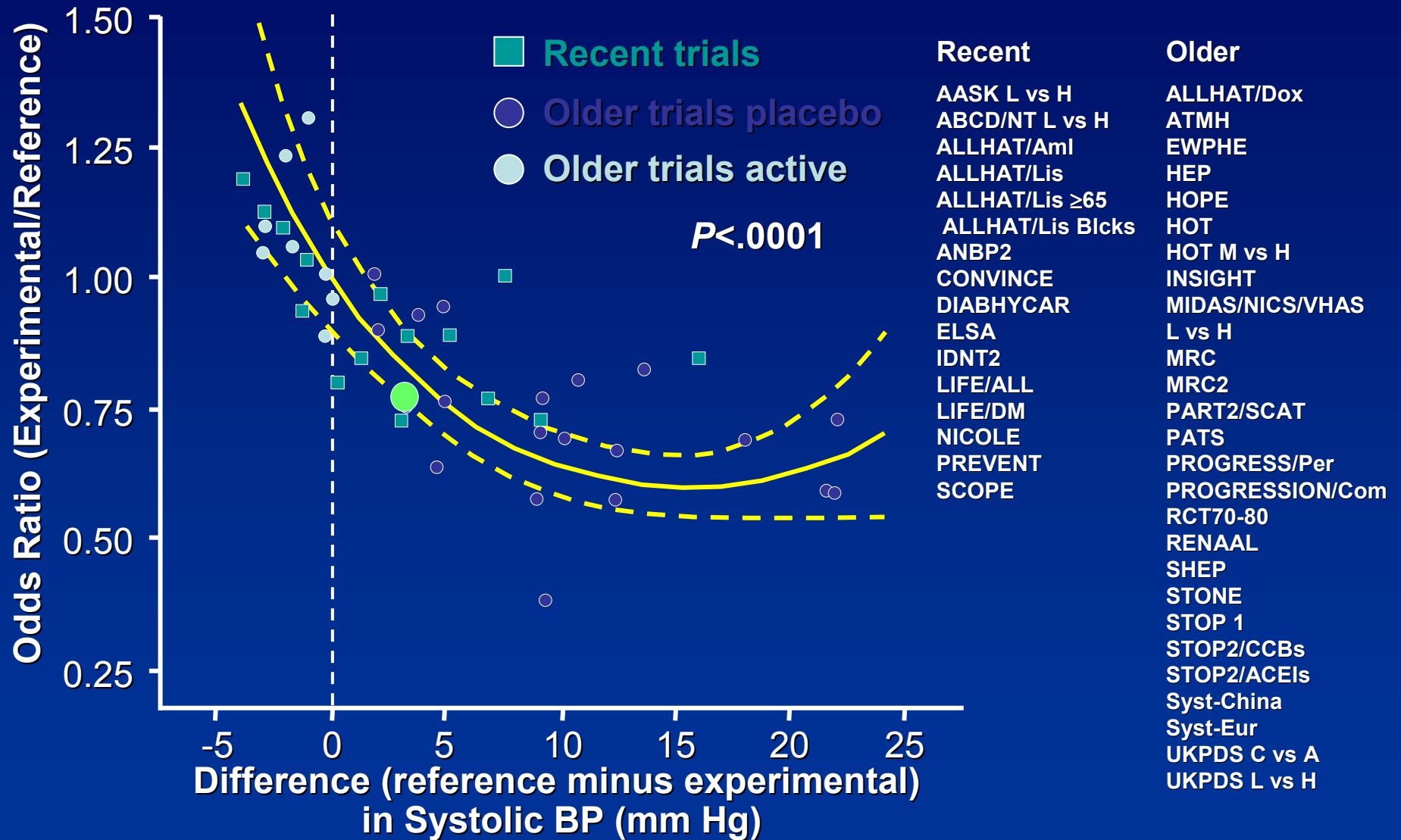
INSIGHT
NORDIL

STOP-1

HAPPHY
MAPHY

TOMHS
VA MONORx

Odds Ratio for CV Events and Systolic BP Difference: Recent and Older Trials

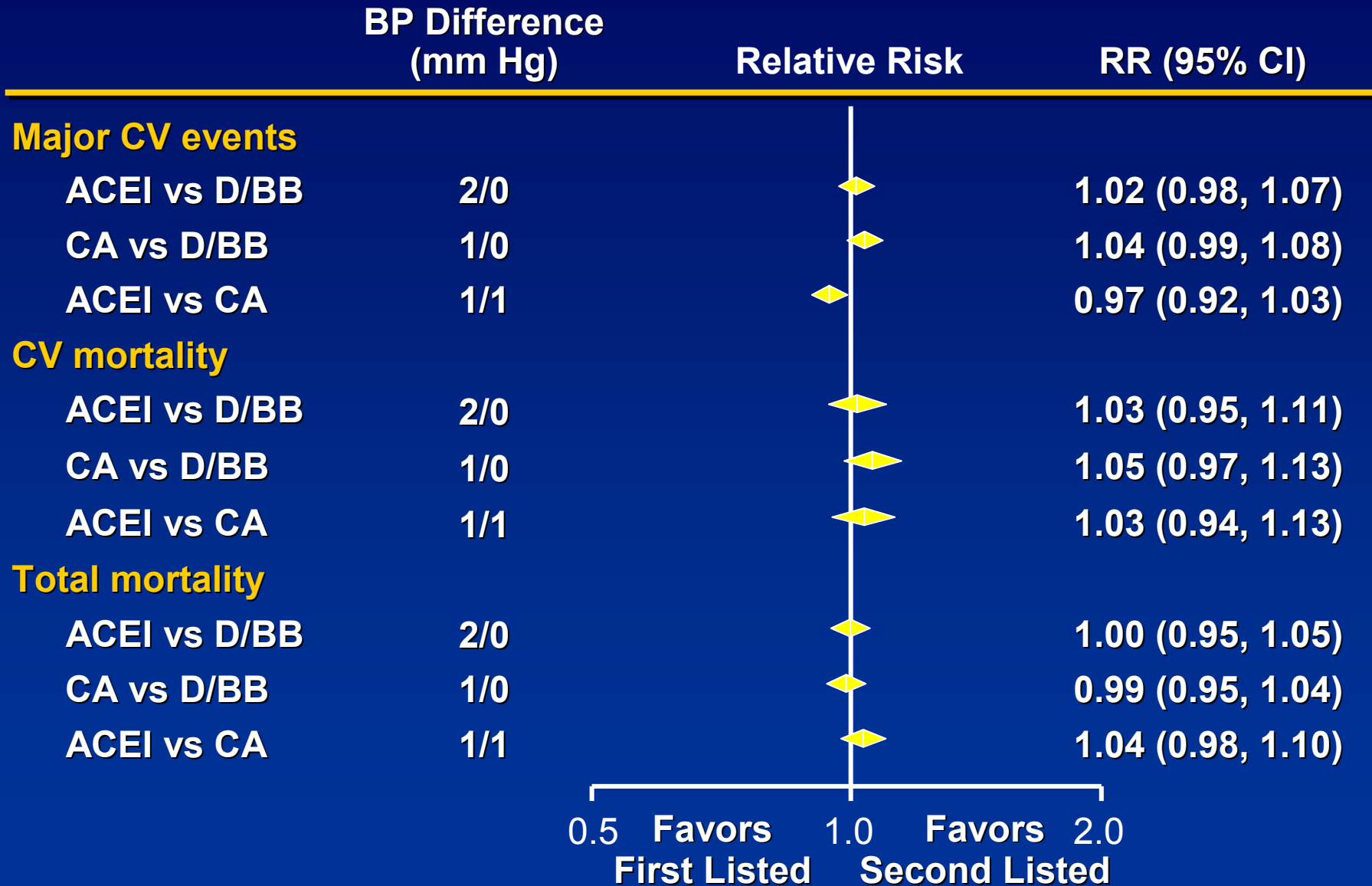


Staessen et al. *J Hypertens.* 2003;21:1055-1076.

Estimated Efficacy of Monotherapy

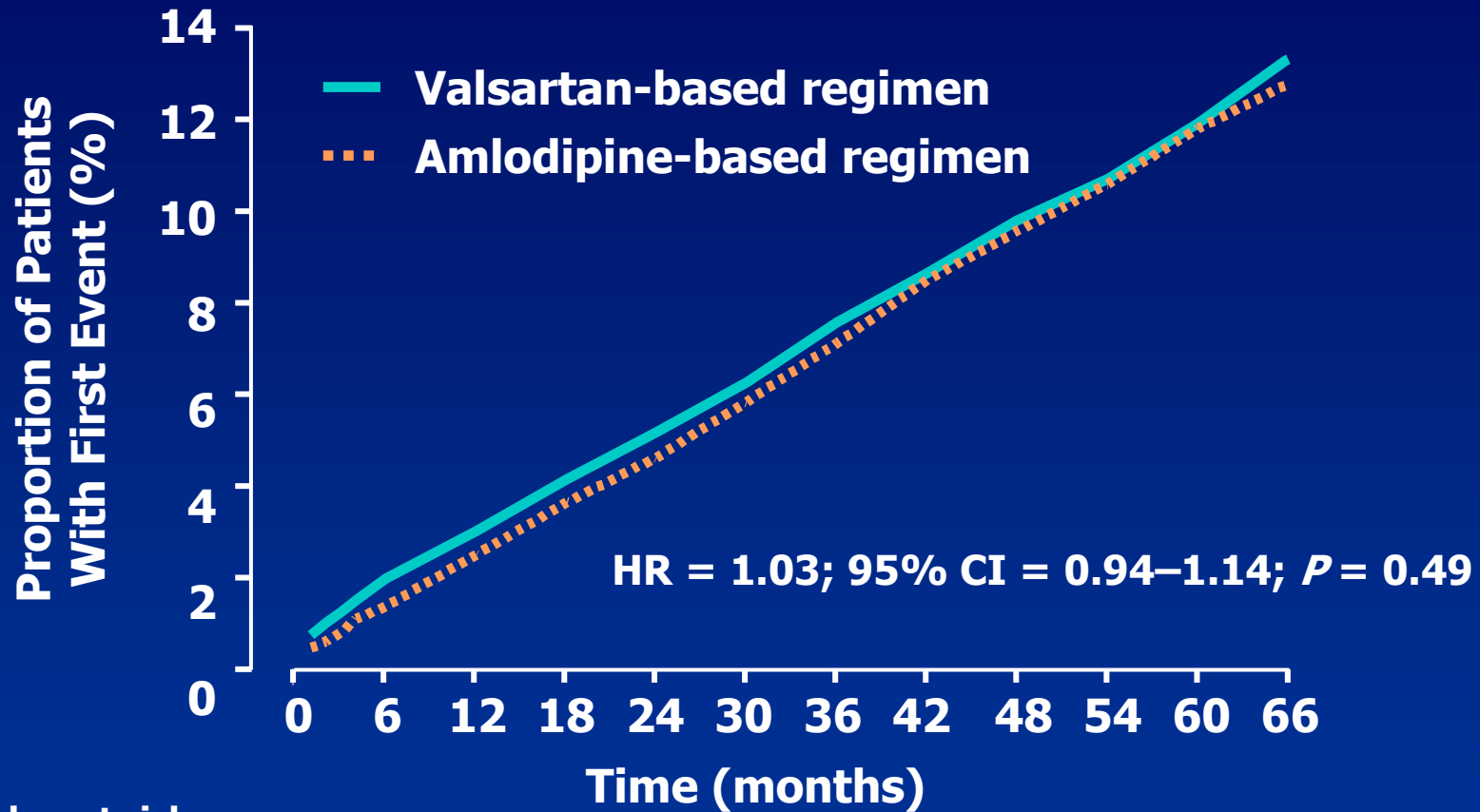
Drug	Responders (%)
Thiazides	50 – 55
β -blockers	45 – 50
ACE inhibitors	50 – 60
Calcium channel blockers	40 – 60
α -blockers	35 – 40

BP-Lowering Treatment Trialists



Blood Pressure Lowering Treatment Trialists' Collaboration. *Lancet*. 2003;362:1527-1535.

VALUE: Primary Composite Cardiac Endpoint



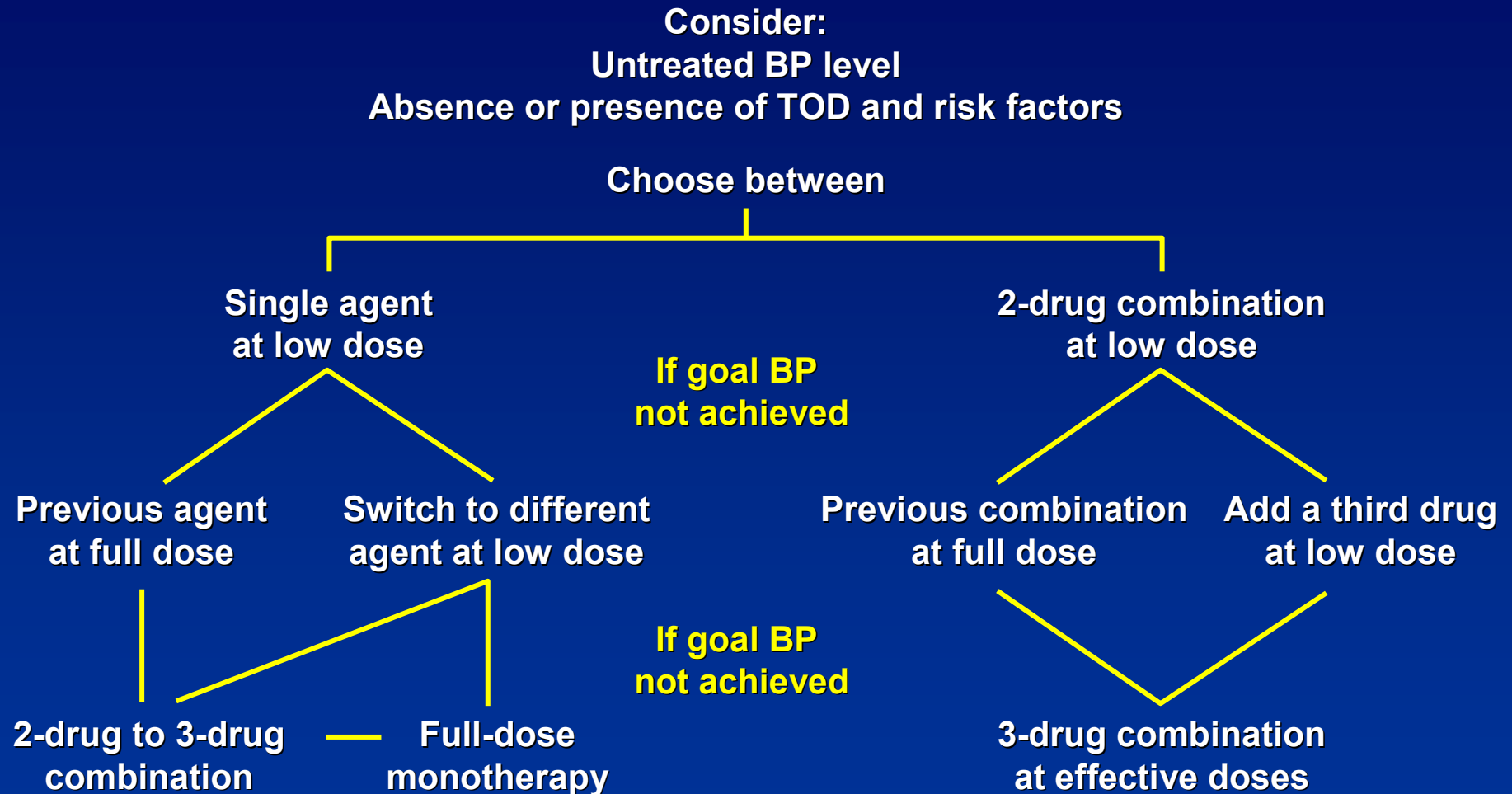
Number at risk

Valsartan 7649 7459 7407 7250 7085 6906 6732 6536 6349 5911 3765 1474

Amlodipine 7596 7469 7424 7267 7117 6955 6772 6576 6391 5959 3725 1474

Julius S et al. *Lancet*. June 2004;363.

ESH 2003: Choice Between Monotherapy and Combination Therapy



Combination Therapy Has Many Advantages

- **Faster achievement of target BP¹**
- **Greater efficacy¹**
- **Higher response rates¹**
- **May make therapy effective in broader population (races, patient types, co-morbidities)^{1,2}**
- **Additive, or synergistic antihypertensive effects through different mechanisms²**

BP=blood pressure.

1. Neutel JM et al. *Am J Hypertens*. 2001;14:286–292.

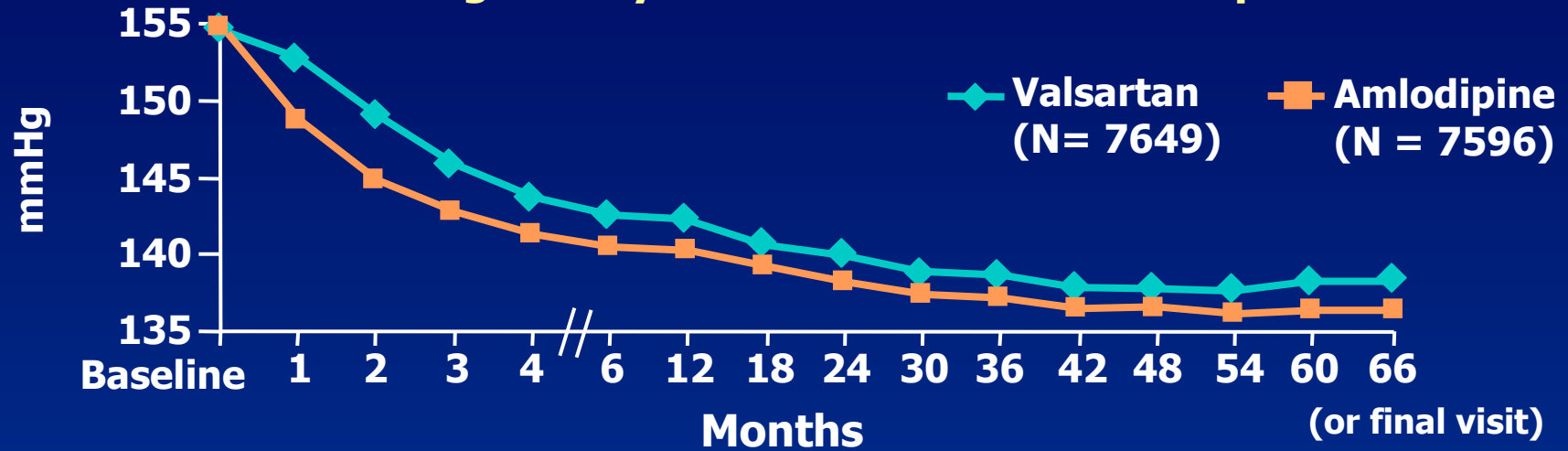
2. Weir MR. *Am J Hypertens*. 1998;11:163S–169S.

Multiple-mechanism Therapy recommended by Guideline

- JNC VII
 - “Most patients with hypertension will require two or more antihypertensive agents to achieve their BP goals”
 - “When BP is more than 20 mmHg above systolic goal or 10 mmHg above diastolic goal, consideration should be given to initiate therapy with 2 drugs, either as separate prescriptions or in fixed-dose combinations”
- New ESH–ESC in 2007
 - “In higher risk hypertension, goal blood pressure should be achieved more promptly, which favours initial combination therapy and quicker adjustment of doses”

VALUE: An Unintended Early Difference In BP ?

Sitting SBP by Time and Treatment Group



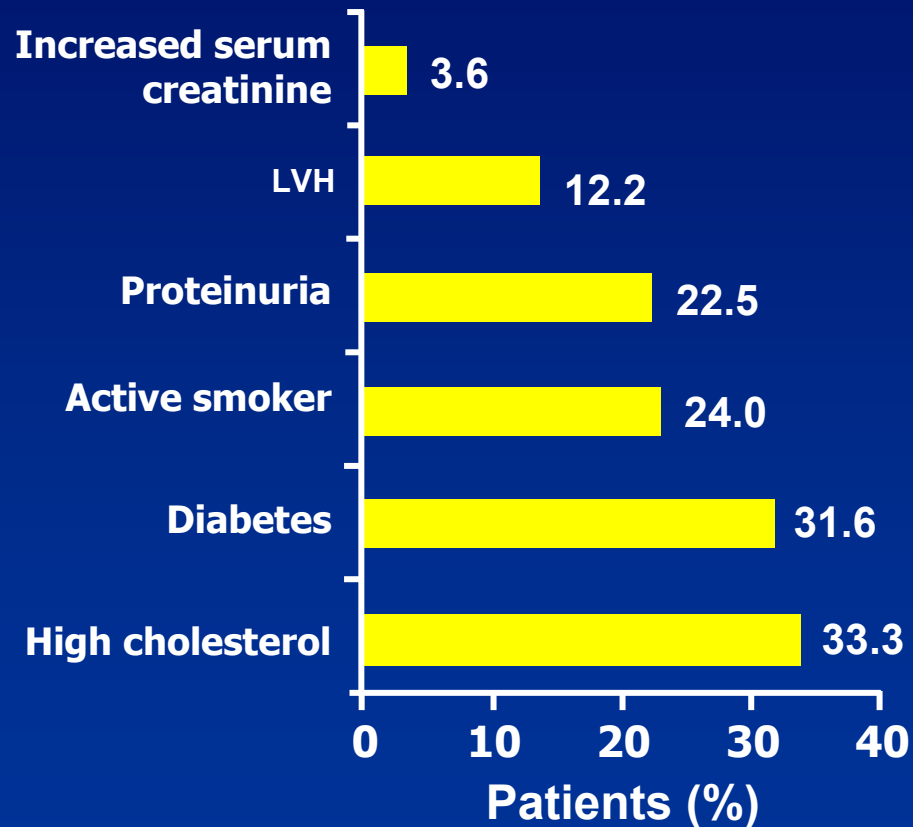
Difference in SBP Between Valsartan and Amlodipine



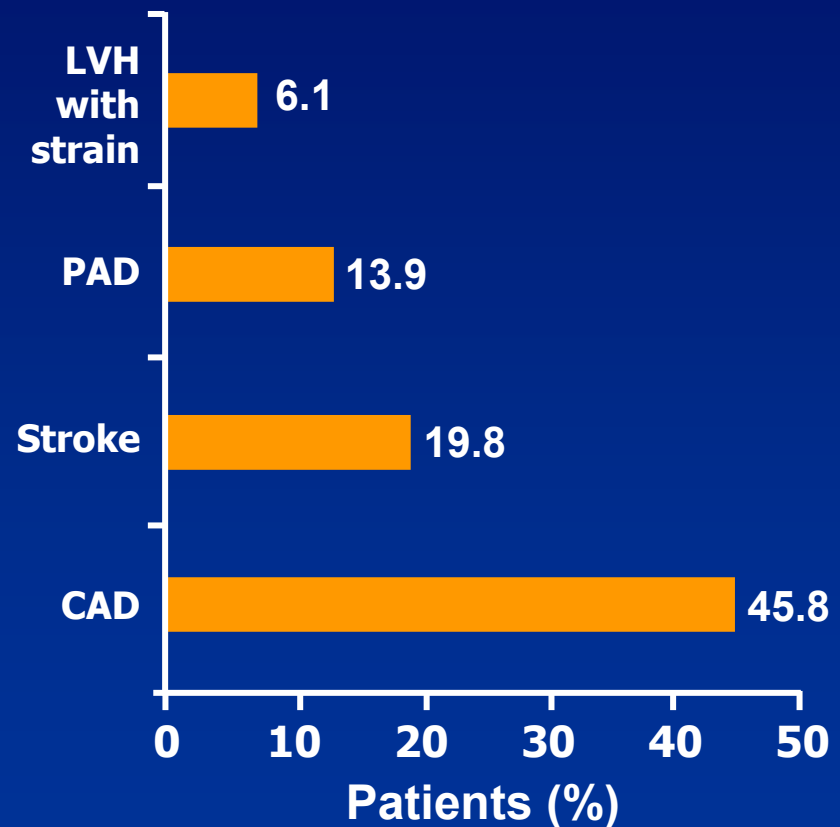
Julius S et al. *Lancet*. June 2004;363.

VALUE: Patient Characteristics

Associated risk factors



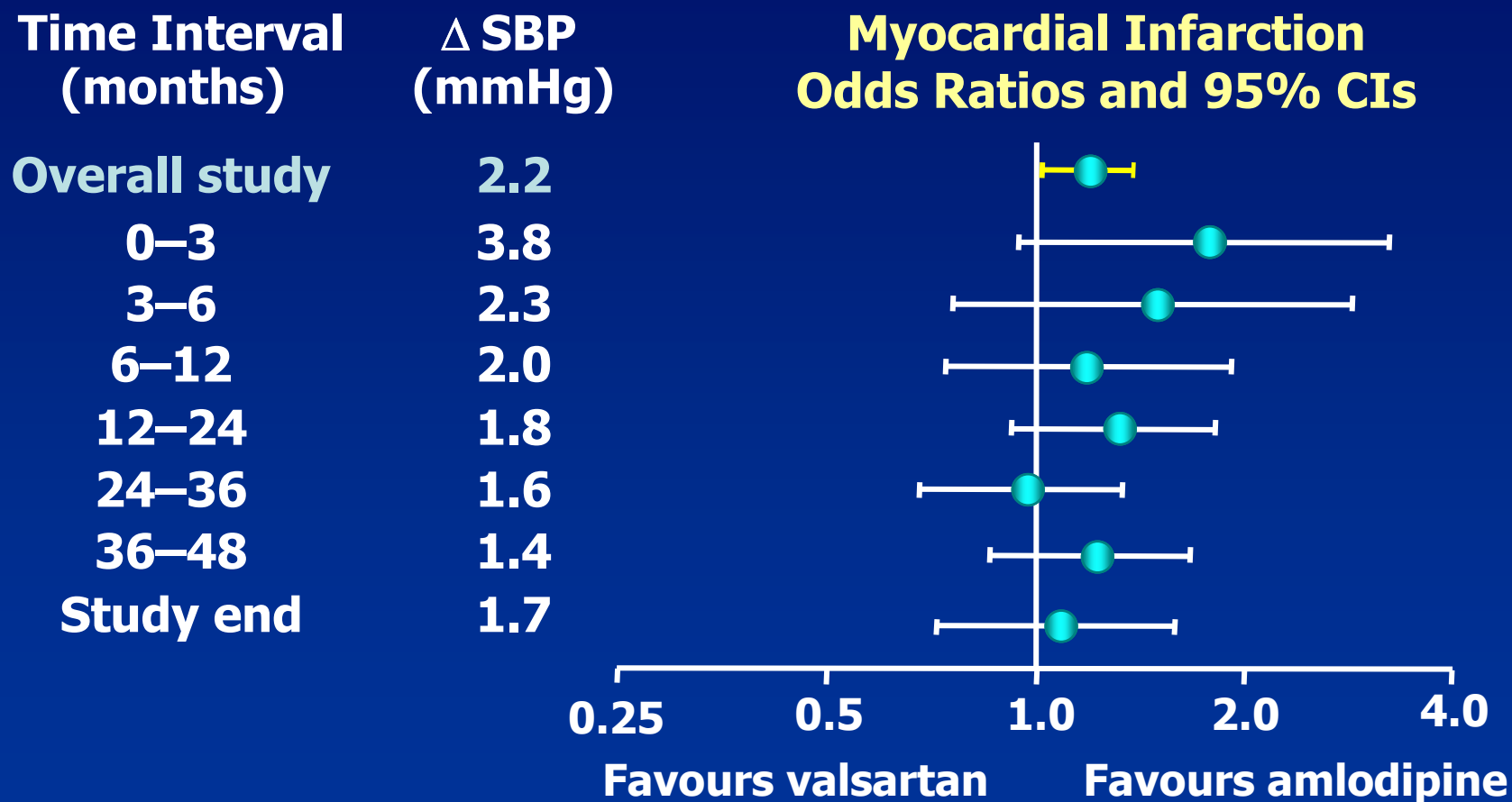
Associated diseases



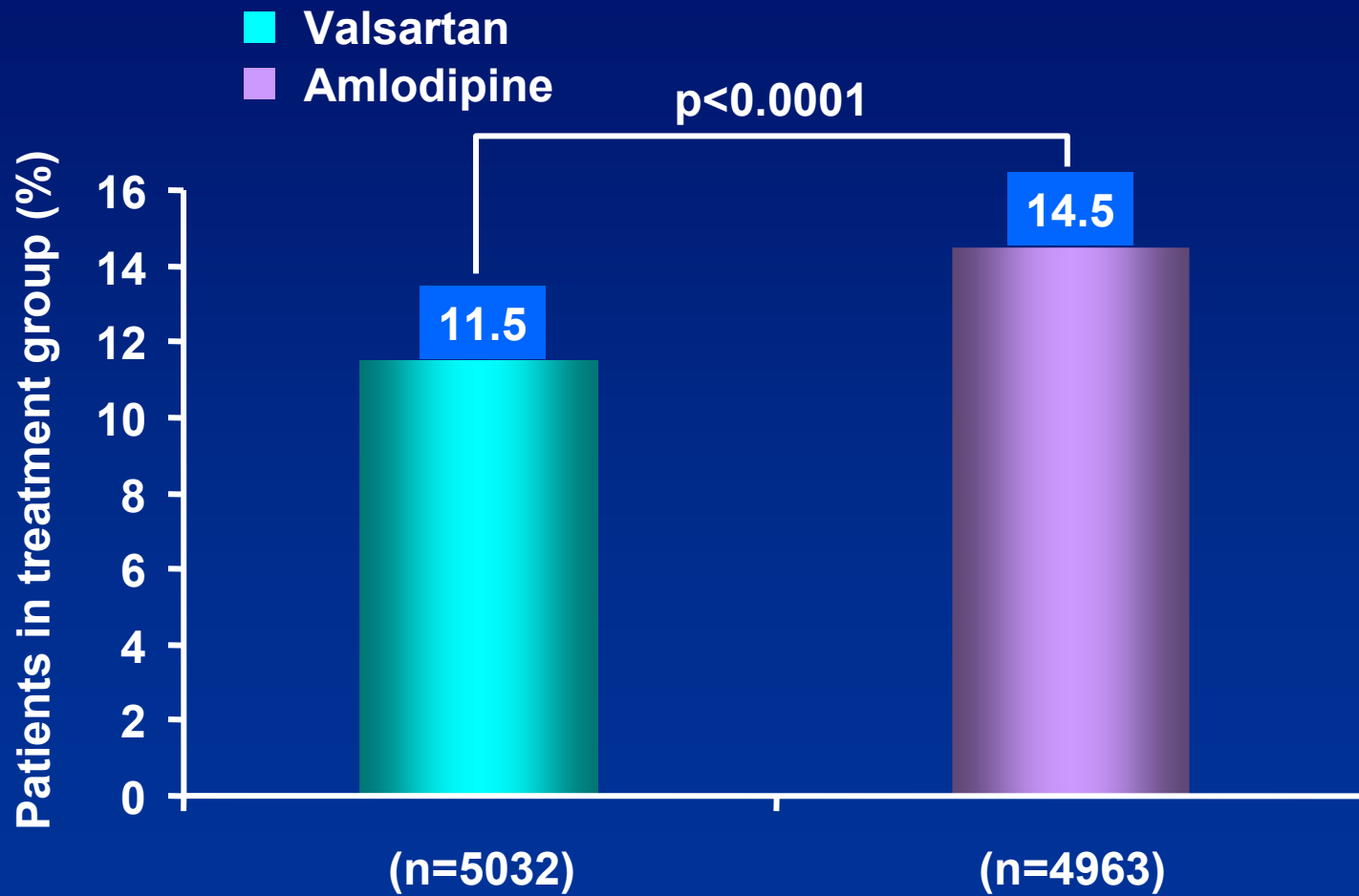
LVH = left ventricular hypertrophy; PAD = peripheral artery disease;
CAD = coronary artery disease

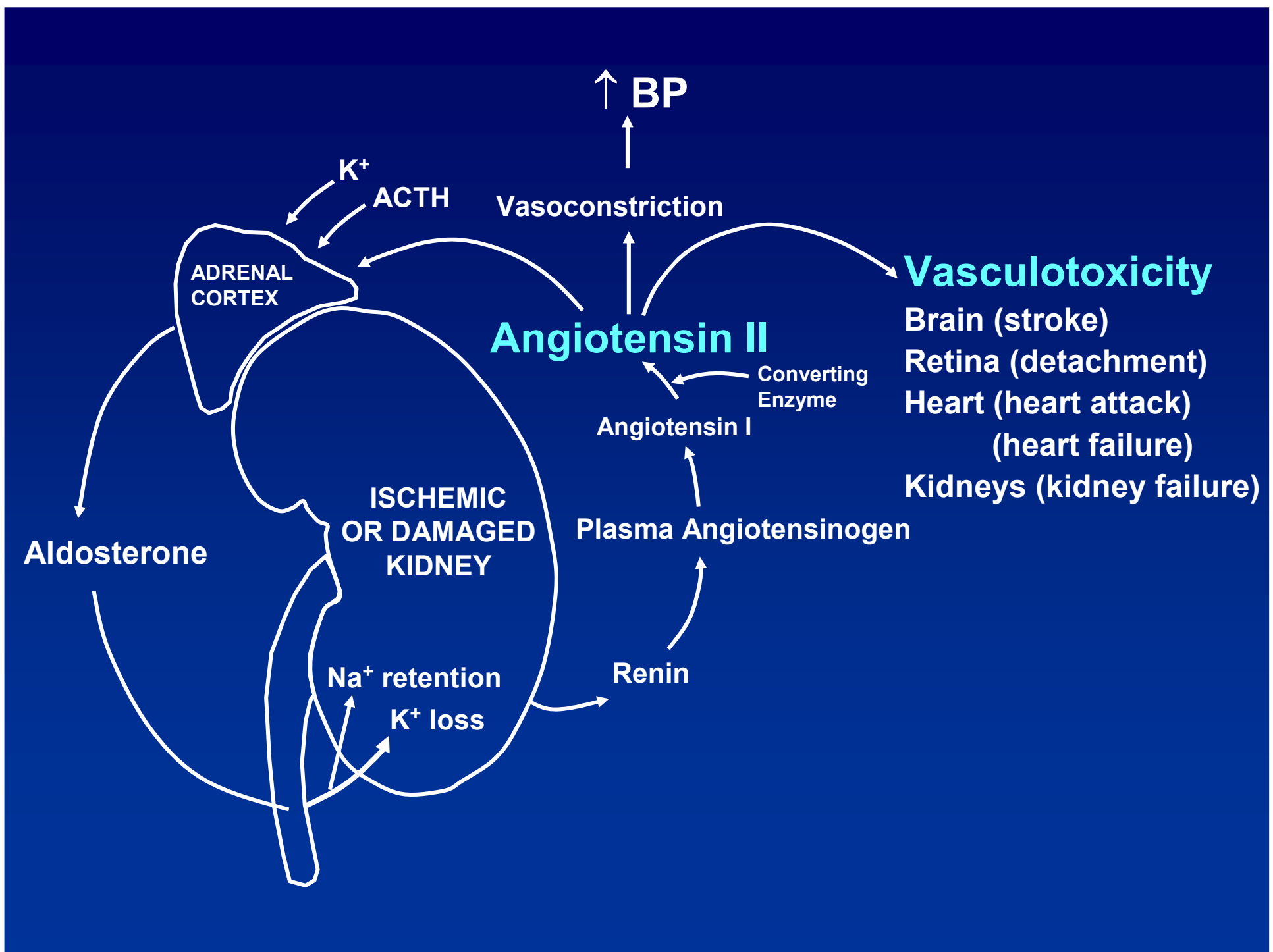
Kjeldsen SE, Julius S et al. Blood Press 2001;10:83–91

VALUE: Outcome and SBP Differences at Specific Time Periods: *Myocardial Infarction*

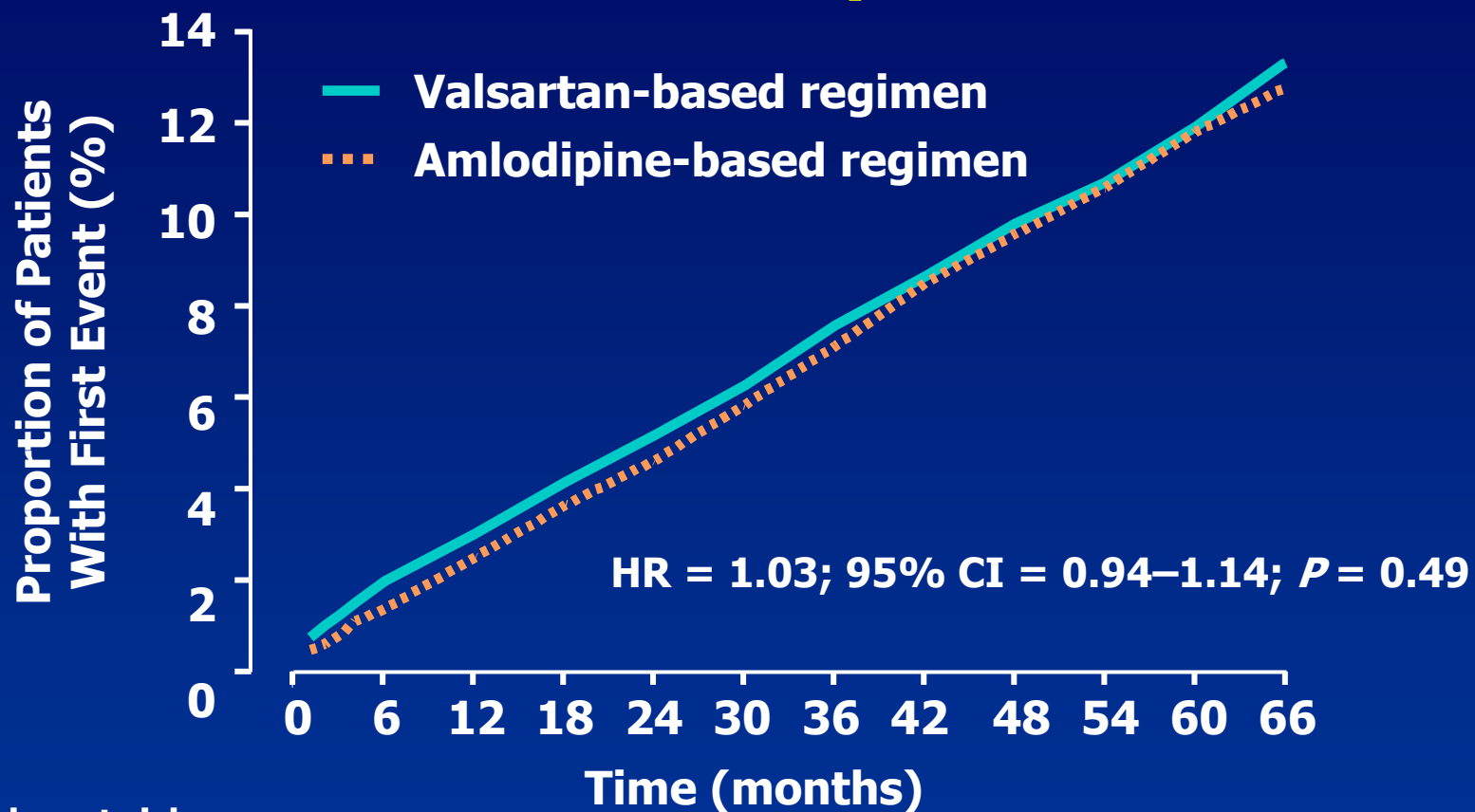


VALUE: New Onset Diabetes Valsartan vs. Amlodipine





VALUE: Primary Composite Cardiac Endpoint



Number at risk

Valsartan 7649 7459 7407 7250 7085 6906 6732 6536 6349 5911 3765 1474

Amlodipine 7596 7469 7424 7267 7117 6955 6772 6576 6391 5959 3725 1474

Julius S et al. *Lancet*. June 2004;363.

Controlled Versus Non-controlled: VALUE Trial

	Combined	Valsartan	Amlodipine
Death	0.79*	0.79*	0.79*
MI	0.86	0.83	0.91
Death+MI+CHF	0.75*	0.76*	0.73*
CHF	0.64*	0.62*	0.64*
Stroke	0.55*	0.60*	0.50*

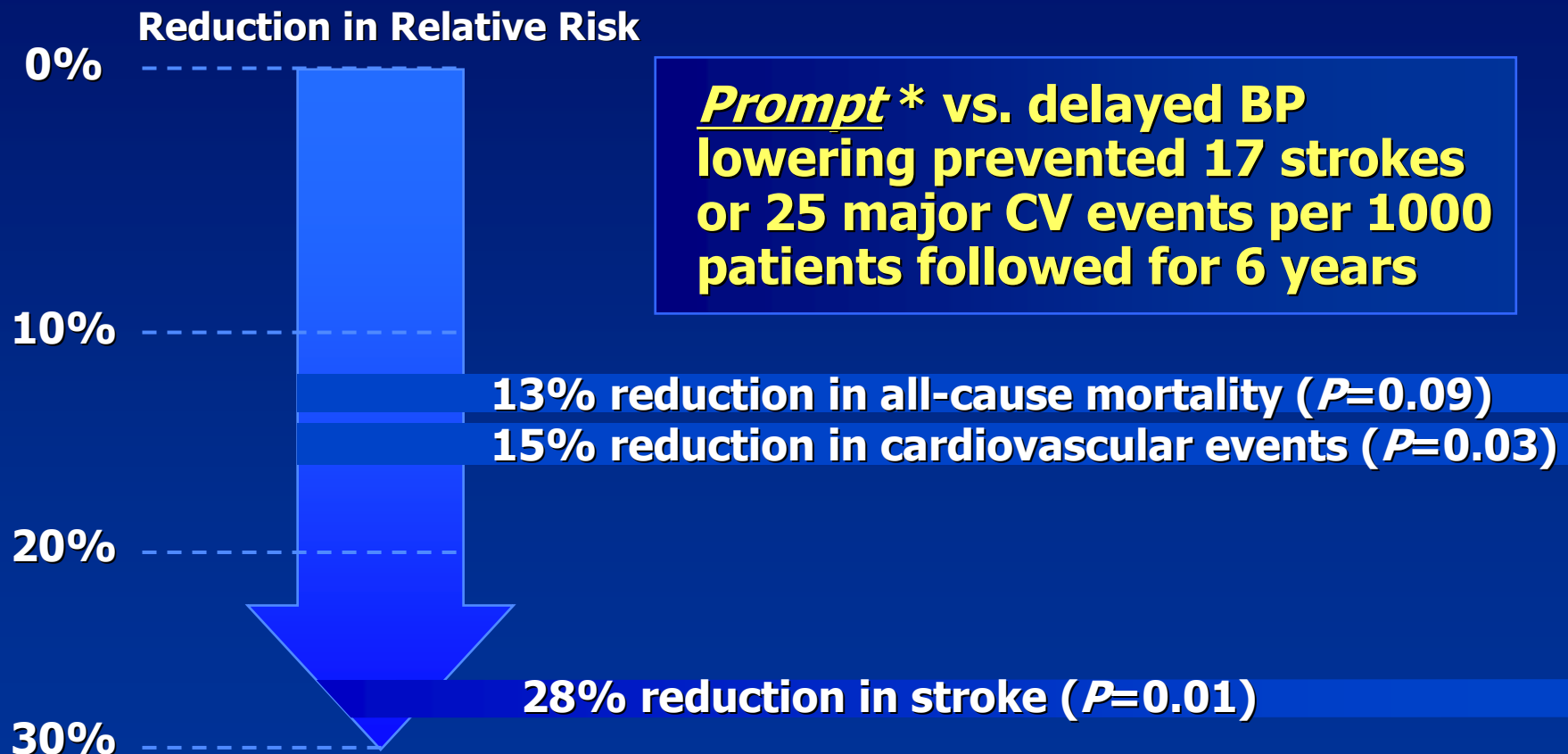
Controlled; Systolic BP < 140 mm Hg by 6 months

Early aggressive BP control is the key to reducing CV events.

Achieved BP rather than drug type was the main determinant of event rates.

And It Is Important to Note the Positive Benefits of Prompt* BP Lowering

Syst-Eur : Risk Reduction



*Prompt in this study was any treatment utilized in the first 2.0 years.
BP=blood pressure; CV=cardiovascular.

Staessen JA et al. *J Hypertens.* 2004;22:847–857.

Prompt BP Lowering Is Valuable to Patients

- **Patient spends less time in high-risk state**
- **Less opportunity for patient and physician to accept inadequate control**
- **Patient adherence increases when BP control is achieved within weeks rather than in months**

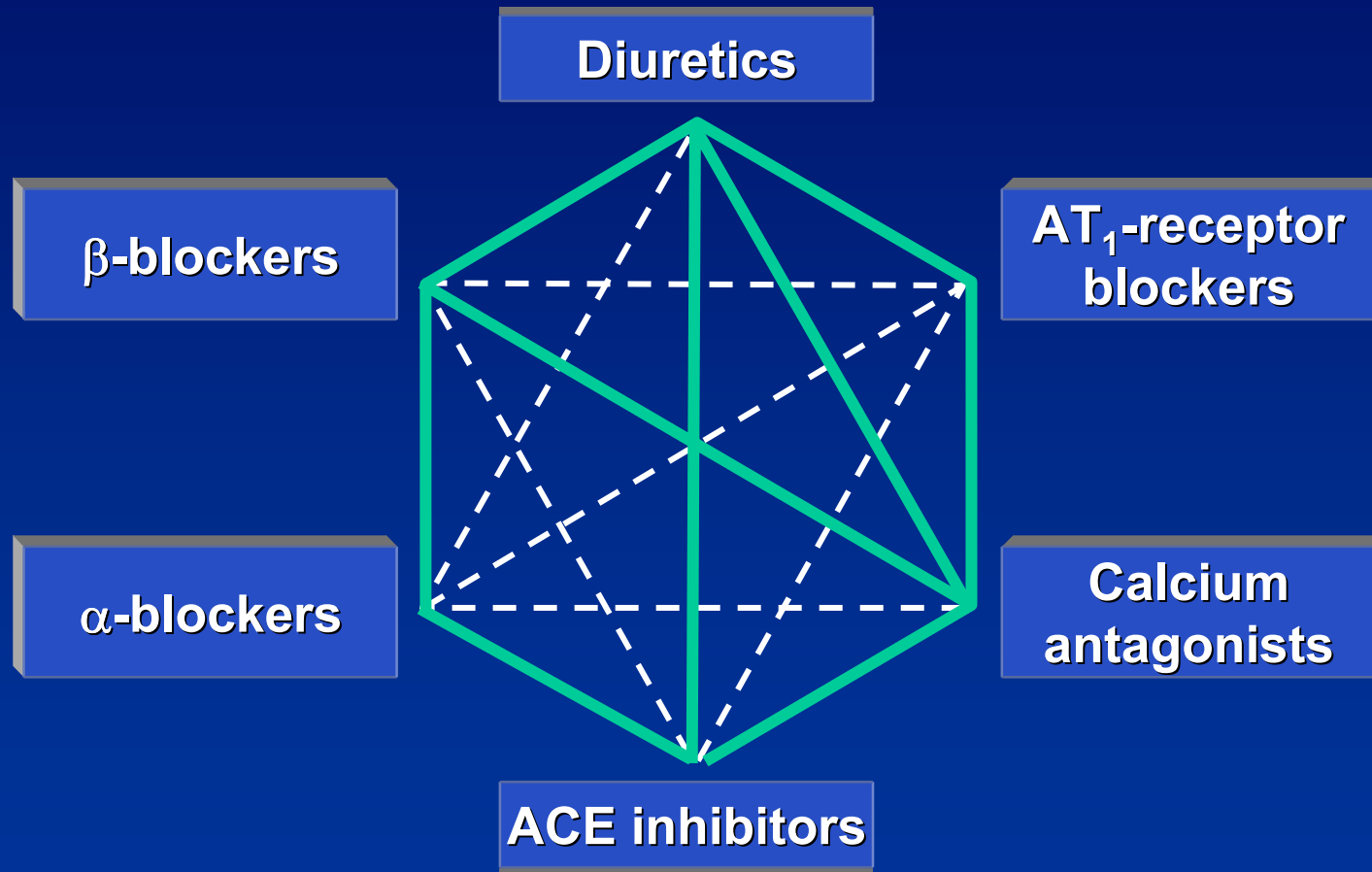
BP=blood pressure.

Neutel JM et al. *Am J Hypertens*. 2001;14:286–292.

Which Therapy Should You Use?

ESH 2003: Possible Combinations of Different Classes of Antihypertensive Agents

The most rational combinations are represented as thick lines

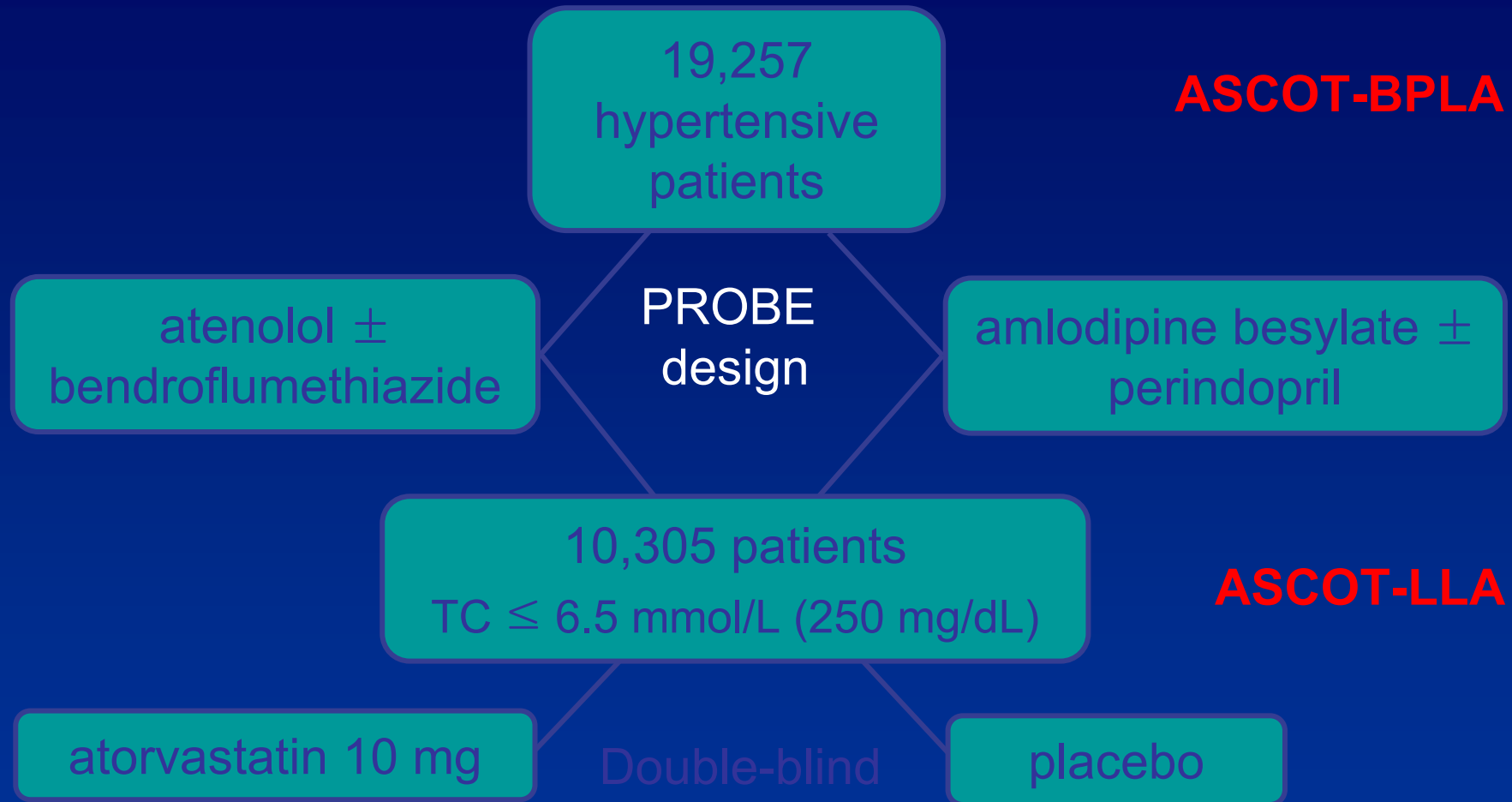


ASCOT- BPLA

Primary Objective

To compare the effect on MI and fatal CHD of the standard antihypertensive regimen (β -blocker \pm diuretic) with a more contemporary regimen (CCB \pm ACE inhibitor)

Study design

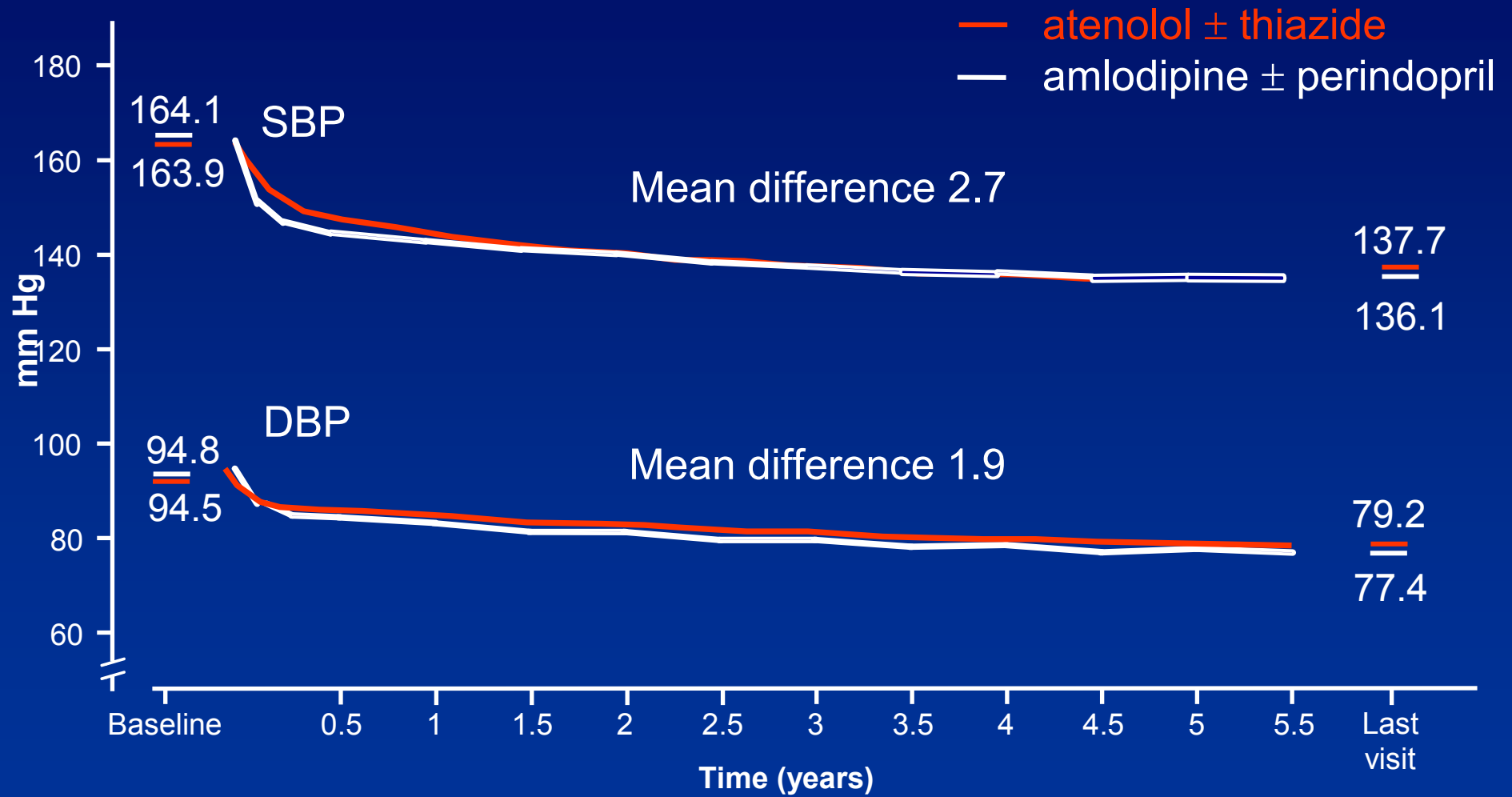


**Investigator-led, multinational
randomised controlled trial**

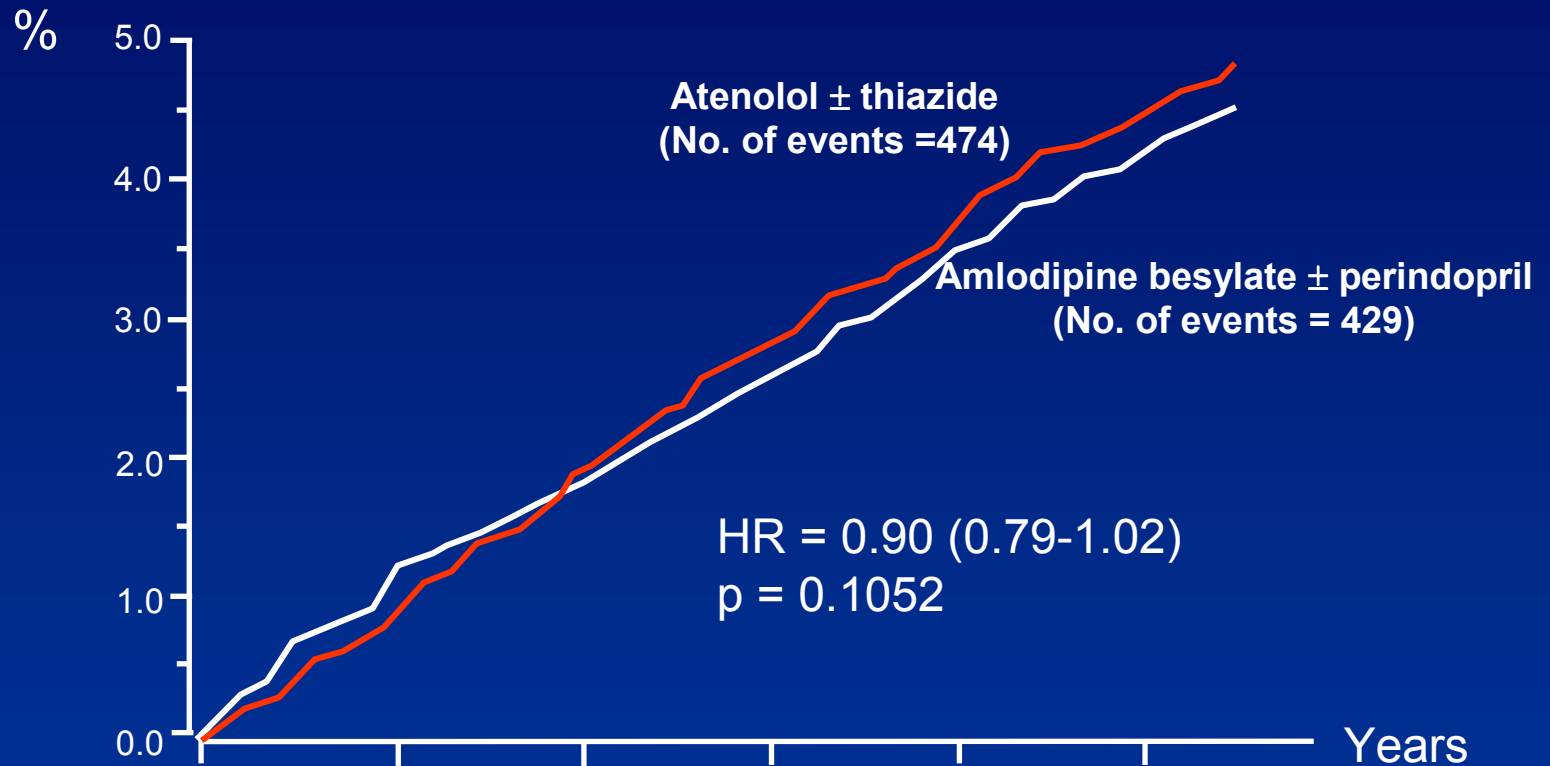
Patient inclusion criteria

- **Screening and baseline BP**
 - **≥ 160/100 mm Hg untreated**
 - **≥ 140/90 mm Hg following treatment with 1 or more drugs**
- **Age 40-79 years**
- *No previous MI or current clinical CHD*
- **3 or more CV risk factors**

Systolic and diastolic blood pressure



Primary end point: Non-fatal MI, fatal CHD



Number at risk

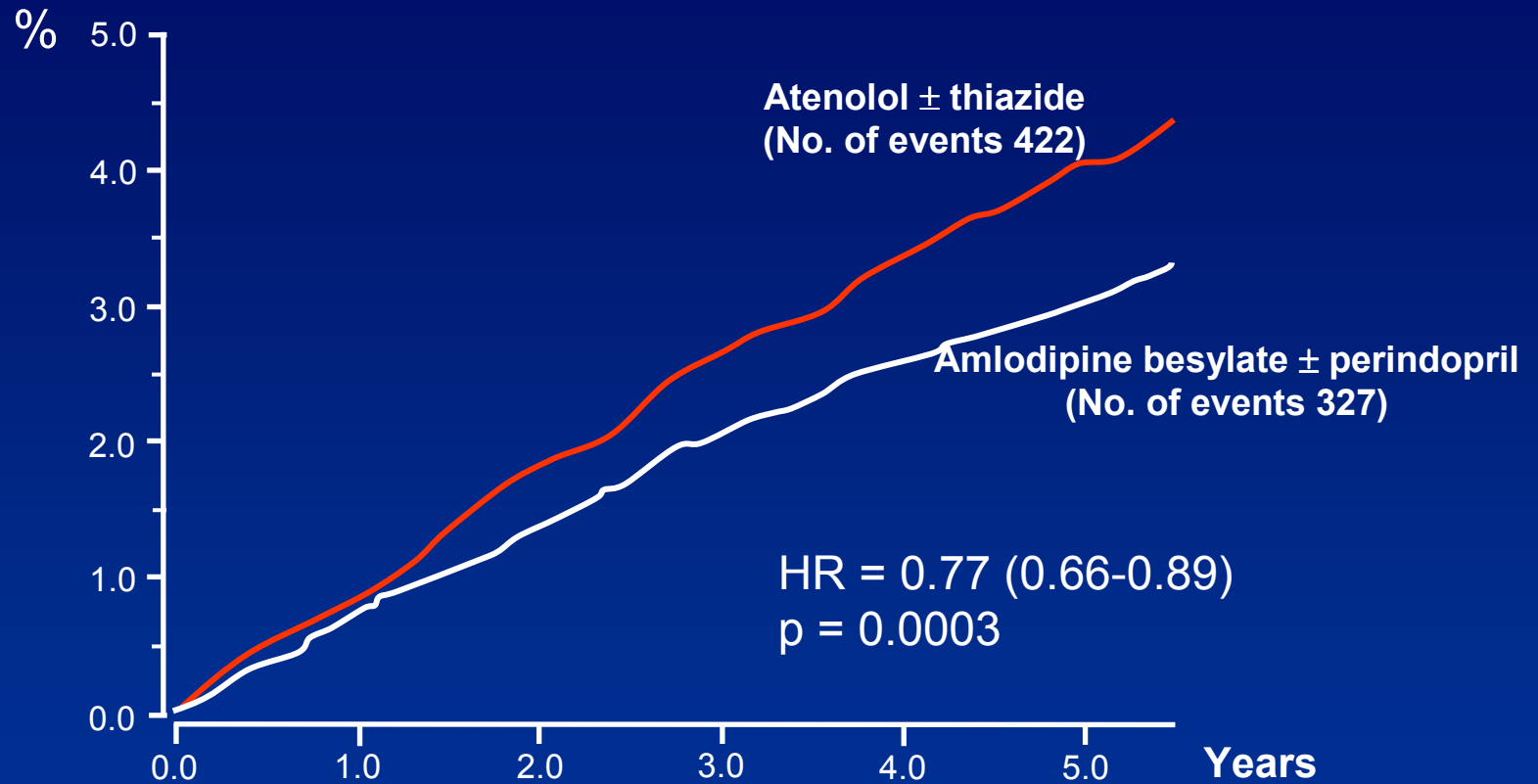
Amlodipine ± perindopril

0.0	1.0	2.0	3.0	4.0	5.0
9639	9475	9337	9168	8966	7863

Atenolol ± thiazide

0.0	1.0	2.0	3.0	4.0	5.0
9618	9470	9290	9083	8858	7743

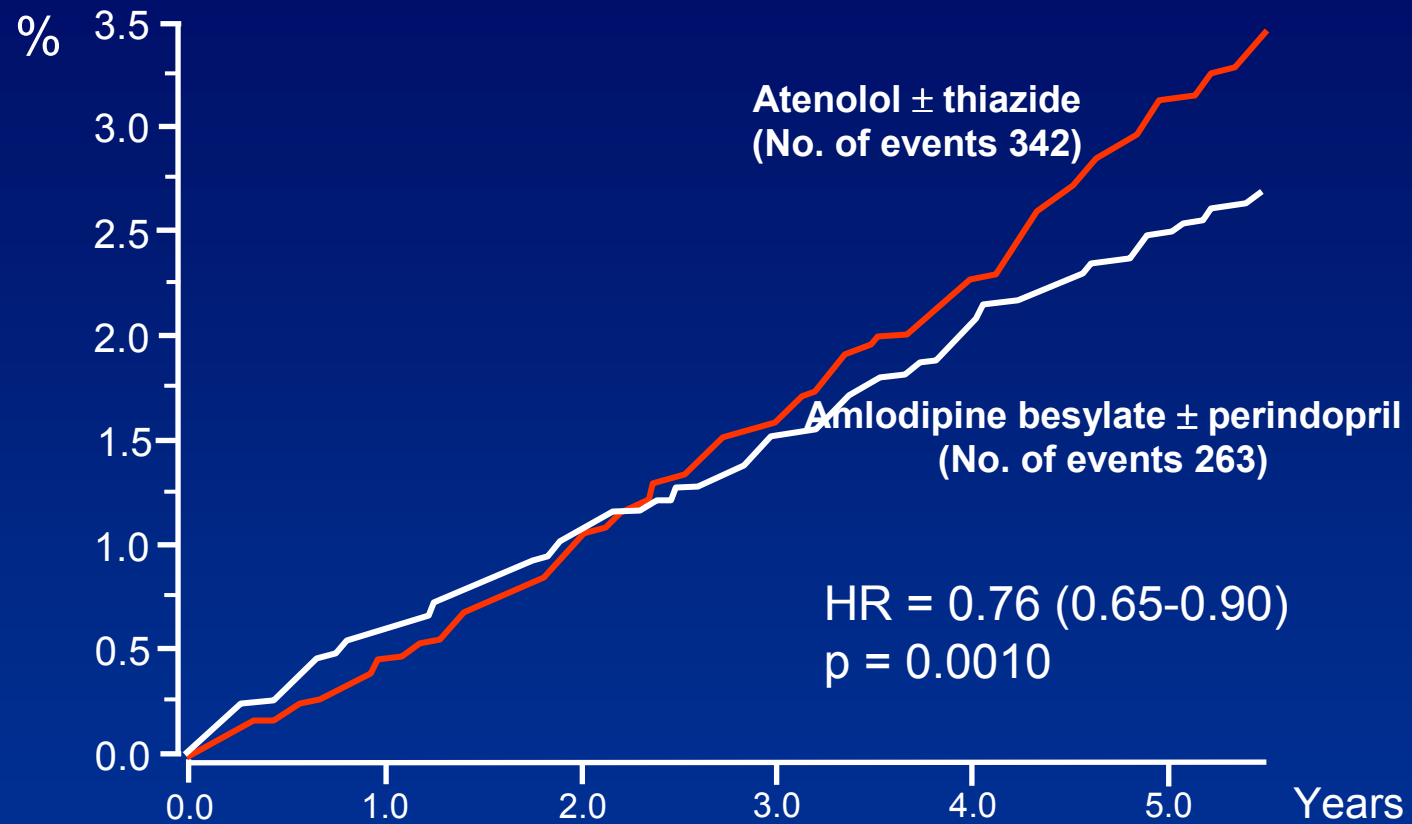
Fatal and non-fatal stroke



Number at risk

Amlodipine ± perindopril	9639	9483	9331	9156	8972	7863
Atenolol ± thiazide	9618	9461	9274	9059	8843	7720

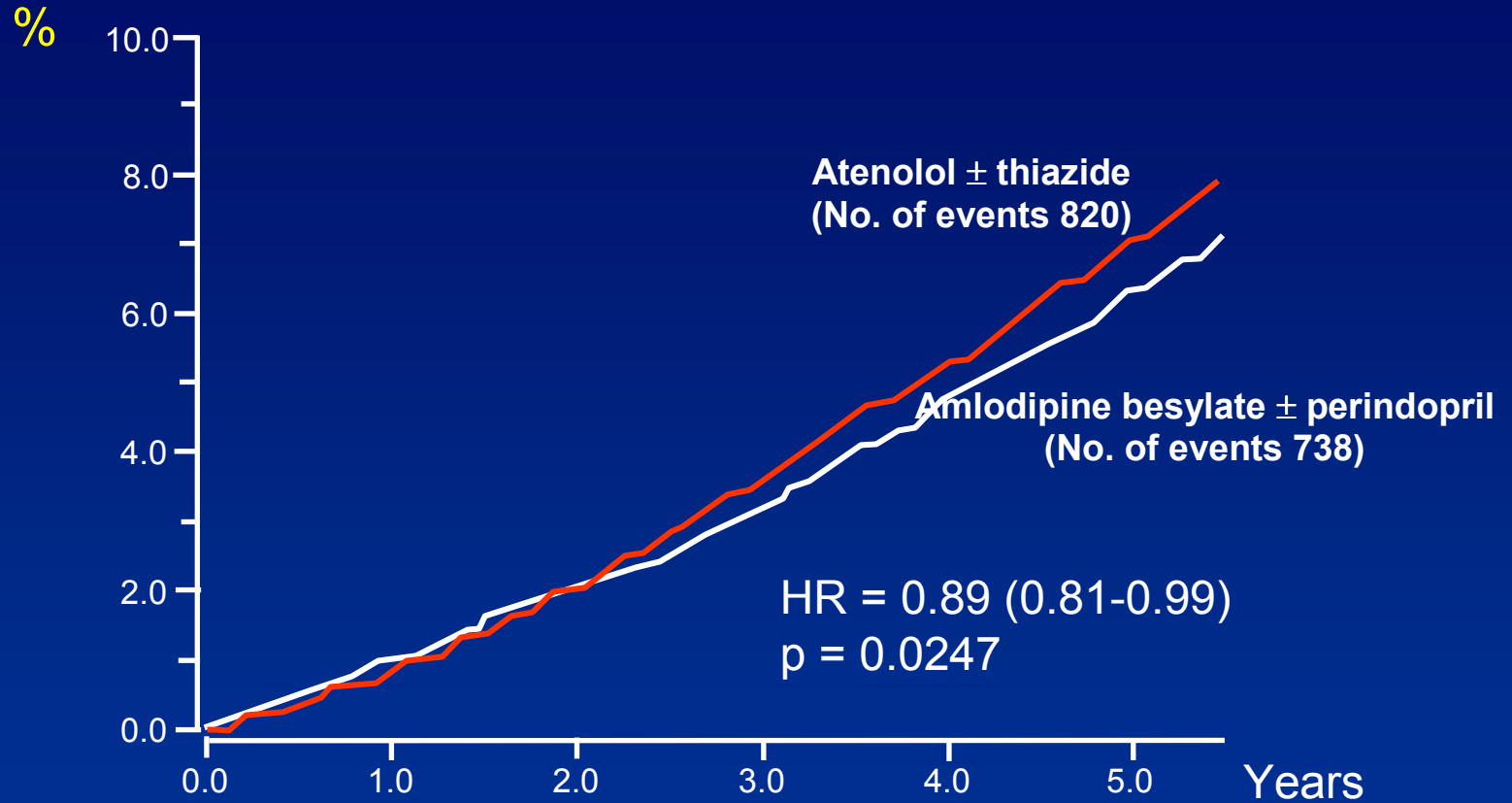
CV mortality



Number at risk

Amlodipine ± perindopril	9639	9544	9441	9322	9167	8078
Atenolol ± thiazide	9618	9532	9415	9261	9085	7975

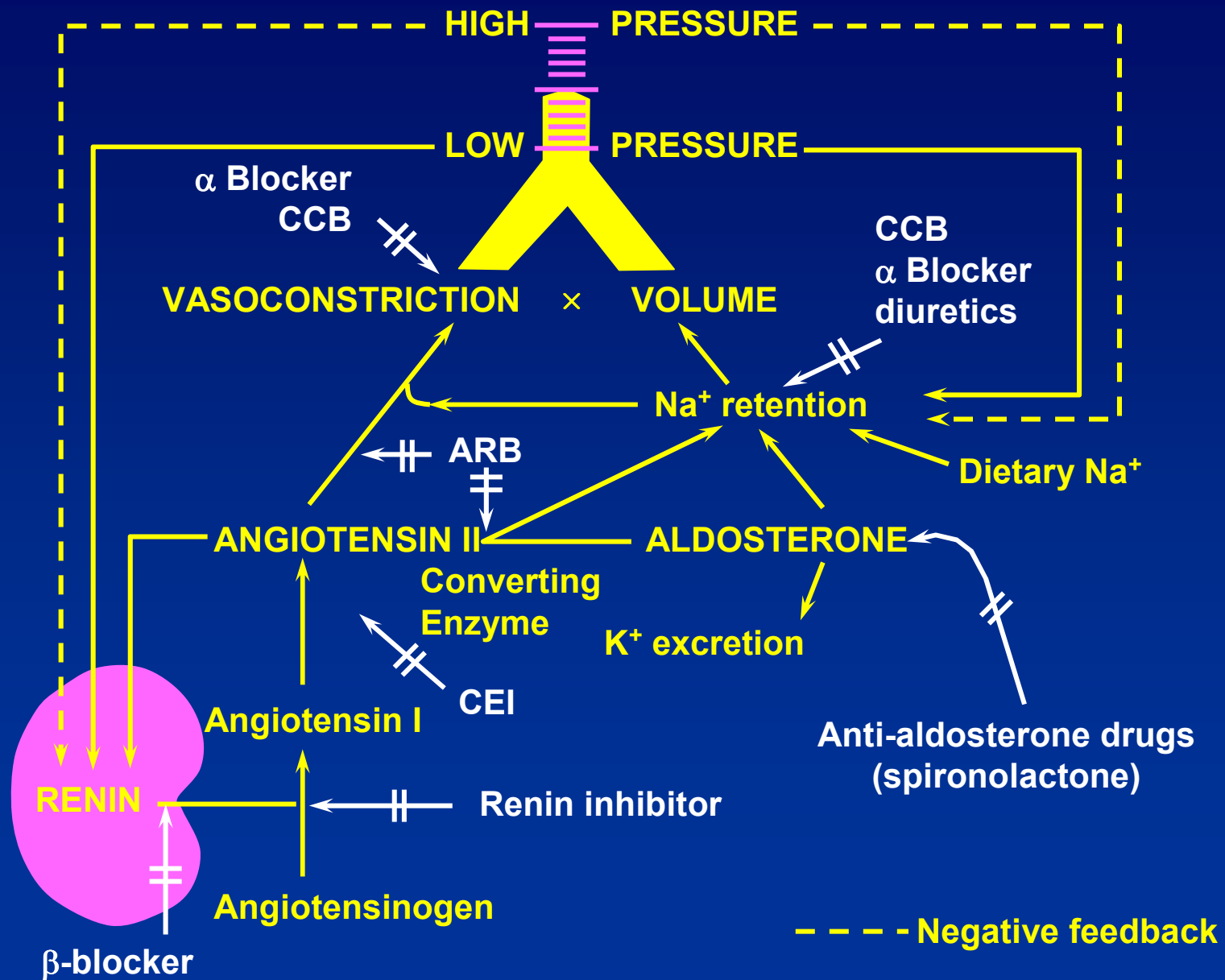
All-cause mortality



Number at risk
 Amlodipine besylate
 ± perindopril
 Atenolol ± thiazide

9639	9544	9441	9332	9167	8078
9618	9532	9415	9261	9085	7975

The Circulating Renin-Angiotensin-Aldosterone System



Superior tolerability of ARBs compared with ACE inhibitors

- **ARBs offer the advantage of more complete blockade of the RAAS**
- **Repeatedly shown to have excellent tolerability, with adverse effect profiles similar to placebo**
- **In particular, the persistent cough that some patients develop with ACE inhibitors is not seen with AIIAs**

Valsartan: Wealth of CV Outcomes Data

VALUE¹

15,245 high-risk HTN patients:
Double-blind, randomized, active-
controlled study vs. amlodipine

Primary outcome: No difference in
composite of cardiac mortality and
morbidity

23% ↓ new-onset diabetes

VALIANT²

14,703 post-myocardial infarction
patients: Double-blind, randomized
study vs. captopril and vs captopril +
valsartan

Primary outcome: No difference vs.
captopril in all-cause mortality

(Valsartan is as effective as standard of
care)

Val-HeFT³⁻⁵

5,010 heart failure II-IV patients:
Double-blind, randomized study vs
placebo

Primary endpoints: Mortality and
combined endpoint of mortality and
morbidity

13% ↓ mortality and morbidity

↓ left ventricular remodeling

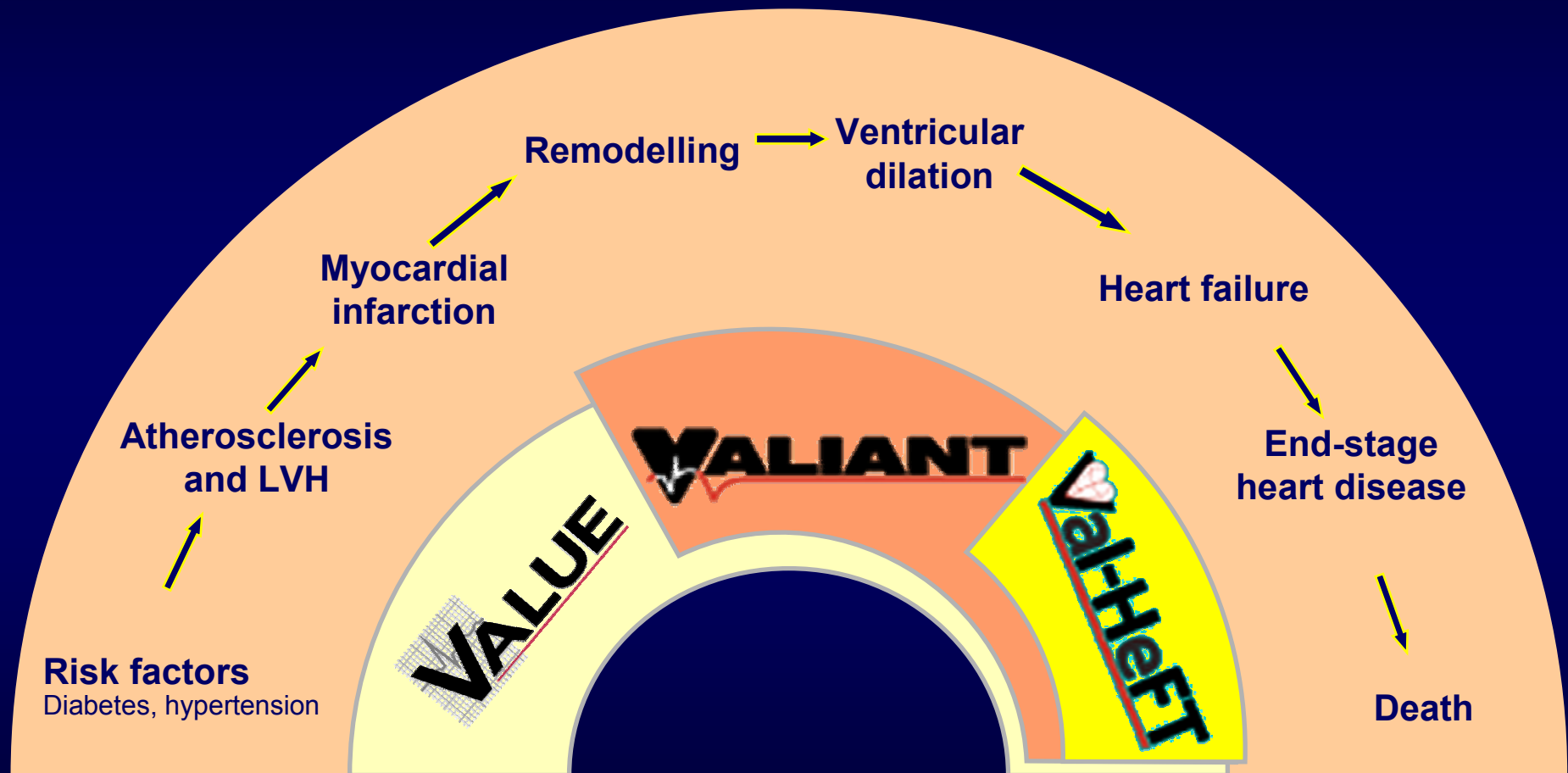
37% ↓ atrial fibrillation occurrence

↓ heart failure signs/symptoms

28% ↓ heart failure hospitalization

¹Julius et al. Lancet 2004;363:2022-31; ²Pfeffer et al. N Engl J Med 2003;349:1893-906; ³Maggioni et al. Am Heart J 2005;149:548-57; ⁴Wong et al. J Am Coll Cardiol 2002;40:970-5; ⁵Cohn et al. N Engl J Med 2001;345:1667-75

The Cardiovascular Continuum From Hypertension to Heart Failure



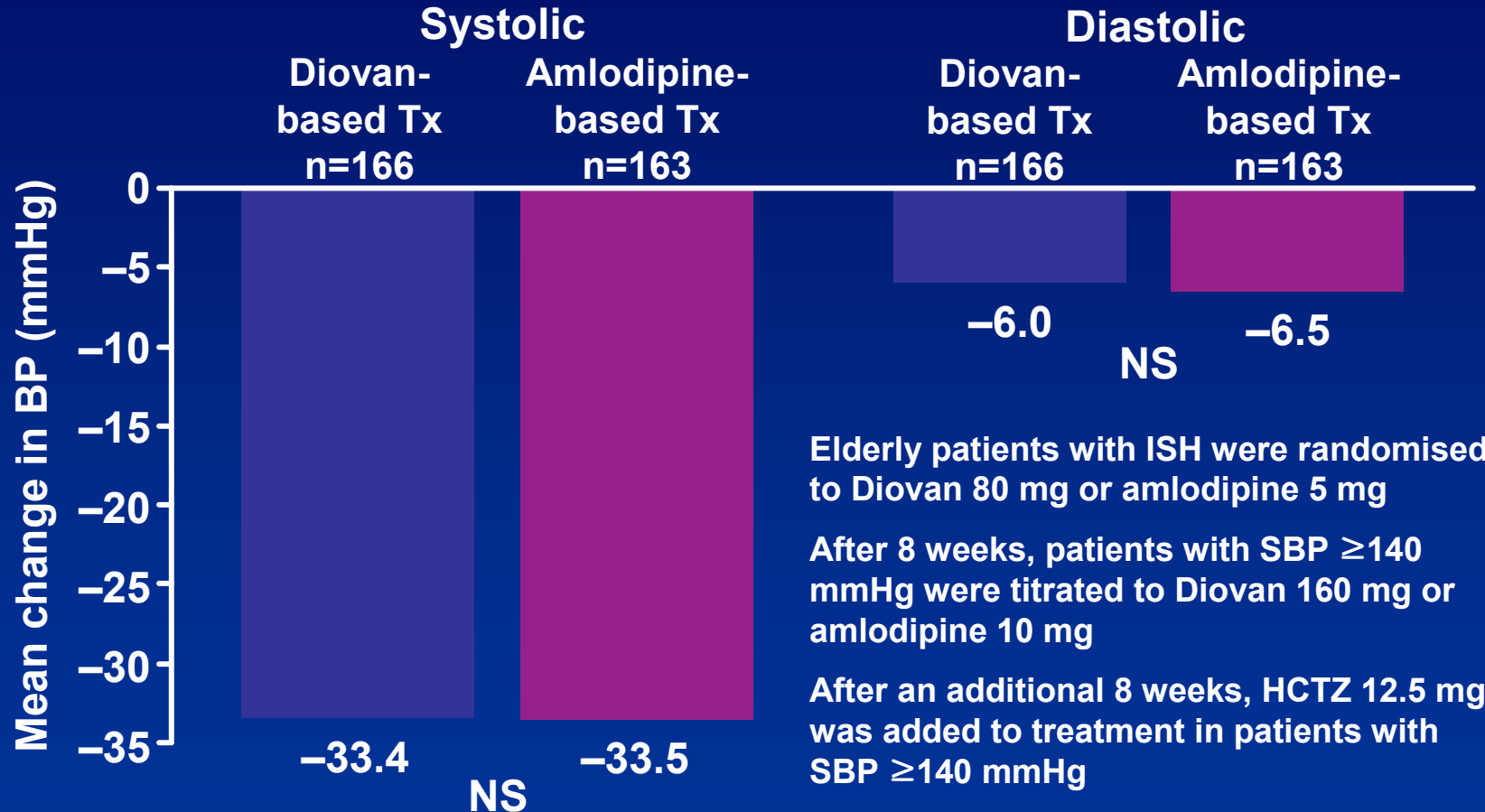
ARB FAMILY



HYPERTENSION OR HEART FAILURE !

Val-Syst Trial: Powerful Double-Digit BP Reductions With Diovan[®]-based Therapy in Patients With ISH

Blood pressure decrease over 24 weeks (mmHg)



Elderly patients with ISH were randomised to Diovan 80 mg or amlodipine 5 mg

After 8 weeks, patients with SBP ≥ 140 mmHg were titrated to Diovan 160 mg or amlodipine 10 mg

After an additional 8 weeks, HCTZ 12.5 mg was added to treatment in patients with SBP ≥ 140 mmHg

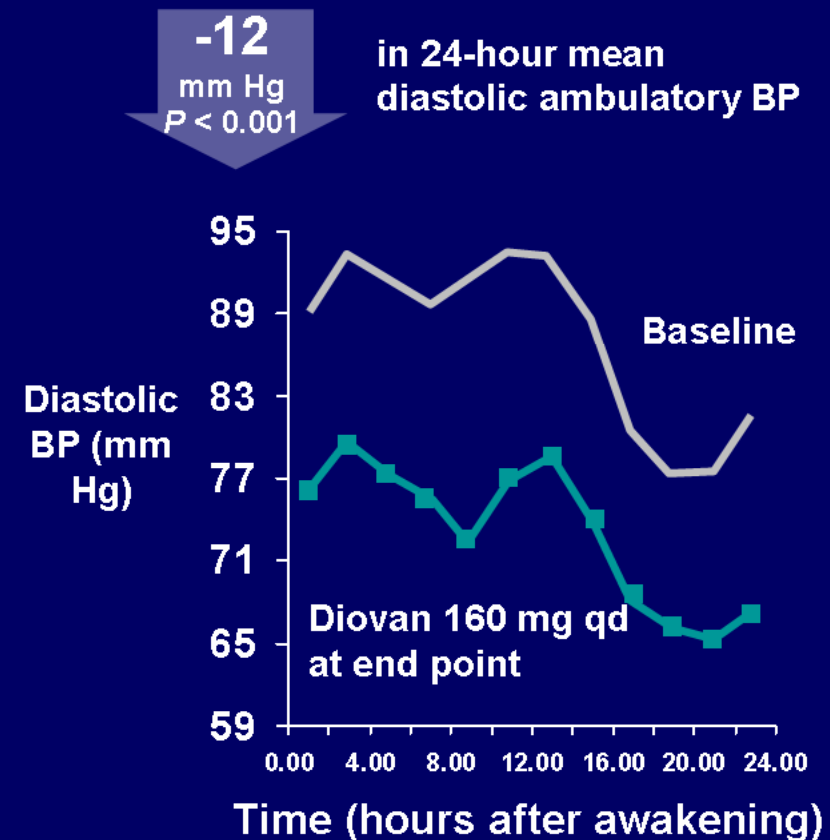
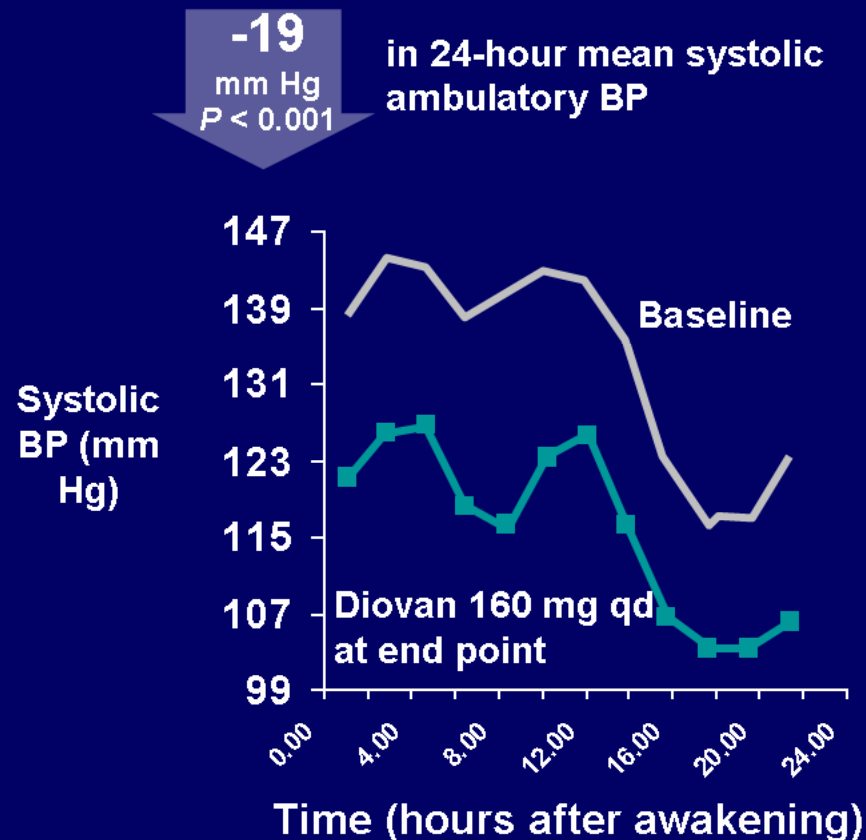
ISH = isolated systolic hypertension

NS = not significant

Malacco E et al. Clin Ther 2003;25:2765-80

Diovan[®] 160 mg qd: Consistent 24-Hour BP Reductions

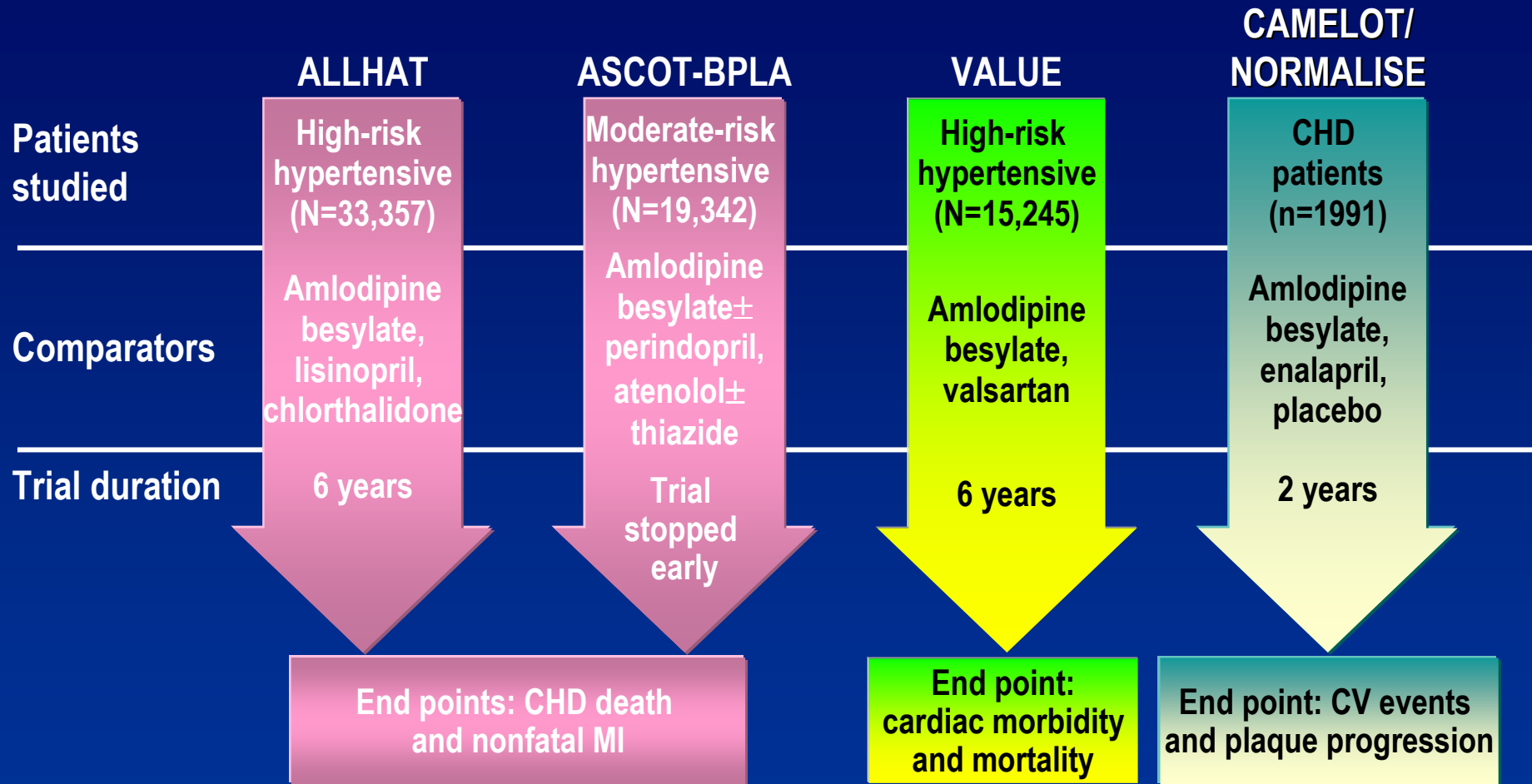
All-Day Efficacy in Previously Untreated Hypertensive Patients



* $P < 0.001$ vs baseline.

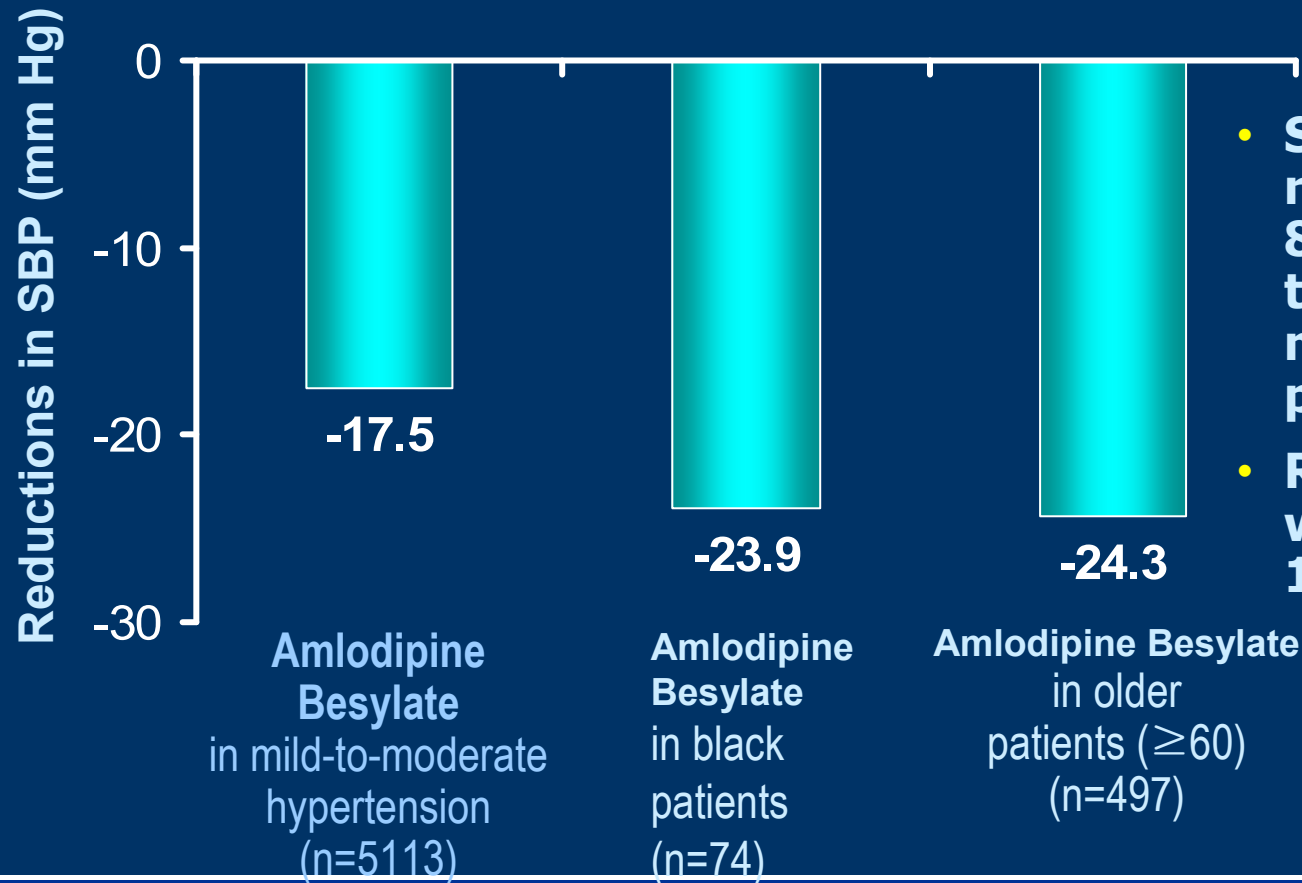
Calvo C et al. *J Hypertens*. 2004;22:837-846.

Amlodipine Extensively Studied in Large Trials



ALLHAT Collaborative Research Group. *JAMA*. 2002;288:2981-2997; Julius et al, for the VALUE trial group. *Lancet*. 2004;363:2022-2031; Sever et al, for the ASCOT Investigators. *J Hypertens*. 2001;19:1139-1147; Nissen et al, for the CAMELOT Investigators. *JAMA*. 2004;292:2217-2226.

Systolic BP in a Broad Range of Patients



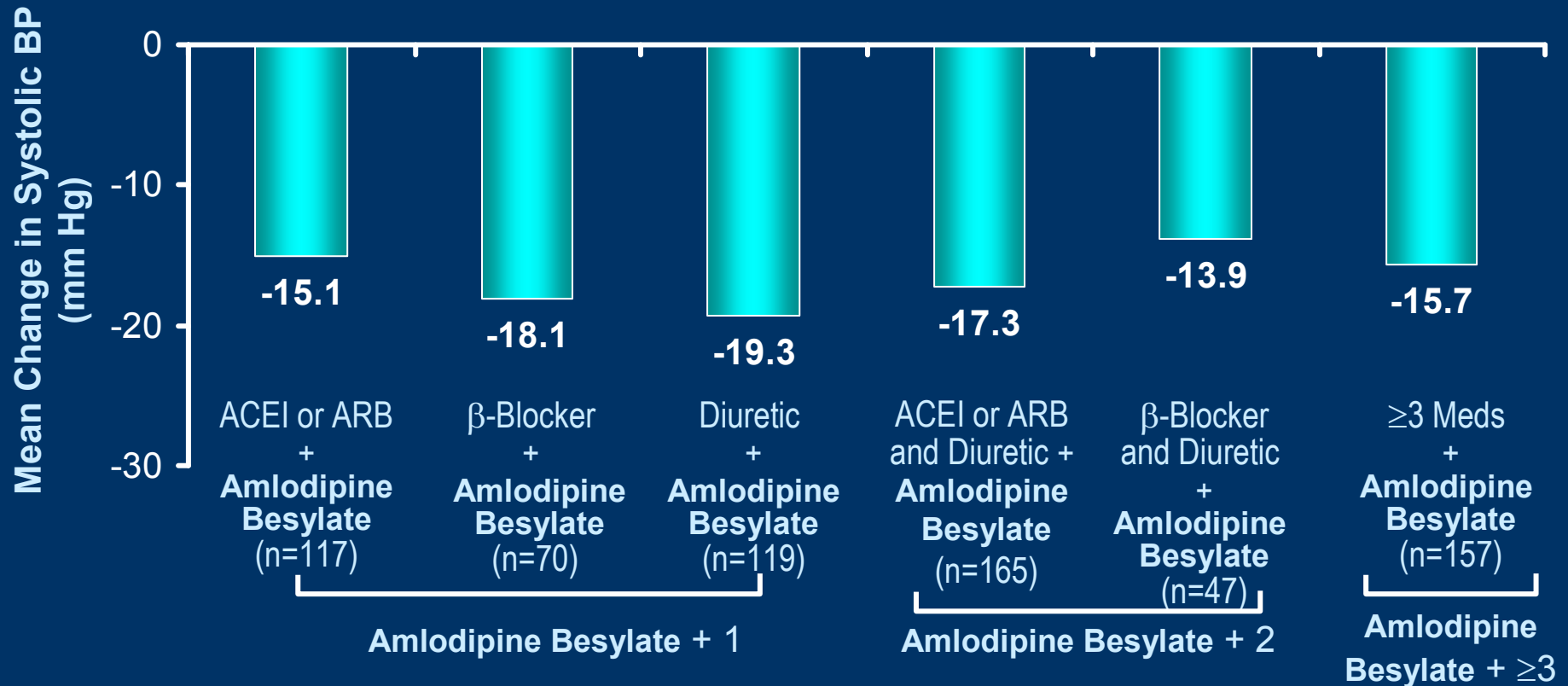
- Systematic retrospective review of 85 controlled clinical trials representing more than 5000 patients
- Reductions in DBP were 12.3, 17.1, and 10.8 mm Hg

SBP=systolic BP.

The magnitude of BP reduction with Norvasc is correlated with the height of pretreatment elevation.

Levine et al. *Clin Ther.* 2003;25:35-57; Data on file. Pfizer Inc, New York, NY.

BP Lowering Effect When Added to Various Antihypertensive Drug Regimens



ACEI=angiotensin-converting enzyme inhibitor; ARB=angiotensin II-receptor blocker.
 $P < .001$ vs baseline regimens.

RAAS Blockade Can Be Considered as a Foundation of Combination Therapy

RAAS Blocker	
CCB*	Diuretic*
<ul style="list-style-type: none">✓ greater BP reduction in many demographic groups✓ complementary effects with other drugs✓ additive efficacy	<ul style="list-style-type: none">✓ greater BP reductions in many demographic groups✓ complementary effects with other drugs, particularly RAAS blockers

*Versus either drug alone.

RAAS=renin-angiotensin-aldosterone system; CCB=calcium channel blocker; BP=blood pressure.

Weir MR. *Am J Hypertens*. 1998;11:163S-169S.

CCB-ARB: Synergy of Counter-regulation

CCB

- Arteriodilation
- Peripheral edema
- Effective in low-renin patients
- Reduces cardiac ischemia

ARB

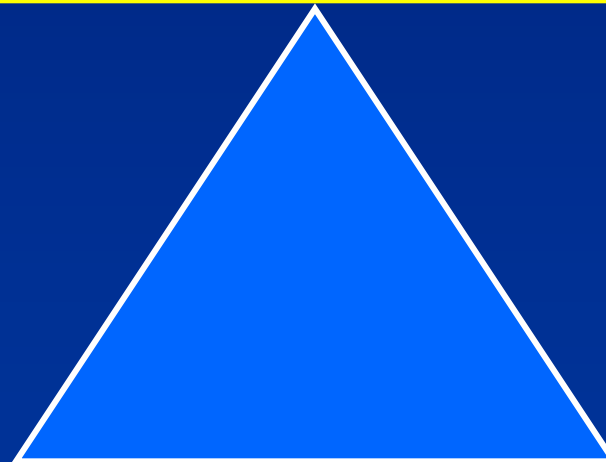
- RAS blockade
- CHF and renal benefits

ARB

- Venodilation
- Attenuates peripheral edema
- Effective in high-renin patients
- No effect on cardiac ischemia

CCB

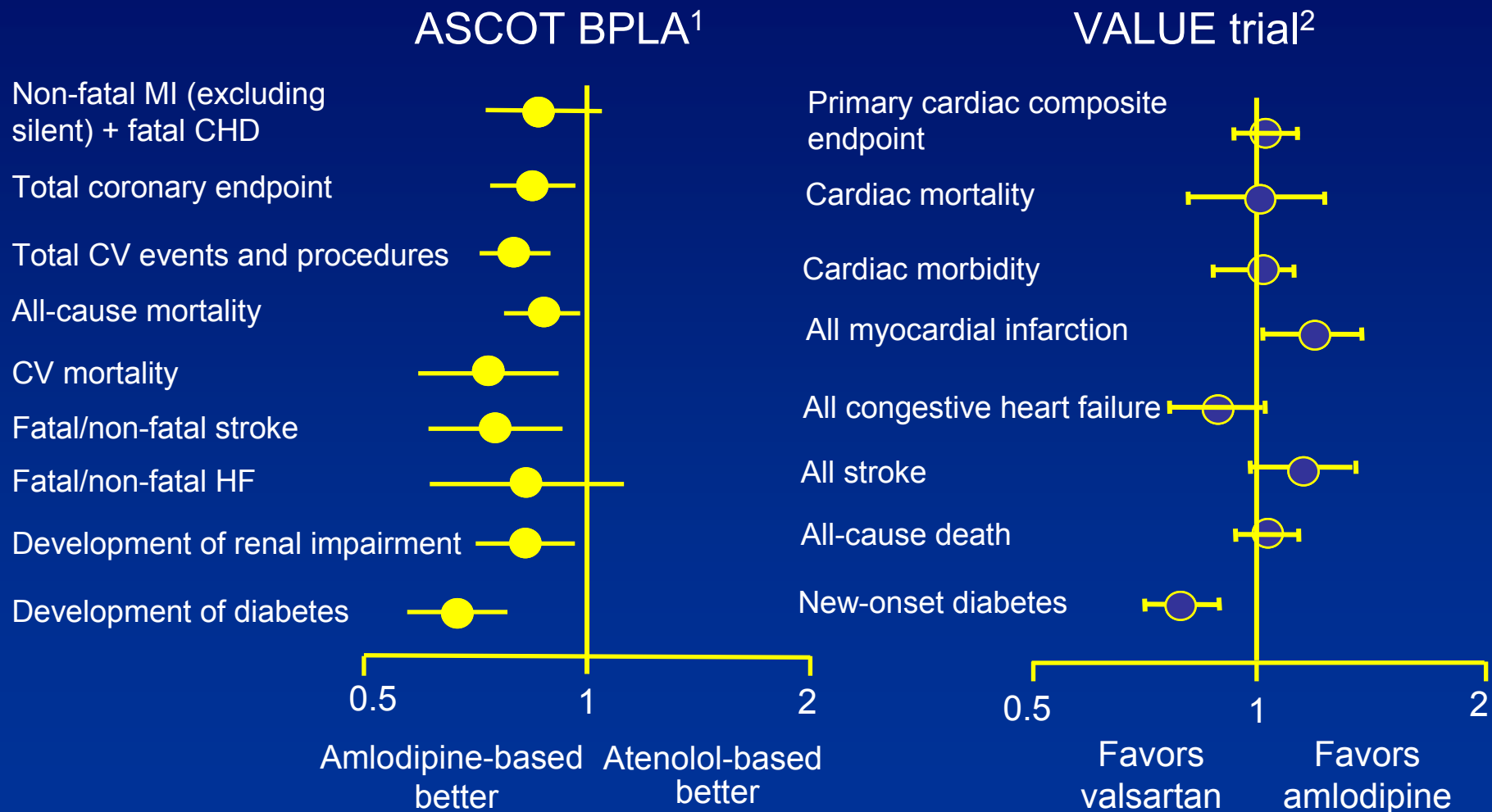
- RAS activation
- No renal or CHF benefits



Why CCB/ARB Combination?

- **CCB/ARB complementary mode of action**
- **CCB induced edema is minimized by ARB**
- **Wealth of CV outcome data for CCB and ARB**

Valsartan and Amlodipine in High-risk Hypertension Have Proven Endpoint Benefits



¹Dahlöf et al. Lancet 2005;366:895–906; ²Julius et al. Lancet 2004;363:2022–31

Case

A typical VALUE study patient

과체중 **67**세 남자 환자

고혈압 진단되어 칼슘길항제와 **ACE** 차단제 투여 중에도
혈압이 조절되지 않아 내원하였음

협심증으로 진단 받았음

신장 **168cm**, 체중 **80kg**, **Body mass Index 28.3**

혈압약 복용 중에도 측정 혈압은 수축기 혈압 **155mmHg**,
이완기 혈압 **88 mmHg**이었음

Case

A typical VALUE study patient

환자에게 적절한 초기 처방은 ?

- 1. Amlodipine 5 mg qd**
- 2. Valsartan 80 mg qd**
- 3. Codigoan 80 mg qd**
- 4. Amlodipine 5 mg and Valsartan 80 mg**