Rationale for the use of Single Pill Combination

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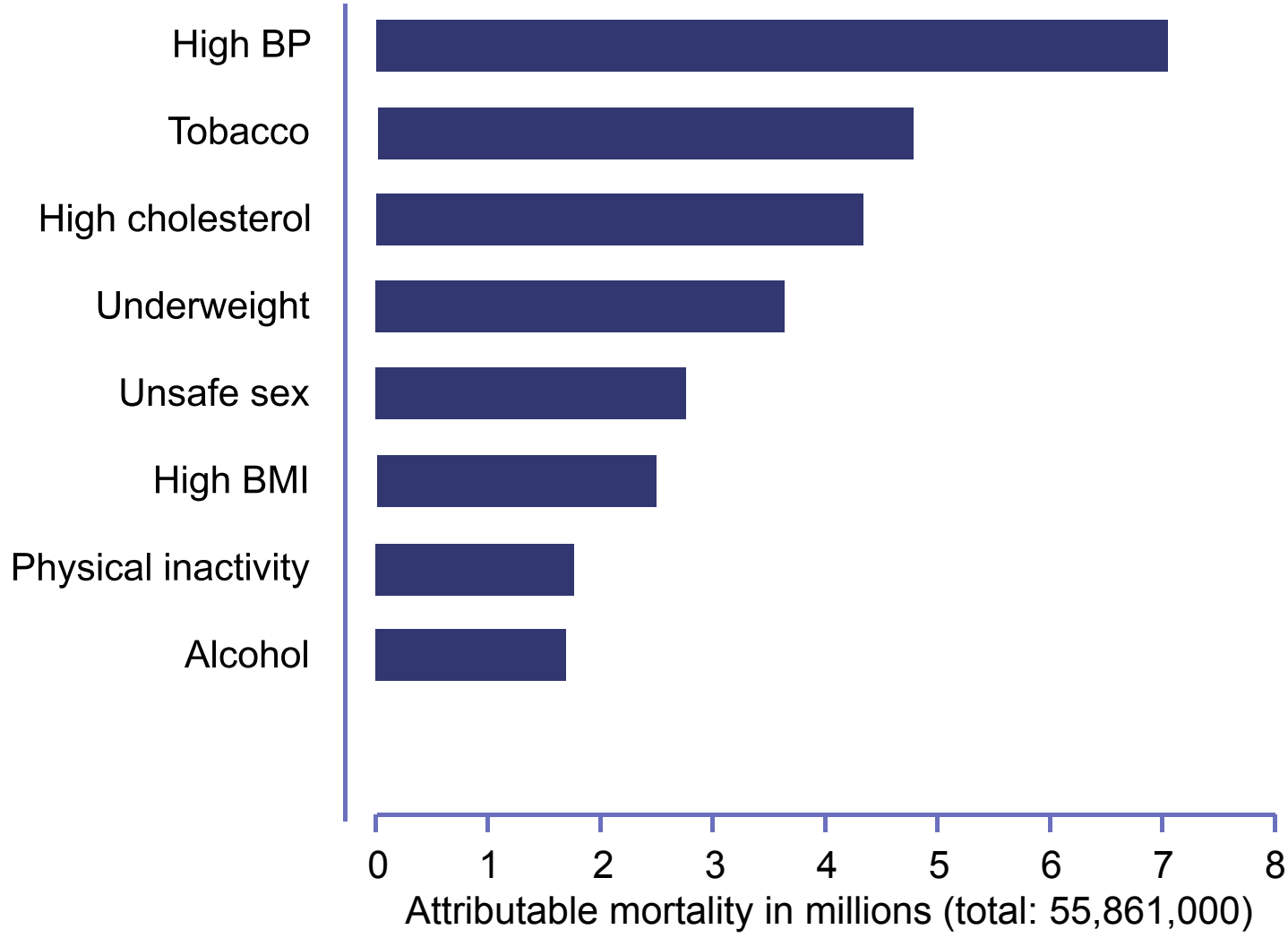
Unmet Need of Hypertension Treatment

Hypertension - # 1 Risk Factor for Global Mortality



BMI = body mass index; BP = blood pressure

Ezzati et al. Lancet 2002;360:1347–60

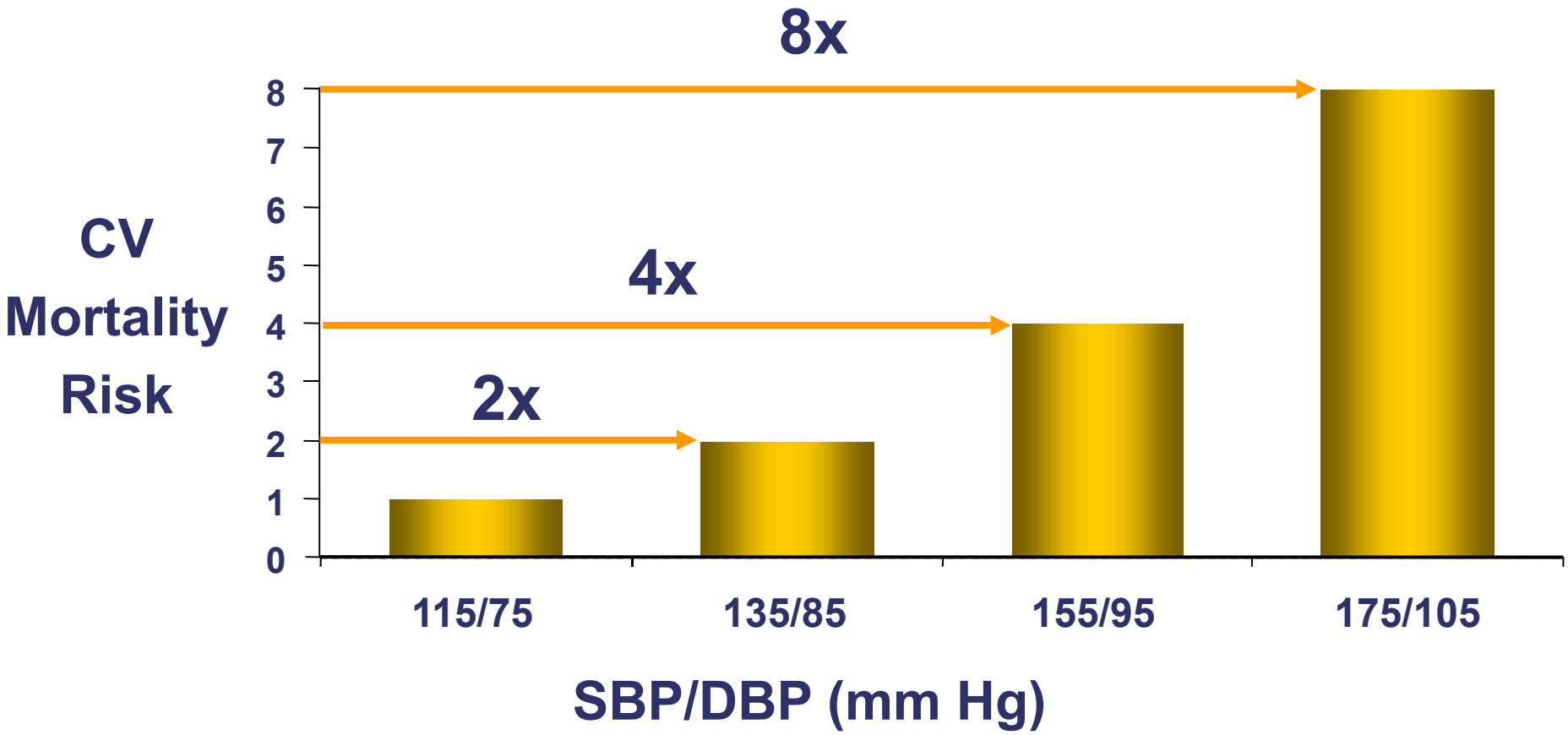
Hypertension – High Prevalence

Hypertension affects approximately 1 billion people worldwide

Number of adults with hypertension is estimated to ⬆ 60% from 2000 to 2025

Kearney et al. Lancet 2005;365:217–23

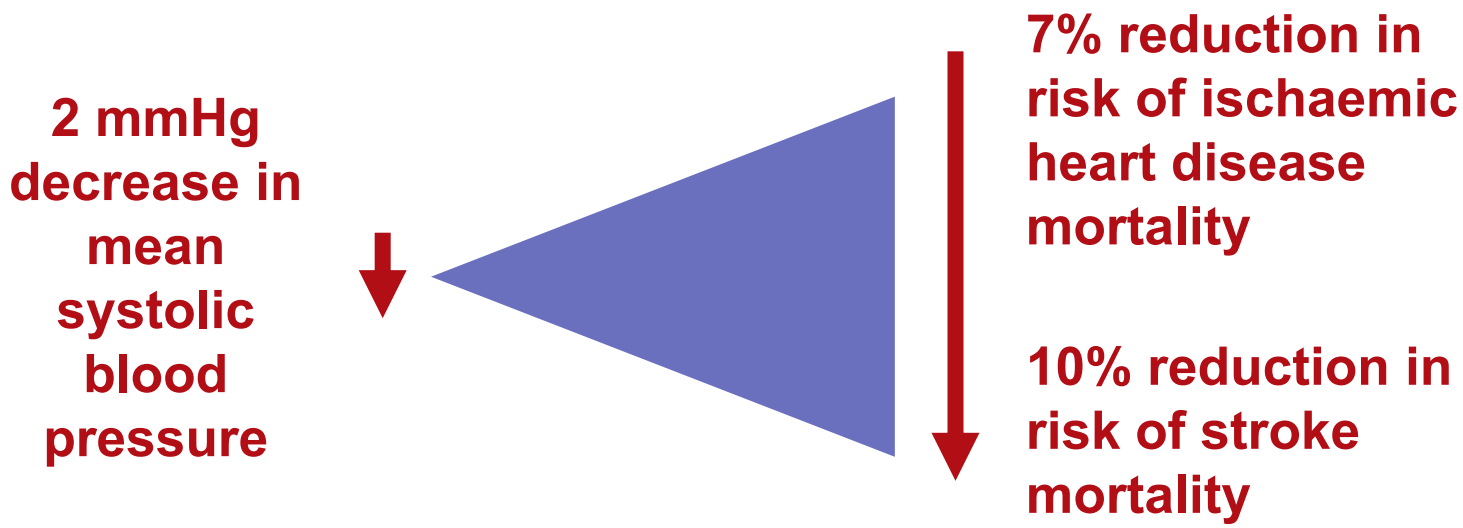
Hypertension – CV Mortality Risk



*Individuals aged 40 to 69 years, starting at blood pressure 115/75 mm Hg

Chobanian AV et al. *JAMA*. 2003;289:2560. Lewington S et al. *Lancet*. 2002;360:1903

Blood Pressure and Risk of Cardiovascular Event



- Meta-analysis of 61 prospective, observational studies
- 1 million adults
- 12.7 million person-years

Lewington et al. Lancet 2002;360:1903–13

Blood Pressure Goal

ESH–ESC & JNC 7 Guidelines

	JNC 7[1]	ESH–ESC[2]
Type of hypertension	**BP goal (mmHg)**	**BP goal (mmHg)**
Uncomplicated	**<140/90**	**130–139/80–85**
Complicated		
Diabetes mellitus	**<130/80**	**130–139/80–85**
Kidney disease	**<130/80***	**130–139/80–85**
Other high risk (stroke, myocardial infarction)	**<130/80**	**130–139/80–85**

*Lower if proteinuria is >1 g/day

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

Global risk assessment

Promotes intensified BP control

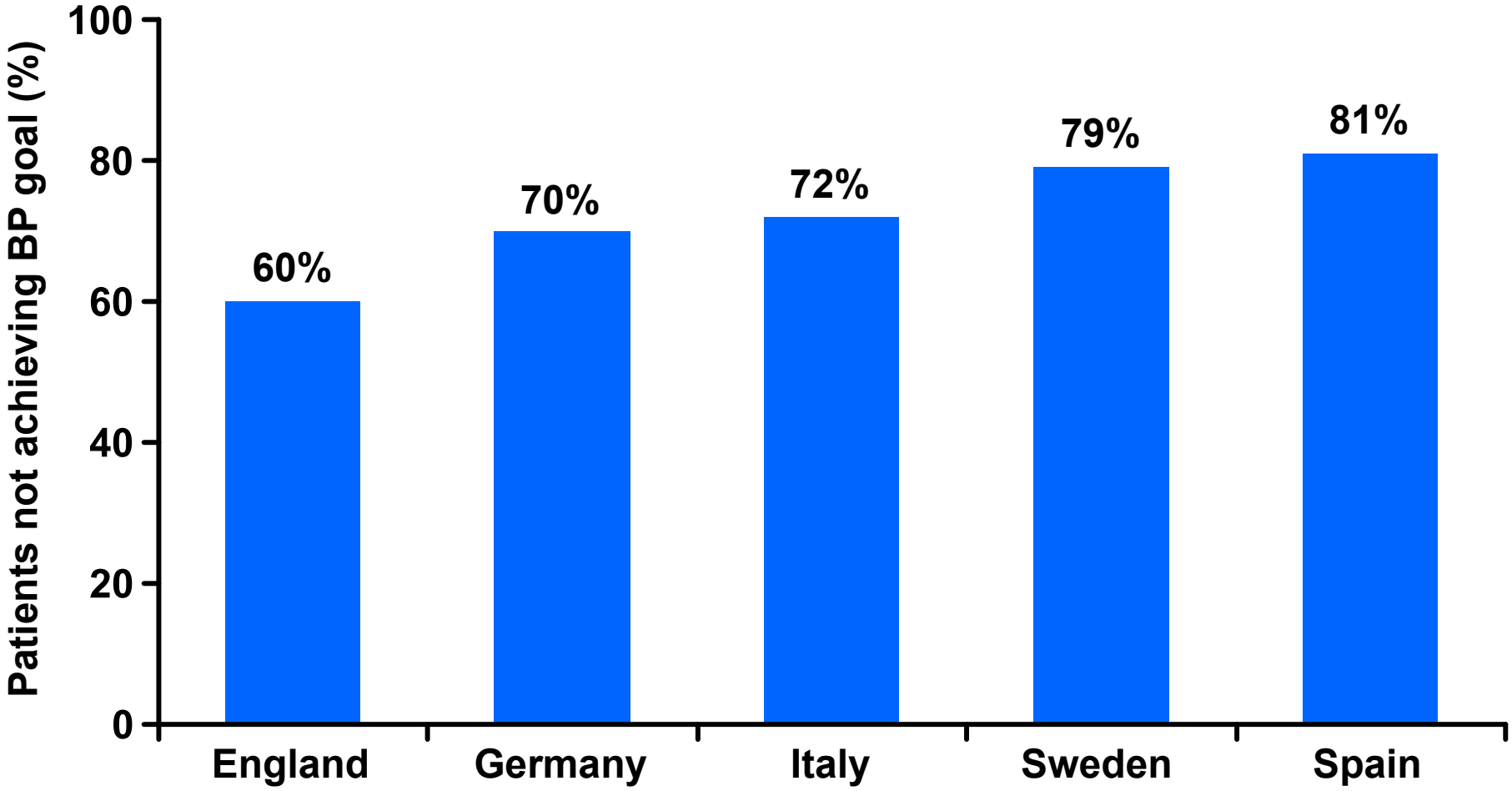
Blood pressure (mmHg)					
Other risk factors OD or disease	Normal SBP 120–129 or DBP 80–84	High normal SBP 130–139 or DBP 85–89	Grade 1 HT SBP 140–159 or DBP 90–99	Grade 2 HT SBP 160–179 or DBP 100–109	Grade 3 HT SBP≥180 or DBP≥110
No other risk factors	No BP intervention	No BP intervention	Lifestyle changes for several months then drug treatment if BP uncontrolled	Lifestyle changes for several weeks then drug treatment if BP uncontrolled	Lifestyle changes + Immediate drug treatment
1–2 risk factors	Lifestyle changes	Lifestyle changes	Lifestyle changes for several weeks then drug treatment if BP uncontrolled	Lifestyle changes for several weeks then drug treatment if BP uncontrolled	Lifestyle changes + Immediate drug treatment
≥3 risk factors, MS or OD	Lifestyle changes	Lifestyle changes and consider drug treatment	Lifestyle changes + Drug treatment	Lifestyle changes + Drug treatment	Lifestyle changes + Immediate drug treatment
Diabetes	Lifestyle changes	Lifestyle changes + Drug treatment			
Established CV or renal disease	Lifestyle changes + Immediate drug treatment	Lifestyle changes + Immediate drug treatment	Lifestyle changes + Immediate drug treatment	Lifestyle changes + Immediate drug treatment	Lifestyle changes + Immediate drug treatment

- **Patients with organ damage, established CVD, DM, Metabolic syndrome or ≥ 3 other risk factors need immediate treatment**

2007 ESC/ESH guideline. 2007;25:1105-1187

BP Control Rates in Europe

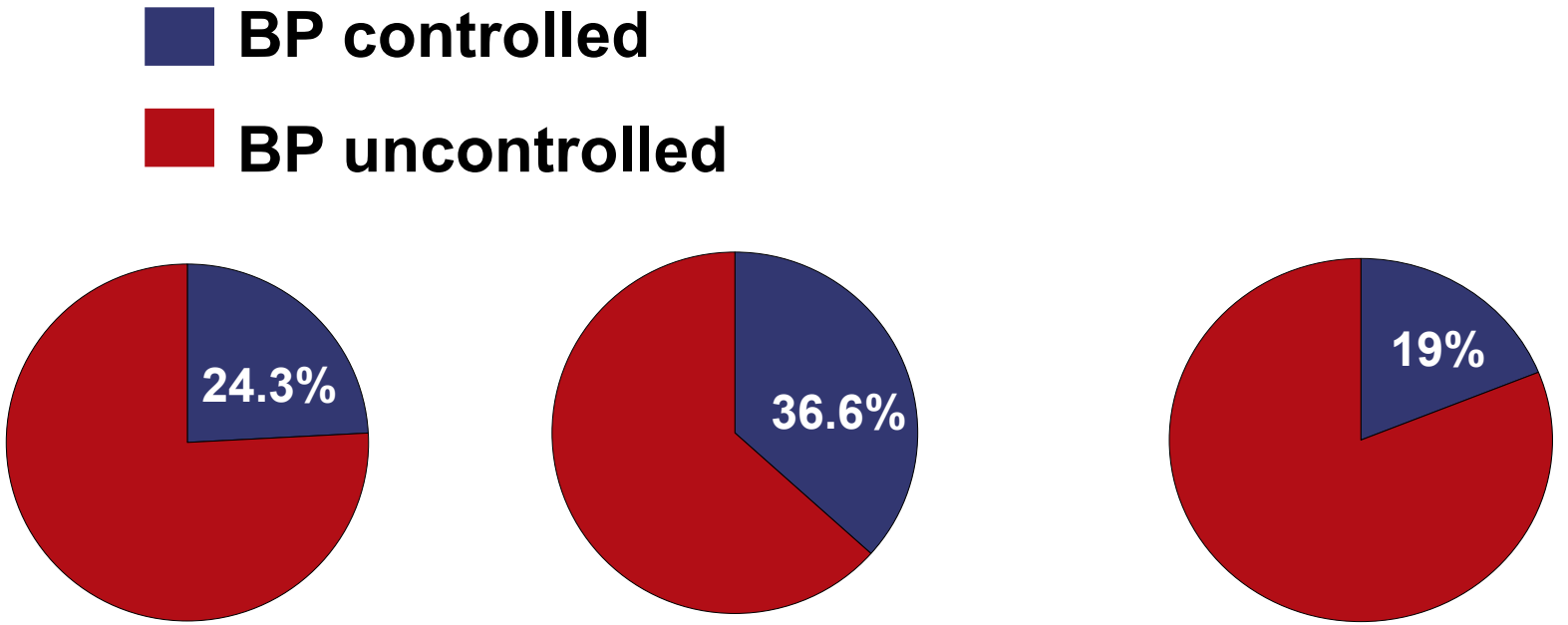
Majorities do not reach the goal



*Treated for hypertension; #BP goal <140/90 mmHg
BP = blood pressure

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

BP Control Rates in Asia



Turkey[1]
(Treated population)

Thailand[2]
(Treated population)

China[3]
(Population aware of their hypertension)

BP = blood pressure

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

Why do we need

Multiple Mechanism Therapy:

Efficacy

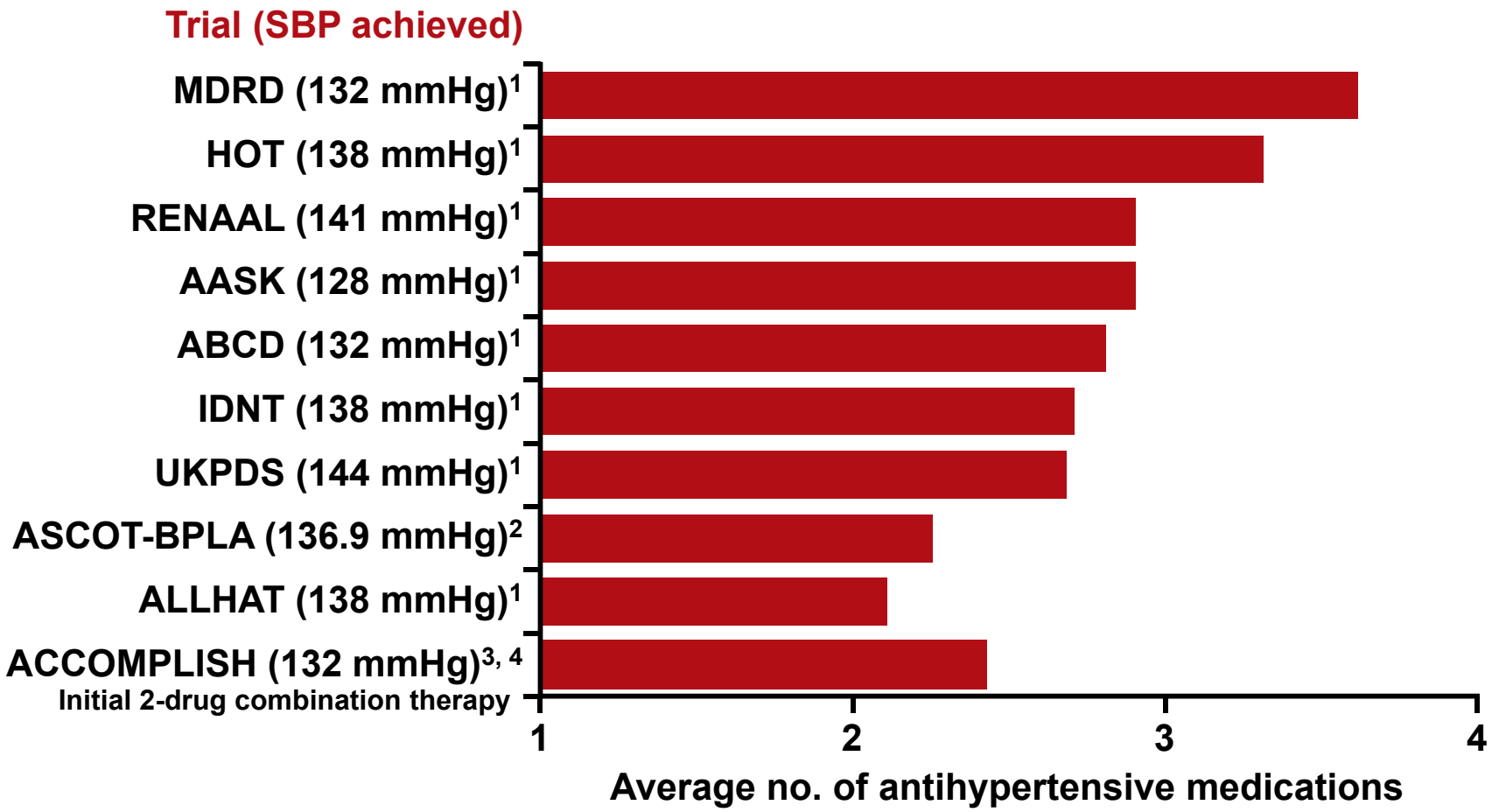
Limitations of Treating with Single Mechanism of Action

- Antihypertensive agents with a single MoA were inadequate to achieve a diastolic BP <95 mmHg in 40–60% of hypertensive patients[1]
- Because hypertension is a multifactorial disease, in most cases at least two antihypertensive agents are needed for patients to achieve BP goal[2]
- As an estimate, 1/3 of patients with hypertension require 2 drugs to achieve BP control* and 1/3 of patients will require 3 or more agents to achieve BP control[3]

*Blood pressure (BP) <140/90 mmHg

[1]Materson et al. N Engl J Med 1993;328:914–21
[2]Milani. Am J Manag Care 2005;11:S220–7
[3]Düsing et al. Vasc Health Risk Manag 2010;6:321–5

Multiple Antihypertensive Agents
Needed to Reach BP Goal in Clinical Trials



SBP = systolic blood pressure

[1]Bakris, et al. Am J Med 2004;116(5A):30S–8; [2]Dahlöf, et al. Lancet 2005;366:895–906
[3]Jamerson, et al. Blood Press 2007;16:80–6; [4]Jamerson, et al. N Engl J Med 2008;359:2417–28

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

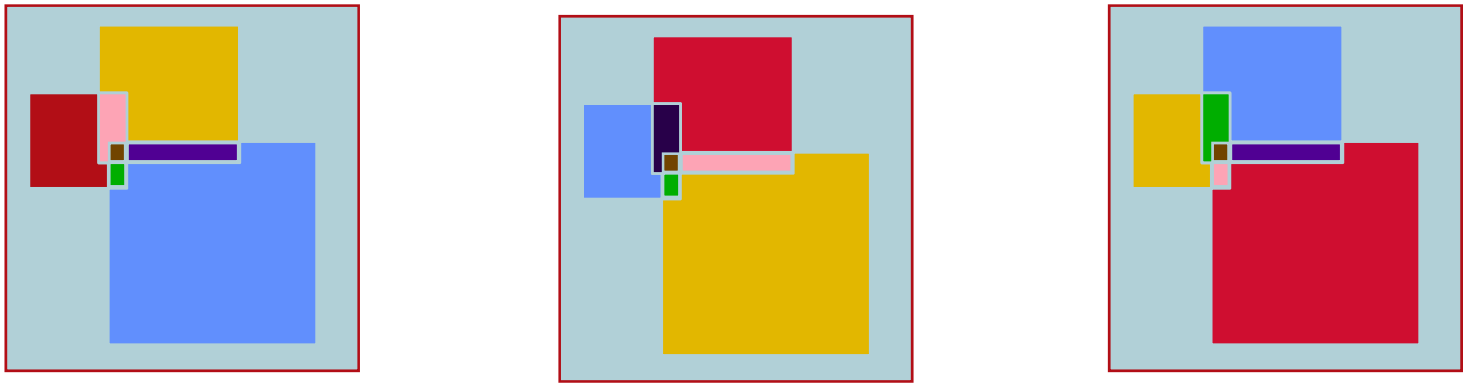
Multiple-mechanism Therapy:
Potential Efficacy Benefits

- Components with a different mechanism of action interact on complementary pathways of BP control[1]
- Each component can potentially neutralize counter-regulatory mechanisms
- Multiple-mechanism therapy may result in BP reductions that are additive[2]

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

Limitations of Treating with Single Mechanism of Action

Patient 1 **Patient 2** **Patient 3**



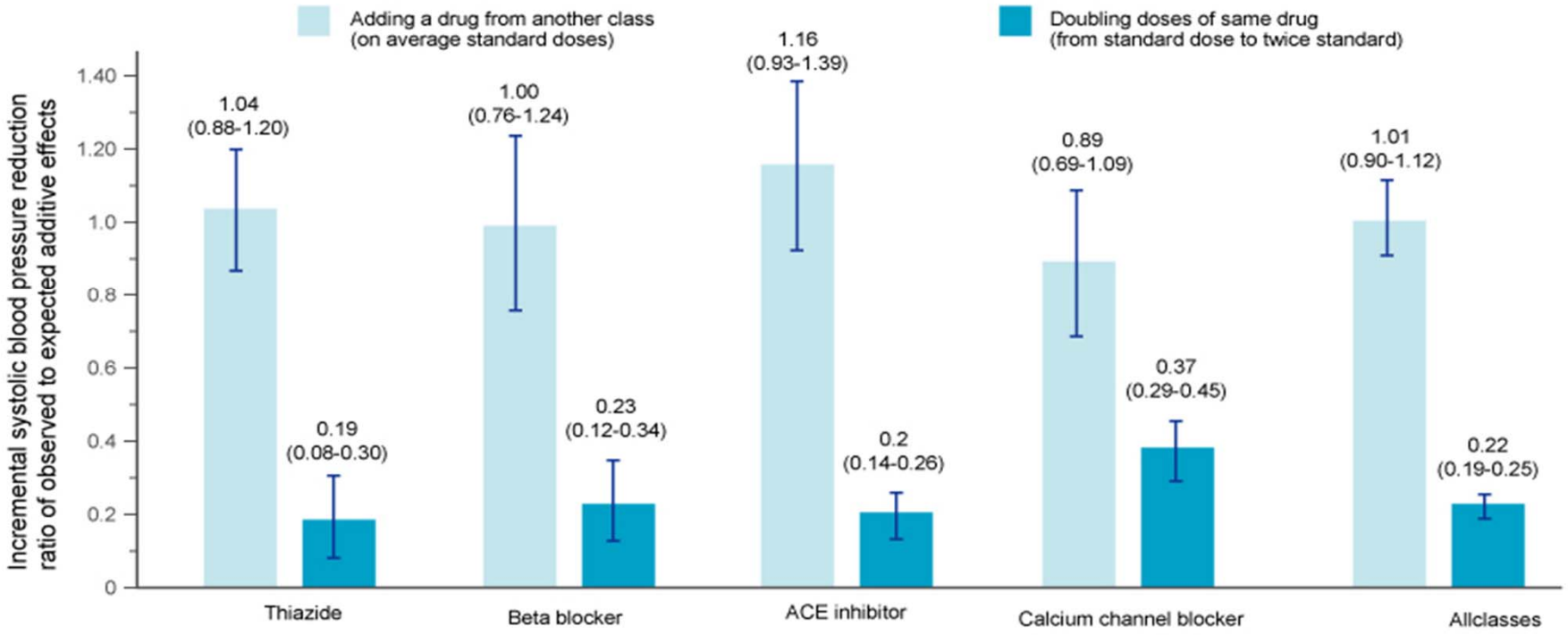
Renin-angiotensin system
Sympathetic nervous system
Total body sodium

B. Waeber, March 2007, with permission

Adding an Antihypertensive Agent

More Effective Than Titrating

combination therapy vs monotherapy
in over 11,000 patients from 42 trials



Wald et al. Am J Med 2009;122:290–300

Adding an Antihypertensive Agent
More Effective Than Titrating

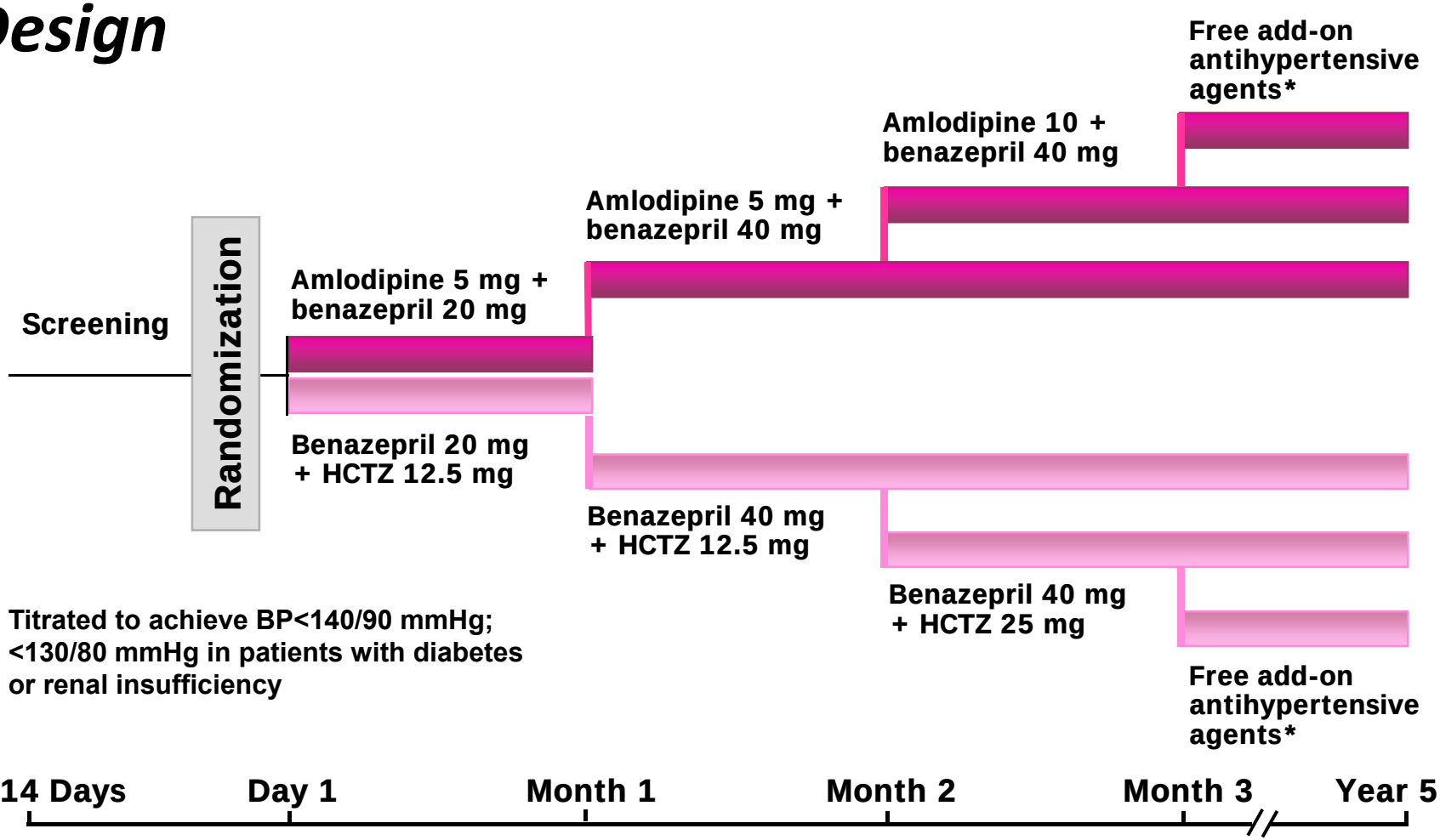
‘The extra blood pressure reduction from combining drugs from 2 different classes is approximately 5 times greater than doubling the dose of 1 drug’

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

ACCOMPLISH Study

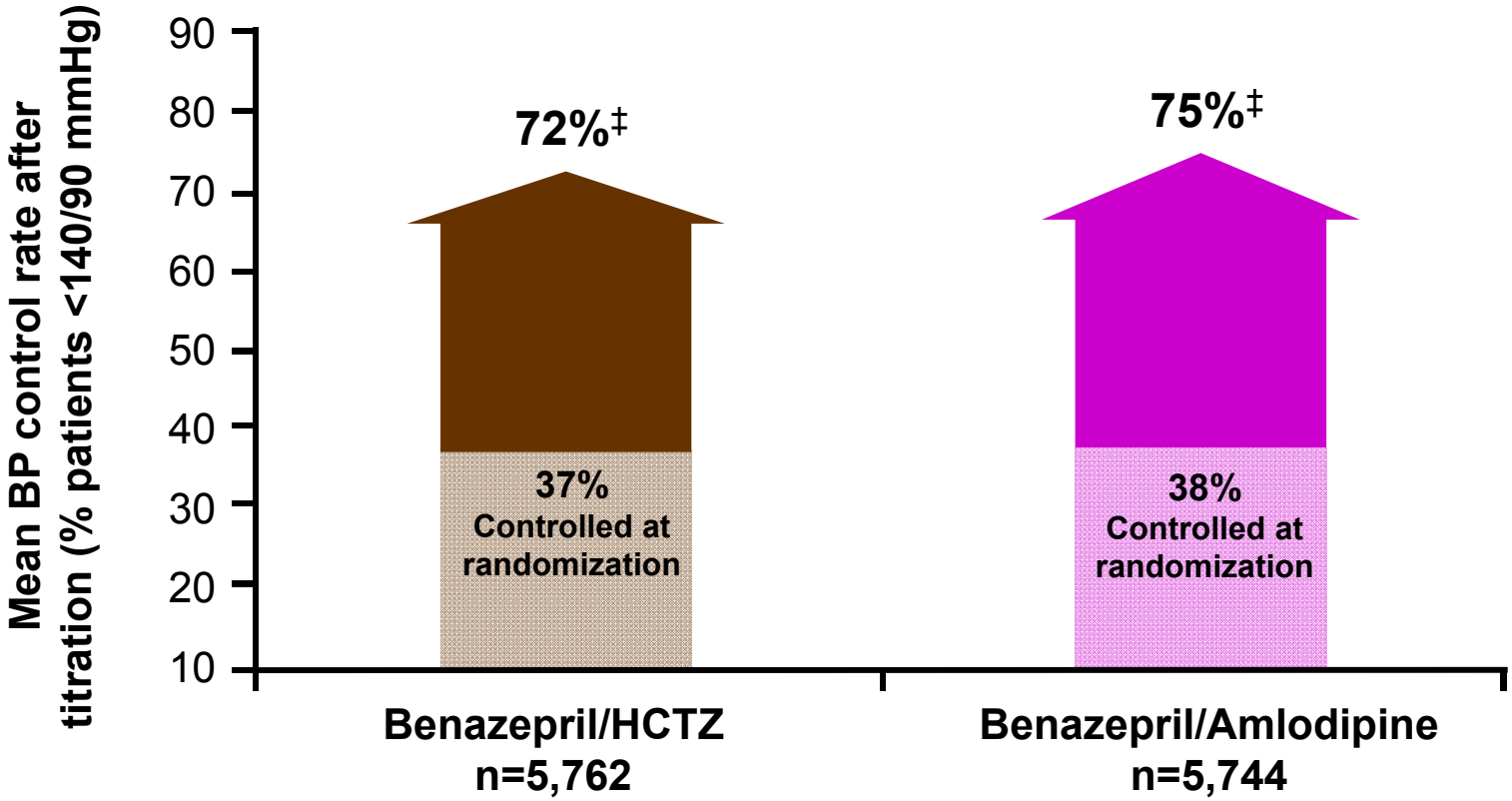
Design



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

ACCOMPLISH Study

Target achieved with Multiple Mechanism Therapy



*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

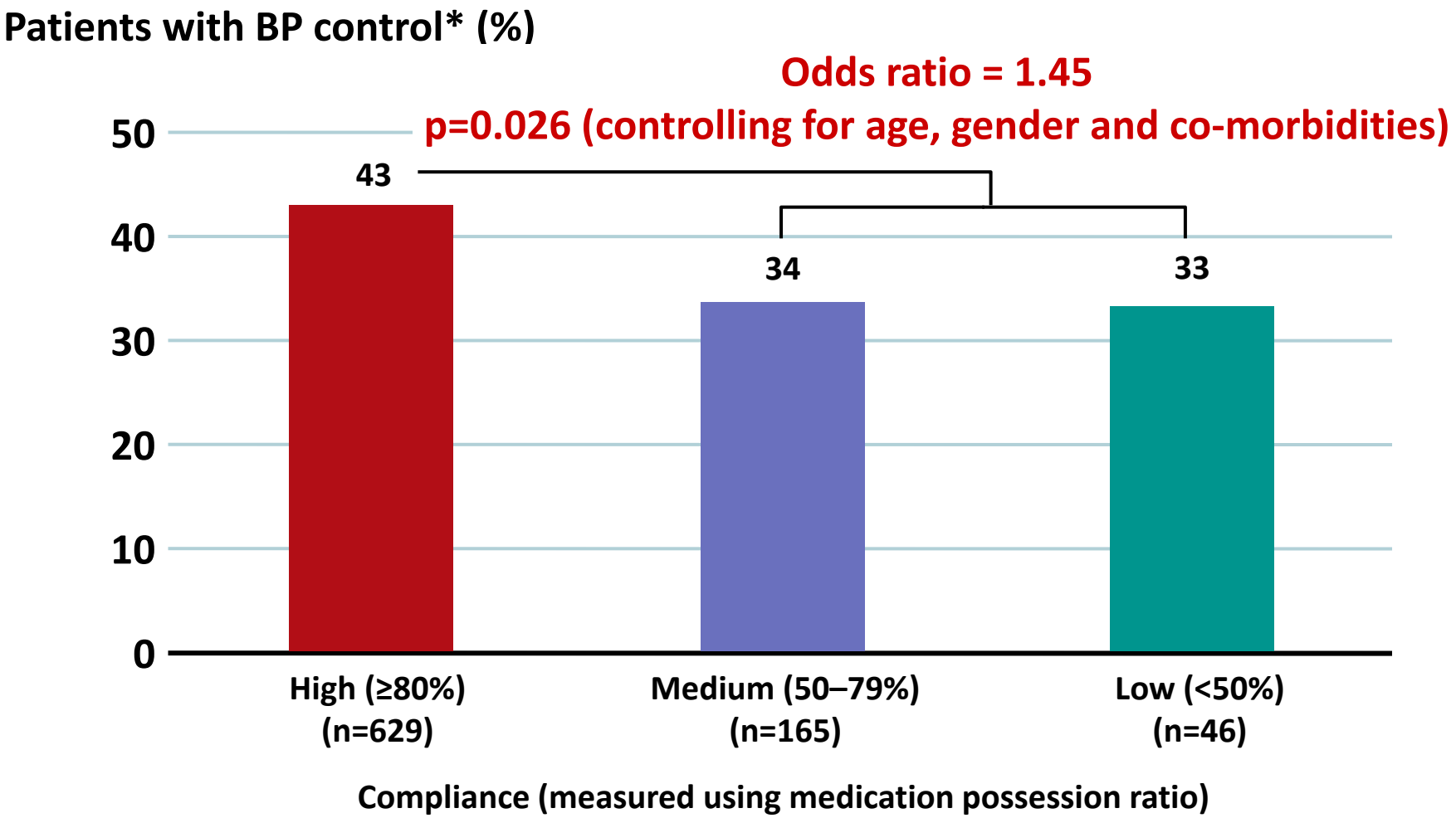
Why do we need

Multiple Mechanism Therapy:

Compliance & Prognosis

Highly Compliant Patients

More Likely to Attain BP Goal



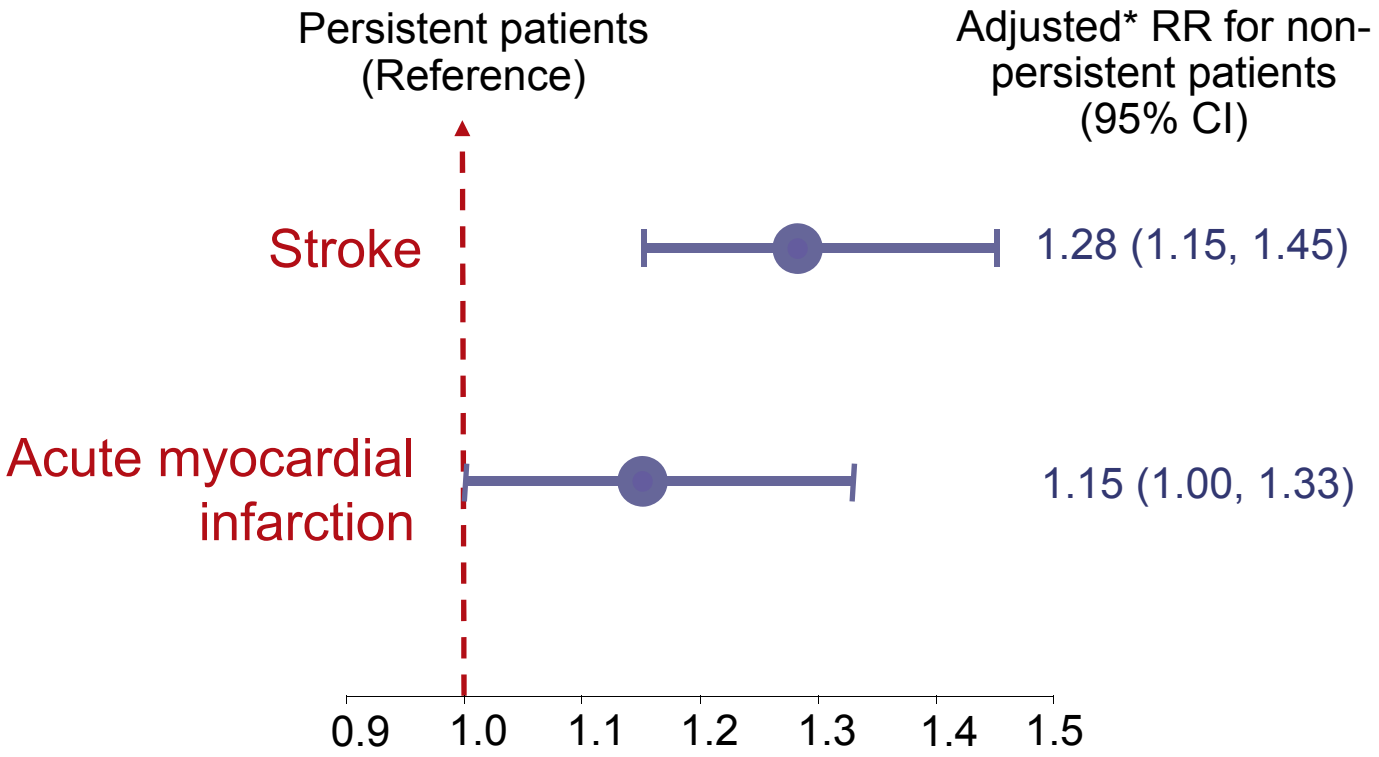
*<140/90 mmHg or <130/85 mmHg for patients with diabetes

Bramley et al. J Manag Care Pharm 2006;12:239–45

Non-persistence with Anti-HT Therapy

Increased Risk of MI and Stroke

77,193 new users of antihypertensive treatment



*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

Adherence to Anti-HT and CV Morbidity

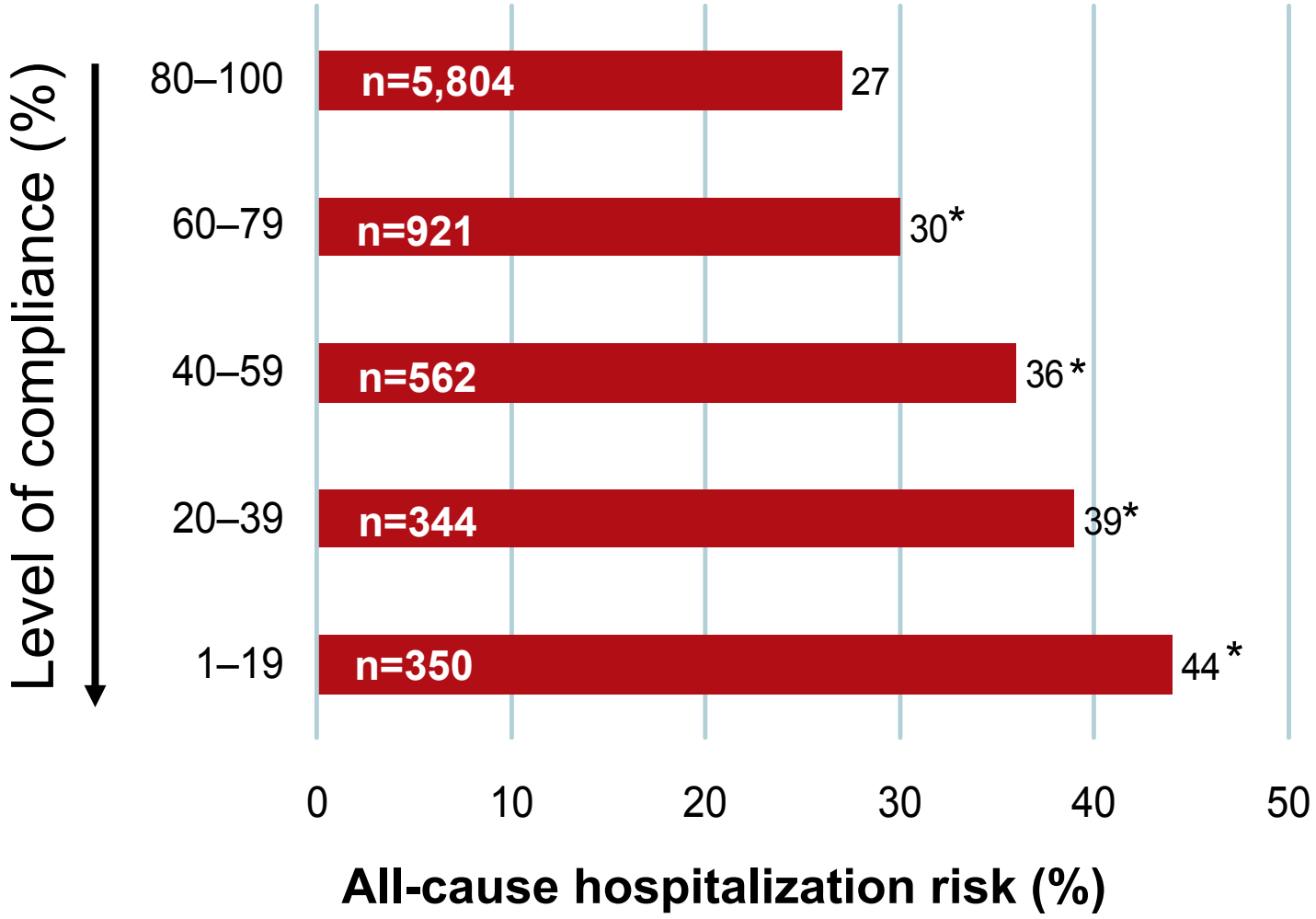
Among 18,806 Newly Diagnosed

Adherence Within 6 mo After Diagnosis	HR* (95% CI)	*P*
Model 1†		
Low (PDC <40%)	1.00	<0.001§
Intermediate (PDC, 40% to 79%)	0.87 (0.73–1.03)	0.117
High (PDC ≥80%)	0.50 (0.35–0.69)	<0.001
Model 2†		
Low (PDC <40%)	1.00	<0.001§
Intermediate (PDC, 40% to 79%)	0.86 (0.71–1.03)	0.109
High (PDC ≥80%)	0.62 (0.40–0.96)	0.032

Circulation. 2009 ;120:1598-1605

Better Compliance with Antihypertensive

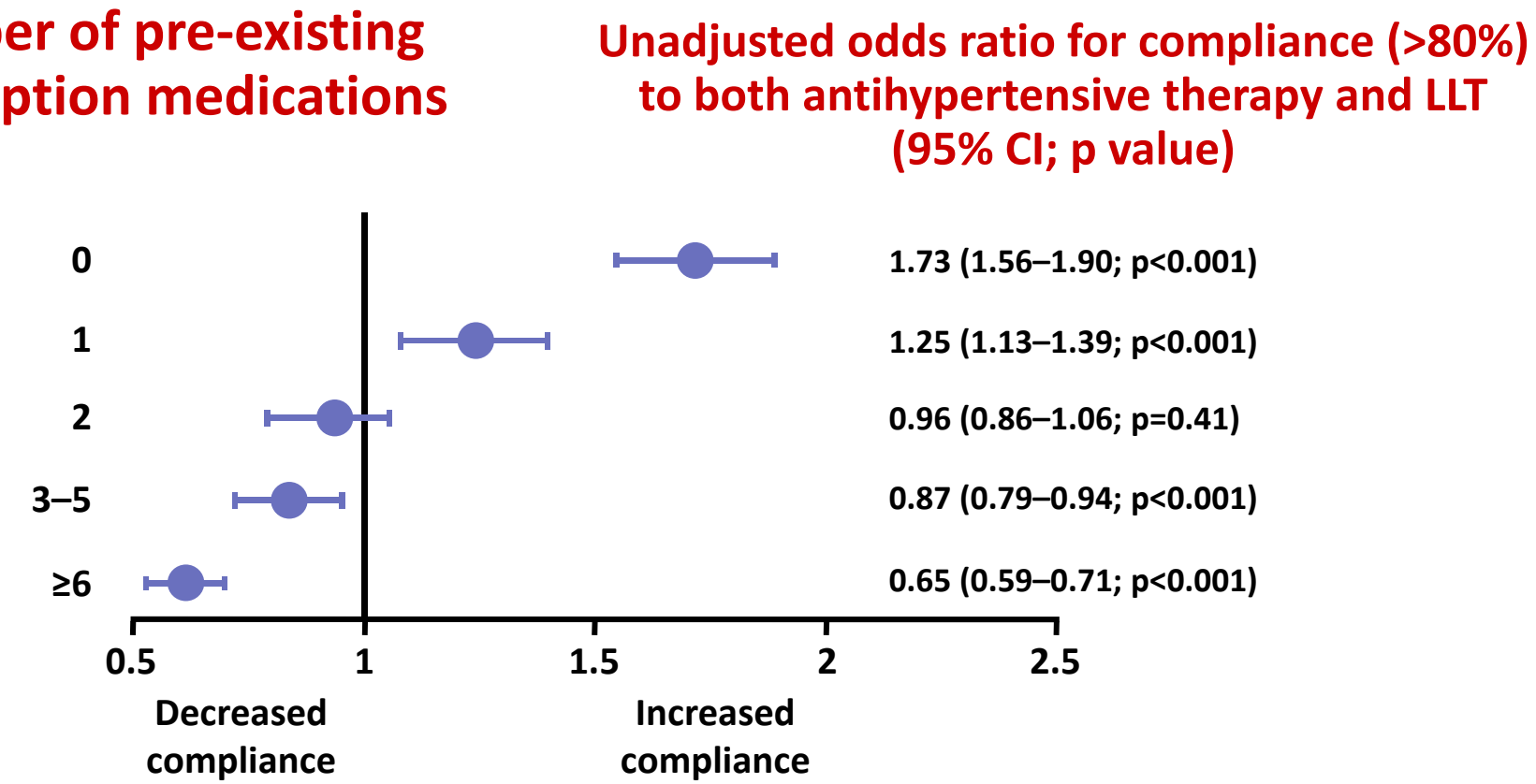
Lower Risk of Hospitalization



*p<0.05 vs 80–100% compliant group

Sokol et al. Med Care 2005;43:521–30

Compliance Decreases
as the Number of Medications Increases



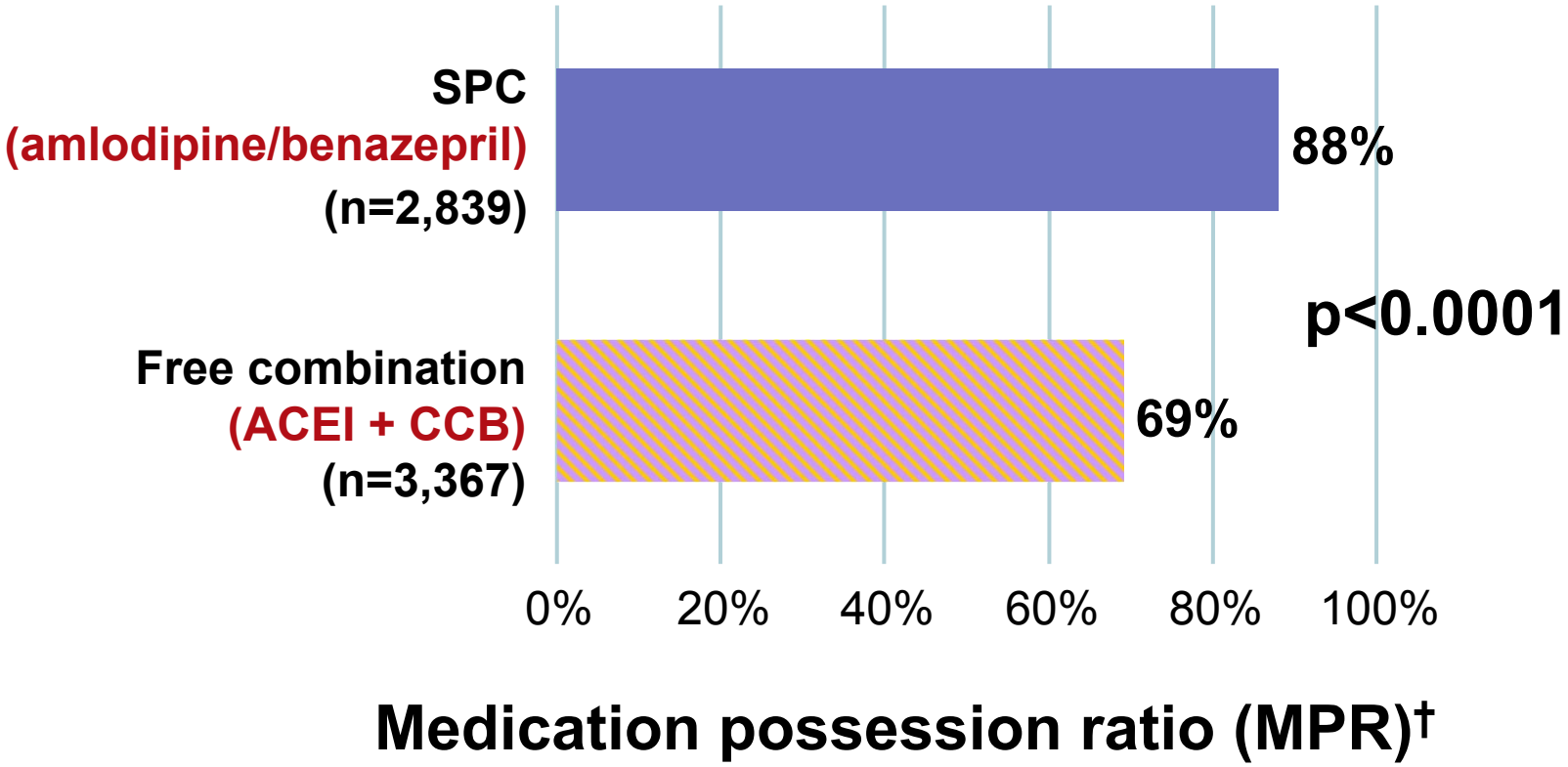
Retrospective cohort study of MCO population. N=8,406 patients with hypertension who added antihypertensive therapy and LLT to existing prescription medications within a 90-day period. Compliance to concomitant therapy: sufficient antihypertensive and LL prescription medications to cover ≥80% of days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

CI=confidence interval; LLT = lipid-lowering therapy

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

Improved Compliance with Single-pill Combination

Vs. Free-combination Therapy



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

ACEI = angiotensin-converting enzyme inhibitor; CCB = calcium channel blocker

Gerbino, Shoheiber.
Am J Health System Pharm 2007;64:1279–83

Multiple-mechanism Therapy:
Potential Tolerability Benefits

Multiple-mechanism therapy

- improved tolerability profile [1,2]

- Components of multiple-mechanism therapy can be given at lower dosages to achieve BP goal than those required as monotherapy: therefore better tolerated[1,2]

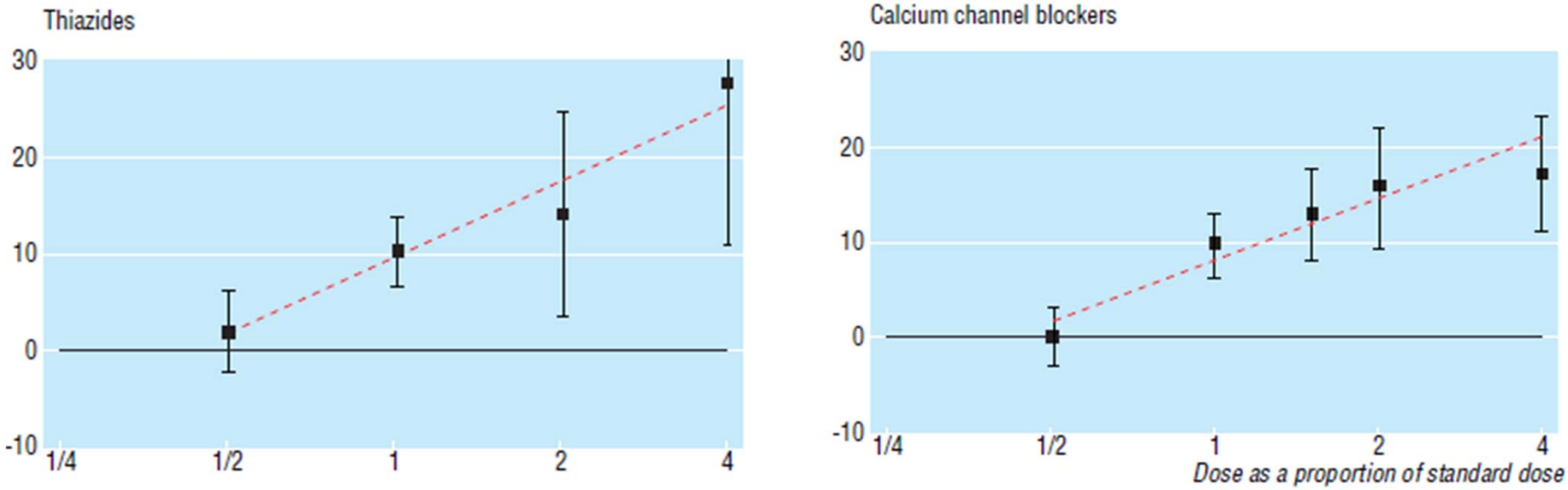
- Compound-specific adverse events can be attenuated [1,2]
  - Renin-angiotensin-aldosterone system blockers may attenuate the edema caused by ca^{++} channel blockers

[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

Lower dose Multiple-mechanism therapy

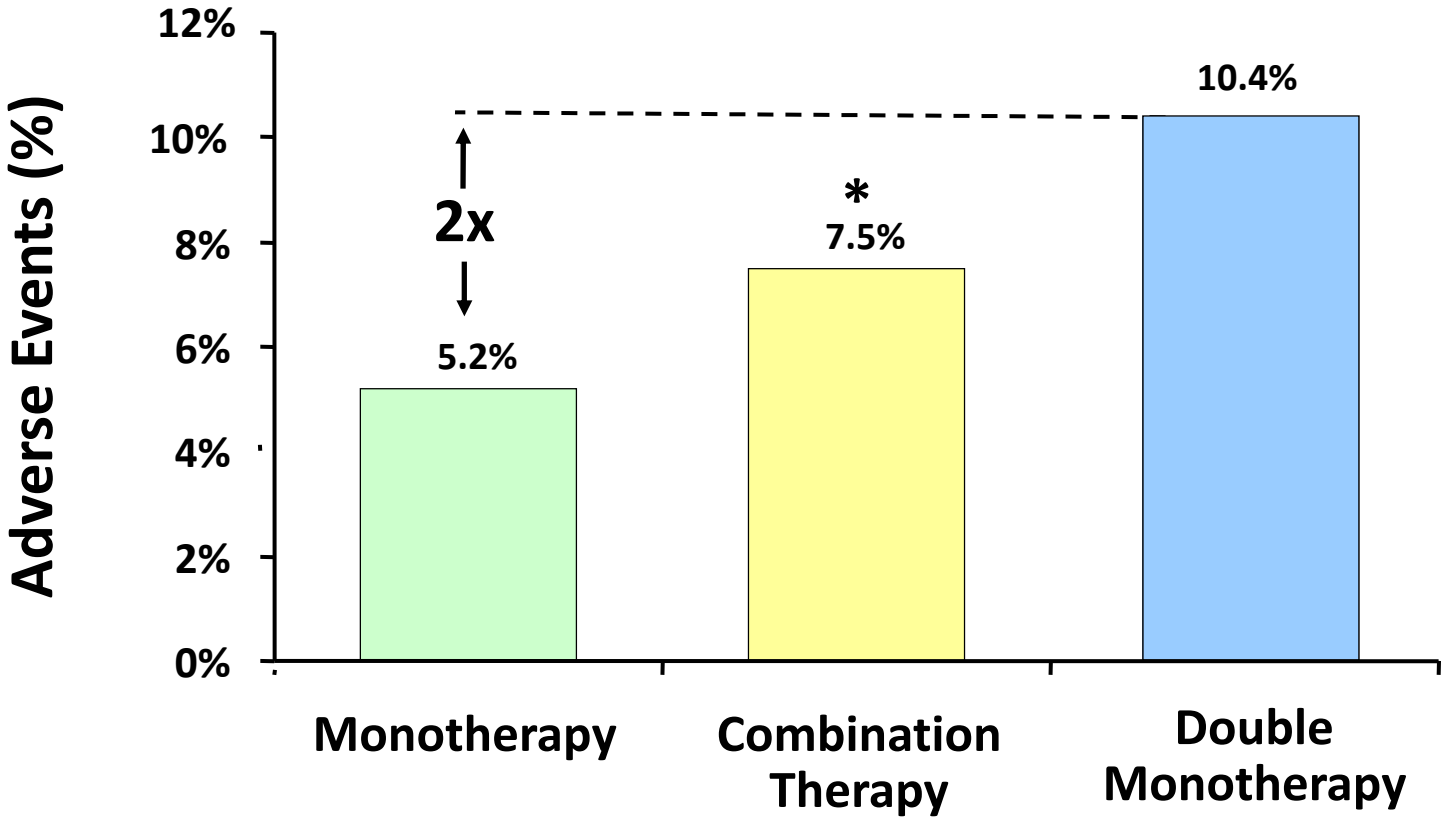
- improved tolerability profile components[1,2]



[1]Sica. Drugs 2002;62:443–62
[2]Quan et al. Am J Cardiovasc Drugs 2006;6:103–13
BMJ 2003;326:1427-31

Multiple-mechanism Therapy:
Reducing Adverse Effects

Combination Therapy Meta-Analysis



******P*<0.03 combination therapy vs expected additive effect**

Law MR, *et al. BMJ.* 2003;326:1427

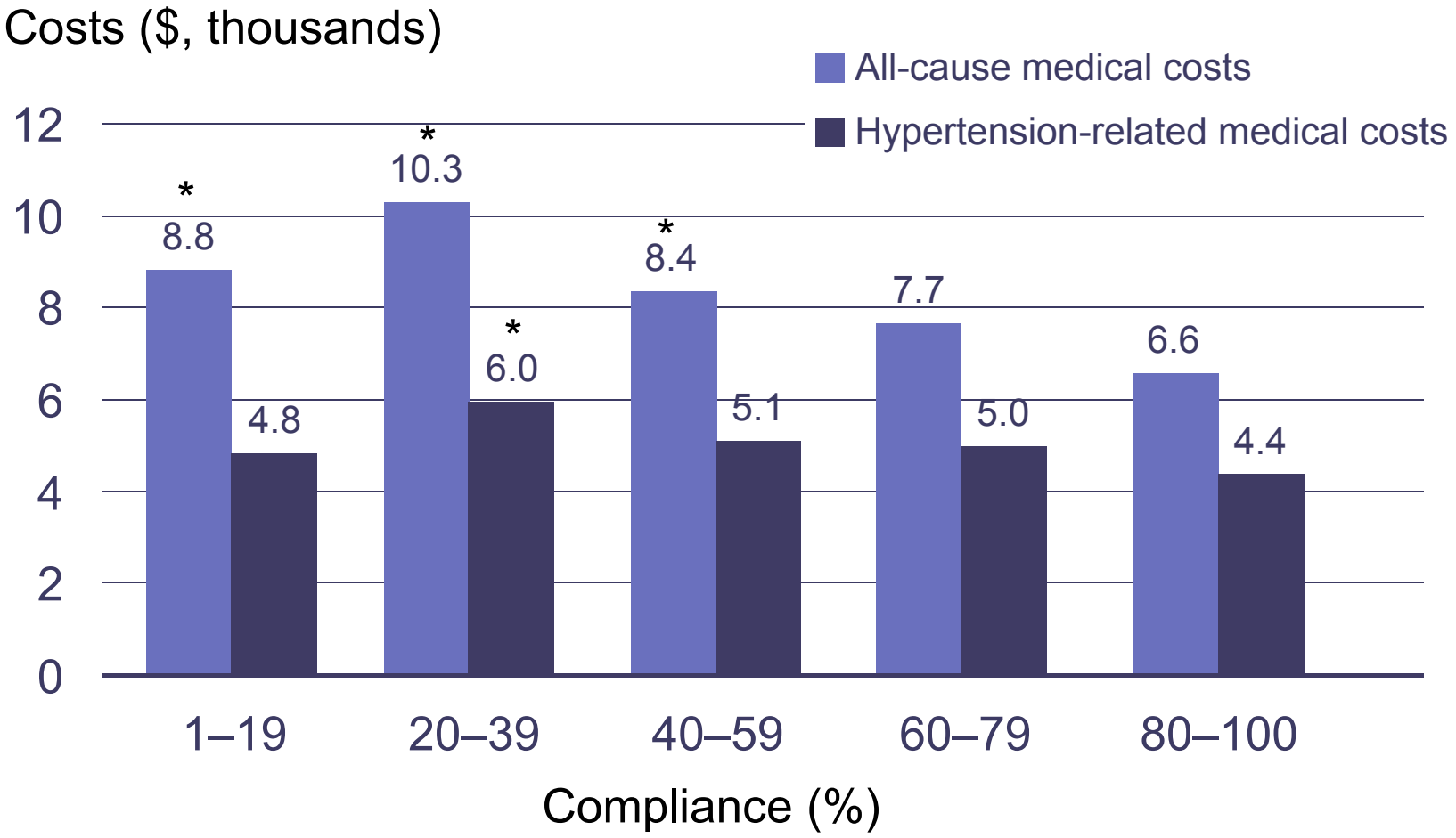
Why do we need

Multiple Mechanism Therapy:

Economics

Better Compliance with Anti-HT Therapy

Decrease in Medical Costs

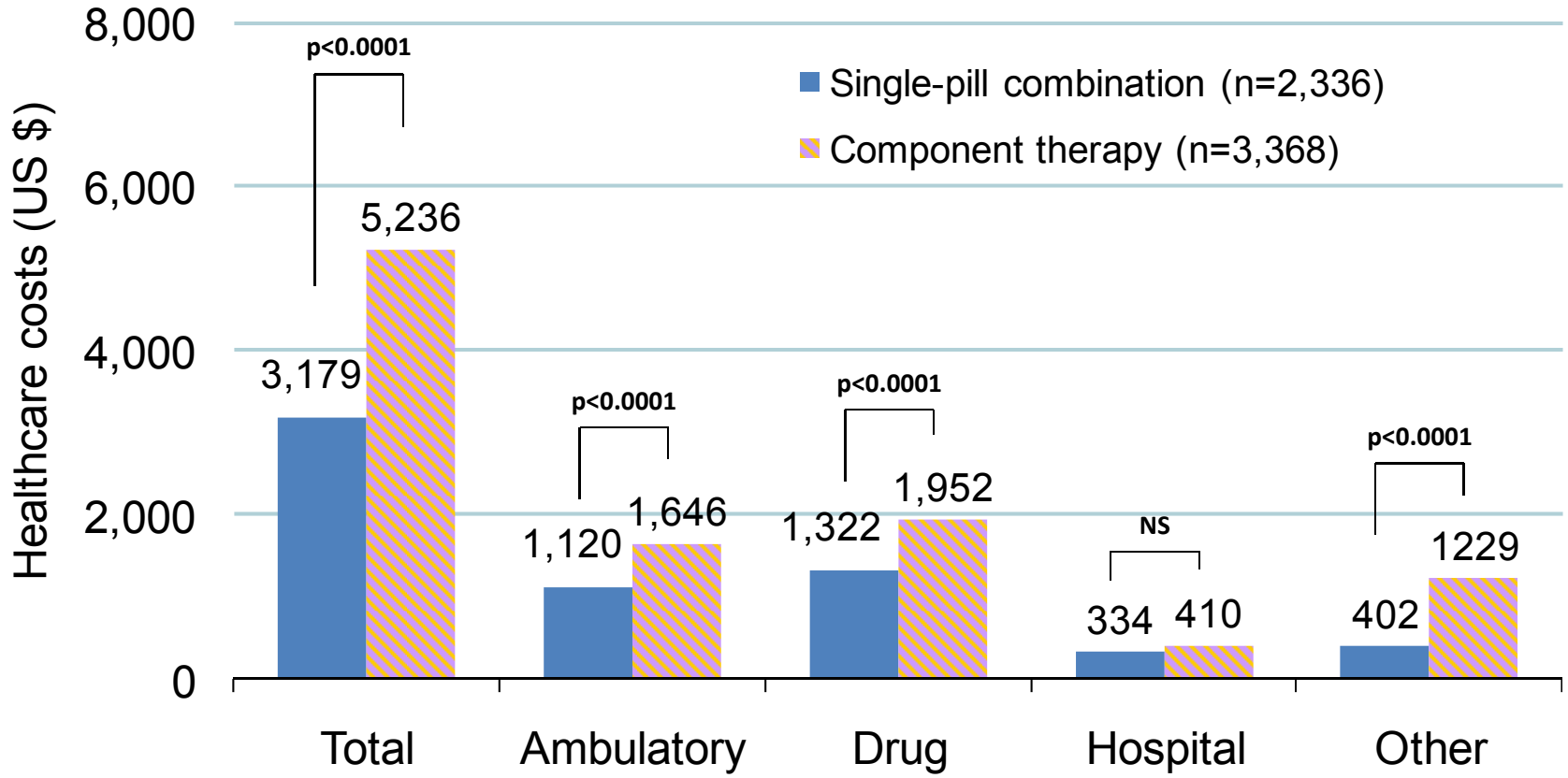


*p<0.05 vs. 80–100% compliant group

Sokol et al. Med Care 2005;43:521–30

Patients with Fixed dose Combinations:

Use Less Resource



NS = not significant

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

Multiple Mechanism Therapy:

Treatment Guidelines

Initiating Combination Therapy Early in Patients with Stage 2 Hypertension or High Risk

- JNC 7 guidelines state[1]:

  '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...'

- 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.'

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

European Guidelines now Recommend
Use of Single-pill Combination Therapy

- 2009 European guidelines

  *'Whenever possible, **use of fixed dose (or single pill) combinations** should be preferred, because simplification of treatment carries advantages for compliance to treatment'*

Mancia et al. Blood Press 2009;18:308–47

Fixed dose combination Advantages:
Vs. Free Combinations

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

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

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

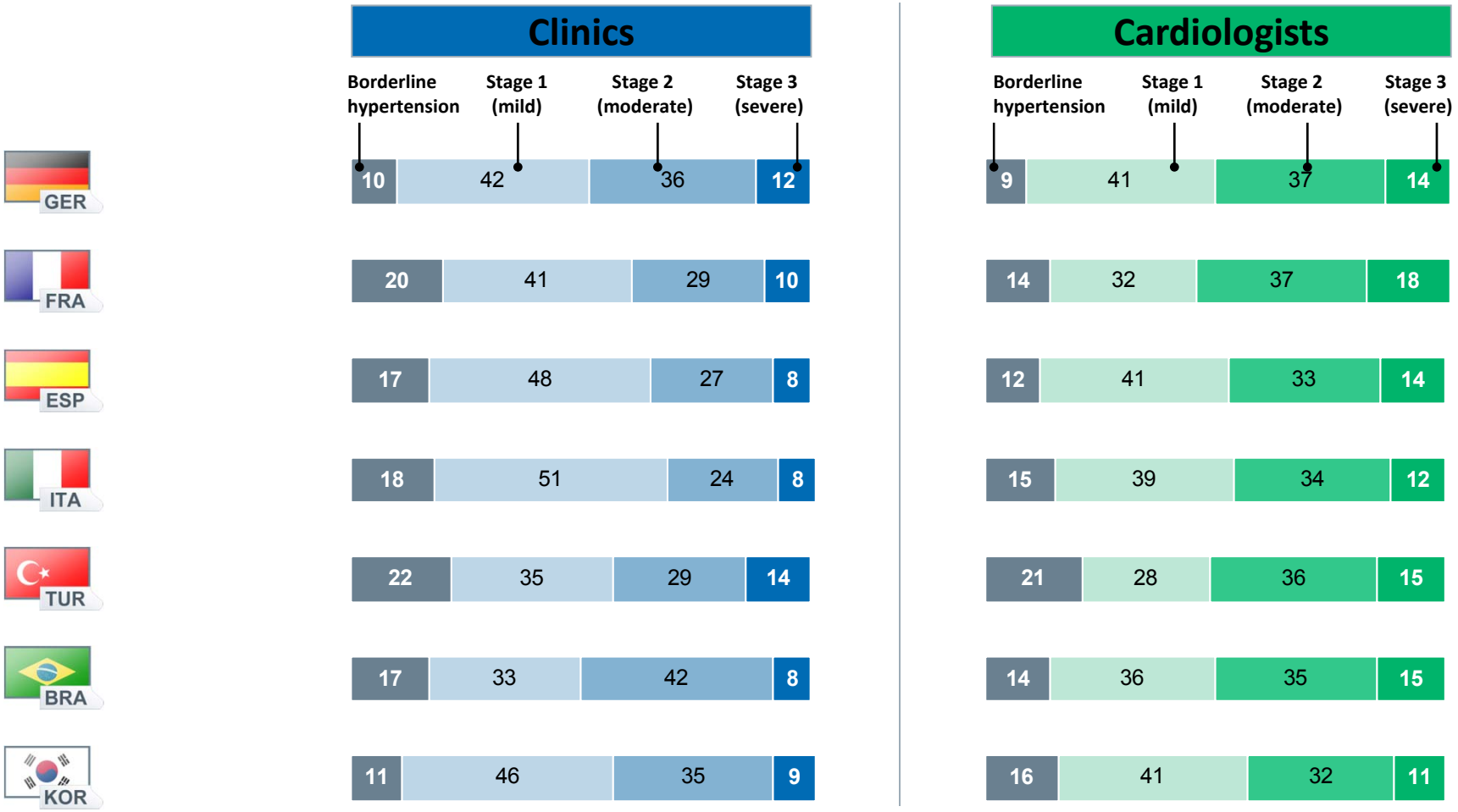
Multiple Mechanism Therapy:

Korean Situation

HTN patients by severity degree

> 40 % of patients are suffered from stage 2 or 3

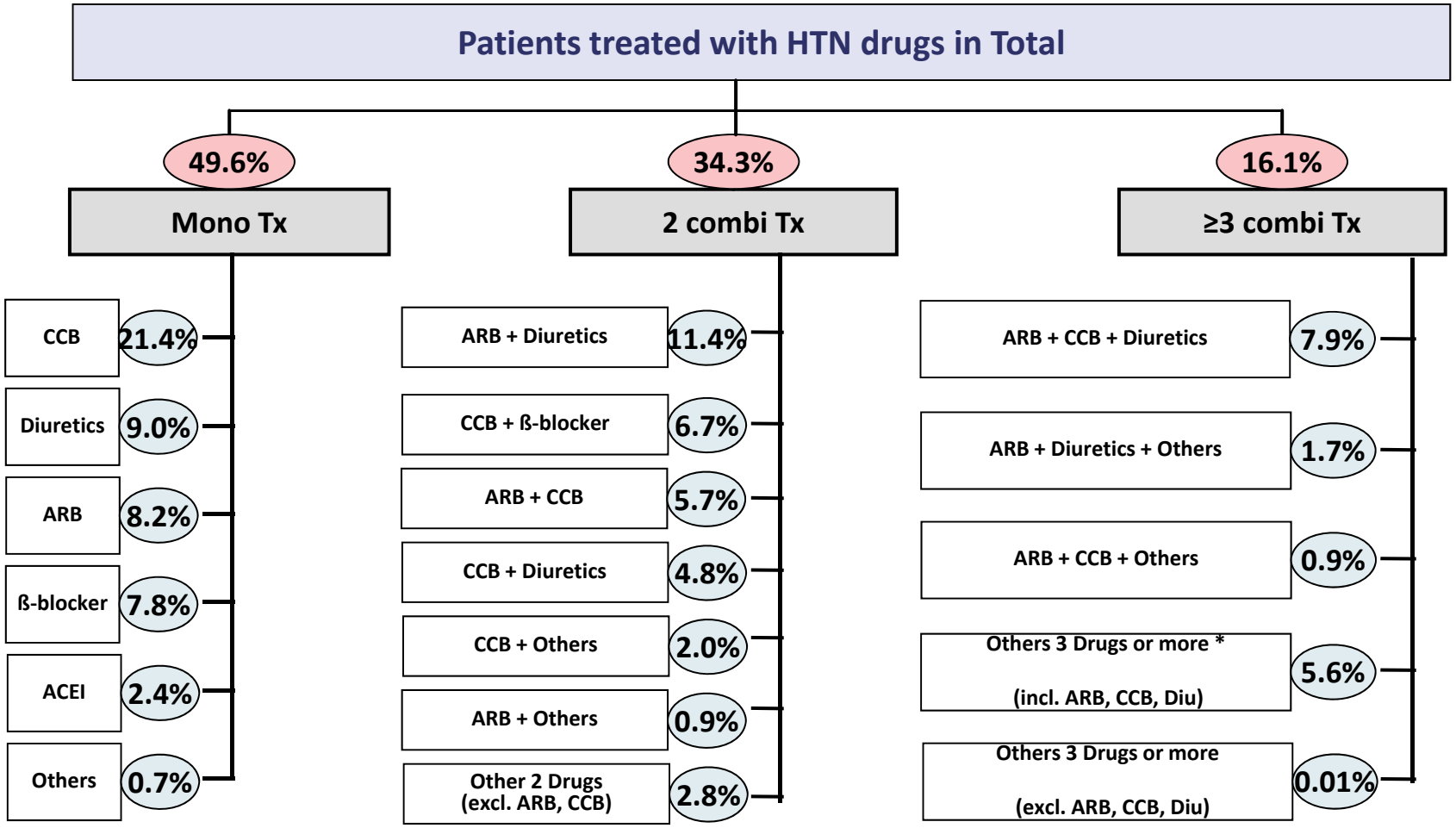
Treated HTN-patients by severity degree (in % of patients)



Data Source) Global CV HTN Tracker study (Nov, 2008)

Current treatment pattern:

Many patients need more than 2 agents



**Combination Therapy = Free combination + SPC (Single Pill Combination)*

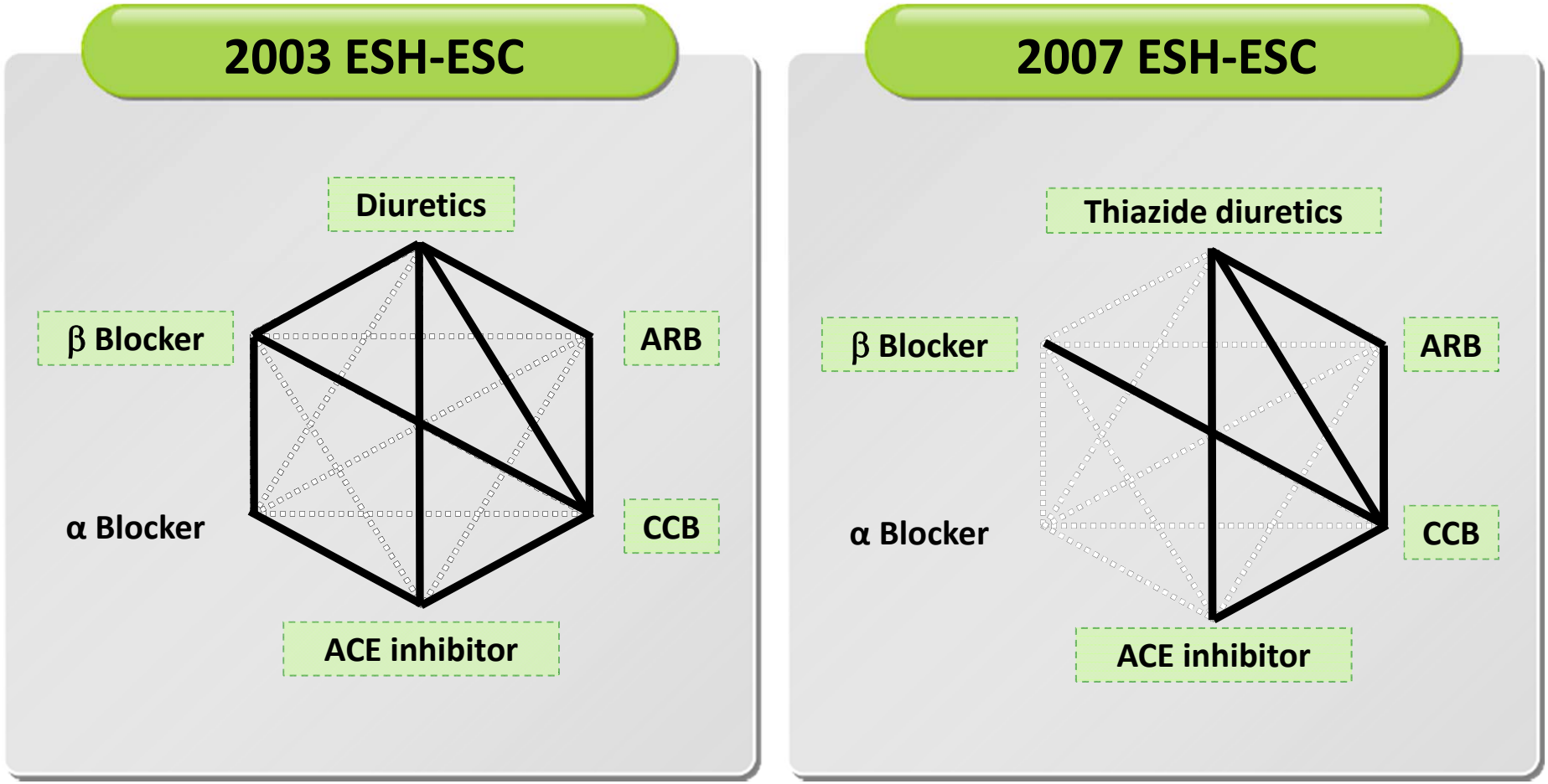
URIS, 1Q 2009

Multiple Mechanism Therapy:

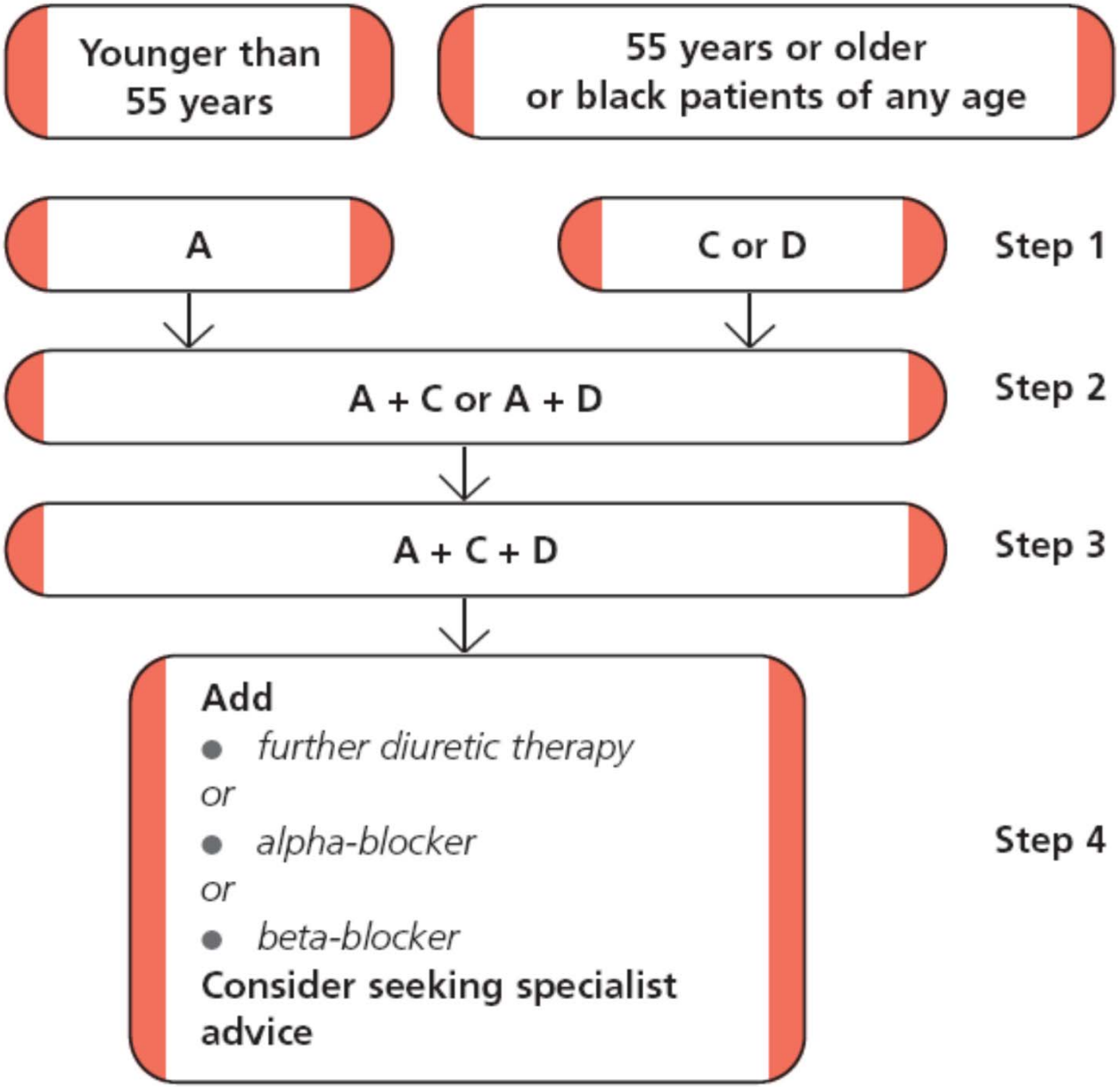
Which Single-pill Combinations?

2007 ESH/ESC Guidelines:

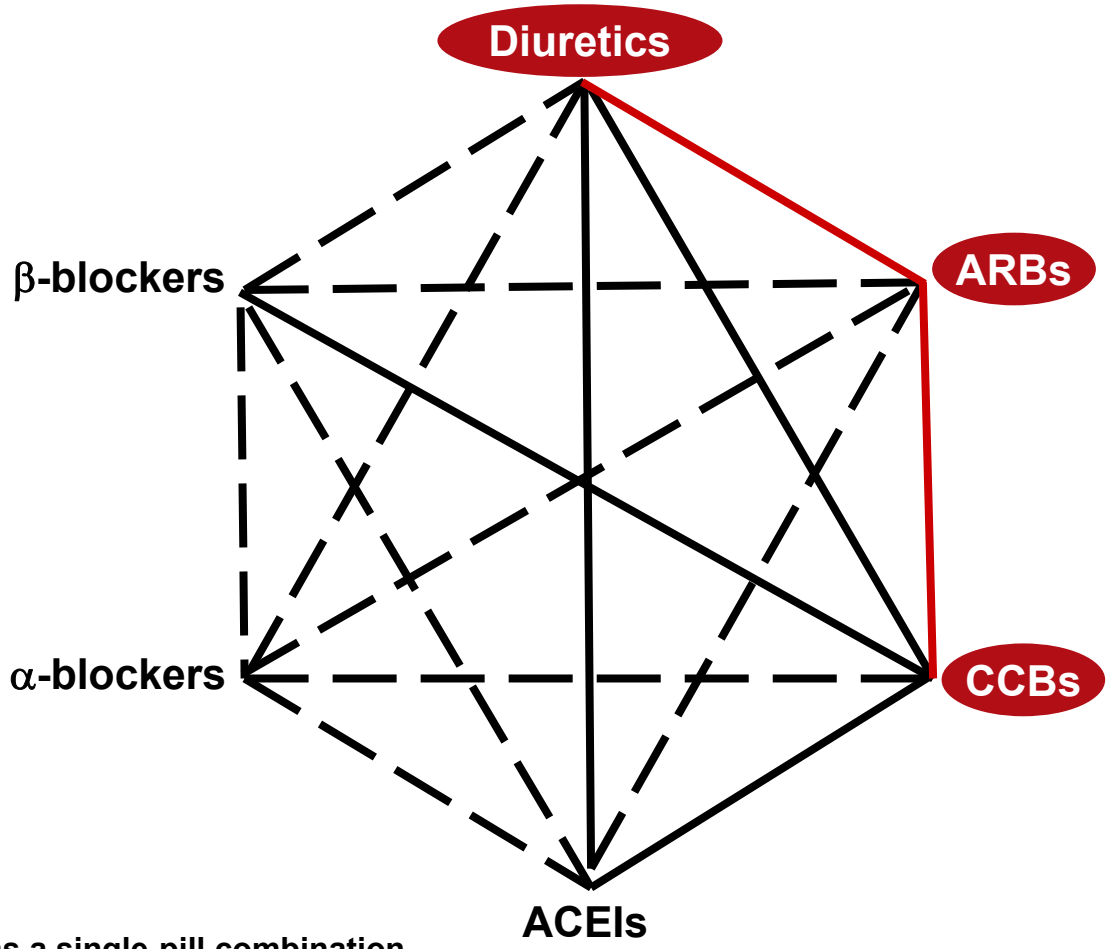
Possible Combinations



A/CD rule


Younger than 55 years
55 years or older or black patients of any age
A
C or D
Step 1
A + C or A + D
Step 2
A + C + D
Step 3
Add
• further diuretic therapy
or
• alpha-blocker
or
• beta-blocker
Consider seeking specialist advice
Step 4

ESH–ESC Recommendations for Combining BP-lowering Drugs and Availability as Single-pill Combinations[1]



- ARB/diuretic and ARB/CCB are rational combinations available in a single pill[1,2]

ACEI = angiotensin-converting enzyme inhibitor;
ARB = angiotensin receptor blocker; CCB = calcium channel blocker

[1]Mancia et al. J Hypertens 2007;25:1105–87;
[2]Mancia et al. Blood Press 2009;18:308–47

Which Single-pill Combinations?

RAAS Blocker Plus Diuretic?

HCTZ Has Been Widely Studied in Hypertension

- First-line recommendation in uncomplicated HT by JNC-7 [1]
- Useful for enhancing efficacy in multi-drug regimens, including in combination with ARBs and CCBs[1]
- The ALLHAT Study: supporting the use of thiazide in HT [2]
- HCTZ has been shown to enhance antihypertensive efficacy when combined with valsartan[3]
  - More than 4,000 patients have been included in the valsartan/HCTZ groups[3]
  - HCTZ resulted in additive decreases in systolic and diastolic BP when combined with valsartan[3]

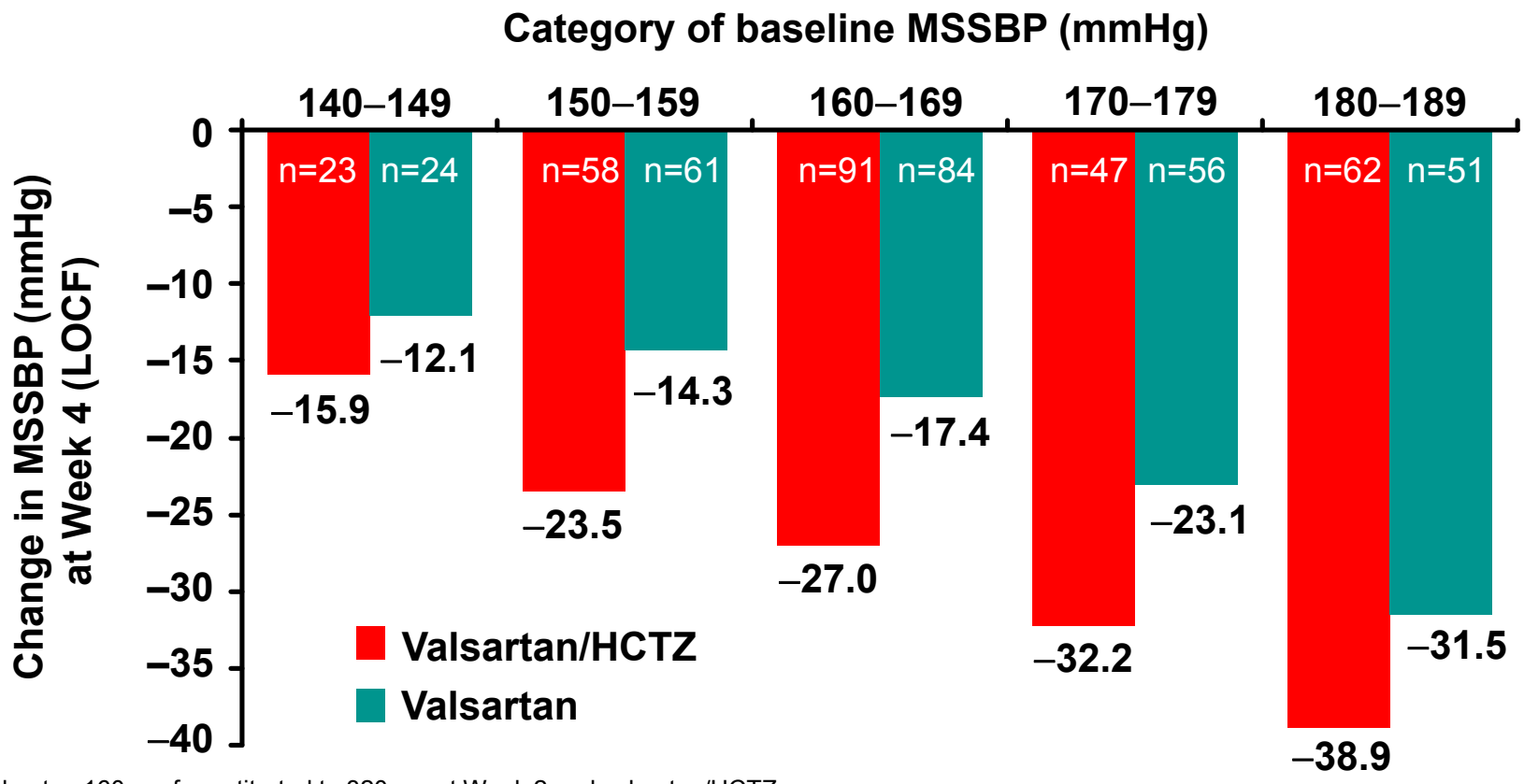
ALLHAT = Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; ARB = angiotensin receptor blocker; CCB = calcium channel blocker; HCTZ = hydrochlorothiazide; JNC = Joint National Committee

[1]Chobanian et al. JAMA 2003;289:2560–72
[2]The ALLHAT investigators. JAMA 2002;288:2981–97
[3]DIOVAN HCT prescribing information. Novartis July 2008

ARB/HCTZ Provides

Systolic BP Reductions Across HT Severities

6-week, double-blind, multicentre, forced-titration study



*Valsartan 160 mg force-titrated to 320 mg at Week 2 and valsartan/HCTZ 160/12.5 mg force-titrated to 160/25 mg and 320/25 mg at Weeks 2 and 4, respectively; BP = blood pressure; DBP = diastolic BP; SBP = systolic BP; MSSBP = mean sitting SBP; LOCF = last observation carried forward; C-DITT = Co-Valsartan Initial Therapy Trial

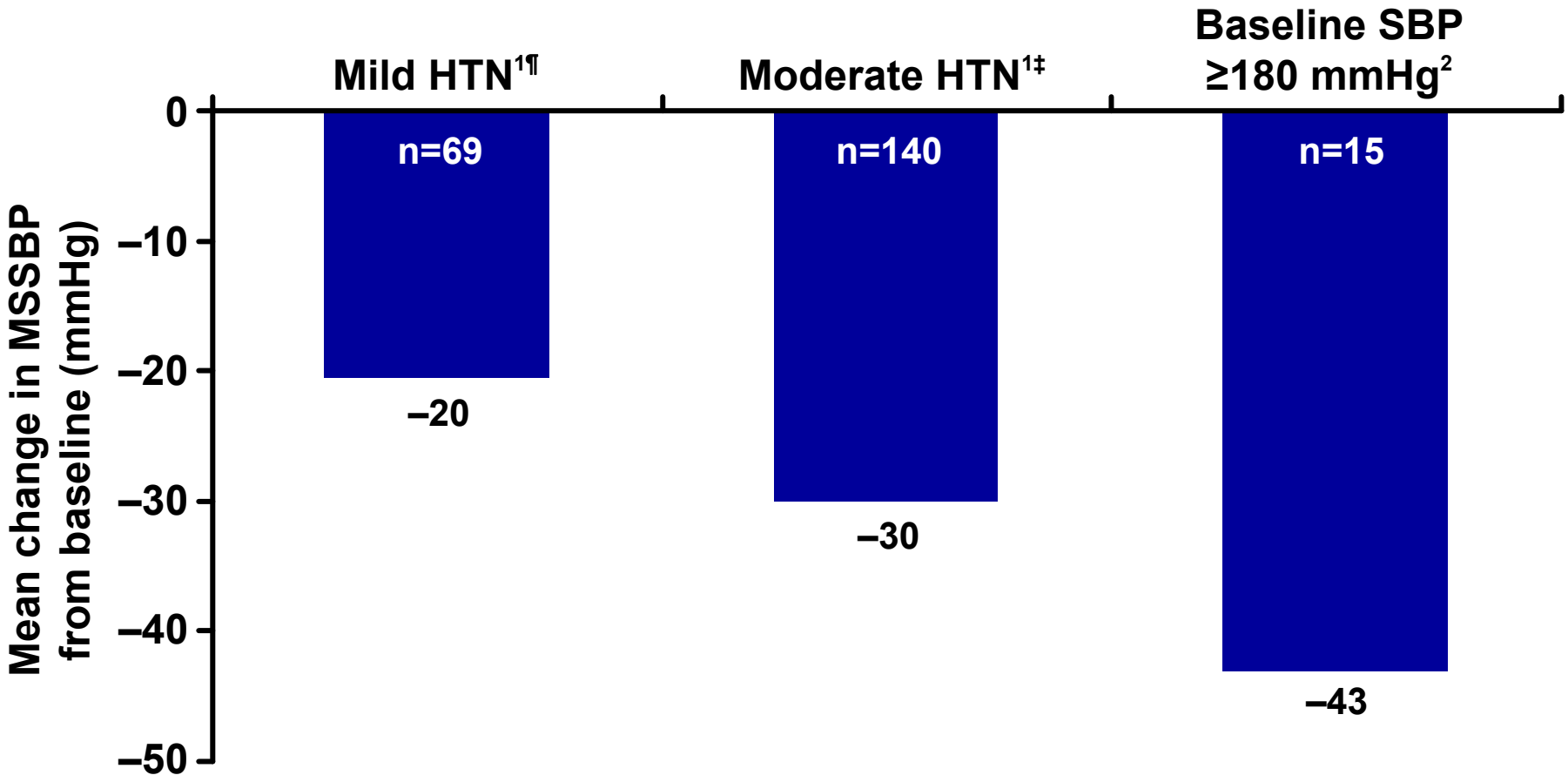
Calhoun et al. Curr Med Opin Res 2008;24:2303–11

Which Single-pill Combinations?

RAAS Blocker Plus CCB?

Amlodipine/Valsartan

Powerful BP Reductions Across HT Severities

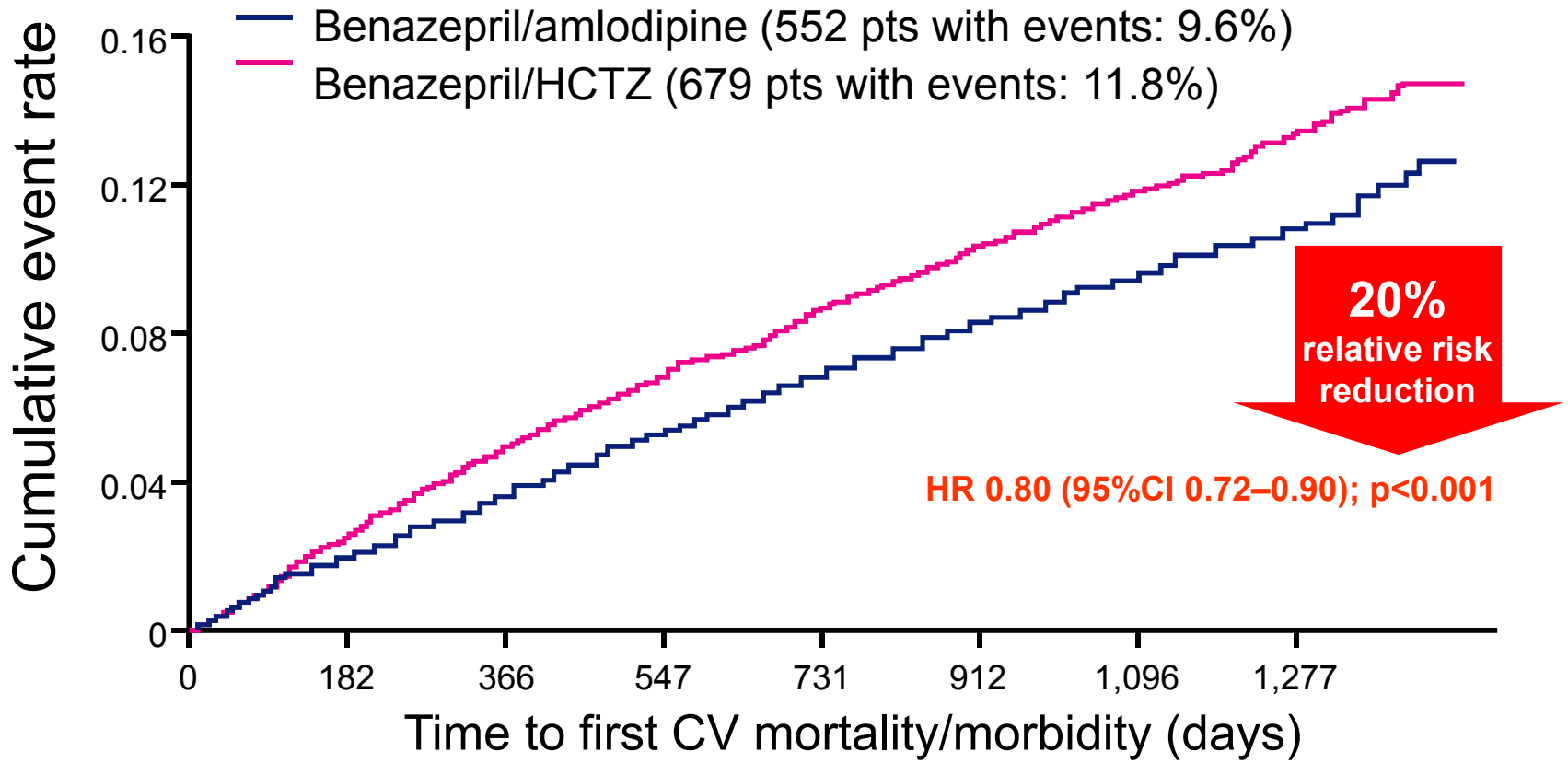


¶DBP 90–99 mmHg, SBP 140–159 mmHg
‡DBP ≥100 mmHg, SBP ≥160 mmHg
BP = blood pressure; DBP = diastolic BP;
SBP = systolic BP; MSSBP = mean sitting SBP

[1]Smith et al. J Clin Hypertens 2007;9:355–64 (Dose 10/160 mg)
[2]Poldermans et al. Clin Ther 2007;29:279–89 (Dose 5–10/160 mg)

ACCOMPLISH:

Superior CV Outcomes with RAAS Blocker/Amlodipine



Months	0	6	12	18	24	30	36	42
Patients at risk (N)								
Benazepril/amlodipine	5,512	5,317	5,141	4,959	4,739	2,826	1,447	
Benazepril/HCTZ	5,483	5,274	5,082	4,892	4,655	2,749	1,390	

ACCOMPLISH = Avoiding Cardiovascular events through COMbination therapy in Patients LIving with Systolic Hypertension; CV = cardiovascular; RAAS = renin-angiotensin-aldosterone system; HCTZ = hydrochlorothiazide

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

Amlodipine

Wealth of Cardiovascular Outcomes Data

PREVENT[1] 825 coronary heart disease (CAD) patients (≥30%): Multicentre, randomized, placebo controlled	Primary outcome: No difference in mean 3 yr coronary angiographic changes vs placebo 35% ↓ hospitalization for HF + angina 43% ↓ revascularization procedures
CAMELOT[2] 1,991 CAD patients (>20%): Double-blind, randomized study vs placebo and enalapril 20 mg	Primary outcome: 31% ↓ in CV events vs placebo 42% ↓ hospitalization for angina 27% ↓ coronary revascularization
ASCOT-BPLA/CAFE[3,4] 19,257 hypertensive patients: Multicentre, randomized, 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 hypertensive patients: Randomized, prospective study vs lisinopril	Primary outcome: No difference in composite of fatal CHD + non-fatal MI vs lisinopril 6% ↓ combined CV disease 23% ↓ stroke

[1]Pitt et al. Circulation 2000;102:1503–10; [2]Nissen et al. JAMA 2004;292:2217–26; [3]Dahlof 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

ARB

Wealth of Cardiovascular Outcomes Data

VALUE[1] 15,245 high-risk hypertension patients; Double-blind, randomized study vs amlodipine	No difference in composite of cardiac mortality and morbidity (primary) 23% ↓ new-onset diabetes
VALIANT[2] 14,703 post-myocardial infarction (MI) patients; Double- blind, randomized 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 (HF) II–IV patients; Double-blind, randomized study vs placebo	13% ↓ morbidity and mortality (primary) ↓ left ventricular remodeling 37% ↓ atrial fibrillation occurrence ↓ HF signs/symptoms 28% ↓ HF hospitalization
JIKEI HEART[6] 3,081 Japanese patients on conventional treatment for hypertension, coronary heart disease (CHD), HF or combination of these; Multicentre, randomized, controlled trial comparing addition of valsartan vs non-angiotensin Type 2 receptor blocker (ARB) to conventional treatment	39% ↓ composite CV mortality and morbidity 40% ↓ Stroke/transient ischemic attack (TIA) 47% ↓ Hospitalization for HF 65% ↓ Hospitalization 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/transient ischemic attack (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;30:2461–9

Summary

- A good proportion of patients require 2 or more antihypertensive medications to reach BP goal[1–3] , especially in the era of global cardiovascular risk management.

- When combination therapy is required,
  - the use of Fixed dose combinations to improve adherence[4]

- When combination therapy is required, most guidelines recommend (when there are no compelling indications)
  - For dual: a combination of a RAAS blocker and a diuretic, or a RAAS blocker and a calcium channel blocker[4]

1. UKPDS BMJ 1998:317:703–13; 2. Cushman et al. J Clin Hypertens 2002;4:393–404;
3. Jamerson et al. Blood Press 2007;16:80–86; 4. Mancia et al. Blood Pressure 2009;18:308–347;