Rationale for the use of Single Pill Combination (SPC) and Asian data of ARB/CCB SPC

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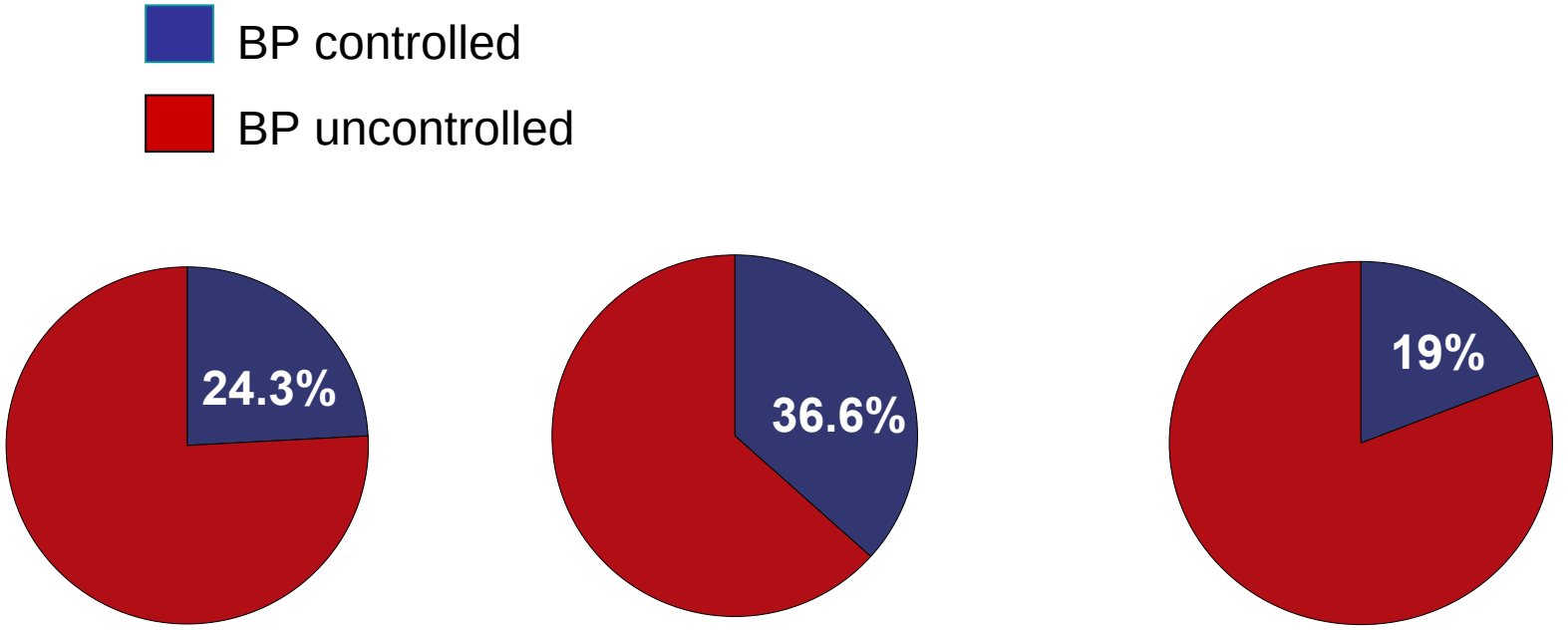
BP Control Rates in Asia



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

Agents with a Single Mechanism of Action: *Limitations*

Materson et al. observed that 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, 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

Multiple-mechanism Therapy:
Potential Efficacy Benefits

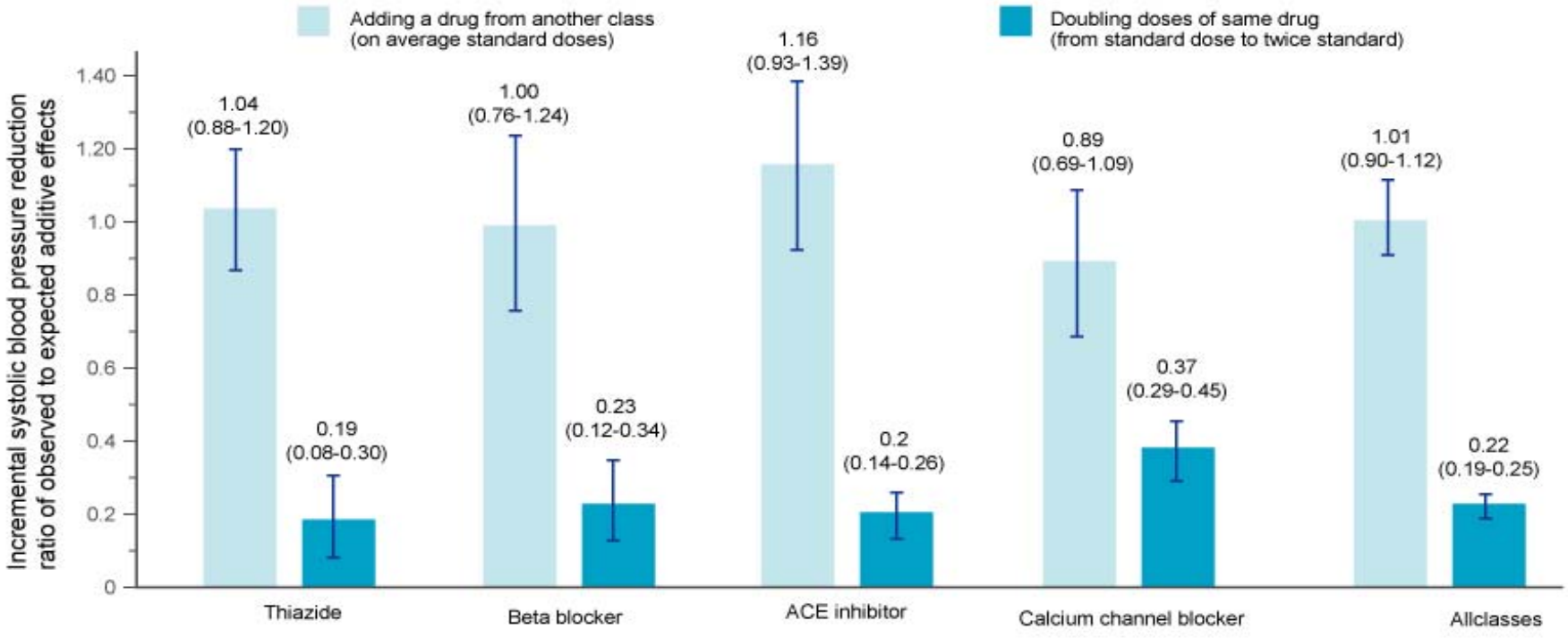
Components with a different mechanism of action interact on complementary pathways of BP control[1]

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

Adding an Antihypertensive Agent
More Effective Than Titrating



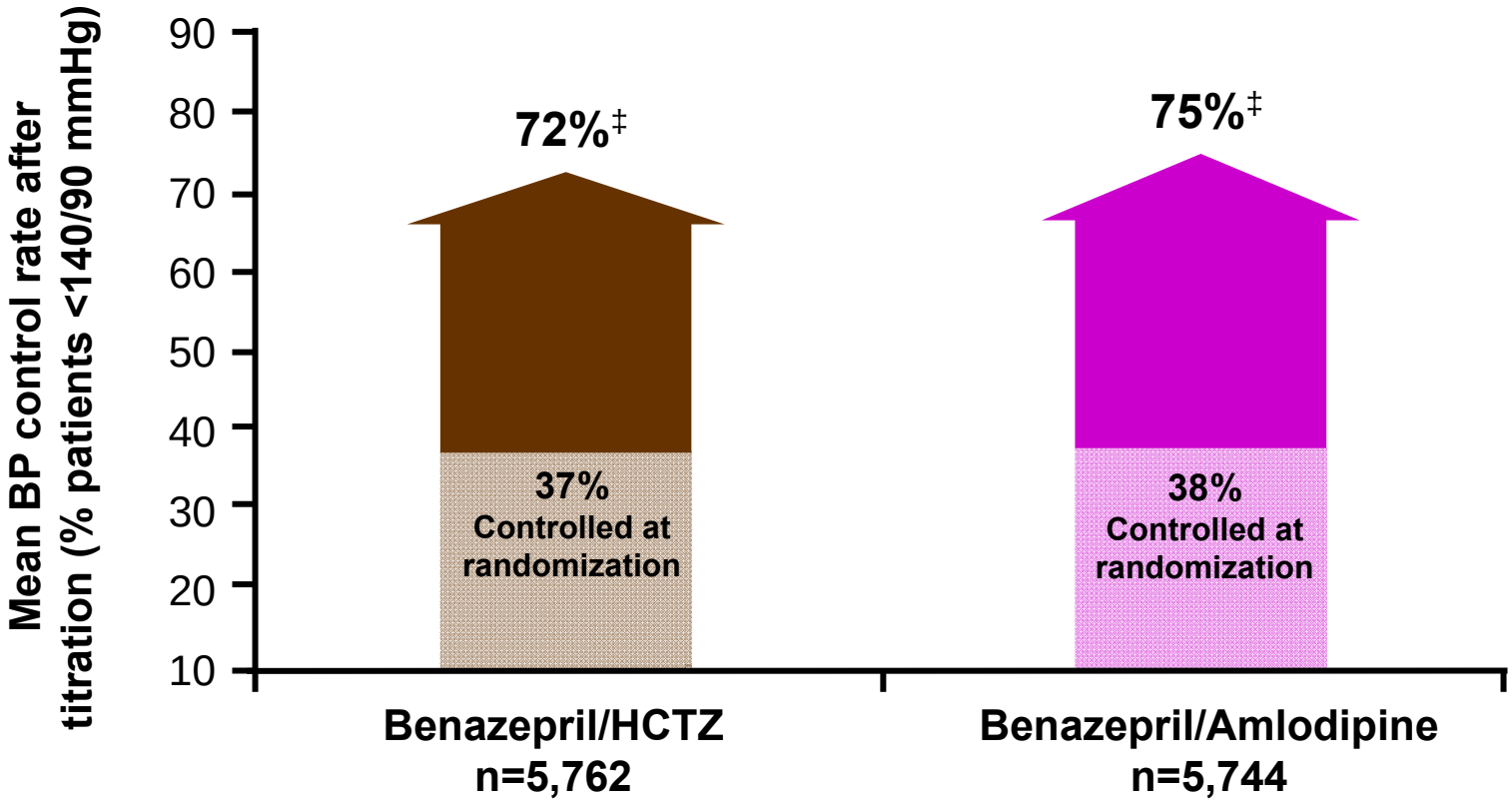
Conclusions from a meta-analysis comparing combination antihypertensive therapy with monotherapy in over 11,000 patients from 42 trials

Wald et al. Am J Med 2009;122:290–300

ACCOMPLISH Study

Target achieved with Multiple Mechanism Therapy

Only ~37% of patients had their BP controlled at baseline despite ~74% of patients receiving ≥2 antihypertensive agents as free combination



*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

Multiple-mechanism Therapy:
Potential Tolerability Benefits

Multiple-mechanism therapy may have an improved tolerability profile compared with its single-mechanism components[1,2]

Components of multiple-mechanism therapy can be given at lower dosages to achieve blood pressure goal than those required as monotherapy ⟶

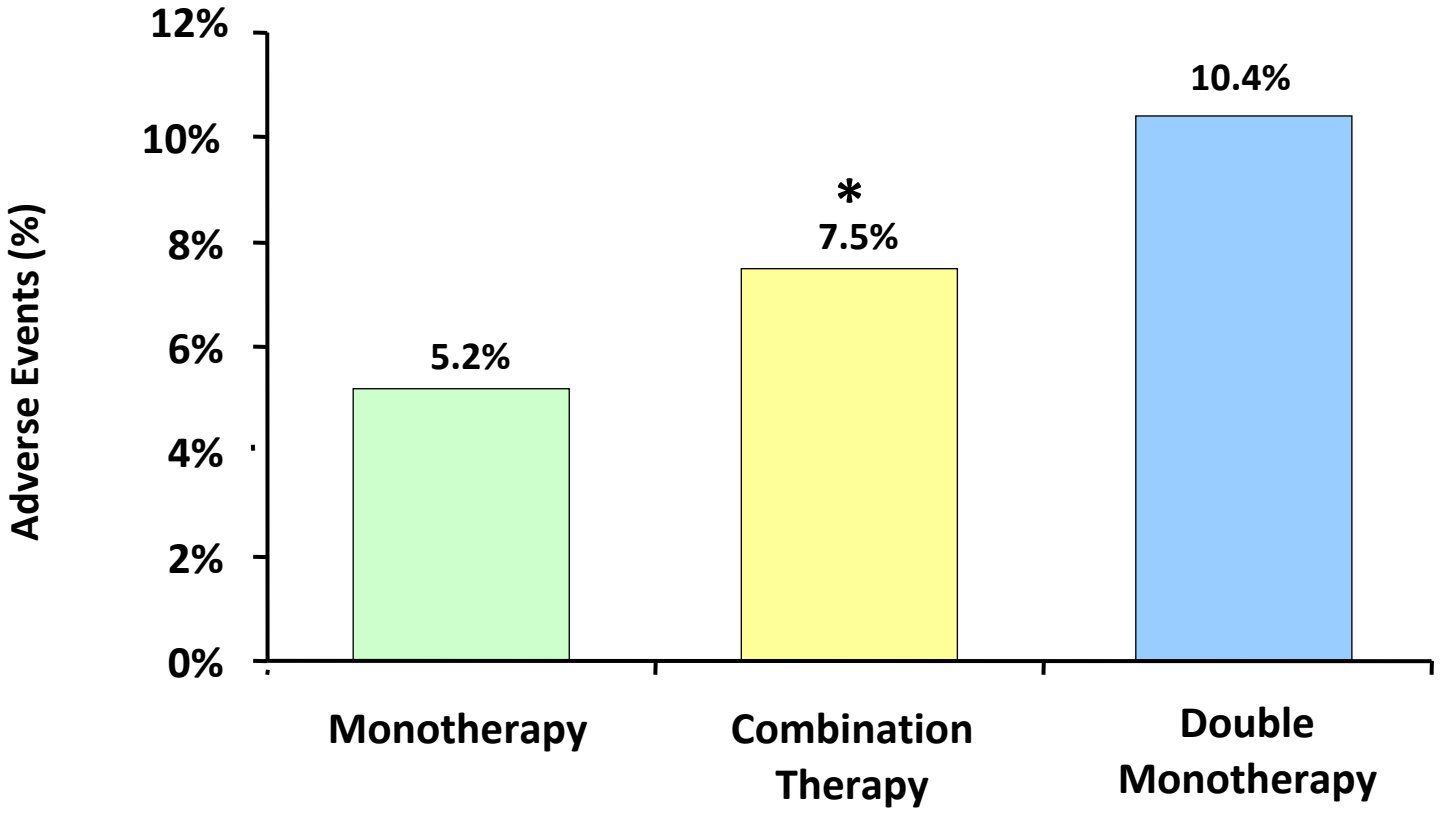
- Better tolerated
- Attenuated compound-specific adverse events

ex) RAAS blockers may attenuate the edema that is caused by CCB

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

Multiple-mechanism Therapy:
Reducing Adverse Effects

Combination Therapy Meta-Analysis



******P*<0.03 combination therapy vs expected additive effect (ie, doubling monotherapy result)**

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

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'

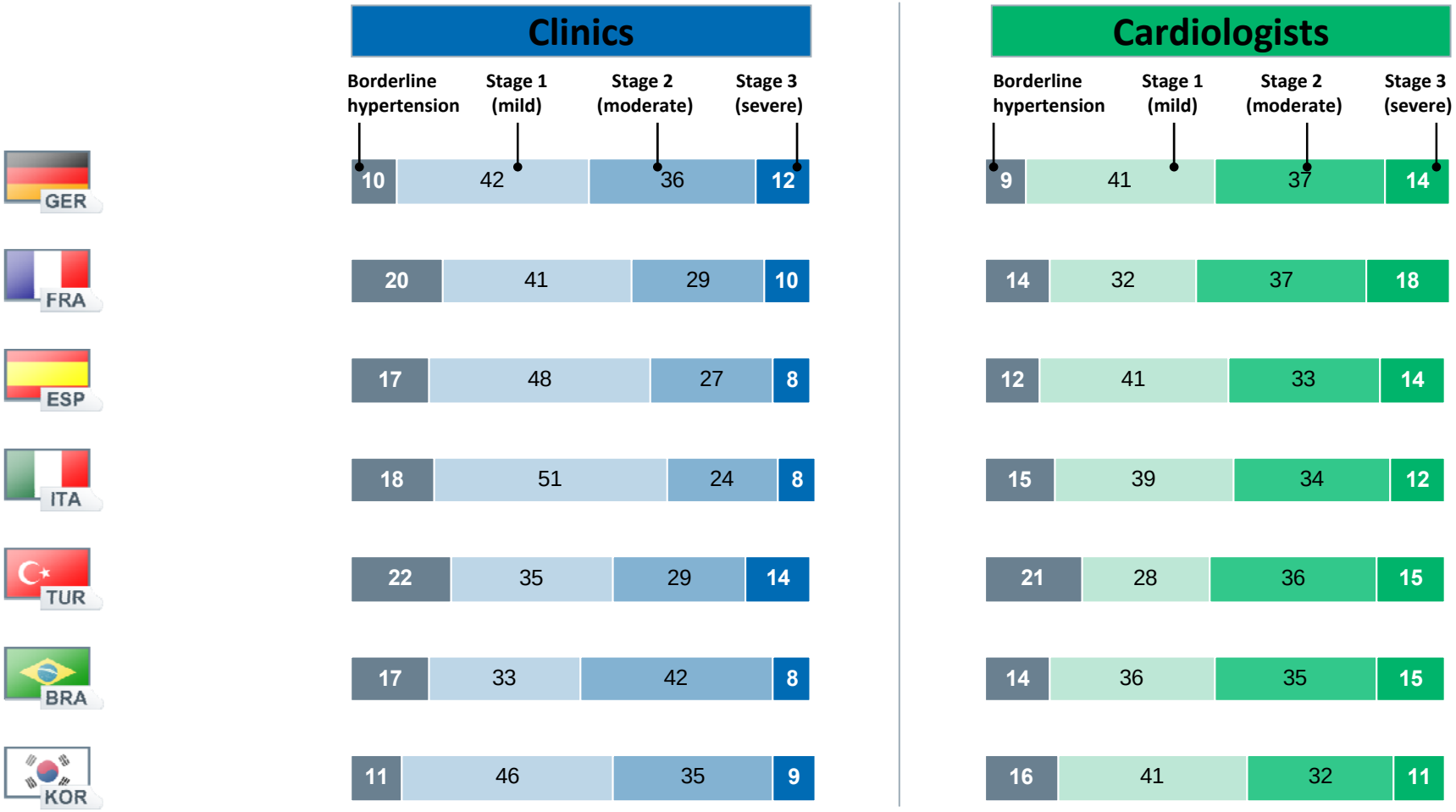
'Whenever possible, use of fixed dose (or single pill) combinations should be preferred, because simplification of treatment carries advantages for compliance to treatment'

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

HTN patients by severity degree

More than 40 % of patients are suffered from stage 2 or 3

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

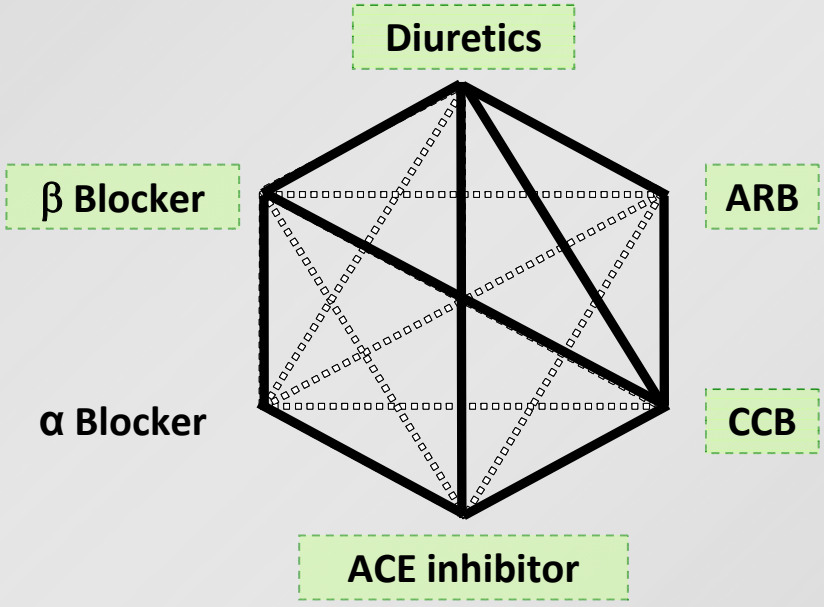


Data Source) Global CV HTN Tracker study (Nov, 2008)

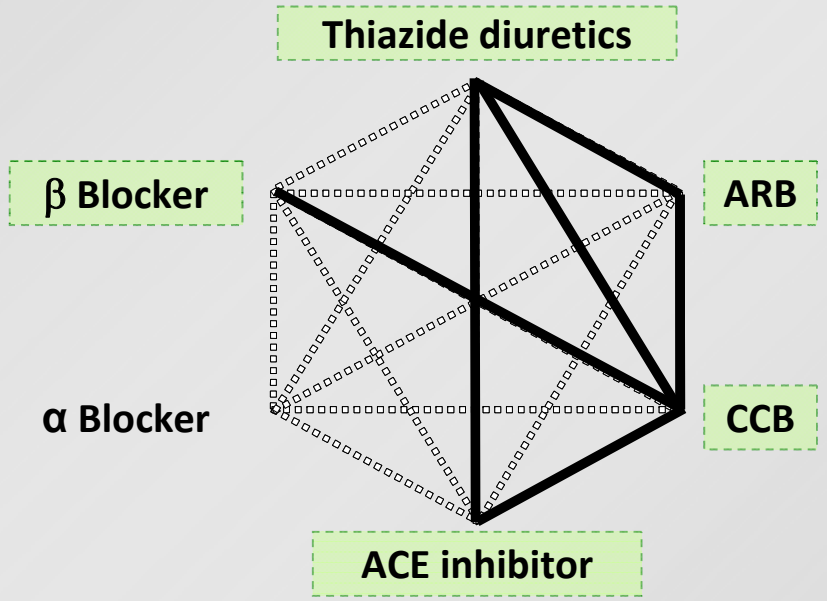
2007 ESH/ESC Guidelines:

Possible Combinations

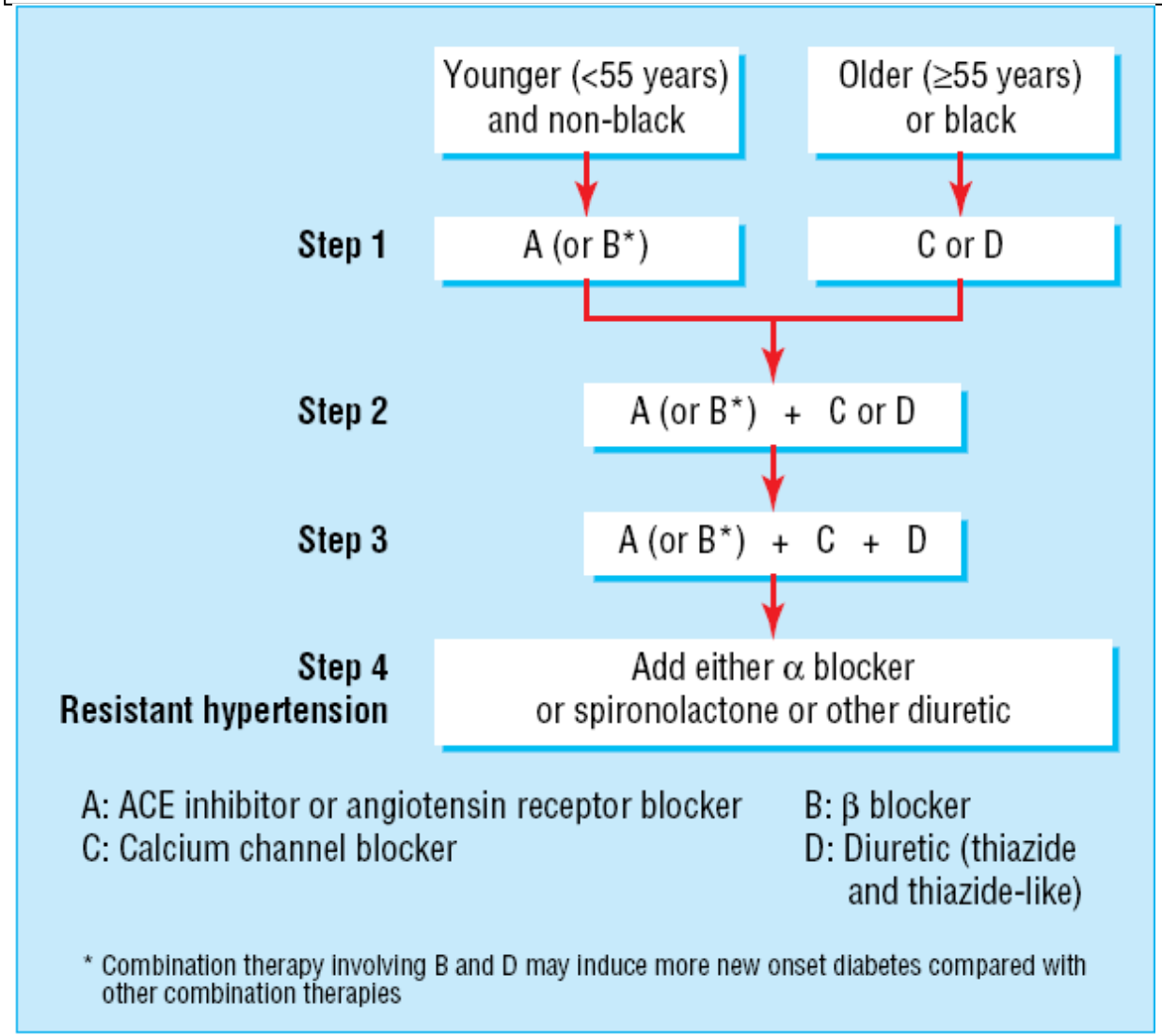
2003 ESH-ESC



2007 ESH-ESC



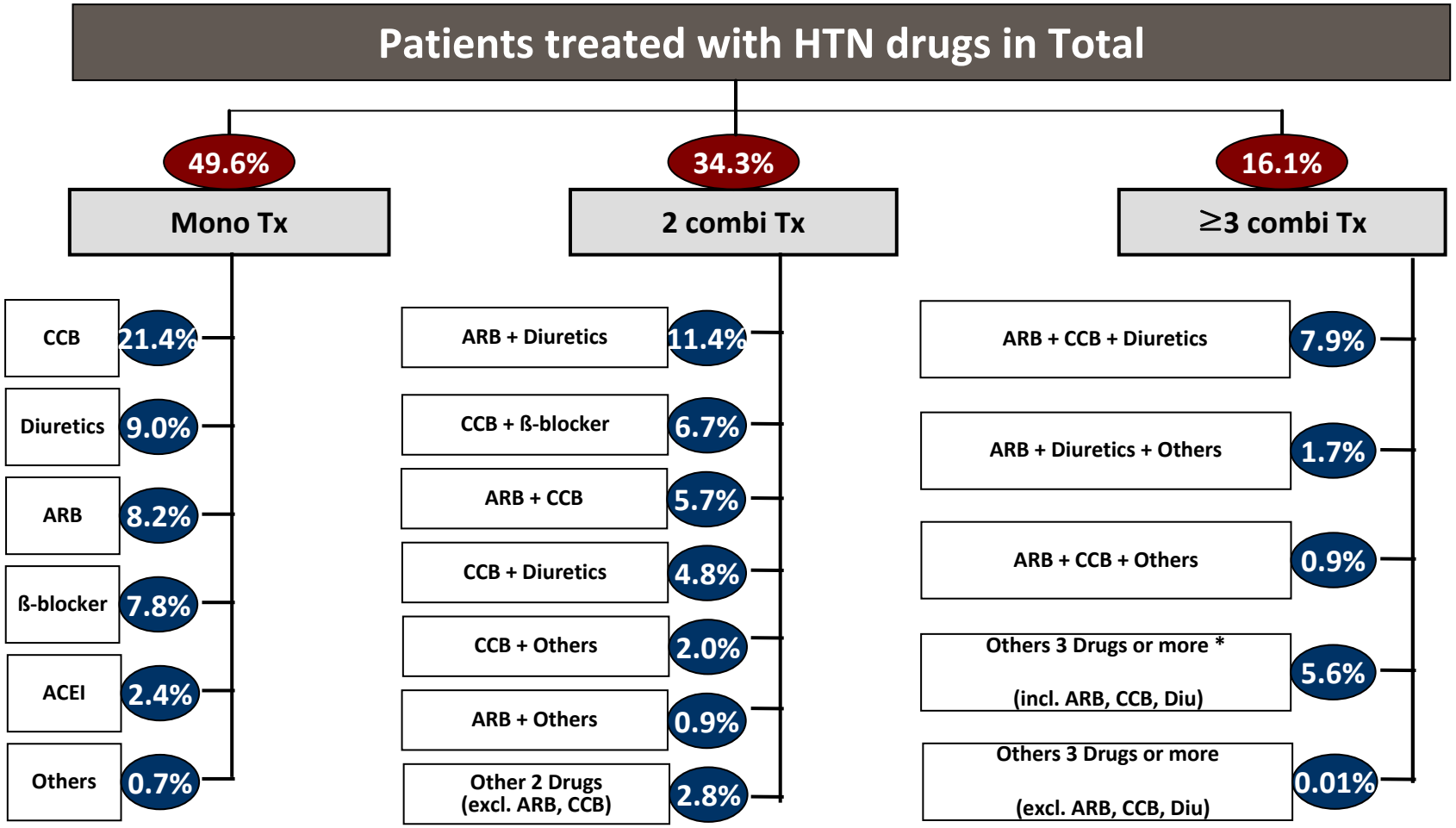
AB/CD rule



2004 BHS IV guideline

Current treatment pattern:

Still many patients need more than 2 agents



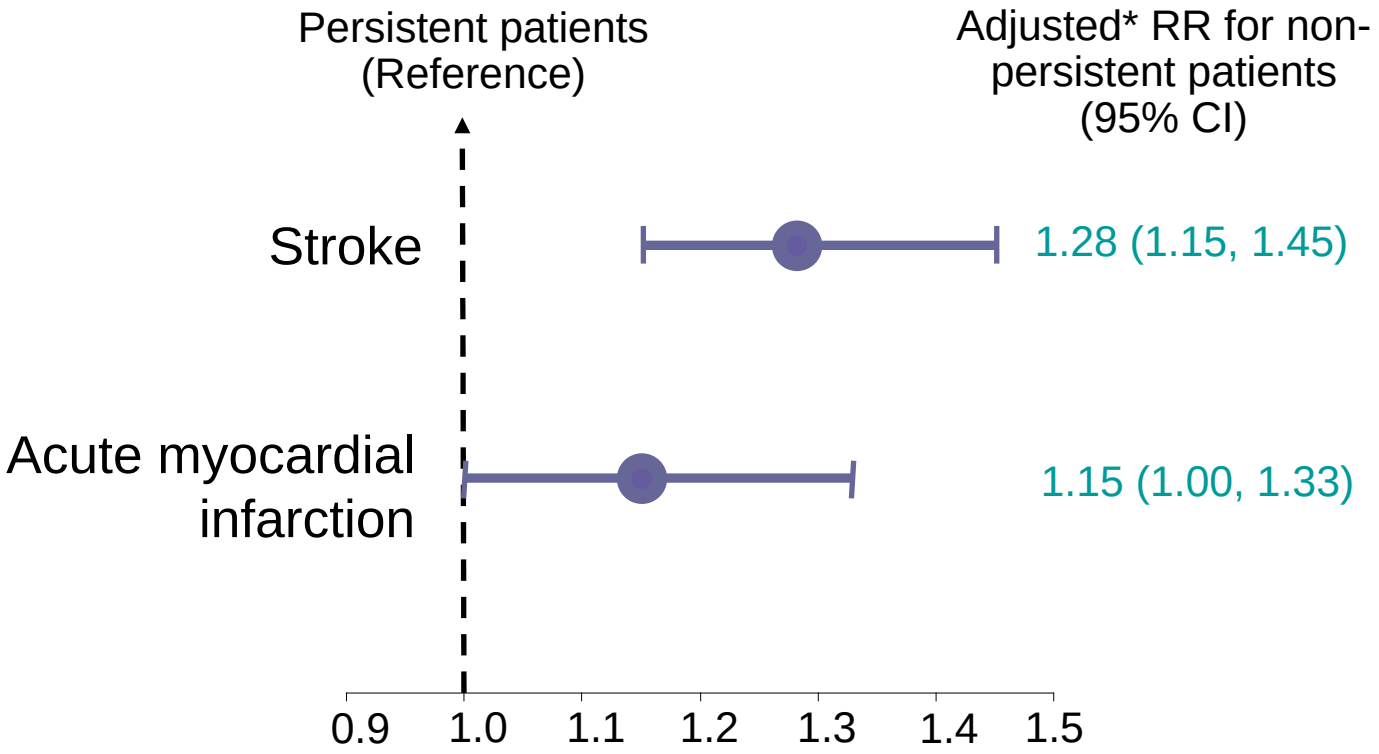
**Combination Therapy = Free combination + SPC (Single Pill Combination)*

URIS, 1Q 2009

Non-persistence with Antihypertensive Therapy

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

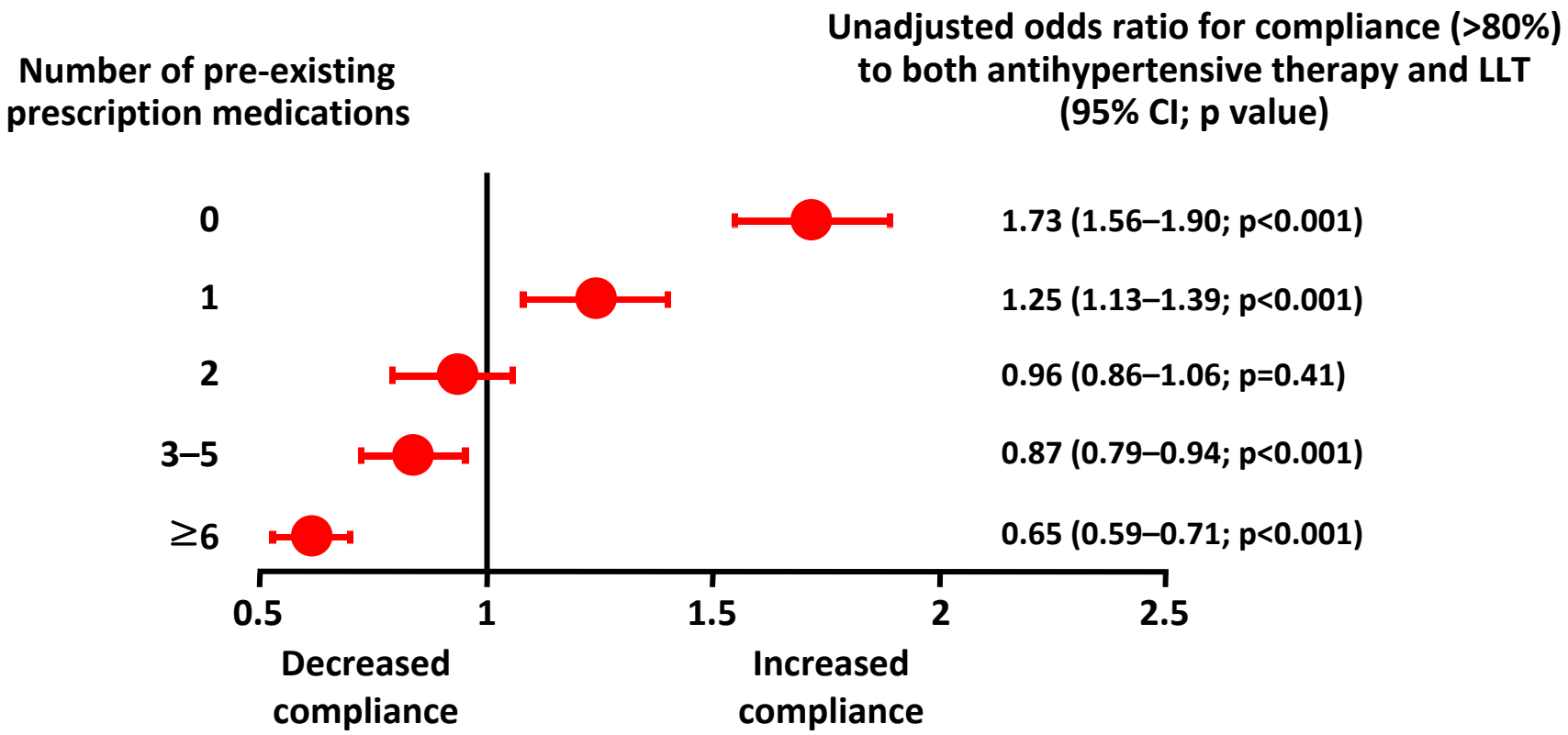
Adherence to Antihypertensives and CV Morbidity

Among 18,806 Newly Diagnosed Hypertensive Patients

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

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

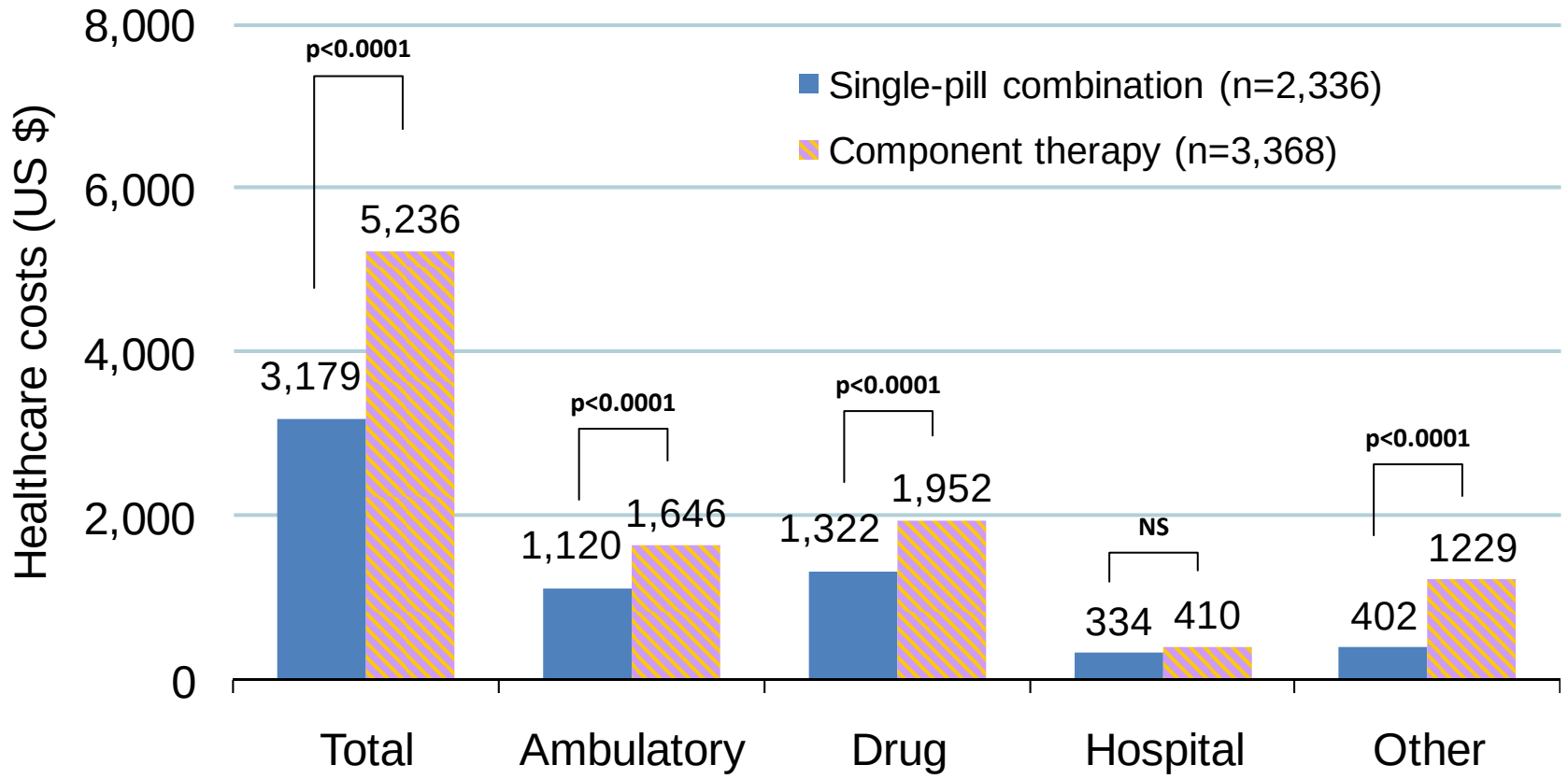
Fixed dose combination Combinations:
Advantages Vs. Free Combinations

	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

Patients Treated with Fixed dose Combinations:
Use Less Resource



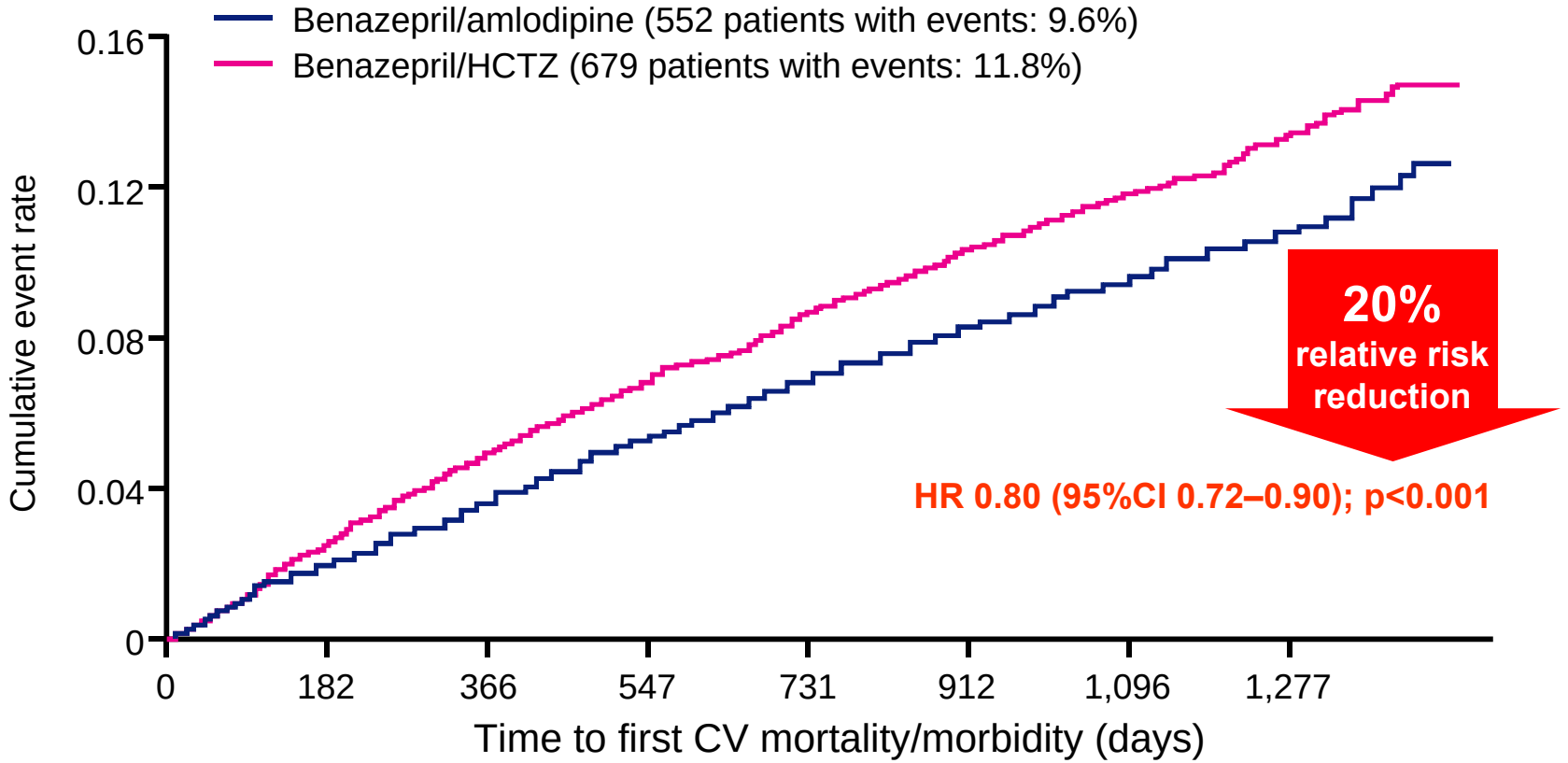
NS = not significant

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

Which Single-pill Combinations?

ACCOMPLISH:

Superior CV Outcomes with RAAS Blocker/Amlodipine Vs. RAAS Blocker/HCTZ



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

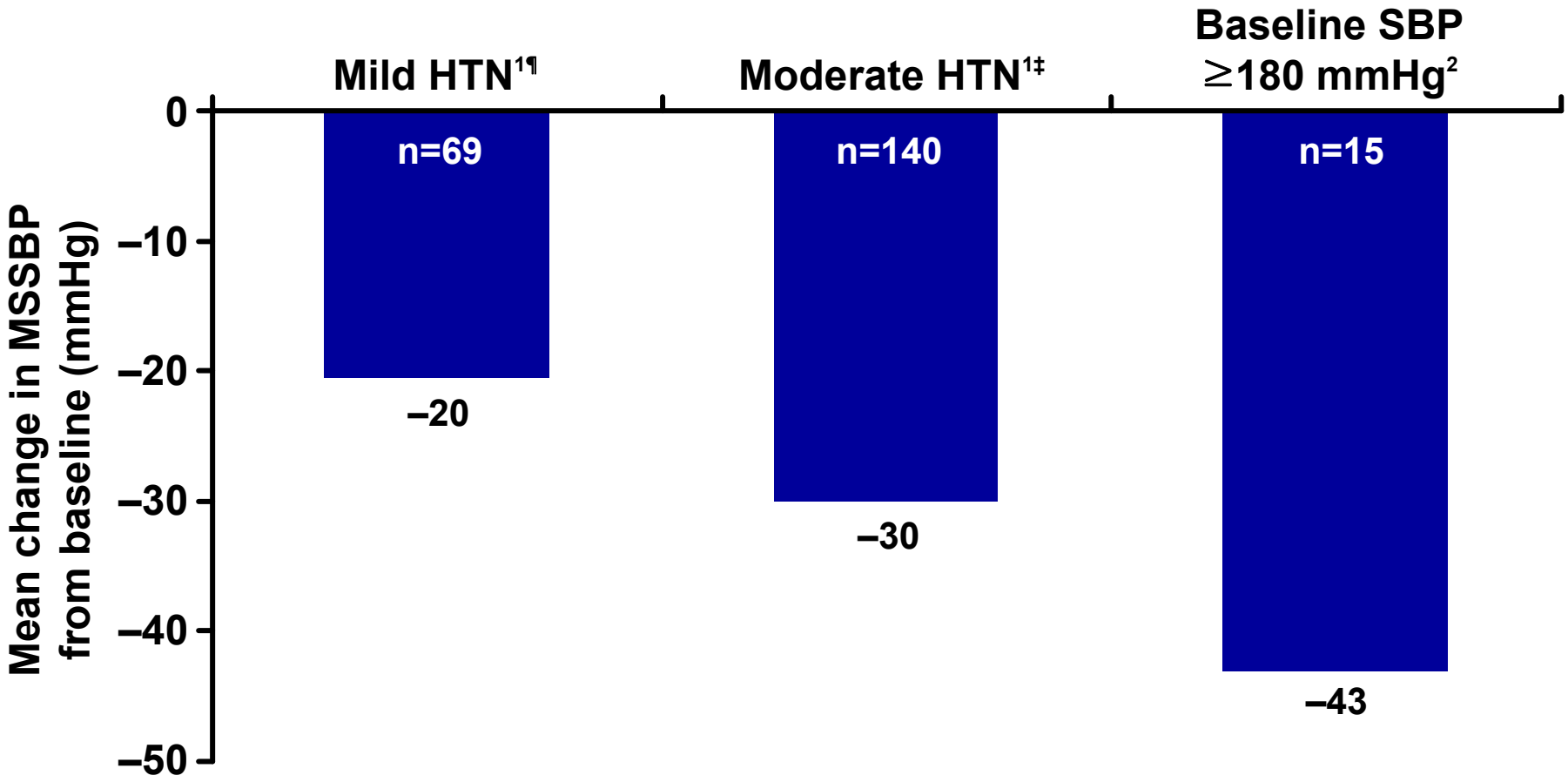
Wealth of Cardiovascular Outcomes Data

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

Amlodipine/Valsartan

Powerful BP Reductions Across Hypertension (HTN) 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)

Effect of ARB/CCB SPC to Asian Patients

Asian Data

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

Objective

To evaluate the efficacy and safety of a single-pill combination of amlodipine/valsartan compared with amlodipine in Asian hypertensive patients inadequately controlled on amlodipine alone

Study Populations

Inclusion Criteria

- Men and Women ≥ 18 and < 86 years with mild-to-moderate essential hypertension (mean sitting DBP ≥ 95 mmHg and < 110 mmHg)

Exclusion Criteria

- Severe hypertension (msDBP ≥ 110 mmHg and/or msSBP ≥ 180 mmHg)
- Secondary hypertension
- A history of hypertensive encephalopathy or cerebrovascular accident; TIA, MI or any type of revascularisation; HF; second or third degree heart block; angina pectoris; significant arrhythmia or valvular heart disease
- Diabetes requiring insulin treatment or poorly controlled type 2 DM
- Known or suspected contraindications or a history of allergy to ARBs or CCBs
- Premenopausal women
- Concomitant use of medications known to have significant effect on BP

Design

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

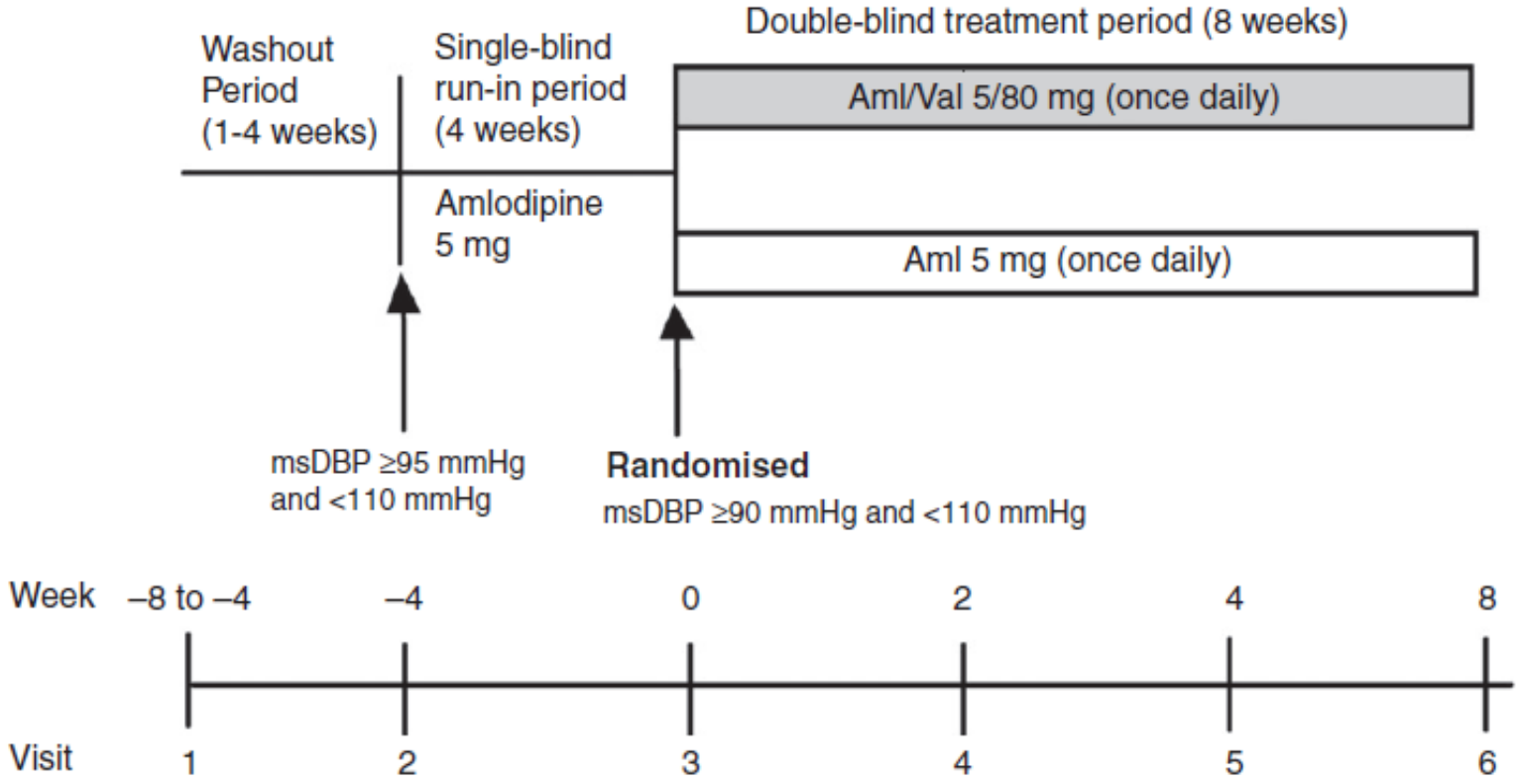


Figure 1. Study design. Aml, amlodipine; Val, valsartan; msDBP, mean sitting diastolic blood pressure.

Patient Disposition

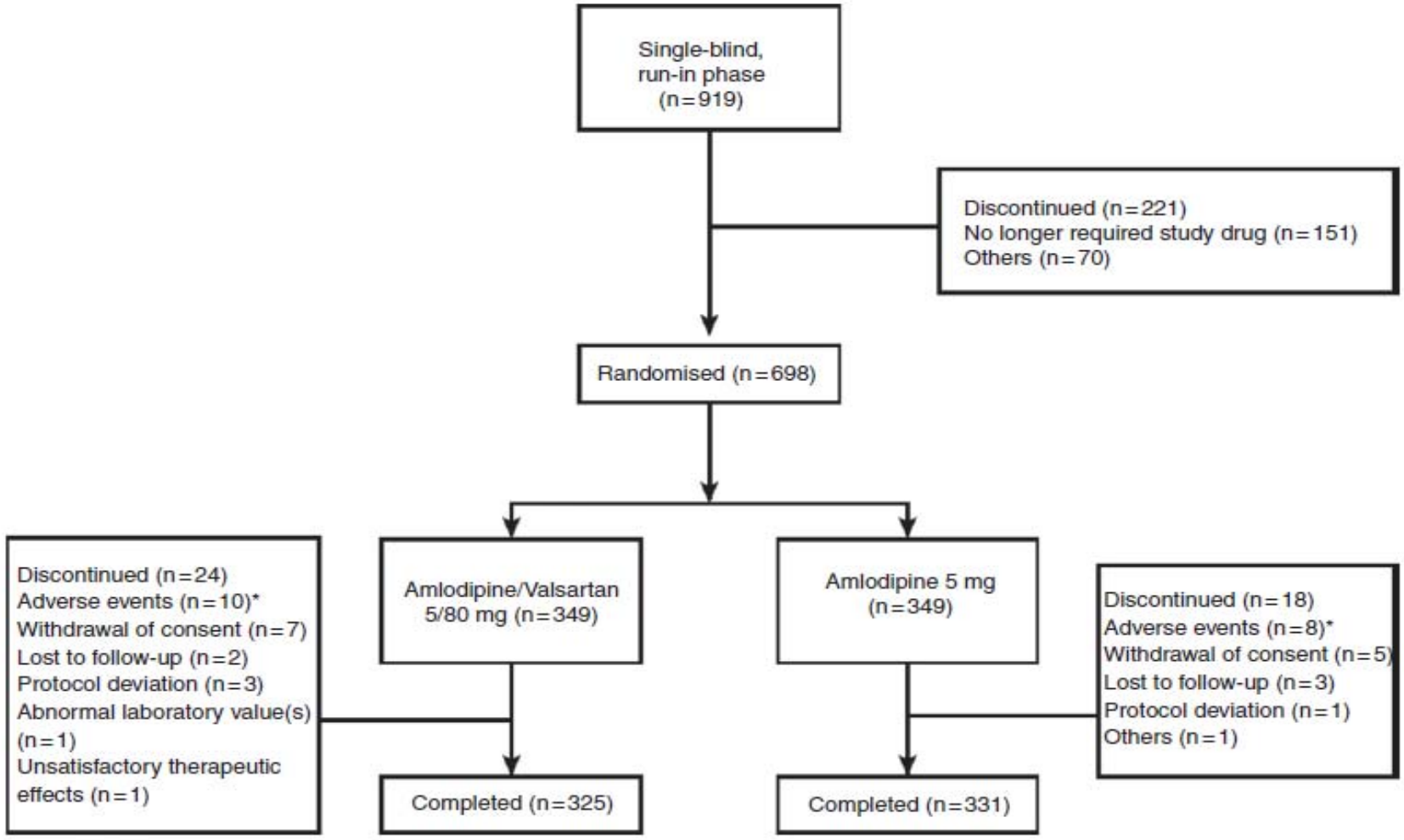


Figure 2. Patient disposition during the treatment period.

Patient Characteristics

Table 1. Patient baseline and demographic characteristics (full-set analysis population).

Category	Aml/Val, 5/80 mg $n = 347$*	Aml 5 mg $n = 349$	*p*-value
Sex, *n* (%)			
Male	213 (61.4)	240 (68.8)	0.041†
Female	134 (38.6)	109 (31.2)	
Age, years	53.4 ± 9.7	54.2 ± 9.1	0.282
Non-elderly (<65 years)	304 (87.6)	305 (87.4)	0.931
Elderly (≥65 years)	43 (12.4)	44 (12.6)	
Race/ethnicity			
Chinese	300 (86.5)	301 (86.2)	0.936
Other	47 (13.5)	48 (13.8)	
BMI, kg/m^2, *n*	25.8 ± 3.1, 344	25.7 ± 3.0, 347	0.580
Type 2 diabetes history, *n* (%)	24 (6.9)	31 (8.9)	0.336
Duration of hypertension (years)	8.3 ± 7.45	8.4 ± 7.88	0.842
Mean sitting DBP (mmHg)	94.5 ± 4.24	94.5 ± 4.28	0.912
Mean sitting SBP (mmHg)	139.8 ± 11.90	139.3 ± 11.38	0.610

*Two patients in the Aml/Val group were excluded from the full-set analysis population for having no post-baseline efficacy assessment.
†Indicates statistical significance at 0.05 level.
Aml, amlodipine; Val, valsartan; BMI, body mass index; DBP, diastolic blood pressure; SBP, systolic blood pressure.

Efficacy Outcomes

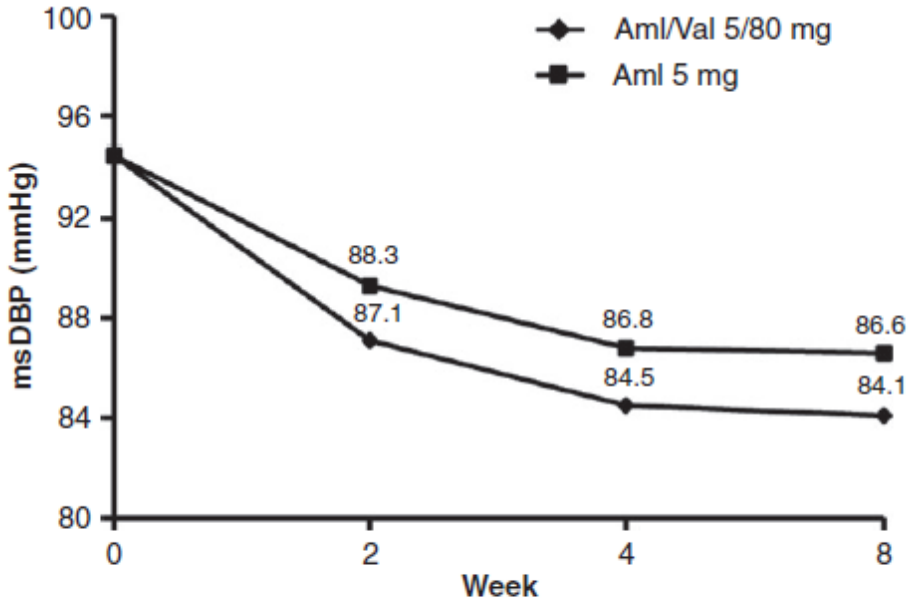


Figure 3. Mean sitting diastolic blood pressure (msDBP) by treatment and week (Full-set analysis population). $p < 0.0001$ for both the treatment groups at week 4 and at week 8. Aml, amlodipine; Val, valsartan; msDBP, mean sitting diastolic blood pressure.

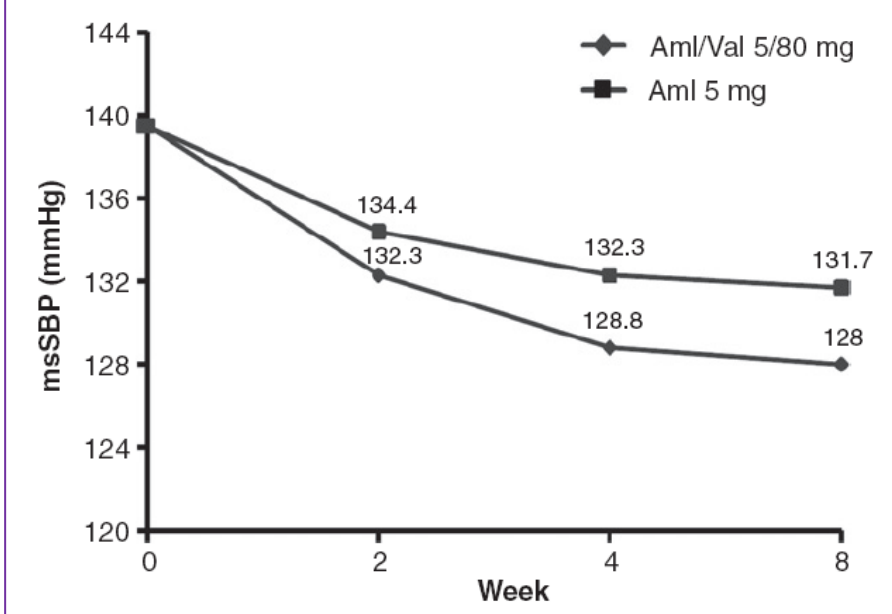


Figure 4. Mean sitting systolic blood pressure (msSBP) by treatment and week (full-set analysis population). $p < 0.0001$ for both the treatment groups at week 4 and at week 8. Aml, amlodipine; Val, valsartan; msSBP, mean sitting systolic blood pressure.

- 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)

Ambulatory BP measurement

Table 3. Change from baseline in mean 24-hour, daytime and nighttime ambulatory BP (mmHg).

	Aml/Val 5/80 mg ($n=41$)		Aml 5 mg ($n=41$)	
	Baseline	Change	Baseline	Change
Mean ambulatory DBP, mean (SD)				
24-hour	88.4 (7.86)	−6.3 (5.85)*	84.5 (7.33)	0.3 (5.82)
Daytime	92.7 (8.40)	−7.2 (6.12)†	88.7 (8.40)	−0.4 (6.81)
Nighttime	79.8 (8.60)†	−4.8 (7.83)†‡	76.2 (7.31)	1.2 (6.78)
Mean ambulatory SBP, mean (SD)				
24-hour	132.2 (10.28)	−7.3 (7.62)*	130.8 (9.68)	−0.2 (8.64)
Daytime	136.9 (11.16)	−8.3 (8.04)†	135.7 (10.61)	−1.1 (9.53)
Nighttime	122.4 (10.70)‡	−5.4 (9.33)†‡	121.4 (10.12)	0.9 (10.02)

*$p<0.0001$ vs. Aml 5 mg; †$p<0.005$ vs. Aml 5 mg; ‡$n=40$.
Aml, amlodipine; Val, valsartan; DBP, diastolic blood pressure; SBP, systolic blood pressure; SD, standard deviation.

- At week 8 endpoint, the reductions in 24-h ambulatory BP from baseline were significant in the Aml/Val group (7.3/6.3mmHg;p<0.0001), whereas the change was not significant with Aml 5mg alone (-0.2/+0.3mmHg; p>0.05)

Ambulatory BP measurement

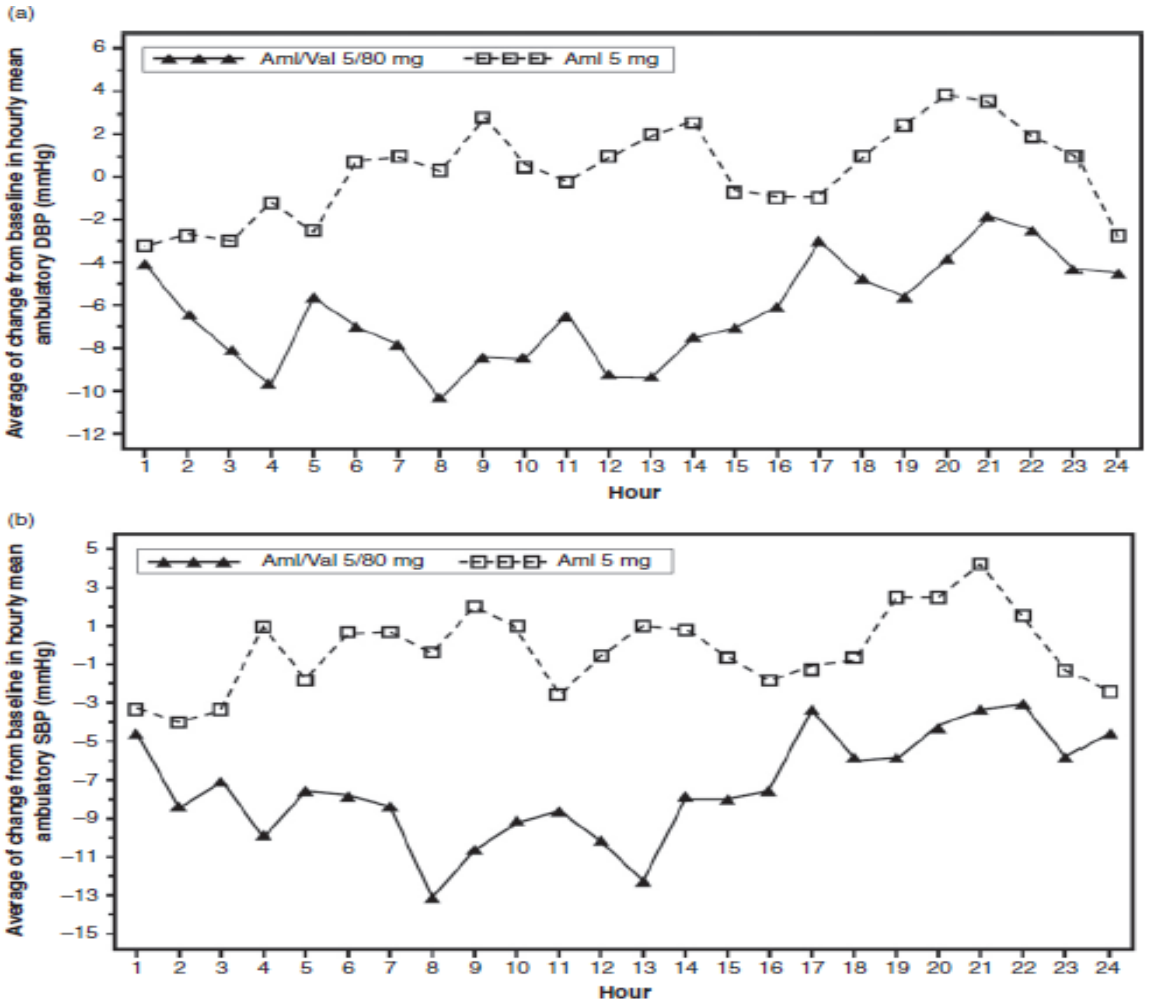


Figure 5. Change from baseline in hourly mean ambulatory BP (full-set analysis population). (a) Mean ambulatory DBP by post-dosing hour and treatment group (b) Mean ambulatory SBP by post-dosing hour and treatment group. Aml, amlodipine; Val, valsartan; DBP, diastolic blood pressure; SBP, systolic blood pressure.

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 $\geq$ 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.

Summary

- 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.

Conclusion

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.