Dukarb®

The Smallest,
But the Strongest !!

성균관의대 강북삼성병원 순환기내과

이종영

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Importance of Intensive BP Lowering

01 BP, Risk Factor for CVD

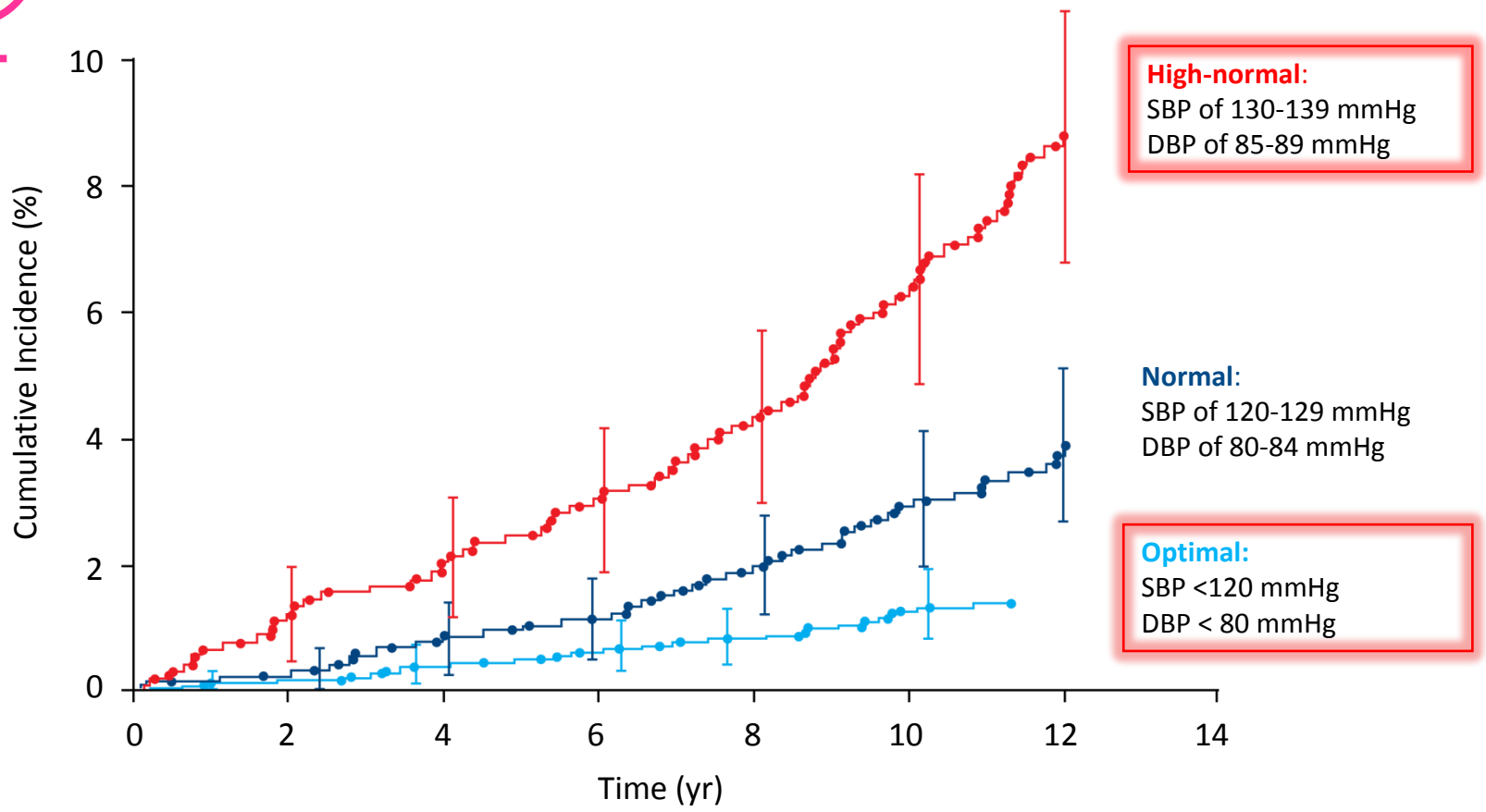
02 Effects of Intensive BP Lowering

- SPRINT
- Meta-analysis Study

03 Management of Hypertension in Korea

BP, Risk Factor for CVD (1)

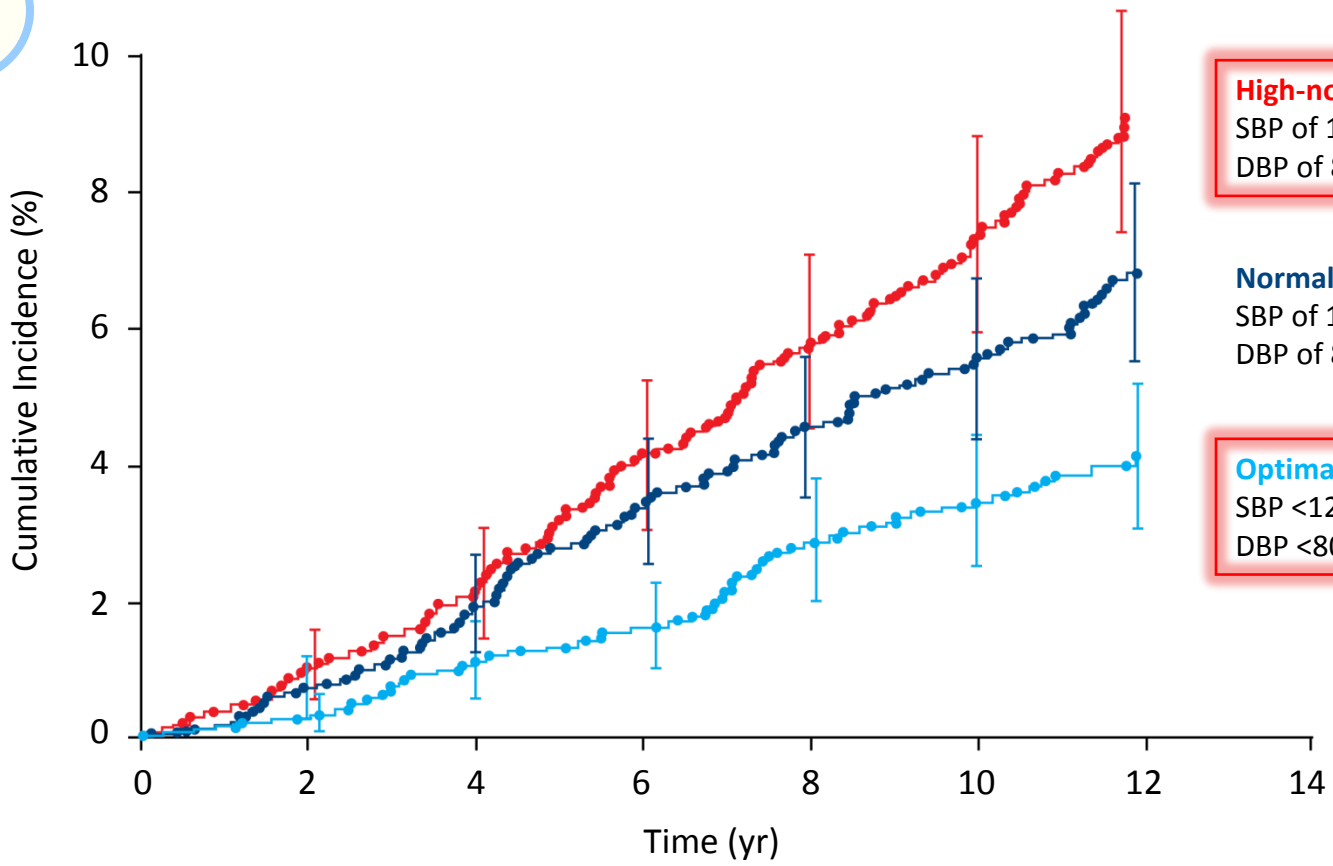
Women



N Engl J Med 2001;345:1291-1297

BP, Risk Factor for CVD (2)

Men



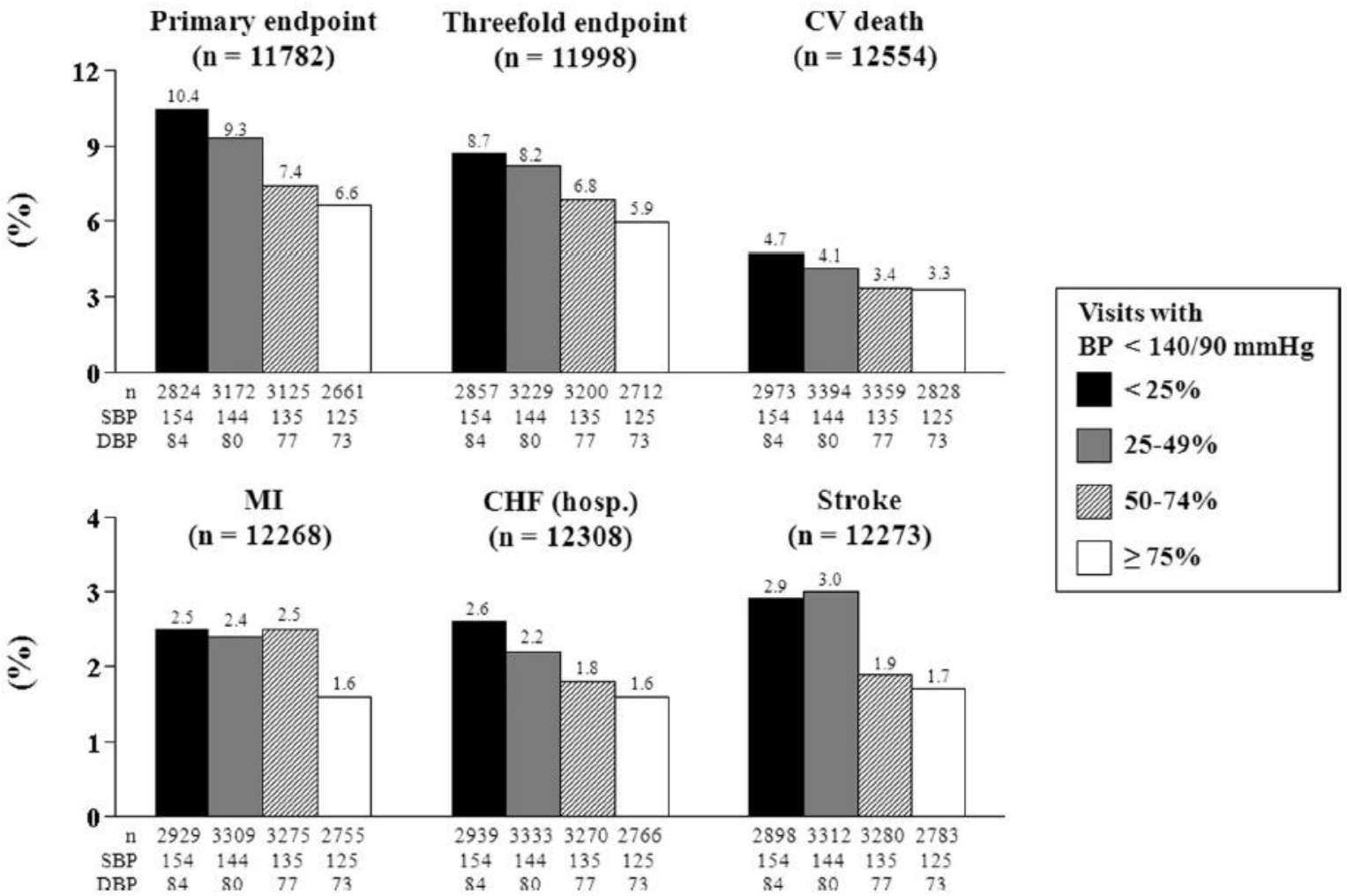
High-normal:
SBP of 130-139 mmHg
DBP of 85-89 mmHg

Normal:
SBP of 120-129 mmHg
DBP of 80-84 mmHg

Optimal:
SBP <120 mmHg
DBP <80 mmHg

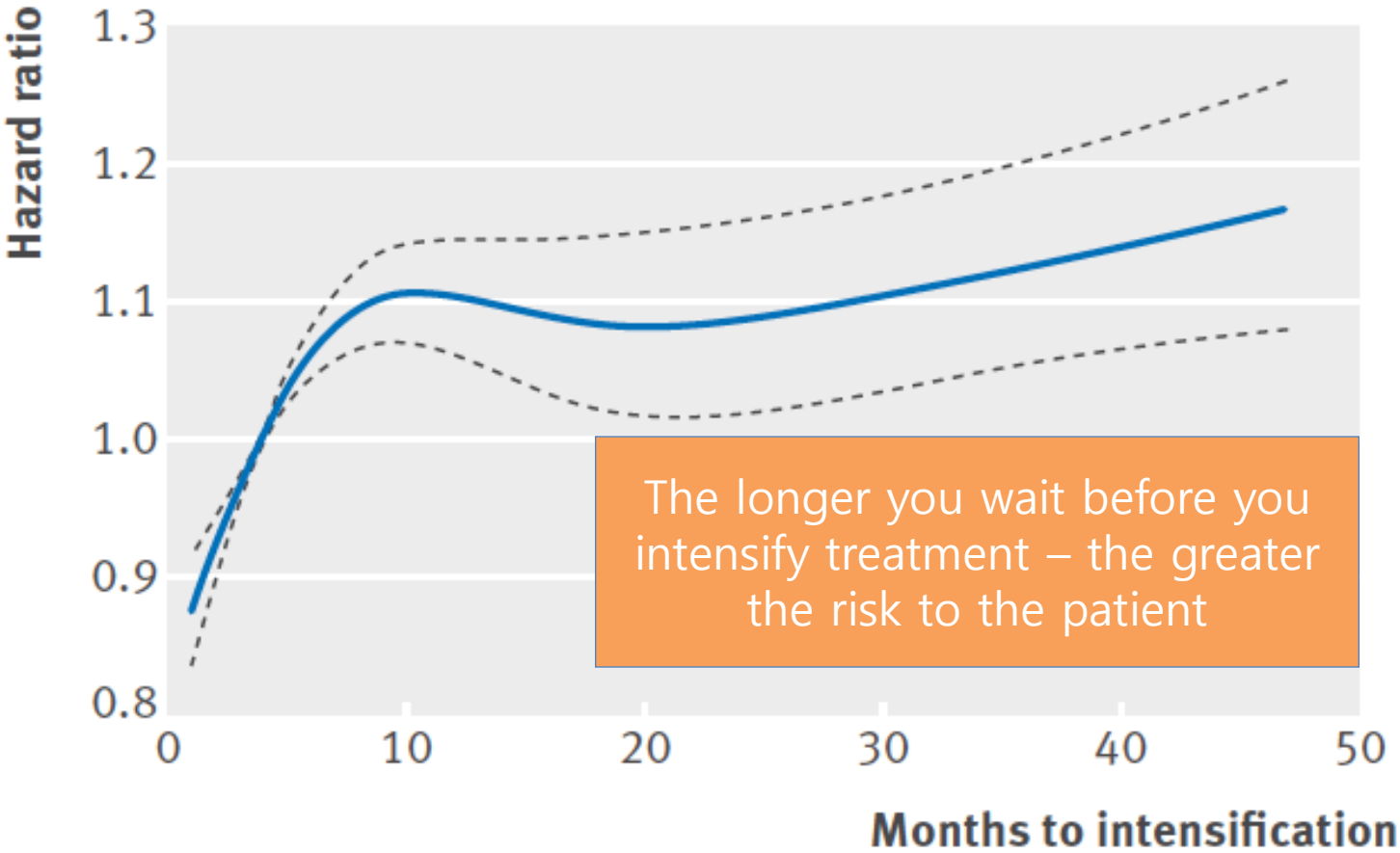
N Engl J Med 2001;345:1291-1297

Time in BP control and Clinical Outcomes



Mancia G, et al. Circulation 2011

Time to treatment Intensification of BP treatment and risk of CV events or death



Xu W, et al. BMJ 2015

Importance of Intensive BP Lowering

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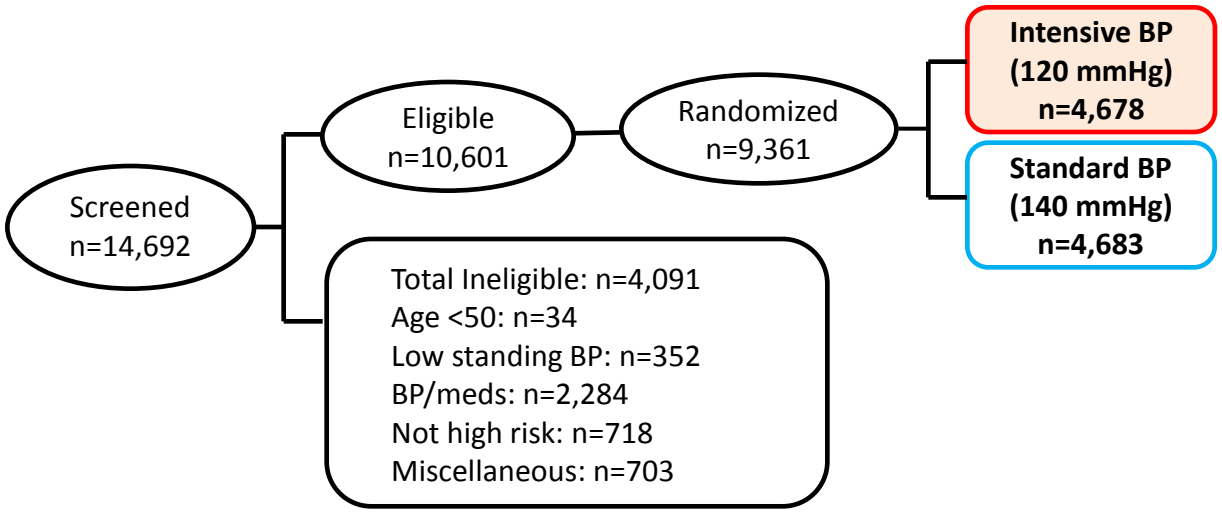
The SBP Intervention Trial (1)

- **The overall enrollment experience**

  - CONSORT(consolidated standards of reporting trials) diagram



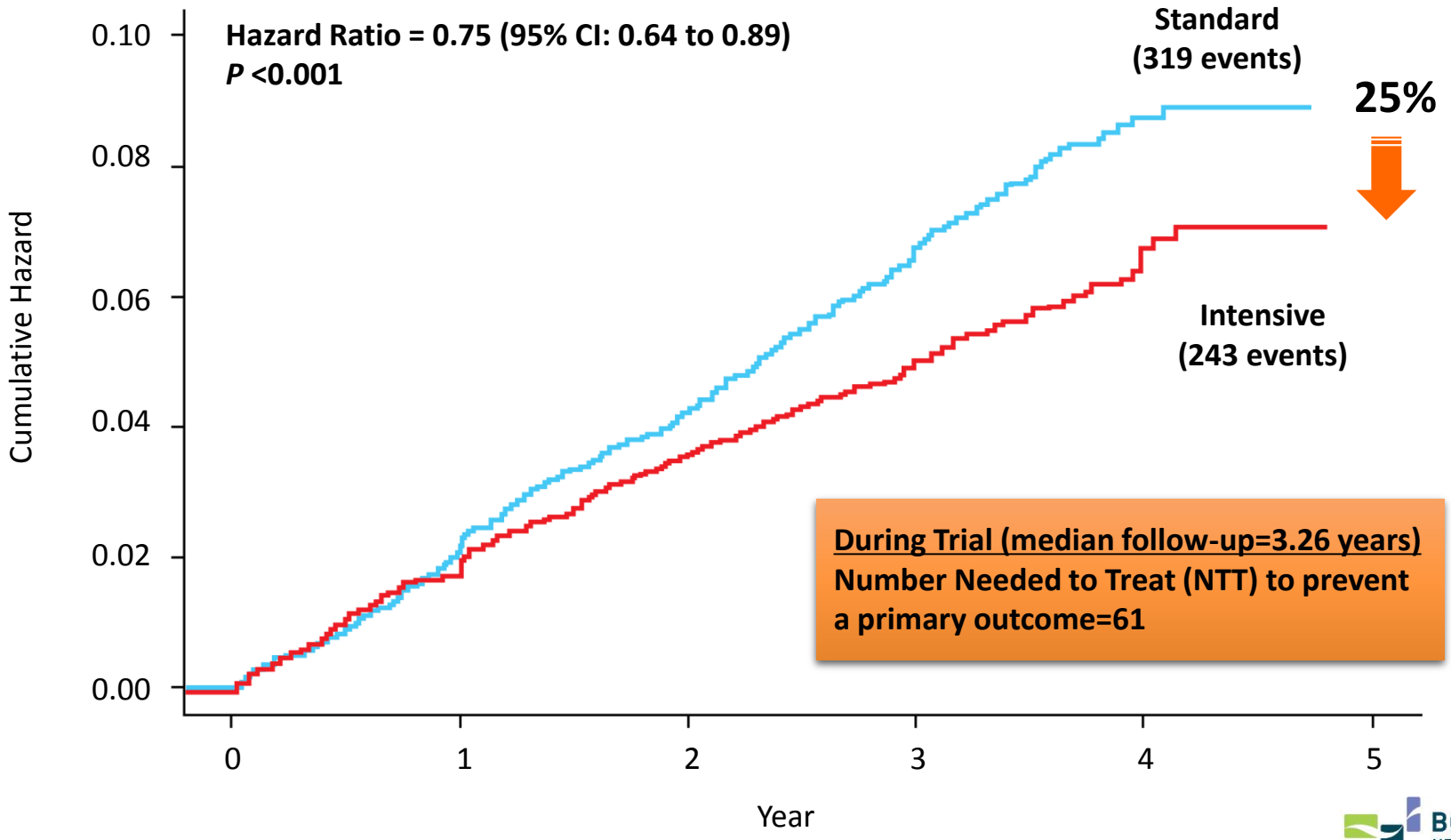
- **Primary outcome**

  − First occurrence of MI, non-MI ACS, Stroke, Acute decompensated HF, CVD death

N Engl J Med 2015;373:2103-2116

The SBP Intervention Trial (2)

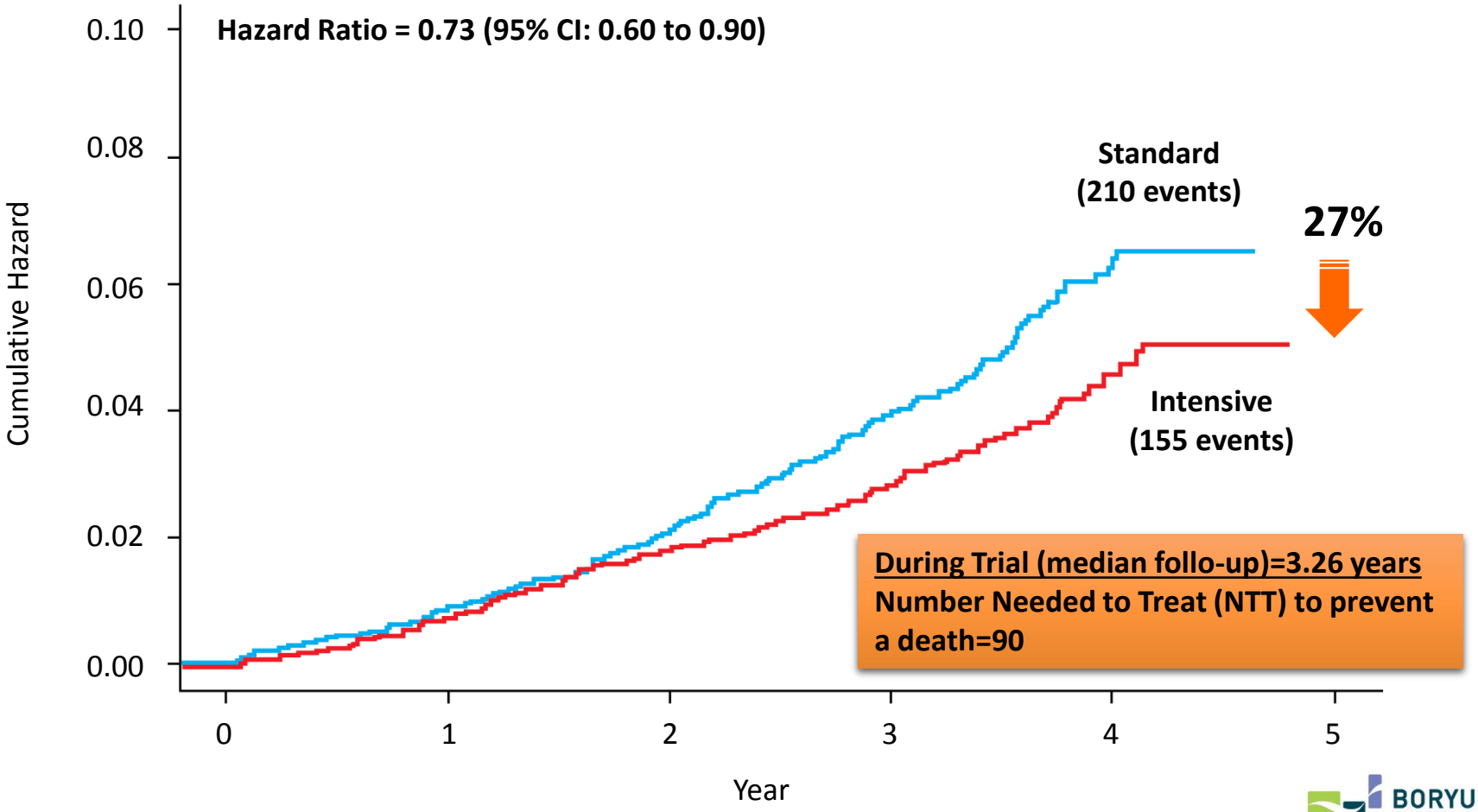
- **Results – Primary outcome**



N Engl J Med 2015;373:2103-2116

The SBP Intervention Trial (3)

- **Results – Death from any cause**

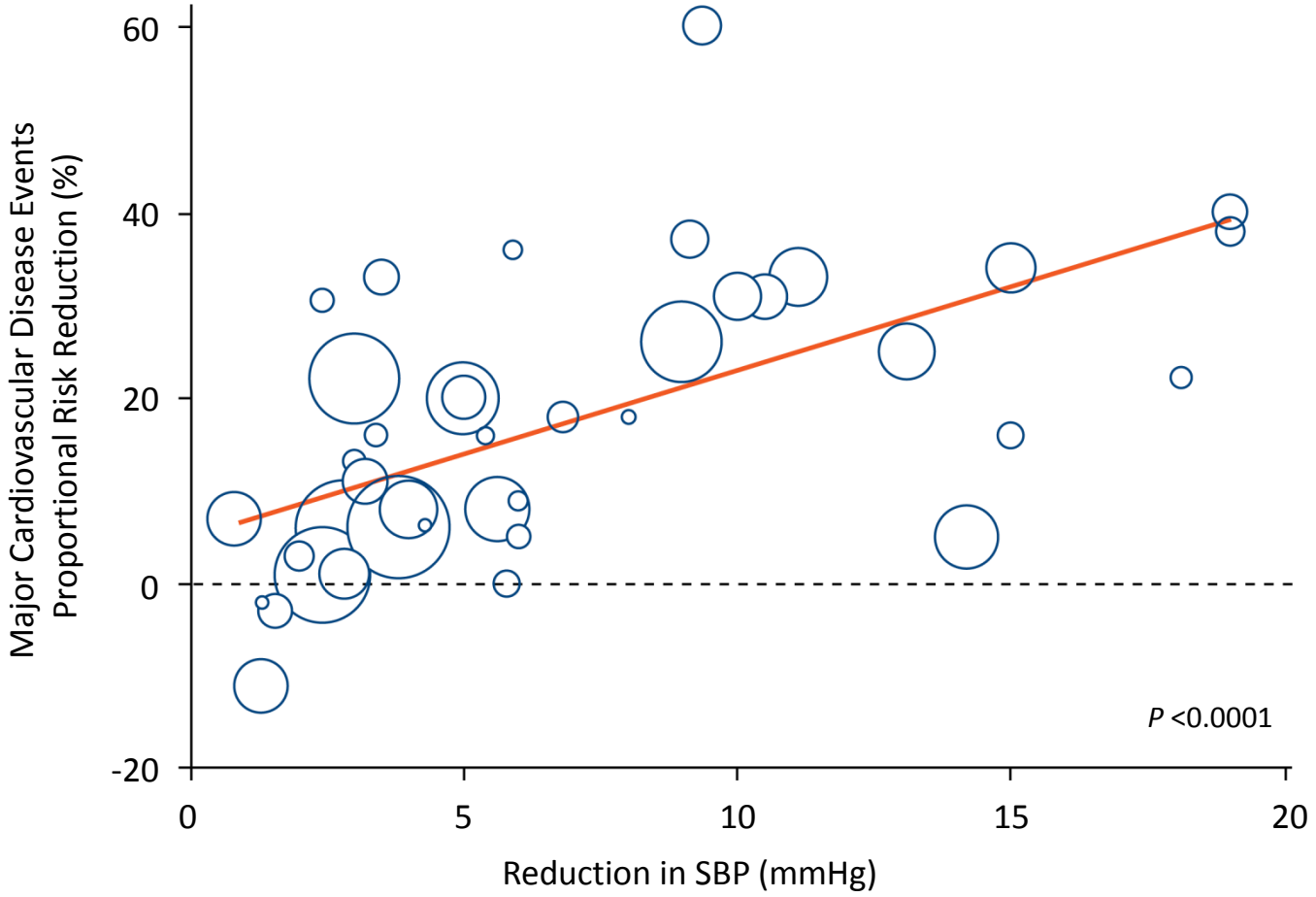


N Engl J Med 2015;373:2103-2116

Meta-analysis

BP Lowering for Prevention of CVD and Death (1)

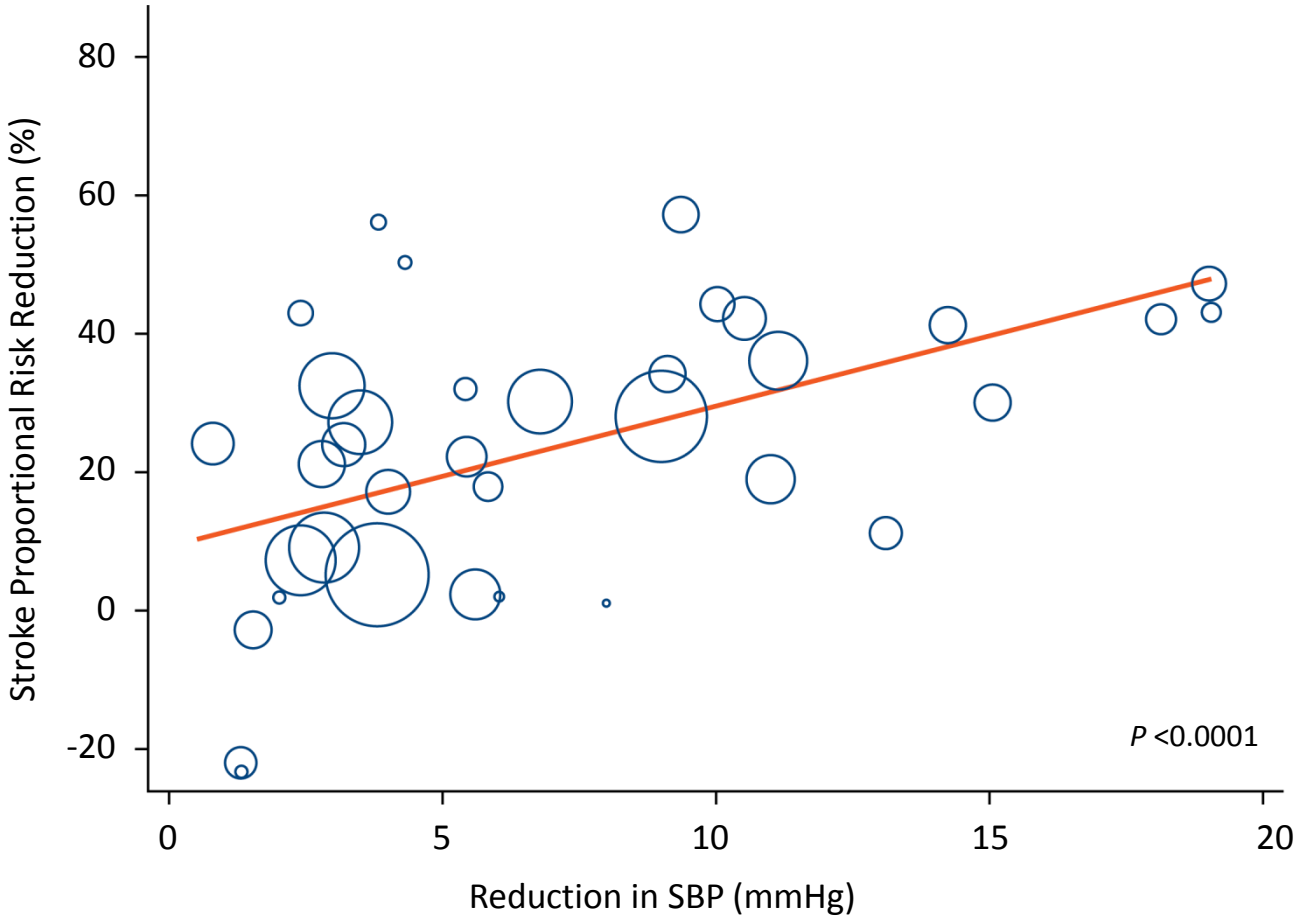
- **Results – Major CVD**



Lancet 2016;387:957-967

BP Lowering for Prevention of CVD and Death (2)

- **Results - Stroke**

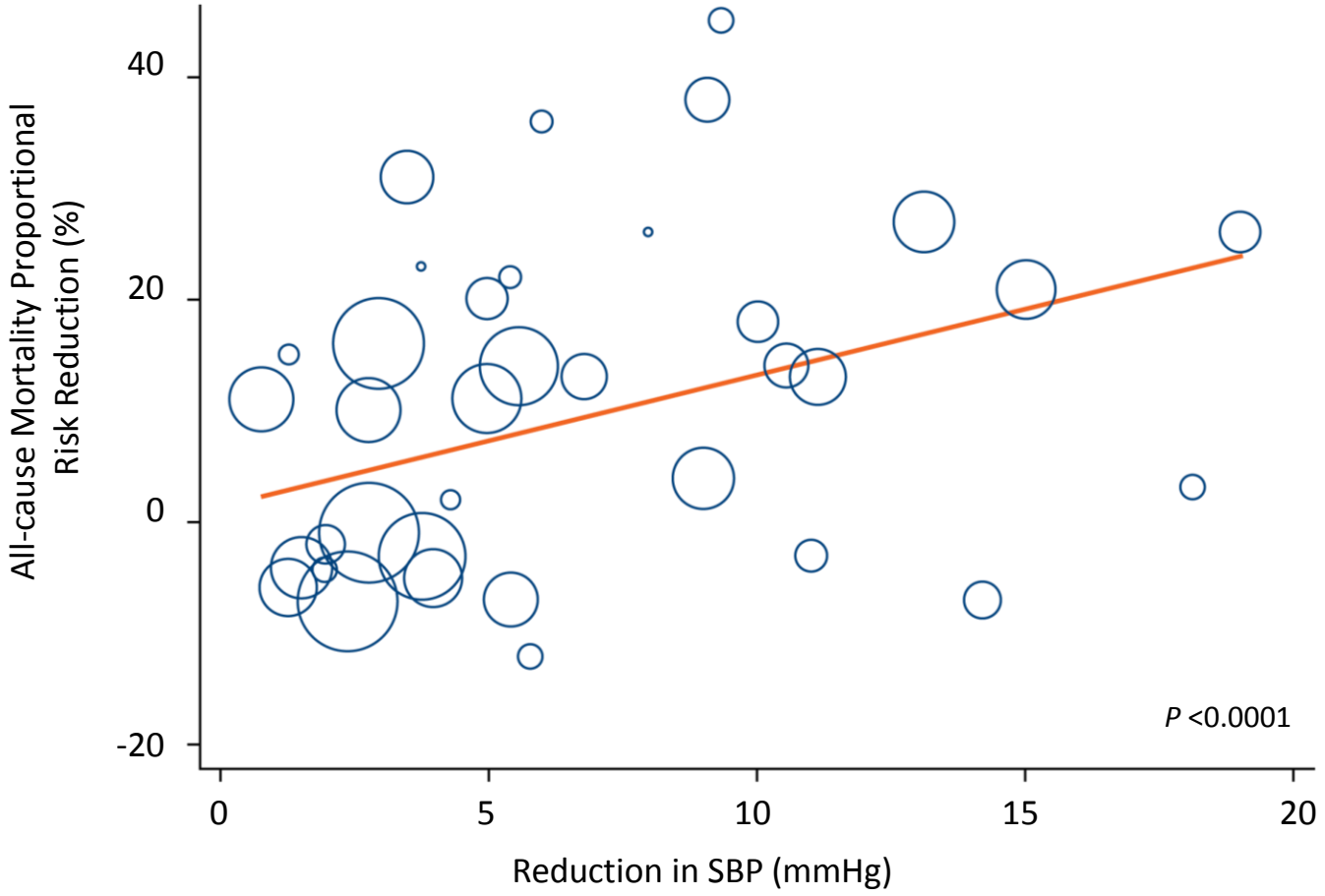


Lancet 2016;387:957-967

Meta-analysis

BP Lowering for Prevention of CVD and Death (3)

- **Results – All-cause mortality**



Lancet 2016;387:957-967

Importance of Intensive BP Lowering

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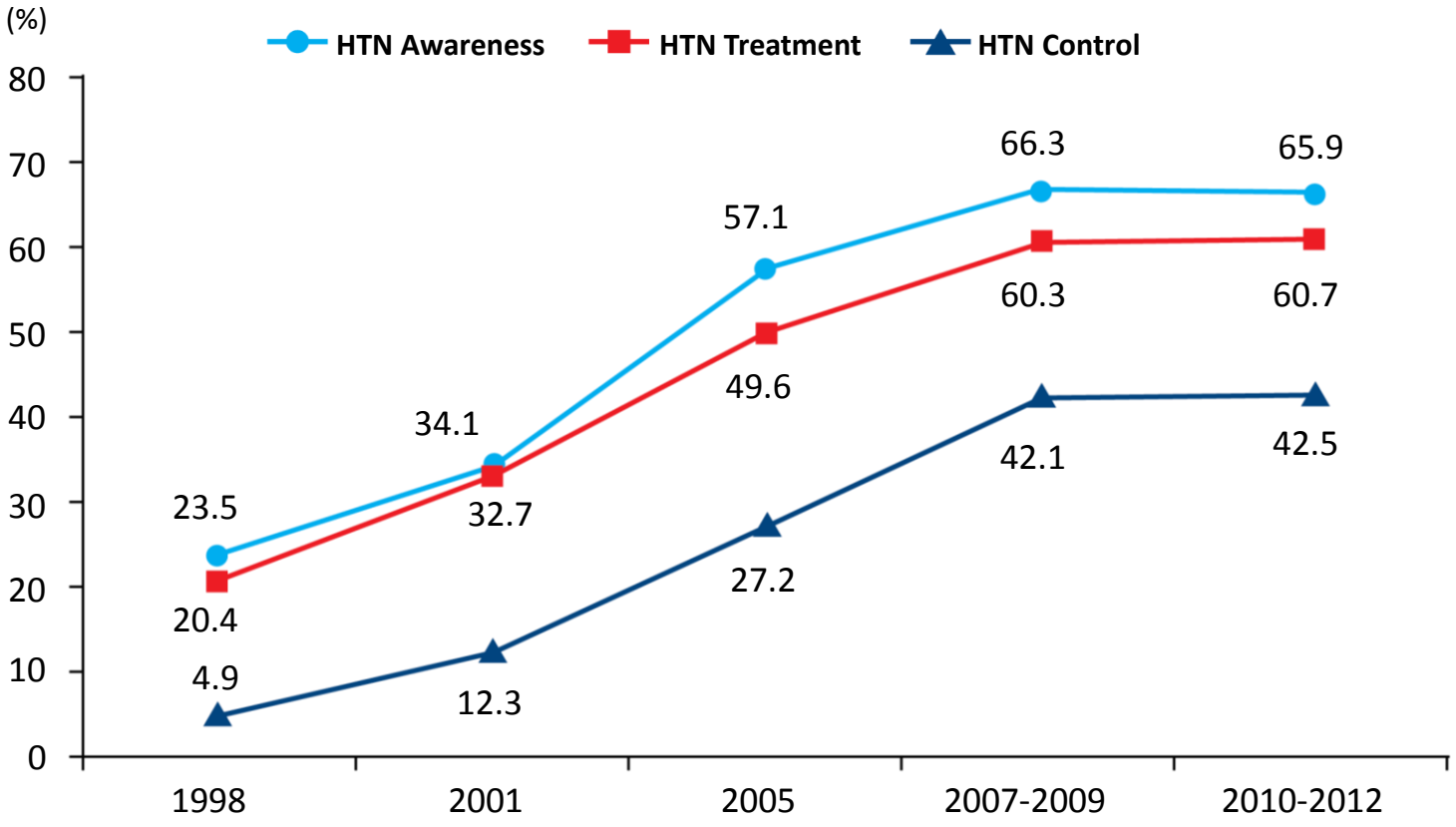
Management of Hypertension in Korea

[Trends in awareness, treatment, control of high BP, over 30 years old, 1998-2012]



KNHANES, Korean National Health and Nutrition Examination Survey

2013 *KNHANES*, *PUBLIC HEALTH WEEKLY REPORT*, *KCDC* 2015;8:477-480

Summary

PRESSURE!!

- **High-normal BP is associated with a more than twofold increase in relative risk from CVD as compared with those with optimal BP**
- **Incidence of primary outcome (composite of CVD events) and all-cause mortality were lowered in intensive BP lowering, than standard BP lowering**
- **In Korea, the hypertension control rate has been increasing since 1998, but the rate has not reached 50% yet**

Efficacy of Combination Therapy

01 Limitation of Monotherapy

02 Effect of Combination Therapy on BP Reduction

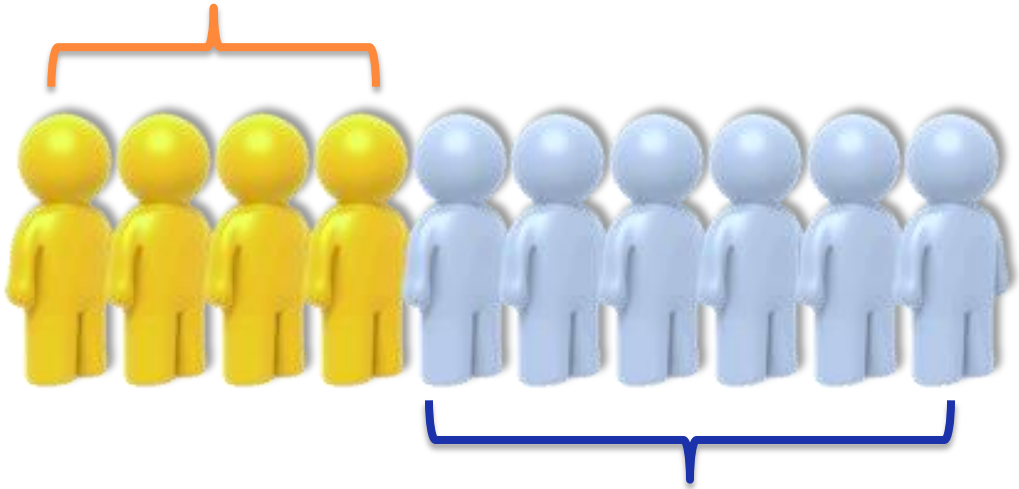
03 Hypertension Guidelines

04 The role of ARB & CCB Combination Therapy

05 Adherence of Single-Pill Combination

Limitation of Monotherapy

40% of hypertension patients are initially treated with monotherapy



BUT, more than 60% of hypertension patients require combination therapy

Am J Manag Care 2005;11:S220-7,
Vasc Health Risk Manag 2010;6:321-325

Efficacy of Combination Therapy

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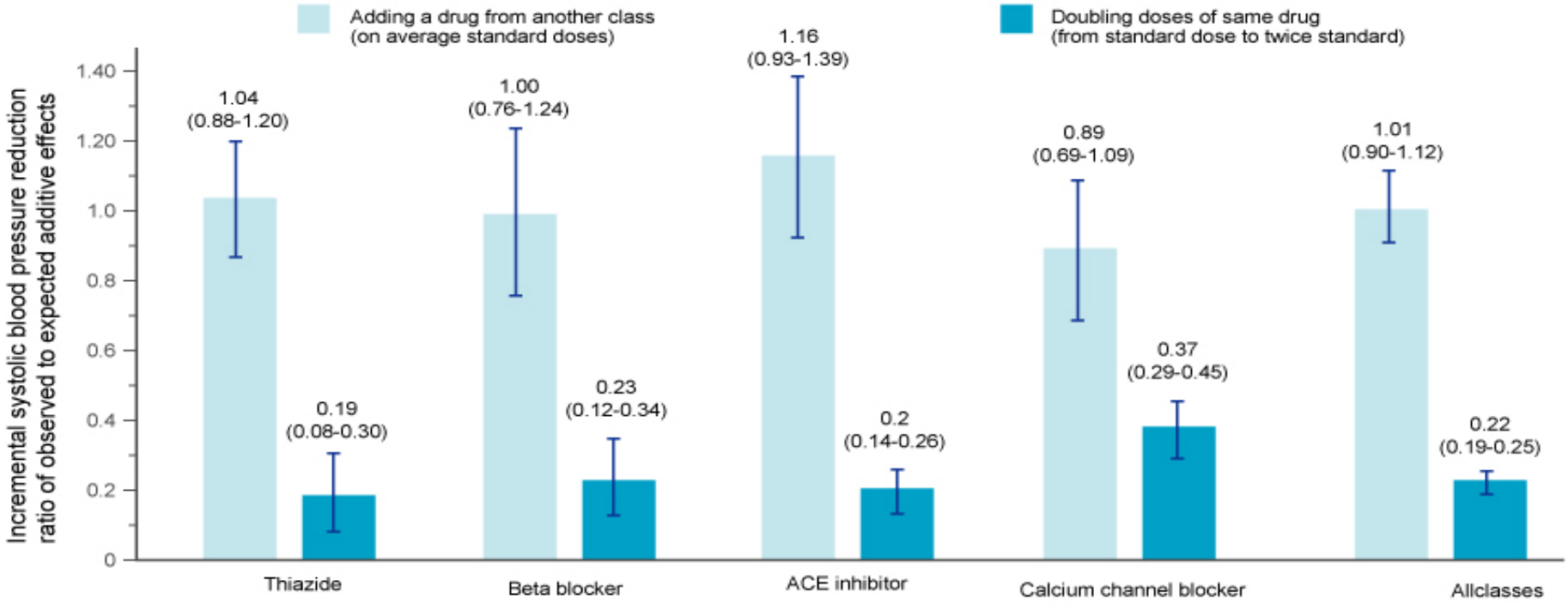
Adding an Antihypertensive Agent is More Effective Than Titrating



'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

Efficacy of Combination Therapy

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Comparison of Target BP in Several Guidelines

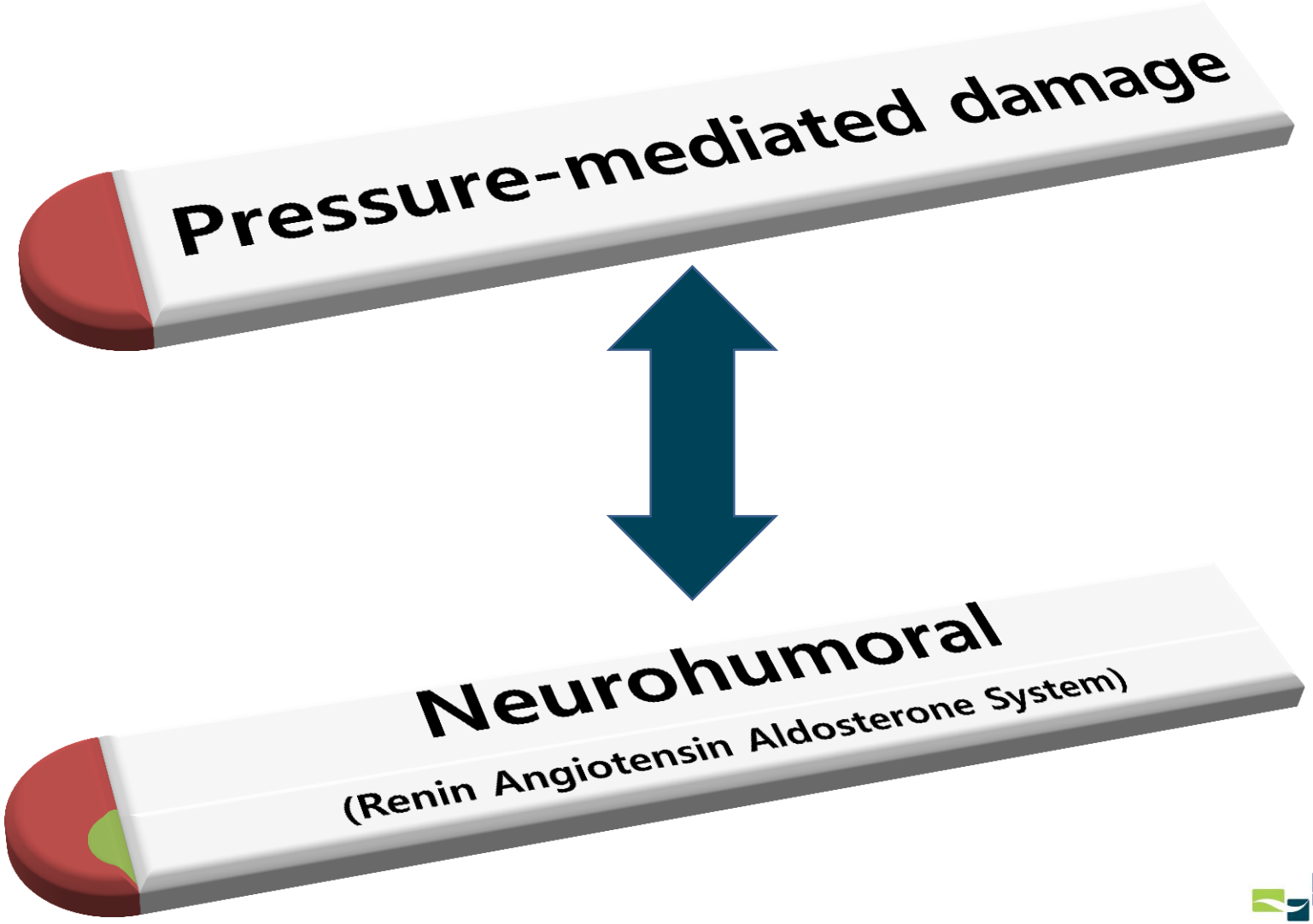
		NICE (2011)	ESH/ESC (2013)	KSH (2013)	JNC 8 (2014)
Target BP (mmHg)	General population	140/90 (Ages <80)	140/90	140/90	140/90 (Ages <60)
	For elderly	150/90 (Ages ≥80)	150/90 (Ages ± 80)	140-150 (DBP ≥60)	150/90 (Ages ≥60)
			140/90 (Ages <80)		
	Adult with diabetes		140/85	140/85	140/90

KSH, The Korean society of hypertension

2013 대한고혈압학회 진료지침 , 2011 NICE

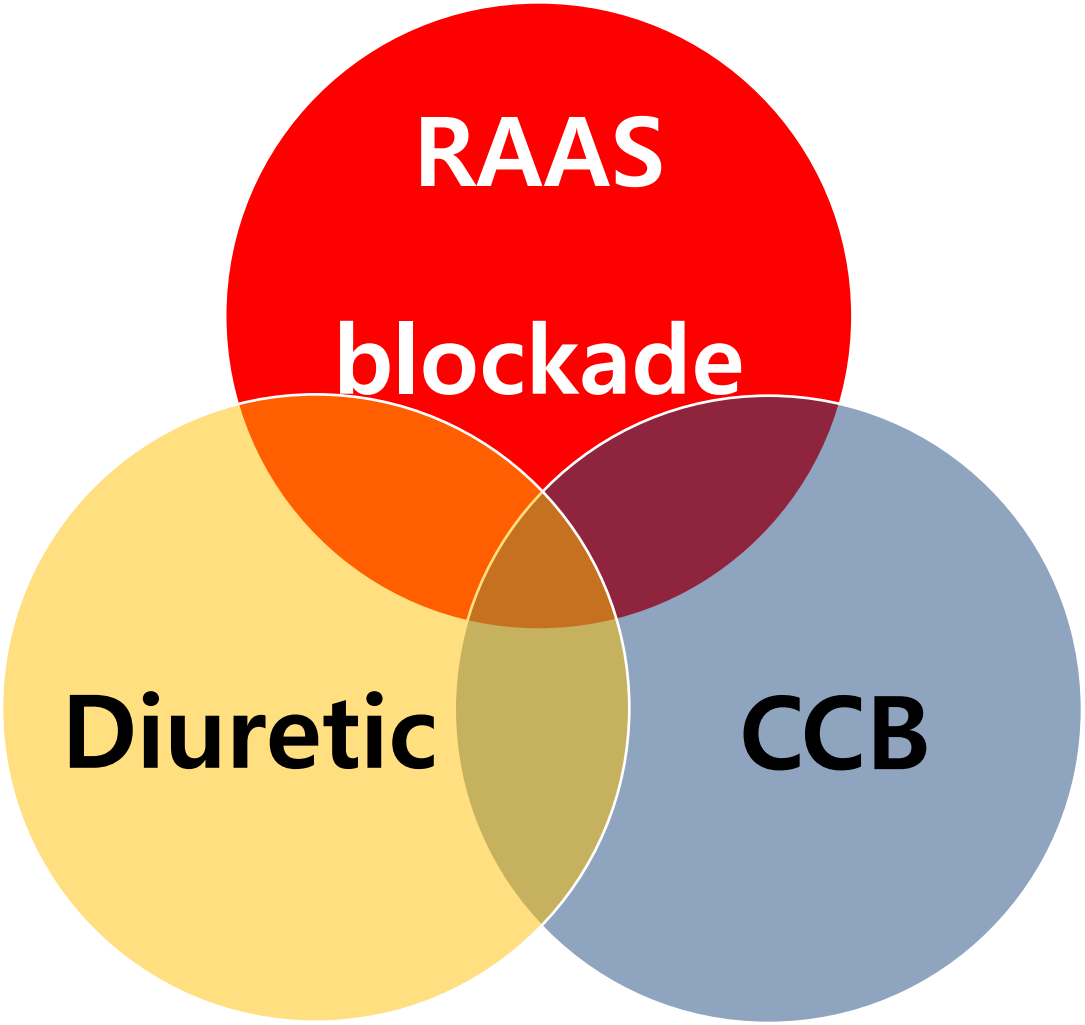
Eur Heart J 2013;34:2159-2219, *JAMA* 2014;311:507-520

Hypertension Pathobiology



Oparil S *et al*. *Annals of Internal Medicine* 2003;139(9):761–76

Evidence-based **combination therapy**



Efficacy of Combination Therapy

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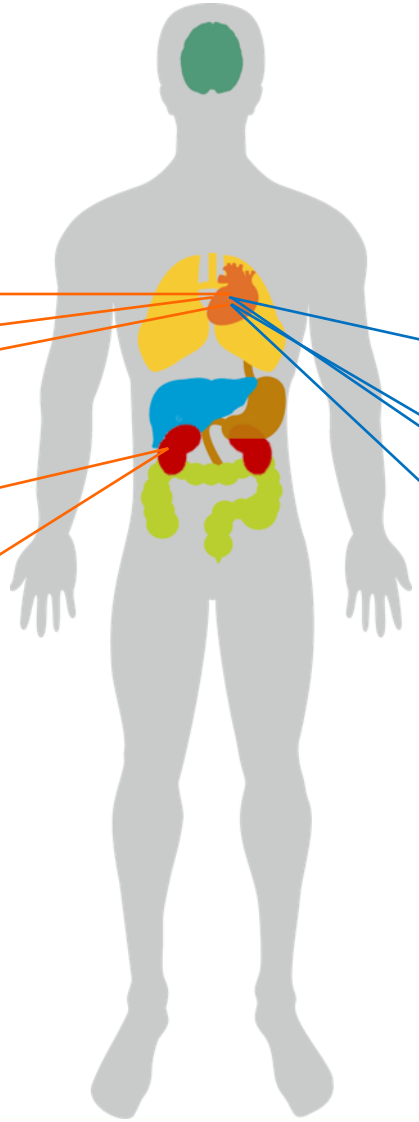
The Role of ARB & CCB Combination Therapy

Dukarb®

ARB

- Post myocardial infarction
- Atrial fibrillation
- Heart failure
- Diabetic nephropathy
- Proteinuria / microalbuminuria



CCB

- Isolated systolic hypertension (elderly)
- Hypertension
- Angina pectoris
- Left ventricular hypertrophy
- Coronary atherosclerosis

- Metabolic syndrome
- ACEi-induced cough

- Pregnancy

BORYUNG 보령제약

Am J Cardiovasc Drugs 2013;13:301-313

The Role of ARB & CCB Combination Therapy

Dukarb®

ARB

Vasodilation

Attenuated peripheral edema

Effective in high-renin patients

No effect cardiac ischemia

RAS ↓

SNS ↓

Synergistic effect

CCB

Arteriodilation

Peripheral edema

Effective in low-renin patients

Reduces cardiac ischemia

RAS ↑

SNS ↑

RAS, Renin-angiotensin system; SNS, Sympathetic nervous system

Vasc Health Risk Manag 2010;6:253-260
Eur Heart J 2011;32:2499-2506

BORYUNG 보령제약

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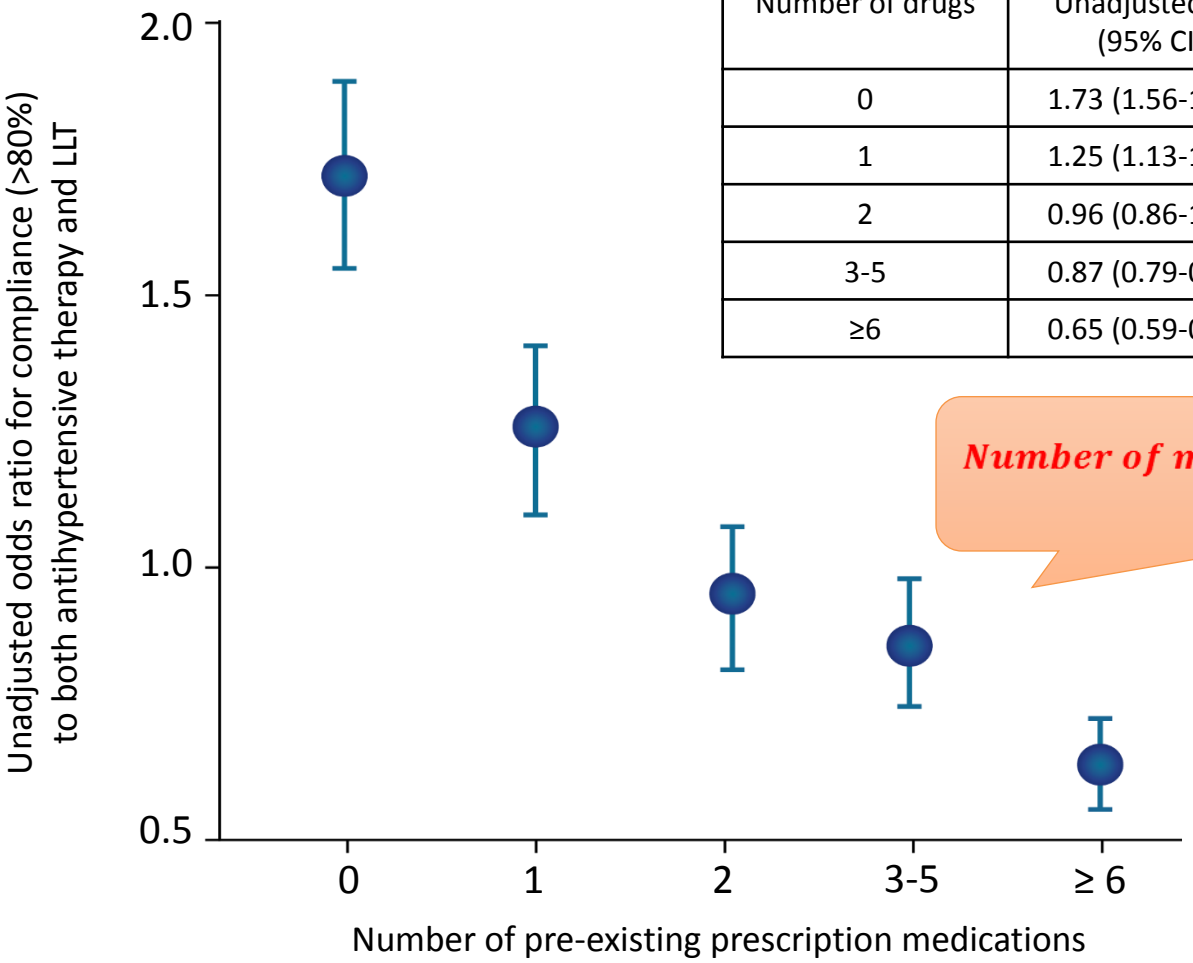
Medication Adherence

Number of drugs	Unadjusted OR (95% CI)	*P* value
0	1.73 (1.56-1.90)	*P* <0.001
1	1.25 (1.13-1.39)	*P* <0.001
2	0.96 (0.86-1.06)	*P* = 0.41
3-5	0.87 (0.79-0.94)	*P* <0.001
≥6	0.65 (0.59-0.71)	*P* <0.001

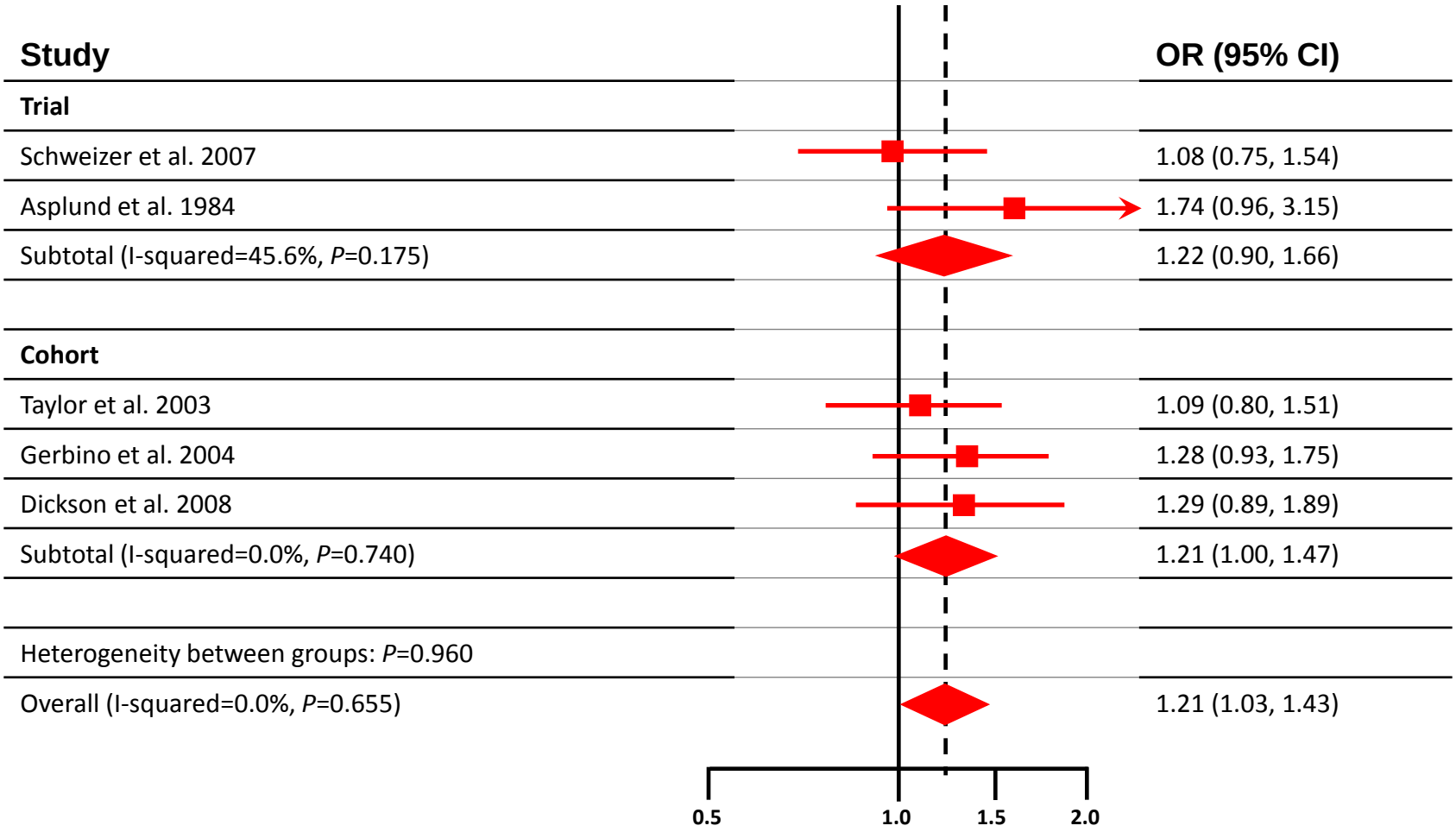


$$Number\ of\ medications \propto \frac{1}{Adherence}$$

LLT, lipid-lowering therapy; OR, odd ratio

Vasc Health Risk Manag 2010;6:321-325
Arch intern med 2005;165:1147-1152

Adherence of single-Pill Combination



Hypertension 2010;55:399-407.

Combination of Fimasartan and Amlodipine : Phase II study

A randomized, double-blind, placebo-controlled, 3 × 3 factorial design, phase II study to evaluate the antihypertensive efficacy and safety of combination of fimasartan and amlodipine in patients with essential hypertension

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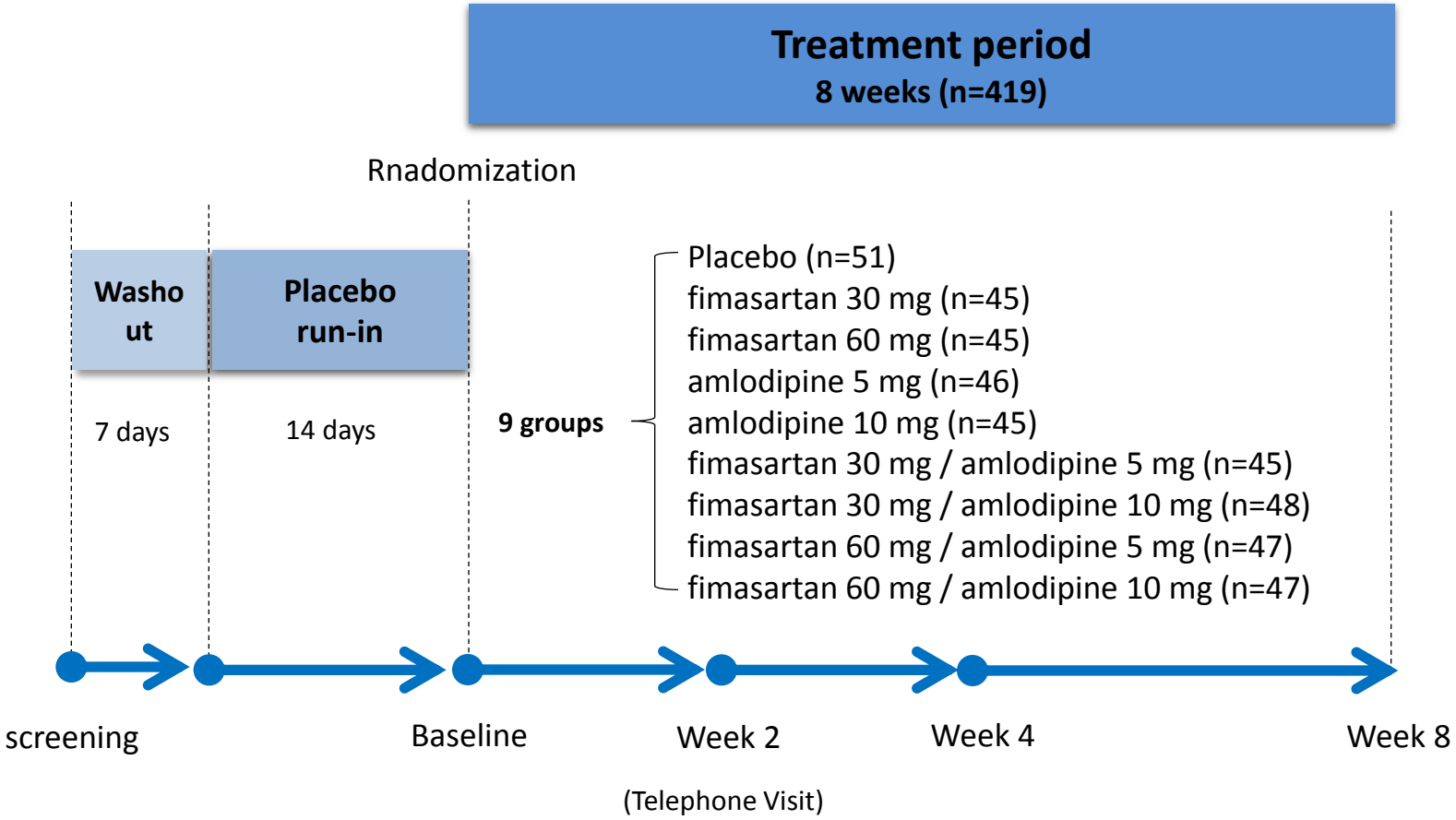
보령제약

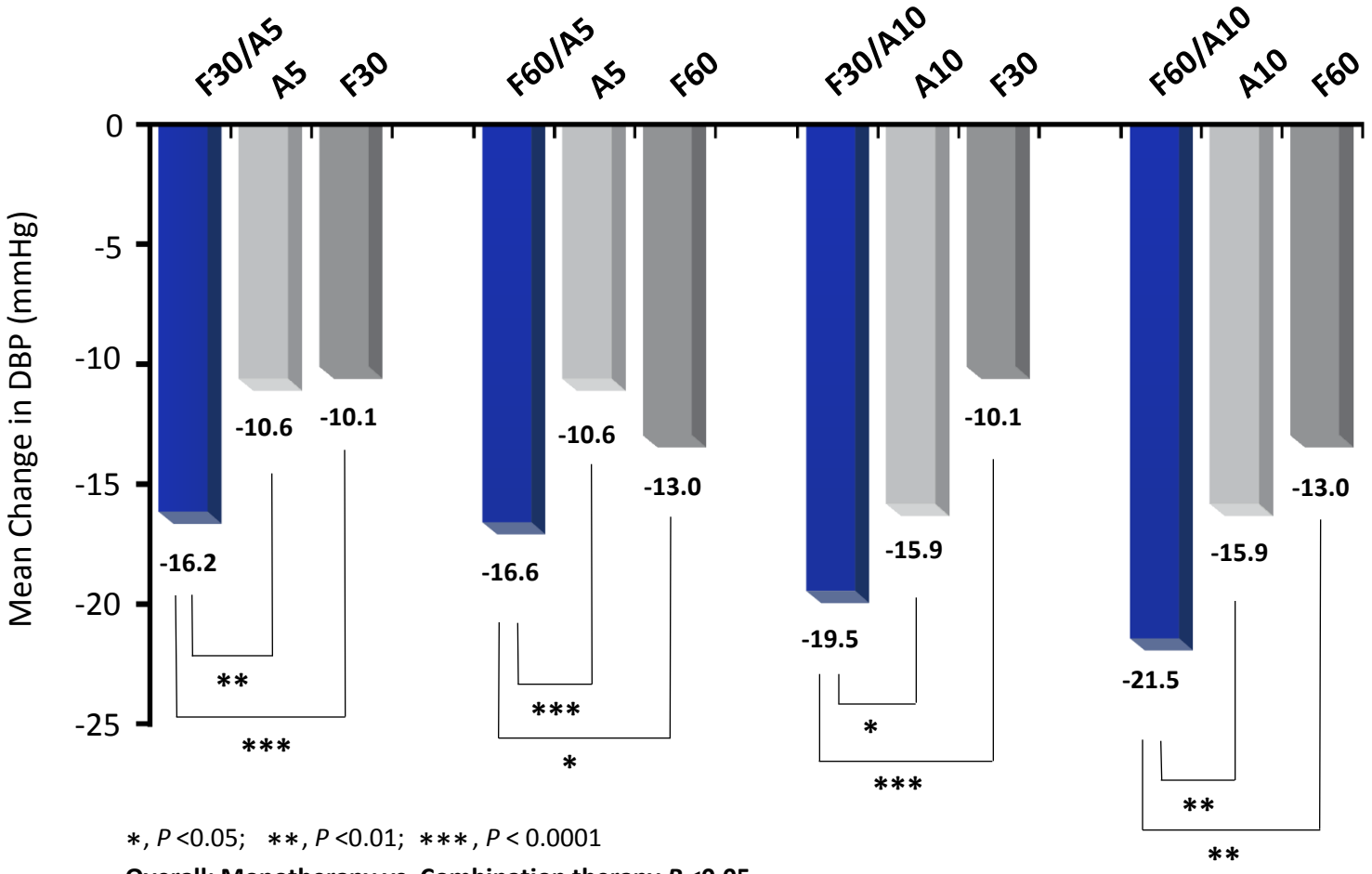
Overall Study Design



Clin Ther 2015;37:2581-2596

Primary Endpoint

Change in mean DBP at week 8



*, P <0.05; **, P <0.01; ***, P < 0.0001

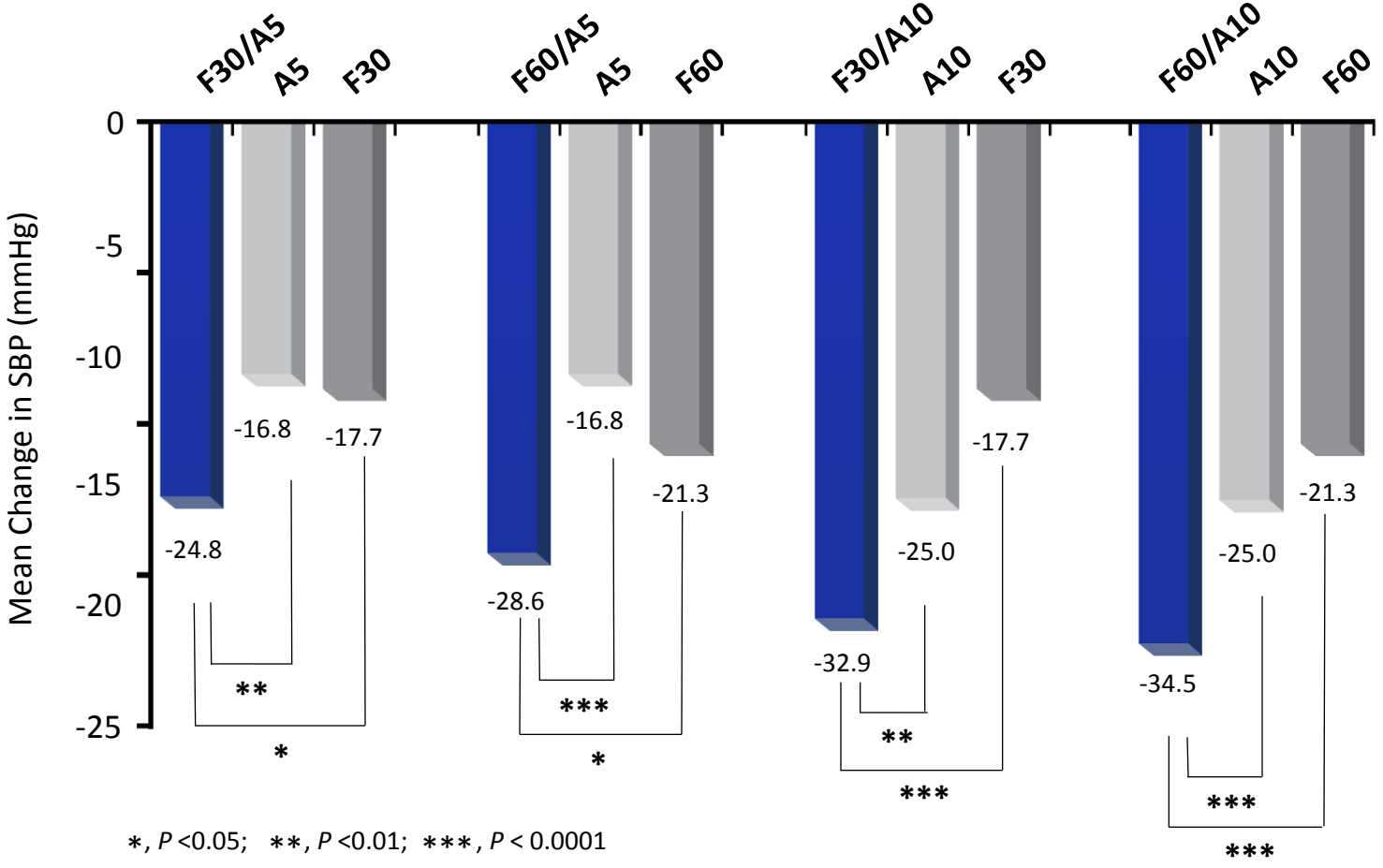
Overall: Monotherapy vs. Combination therapy P <0.05

F, fimasartan; A, amlodipine

Clin Ther 2015;37:2581-2596

Secondary Endpoint

Change in mean SBP at week 8



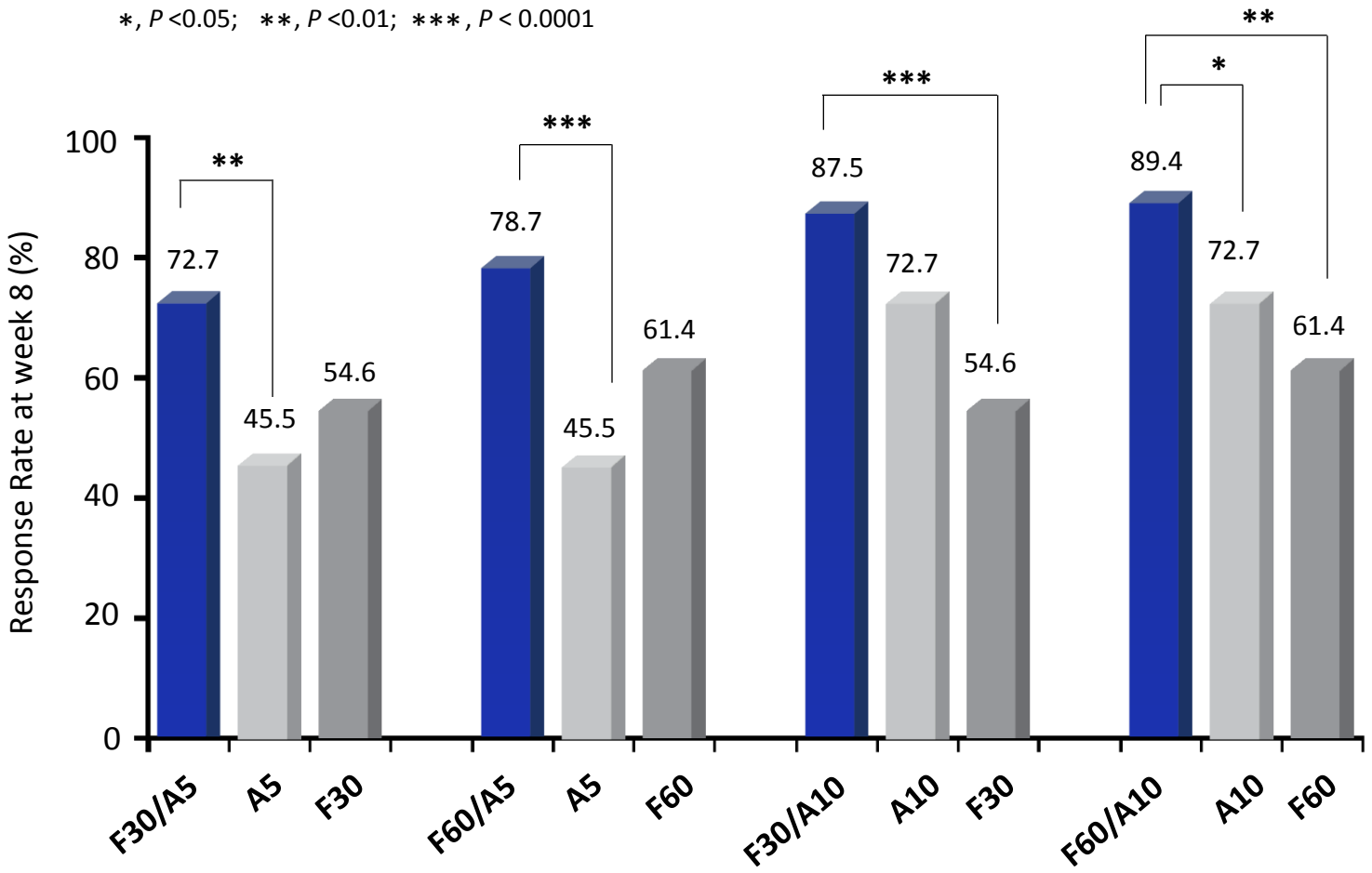
*, P <0.05; **, P <0.01; ***, P < 0.0001

Overall: Monotherapy vs. Combination therapy P <0.05

F, fimasartan; A, amlodipine

Clin Ther 2015;37:2581-2596

Results [Response rate]



F, fimasartan; A, amlodipine

Clin Ther 2015;37:2581-2596

Results [Safety]

	Placebo (n=51)	F-mono (n=90)	A-mono (n=91)	F/A (n=187)	Total (n=419)
TEAEs	6(11.8) [10]	20(22.2) [32]	14(15.4) [16]	35(18.7) [48]	75(17.9) [106]
P-value [1]					0.0884
SAEs	0(0.00) [0]	2(2.2) [2]	2(2.2) [2]	0(0.00) [0]	4(0.95) [4]
P-value [2]					0.0799
ADRs	2(3.9) [3]	3(3.3) [4]	3(3.3) [4]	8(4.3) [9]	16(3.82) [20]
P-value [2]					0.9921

[1] Difference between treatment group(chi-square test)
[2] Difference between treatment group(Fisher's exact test)
SAEs include erythema nodosum, ligament rupture, contusion, intervertebral disc protrusion

F-mono, fimasartan monotheraphy; A-mono, amlodipine monotherapy; F/A, fimasartan/amlodipine combination therapy;
TEAEs, Treatment Emergent Adverse Events; SAEs, Serious Adverse Events; ADRs, Adverse Drug Reactions

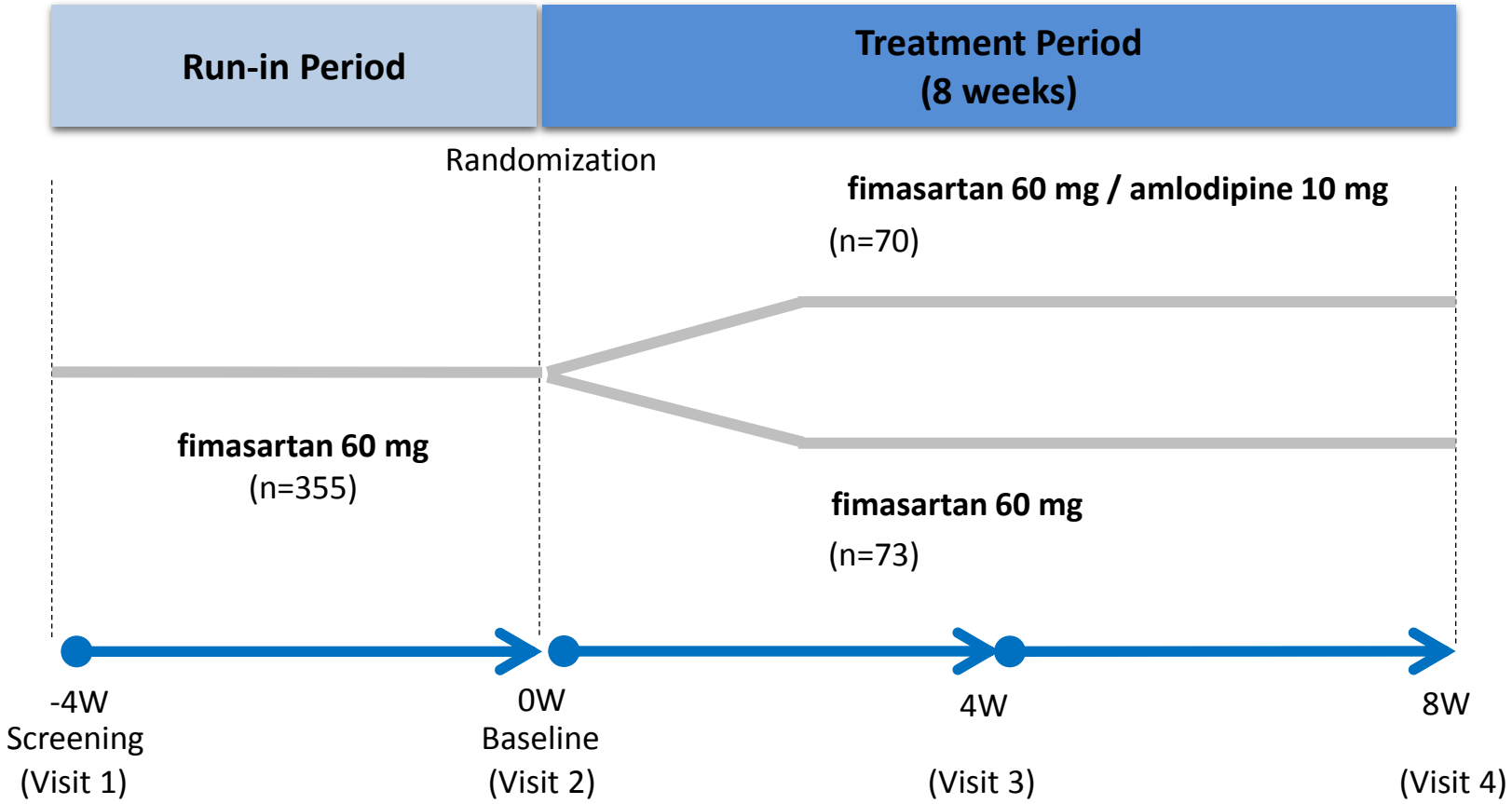
Clin Ther 2015;37:2581-2596

Combination of Fimasartan and Amlodipine : Phase III study

A randomized, double-blind, multicenter, phase III study to evaluate the efficacy and safety of combination of fimasartan/amlodipine versus fimasartan monotherapy in patients with essential hypertension who fail to respond adequately to fimasartan monotherapy

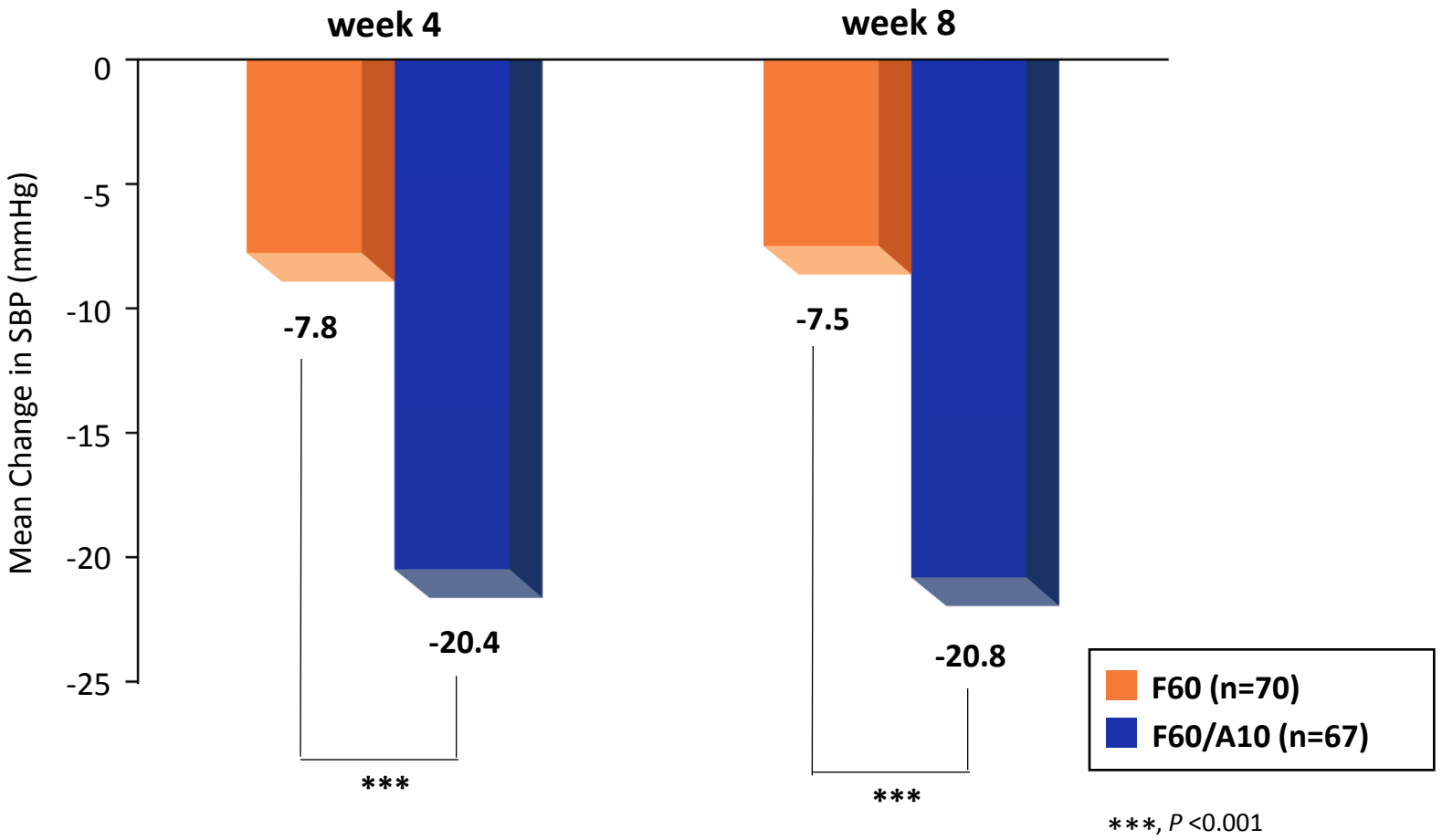
BORYUNG
보령제약

Overall Study Design



Data on file

Results [Change in SBP]

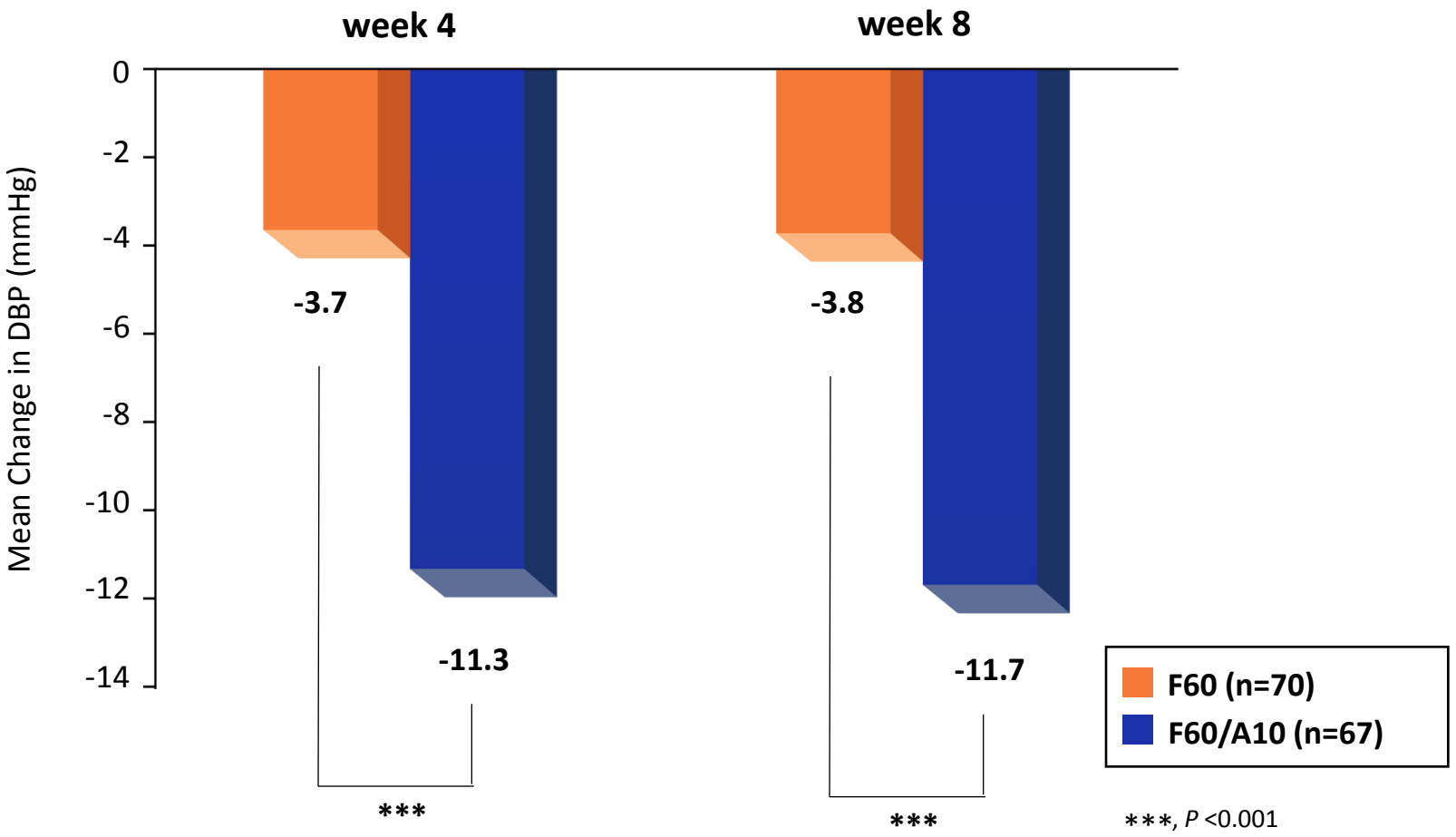


***, *P* <0.001

F, fimasartan; A, amlodipine

Data on file

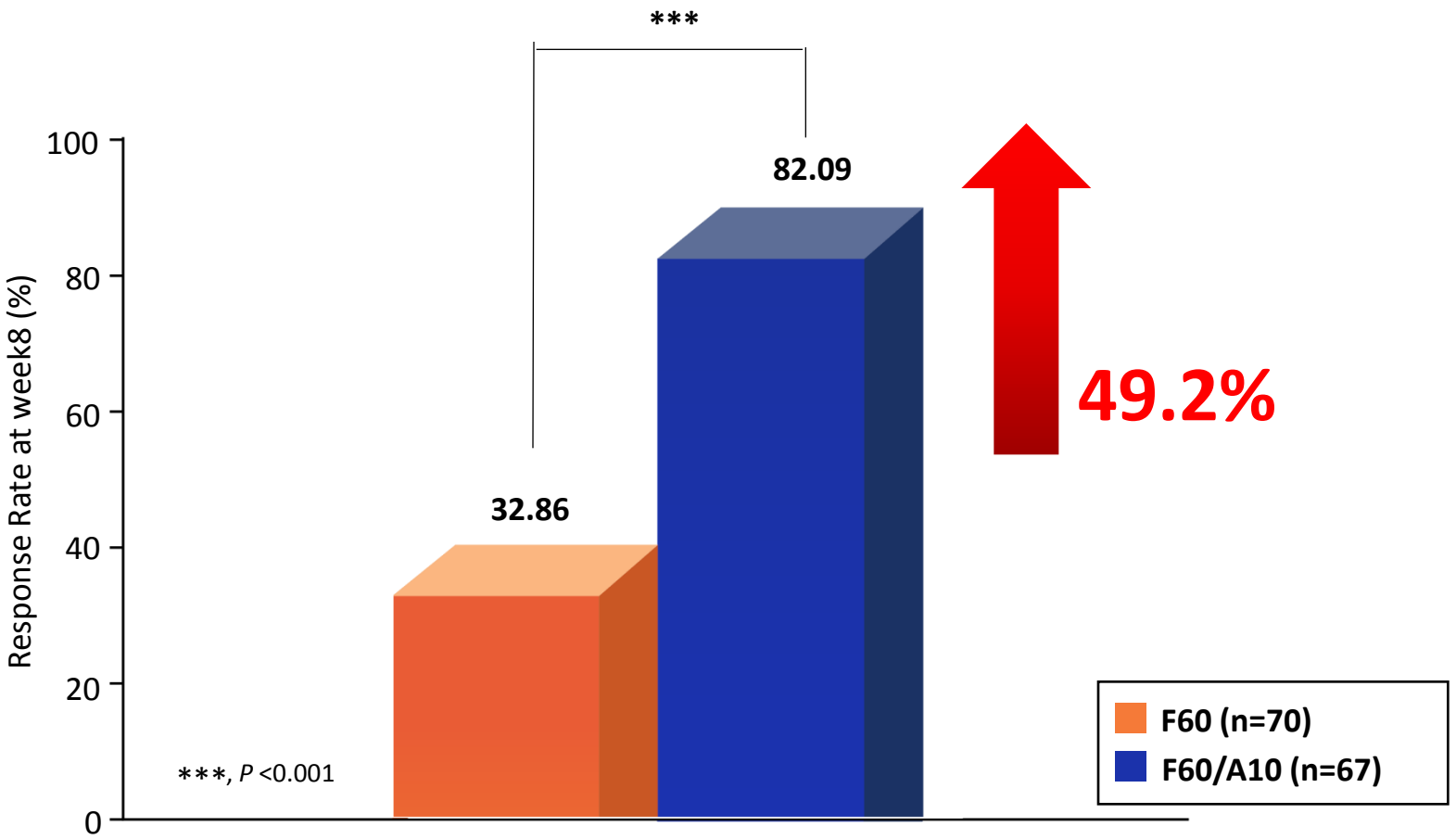
Results [Change in DBP]



F, fimasartan; A, amlodipine

Data on file

Results [Response rate]



F, fimasartan; A, amlodipine

Data on file

Results [Safety]

	F60 (n=73)	F60/A10 (n=70)	TOTAL (n=143)	*P*-value [1)]
TEAEs	14 (19.18) [19]	18 (25.71) [28]	32 (22.38) [47]	0.3485 (c)
SAEs	0	0	0	
ADRs	6 (8.22) [9]	3 (4.29) [4]	9 (6.29) [13]	0.4944 (f)

TEAEs, Treatment-Emergent Adverse Events; SAEs, Serious Adverse Events; ADRs, Adverse Drug Reaction

Data on file

Dukarb® for Efficacy, Safety, Cost-effectiveness, Adherence

01 Comparison of Efficacy

02 Comparison of Safety

03 Comparison of Cost

04 Comparison of Pill Size

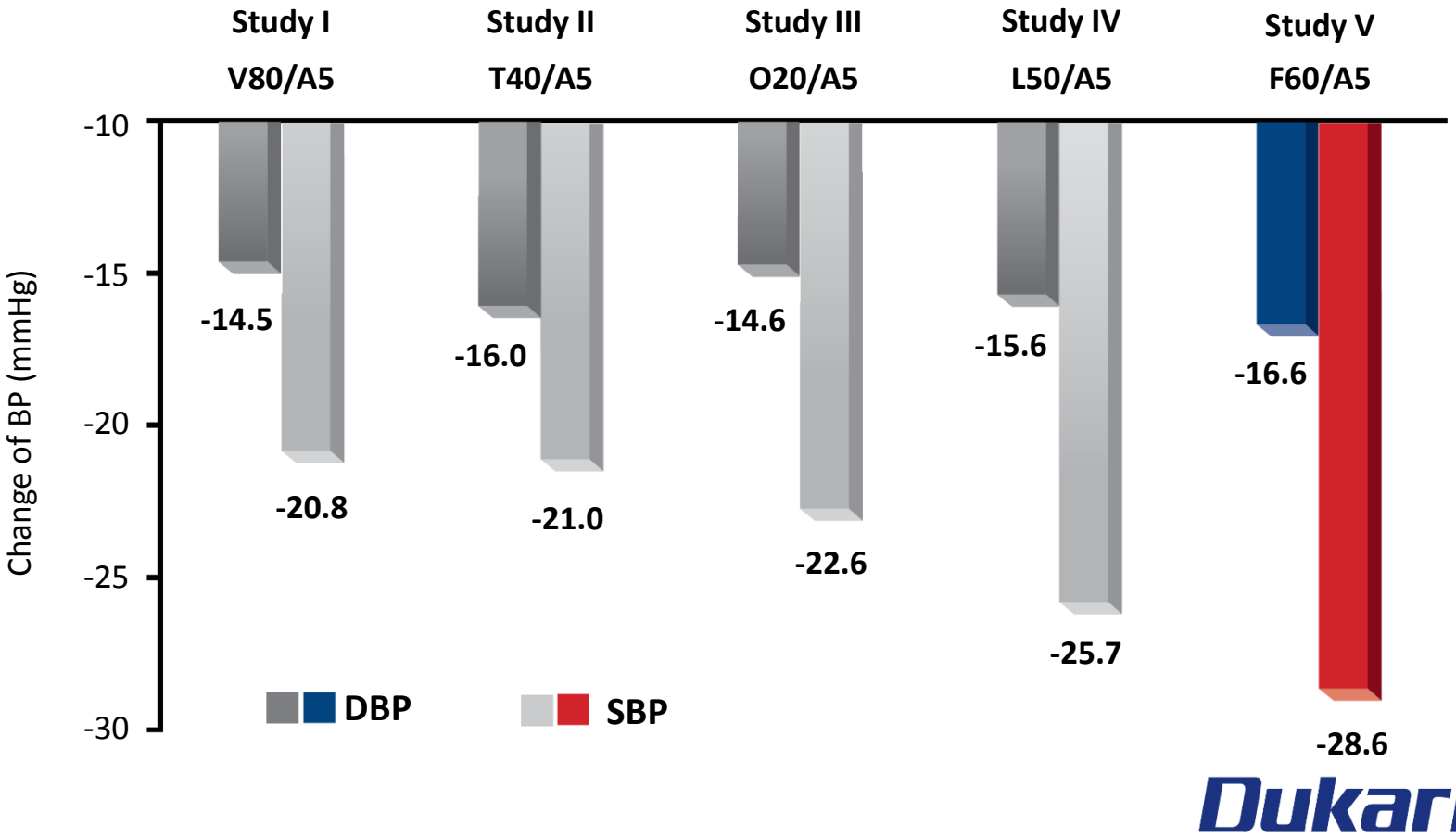
Comparison of Efficacy (1)

		Study I	Study II	Study III	Study IV	Study V
Design		Multicenter, double-blind, randomized placebo controlled, parallel-group trials (Multinational)	Multicenter, randomized, double-blind, double-dummy, placebo-controlled, 4 × 4 factorial design trial (Multinational)	Multicenter, double-blind, randomized, placebo-controlled, factorial study (US)	Multicenter, double-blind, randomized, phase II study (Korea)	**Multicenter, double-blind, randomized, placebo-controlled, 3x3 factorial study (Korea)**
Treatment		V80/A5 (n=127)	T40/A5 (n=141)	O20/A5 (n=161)	L50/A4 (n=38)	**F60/A5 (n=47)**
Duration		8 weeks	8 weeks	8 weeks	8 weeks	**8 weeks**
Baseline (mmHg)		SBP 153.2 DBP 99.1	SBP 153.2 DBP 101.7	SBP 163.8 DBP 101.7	SBP 158.4 DBP 101.5	**SBP 159 DBP 99.2**
Inclusion Criteria	**BP (mmHg)**	DBP >95 and <110	DBP ≥95 and ≤119	DBP: 95 to 120	DBP ≥95 and <115	**90 ≤ DBP < 114**
	Patients	Essential hypertension	Stage I or II hypertension	Stage II hypertension	Essential hypertension	**mild to moderate hypertension**
Primary endpoint		Change from baseline in DBP at the end of the study	Change in DBP At week 8	Change from baseline in mean DBP at week 8	Mean change from baseline in DBP after 8 weeks of treatment	**Change in DBP from baseline and at week 8**

L, losartan; A, amlodipine; V, valsartan; O, olmesartan; F, fimasartan

Clin Ther 2007;29:563-580, *J Clin Hypertens (Greenwich)* 2009;11:207-213, *Clin Ther* 2008;30:587-604, *Am J Cardiovasc Drugs* 2012;12:35-47, *Clin Ther* 2015;37:2581-2596

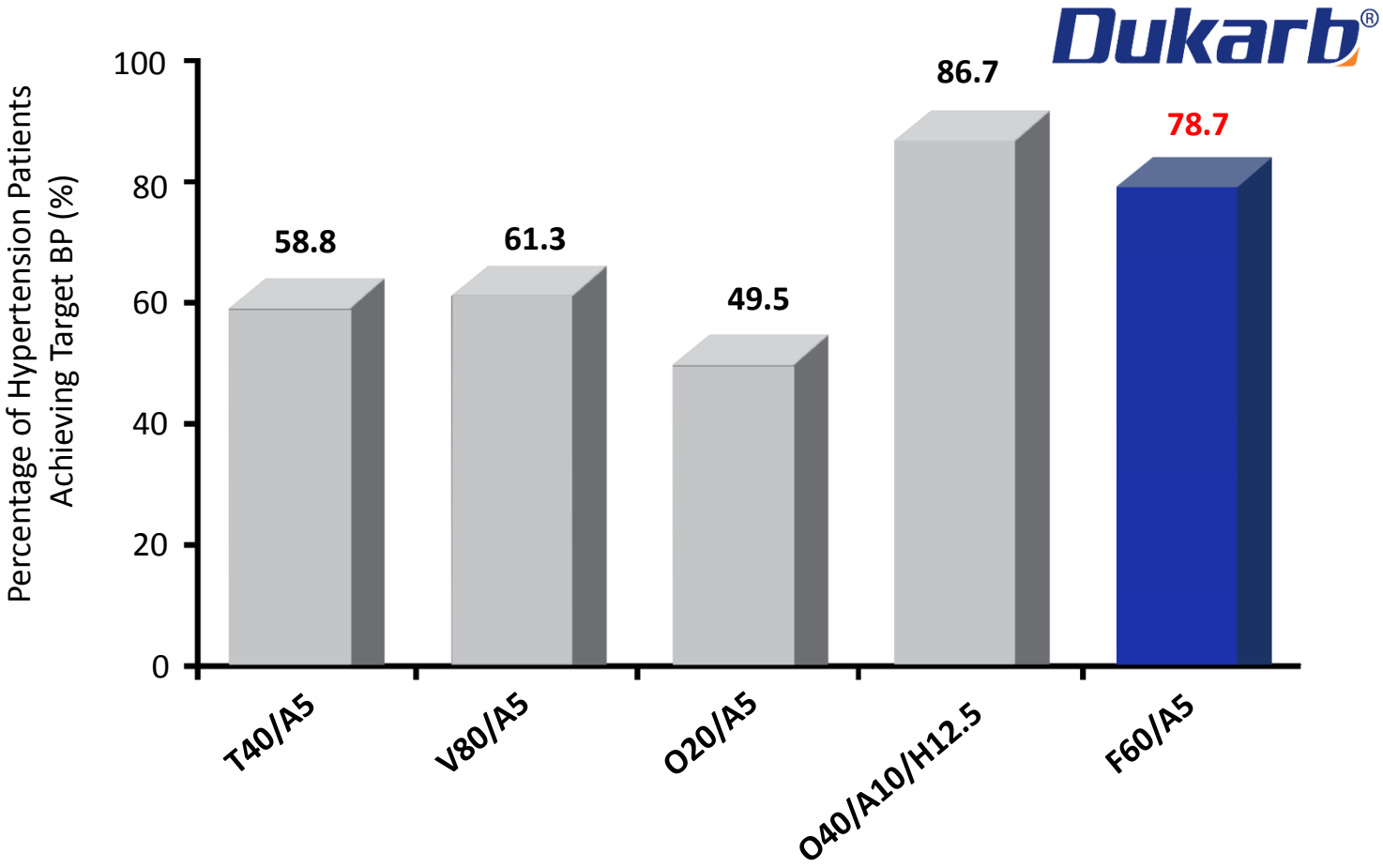
Comparison of Efficacy (2)



L, losartan; A, amlodipine; V, valsartan; O, olmesartan; F, fimasartan

Clin Ther 2007;29:563-580, *J Clin Hypertens (Greenwich)* 2009;11:207-213, *Clin Ther* 2008;30:587-604, *Am J Cardiovasc Drugs* 2012;12:35-47, *Clin Ther* 2015;37:2581-2596

Comparison of Efficacy (3)



T, telmisartan; A, amlodipine; V, valsartan; O, olmesartan; H, hydrochlorothiazide; F, fimasartan

Data on file, *Vascular Health and Risk Management* 2011;7:183-192,
International Journal of Hypertension 2013, *Journal of Hypertension* 2013;31:1245-1255,
Internaional Journal of Cardiology 2013;167:2024-2030

Dukarb® for Efficacy, Safety, Cost-effectiveness, Adherence

01 Comparison of Efficacy

02 Comparison of Safety

03 Comparison of Cost

04 Comparison of Pill Size

Comparison of Safety (1)

Dukarb

Common ARB Adverse Events

Dizziness, headache, drowsiness, nausea, rash, vomiting, diarrhea, cough, elevated K^+ levels, low BP, muscle or bone pain, etc.

Common CCB Adverse Events

Dizziness, headache, drowsiness, nausea, rash, constipation, edema(legs, feet), low BP, etc.

Fimasartan+amlodipine combination therapy showed similarity in terms of safety features compares to other combination agents

Drug-related Adverse events(%)	
L50/A5	6.5%
O40/A5	7.5%
T80/A5	8.7%
F60/A5	6.4%

L, losartan; A, amlodipine; O, olmesartan; T, telmisartan; F, fimasartan

Clin Ther 2011;33:1953–1963, *Curr Med Res Opin* 2010;26:1705-1713, *Clin Drug Invest* 2009;29:11-25, *J Clin Hypertens* 2011;13:459-466, *Clin Ther* 2015;37:2581-2596

BORYUNG 보령제약

Comparison of Safety (2)

Dukarb® is non hygroscopic medication

취급상의 주의사항

1. 이 약은 습기에 약하므로, 원래의 포장 상태대로 보관하시고 복용 직전에 알루미늄 호일을 개봉하십시오.

2. 이 약의 지정된 보관 온도는 1-30℃입니다.
30 ℃를 초과하는 고온에 노출되지 않도록 주의하십시오

Dukarb® for Efficacy, Safety, Cost-effectiveness, Adherence

01 Comparison of Efficacy

02 Comparison of Safety

03 Comparison of Cost

04 Comparison of Pill Size

Comparison of Cost

Dukarb® is the most cost-effective ARB & CCB SPC Therapy

	ARB + CCB	Single-Pill Combination
L100/A5	1,335	944
O40/A5	844	758
T80/A5	927	1,053
V160/A5	1,336	988
F60/A5	**1,031**	**808**

(원단위, 개당 단가)

L, losartan; A, amlodipine; O, olmesartan; T, telmisartan; V, valsartan; F, fimasartan

약학정보원, http://www.health.kr/

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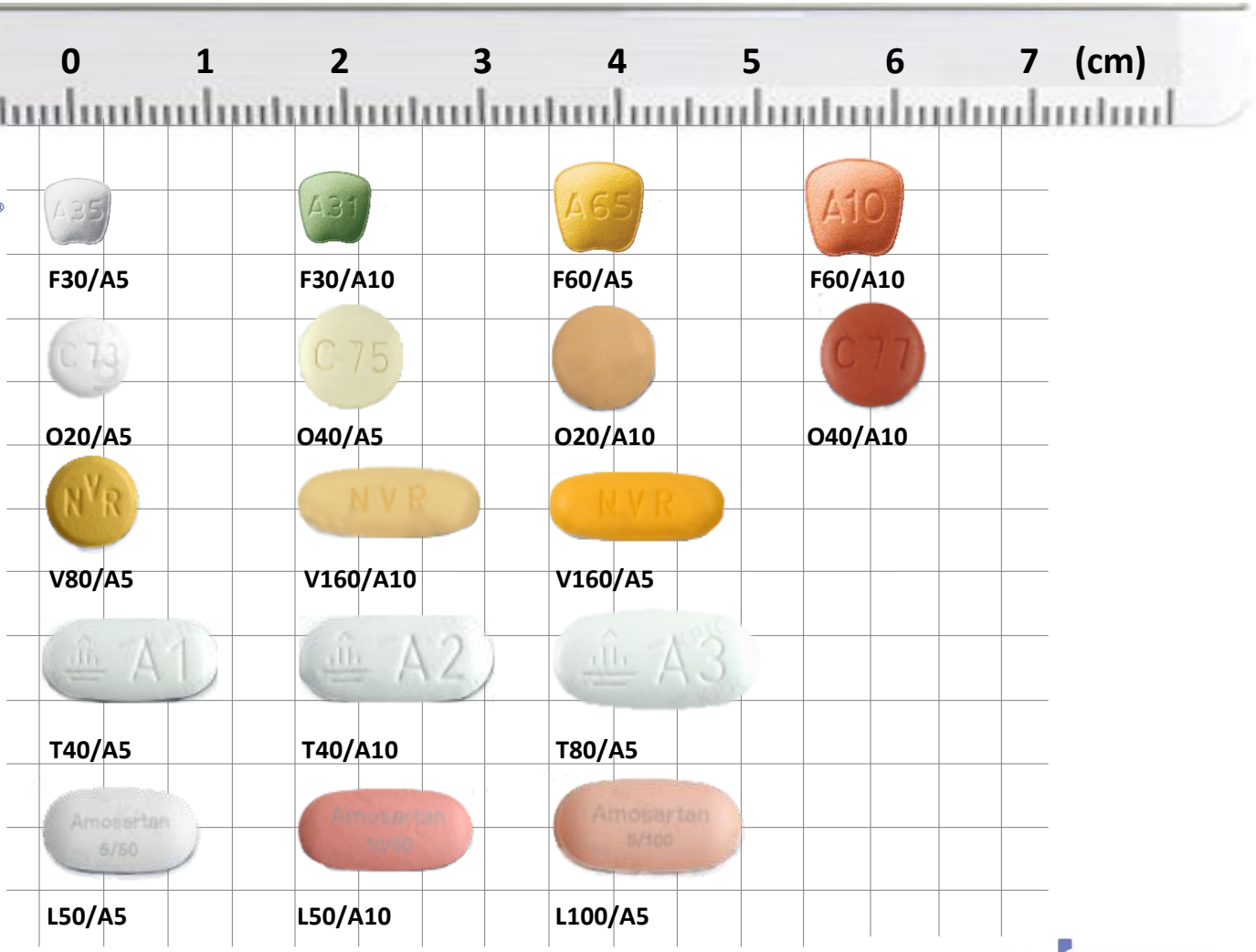
Comparison of Pill Size

Dukarb®
The smallest
SPC



약학정보원, http://www.health.kr/

Summary

- **Fimasartan and amlodipine combination therapy superior reduction in BP compared with other ARB & CCB combination therapies**
- **Non-hygroscopic medication, Dukar b , is the smallest and most cost-effective available ARB & CCB SPCs** Dukarb®

Thank you

BORYUNG
보령제약

Dukarb®