Achieve Best Controls with Fixed Dose Combination for High Blood Pressure

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Cardiovascular Center

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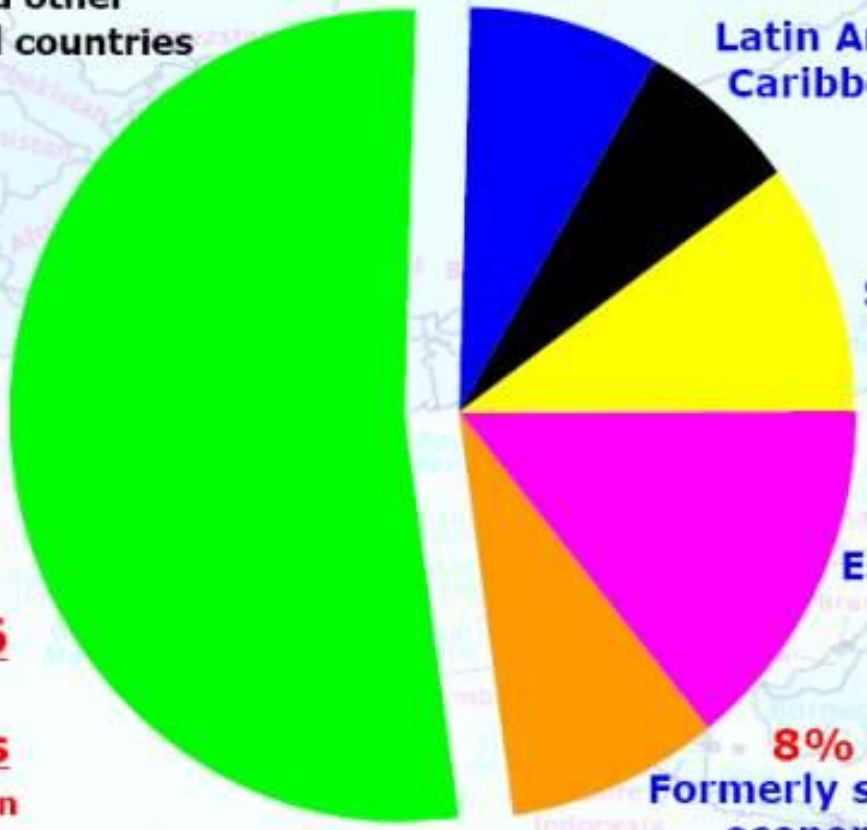
1. What is the burden of disease and why is controlling BP important?

Death by cause in the World:2008 WHO data

World	Deaths in millions	% of deaths
Ischaemic heart disease	7.25	12.8%
Stroke and other cerebrovascular disease	6.15	10.8%
Lower respiratory infections	3.46	6.1%
Chronic obstructive pulmonary disease	3.28	5.8%
Diarrhoeal diseases	2.46	4.3%
HIV/AIDS	1.78	3.1%
Trachea, bronchus, lung cancers	1.39	2.4%
Tuberculosis	1.34	2.4%
Diabetes mellitus	1.26	2.2%
Road traffic accidents	1.21	2.1%

Asian Contribution for Global Burden of CVD



Asia

Countries: 46

Population: 3.8 billions

60.5% world population

Murray C J L and Lopez D The Lancet 1997; 349:1269

The Burden of CVD in Asia:

Stroke Deaths by Country, 2002

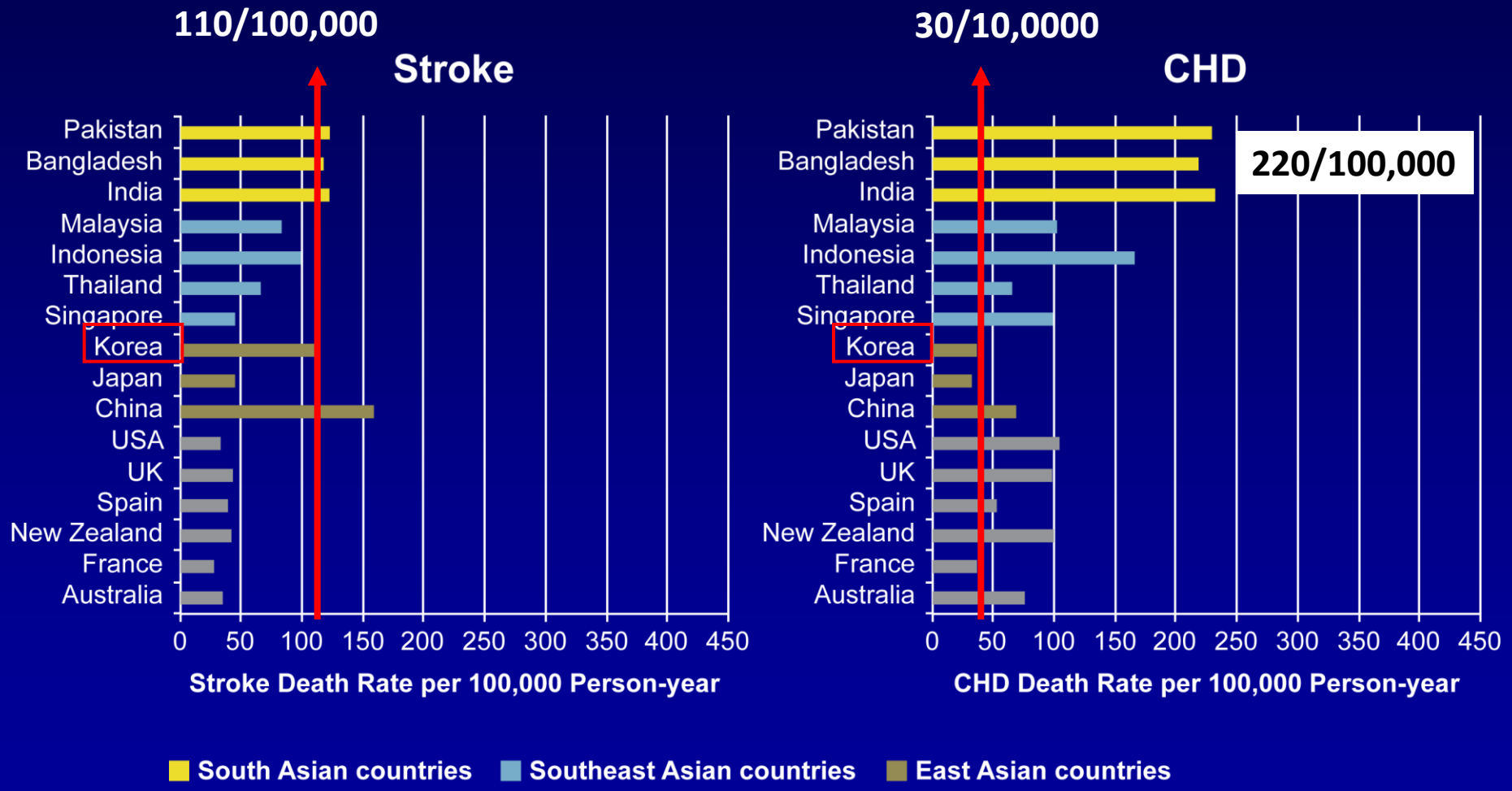
WHO CVD Atlas. 2002. WHO Stroke Atlas. 2002.

The Burden of CVD in Asia:

CHD Deaths by Country, 2002

WHO CVD Atlas. 2002. WHO Stroke Atlas. 2002

Age-Standardized Stroke and CHD Death Rates by Country, 2002



Ueshima H et al. *Circulation*. 2008;118:2702-2709.

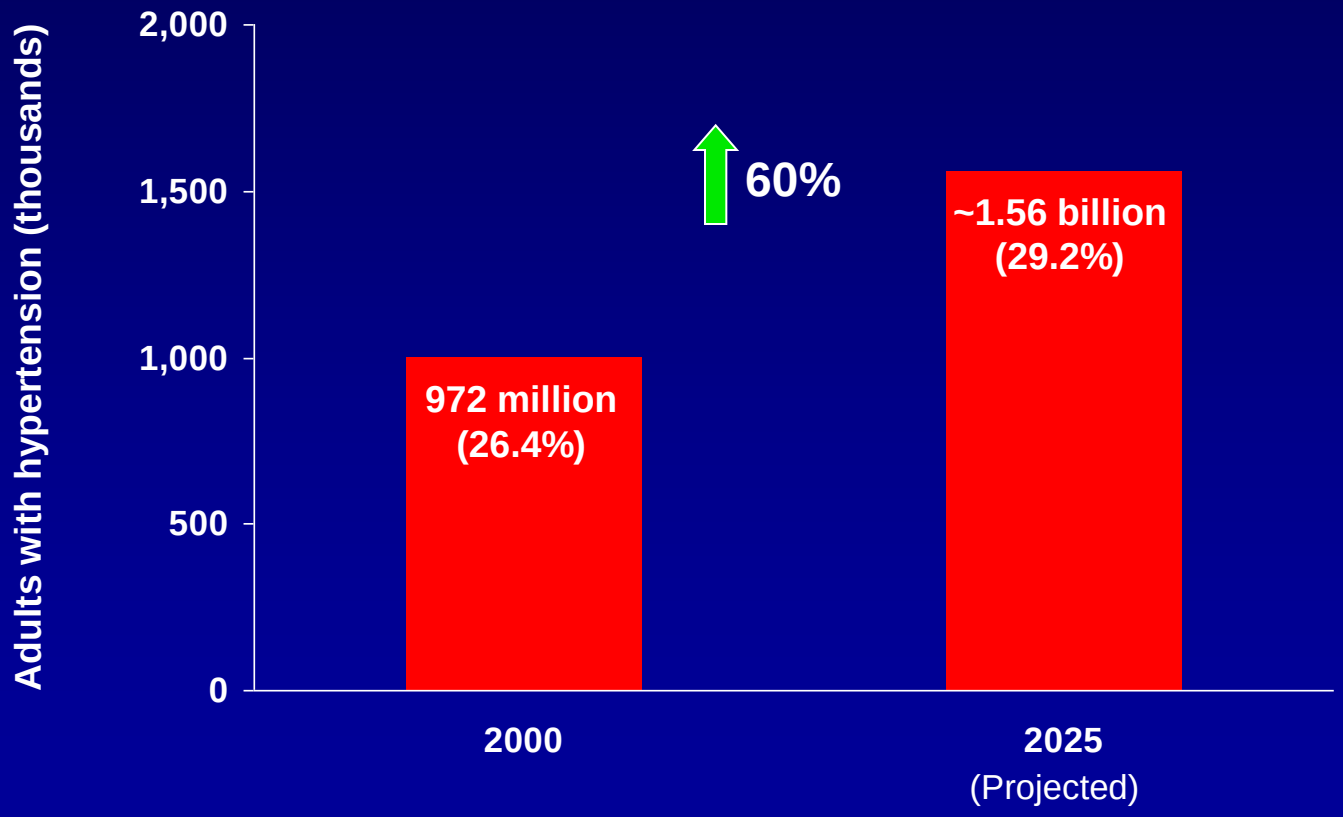
Two major CV risk factors in Asia: Blood pressure and Lipid

	Risk Factor	Global	Developed coutry	Developing country
Ischemic Heart Disease	High Blood Pressure	45%	48%	44%
	High cholesterol	48%	57%	46%
	Obesity	18%	27%	16%
	Low fruit and vegetable intake	28%	19%	30%
	Physical inactivity	21%	21%	21%
	Smoking	17%	23%	15%
Stroke	High Blood Pressure	54%	56%	54%
	High cholesterol	16%	25%	15%
	Obesity	12%	20%	10%
	Low fruit and vegetable intake	11%	9%	11%
	Physical inactivity	7%	8%	6%
	Smoking	13%	21%	12%

Lopez AD et al. Global burden of disease and risk factors. Washington, DC: World Bank; 2006.

Global Prevalence of Hypertension

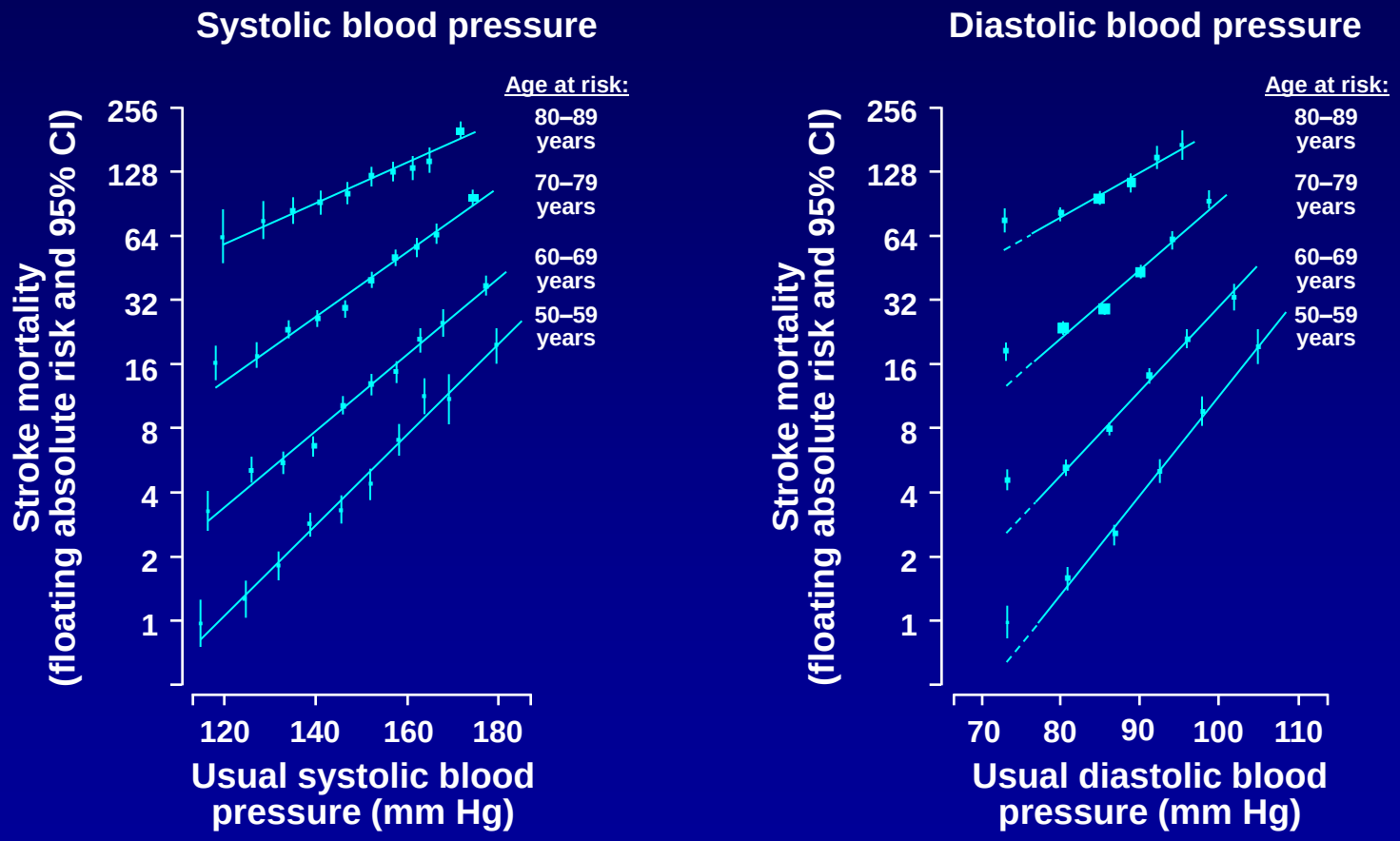
More than a quarter of the world's adult population had hypertension in 2000, and the number of adults with hypertension is expected to increase 60% by 2025.



Kearney PM, et al. *Lancet*. 2005;365(9455):217-223.

The Relationship of Stroke Mortality for Different Age Groups and Blood Pressure Ranges

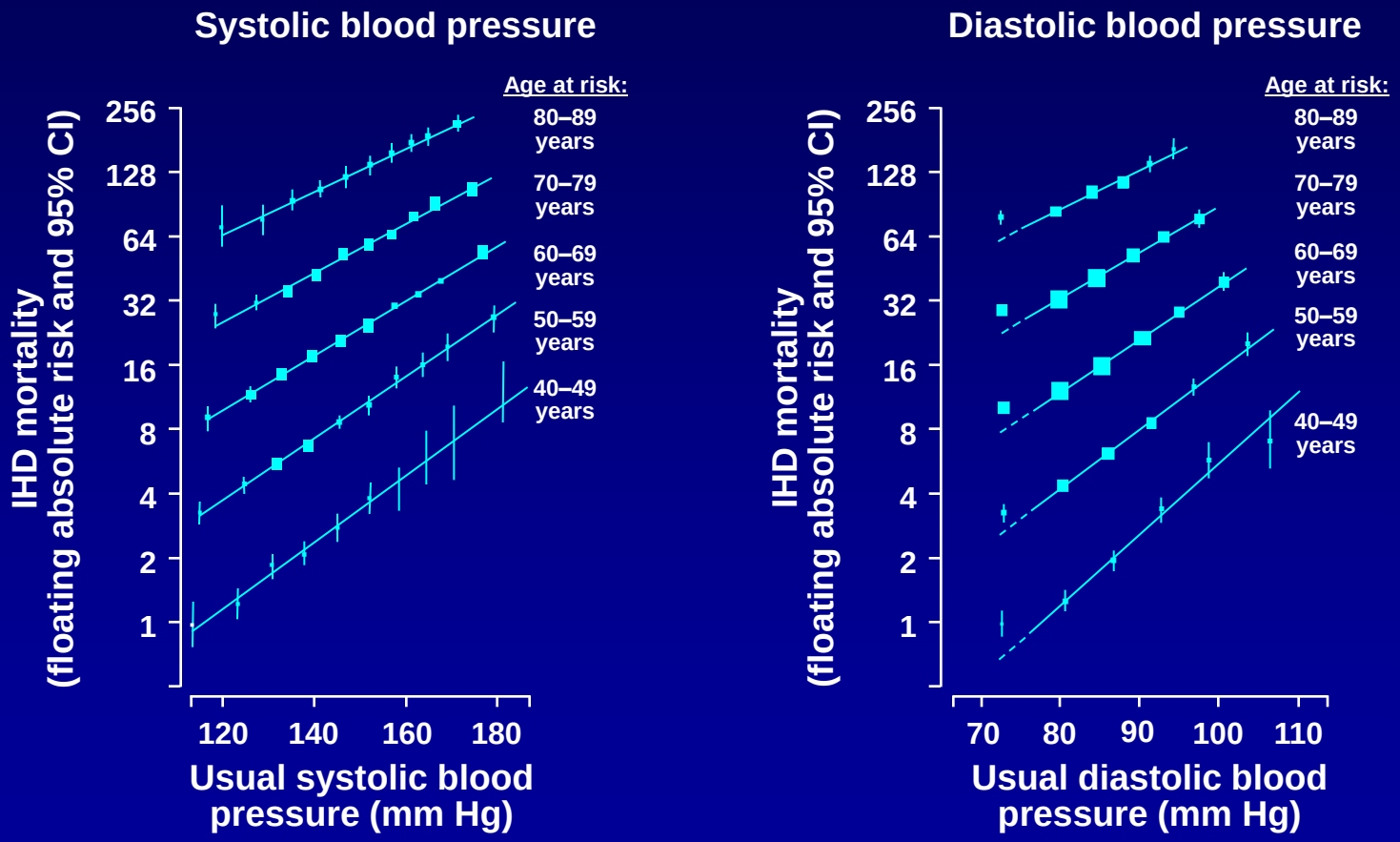
The relationship of stroke mortality to blood pressure is strong and direct at all ages.



The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Chobanian AV, et al. *Hypertension.* 2003;42:1206-1252.

The Relationship of Ischemic Heart Disease Mortality for Different Age Groups and Blood Pressure Ranges

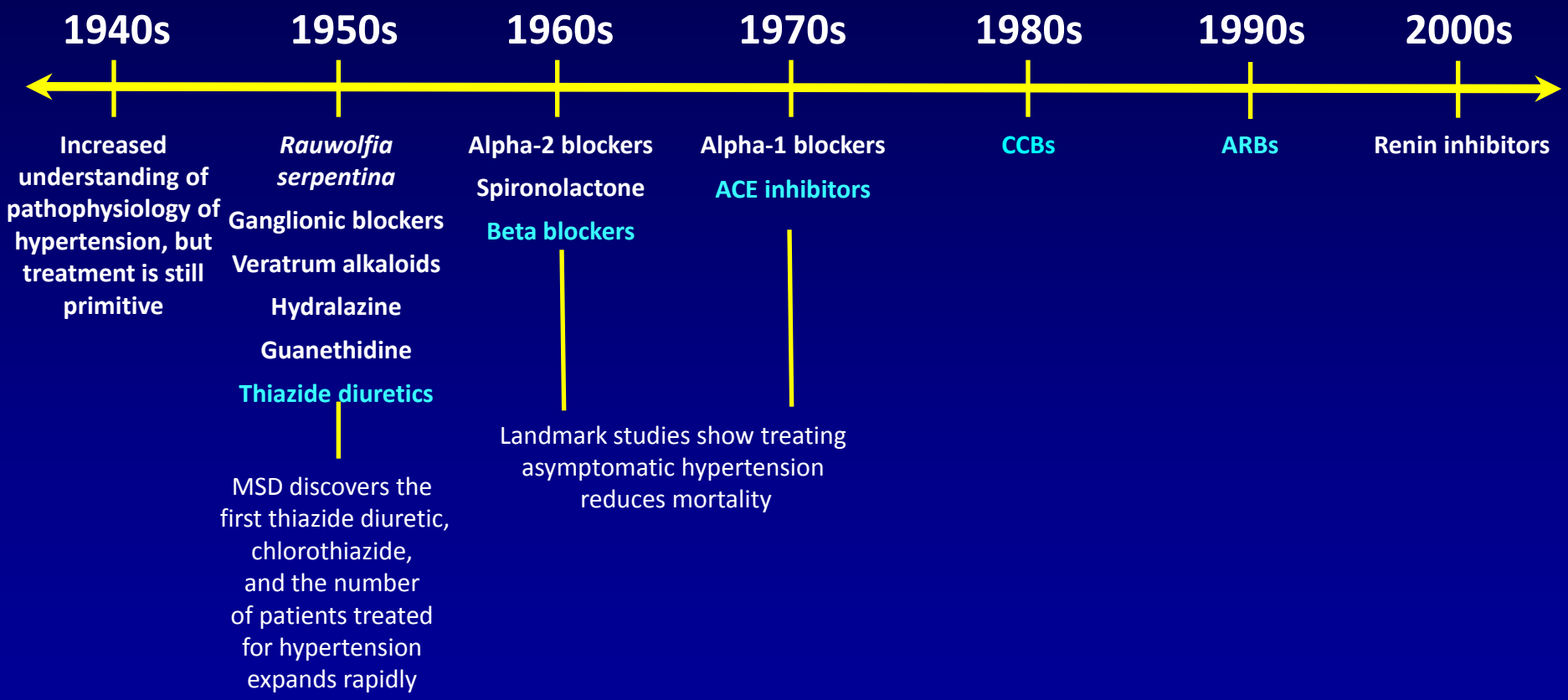
The relationship of ischemic heart disease mortality to blood pressure is strong and direct at all ages.



The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Chobanian AV, et al. *Hypertension* 2003;42:1206-1252.

2. What do the guidelines say about Hypertension management and Combination Therapy

History of Hypertension Knowledge and Innovation



Chobanian: AV. *N Engl J Med.* 2009; 361:878-887.

ACE = angiotensin-converting enzyme; CCB = calcium channel blocker; ARB = angiotensin II receptor blocker.

Evolution of hypertension management guideline evolution in US

1977:JNC I

1980:JNC II } DBP<90mmHg

1984:JNC III

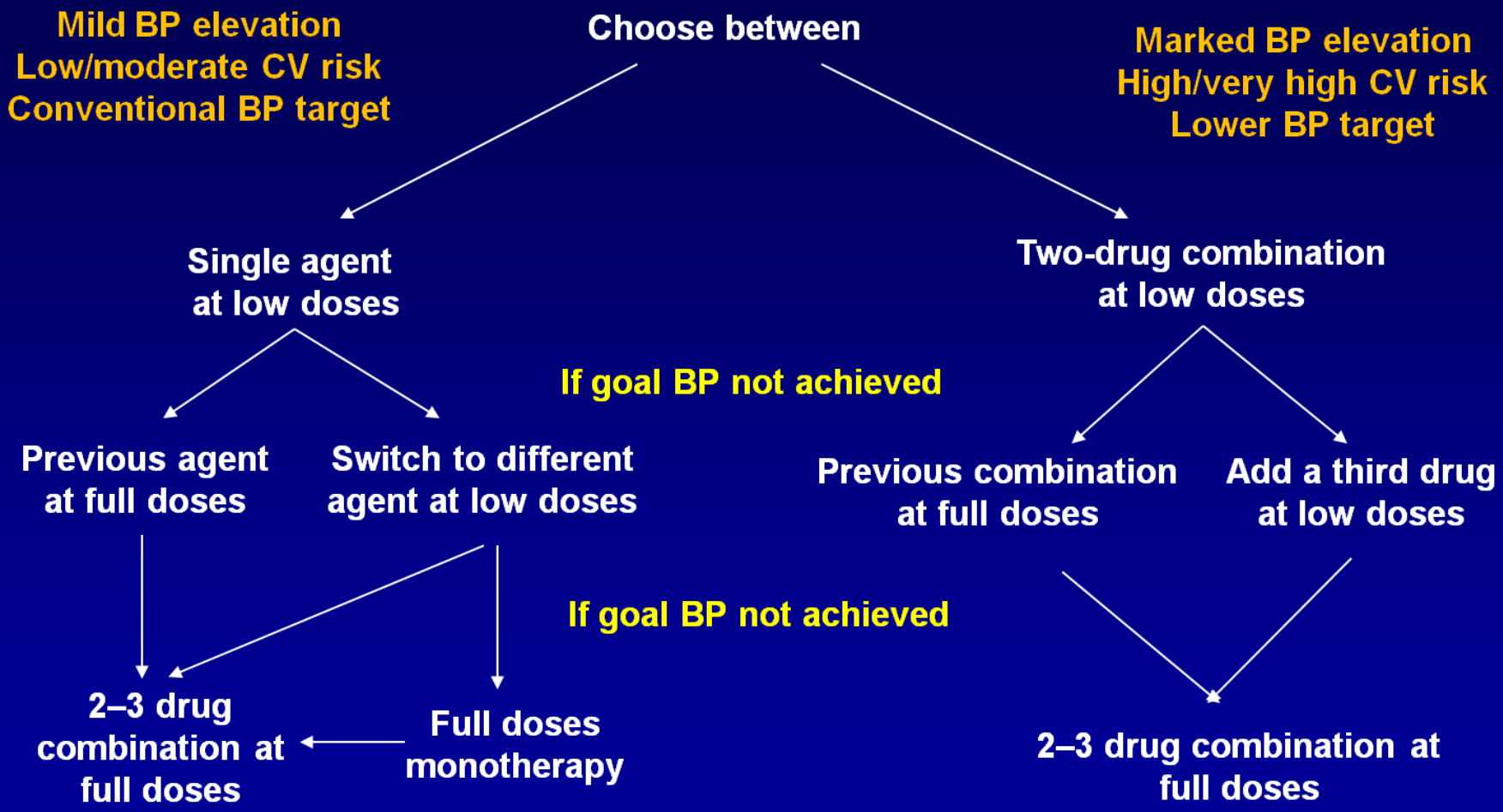
1988:JNC IV → BP<140/90mmHg

1993:JNC V → Different BP goal by baseline BP level

1997:JNC VI → Different BP goal by RFs:140/90, 130/85 or 125/75

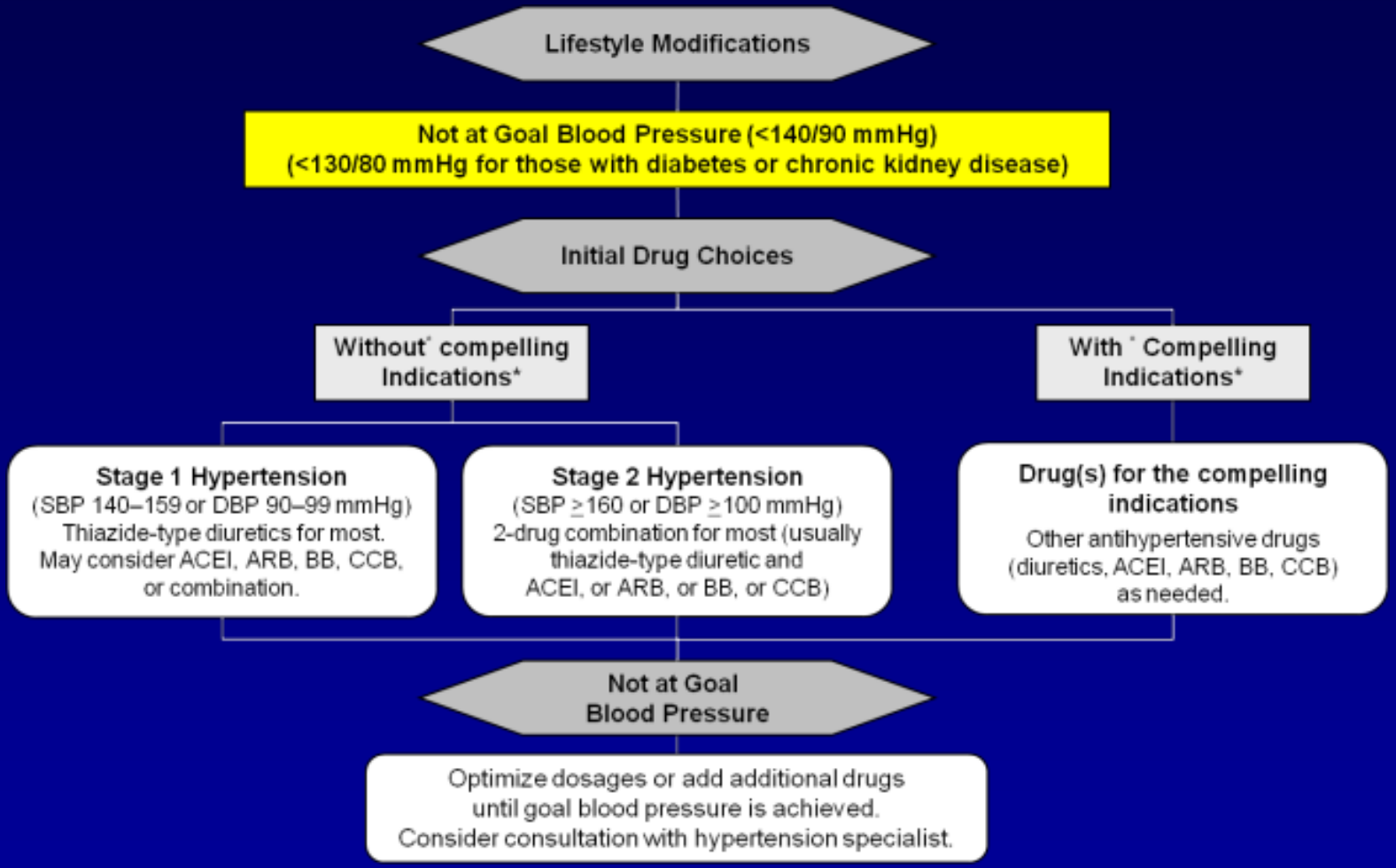
2003:JNC VII → Different BP goal by RFs:140/90 or 130/80

ESH/ESC 2007 Guidelines Algorithm for the Treatment of Hypertension



ESH = European Society of Hypertension; ESC = European Society of Cardiology; BP = blood pressure; CV = cardiovascular.
Mancia G, et al. *J Hypertens*. 2007;25:1105-1187.

JNC 7 2003 Guidelines
Algorithm for the Treatment of Hypertension



JNC = Joint National Committee; ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; BB = beta blocker; CCB = calcium channel blocker; DBP = diastolic blood pressure; SBP = systolic blood pressure.

The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Chobanian AV, et al. *Hypertension* 2003;42:1206-1252.

Potential Benefits of Combining Antihypertensive Agents into a Fixed-Dose Combination

Benefit	Reason(s)
• More rapid achievement of goal blood pressure compared with monotherapy	• Greater antihypertensive efficacy
• Lower rate of adverse events	• Action of one agent ameliorates adverse effects of the other
• Less need to modify antihypertensive regimen	• Target blood pressure reached more quickly
• Lower overall cost	• Lower prescription costs and fewer physician visits because of reduced need for regimen modification
• Improved patient compliance	• Simpler dosing regimen and reduced medication burden
• More effective than monotherapy, and at least as effective as free combination of same agents	• Combination blocks more than one pathophysiologic pathway

Oparil S, et al. *Postgrad Med*. 2009;121:25-39.

Guideline Recommendations Regarding Initial Use of Combination Therapy

JNC 7	>20/10 mm Hg
ESH	>20/10 mm Hg OR high cardiovascular risk
AHA	SBP ≥160 mm Hg or DBP ≥100 mm Hg irrespective of the BP goals
NKF K/DOQI	SBP >20 mm Hg above goal according to the stage of CKD and CVD risk

JNC 7, Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.
ISHIB, International Society on Hypertension in Blacks.
ESH, European Society of Hypertension.
AHA, American Heart Association.
NKF K/DOQI, National Kidney Foundation Kidney Disease Outcomes Quality Initiative.

1. Chobanian AV, et al. *Hypertension*. 2003;42:1206-1252. 2. Douglas JG, et al. *Arch Intern Med.* 2003;163: 525-541.
3. K/DOQI. *Am J Kidney Dis*. 2004;43 (suppl 1):S65-S230. 4. Mancia G, et al. *J Hypertens*. 2007;25:1105-1187.
5. Rosendorff C, et al. *Circulation*. 2007;115;2761-2788.

3. What is the rationale for adding a CCB to a RAS blocker?

Why is a CCB Preferred to a Diuretic?

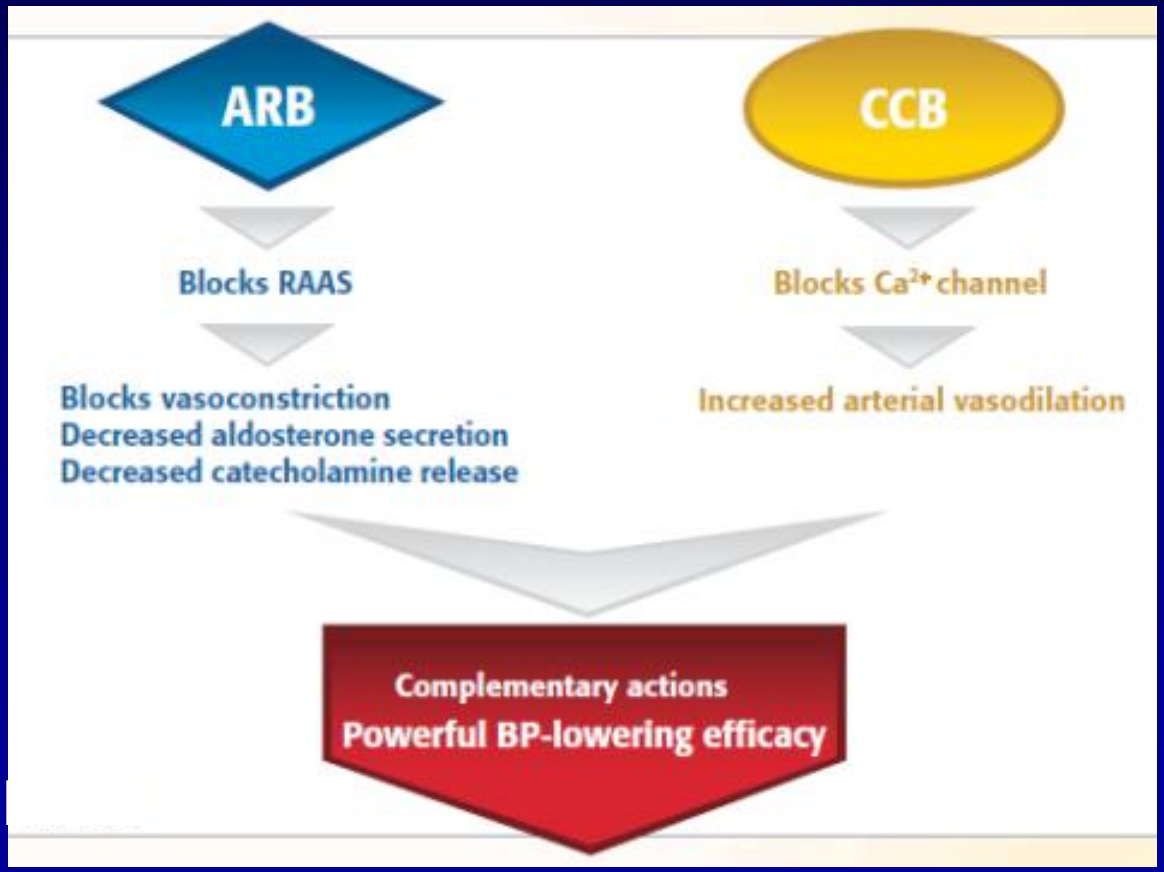
- CCB (usually amlodipine) was the most cost-effective treatment option for treating hypertension unless the patient had heart failure or was at high risk of developing heart failure – i.e. older patient ≥75yrs
- CCB is metabolically neutral – easy to use
- CCB is best at reducing blood pressure variability and BP variability is an independent predictor of clinical outcomes - especially stroke
- At step 2, the combination of A + C was superior to A + D at preventing clinical outcomes

CCB = calcium channel blocker

Krause T, et al. *BMJ*. 2011 Aug 25;343:d4891.

Rationale for Combination of an ARB and CCB in the Treatment of Hypertension

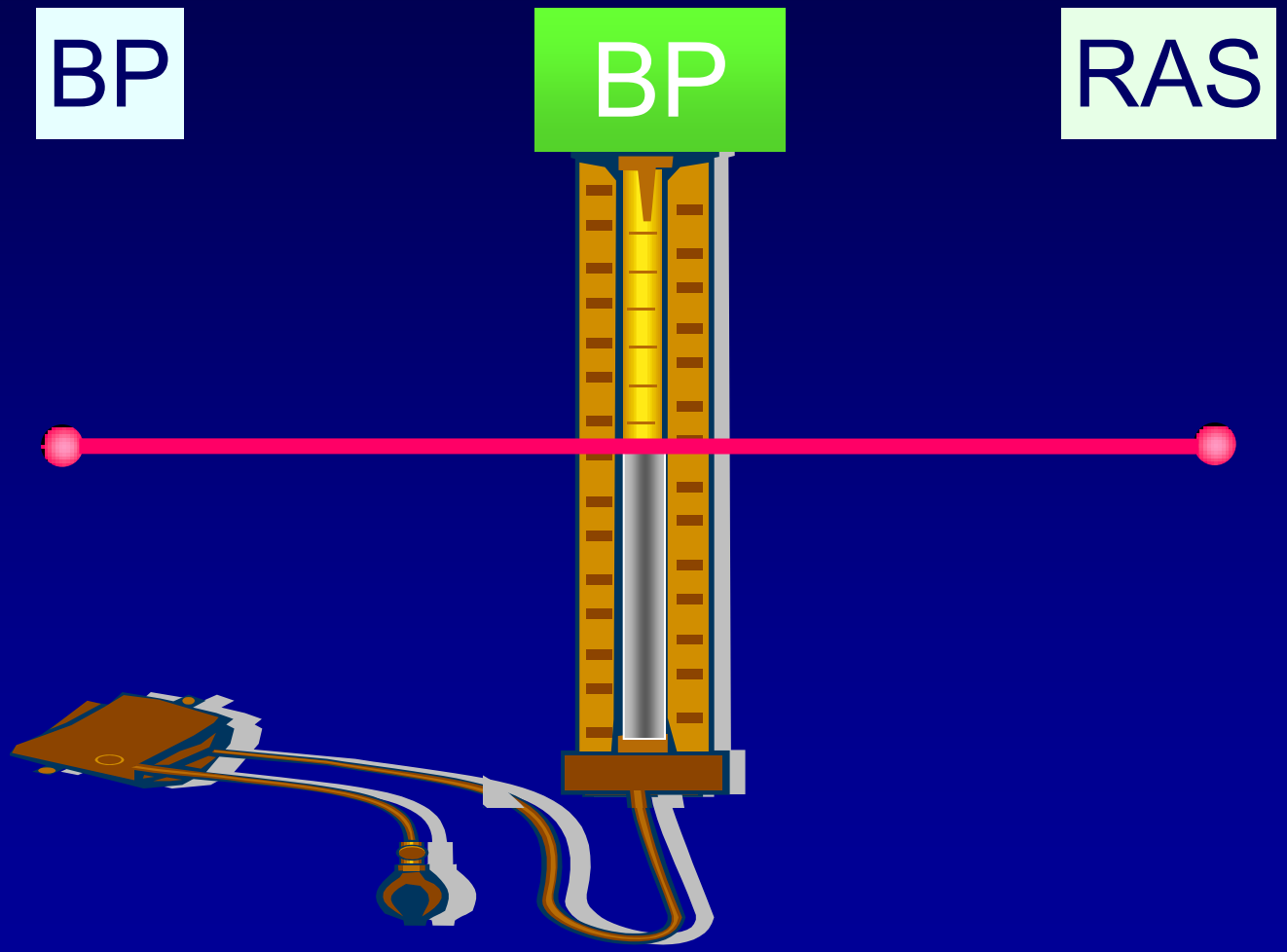
A powerful, complementary combination of 2 proven MOAs



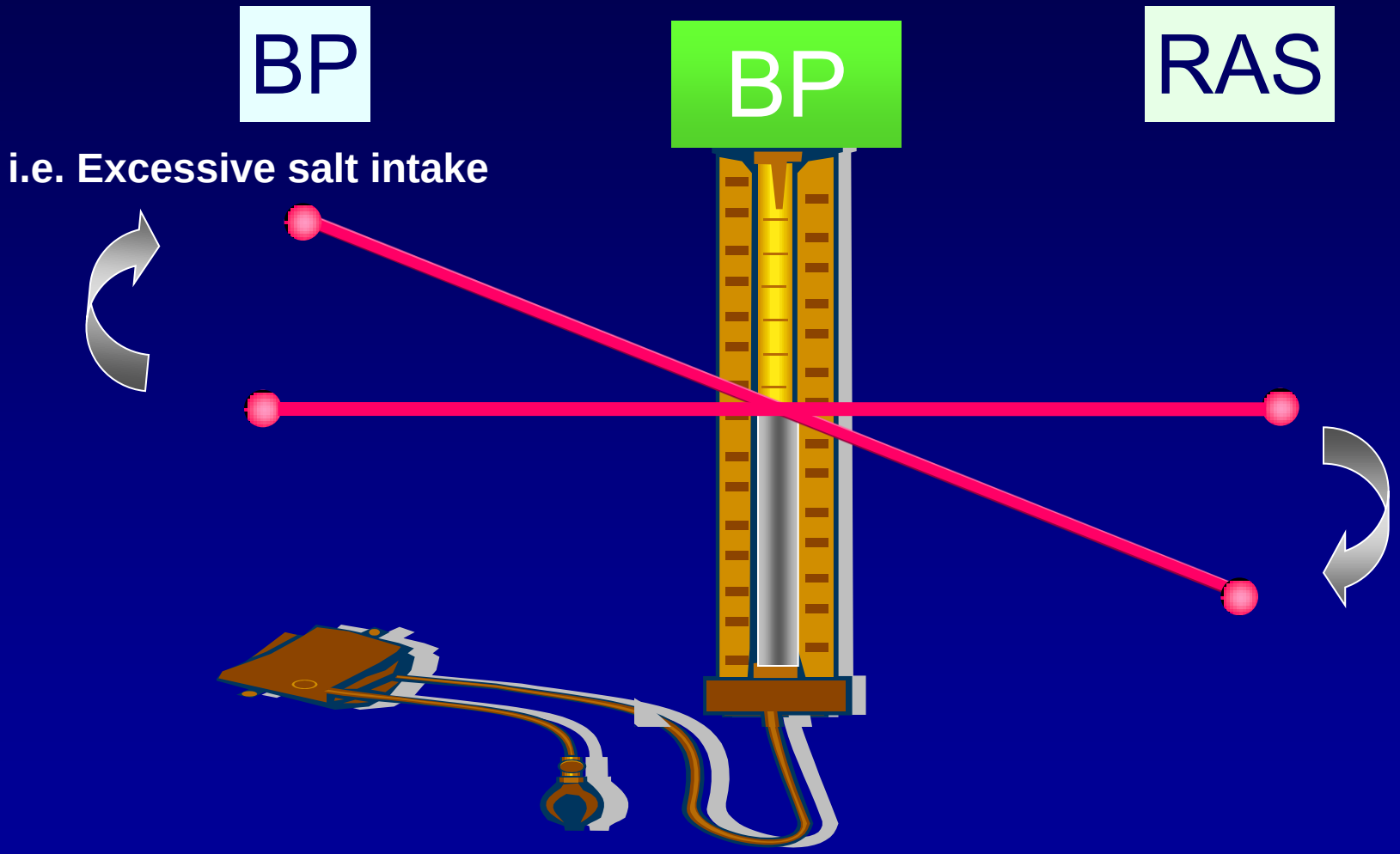
MOA=mechanism of action; ARB=angiotensin II receptor blocker; CCB=calcium channel blocker; BP=blood pressure; Ca=calcium; RAAS=renin-angiotensin-aldosterone system.

Oparil S and Weber M. *Postgrad Med*. 2009;121:25-39.

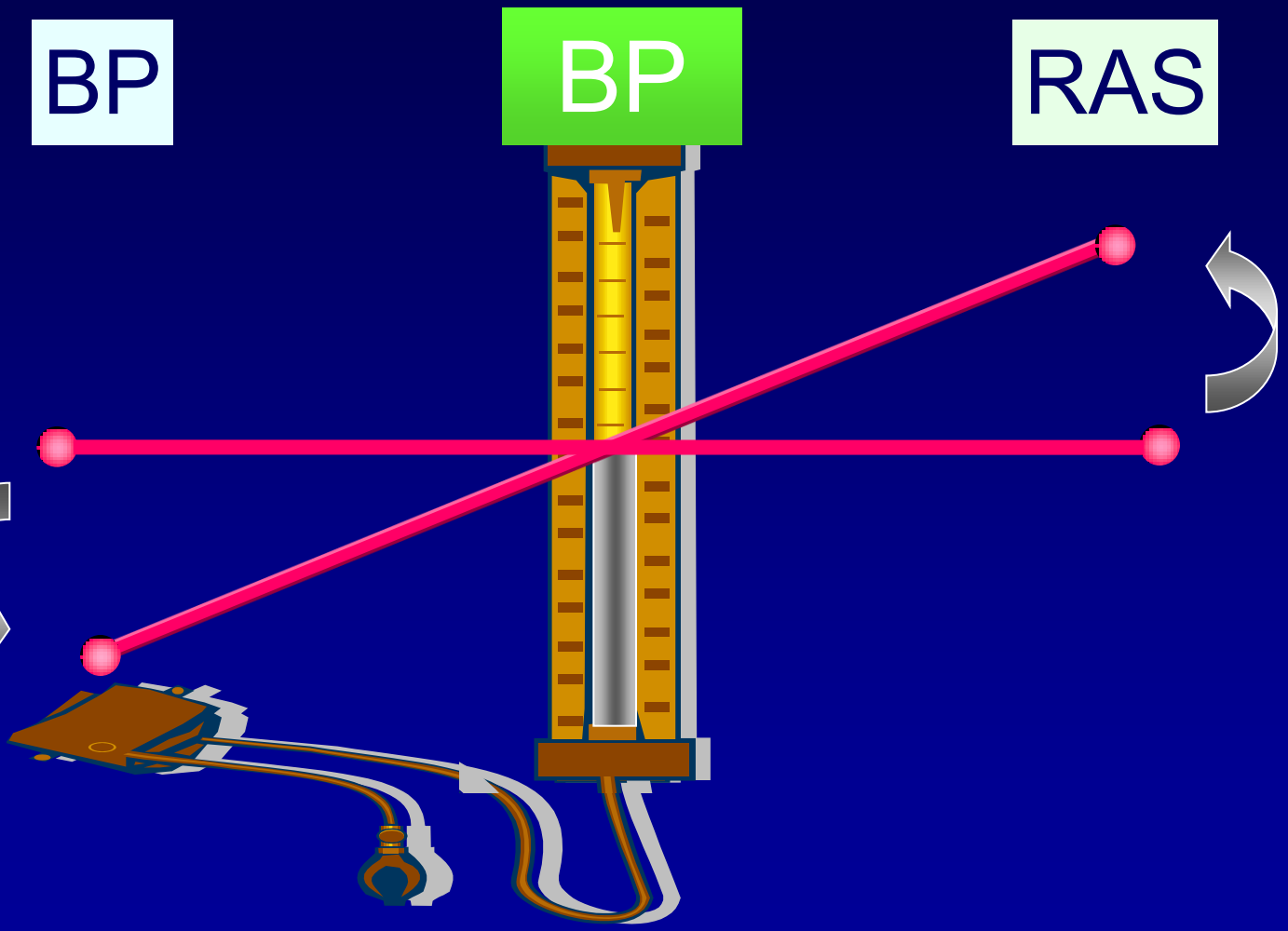
Blood pressure regulation and Renin-Angiotensin System



Blood pressure regulation and Renin-Angiotensin System

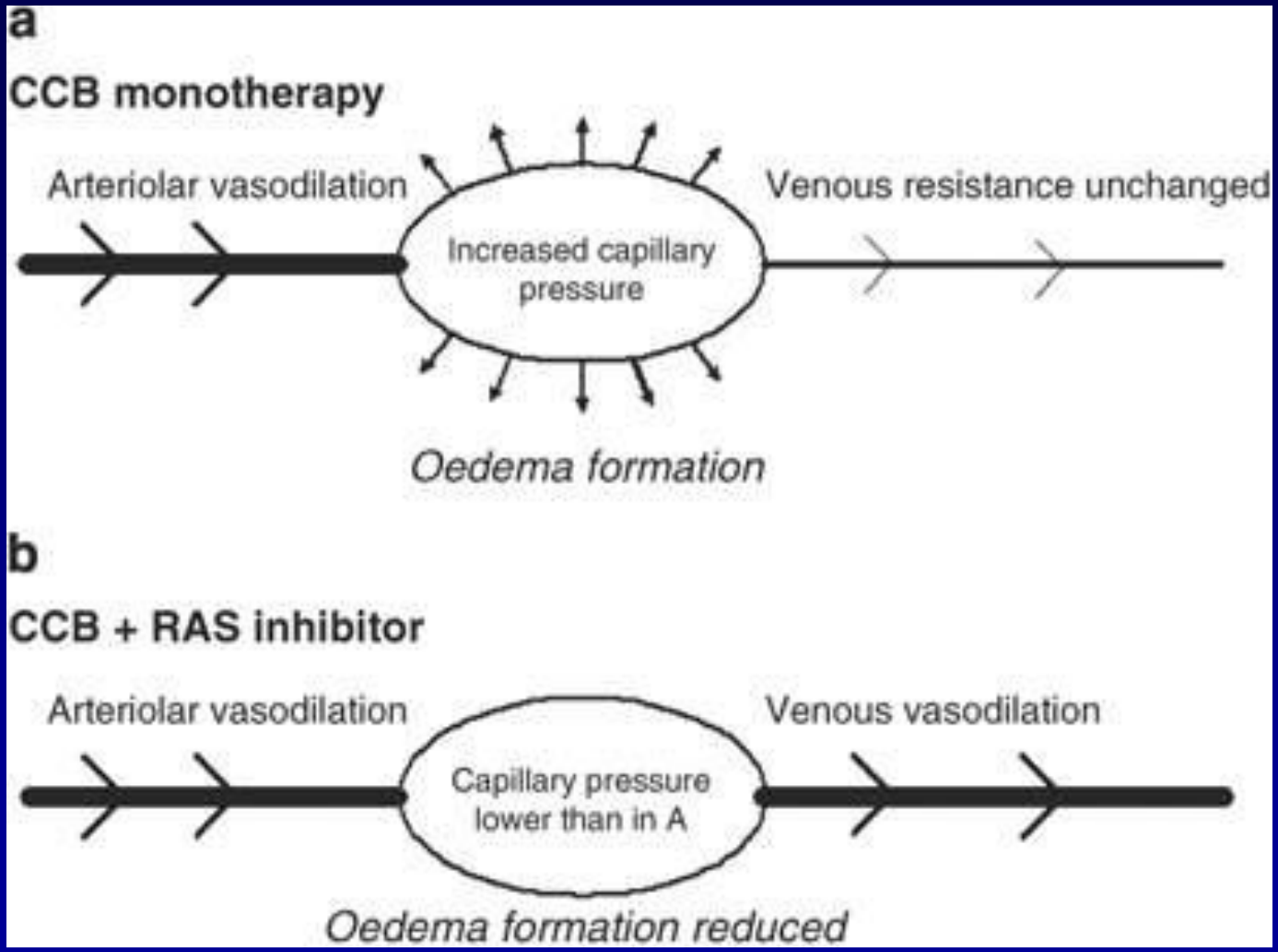


Blood pressure regulation and Renin-Angiotensin System



Sodium restriction
Diuretics
Vasodilation by CCB

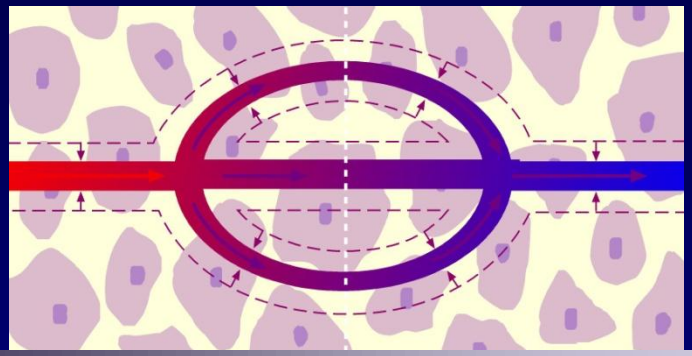
Mitigation of CCB-related edema in hypertension by combining RAS blockers and CCB



Journal of Human Hypertension **23, 503-511 (August 2009) |doi:10.1038/jhh.2008.157**

Complementary Effects of a CCB/RAS Inhibitor:
Reduction of CCB-associated Edema

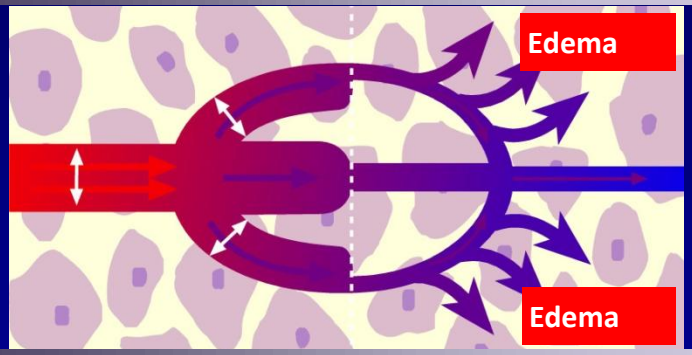
I.



Arterial hypertension

- Constricted blood vessels, high resistance

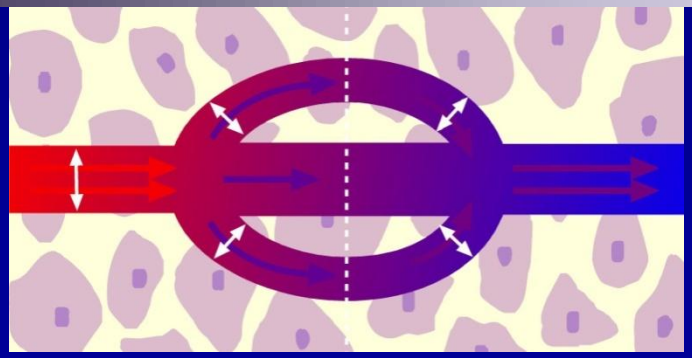
II.



CCBs

- BP reduction due to arterial vasodilation
- Tendency towards edema due to absent venodilation
- BP reduction stimulates RAS and increases Ang II level

III.

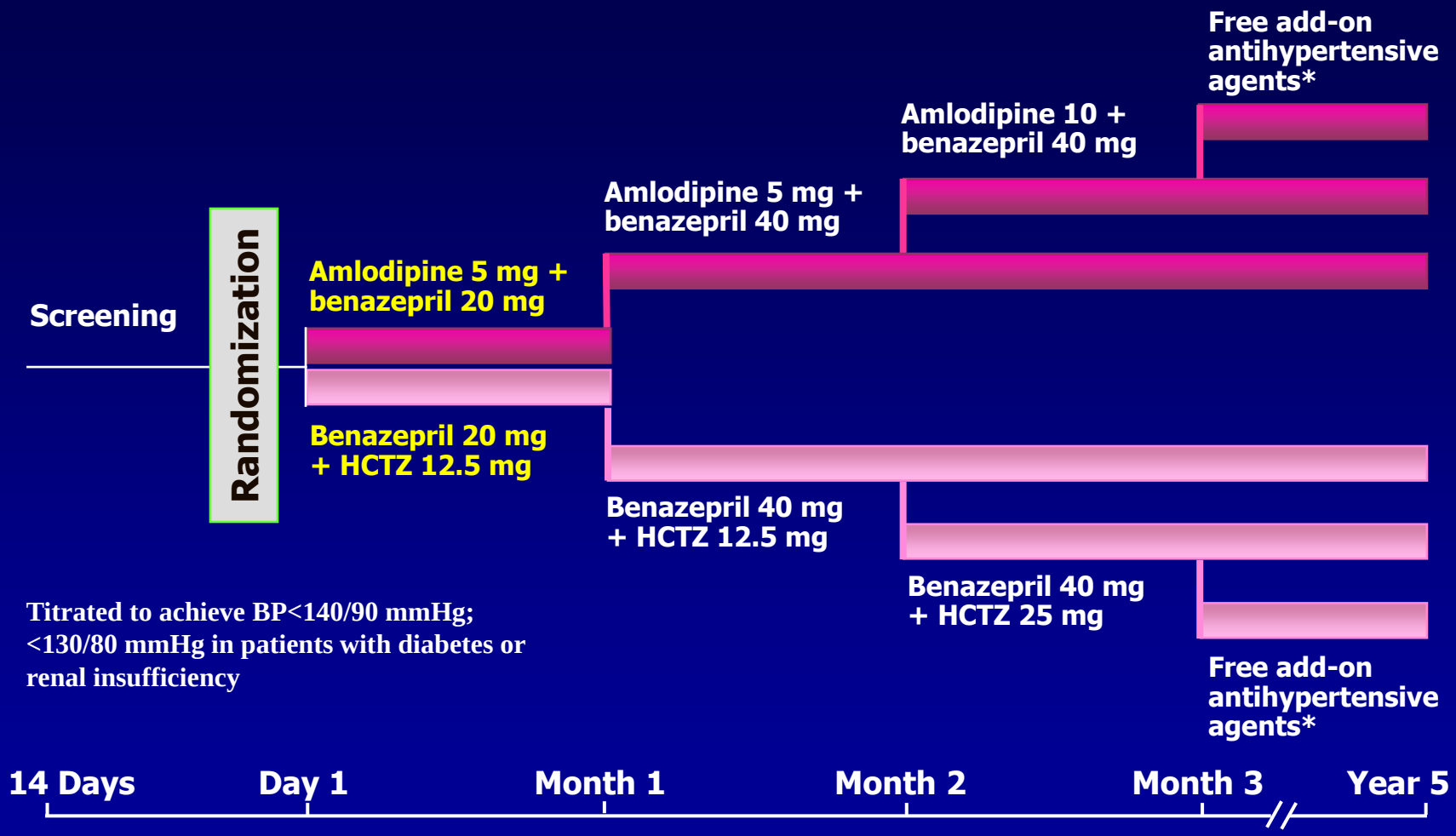


CCBs + RAS inhibitors*

- Blockade of RAS inhibits effects of angiotensin II, giving rise to additional BP reduction
- Additional venodilation by RAS inhibitors reduces edema

*Angiotensin receptor blockers or angiotensin-converting enzyme inhibitors

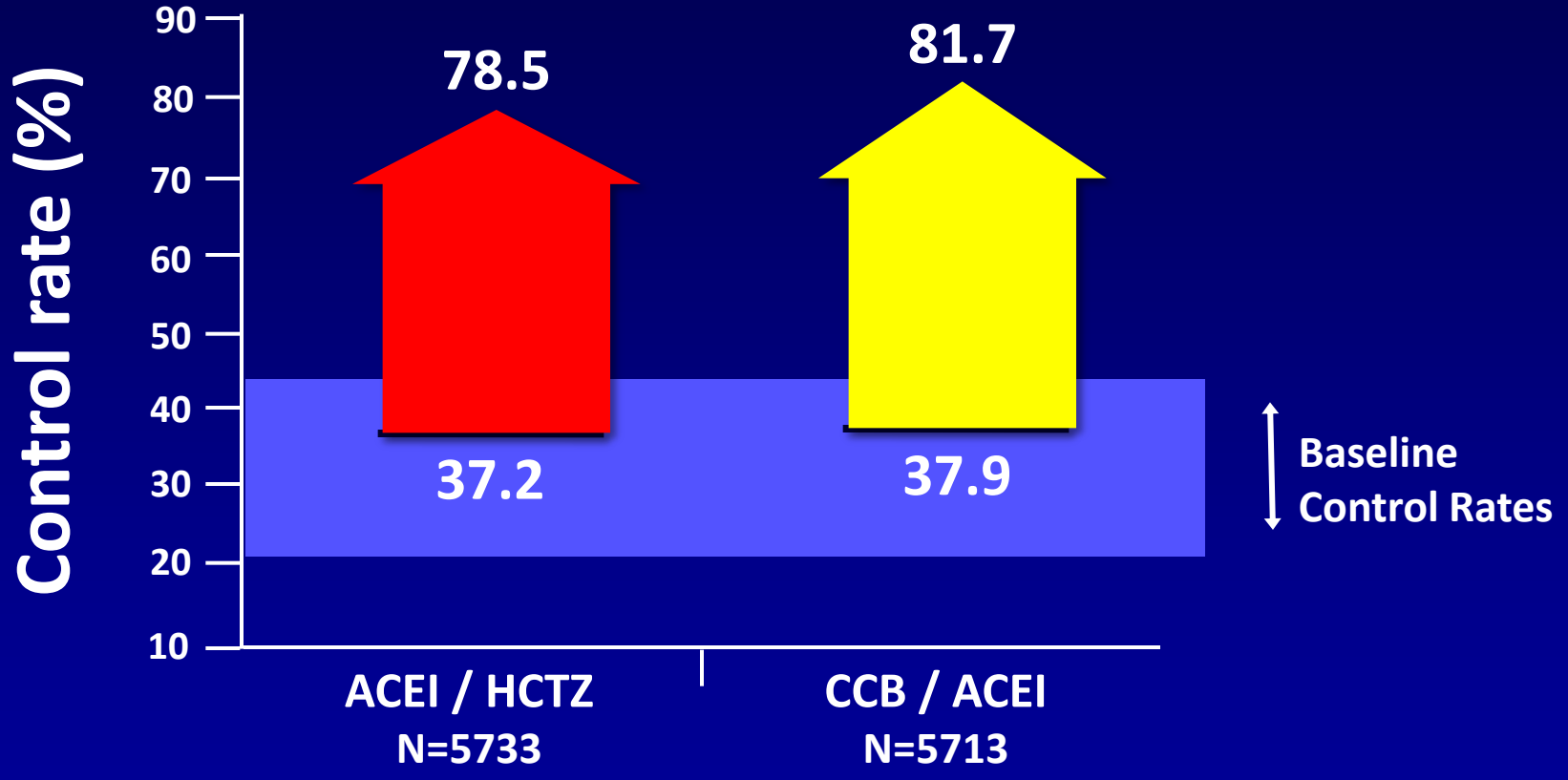
ACCOMPLISH : Design



*Beta blockers; alpha blockers; clonidine; (loop diuretics).

Jamerson KA et al. *Am J Hypertens*. 2003;16(part2)193A

Control Rates with Initial Combination Therapy

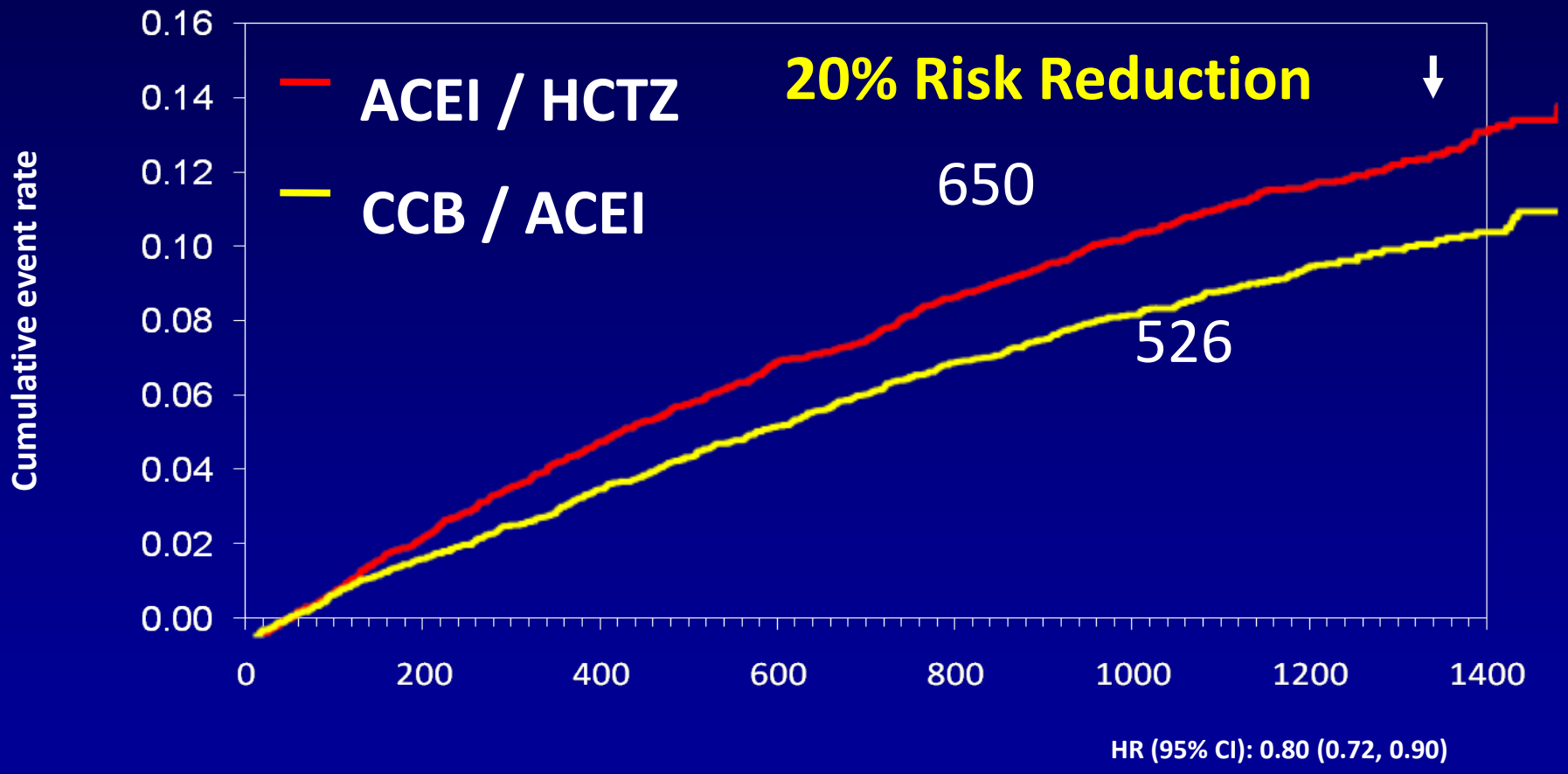


P<0.001 at 30 months follow-up

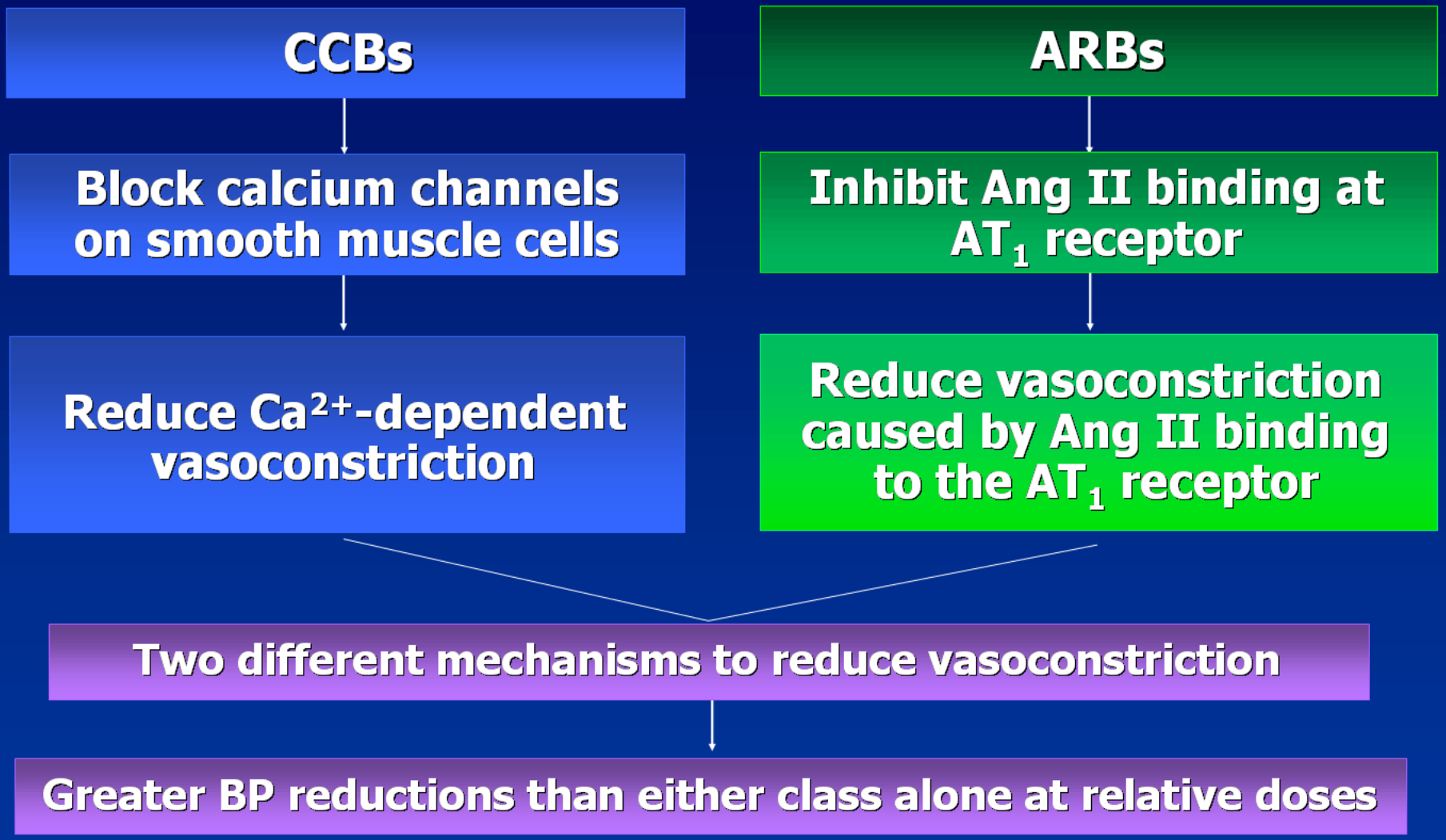
Control defined as <140/90 mmHg

ACCOMPLISH

Kaplan Meier for Primary Endpoint



CCBs and ARBs: Mechanisms of Action in the Treatment of Hypertension

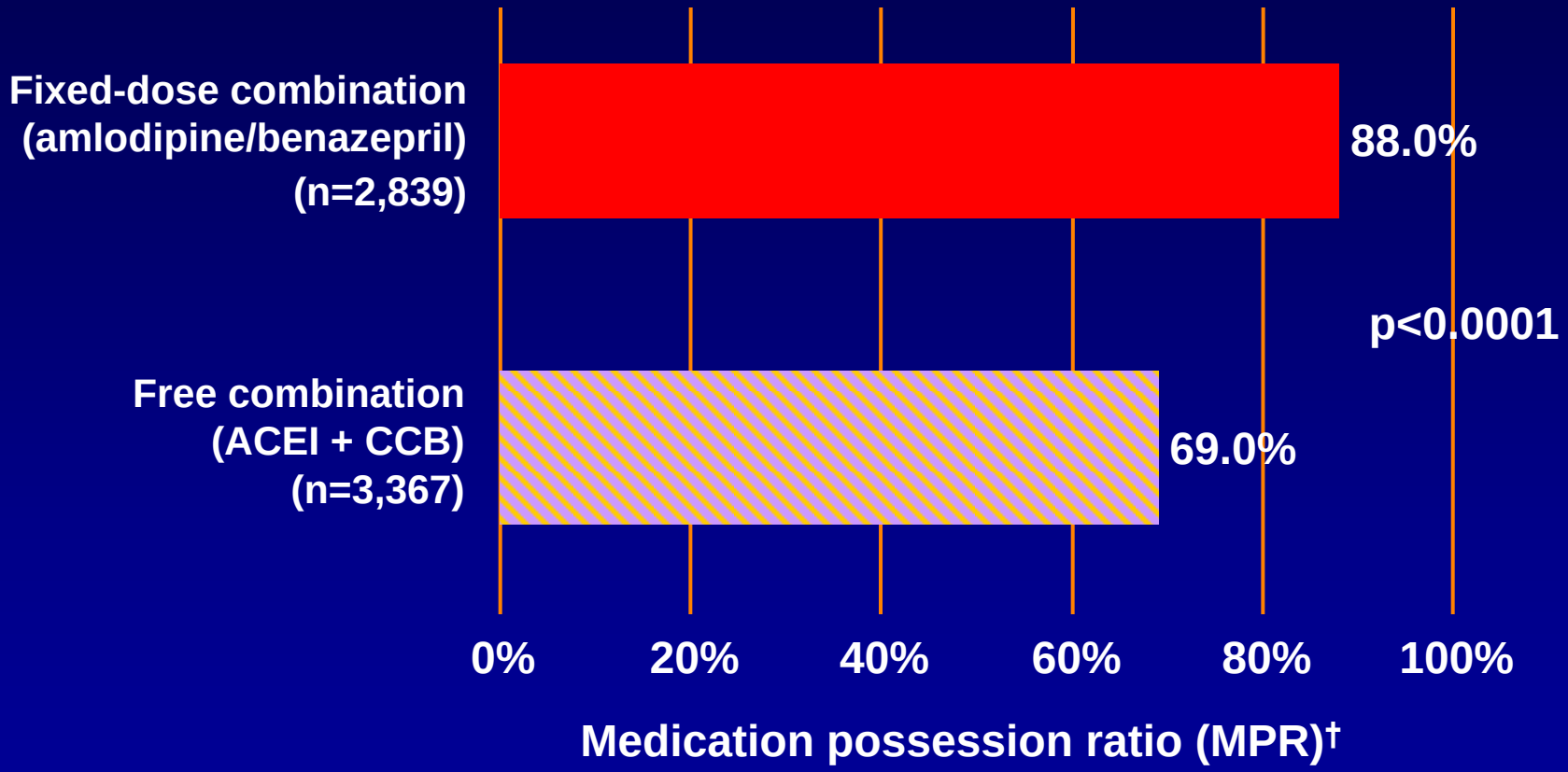


1. Berkels R et al. *Cardiovasc Drug Rev*. 1999;17:179–186.
2. Unger T. *Am J Cardiol.* 2002;89(suppl):3A–10A.

Ang II=angiotensin II

4. Is there an advantage of the Fixed Dose Combination?

Improved Compliance with Fixed-dose Combination Therapy Compared with Free-combination Therapy



†Defined as the total number of days of therapy for medication dispensed/365 days of study follow-up

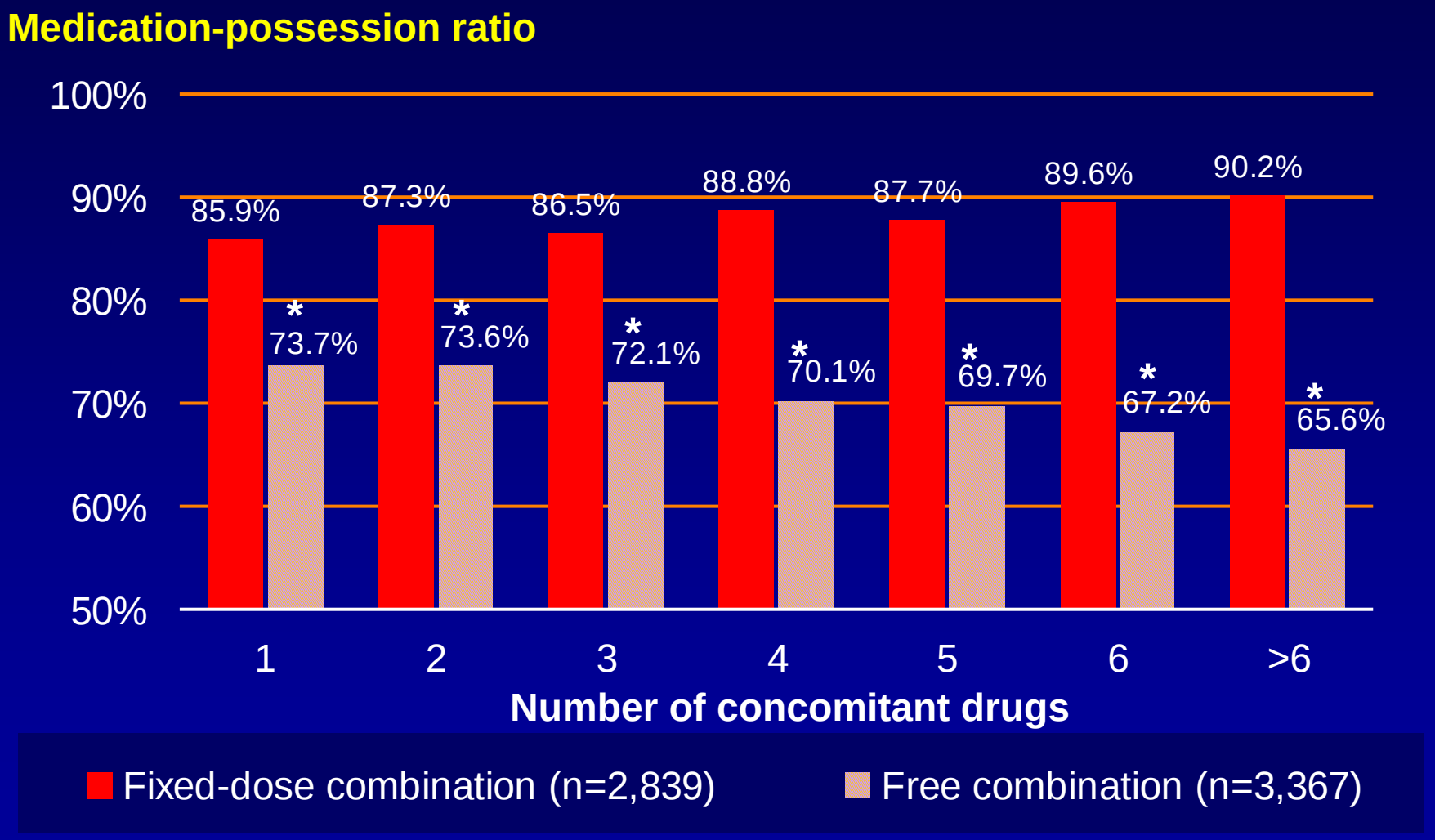
Wanovich et al. Am J Hypertens 2004;17:223A (poster)

ADVANTAGES OF FIXED VERSUS FREE COMBINATIONS OF TWO ANTIHYPERTENSIVE DRUGS

	Fixed	Free
Simplicity of treatment	+	–
Compliance	+	–
Efficacy	+	+
Tolerability	+*	–
Price	+	–
Flexibility	–	+

*Lower doses generally used in fixed-dose combinations
+ = potential advantage

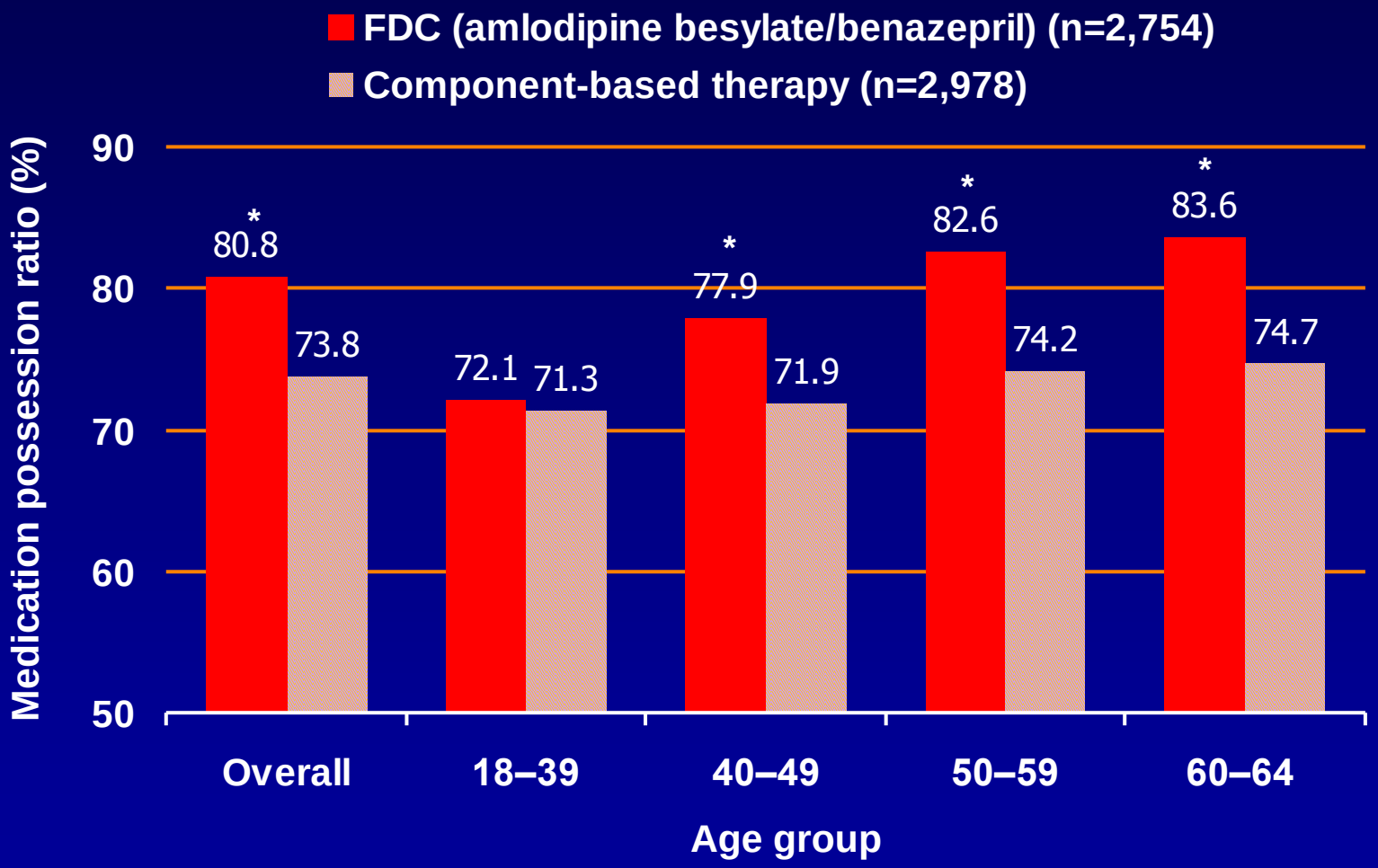
Fixed-dose Combinations Improve Compliance Regardless of Concomitant Medications



*p<0.0001

Wanovich et al. Am J Hypertens 2004;17:223A (poster)

Fixed-dose Combinations Improve Compliance Regardless of Age



*p<0.001

A large managed care database analysis (n=5,732)

Taylor et al. Congest Heart Fail 2003;9:324–32

5. Do we need to consider body types before prescribing anti-HTN medication?

CCB versus Diuretic (depends on body size)

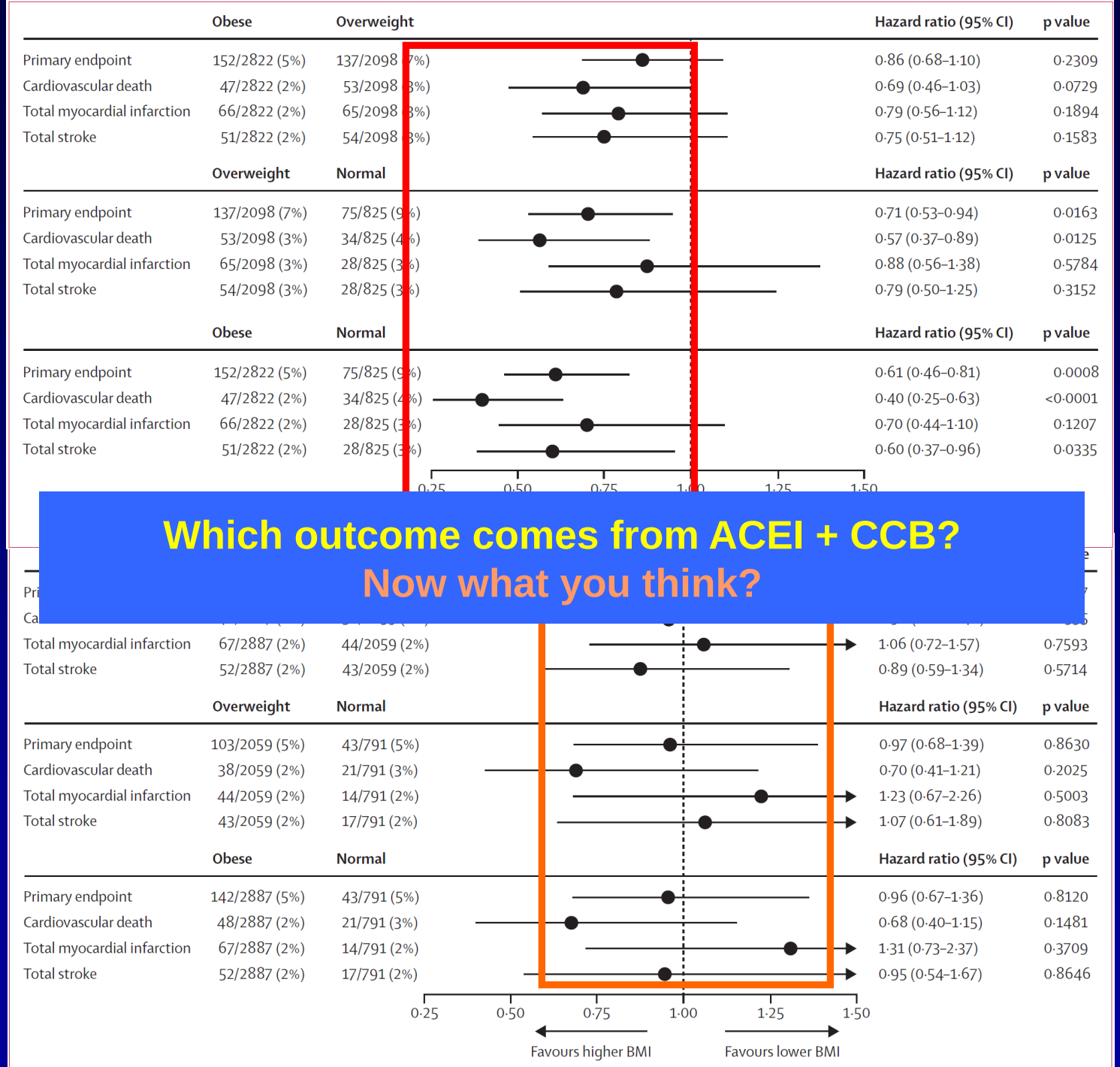
(sub-analysis of the ACCOMPLISH randomized controlled trial)

Dose the type of hypertension treatment affects patients' cardiovascular Outcomes according to their body size?

- Methods

-> divided obese (BMI ≥30, n=5,709), overweight (≥25 to <30, n=4,157), or normal weight (<25, n=1,616) categories

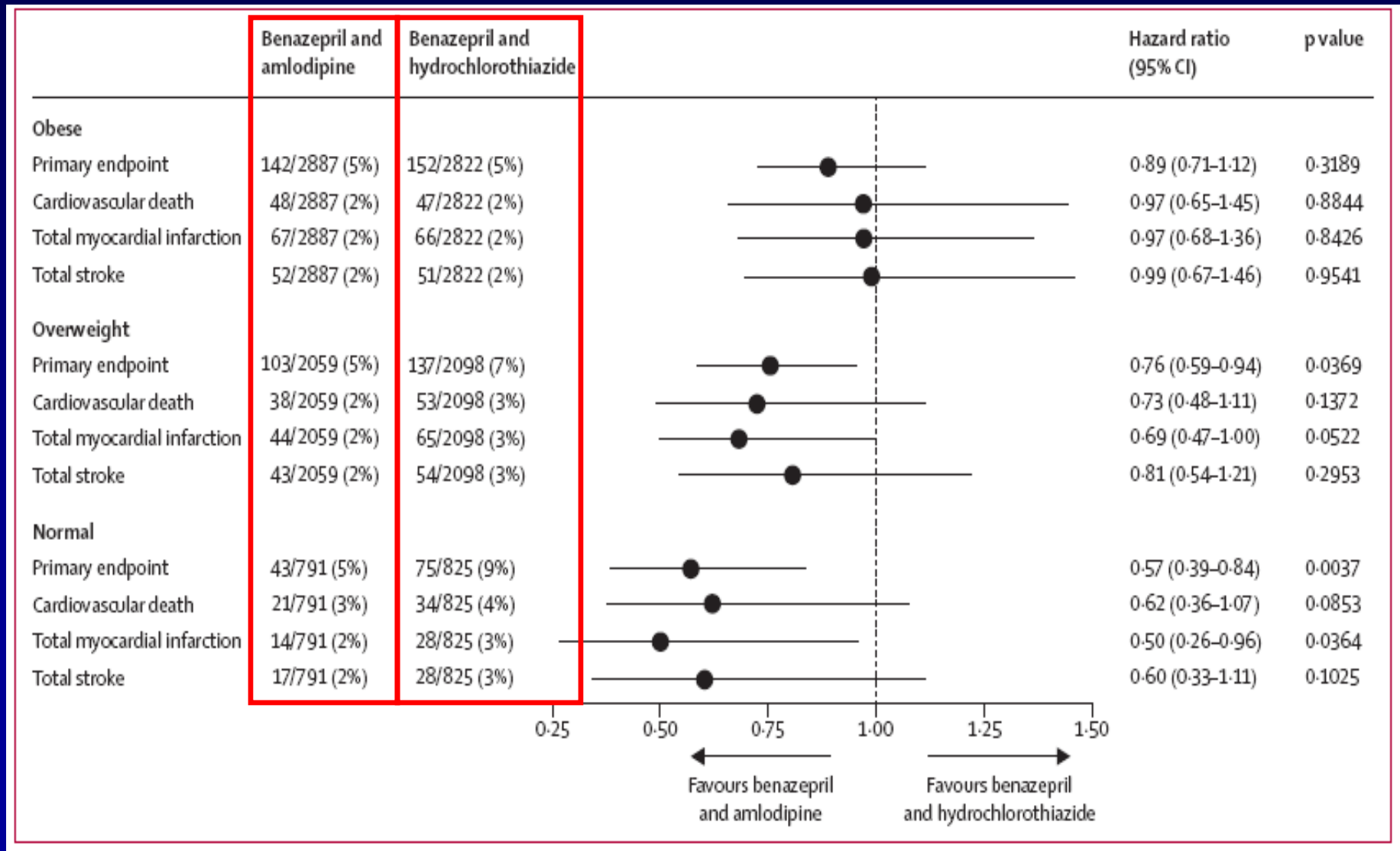
-> It is compared event rates (adjusted for age, sex, diabetes, previous cardiovascular events, stroke, chronic kidney disease) for the primary endpoint of cardiovascular death or non-fatal myocardial infarction or stroke



Which outcome comes from ACEI + CCB?

Now what you think?

Comparison of event rates within obese, overweight, and normal weight categories



Do we need to consider body types before prescribe a medication?

Thiazide-based treatment gives less cardiovascular protection in normal weight than obese patients, but amlodipine based therapy is equally effective across BMI subgroups and thus offers superior cardiovascular protection in non-obese hypertension.

(sub-analysis of the ACCOMPLISH randomized controlled trial)

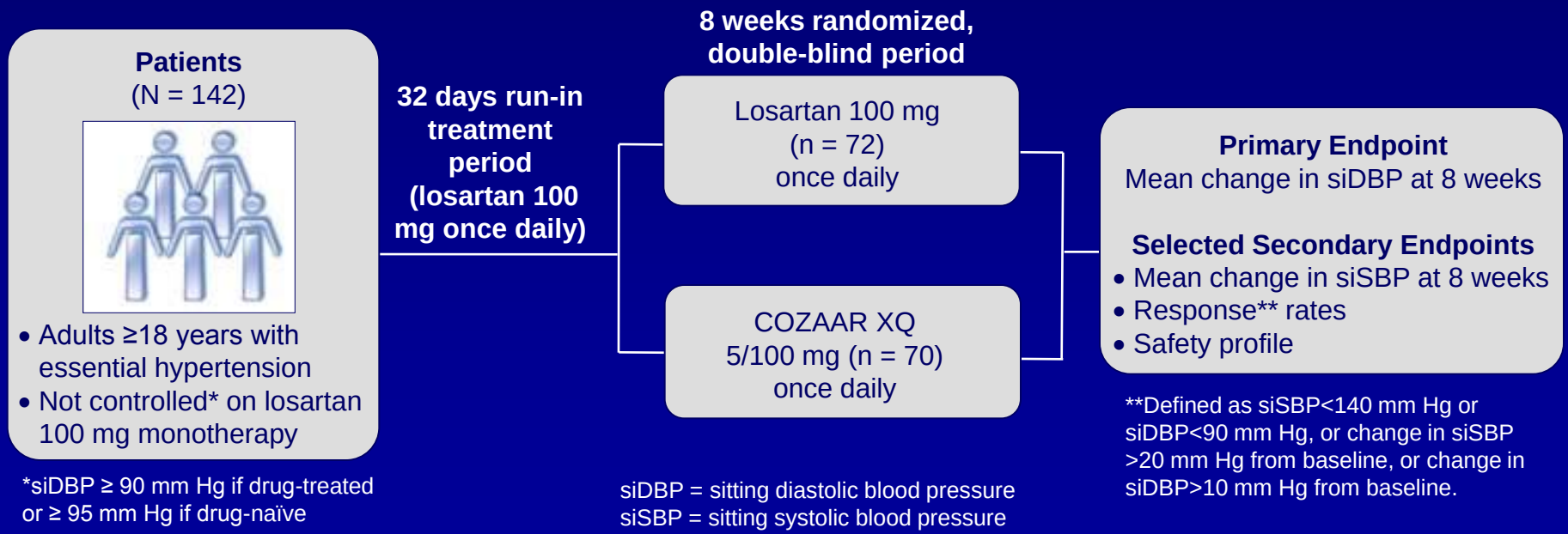
6. What are the clinical efficacy data for COZAAR XQ™ ?

(Amlodipine Camsylate and Losartan Potassium)

A Fixed-Dose Combination Therapy for Hypertension

COZAAR XQ: Uncontrolled on Losartan 100 mg* Study Design

- **Objective**
  - Evaluate the efficacy and safety of COZAAR XQ 5/100 mg vs. losartan 100 mg in patients with essential hypertension inadequately controlled on losartan 100 mg
- **Study Design**
  - 8-week, multicenter, randomized, double-blind phase III clinical study



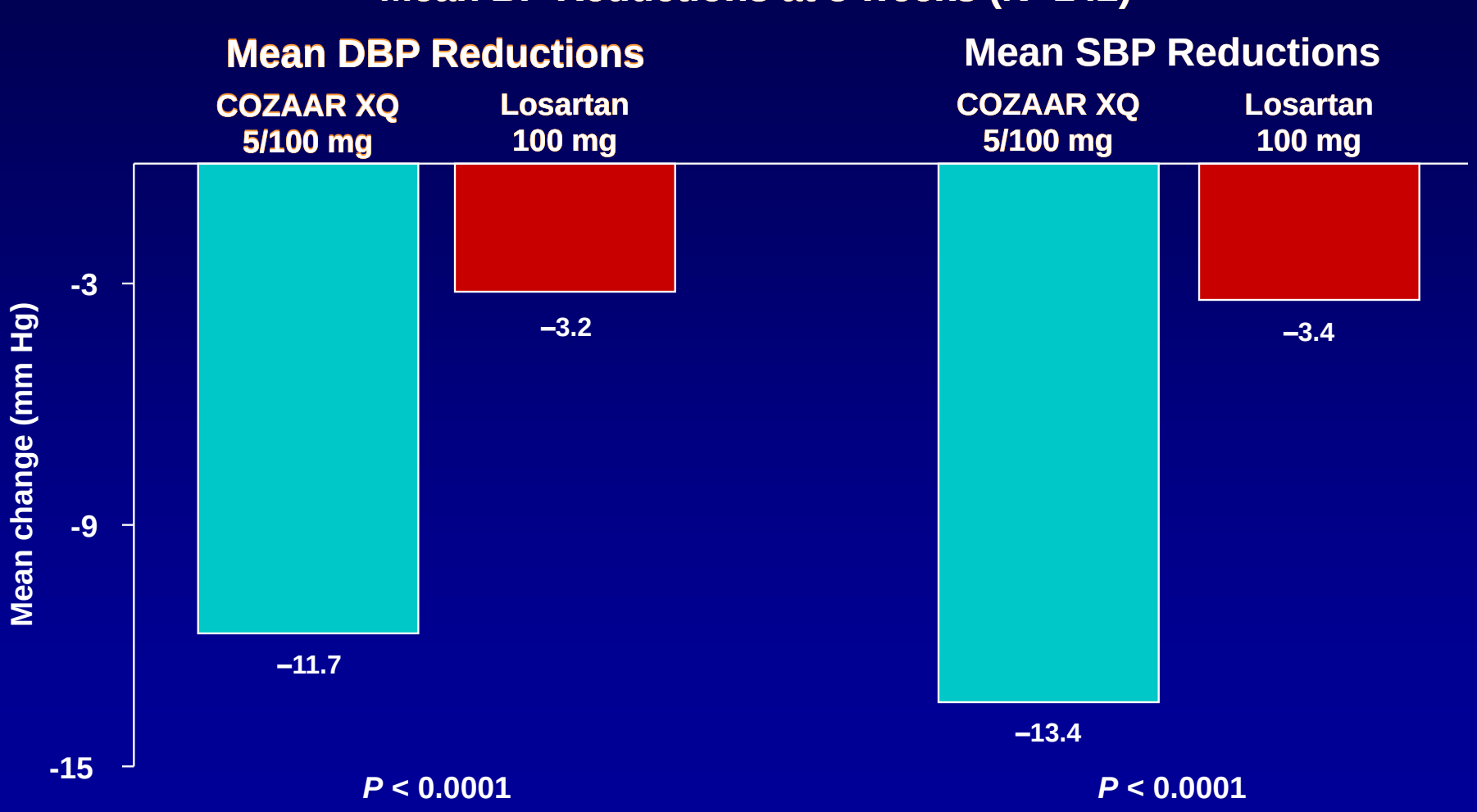
Reference : 1. Hong BK, et al. Am J Cardiovasc Drugs. 2012;12(3):189-195.

COZAAR XQ: Uncontrolled on Losartan 100 mg Inclusion and Exclusion Criteria

- **Selected Inclusion Criteria**
  - Patients 18 years of age or older with essential hypertension (DBP ≥ 90 mm Hg if drug-treated or ≥ 95 mm Hg if drug-naïve).
  - Non-responders to 4 weeks of treatment with losartan 100 mg monotherapy (sitting DBP≥ 90).
- **Selected Exclusion Criteria**
  - Secondary hypertension
  - A difference in sitting systolic BP measurements ≥20 mm Hg or diastolic BP ≥10 mm Hg between the highest and lowest measurements after 3 measurements
  - Known hypersensitivity to dihydropyridine CCBs or ARBs
  - Mean sitting SBP ≥ 200 mm Hg or mean sitting DBP ≥ 120 mm Hg at screening and mean siSBP ≥ 180 mm Hg or mean sitting DBP ≥ 120 mm Hg after 4 weeks of losartan potassium 100 mg treatment.
  - Clinically significant renal, metabolic, or hepatic disease
  - Severe heart disease or severe neurovascular disease
  - Uncontrolled diabetes mellitus
  - Pregnant or nursing women

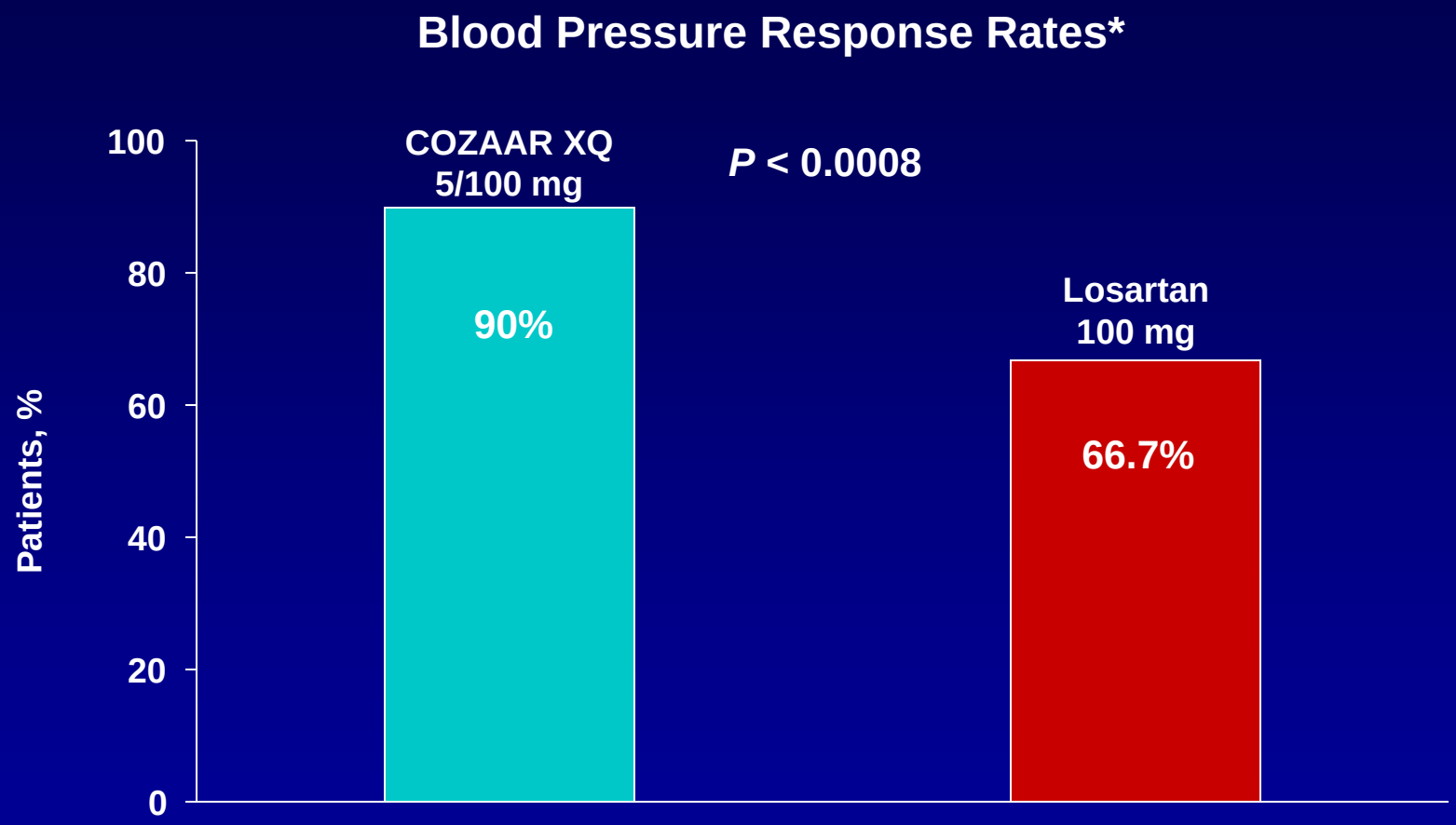
Reference : 1. Hong BK, et al. Am J Cardiovasc Drugs. 2012;12(3):189-195.

COZAAR XQ: Uncontrolled on Losartan 100 mg
Mean Reductions in DBP (Primary Endpoint) and SBP



Reference : 1. Hong BK, et al. Am J Cardiovasc Drugs. 2012;12(3):189-195.

COZAAR XQ: Uncontrolled on Losartan 100 mg Additional Efficacy Results



*The rate of patients who achieved any of the following predefined targets: 1) systolic BP <140 mm Hg or diastolic BP <90 mm Hg, 2) a reduction in systolic BP >20 mm Hg from baseline, or 3) a reduction in diastolic BP >10 mm Hg from baseline.

Reference : 1. Hong BK, et al. Am J Cardiovasc Drugs. 2012;12(3):189-195.

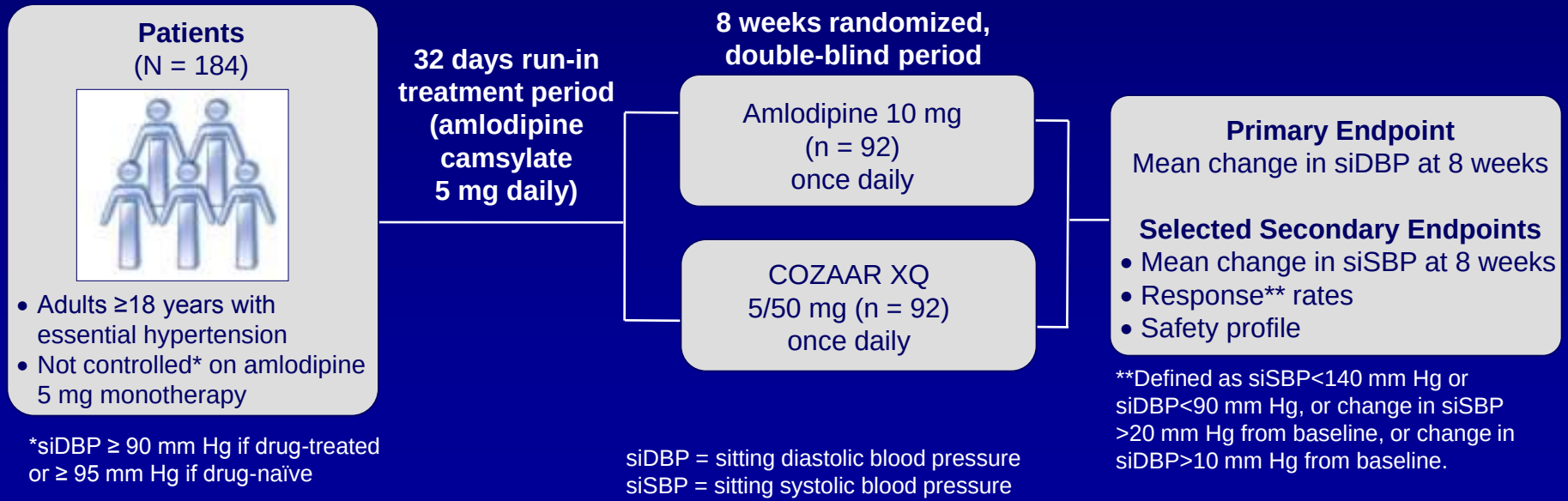
COZAAR XQ: Uncontrolled on Losartan 100 mg Safety Profile Results (After Randomization)

	COZAAR XQ 5/100 mg (n=70)	Losartan 100 mg (n=72)	P value
Subjects with AEs	21 (30.0%)	16 (22.2%)	0.2911
Number of AEs	25	25	
Number of serious AEs	0	1 (1.4%)	0.2306
Severity of AEs			
Mild	19 (27.1%)	15 (20.8%)	0.5294
Moderate	2 (2.9%)	1 (1.4%)	
Severe	0	0	
AEs leading to discontinuation	1 (1.4%)	0	0.4930
Drug-related AEs	5 (7.1%)	9 (12.5%)	0.2844
Deaths	0	0	

Reference : 1. Hong BK, et al. Am J Cardiovasc Drugs. 2012;12(3):189-195.

COZAAR XQ: Uncontrolled on Amlodipine 5 mg* Study Design

- **Objective**
  - Compared the efficacy and safety of COZAAR XQ 5/50 mg to amlodipine 10 mg in patients with essential hypertension inadequately controlled on amlodipine 5 mg
- **Study Design**
  - 8-week, multicenter, randomized, double-blind phase III clinical study



*siDBP ≥ 90 mm Hg if drug-treated or ≥ 95 mm Hg if drug-naïve

siDBP = sitting diastolic blood pressure
siSBP = sitting systolic blood pressure

**Defined as siSBP<140 mm Hg or siDBP<90 mm Hg, or change in siSBP >20 mm Hg from baseline, or change in siDBP>10 mm Hg from baseline.

Kang S-M et al. *Clin Ther* 2011;33(12):1953-1963.

COZAAR XQ: Uncontrolled on Amlodipine 5 mg Inclusion and Exclusion Criteria

- **Selected Inclusion Criteria**
  - Adults aged 18 or older with essential hypertension with uncontrolled essential hypertension [a sitting DBP ≥90 mm Hg in drug-treated patients and ≥95 mm Hg in drug-naïve patients]
  - Non-responders to 4 weeks of treatment with open-label amlodipine 5 mg monotherapy (DBP ≥90 mm Hg)
- **Selected Exclusion Criteria**
  - Secondary hypertension
  - A difference in sitting systolic BP measurements ≥20 mm Hg or diastolic BP ≥10 mm Hg between the highest and lowest measurements after 3 measurements
  - Known hypersensitivity to dihydropyridine CCBs or ARBs
  - Mean sitting SBP ≥ 200 mm Hg or mean sitting DBP ≥ 120 mm Hg at screening and mean siSBP ≥ 180 mm Hg or mean sitting DBP ≥ 120 mm Hg after 4 weeks of amlodipine 5 mg treatment.
  - Clinically significant renal, metabolic, or hepatic disease
  - Severe heart disease or severe neurovascular disease
  - Uncontrolled diabetes mellitus
  - Pregnant or nursing women

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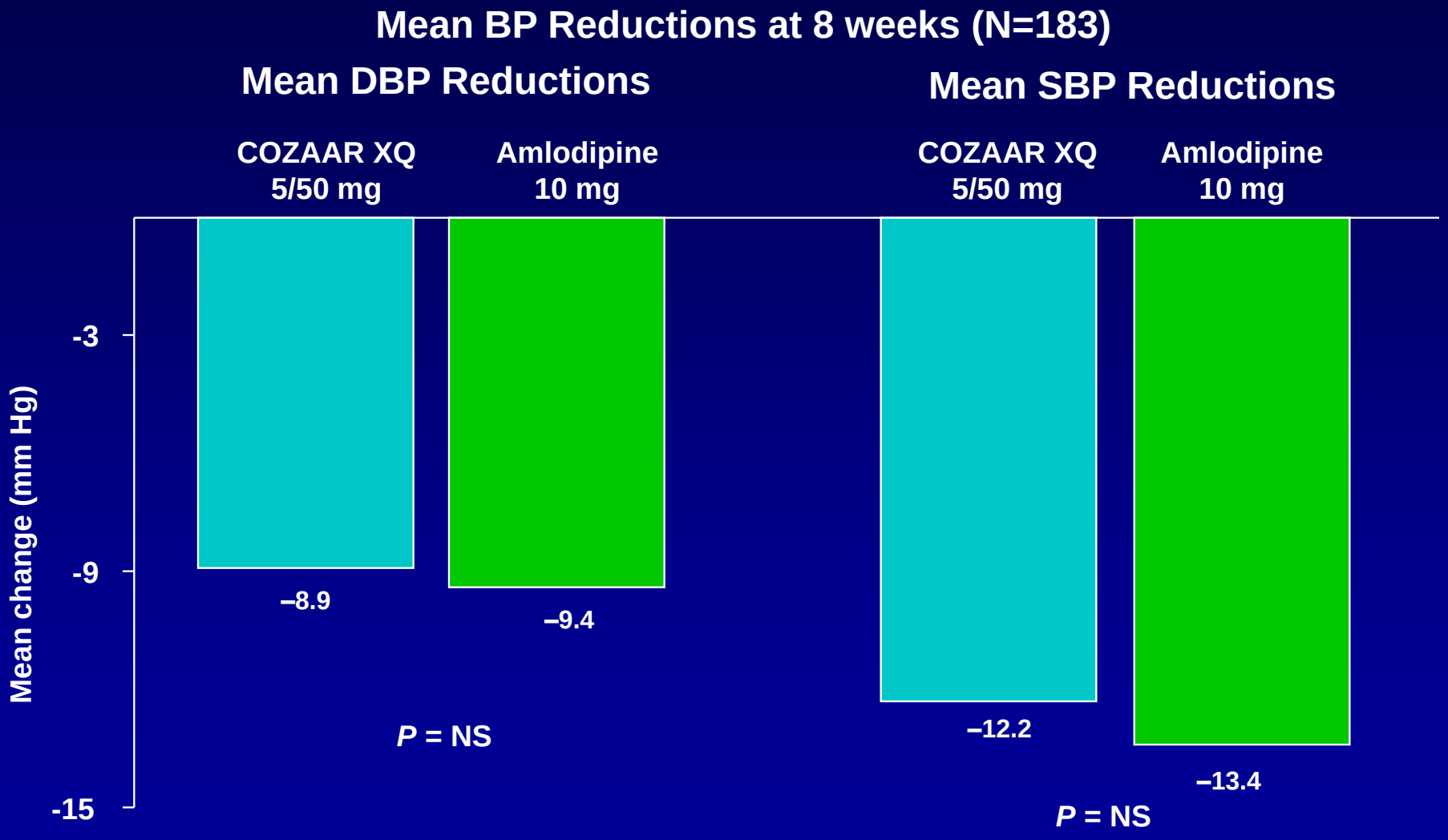
COZAAR XQ: Uncontrolled on Amlodipine 5 mg
Mean Reductions in DBP (Primary Endpoint) and SBP



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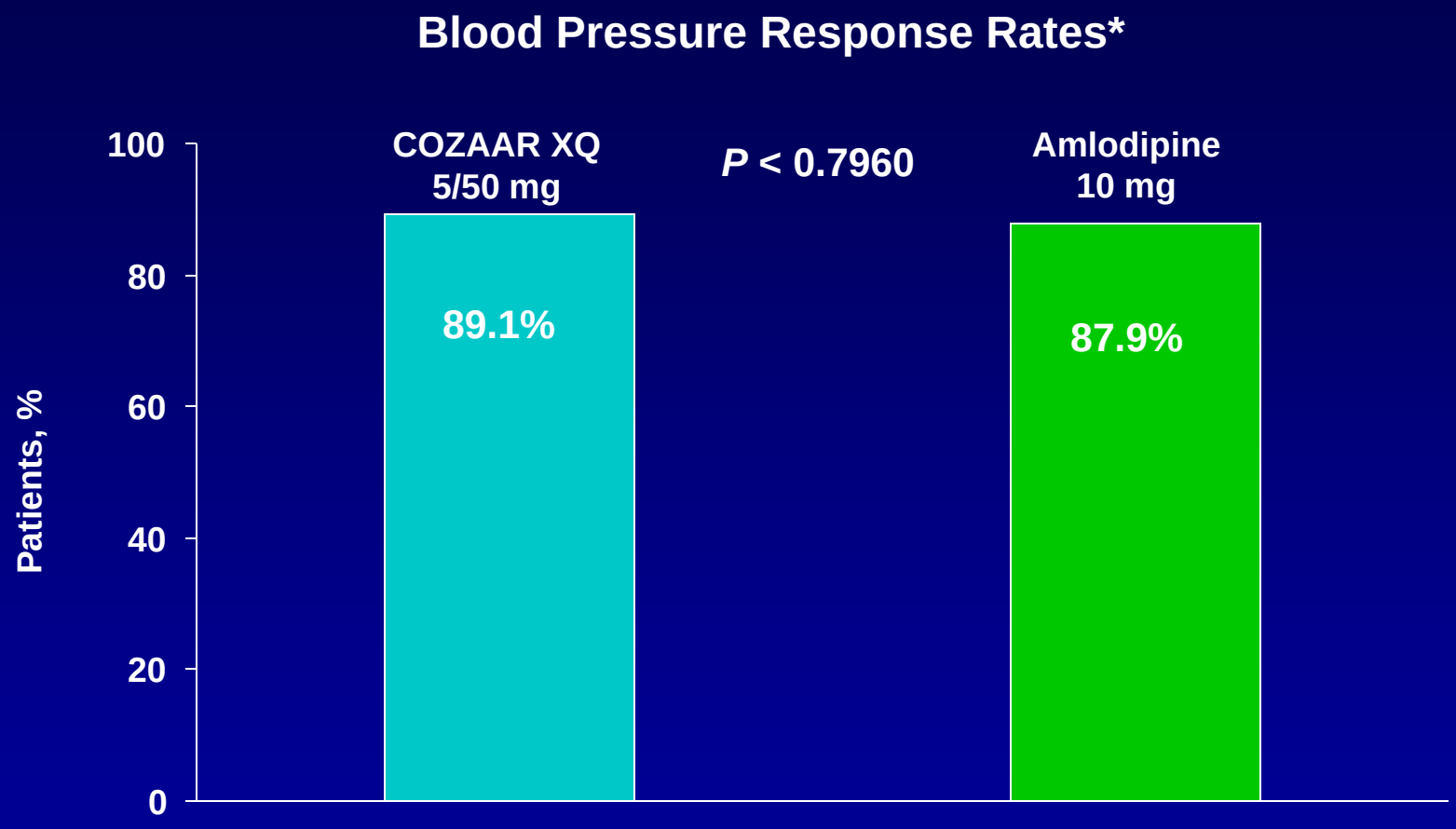
COZAAR XQ: Uncontrolled on Amlodipine 5 mg Additional Efficacy Results



*The rate of patients who achieved any of the following predefined targets: 1) systolic BP <140 mm Hg or diastolic BP <90 mm Hg, 2) a reduction in systolic BP >20 mm Hg from baseline, or 3) a reduction in diastolic BP >10 mm Hg from baseline.

Kang S-M et al. *Clin Ther* 2011;33(12):1953-1963.

COZAAR XQ: Uncontrolled on Amlodipine 5 mg Safety Profile Results

	COZAAR XQ 5/50 mg (n=92)	Amlodipine 10 mg (n=92)	P value
Subjects with AEs	20 (21.7%)	24 (26.1%)	0.49
Number of AEs	38	31	-
Number of serious AEs	1 (1.1%)	1 (1.1%)	1.00
Severity of AEs			0.6907
Mild	15 (16.3%)	21 (22.8%)	
Moderate	3 (3.3%)	2 (2.2%)	
Severe	2 (2.2%)	1 (1.1%)	
AEs leading to discontinuation	0	2 (2.2%)	0.50
Drug-related AEs	6 (6.5%)	10 (10.9%)	0.30
Deaths	0	0	

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Summary

- The burden of CV disease is huge. Hypertension management is key in reducing risk of mortality from CV diseases.
- The guidelines advocate use of combination agents to more effectively reduce BP.
- CCB + RAS blockade combination showed superior outcome compared with Diuretics + RAS blockade in the ACCOMPLISH trial
- CCB + RAS blockade is effective for BP control irrespective of Body Mass Index (BMI).
- FDC improves compliance to medication, enhances BP lowering effects and reduces potential side effects

Summary

- COZAAR XQ has been shown to be effective in patients with hypertension:
  - Whose BP was uncontrolled with amlodipine 5 mg
    → COZAAR XQ 5/50 mg
  - Whose BP was uncontrolled with losartan 100 mg
    → COZAAR XQ 5/100 mg
- In controlled clinical trials, <1% of patients taking COZAAR XQ reported peripheral edema