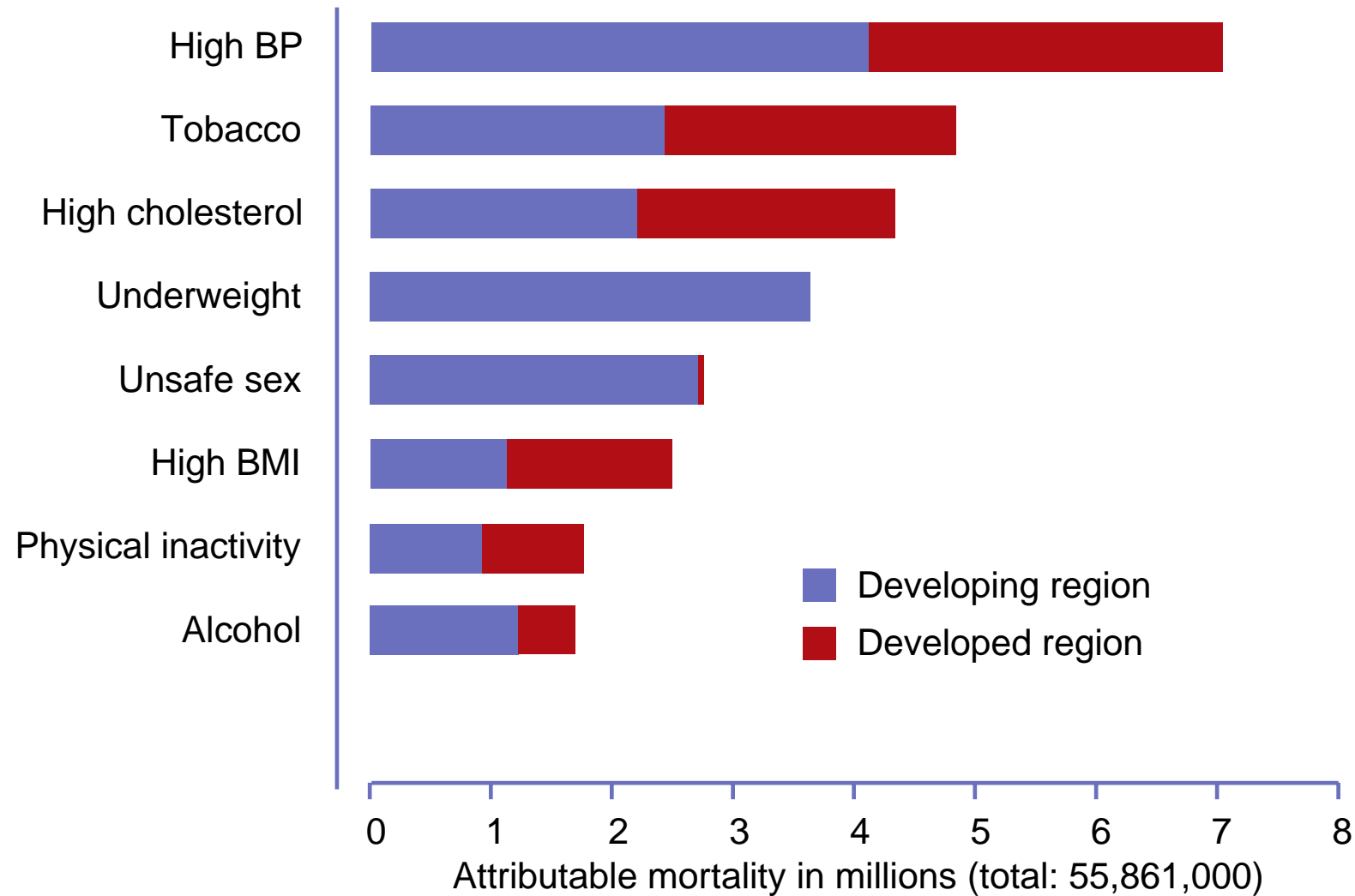


***Explore the Rationale for the Dual
Mechanism CCB/ARB Approach
in Hypertension Management***

Jeong Bae Park, MD,PhD

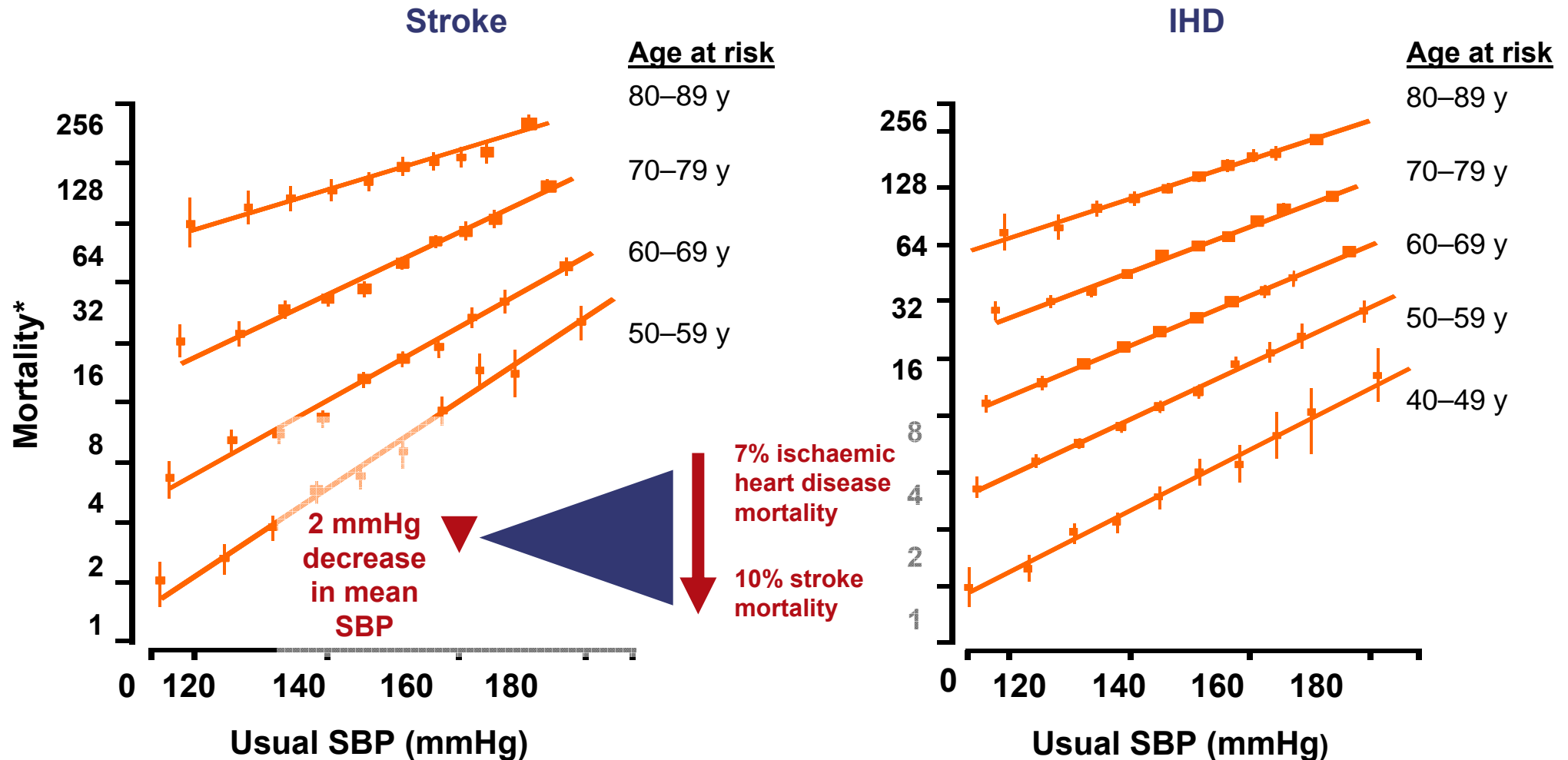
**Dept of Med/Cardiology, Cheil General Hospital,
Kwandong University College of Medicine**

Global Mortality 2000: Impact of Hypertension and Other Health Risk Factors



Adapted from The Lancet, 360, Ezzati et al. pp. 1347–60. Copyright © 2002, with permission from Elsevier

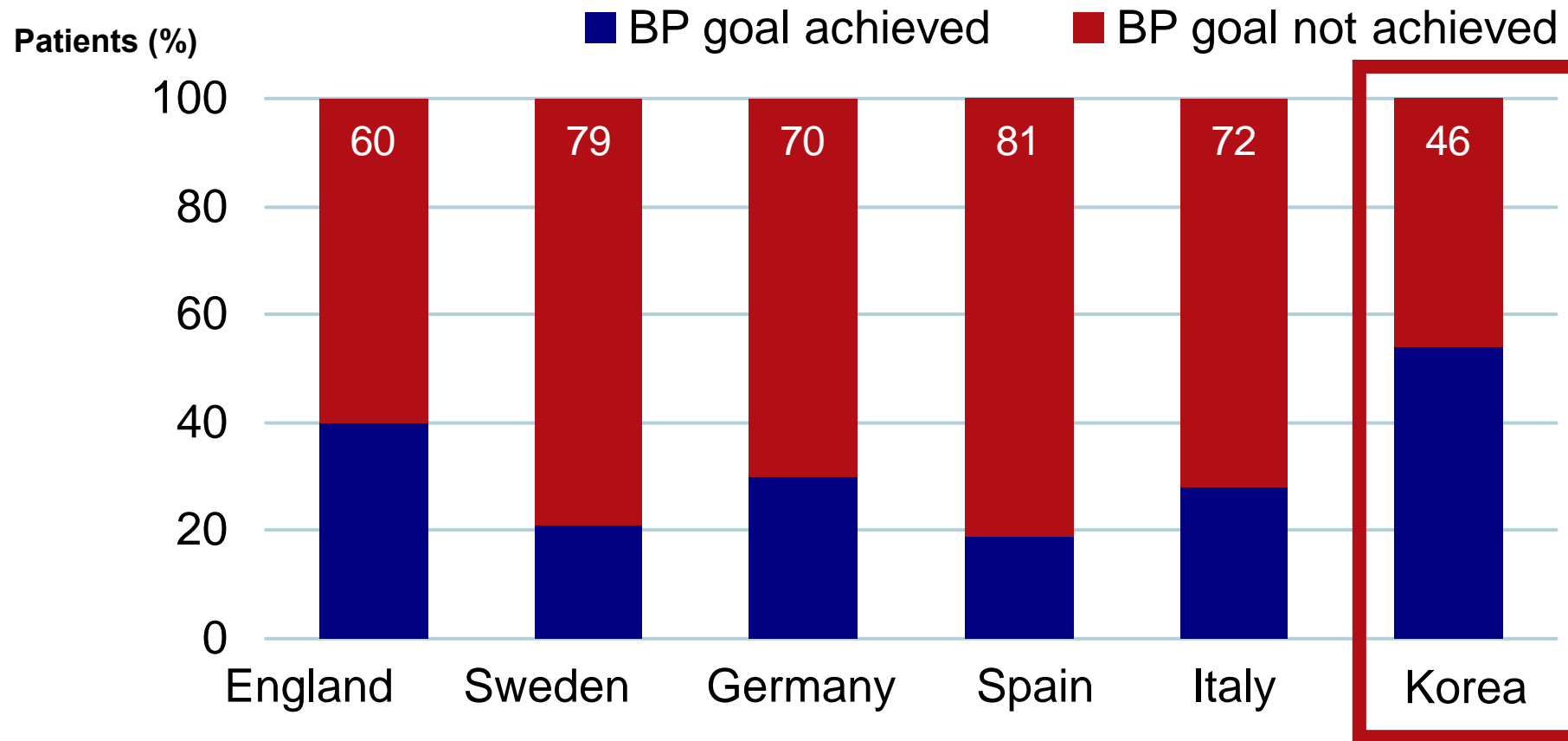
Stroke and Ischemic Heart Disease (IHD) Mortality Rate in Each Decade of Age, Versus Usual Systolic BP at the Start of that Decade



Reproduced from The Lancet, 360, Lewington et al. pp. 1903-13
 Copyright © 2002, with permission from Elsevier

*Floating absolute risk and 95% CI

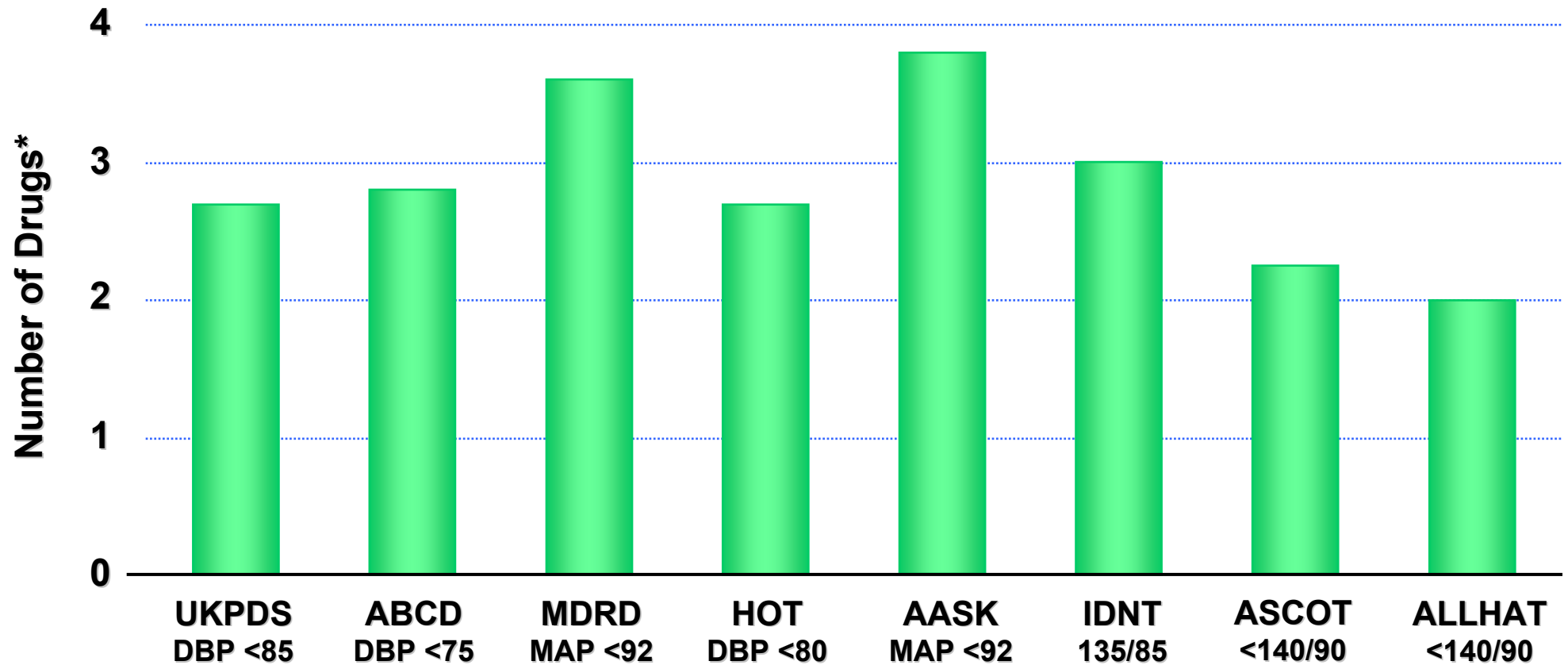
Half of Hypertensive Patients still not at goal



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

Source: Wolf-Maier et al. Hypertension 2004;43:10–17;
Korea National Health and Nutrition Survey 2005

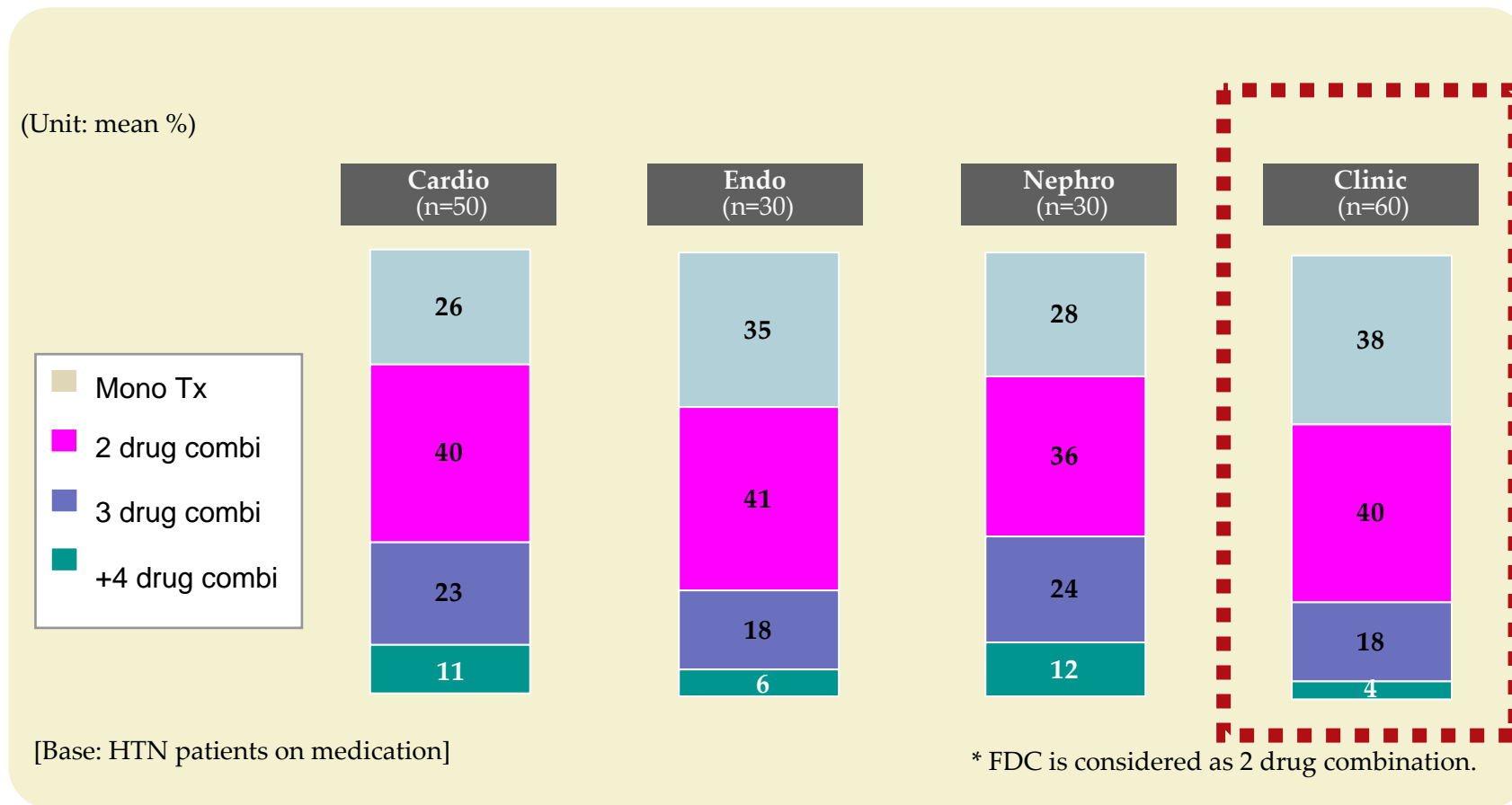
Multiple Antihypertensive Drugs Required to Achieve Target BP



*UKPDS, ABCD, MDRD, HOT, AASK, IDNT, ASCOT=average; ALLHAT=mean.

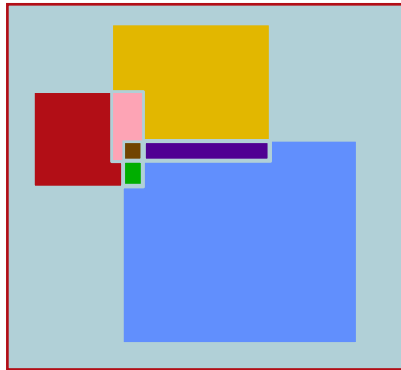
>60-70% patients need 2 or more anti-hypertensive agents in Korea Practice.

- 2 drug combination Rx takes the largest portion across all the specialties.

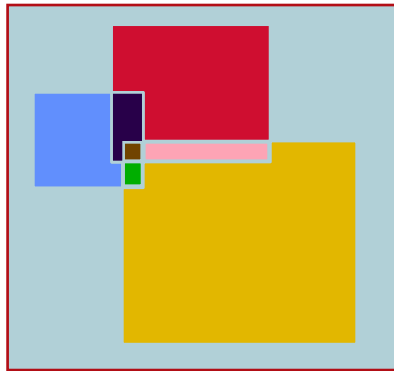


Blood Pressure has Multiple Regulatory Pathways

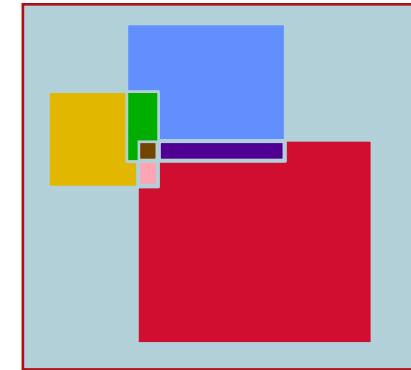
Patient 1






Patient 2



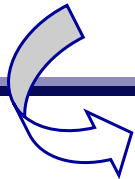
Patient 3



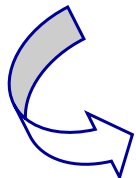
-  Sympathetic nervous system
-  Renin-angiotensin system
-  Total body sodium

Contemporary Hypertension and its Therapeutic Strategy

- Understand burden of Hypertension
 - **Poor Treatment and control rates**
- Rationale for Multiple-mechanism Therapy in Hypertension
 - **Inadequacy of agents with a single mechanism of action**

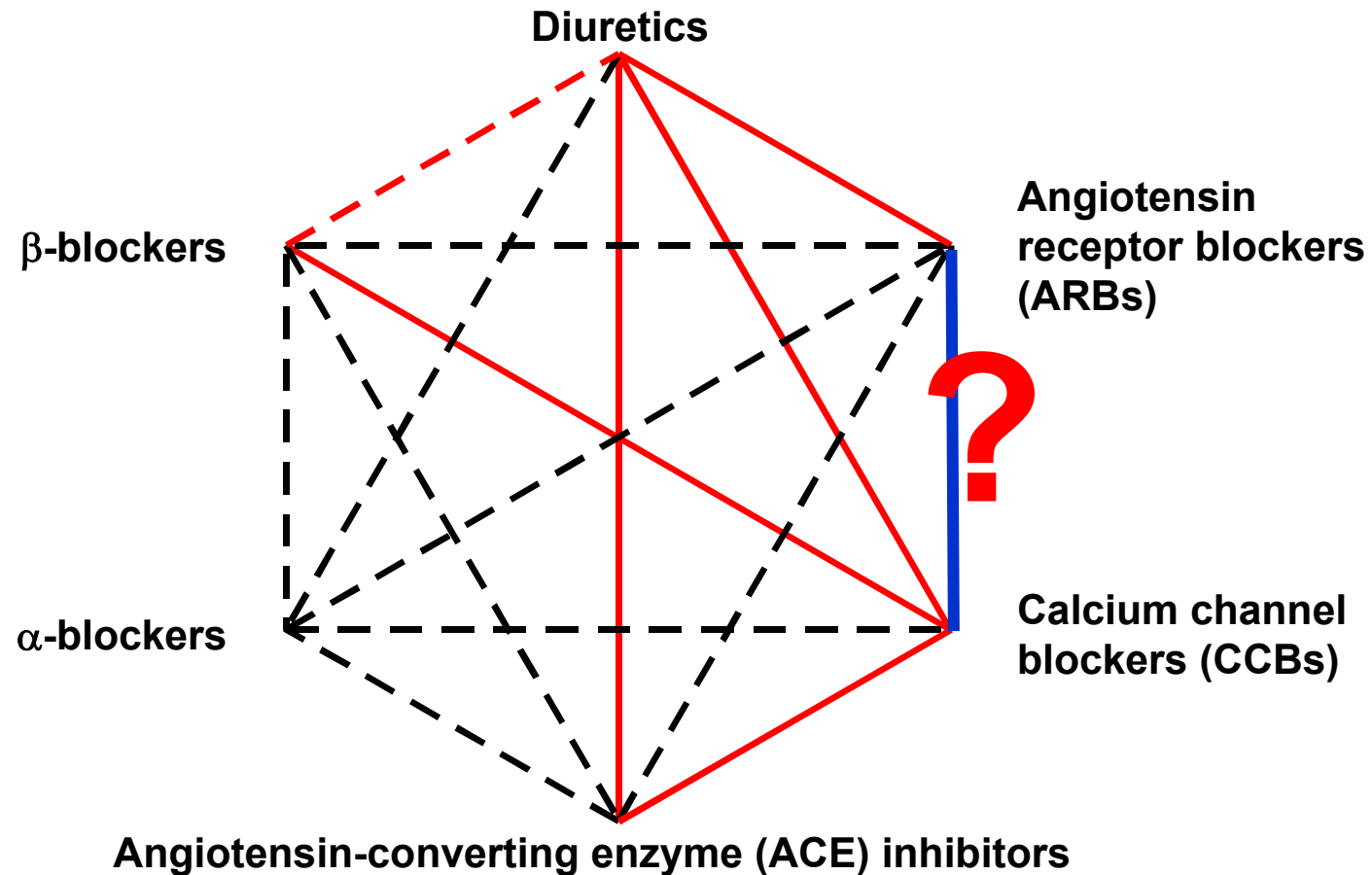


Inadequacy of Single MOA approach



Advantages of Multiple-mechanism Therapy

ESH–ESC Recommendations for **6** Combining BP-lowering Drugs and Availability as Fixed-dose Combinations



— Available as a fixed-dose combination

- - - Less frequently used/combination used as necessary

A Notable Absentee From Currently Available Dual-Mechanism Agents is the CCB–ARB

■ Angiotensin-converting enzyme (ACE) inhibitor and CCB

- Benazepril + amlodipine (Lotrel)
- Trandolapril + verapamil (Tarka)
- Ramipril + felodipine (Unimax)

■ ACE inhibitor and diuretic

- Benazepril + HCTZ (Lotensin HCTZ)
- Captopril + HCTZ (Capoten HCTZ)

■ ARB and diuretic

- Valsartan + HCTZ (Diovan HCTZ/Co-Diovan)
- Losartan + HCTZ (Hyzaar HCTZ)

■ β -blocker and diuretic

- Atenolol + chlorthalidone (Tenoretic)
- Metoprolol + HCTZ (Lopressor HCT)

■ β -blocker and CCB

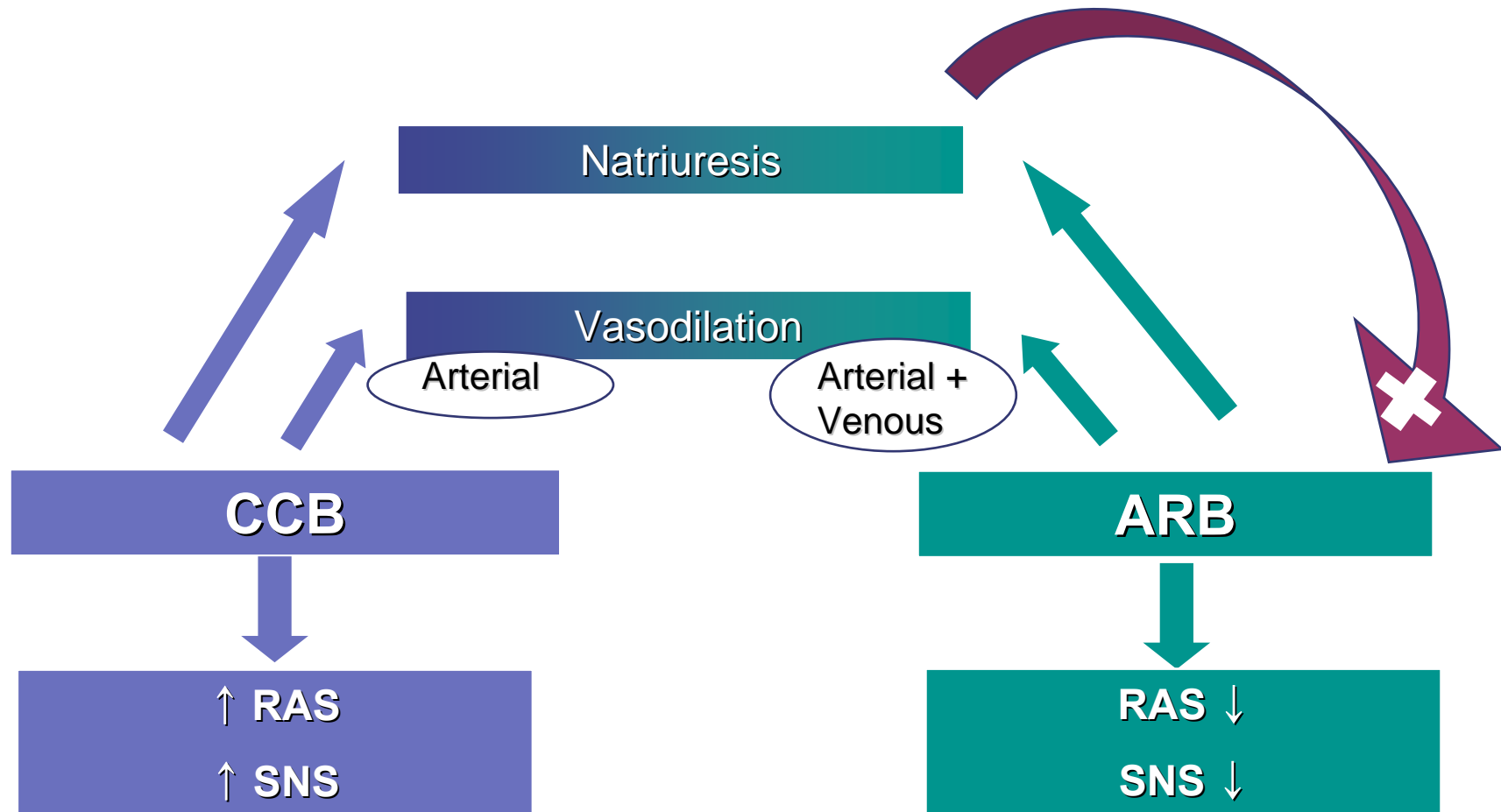
- Metoprolol + felodipine (Logimax)
- Atenolol + nifedipine (Nif-Ten)

● CCB and diuretic

- Nifedipine + mefruside (Sali-Adalat)

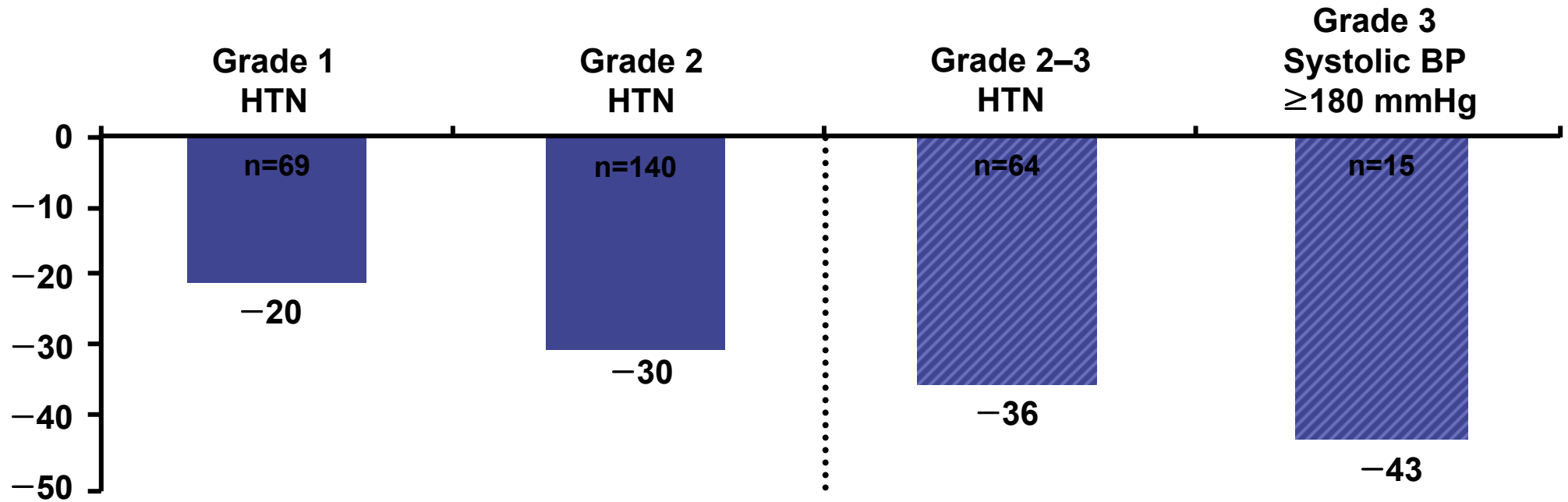
Notable absentee is a
CCB + ARB

Interaction of CCBs and ARBs on Vascular and Renal Function, SNS and RAS Activity



Amlodipine/Valsartan: BP Lowering Across All Grades of Hypertension

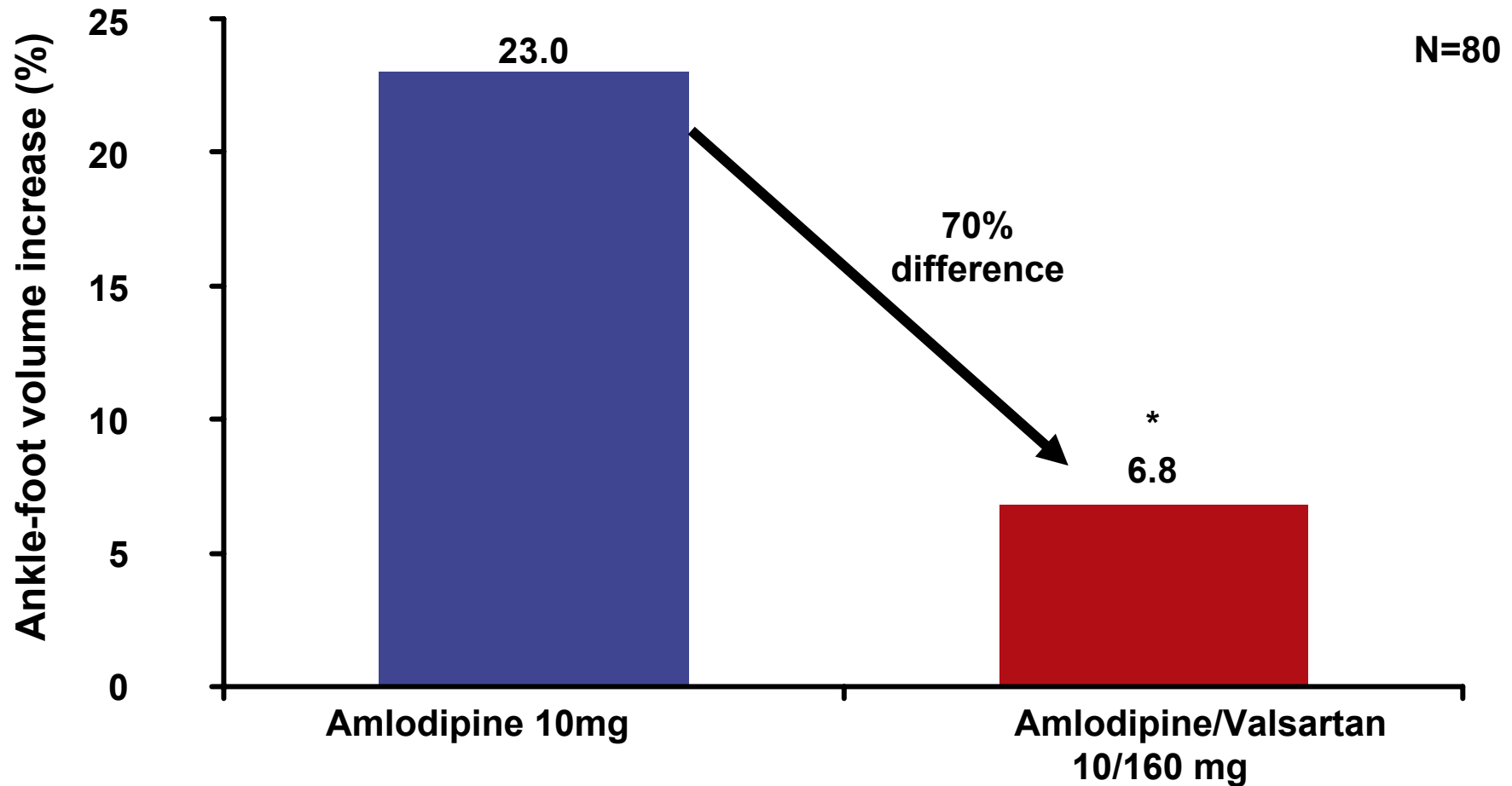
Mean change in MSSBP from baseline (mmHg)



DBP reduction (mmHg)	-17	-18	-29	-26
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Data from Smith et al. J Clin Hypertens 2007;9:355-64. Dose 10/160 mg
Data from Poldermans et al. Clin Ther 2007;29:279-89. Dose 5-10/160 mg

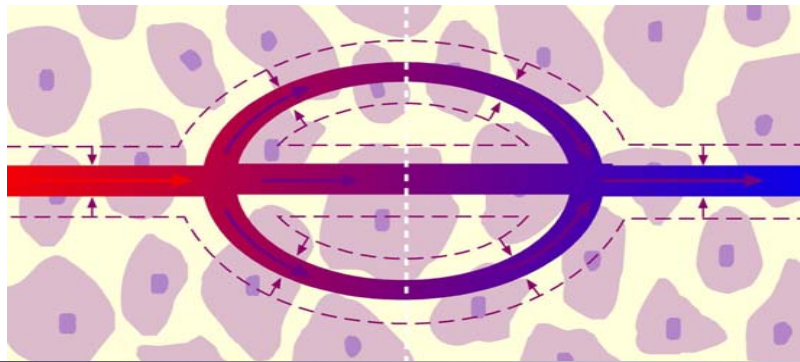
Reduced Fluid Retention with Amlodipine/Valsartan Compared with Amlodipine Monotherapy



*p<0.01 vs. amlodipine, n=80

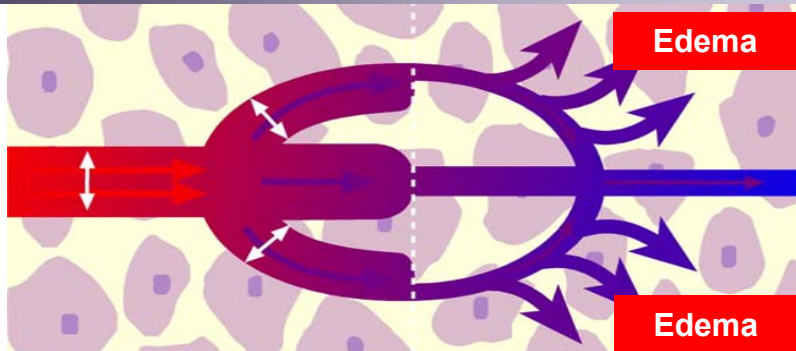
Fogari et al. J Hum Hypertens 2007;21:220-4

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



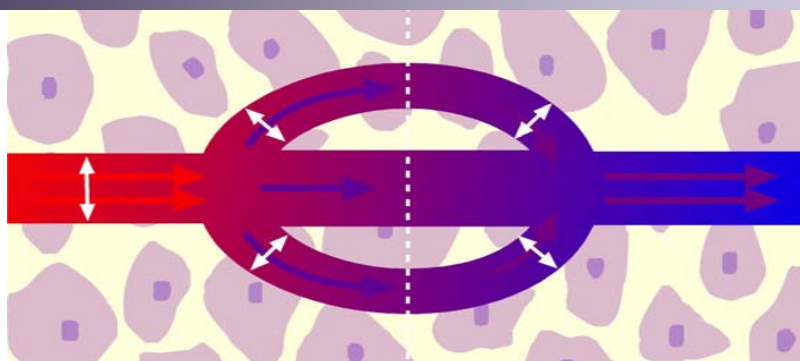
Arterial hypertension

- Constricted blood vessels, high resistance



CCBs

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

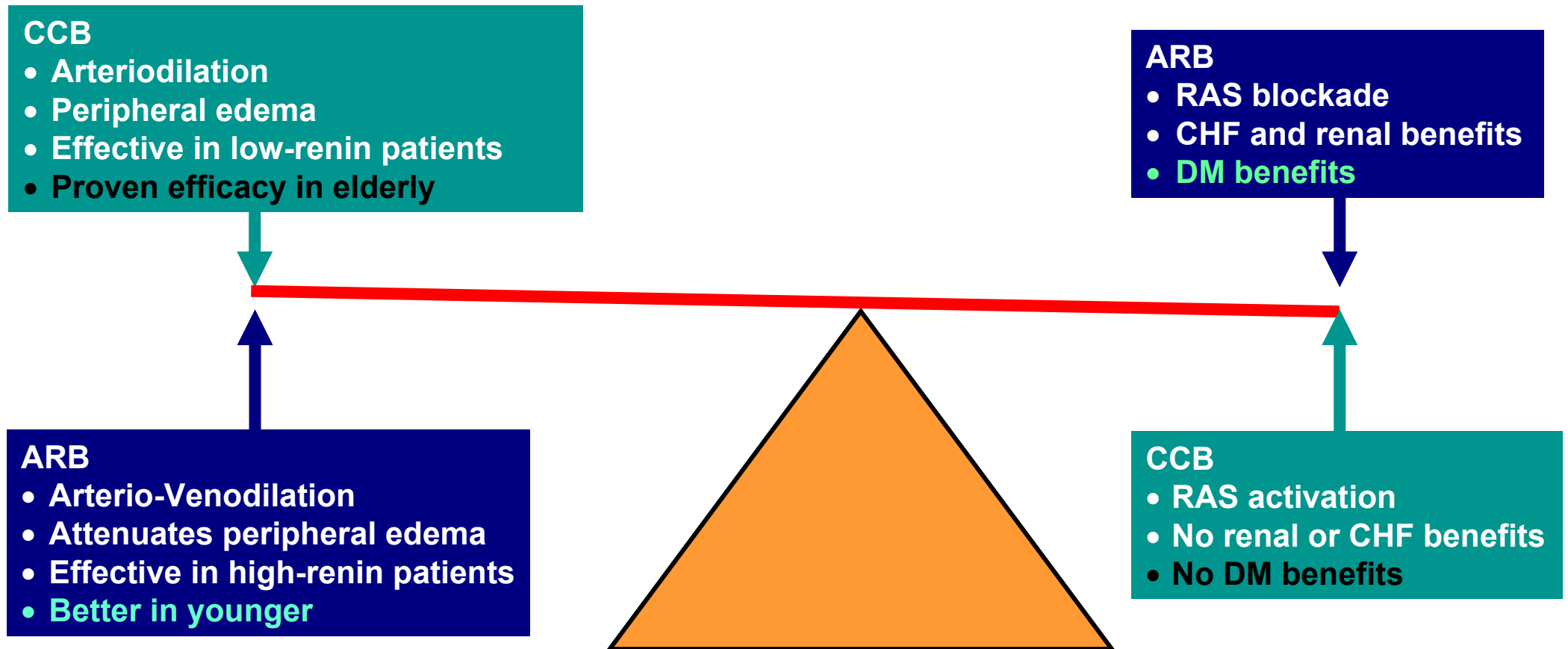


CCBs + RAS inhibitors*

- 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

CCB/ARB: Synergy of Counter-regulation



ACCOMPLISH [RAAS+CCB vs. RAAS+HCTZ]

Avoiding Cardiovascular Events through COMbination Therapy in Patients Living with Systolic Hypertension

A prospective, double-blind, randomized, trial

to compare the effects of

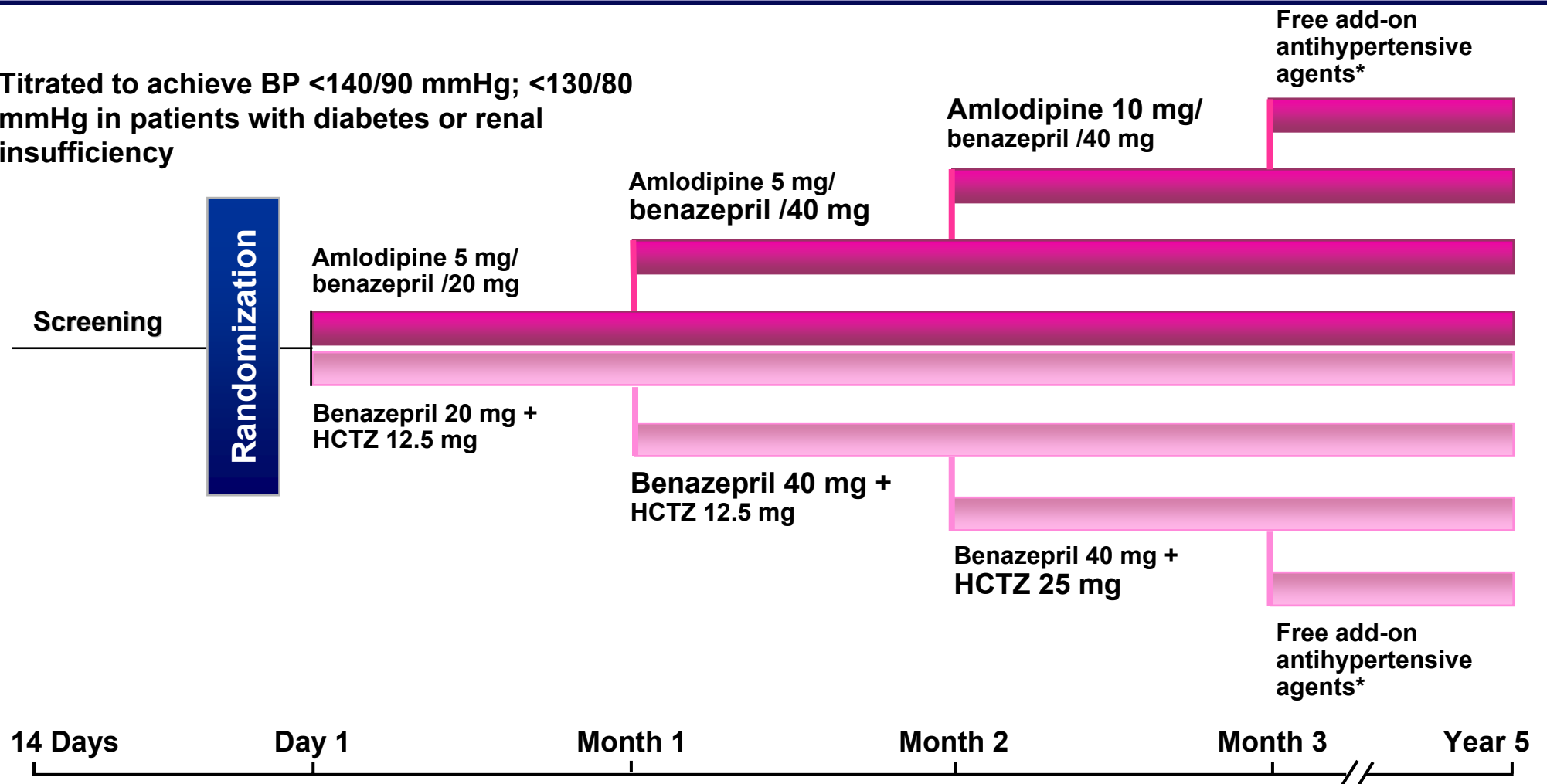
amlodipine / benazepril vs. benazepril / thiazide

on the reduction of CV morbidity and mortality

in patients with high risk hypertension

ACCOMPLISH: Design

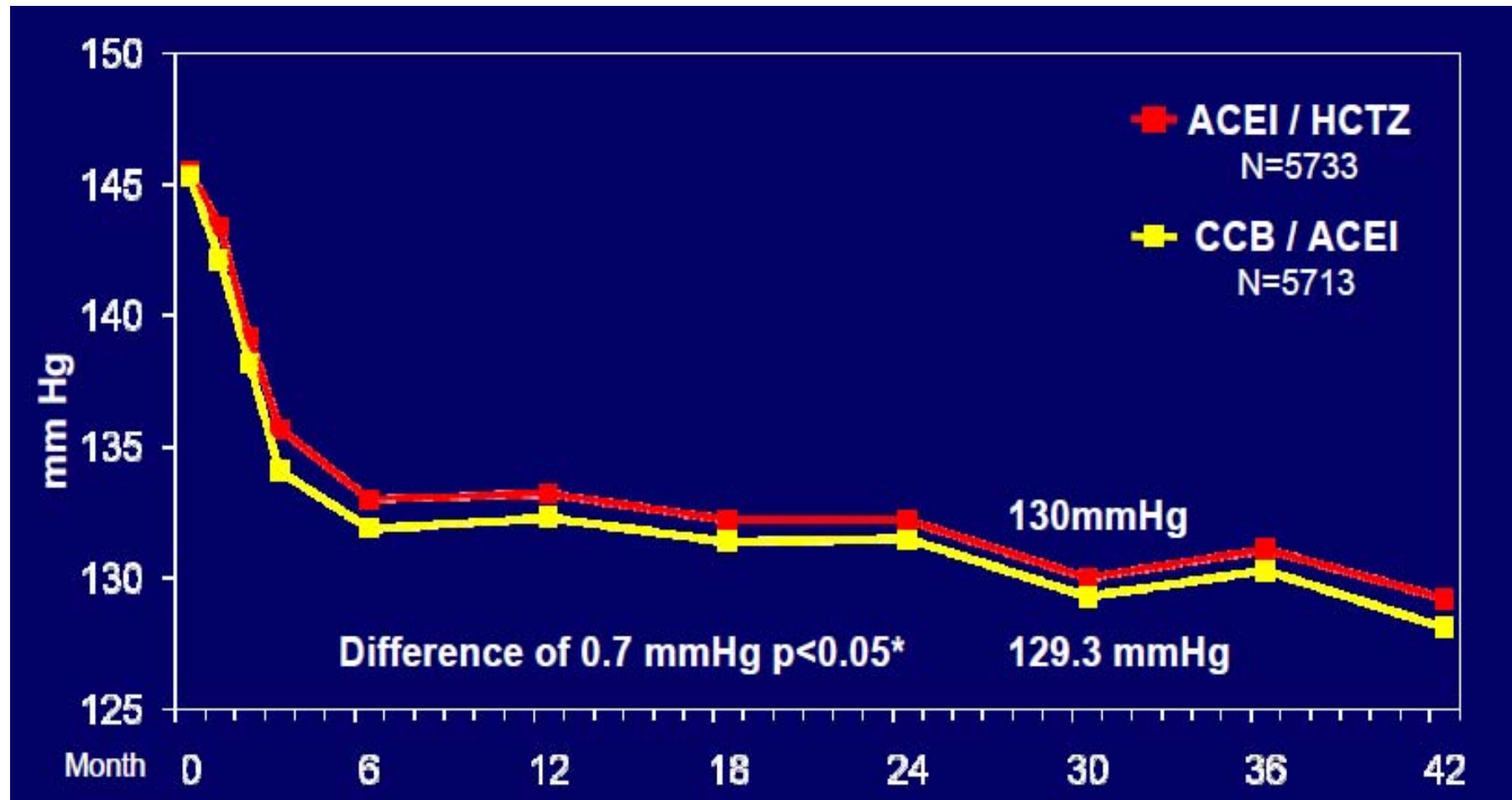
Titrated to achieve BP <140/90 mmHg; <130/80 mmHg in patients with diabetes or renal insufficiency



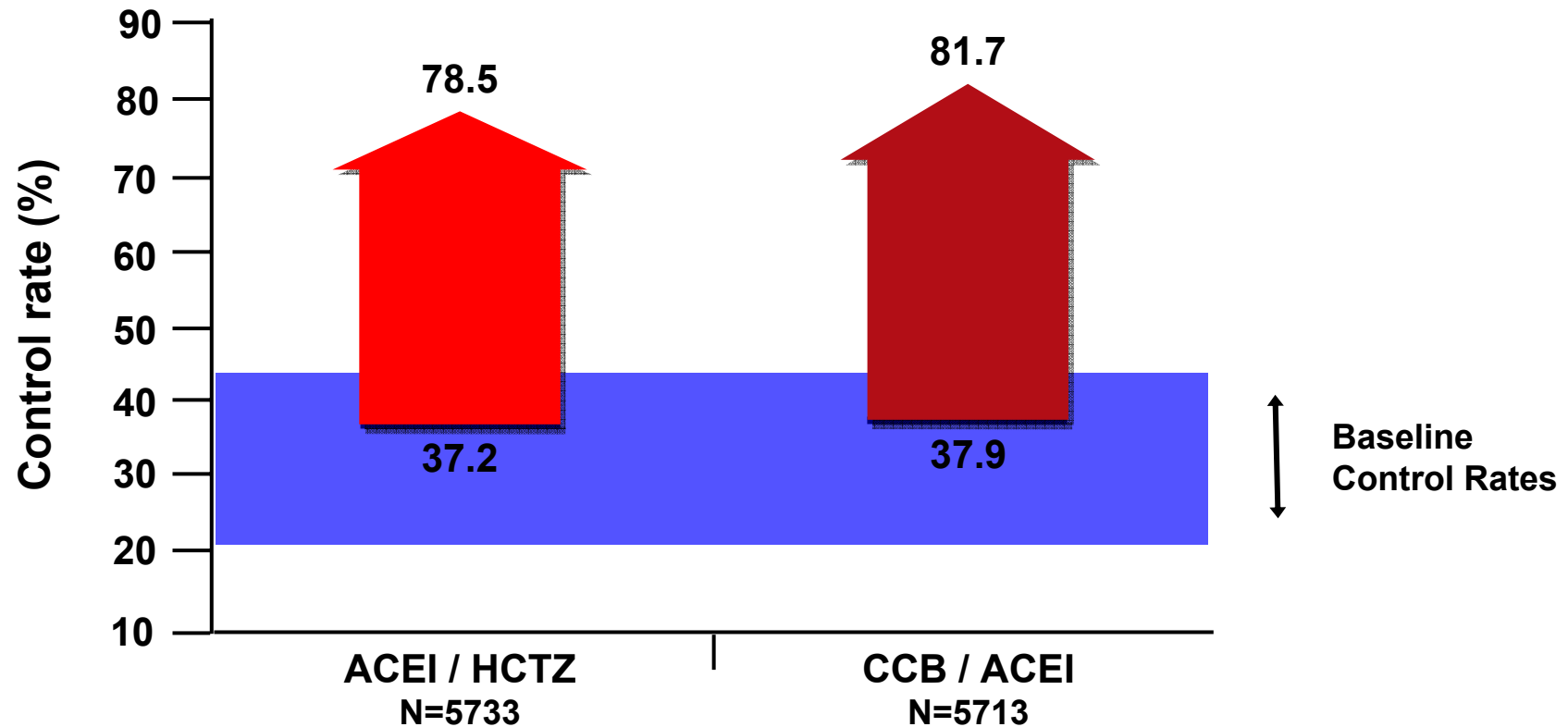
*Beta blockers; alpha blockers; clonidine; loop diuretics.

Jamerson KA et al. *Am J Hypertens*. 2004;17:793–801.

Systolic Blood Pressure over Time



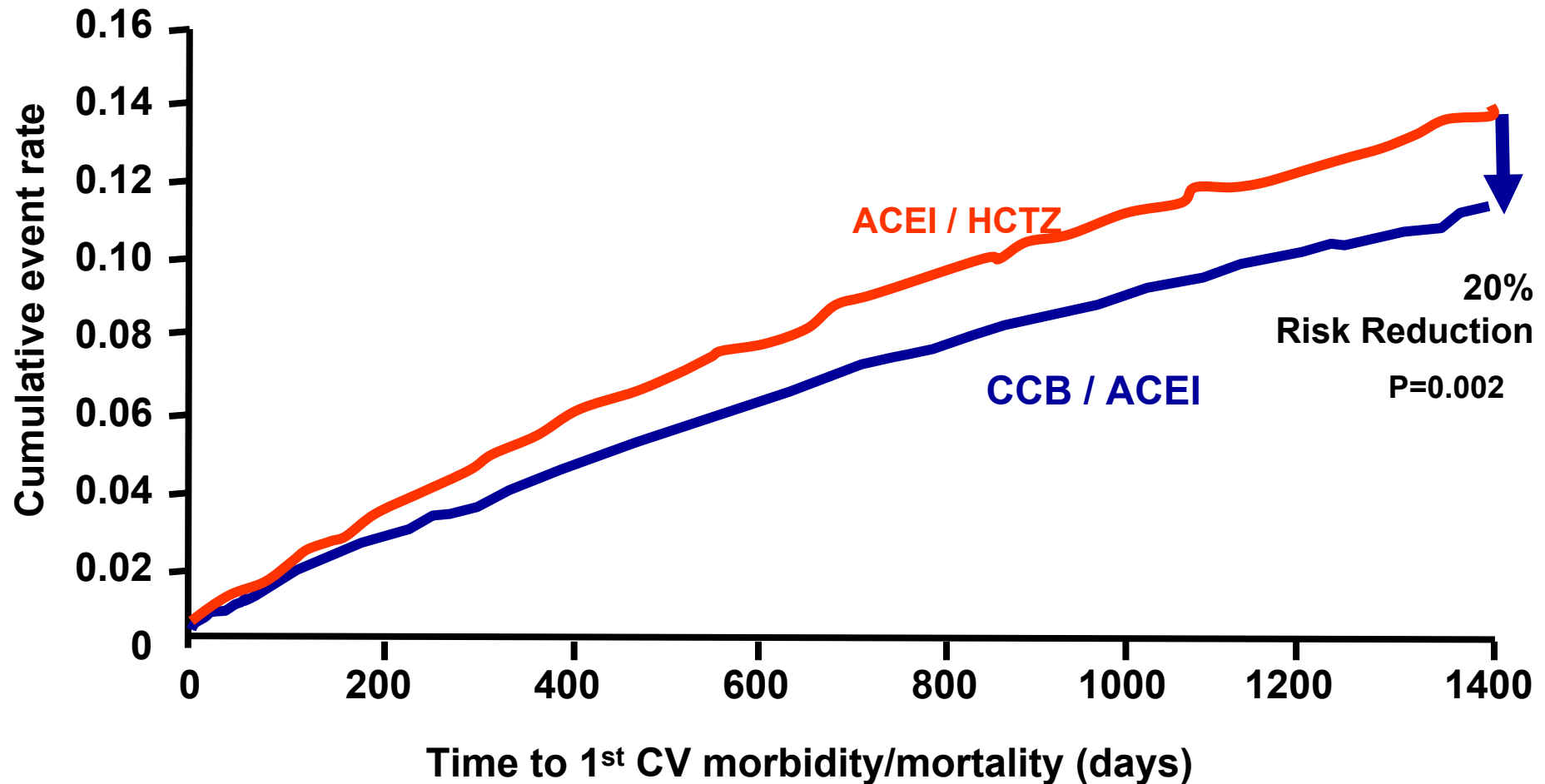
ACCOMPLISH: Exceptional Control Rates with Initial Combination Therapy



P<0.001 at 30 months follow-up
Control defined as <140/90 mmHg

2008 ACC

Kaplan Meier for Primary Endpoint



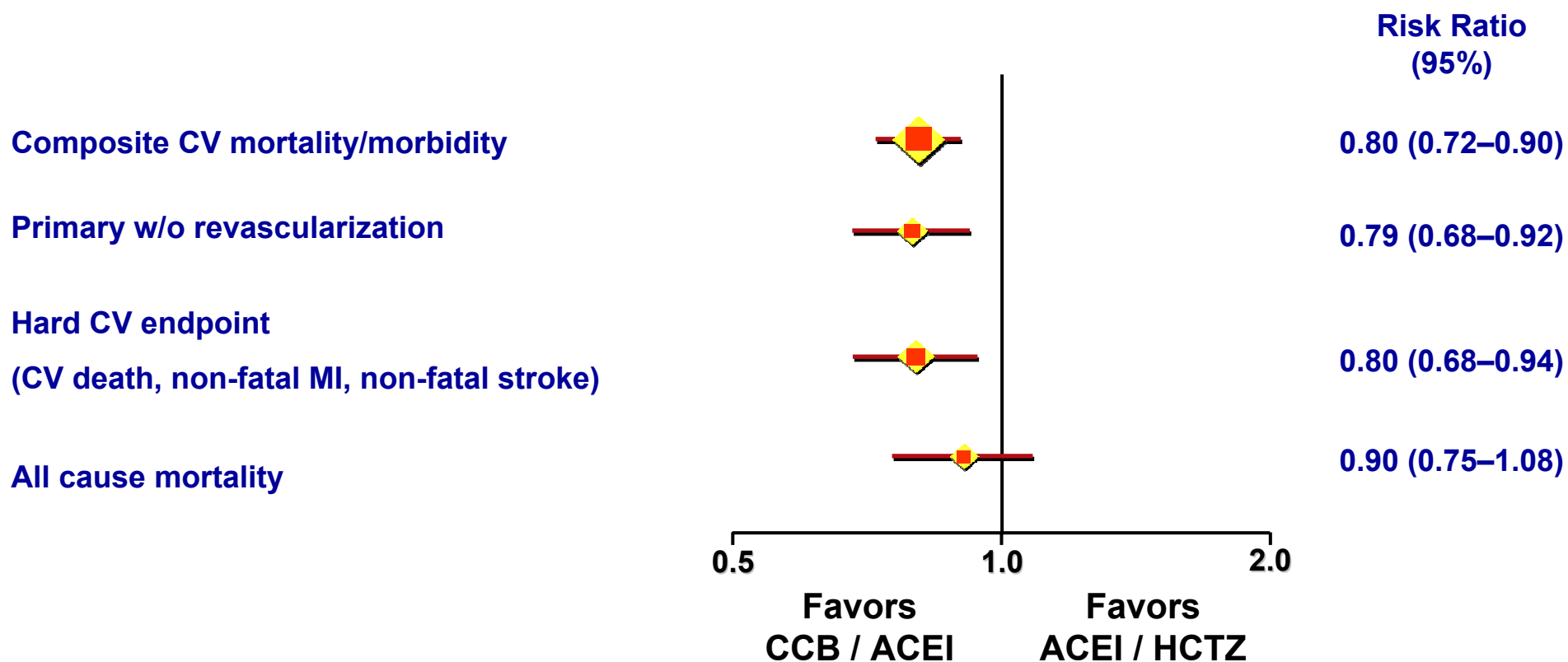
HR (95% CI): 0.80 (0.72, 0.90)
INTERIM RESULTS Mar 08

2008 ACC

Primary and Other Endpoints

Incidence of adjudicated primary endpoints, based upon cut-off analysis date 3/24/2008

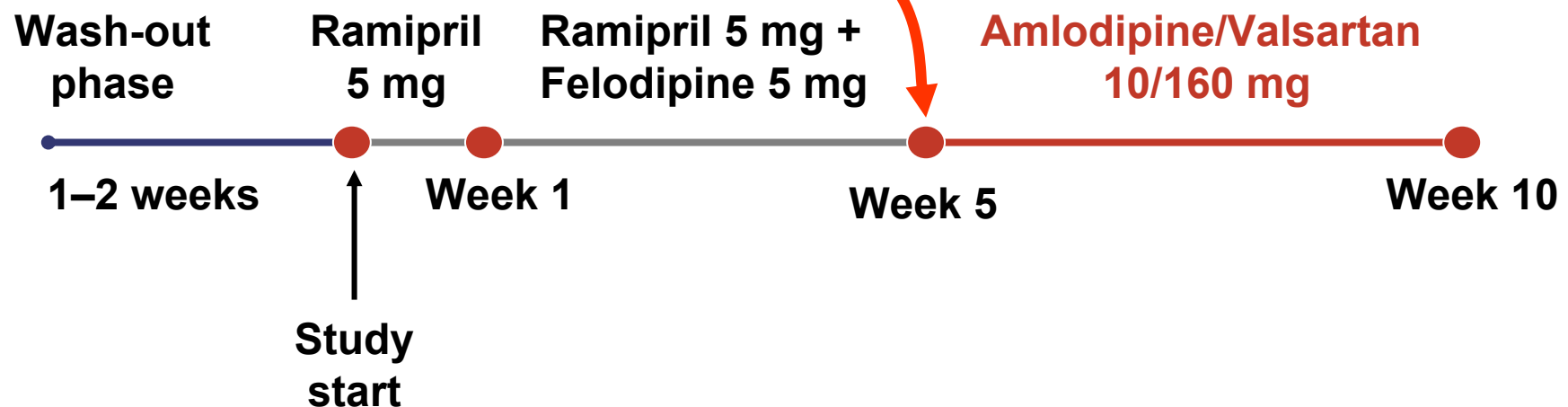
(Intent-to-treat population)



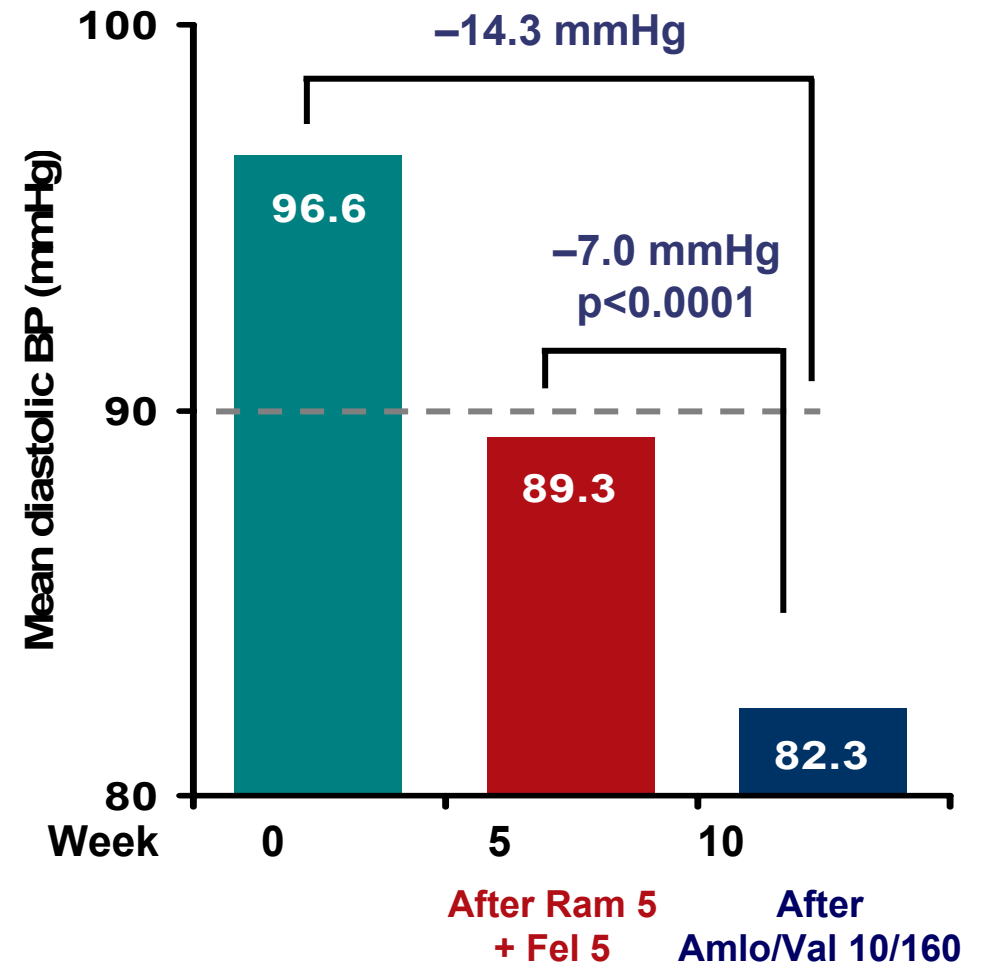
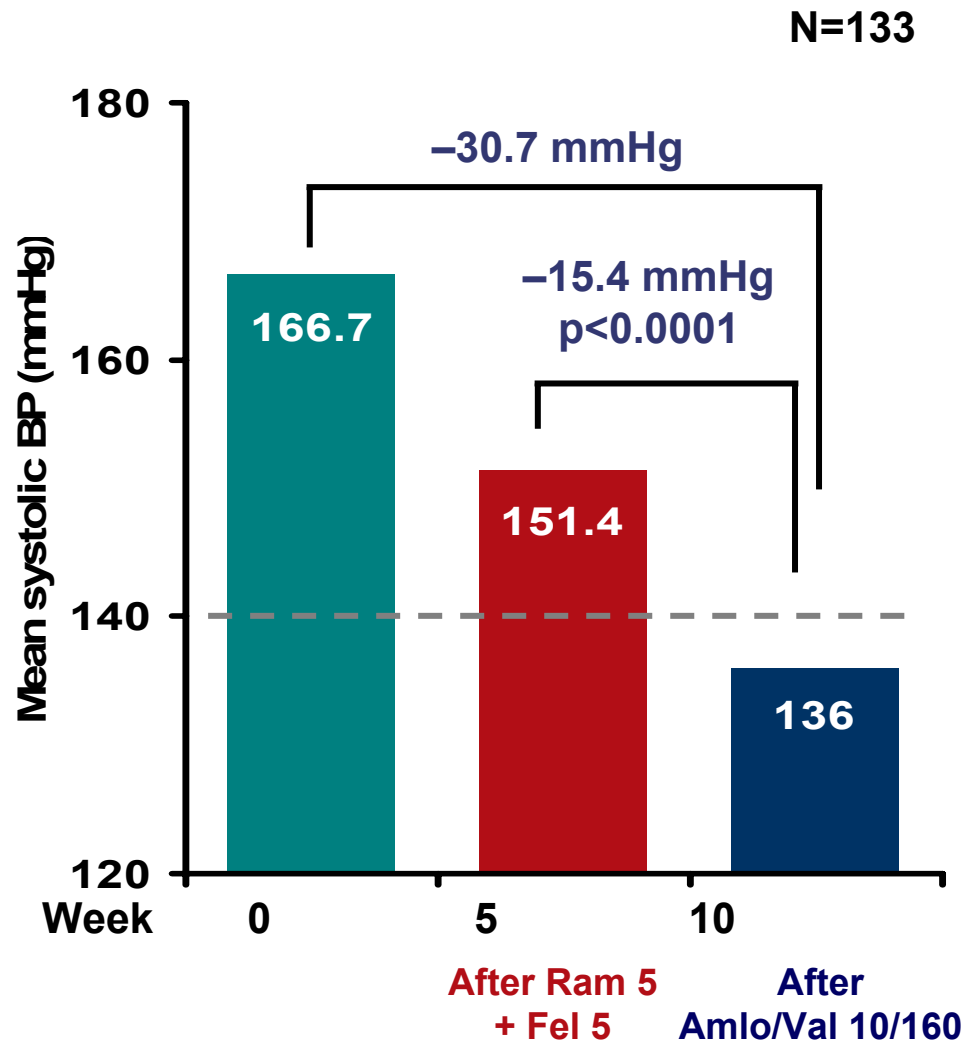
EXPRESS-C Study Design

Non-responders to Combination Therapy (Ramipril/Felodipine)

- 133 patients in 16 centers
- Open, sequential, non-responder study including patients with moderate hypertension (160 mmHg < SBP < 180 mmHg)
- Initial treatment: ramipril 5 mg + felodipine 5 mg (highest permitted dosage in fixed-dose combination)
- **Uncontrolled patients** (n=105) (SBP >140 mmHg) were treated with Amlodipine/Valsartan 10/160 mg for another 5 weeks



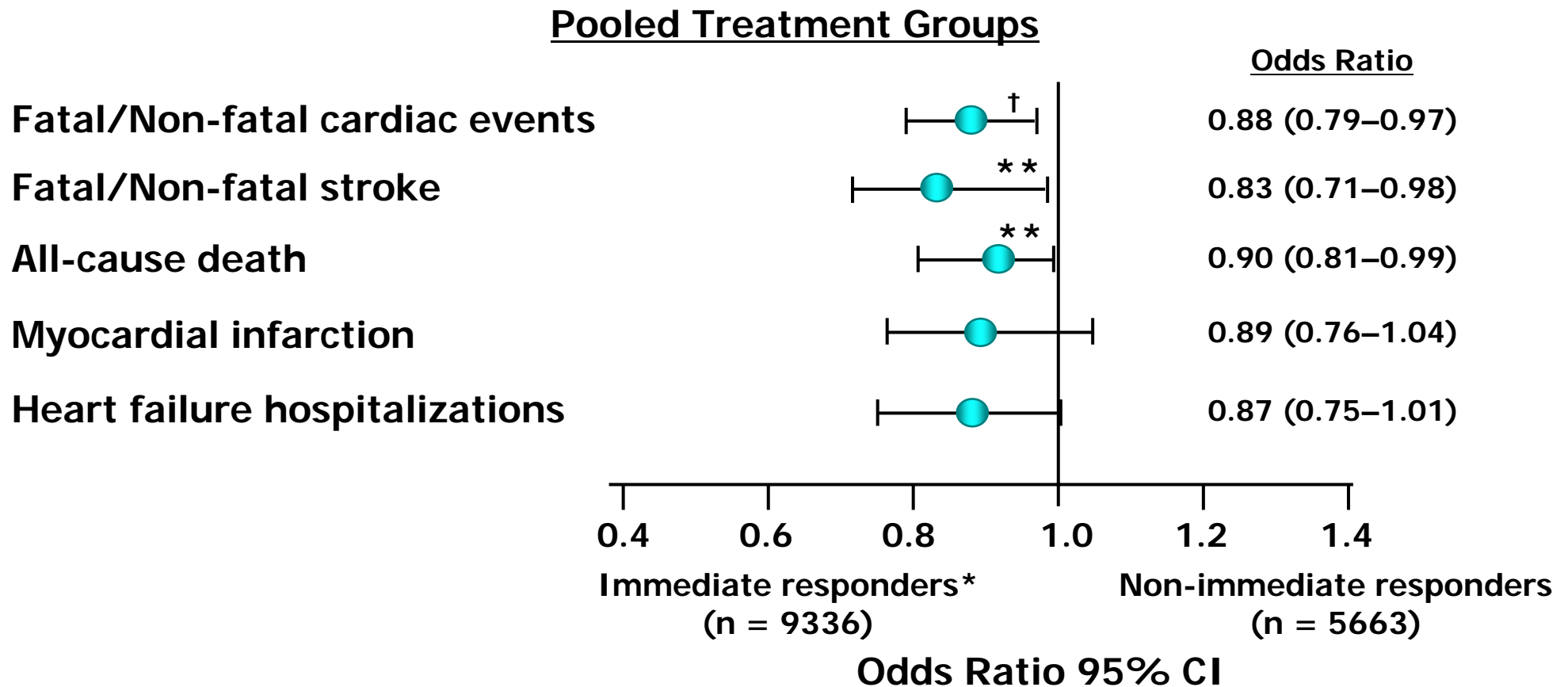
Additional Reduction in BP with Amlodipine/Valsartan in Non-responders to Ramipril/Felodipine



Open, sequential, non-responder, 10-week study

Trenkwalder et al. DMW 2006;131:S164

VALUE Suggests Immediate BP Control Reduce Cardiac M&M



*Those not on previous treatment: SBP \downarrow \geq 10 mmHg at one month;
those on previous treatment: SBP \leq baseline at one month.

** $P < 0.05$; † $P < 0.01$.

Weber MA et al. *Lancet*. 2004;363:2047–49.

SHIFT : The Art of Combination Therapy

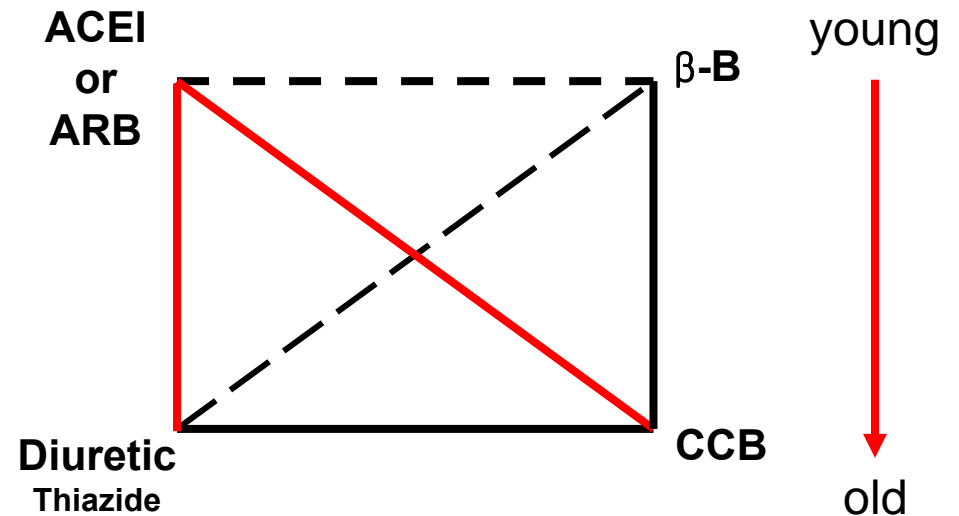
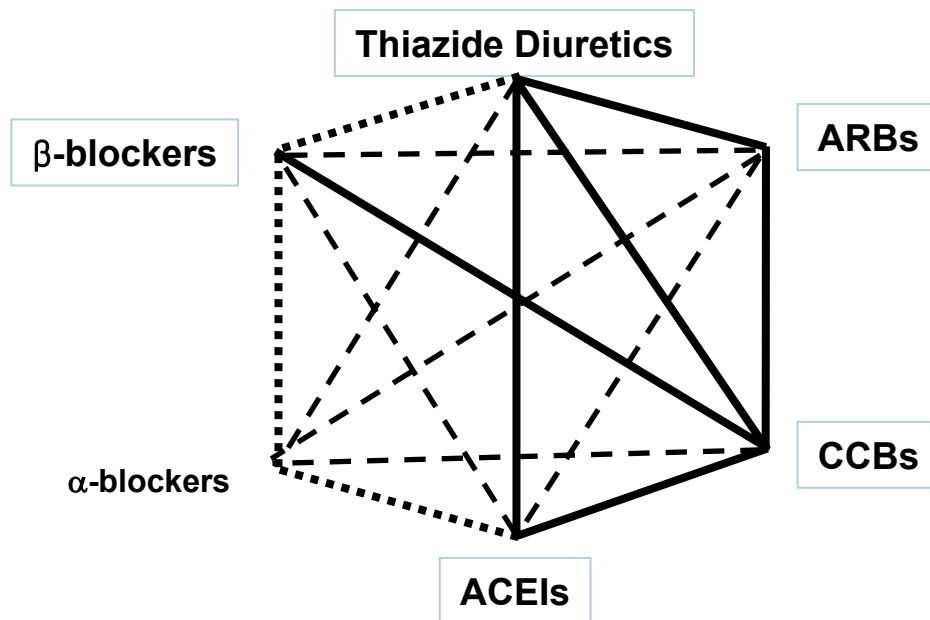
2007

ESH-ESC

2008

ACCOMPLISH

— Recommend
— Permissible
..... little recommend



Adapted from European Society for Hypertension-European Society of Cardiology Guidelines Committee. *J Hypertens.* 2003;21:1011–1053.

Park JB 2008 Apr

Many Advantages of Combinations “ARB + CCB” Over Monotherapy for Hypertension

Efficacy

+

Safety

+

Compliance

Faster achievement
of target BP
Higher control rates

Potential
for fewer side effects

Improved compliance
by simple,
convenient
regimen

Increased potential for end-organ protection

Improved CV outcomes