What is the Most Powerful Solution for Hypertension Patients

Keimyung University Dongsan Medical Center

Nam, Chang-Wook

Contents

Why hypertension?

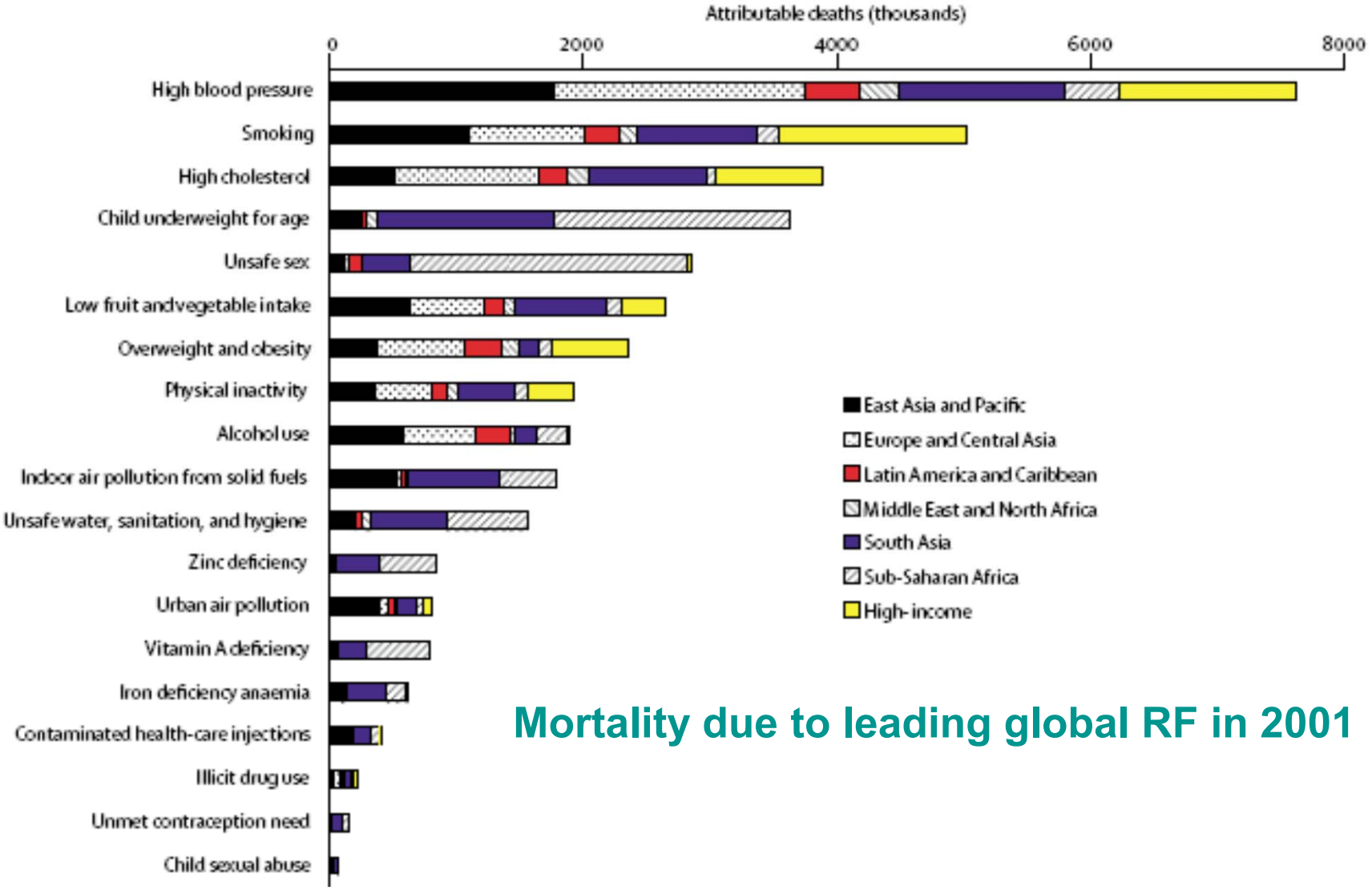
Hypertension is a Highly Prevalent Disease

Hypertension affects approximately 1 billion people worldwide

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

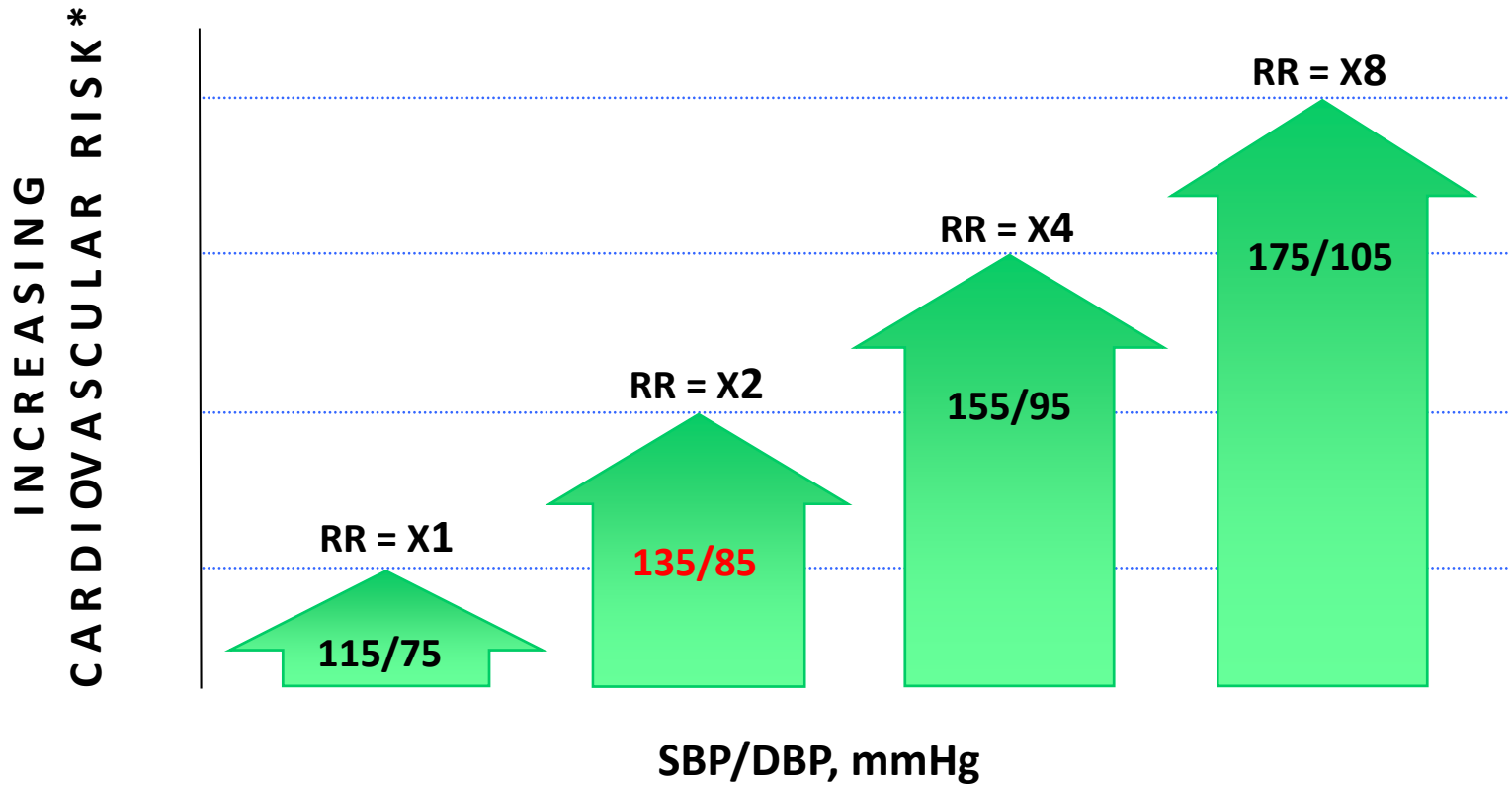
Kearney et al. Lancet 2005;365:217–23

Hypertension is No1 killer in the world



Mortality due to leading global RF in 2001

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

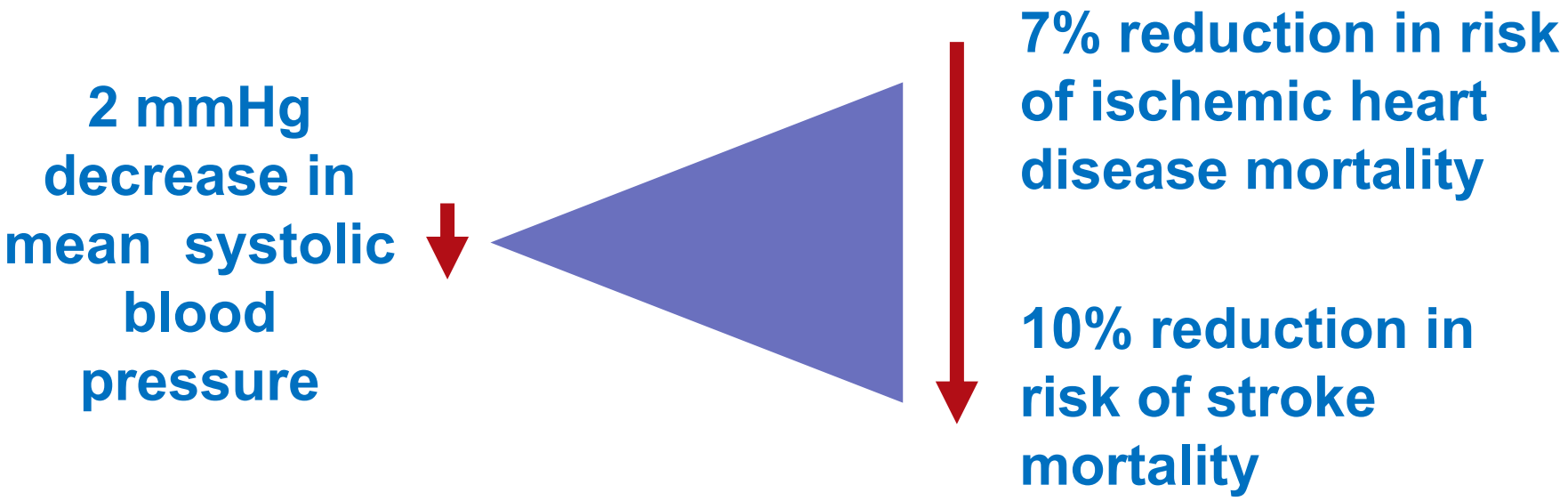


BP=blood pressure.

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

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

Blood Pressure Reduction of 2 mmHg Decreases the Risk of Cardiovascular Events by 7–10%



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

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

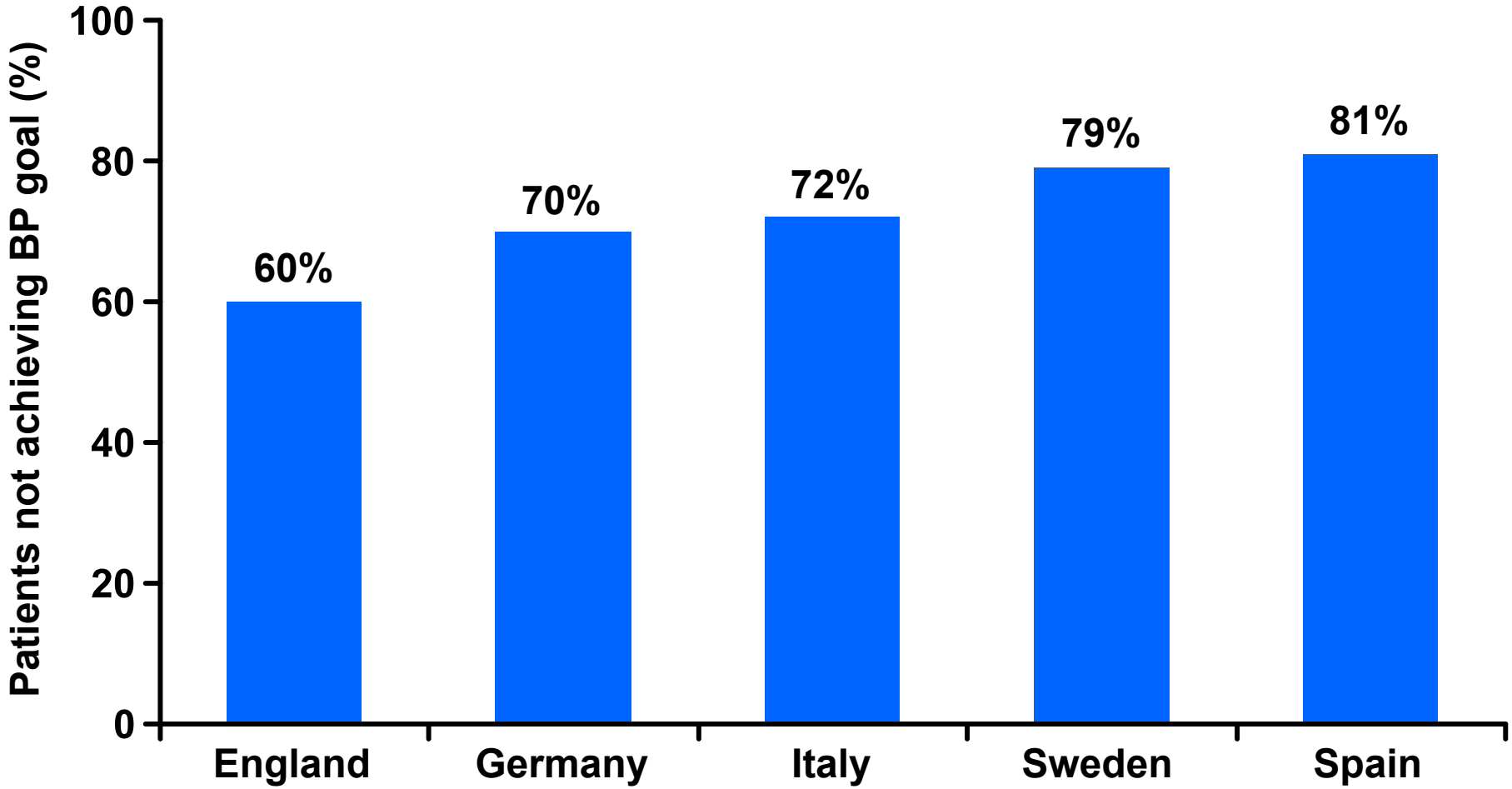
ESH–ESC and JNC 7 Guidelines Recommendations for BP Goals

	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**

BP = blood pressure; ESH = European Society of Hypertension; ESC = European Society of Cardiology;
JNC = Joint National Committee
*Lower if proteinuria is >1 g/day

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

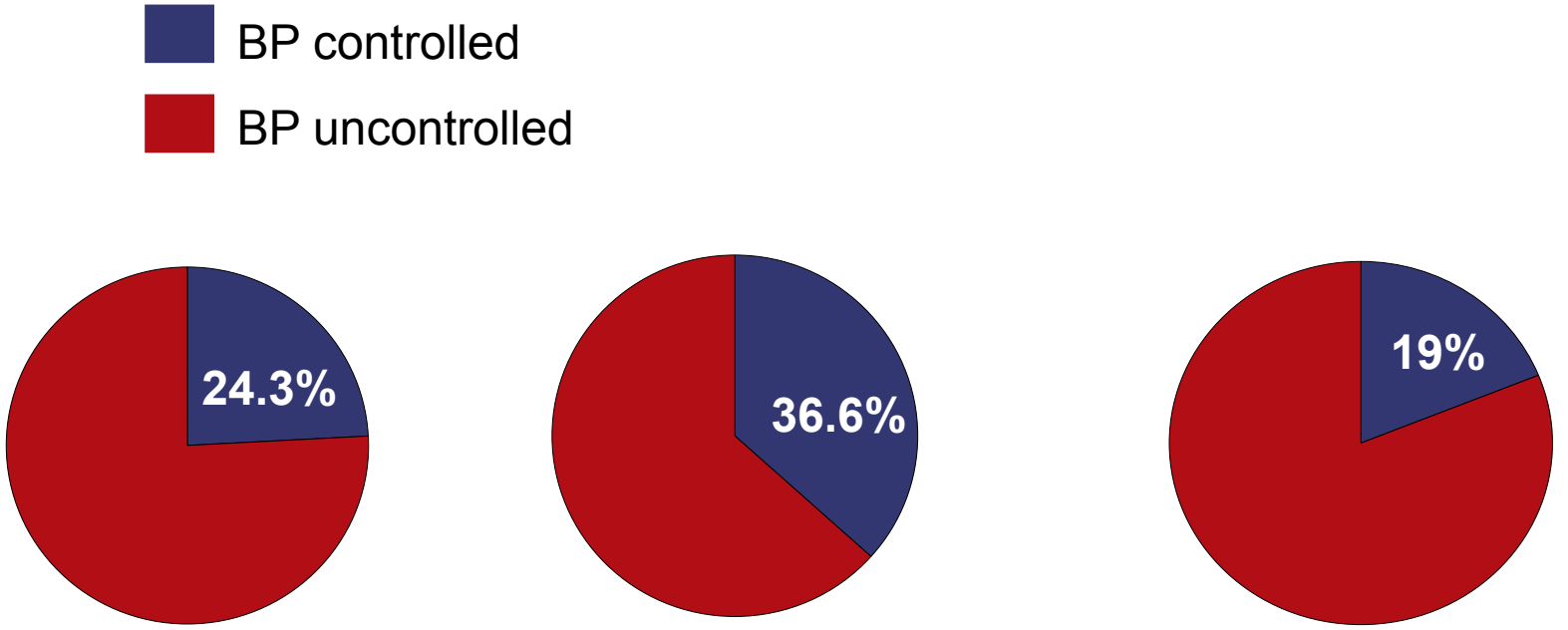
But, Hypertension Control Rate in Real World



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

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

BP Control Rates in Hypertensive Patients in Developing Economies



Turkey[1]
(Treated population)

Thailand[2]
(Treated population)

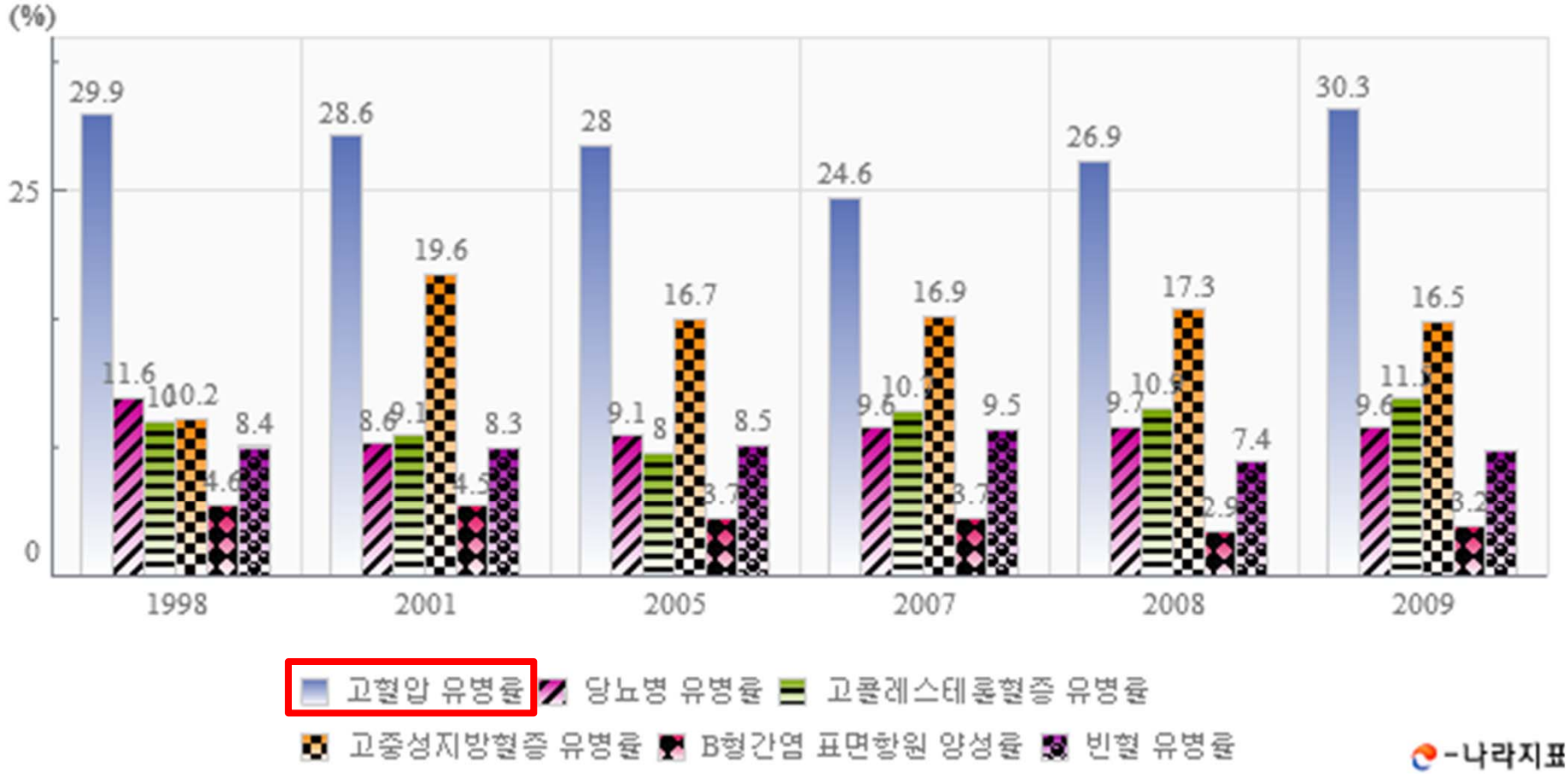
China[3]
(Population aware of their hypertension)

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

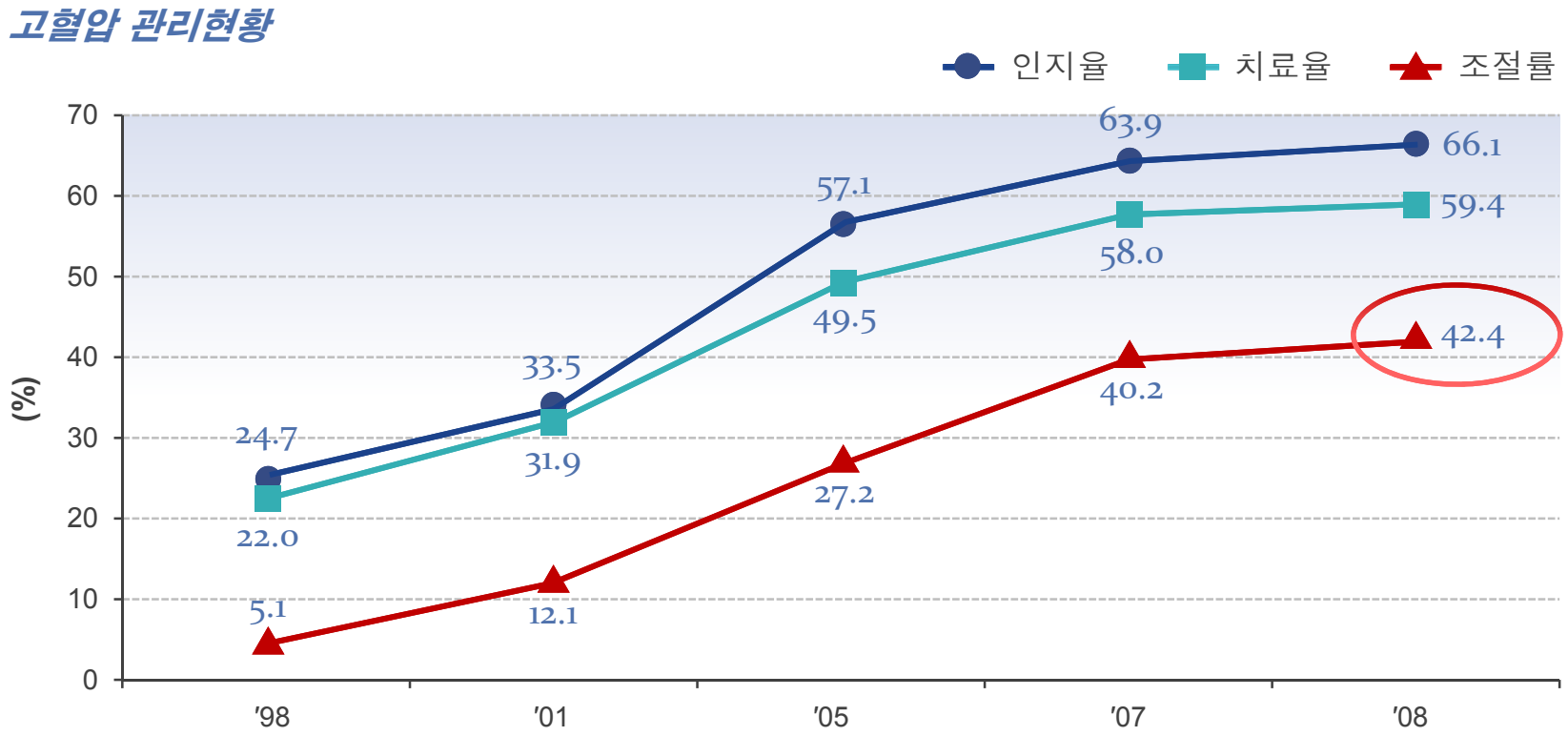
What about in Korea?

우리나라 만성질환 유병률 추이: 검진



출처 : **2009** 국민건강통계, 보건복지부 질병관리본부

BP Control Rates in Hypertensive Patients in Korea



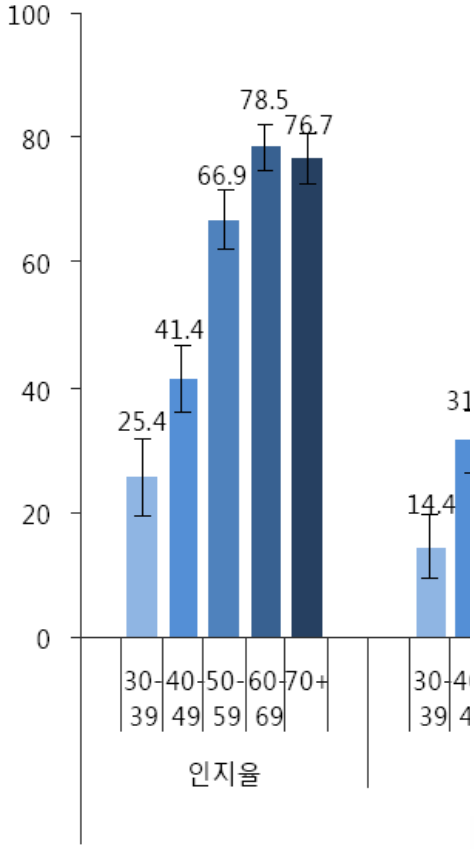
※인지율 : 고혈압 유병자 중 의사로 부터 고혈압 진단을 받은 분율, 만 30세 이상

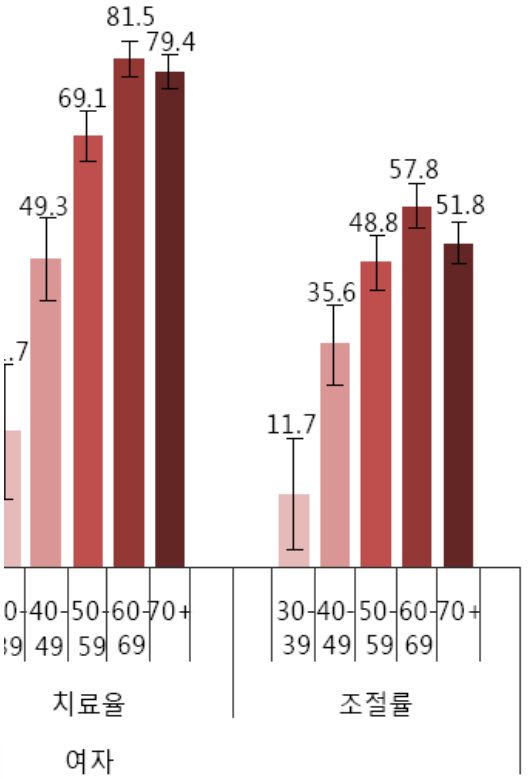
치료율 : 고혈압 유병자 중 혈압강하제를 한 달에 20일 이상 복용한 분율, 만 30세 이상

조절률 (유병자 기준) : 고혈압 유병자중 수축기 혈압 140 mmHg 미만이면서 이완기 혈압 90 mmHg 미만인 분율, 만 30세 이상

※ 2005년 고혈압추정인구 (2005년 추계인구 X 2005년 고혈압 유병률)로 연령표준화

BP Control Rates in Hypertensive Patients in Korea





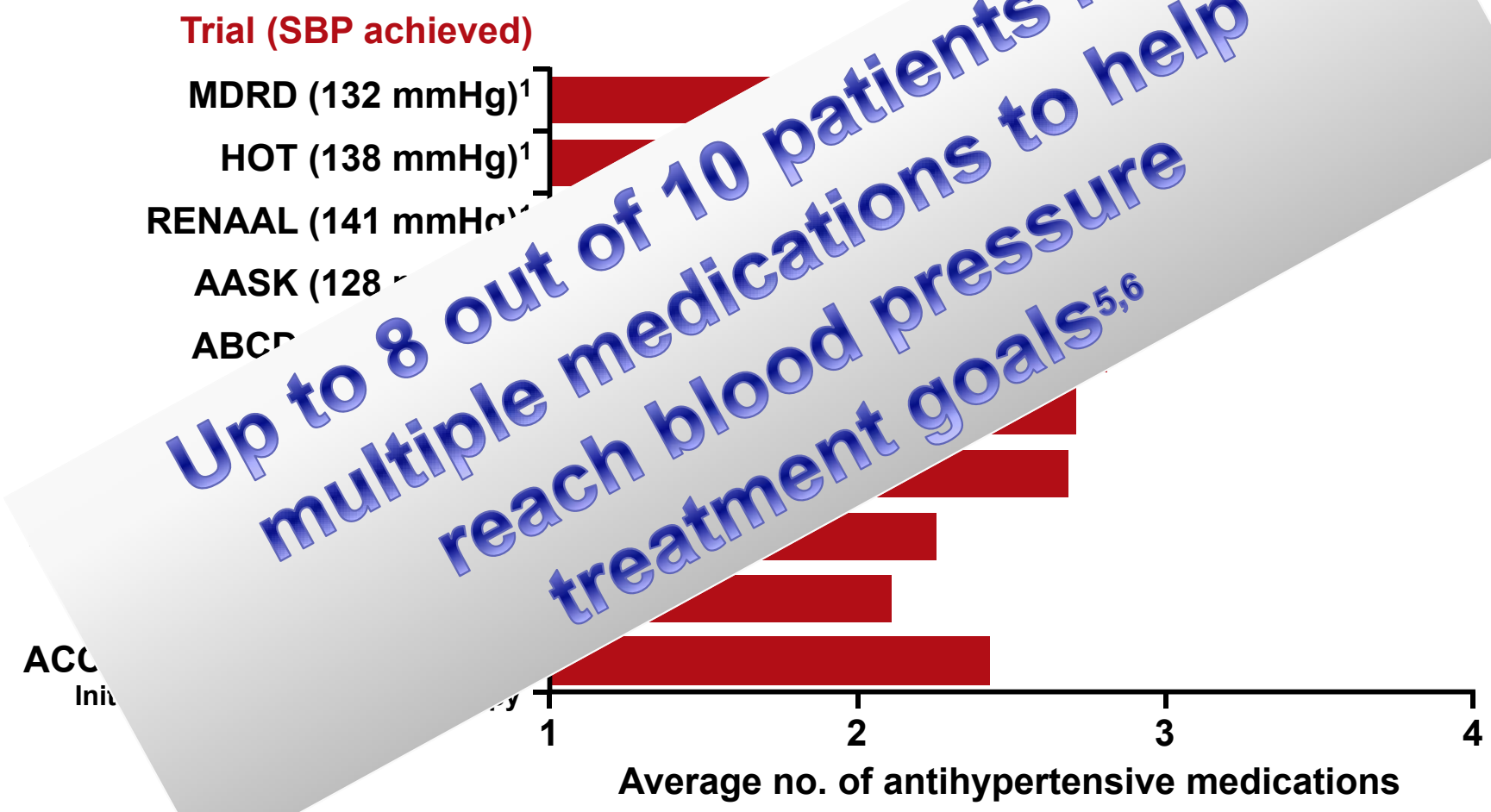
※고혈압 인지율 : 고혈압 유병지
※고혈압 치료율 : 고혈압 유병지
※고혈압 조절률 : 고혈압 유병지
※2011년 남자 팔높이 83cm, 여지
※2008-2010년 통합산출

)세이상
g 미만인 분율, 만30세이상
후 측정치는 보정 산출(13p 참고)

출처 : 201- 국민건강통계, 국민건강영양조사 제 5기 (2010_ 자료

Why combinations therapy?

Multiple Antihypertensive Agents are Needed to Reach [illegible] Goal



Up to 8 out of 10 patients need multiple medications to help reach blood pressure treatment goals[5,6]

[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;359:2417–2,
[5]Dahlof et al. Lancet 2005;366:895–906,[6]Pepine et al. JAMA 2003;290:2805–16

Limitations of Agents with a Single Mechanism of Action

- **Materson et al. observed that antihypertensive agents with a single mechanism of action were inadequate to achieve a diastolic BP <95 mmHg in 40–60% of hypertensive patients[1]**
- **Because hypertension is a multi-factorial disease, in most cases at least two antihypertensive agents are needed for patients to achieve BP goal[2]**
- **As an estimate, one-third of patients with hypertension require 2 drugs to achieve BP control* and one-third of patients will require 3 or more antihypertensive 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

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

Combination Therapy: Why?

- **Hypertension is heterogeneous in its response to treatment and a combination of two drugs will increase the likelihood of response by multiple mechanism.**
- **There may be enhancement of each drugs antihypertensive effect which may be synergistic rather than simply additive.**
- **By keeping both drugs at low dose the incidence of side effect from each may be minimized.**
- **Improving Drug Compliance**

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]:**

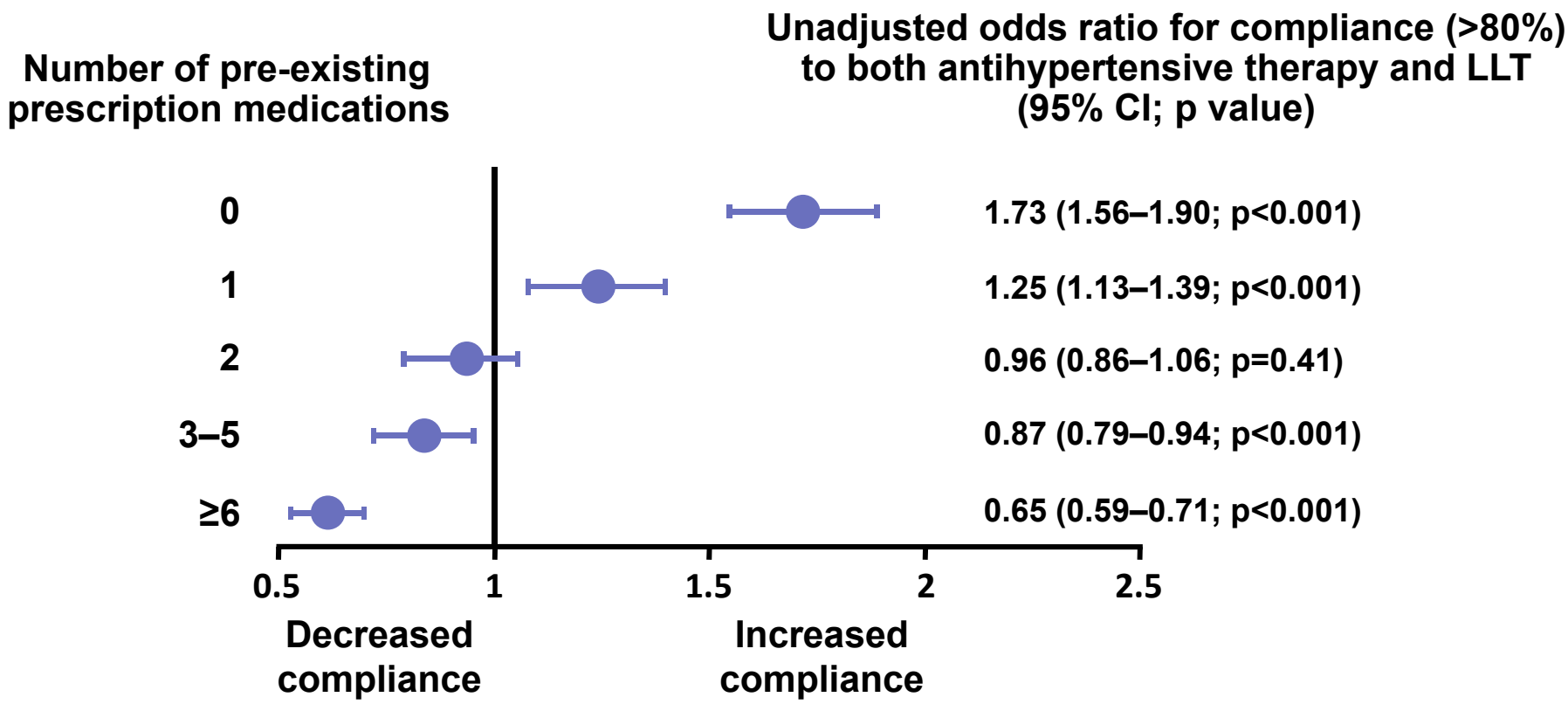
  'The combination of two antihypertensive drugs may offer advantages also for treatment initiation, particularly in patients at high cardiovascular risk in which early BP control may be desirable.'

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

Why Single-pill Combinations?

Compliance Decreases as the Number of Medications Increases

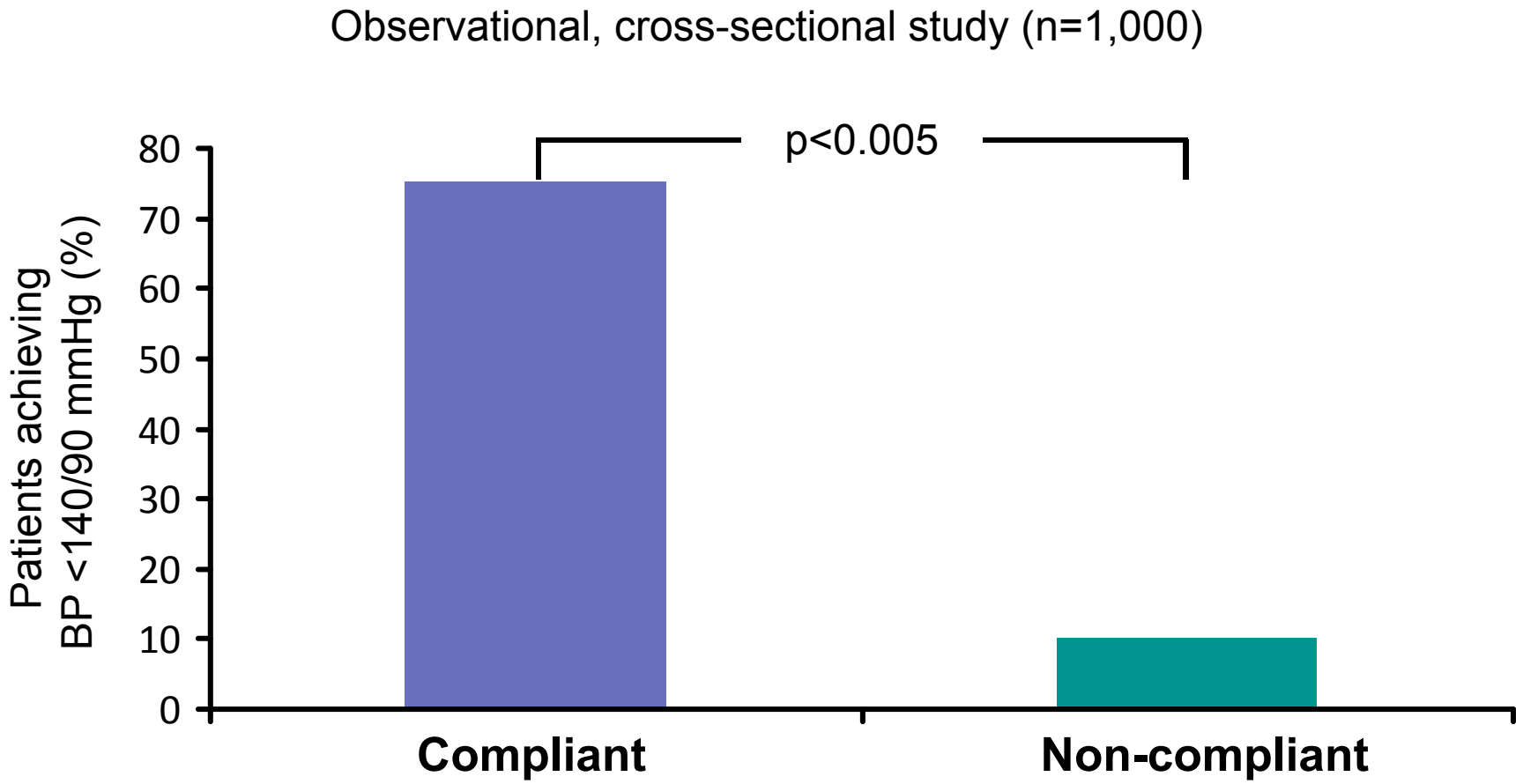


Retrospective cohort study of MCO population. N=8,406 patients with hypertension who added antihypertensive therapy and LLT to existing prescription medications within a 90-day period. Compliance to concomitant therapy: sufficient antihypertensive and LL prescription medications to cover ≥80% of days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

CI=confidence interval; LLT = lipid-lowering therapy

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

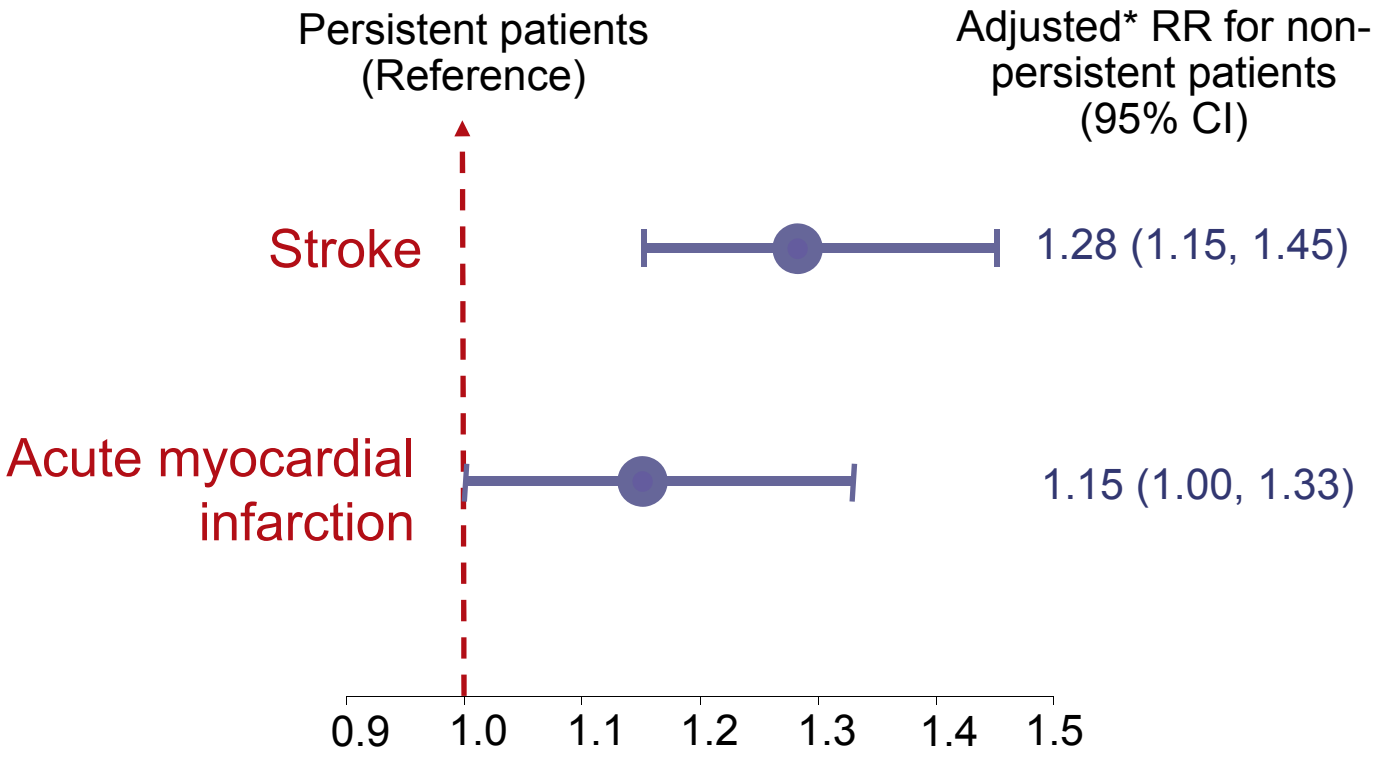
Compliance with Antihypertensive Therapy Results in More Patients Achieving Blood Pressure (BP) Goal (<140/90 mmHg)



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

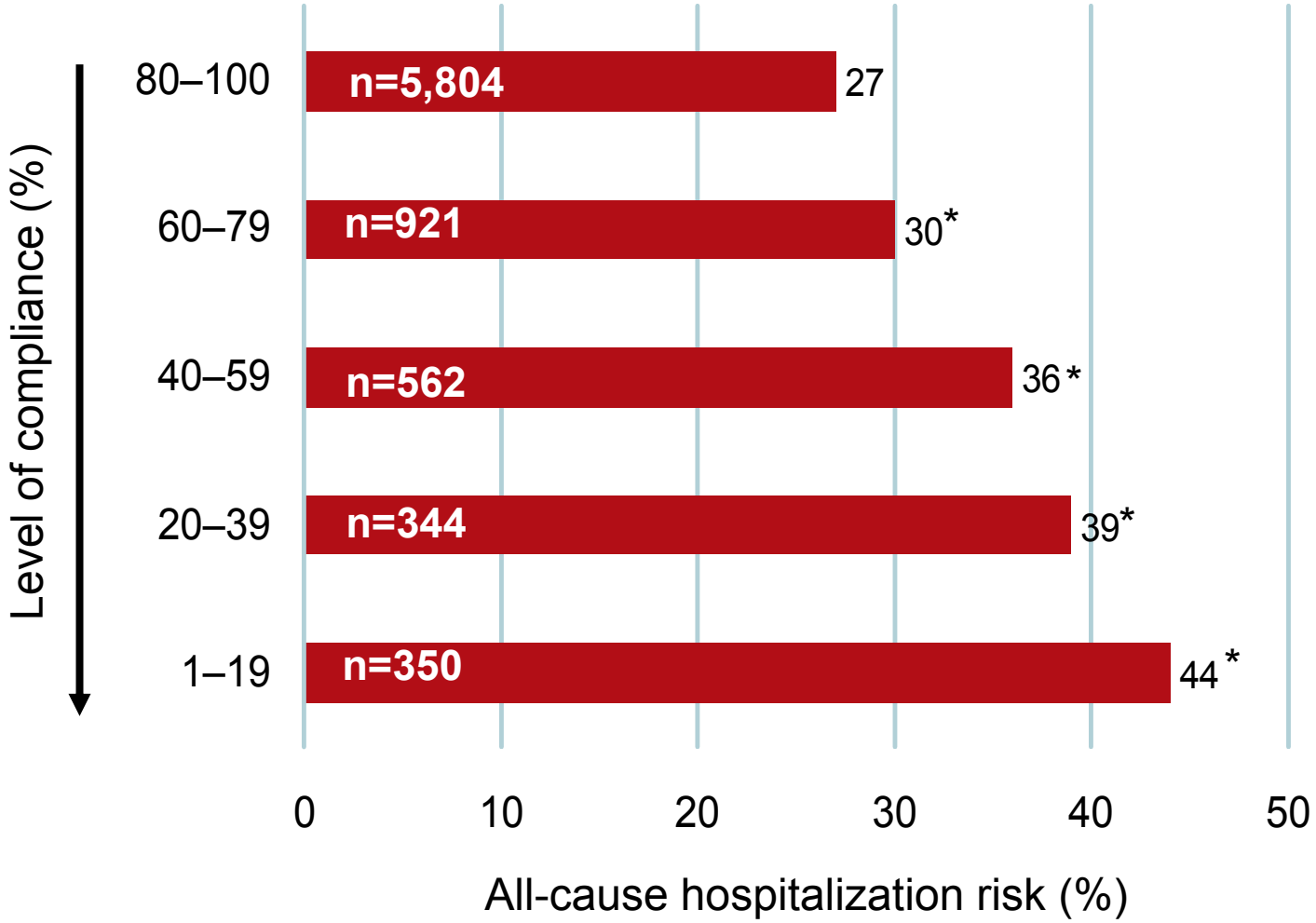
Data based on 77,193 new users of antihypertensive treatment identified in the PHARMO record linkage system



*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

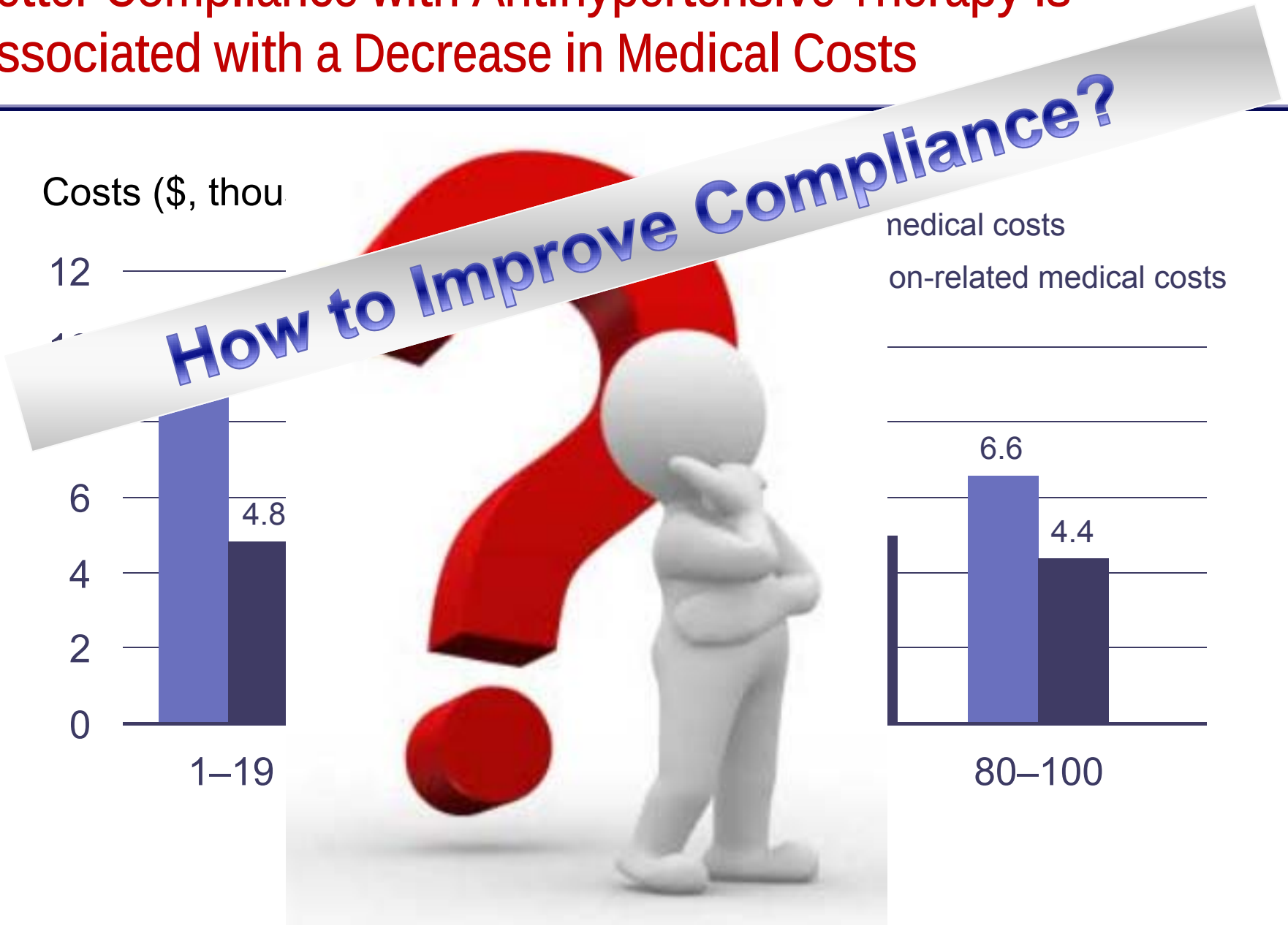
Better Compliance with Antihypertensive Drugs is Associated with a Lower Risk of Hospitalization



*p<0.05 vs 80–100% compliant group

Sokol et al. Med Care 2005;43:521–30

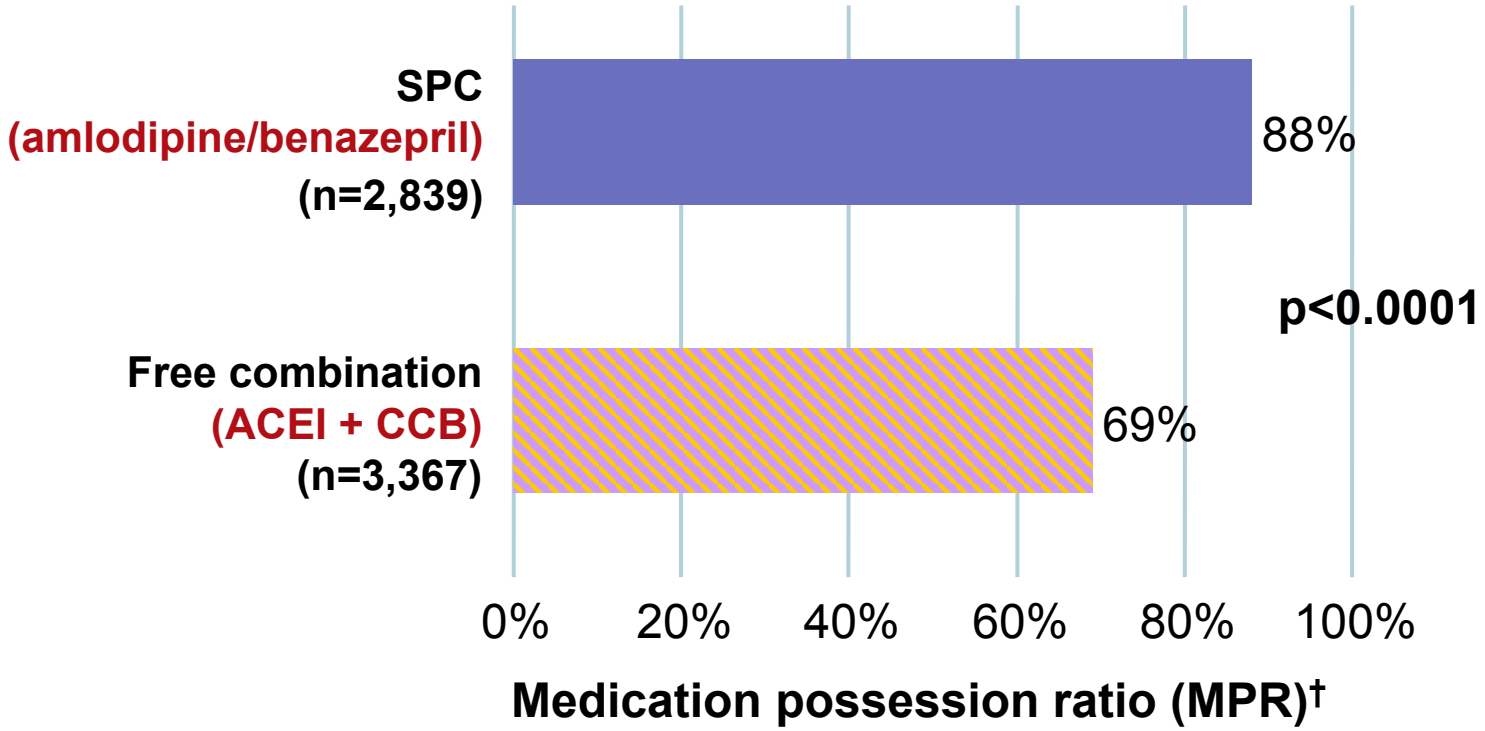
Better Compliance with Antihypertensive Therapy is Associated with a Decrease in Medical Costs



*p<0.05 vs. 80–100% compliant group

Sokol et al. Med Care 2005;43:521–30

Improved Compliance with Single-pill Combination (SPC) Therapy Compared with Free-combination Therapy

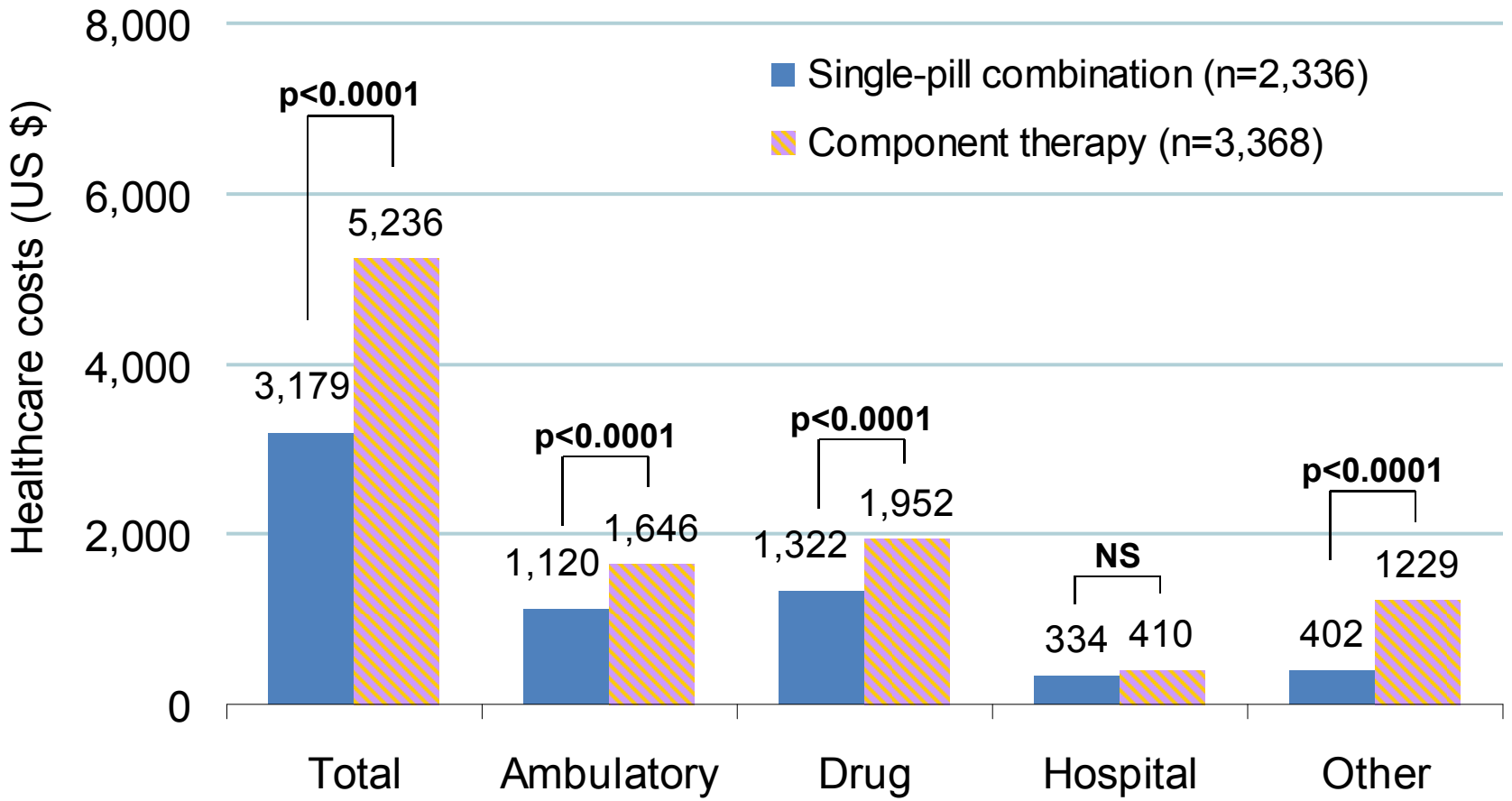


†Defined as the total number of days of therapy for medication dispensed/365 days of study follow-up

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

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

Patients Treated with Single-pill Combinations Use Less Resource

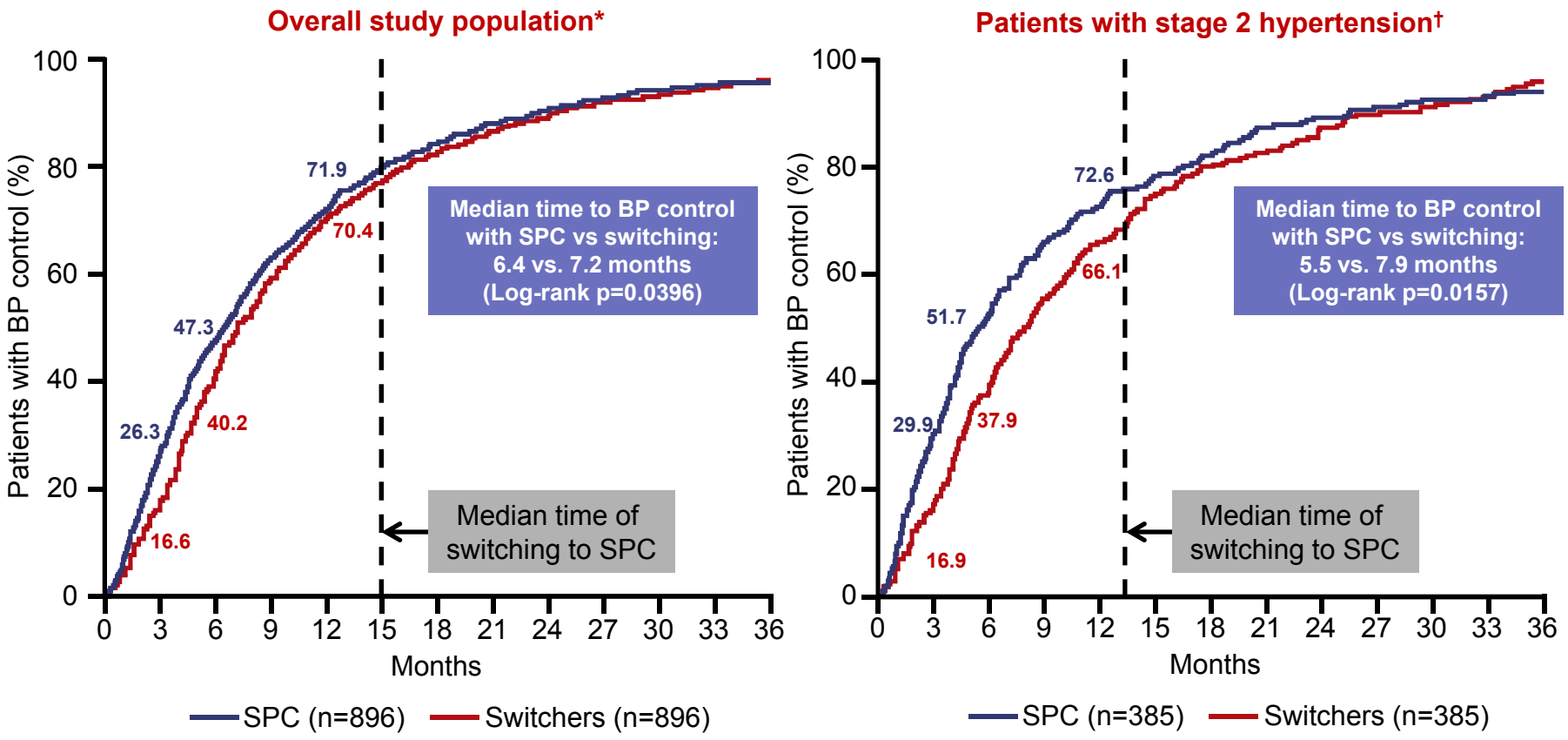


NS = not significant

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

Initiating treatment with a single-pill combination (SPC) is associated with more rapid BP control vs switching to an SPC after initial monotherapy

Retrospective (real-world), matched-cohort study of patients with hypertension



SPC = patients initiated on SPC therapy for at least 60 days. Switchers = patients initiated on monotherapy for at least 60 days, subsequently switched to SPC therapy for at least 60 days.
*Mean blood pressure (BP) at baseline (overall population) = 153/88 mmHg; †SBP ≥160/100 mmHg.
BP control = <140/90 mmHg, or <130/80 mmHg for patients with compelling indications.
SPCs = angiotensin-converting enzyme inhibitor (ACEI)/calcium channel blocker (CCB), angiotensin receptor blocker (ARB)/CCB, ACEI/diuretic, ARB/diuretic

Gradman et al. Poster presented at the American Society of Hypertension, New York, 21–24 May 2011

Initiating therapy with SPC is associated with improved BP control and lower risk of developing a CV event vs switching to combination therapy

- Retrospective (real-world), matched-cohort study (2,432 patients in each of the single-pill combination (SPC) and switcher/add-on cohorts); mean blood pressure (BP) at baseline in each study group: 149/83 mmHg
- More patients achieved BP control* in the SPC vs switcher/add-on cohort at months 3 (24.7% vs 20.4%), 6 (46.6% vs 42.4%, and 12 (72.0% vs 69.1%), resulting in a shorter median time to BP goal: 6.5 vs 7.0 months, respectively; log-rank p=0.0367

	No. of patients with event		Incidence rate (No. of patients with an event per 100 person-years)		Conditional Poisson [Ref: Switcher/Add-on]	
	SPC (n=2,432)	Switch (n=2,432)	SPC (n=2,432)	Switch (n=2,432)	IRR (95% CI)	p value
Acute MI	82	129	1.29	1.79	0.45 (0.32–0.64)	<0.0001
Stroke	357	426	6.14	6.53	0.85 (0.70–1.02)	0.0814
Hospitalization for HF	83	135	1.30	1.87	0.46 (0.33–0.64)	<0.0001
Overall	454	573	8.00	9.13	0.72 (0.61–0.84)	<0.0001
Overall (with death)	473	587	8.34	9.36	0.74 (0.63–0.86)	0.0001

IRR = incidence rate ratio of cardiovascular (CV) events (incidence rate of CV event [SPC cohort]/incidence rate of CV event [Switcher/Add-on cohort]. SPC or free combinations = angiotensin-converting enzyme inhibitor (ACEI)/calcium channel blocker (CCB), angiotensin receptor blocker (ARB)/CCB, ACEI/diuretic, ARB/diuretic.

*<140/90 mmHg, or <130/80 mmHg for patients with compelling indications. SPC = patients initiated on SPC therapy for at least 60 days. Switchers/add-on = patients initiated on monotherapy for at least 60 days, subsequently switched to combination therapy/added a second agent for at least 60 days.
HF = heart failure; MI = myocardial infarction

Gradman et al. Poster presented at the American Society of Hypertension, New York, 21–24 May 2011

European Guidelines now Recommend use of Single-pill Combination Therapy

- 2009 European guidelines state:

  *'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'*

  *'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

Benefits of Single-pill Combinations

- Up to **8 out of 10 patients need multiple medications** to help reach blood pressure (BP) treatment goals[1,2]
- When combining antihypertensive agents, the use of single-pill combinations (SPCs) is **supported by guidelines**, due to compliance advantages, and could lead to **improved efficacy, better outcomes and reduced overall costs**[3–5]
- A renin-angiotensin-aldosterone system **(RAAS) blocker**/calcium channel blocker (**CCB**) and **RAAS blocker/diuretic** represent rational and effective combinations, and **are recommended by guidelines**[3]
- SPC therapy with valsartan/hydrochlorothiazide (HCTZ) and with amlodipine/valsartan are associated with powerful BP-lowering efficacy,[6–8] and the individual components/classes are supported by a wealth of outcomes evidence/use in clinical trials[1,9,10]
- In the proportion of patients who require more than two agents, SPC therapy with valsartan/amlodipine/HCTZ provides superior BP reductions compared with dual therapy and is well tolerated[11]

[1]Dahlof et al. Lancet 2005;366:895–906; [2]Pepine et al. JAMA 2003;290:2805–16; [3]Mancia et al. Blood Press 2009;18:308–47
[4]Yiannakopoulou et al. Eur J Cardiovasc Prev Rehabil 2005;12:243–9; [5]Sokol et al. Med Care 2005;43:521–30
[6]Calhoun et al. Curr Med Opin Res 2008;24:2303–11; [7]Smith et al. J Clin Hypertens 2007;9:355–64
[8]Poldermans et al. Clin Ther 2007;29:279–89; [9]The ALLHAT investigators. JAMA 2002;288:2981–97
[10]Julius et al. Lancet 2004;363:2022–31; [11]Calhoun et al. Hypertension 2009;54:32–9

Why A+C Single-pill Combinations?

Optimal combination therapy

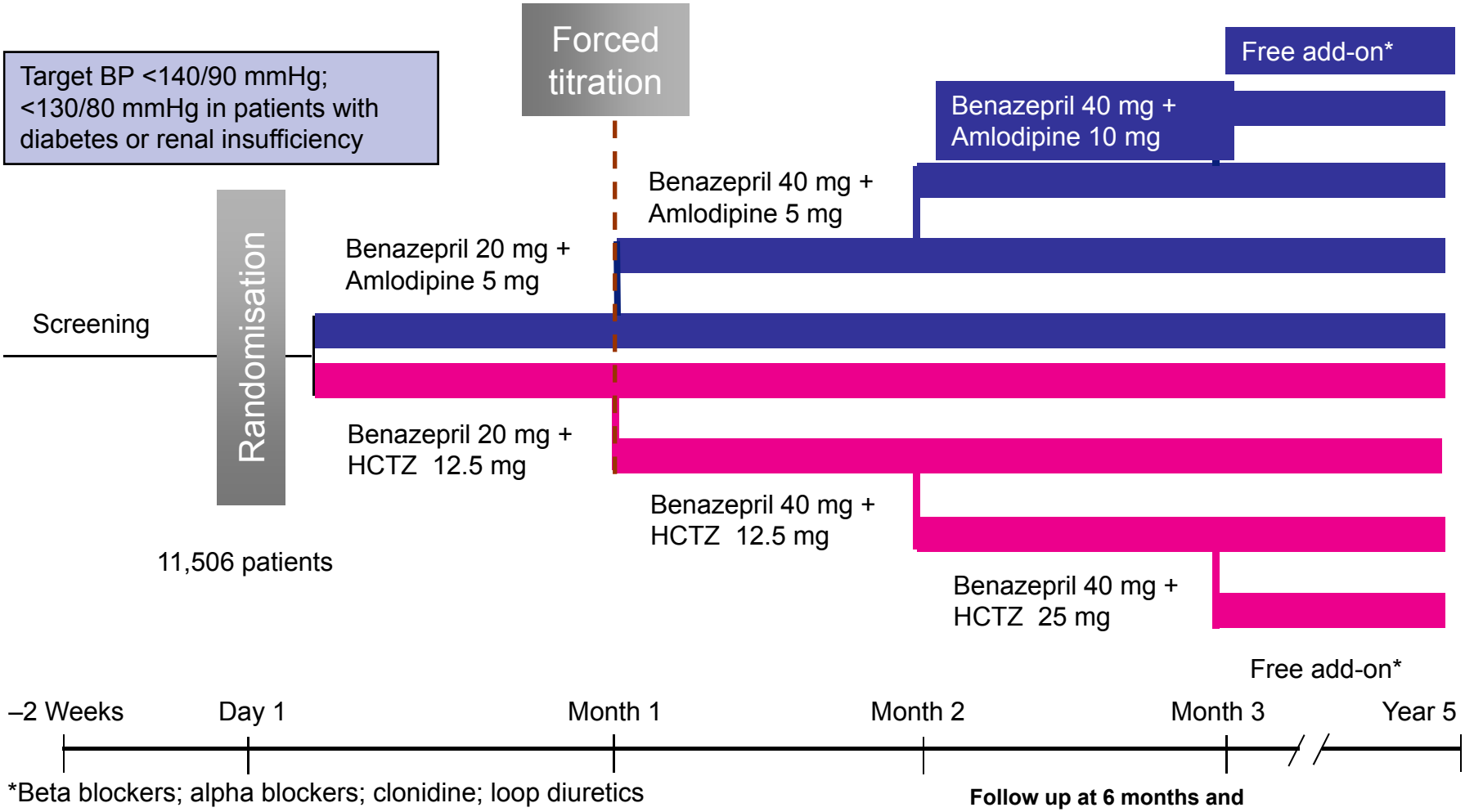
Table I Drug combinations in hypertension: recommendations

Preferred
ACEInhibitor/diuretic
ARB/diuretic
ACE-Inhibitor/CCB
ARB/CCB
Acceptable
Beta-blocker/diuretic
CCB (dihydropyridine)/beta-blocker
CCB/diuretic
Renin inhibitor/diuretic
Renin inhibitor/CCB
Dihydopyridine CCB/non-dihydropyridine CCB

European Heart Journal 2011, doi:10.1093/eurheartj/ehr177

ACCOMPLISH: the First Outcomes Trial to Compare Two Single-pill Combination-based Therapies

Prospective, randomized, double-blind, event-driven trial



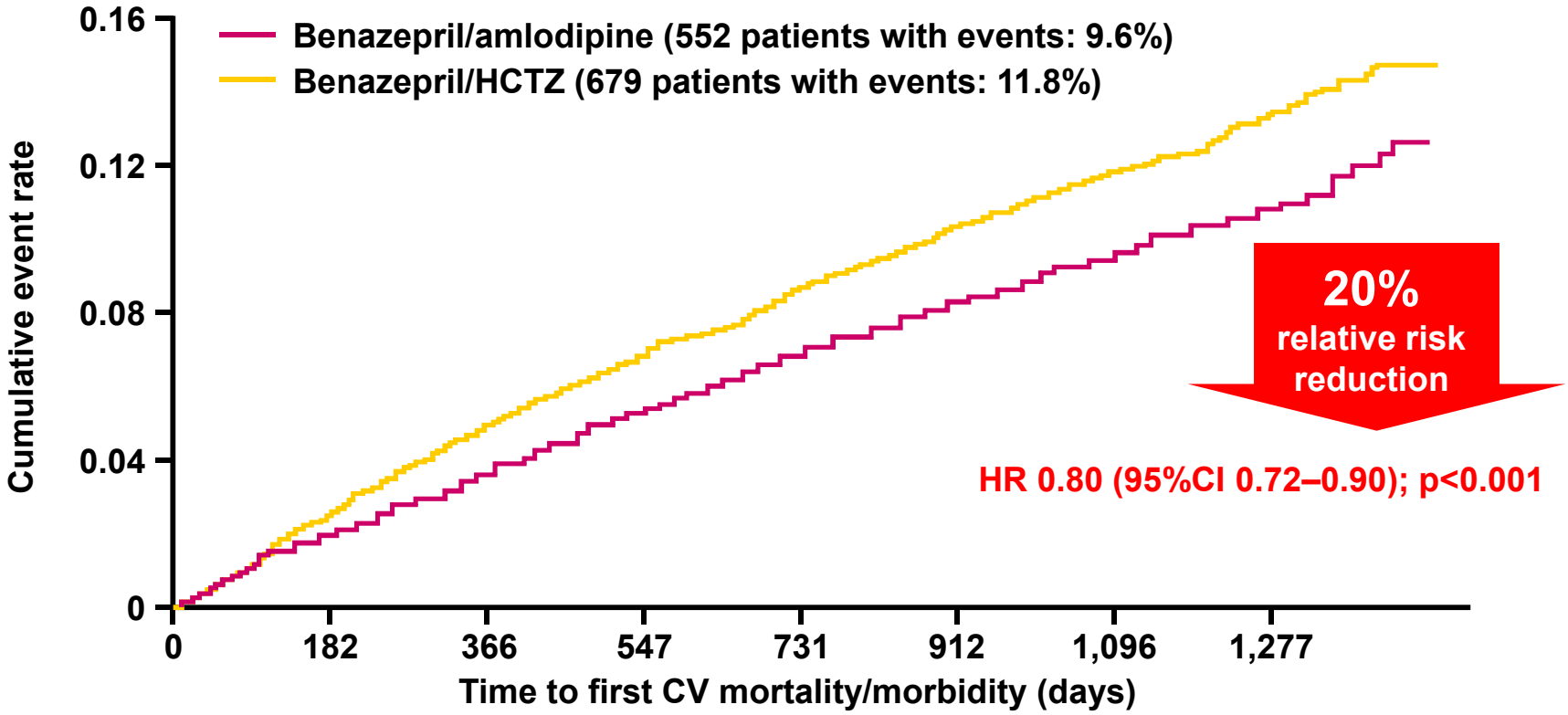
*Beta blockers; alpha blockers; clonidine; loop diuretics

Follow up at 6 months and every 6 months thereafter

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

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

ACCOMPLISH: the First Outcomes Trial to Compare Two Single-pill Combination-based Therapies

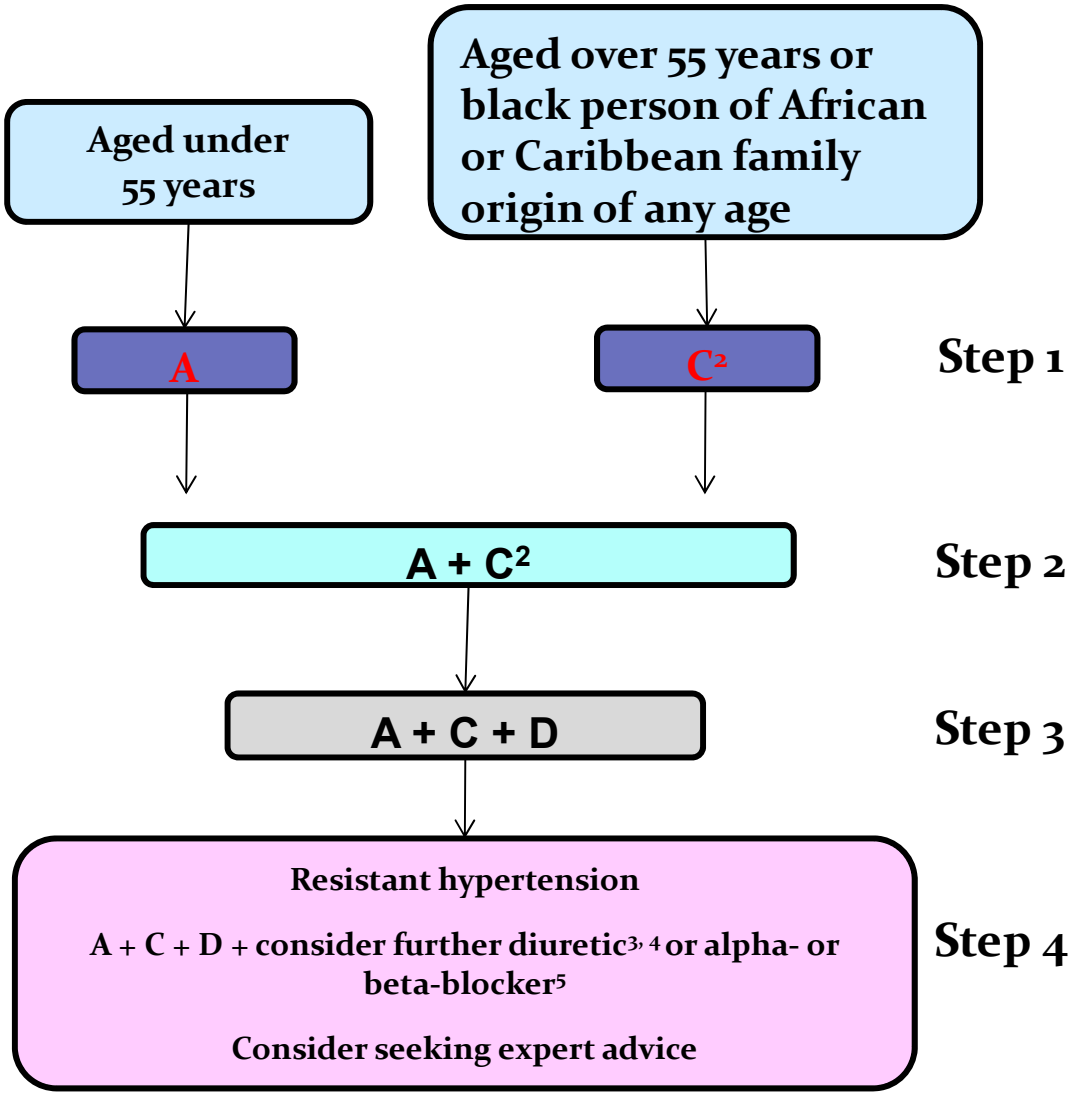


Months	0	6	12	18	24	30	36	42
Patients at risk (N)								
Benazepril/amlodipine	5,512	5,317	5,141	4,959	4,739	2,826	1,447	
Benazepril/HCTZ	5,483	5,274	5,082	4,892	4,655	2,749	1,390	

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

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

2011 NICE guideline



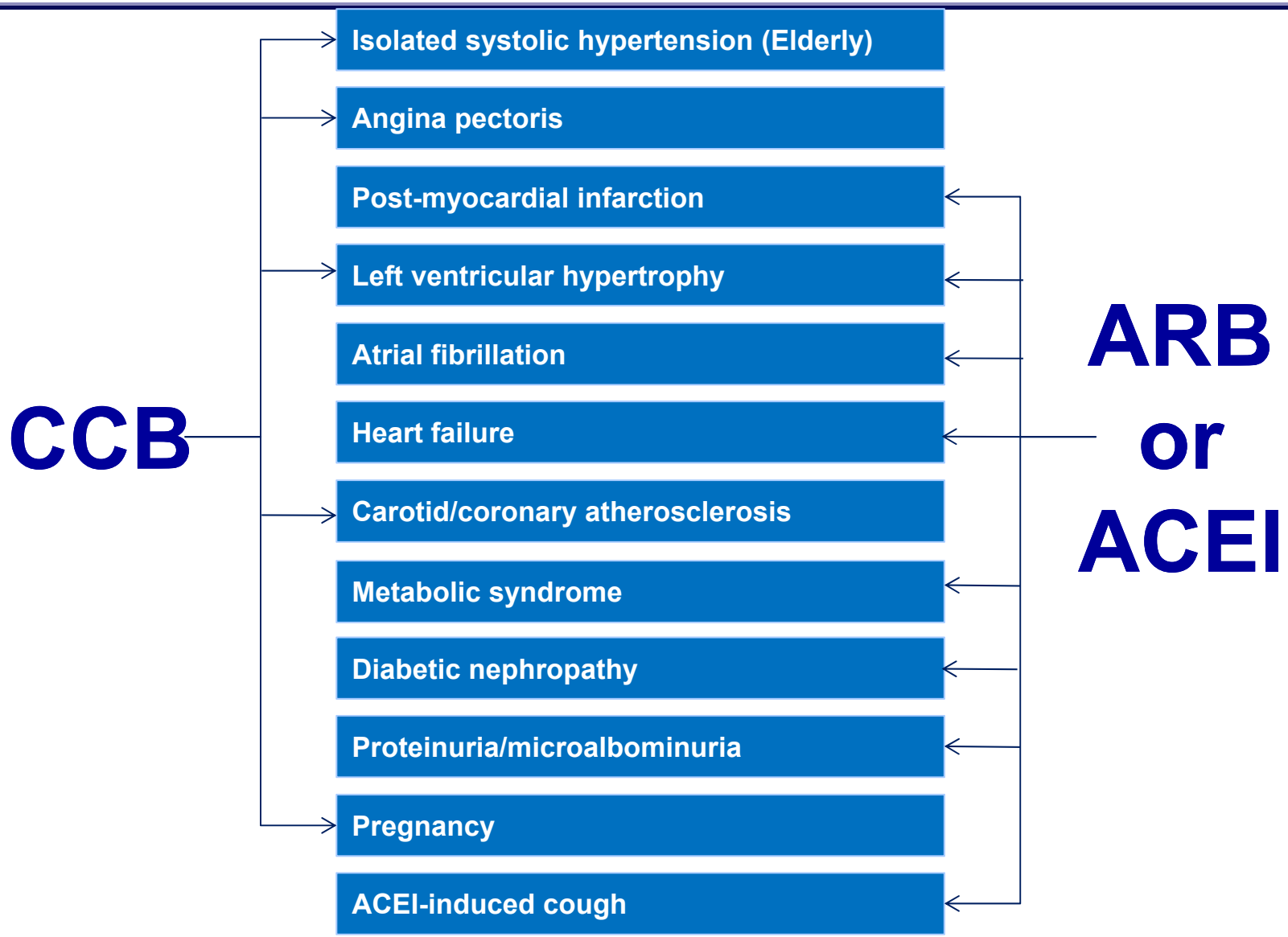
Summary of antihypertensive drug treatment

Key
A – ACE inhibitor or low-cost angiotensin II receptor blocker (ARB)[1]
C – Calcium-channel blocker (CCB)
D – Thiazide-like diuretic

BHS British Hypertension Society

NHS National Institute for Health and Clinical Excellence

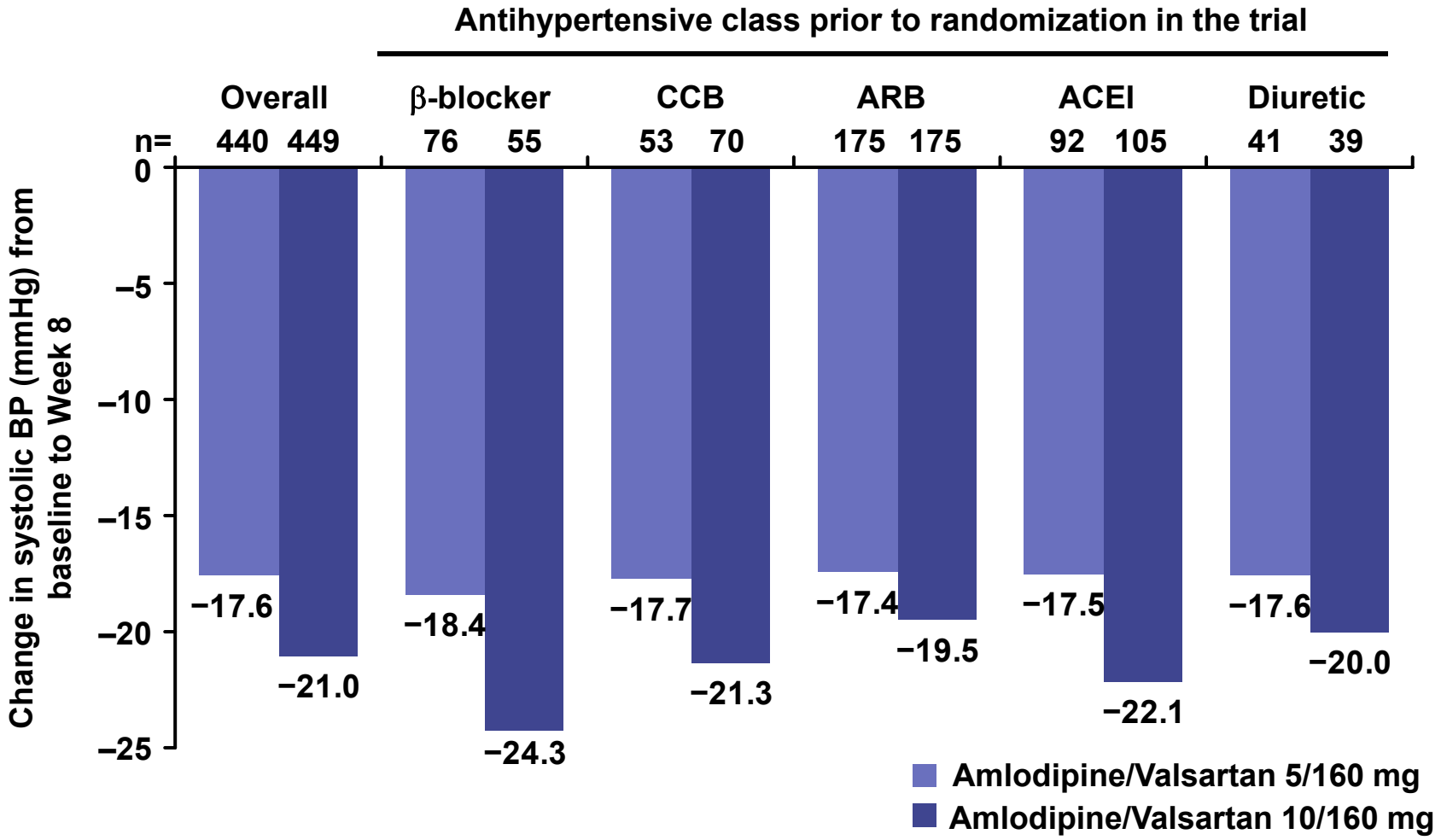
Conditions favoring the use of C and A According to the 2007 ESH/ESC recommendations.



Mancia. et al. J Hypertens. 2007;25:1105-1187

Clinical Evidence with Amlodipine/Valsartan

Incremental BP Drops After Direct Switch to Amlodipine/Valsartan in Patients Previously Uncontrolled on Monotherapy

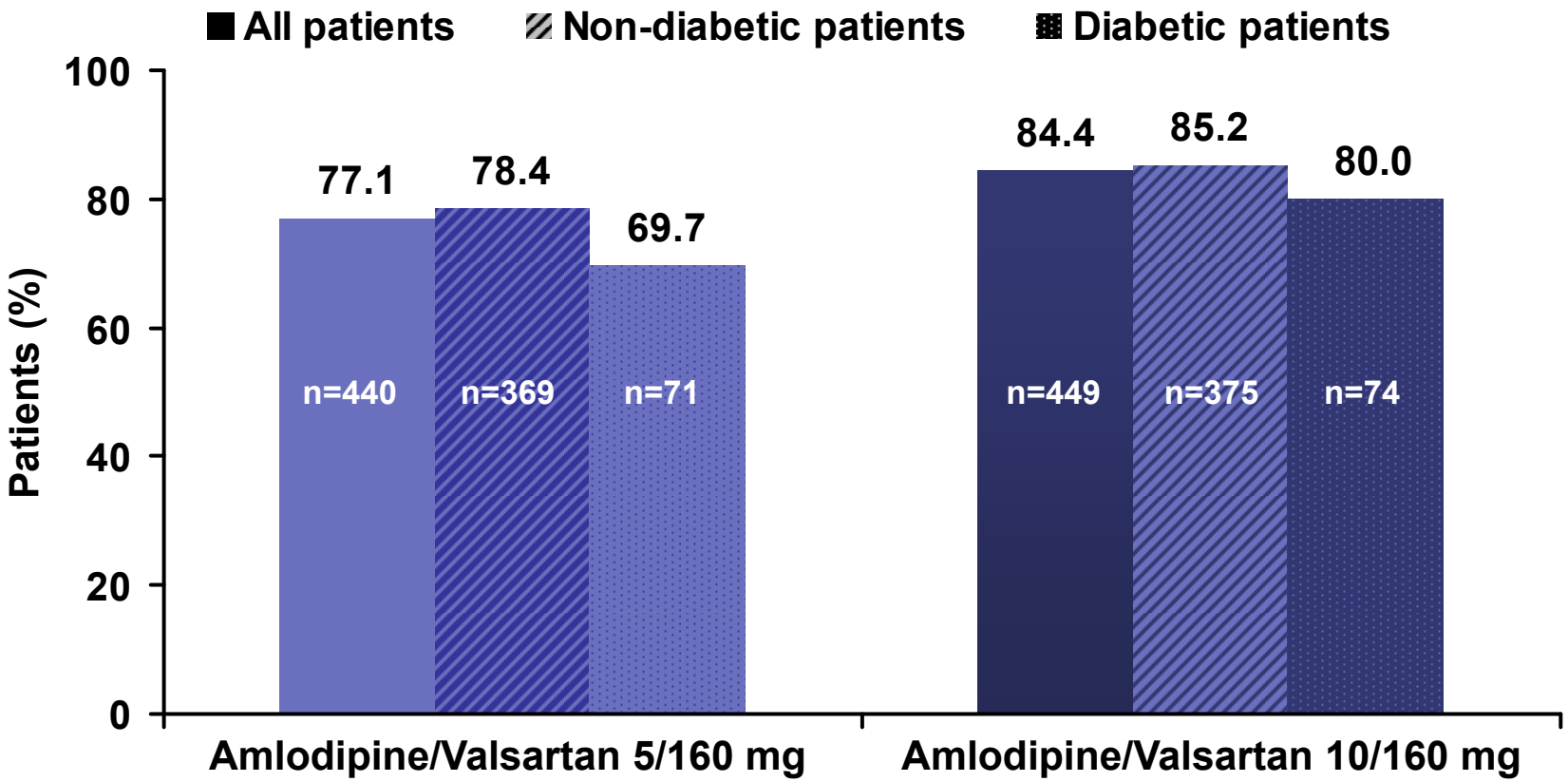


Baseline BP: 150/91 mmHg

Randomized, double-blind, multinational parallel-group, 16-week study

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

Amlodipine/Valsartan: Up to 9 Out of 10 Patients Reach BP Goal <140/90 mmHg

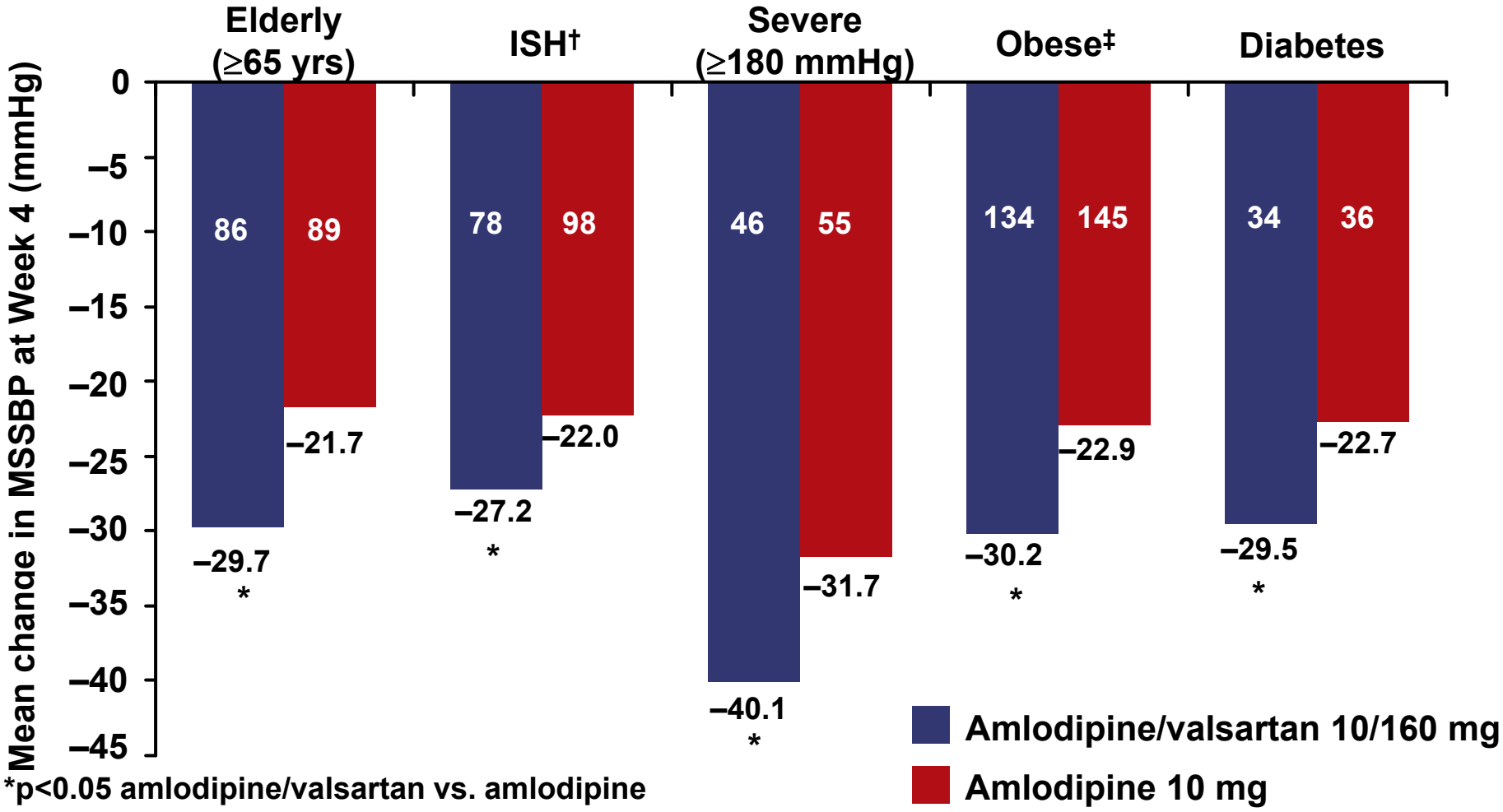


Diabetic patients with BP <130/80 mmHg at Week 8 were 47.0% and 49.2% for 5/160 mg and 10/160 mg doses, respectively

Data shown are at Week 8
No hydrochlorothiazide add-on was permitted until after Week 8
Randomized, double-blind, multinational, parallel-group, 16-week study

Adapted from
Allemann et al. J Clin Hypertens 2008;10:185–94

Amlodipine/Valsartan: Superior BP-lowering Efficacy versus Amlodipine Monotherapy Across Diverse Patient Populations



*p<0.05 amlodipine/valsartan vs. amlodipine monotherapy

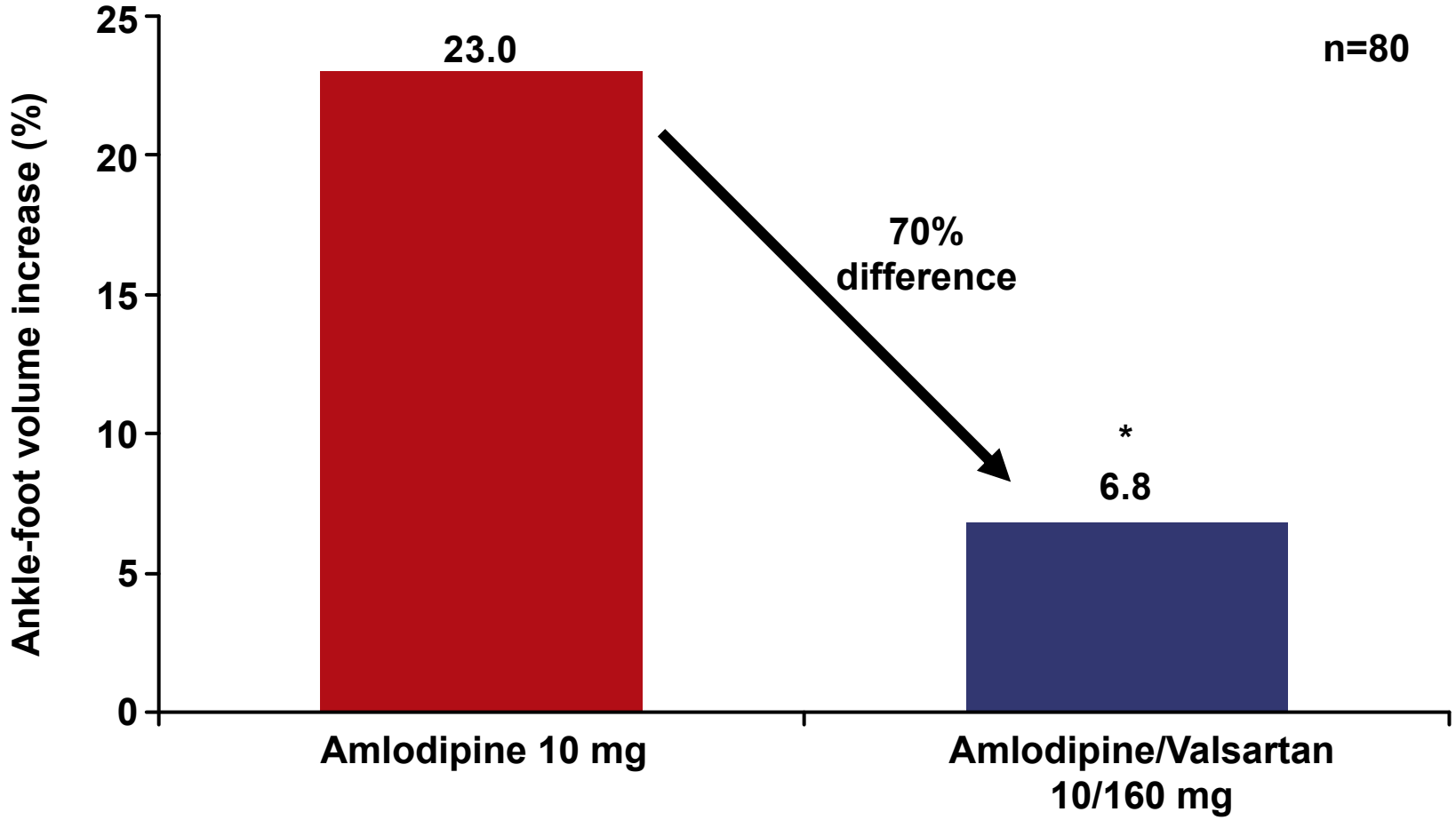
MSSBP = mean sitting systolic BP

†ISH = isolated systolic hypertension (≥140 and <90 mmHg)

‡Obese defined as body mass index ≥30 kg/m^2

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

Amlodipine/Valsartan Significantly Reduces Peripheral Edema versus Amlodipine Monotherapy



*p<0.01 vs. amlodipine
Randomized, cross-over study in 80 patients

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

Symptomatic Hypotension Occurs at Very Low Frequency with Amlodipine/Valsartan

0.3% or fewer reports of symptomatic hypotension in elderly† patients

0.4% or fewer reports of symptomatic hypotension in non-elderly‡ patients

Prespecified and post-hoc sub-group analysis of two double-blind, randomized, placebo-controlled studies
Data shown represent the incidence of reported symptomatic hypotension symptoms (adverse events related to low blood pressure, such as syncope, hypotension, orthostatic hypotension, postural dizziness, or lightheadedness)
In elderly patients the incidence of dizziness was 1.9%
†Elderly patients were ≥65 years of age.
‡Non-elderly patients were 18–64 years of age.

Smith et al. J Clin Hypertens 2007;9:355-364

Exforge Asian Data

Efficacy and safety of a single-pill combination of amlodipine/valsartan in Asian hypertensive patients inadequately controlled with amlodipine monotherapy

Current Medical Research & Opinion 2010;26(7):1705-1713

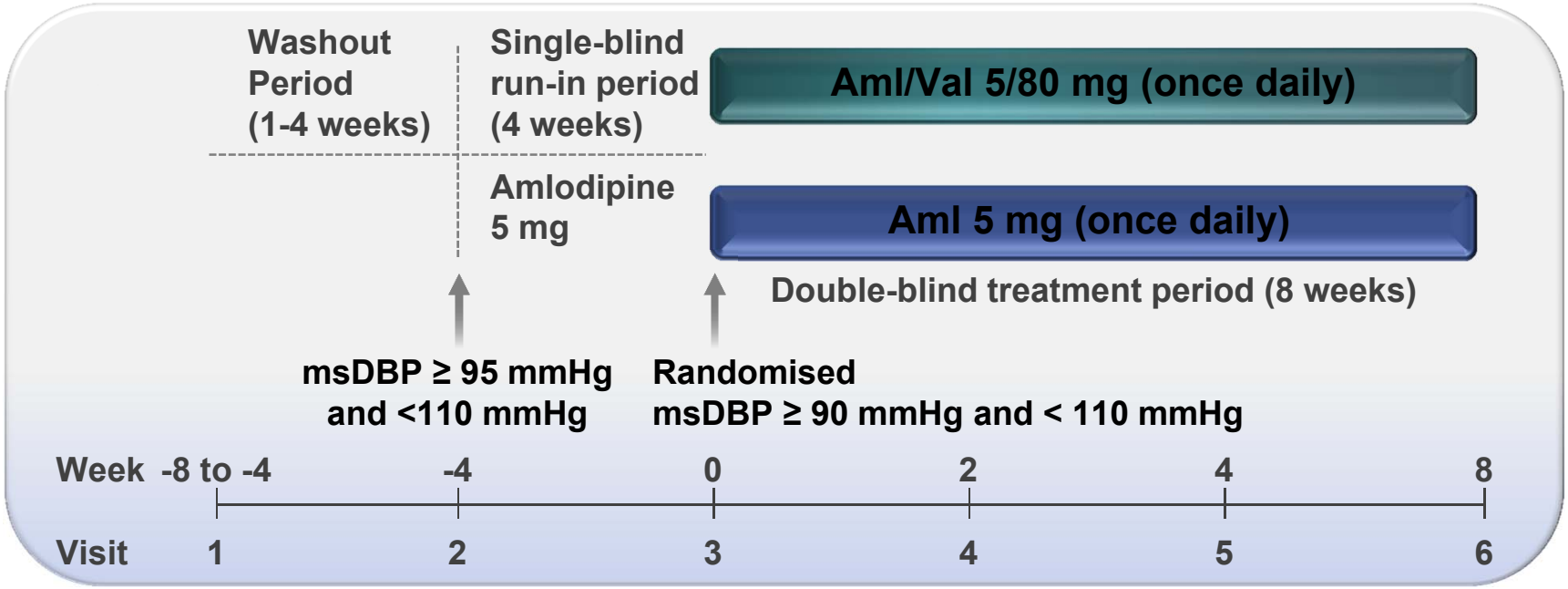
Design

8 week, randomized, double-blind, double-dummy, active-controlled, parallel-group study conducted across 20 centres in Asia (12 in China, 5 in Korea, 3 in Singapore)

Objective : ***To assess the efficacy and safety of SPC of Aml/Val vs. Aml in Asian***

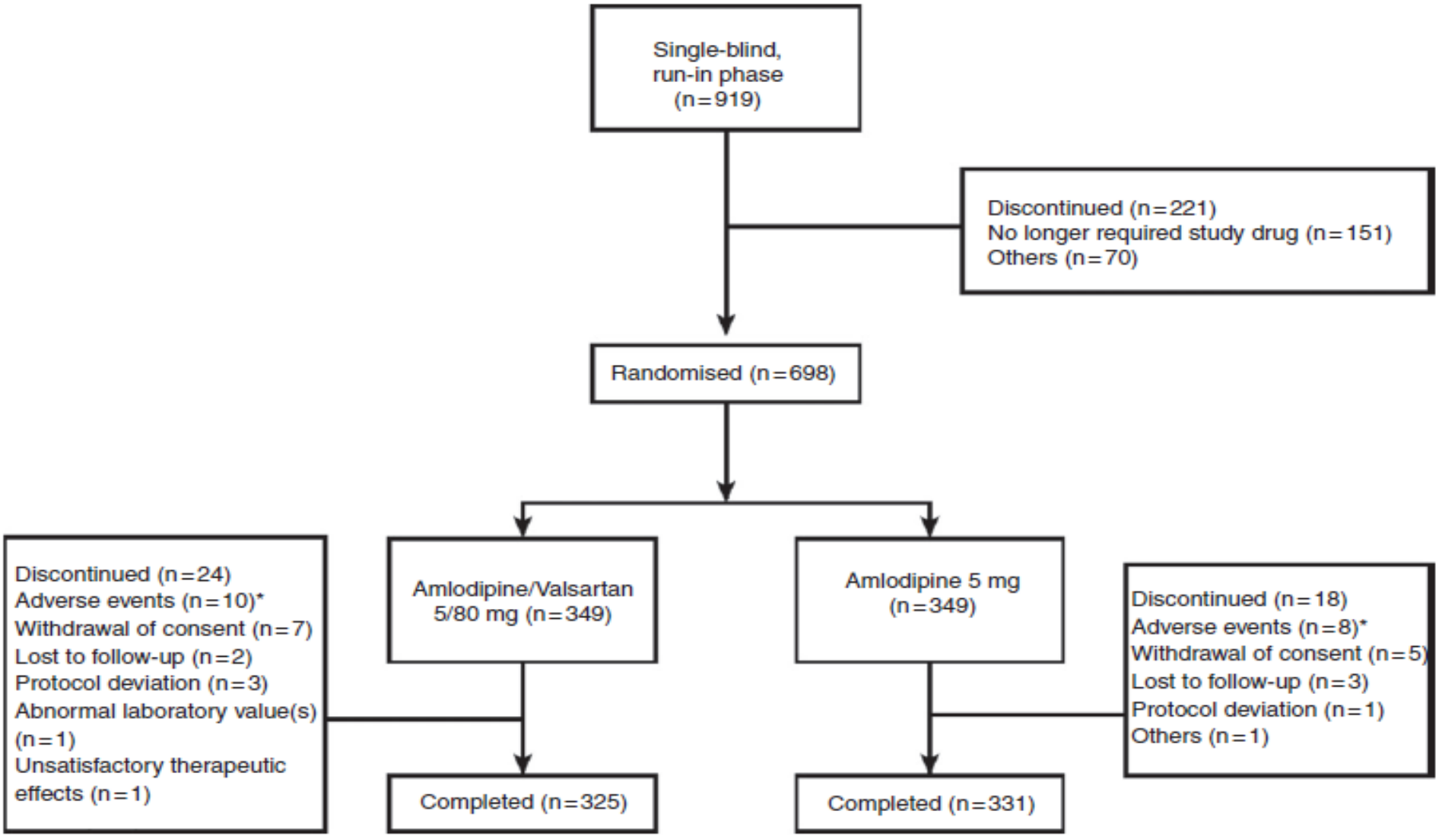
Population: Asian(18~85years) with mild-to-moderate essential hypertension (mean sitting DBP ≥ 95 mmHg and < 110 mmHg)

Endpoint: Change in msDBP, msSBP from baseline to week 8 endpoint
BP control rate (5140/90 mmHg) at week 8 endpoint.



Study design. Aml, amlodipine; Val, valsartan; msDBP, mean sitting diastolic blood pressure.

Patient Disposition



* All adverse events (including SAE)

Efficacy Outcomes

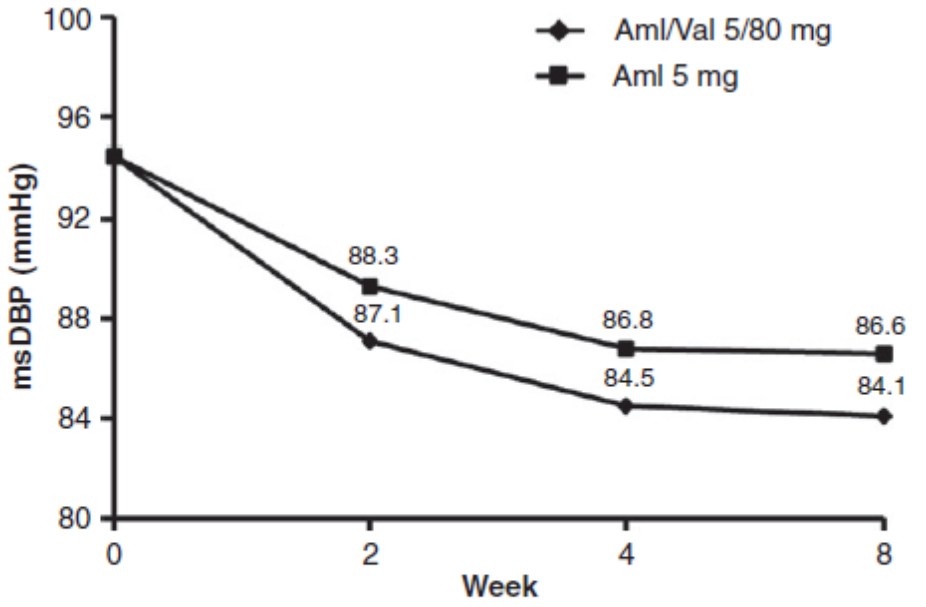


Figure 3. Mean sitting diastolic blood pressure (msDBP) by treatment and week (Full-set analysis population). $p < 0.0001$ for both the treatment groups at week 4 and at week 8. Aml, amlodipine; Val, valsartan; msDBP, mean sitting diastolic blood pressure.

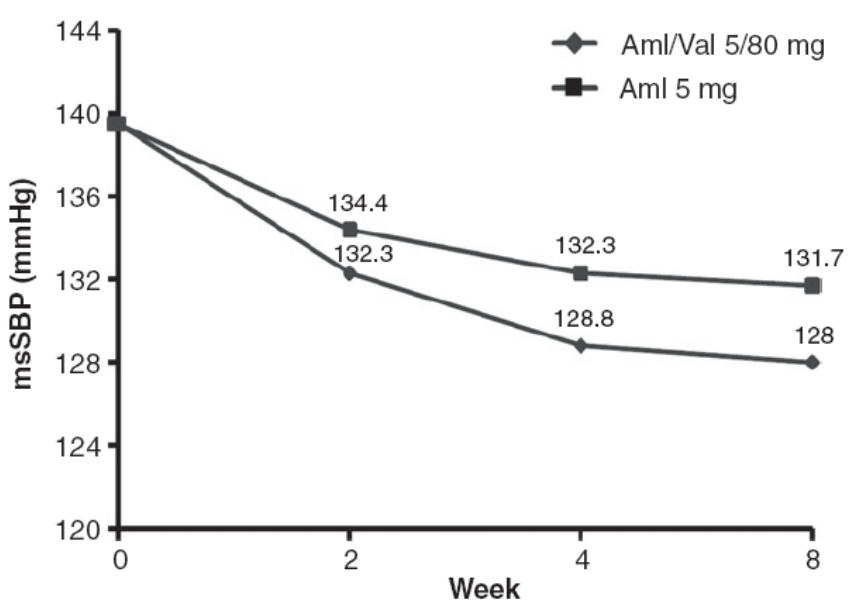


Figure 4. Mean sitting systolic blood pressure (msSBP) by treatment and week (full-set analysis population). $p < 0.0001$ for both the treatment groups at week 4 and at week 8. Aml, amlodipine; Val, valsartan; msSBP, mean sitting systolic blood pressure.

- **The Benefit of combination therapy was observed as early as week 2 and sustained until week 8**
- **Response Rates : 79.3% vs. 66.8% (p<0.0001)**
- **BP Control Rates : 69.2% vs. 57.6% (p=0.0013)**

Safety

Table 4. Overall incidence of adverse events during the double-blind treatment period.

	Aml/Val 5/80 mg *n* = 349 *n* (%)	Aml 5 mg *n* = 349 *n* (%)
Any adverse event	88 (25.2)	86 (24.6)
Deaths	0 (0.0)	0 (0.0)
SAEs	4 (1.1)	2 (0.6)
AEs leading to discontinuation	10 (2.9)	7 (2.0)
Drug-related AE discontinuations	7 (2.0)	5 (1.4)
SAE discontinuation	0 (0.0)	1 (0.3)
AEs ≥ 2%		
Hyperlipidaemia	15 (4.3)	11 (3.2)
Dizziness	10 (2.9)	7 (2.0)
Abnormal hepatic function	8 (2.3)	5 (1.4)

Aml, amlodipine; Val, valsartan; AE, adverse event; SAE, serious adverse event.

- **The overall incidence of AE s was similar in both the groups.**
- **The most frequent AE s were hyperlipidaemia and dizziness.**

Conculusion

- **Once-daily treatment with the single-pill combination of Aml/Val resulted in clinically and statistically significant additional BP reductions and greater BP control than Aml in Asian hypertensive patients inadequately controlled on Aml monotherapy**

- **Consistent with the previous findings in non-Asian cohorts, the combination was well-tolerated.**

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Thank you