CCB Reappraisal

CCB as the first line for the East-Asians

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Korea University Medical School

일본의 국화(國花)는 ?

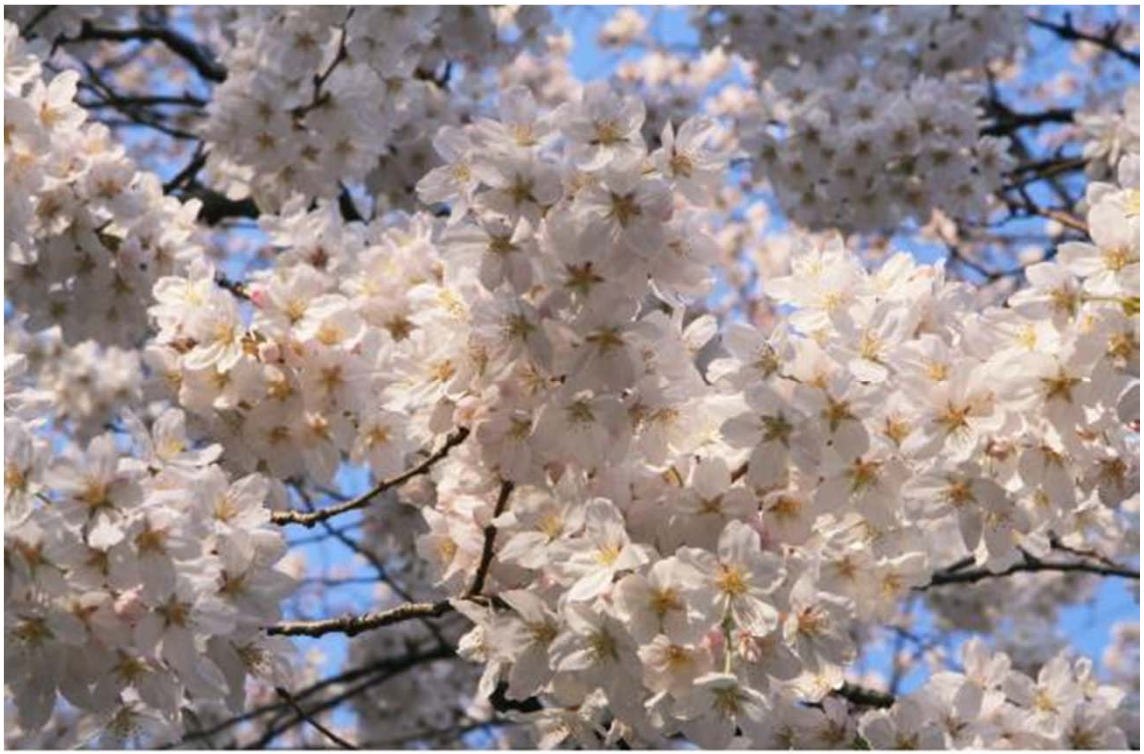
일본(日本)의 국화(國花)

- 정확히 말하면, 日本에는 국화(國花)가 없다.

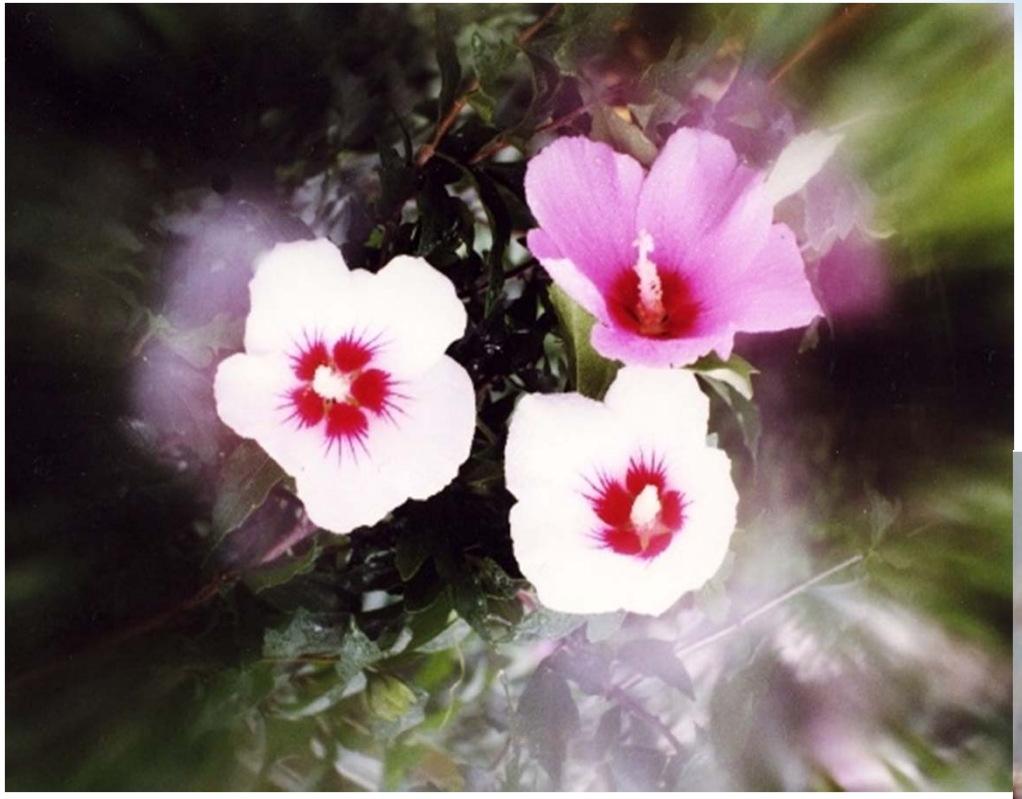
- 황실(皇室)을 상징하는 꽃으로 국화(菊花)가 있을뿐. 따라서 외국에 나가있는 日本의 대사관 정문에도 황금색의 국화문양(紋様)이 있을 뿐이다.

벚꽃의 원산지는?

❖왕벚나무는 한국 제주도 원산



한국의 국화(國花)



Agenda

- The evidence on CCBs over the world
- The evidence on CCBs over the eastern Asian region
- The mechanisms for the benefit of CCBs

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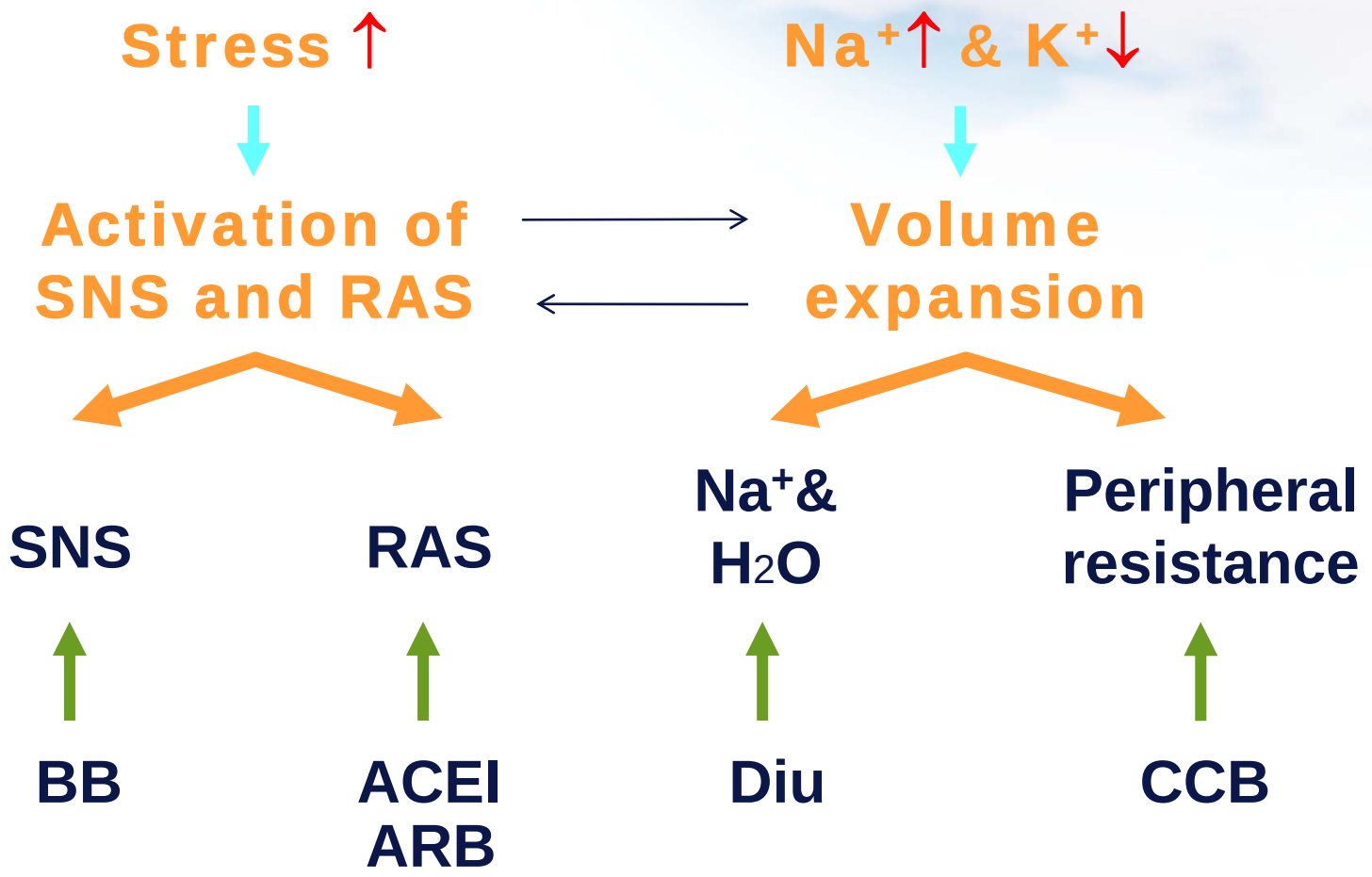
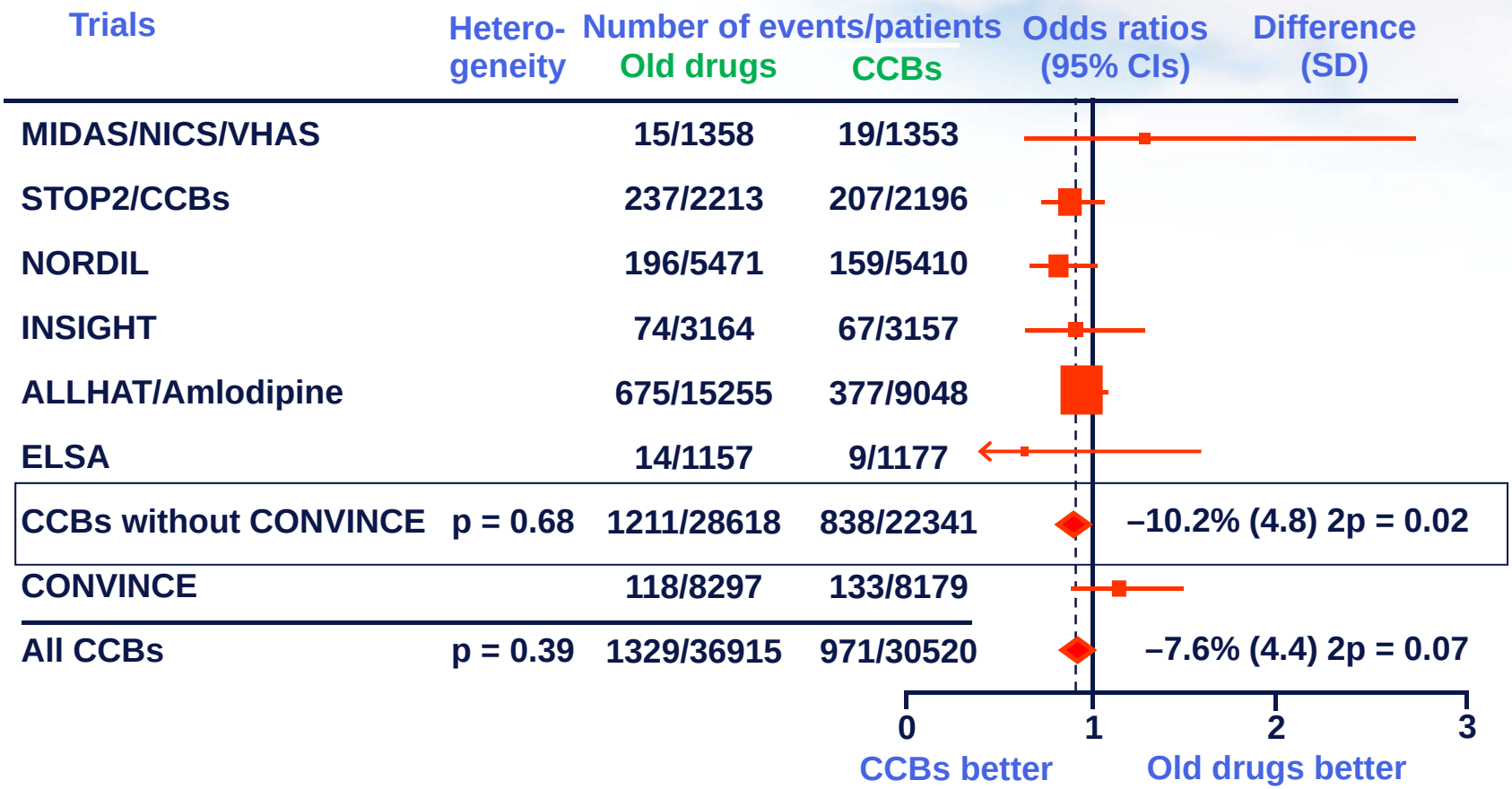
- **The evidence on CCBs over the world**
- **The evidence on CCBs over the eastern Asian region**
- **The mechanisms for the benefit of CCBs**

Regulatory mechanisms of BP and antihypertensive drug classes



META-ANALYSES OF EARLY TRIALS ON CCBS OVER THE WORLD

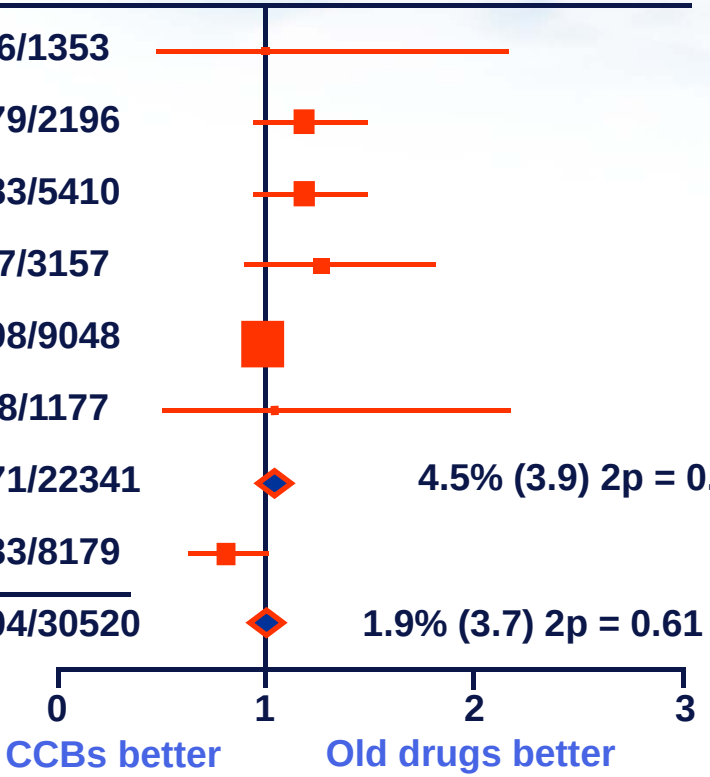
CCBs *vs.* diuretics/β-blockers: Fatal and nonfatal stroke



Staessen JA, et al. Lancet 2001;37:1305-15. Staessen JA et al. J Hypertens 2003;21:1055-76.

CCBs *vs.* diuretics/β-blockers: Fatal and nonfatal MI

Trials	Hetero-geneity	Number of events/patients Old drugs	CCBs	Odds ratios (95% CIs)	Difference (SD)
MIDAS/NICS/VHAS		16/1358	16/1353		
STOP2/CCBs		154/2213	179/2196		
NORDIL		157/5471	183/5410		
INSIGHT		61/3164	77/3157		
ALLHAT/Amlodipine		1362/15255	798/9048		
ELSA		17/1157	18/1177		
CCBs without CONVINCE	p = 0.38	1767/28618	1271/22341		4.5% (3.9) 2p = 0.26
CONVINCE		166/8297	133/8179		
All CCBs	p = 0.14	1933/36915	1404/30520		1.9% (3.7) 2p = 0.61

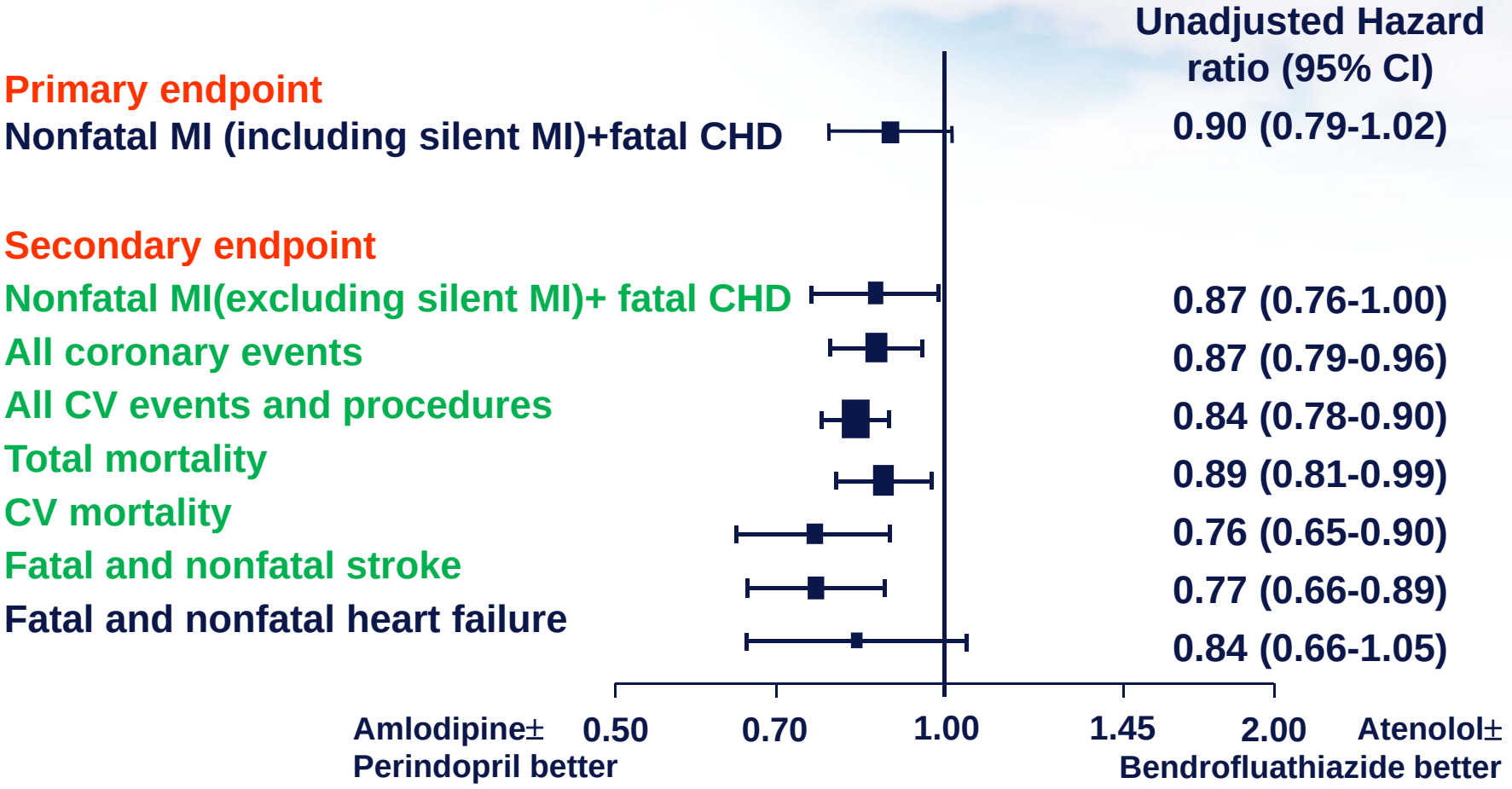


Staessen JA, et al. Lancet 2001;37:1305-15. Staessen JA et al. J Hypertens 2003;21:1055-76.

THE RECENT TRIALS OR ANALYSES ON CCBS OVER THE WORLD

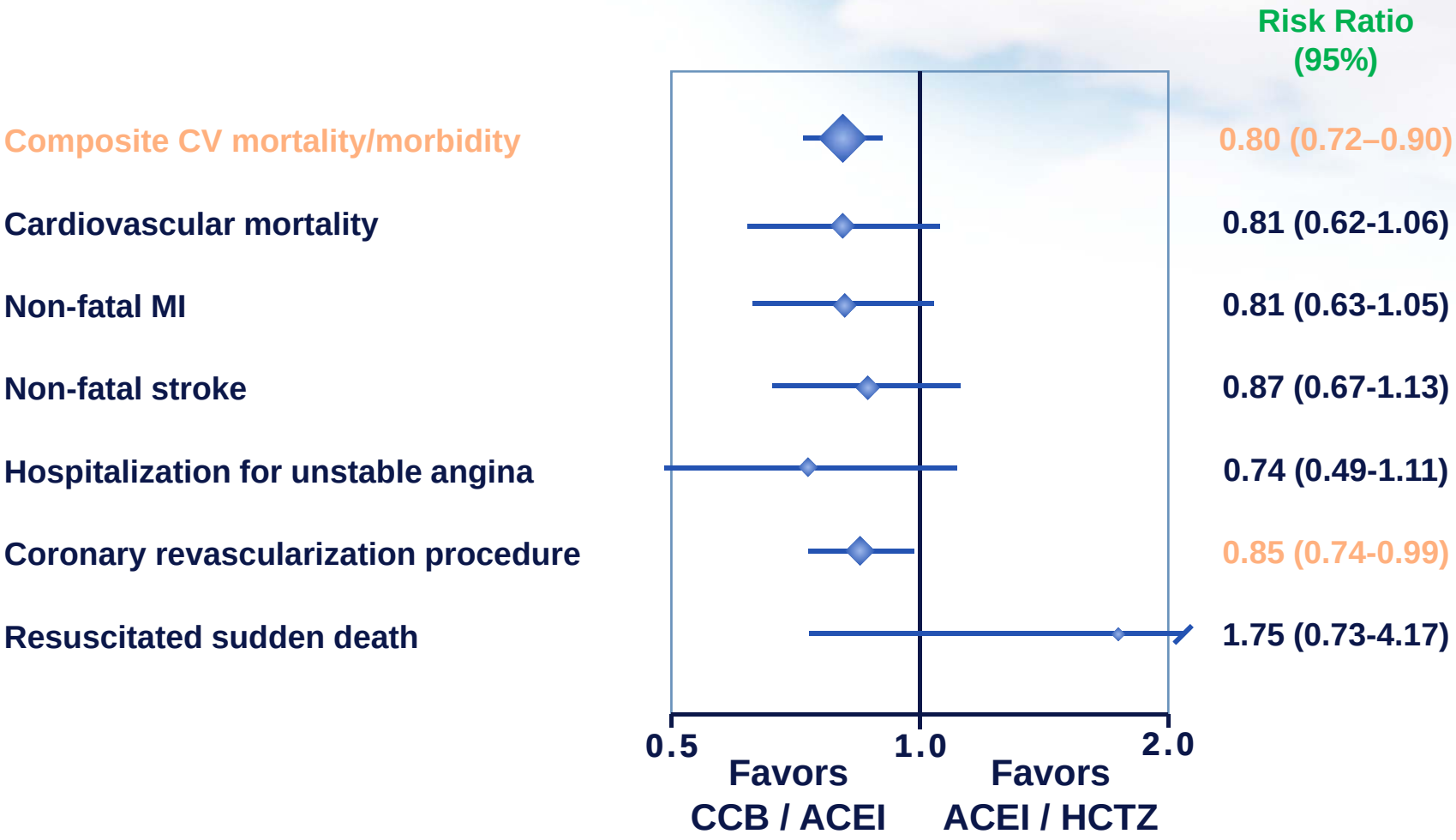
- **ASCOT:** *vs* a β-blocker, atenolol
- **ACCOMPLISH:** *vs* a diuretic, HCZ
- **ALLHAT:** *vs* an ACEI, lisinopril
- **VALUE:** *vs* an ARB, valsartan

ASCOT-BPLA: Primary and secondary endpoints

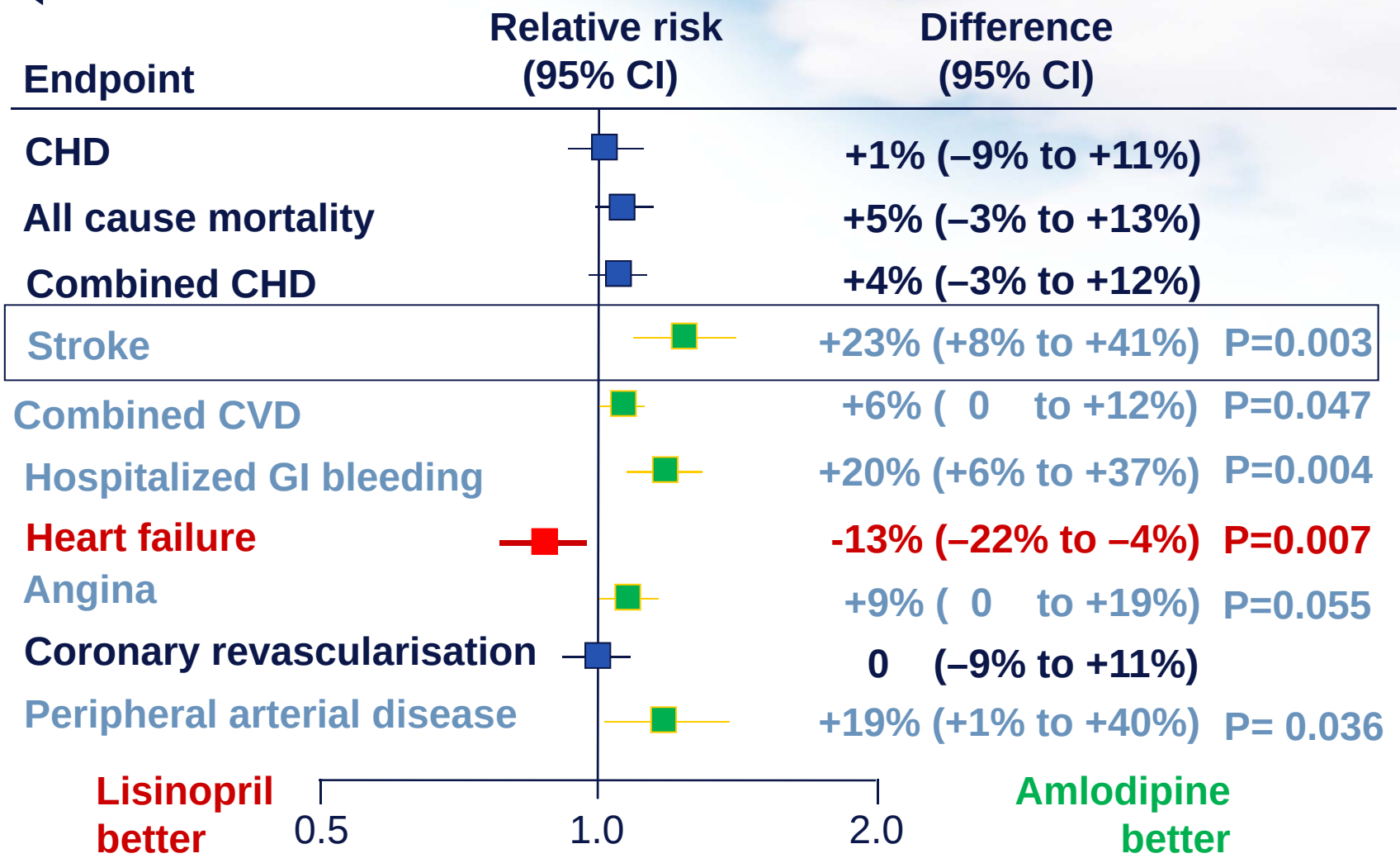


Dahlöf B et al. Lancet 2005:366;895-906.

ACCOMPLISH:
Primary endpoint and components

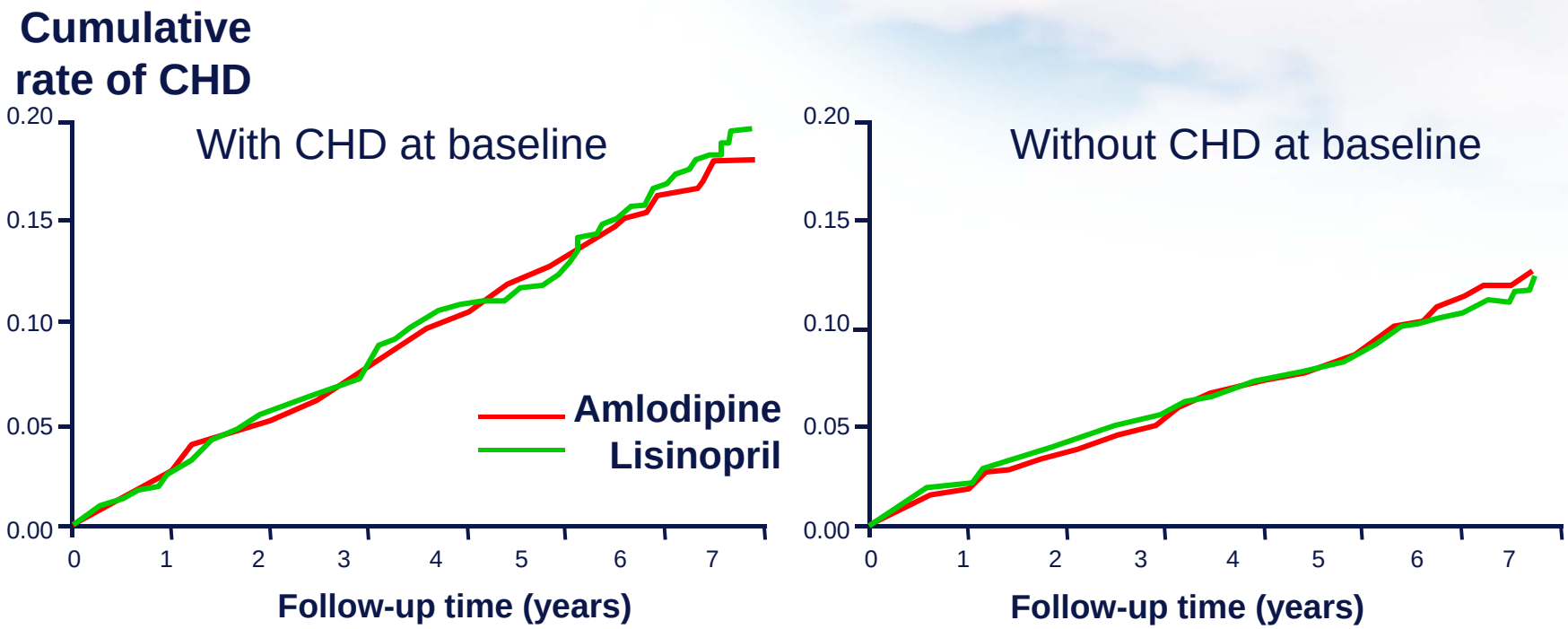


ALLHAT：Lisinopril *vs.* Amlodipine



Leenen FHH, et al. Hypertension 2006;48:374-384.

ALLHAT: Incidence of MI and fatal CHD

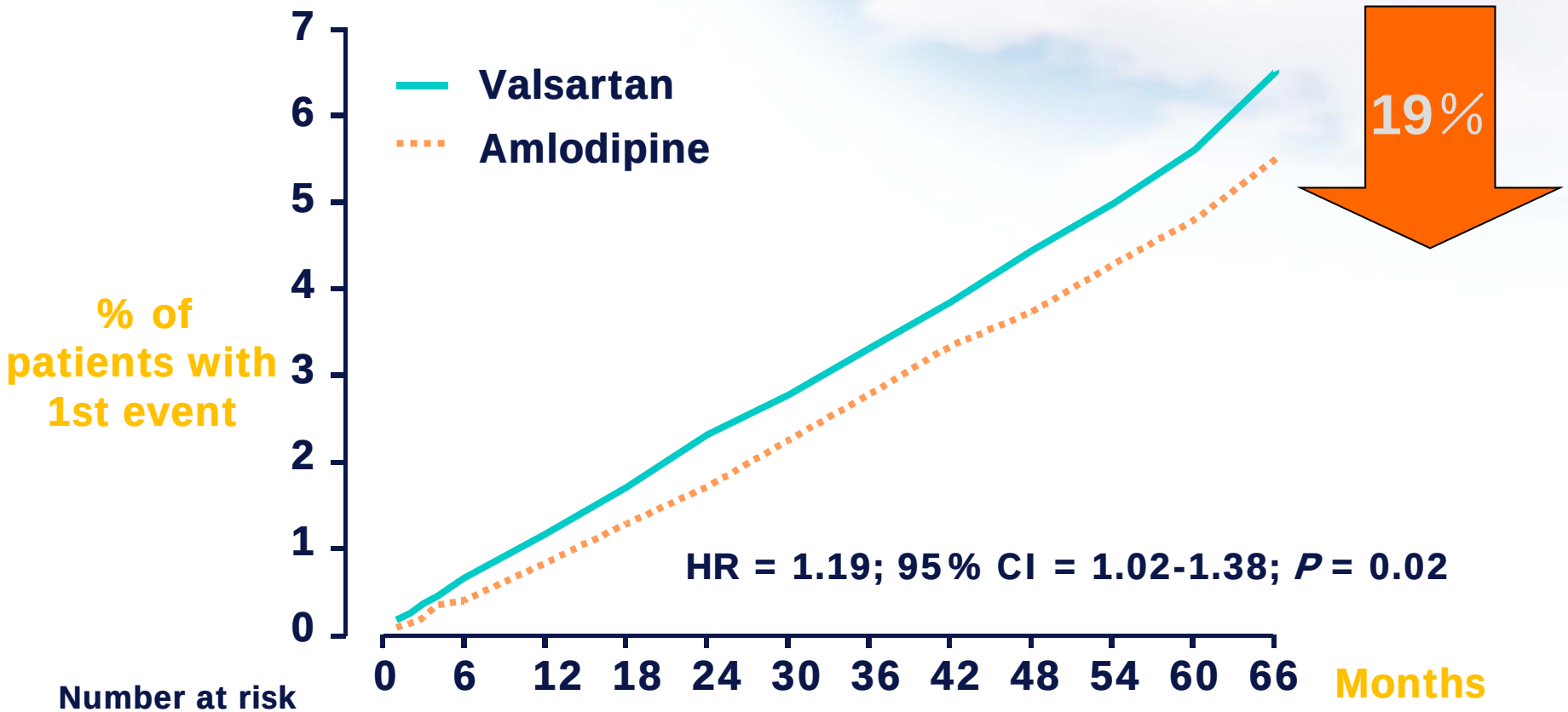


	RR(95%CI)	*P*
lis/am	1.06(0.99-1.32)	0.69

	RR(95%CI)	*P*
lis/aml	0.98(0.88-1.13)	0.78

Leenen FHH, et al. Hypertension 2006;48:374-384.

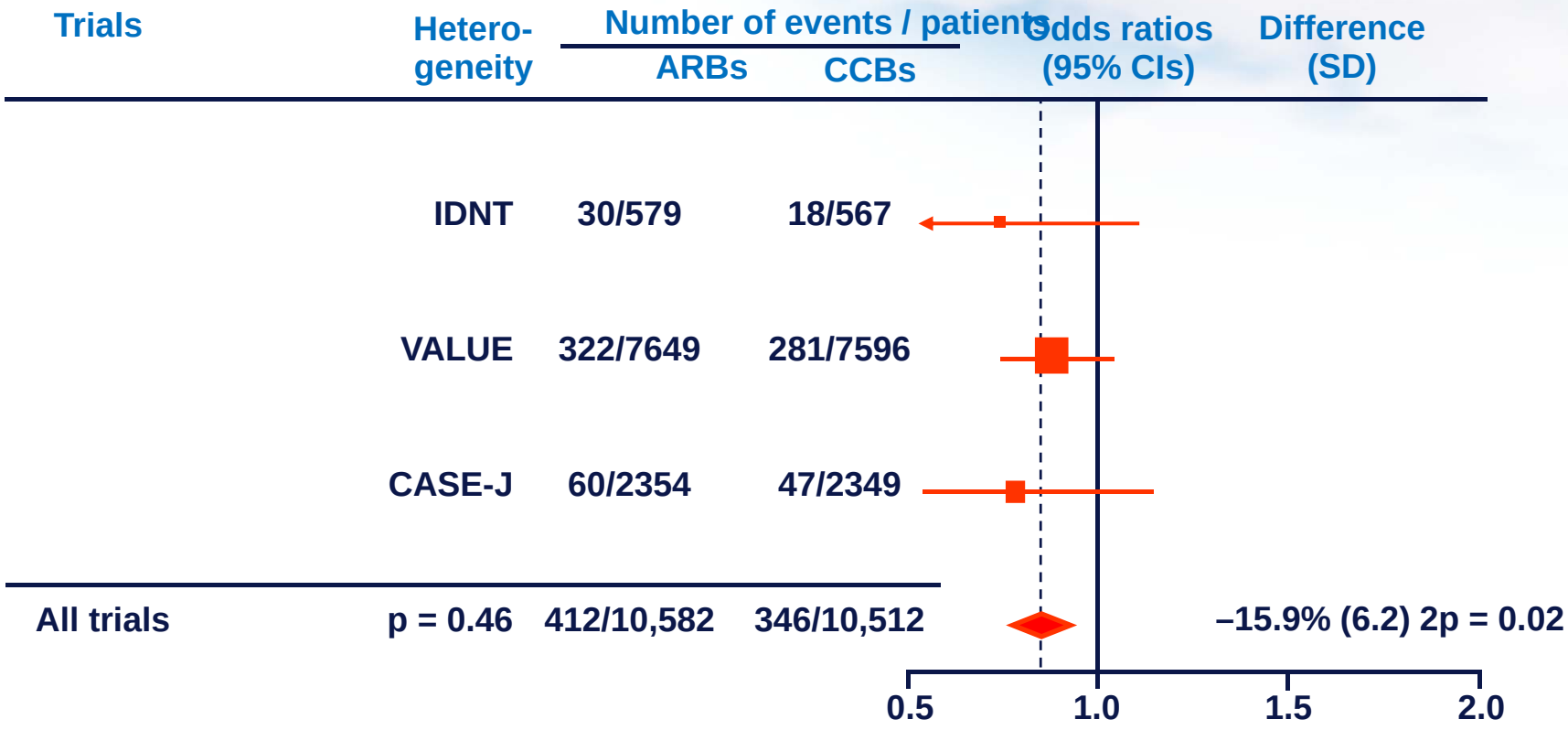
VALUE: Fatal and nonfatal MI



Number at risk												
Valsartan	7649	7499	7458	7319	7177	7016	6853	6680	6504	6078	3864	1520
Amlodipine	7596	7497	7458	7332	7205	7065	6905	6727	6562	6141	3840	1532

Julius S et al. *Lancet*. June 2004;363.

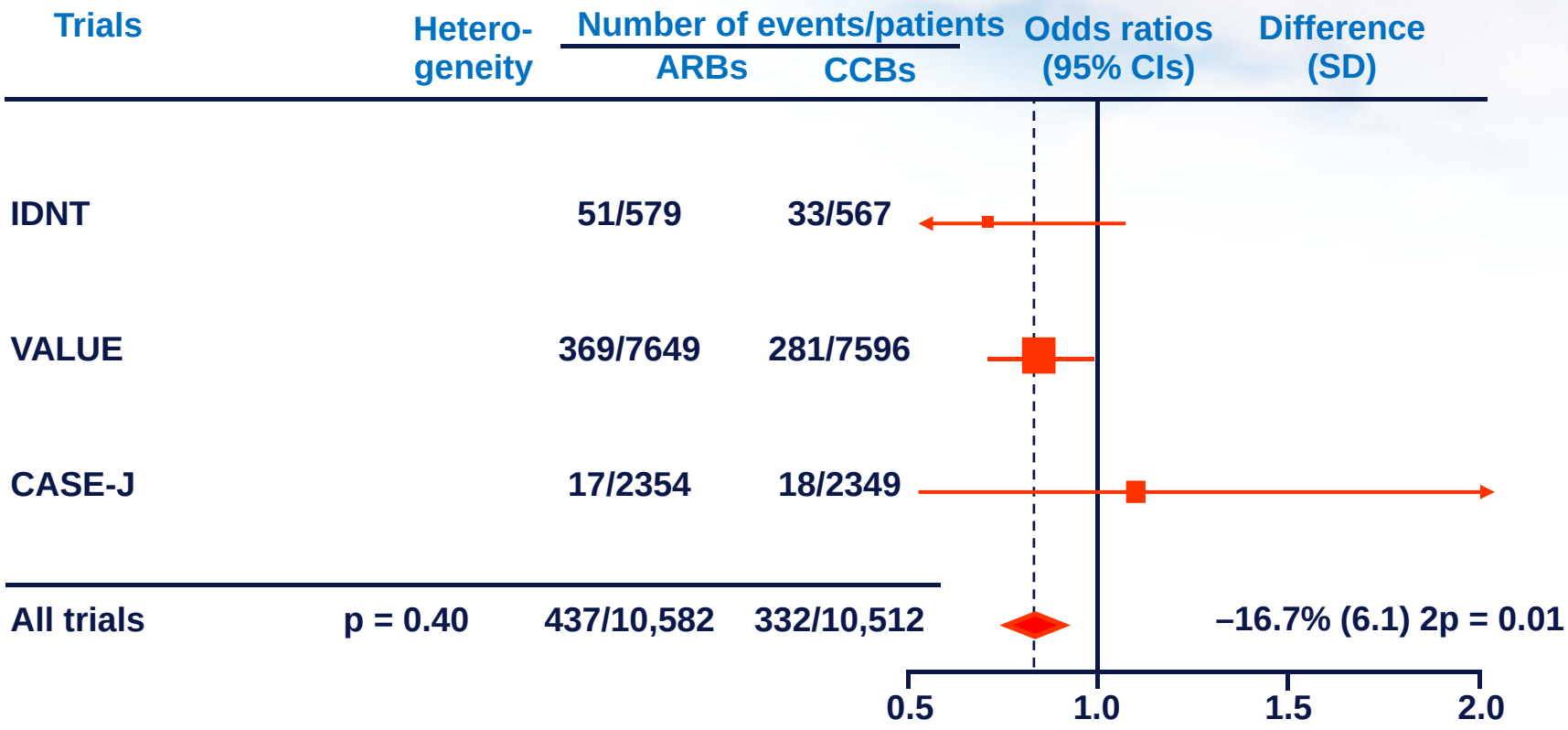
Amlodipine *vs.* ARBs*: Fatal and nonfatal stroke



* Irbesartan, valsartan, and candesartan

Wang JG et al. Hypertension 2007; 50:333-339.

Amlodipine *vs.* ARBs*: Fatal and nonfatal MI



* Irbesartan, valsartan, and candesartan

Wang JG et al. Hypertension 2007; 50:333-339.

Agenda

- The evidence on CCBs over the world
- **The evidence on CCBs over the eastern Asian region**
- The mechanisms for the benefit of CCBs

Summary of the evidence on CCBs over the Asian region

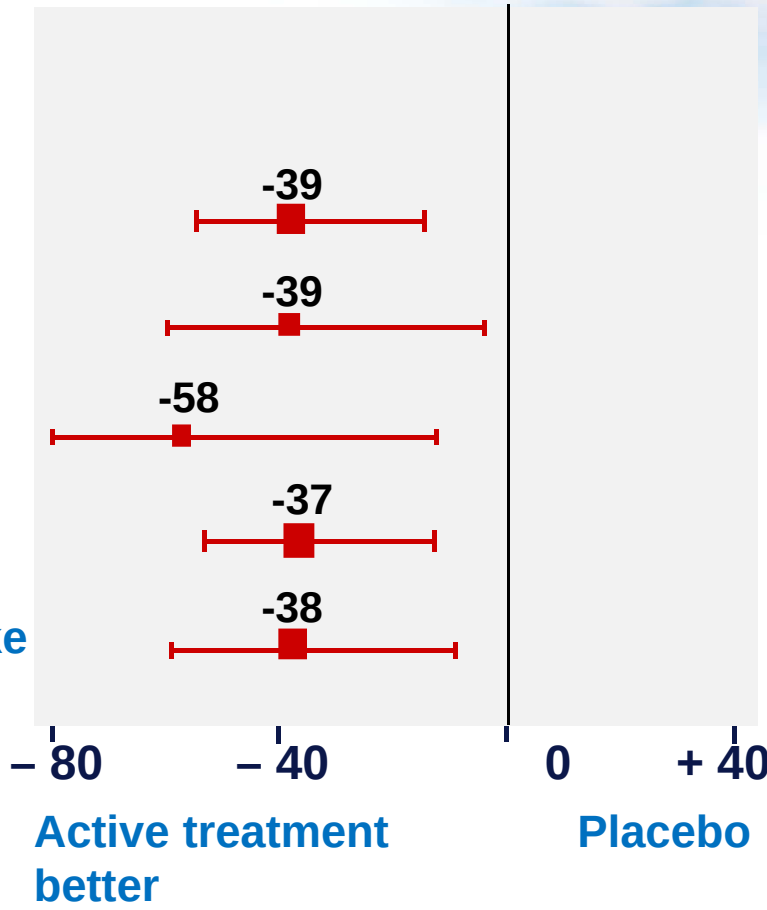
- Syst-China: nitrendipine *vs* a placebo
- FEVER: felodipine+HCTZ *vs* HCTZ+placebo
- CASE-J: amlodipine *vs* candesartan
- CHIEF: amlodipine+telmisartan *vs* amlodipine+diuretics

Syst-China

Systolic Hypertension in China Trial

J Hypertens 1998; 16:1823-1829.
Arch Intern Med 2000; 160:211-220.

Syst-China: Fatal and non-fatal endpoints



	Placebo (n=1141)	Active treatment (n=1253)
Total mortality	82	61
CV mortality	44	33
Stroke mortality	20	10
All CV events	94	74
Fatal and non-fatal stroke	59	45

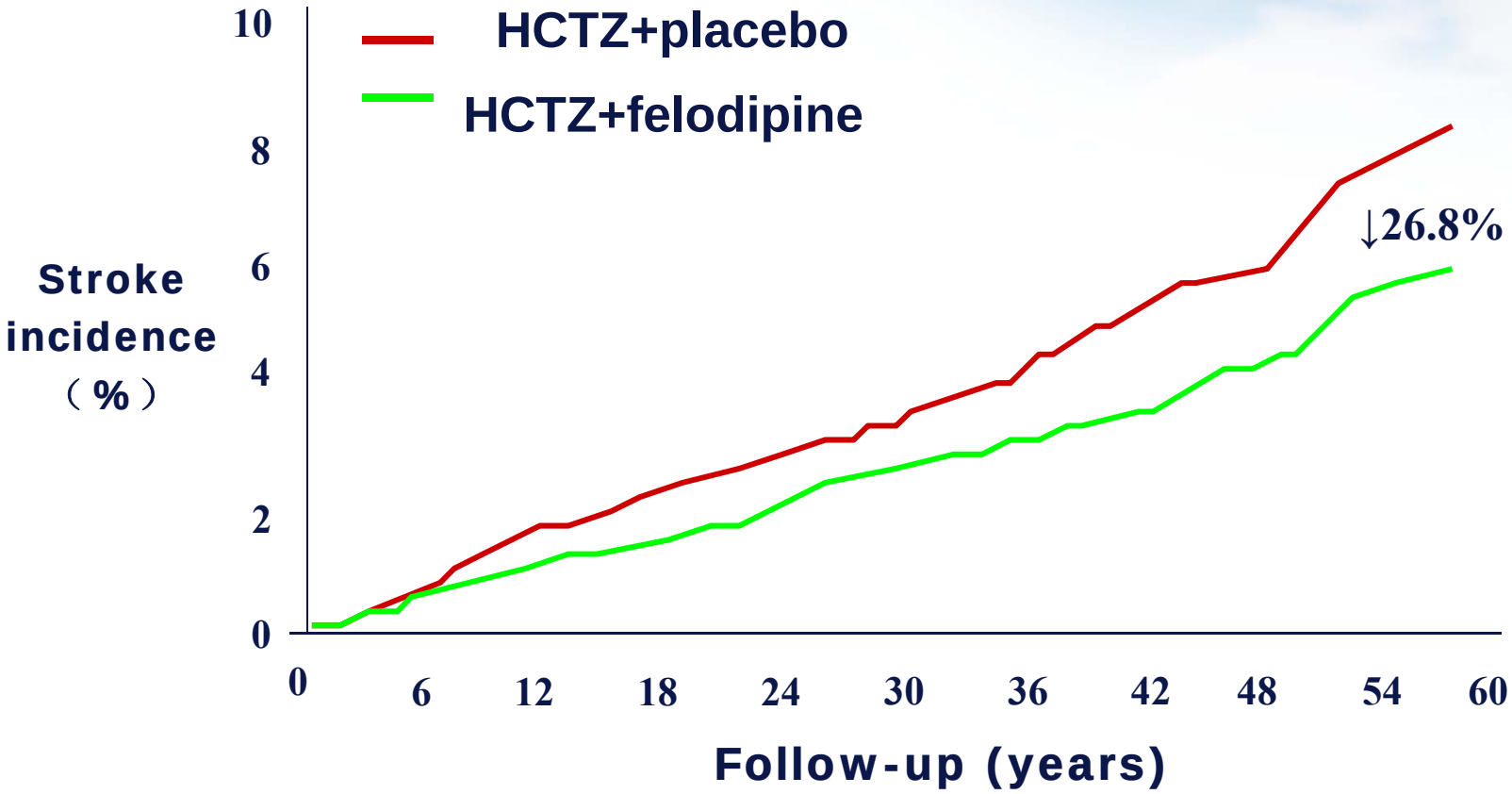
Liu LS et al. J Hypertens 1998;16:1823-1829.

FEVER

Felodipine Event Reduction Trial

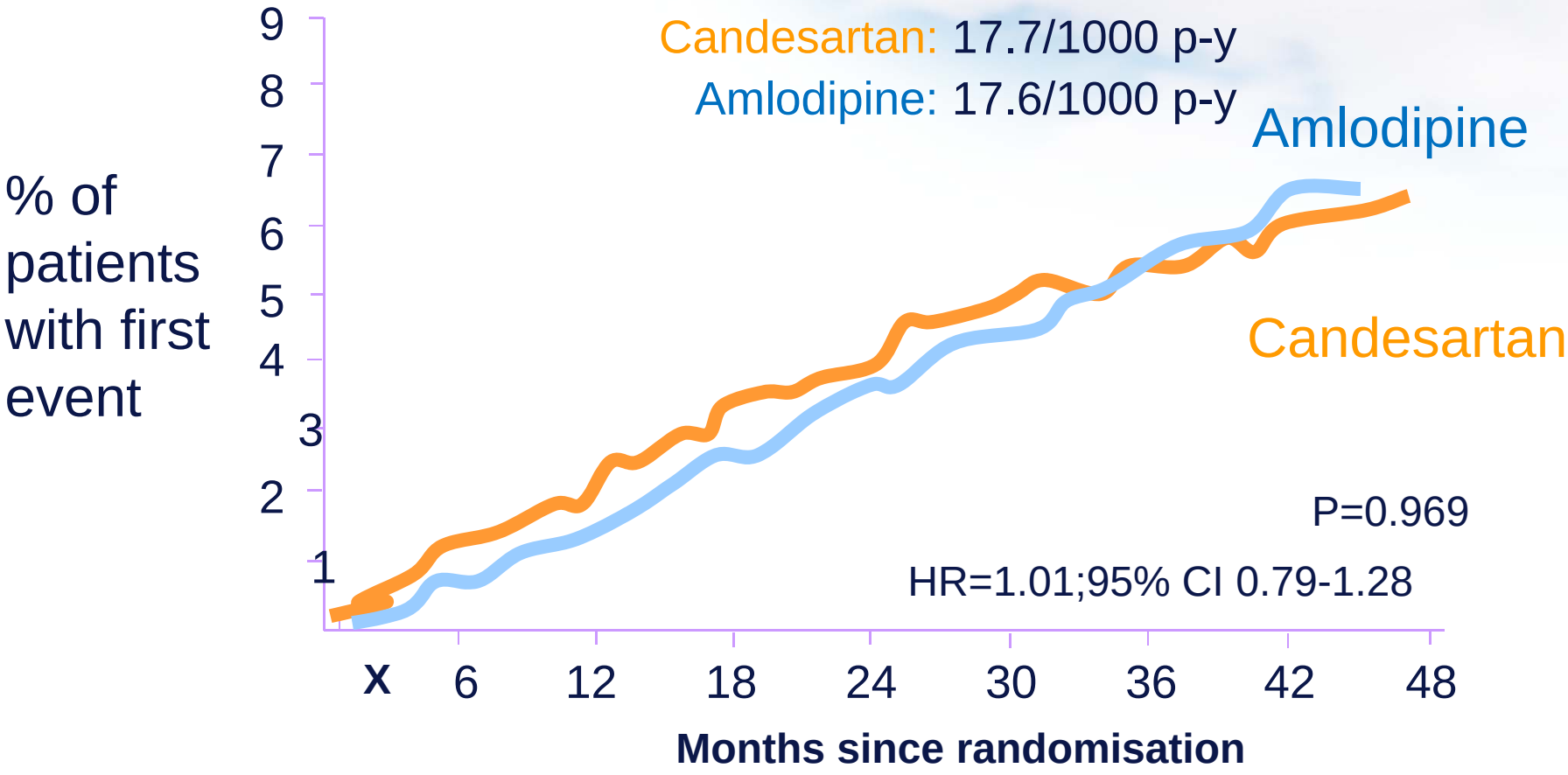
J Hypertens 2005;23:2157-2172.

FEVER：Fatal and nonfatal stroke



Liu LS et al. J Hypertens 2005;23:2157-2172.

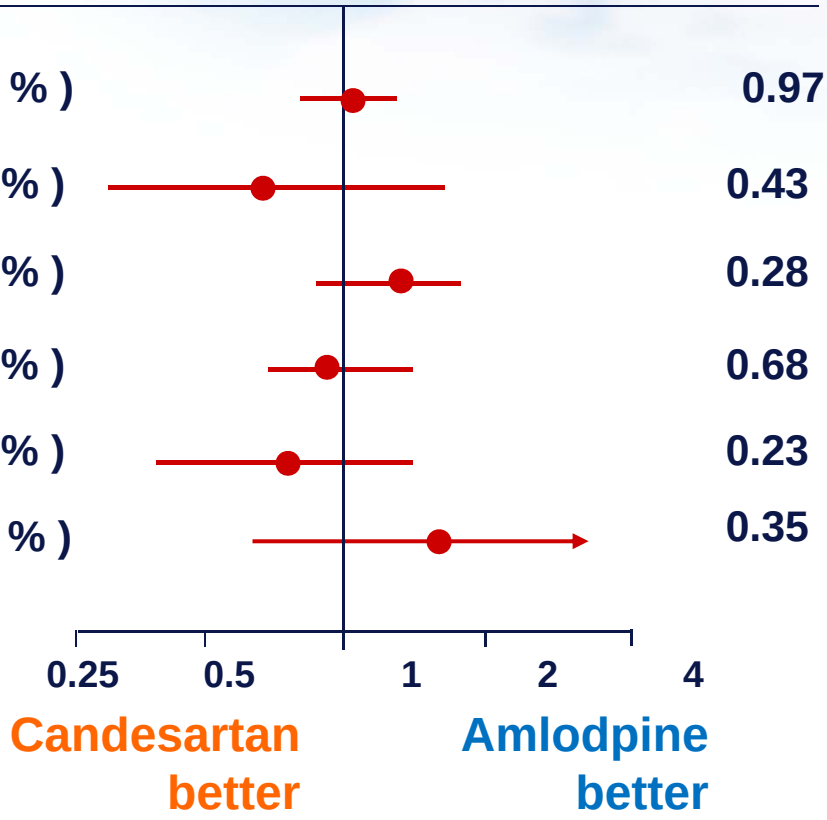
CASE-J：Primary composite CV endpoint



Ogihara T et al. Hypertension. 2008;51:393-8.

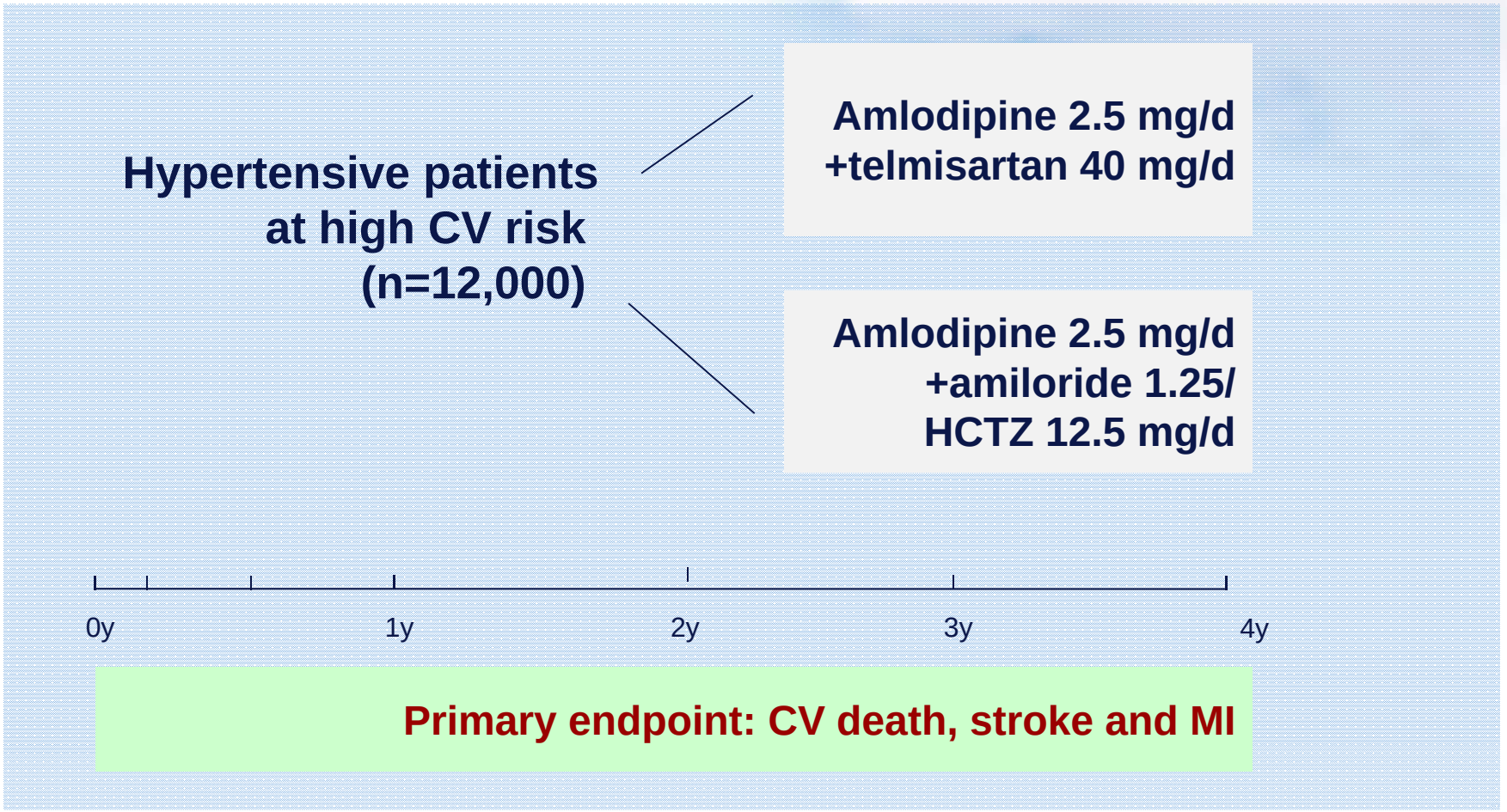
CASE-J：Candesartan vs amlodipine

Events	Candesartan (n=2354)	Amlodipine (n=2349)	P value
CV composite	134 (5.7 %)	134 (5.7 %)	0.97
Sudden death	11 (0.5 %)	15 (0.6 %)	0.43
Cerebrovascular	61 (2.6 %)	50 (2.1 %)	0.28
Cardiac	43 (1.8 %)	47 (2.0 %)	0.68
Renal	19 (0.8 %)	27 (1.1 %)	0.23
Other vascular	11 (0.5 %)	7 (0.3 %)	0.35



Ogihara T et al. Hypertension. 2008;51:393-8.

Chinese Hypertension Intervention Efficacy (CHIEF): General design



Clear recommendations

- If no compelling indications or contraindications, simply start with CLASSIC (**A**mlodipine), with the possible replacement of or combination with FASHION (**A**RB/**A**CEI).
- The **A**+**A** partnership.

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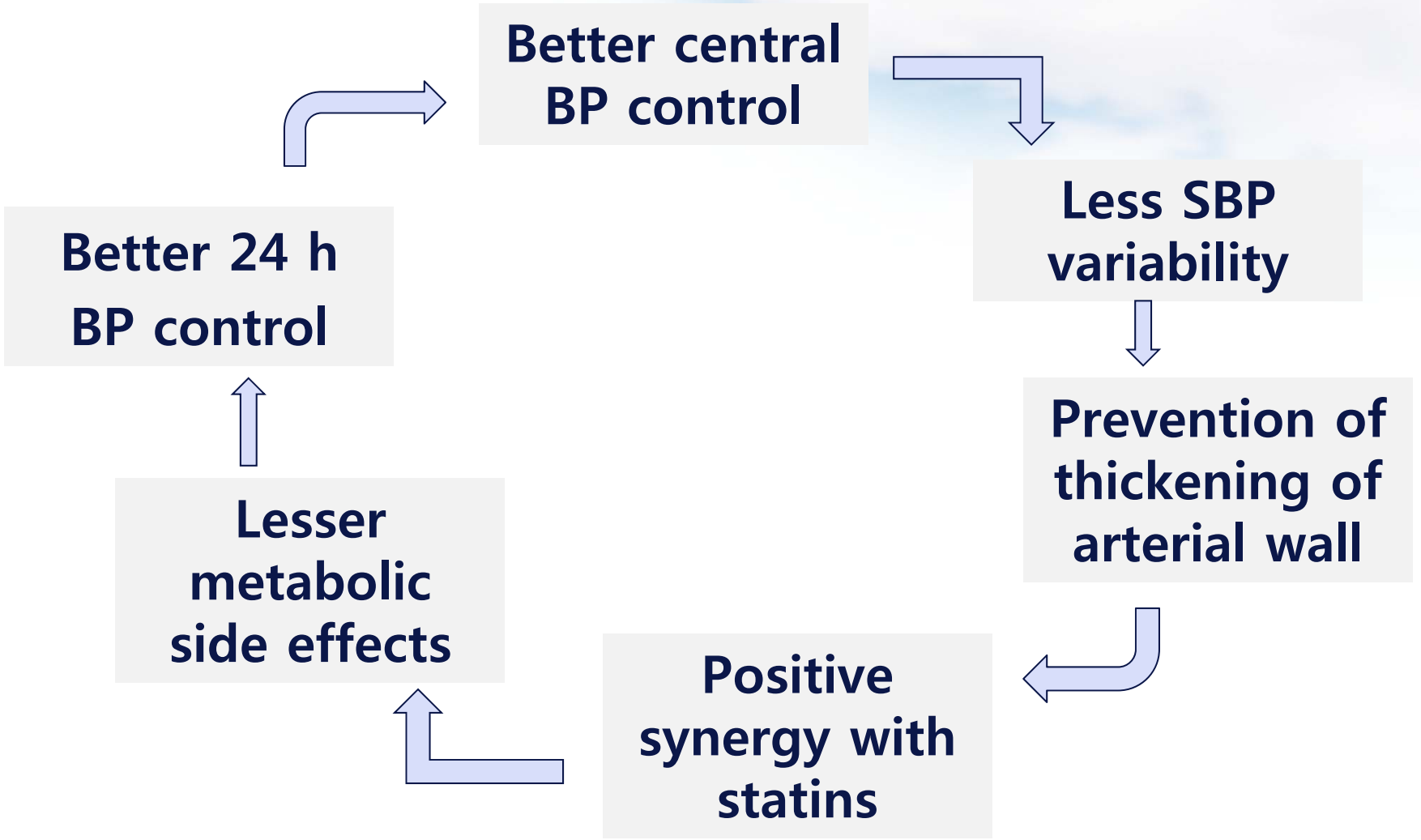
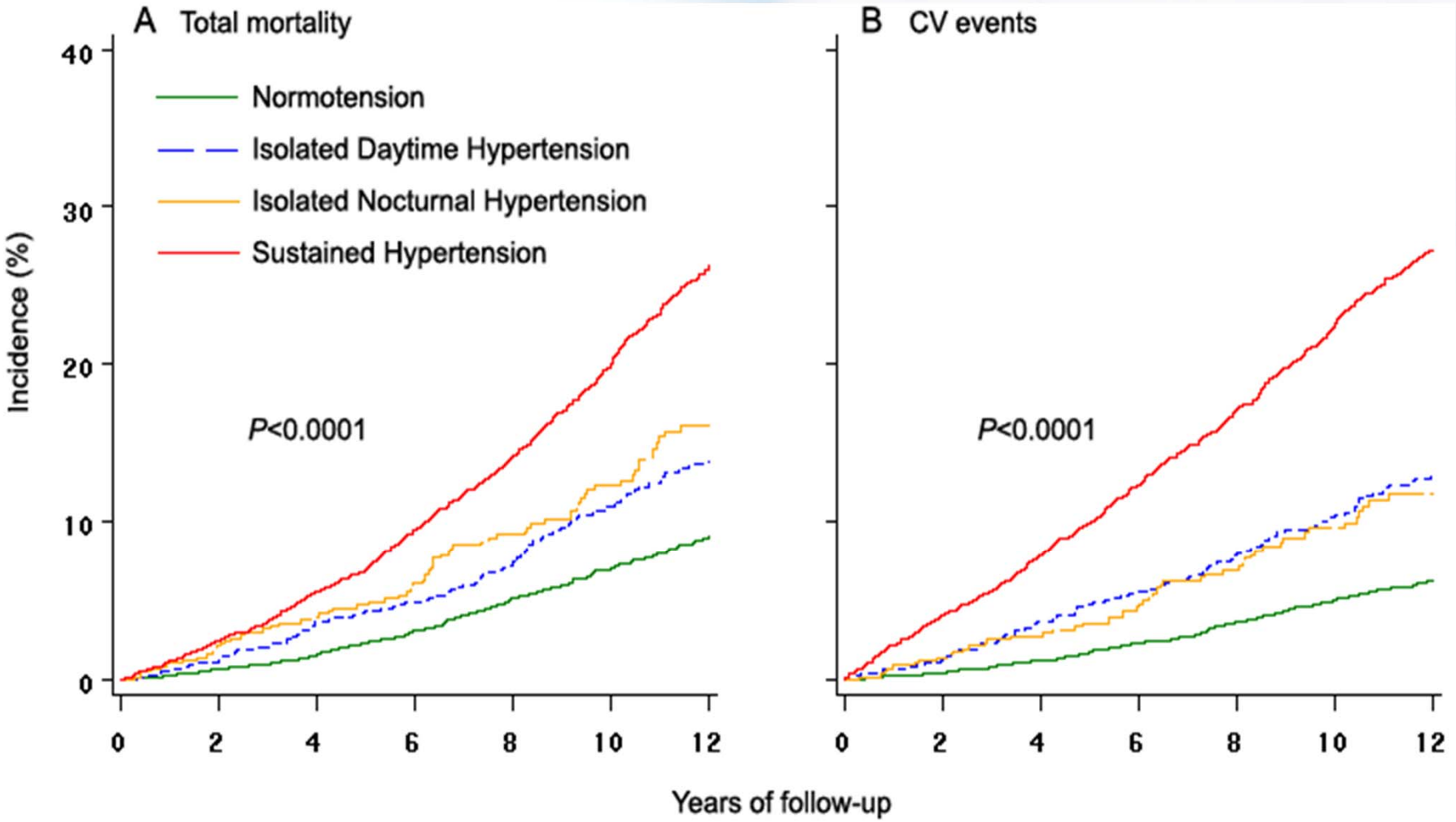
Possible mechanisms for the benefit of CCBs



IDACO*: Prognosis of various forms of ambulatory hypertension



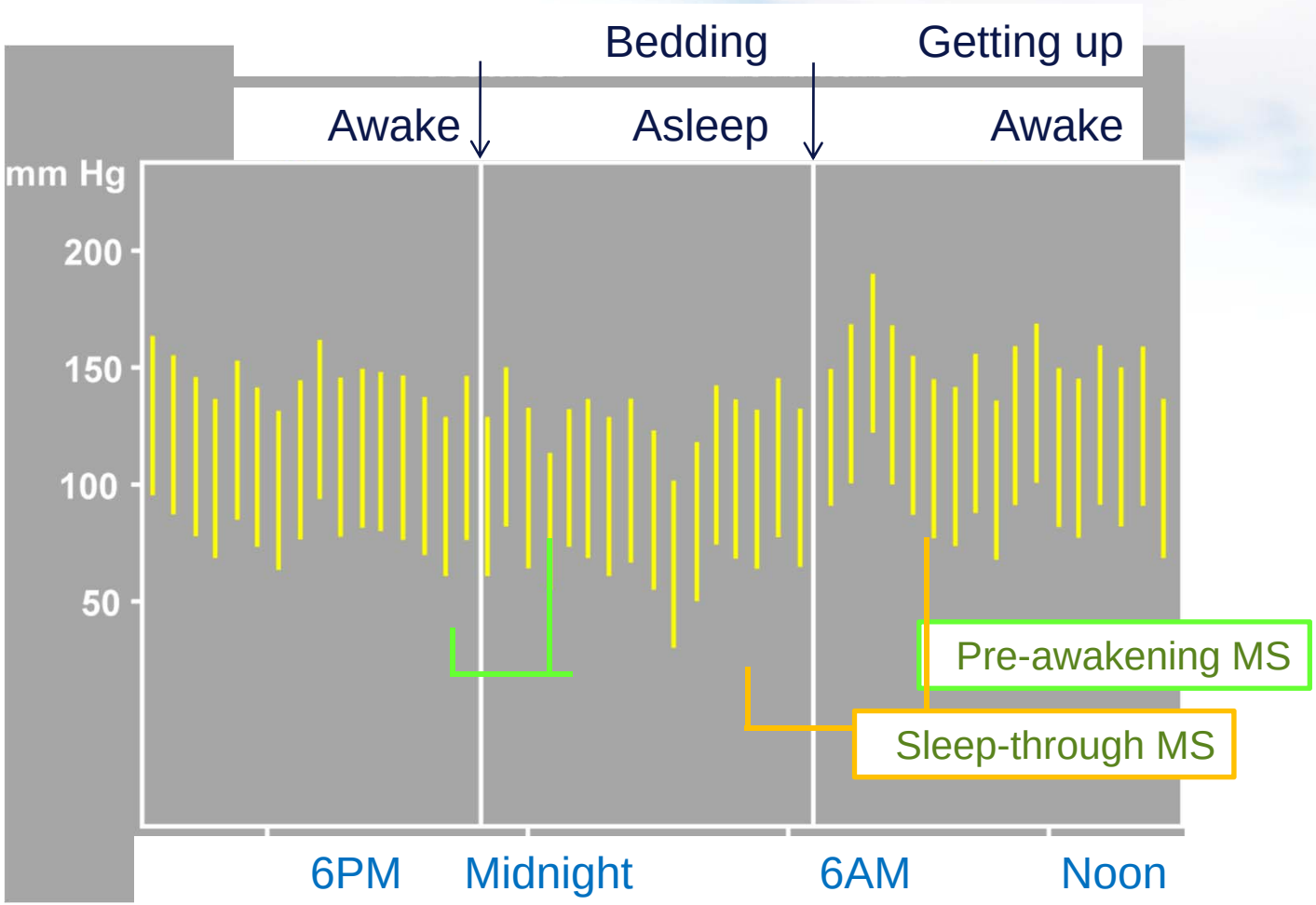
*IDACO; International Database of Ambulatory Blood Pressure in relation to Cardiovascular Outcome

Fan HQ, et al. J Hypertens 2010; Epub.

O1 In the next 3 slides, I will show you the characteristics of the participants. In 204 men and 223 women, age averaged 44 years. two third of men consumed alcohol and cigarettes. About 20% of women drank alcohol but none smoked. The prevalence of hypertension was about 25% and only about 10% took antihypertensive drugs.

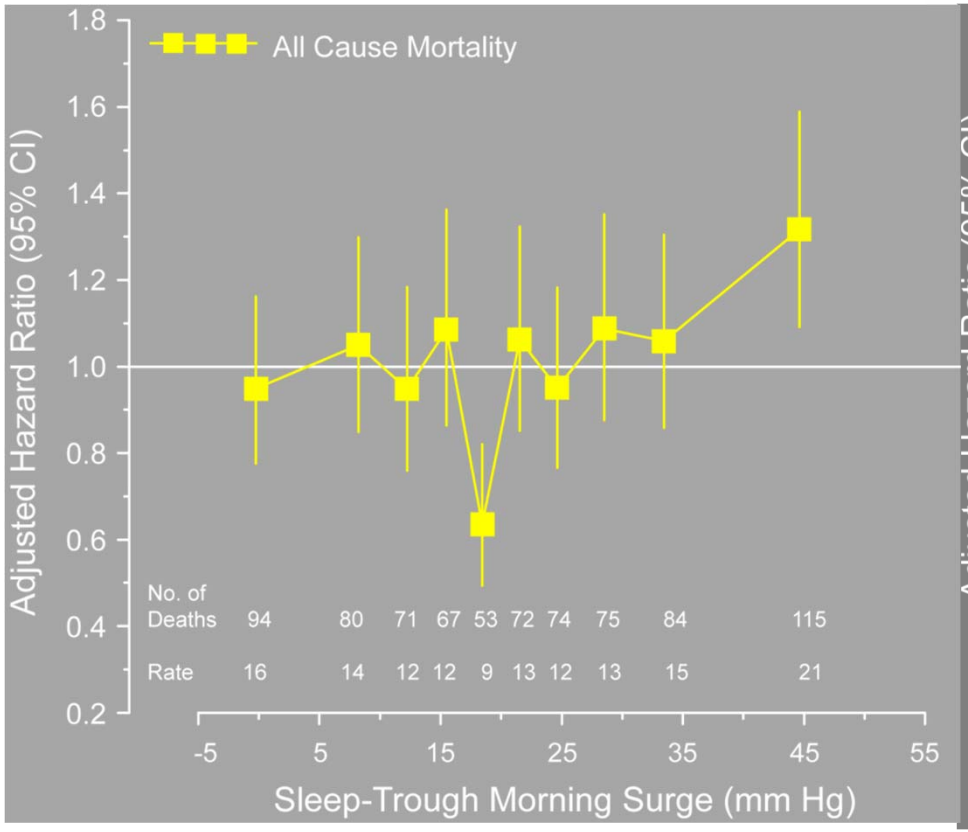
Owner, 2005-06-03

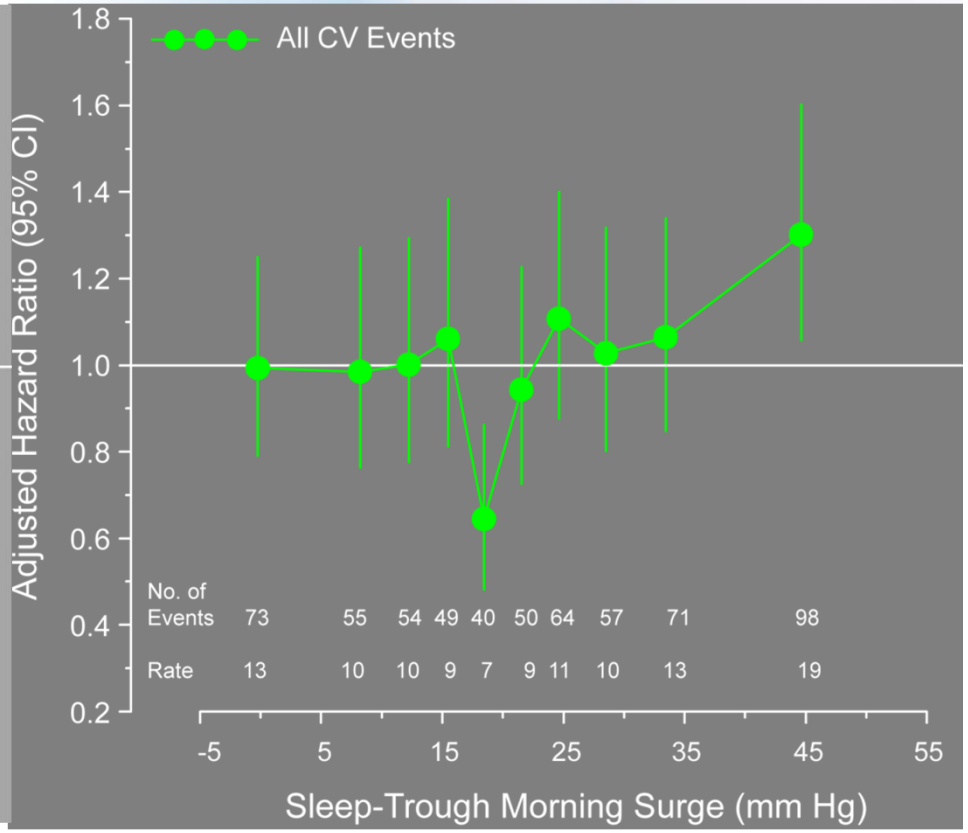
IDACO: Morning BP surge



Kario K et al. Circulation 2003;107:1401-1406.

IDACO: Risk according to the level of morning BP surge

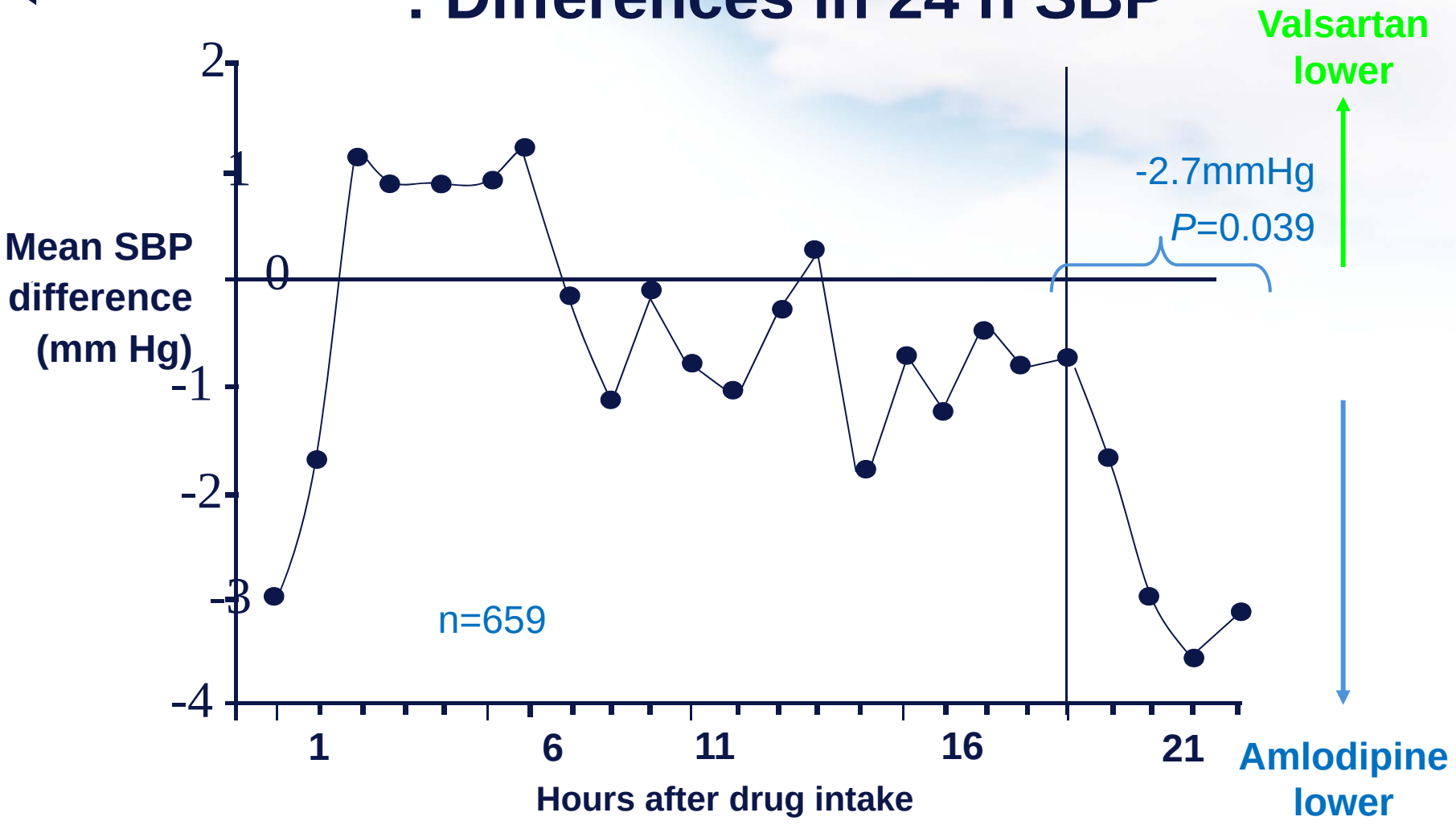




Li Y, et al. Hypertension 2010;55:1040-1048.

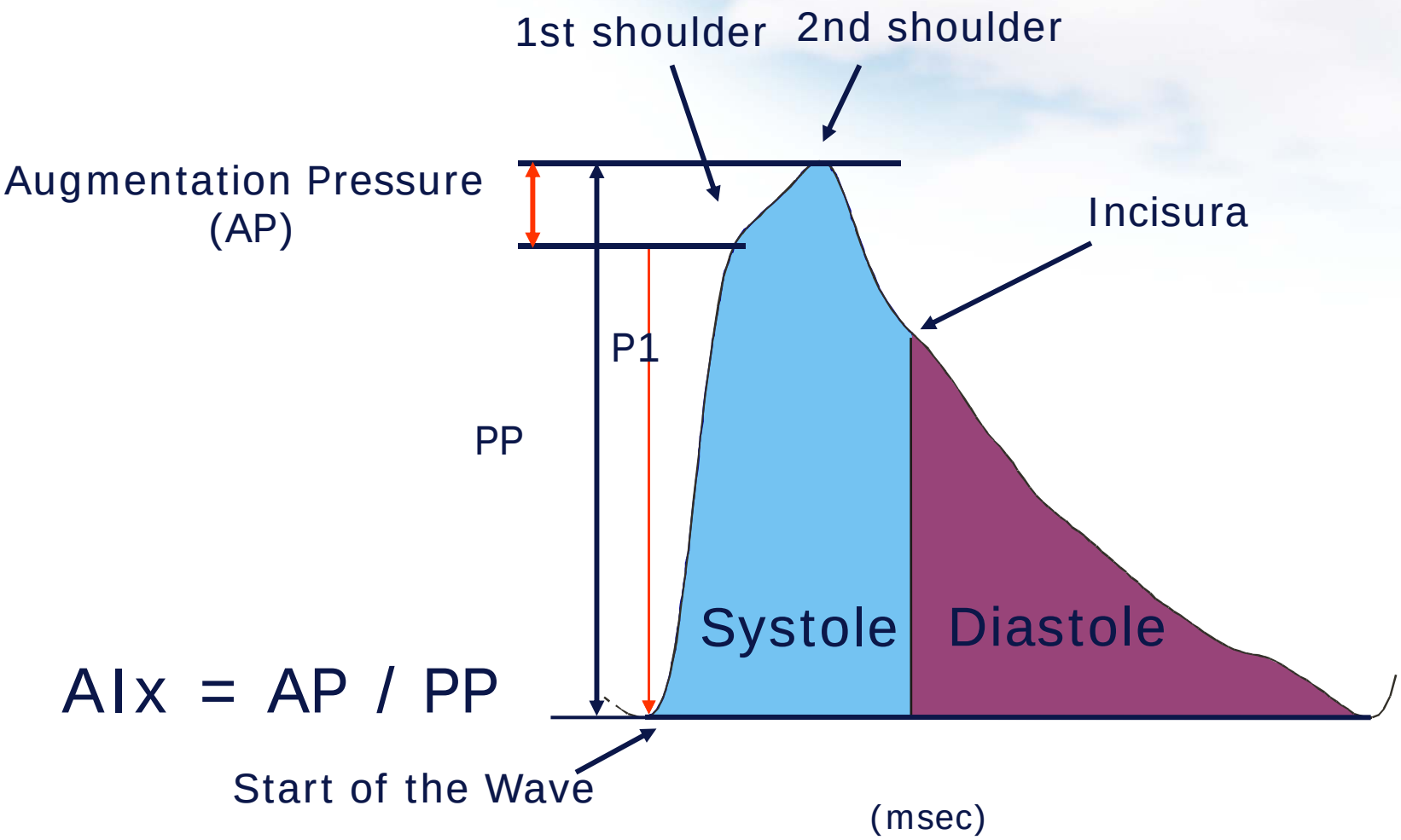
VALUE ABPM substudy

: Differences in 24 h SBP



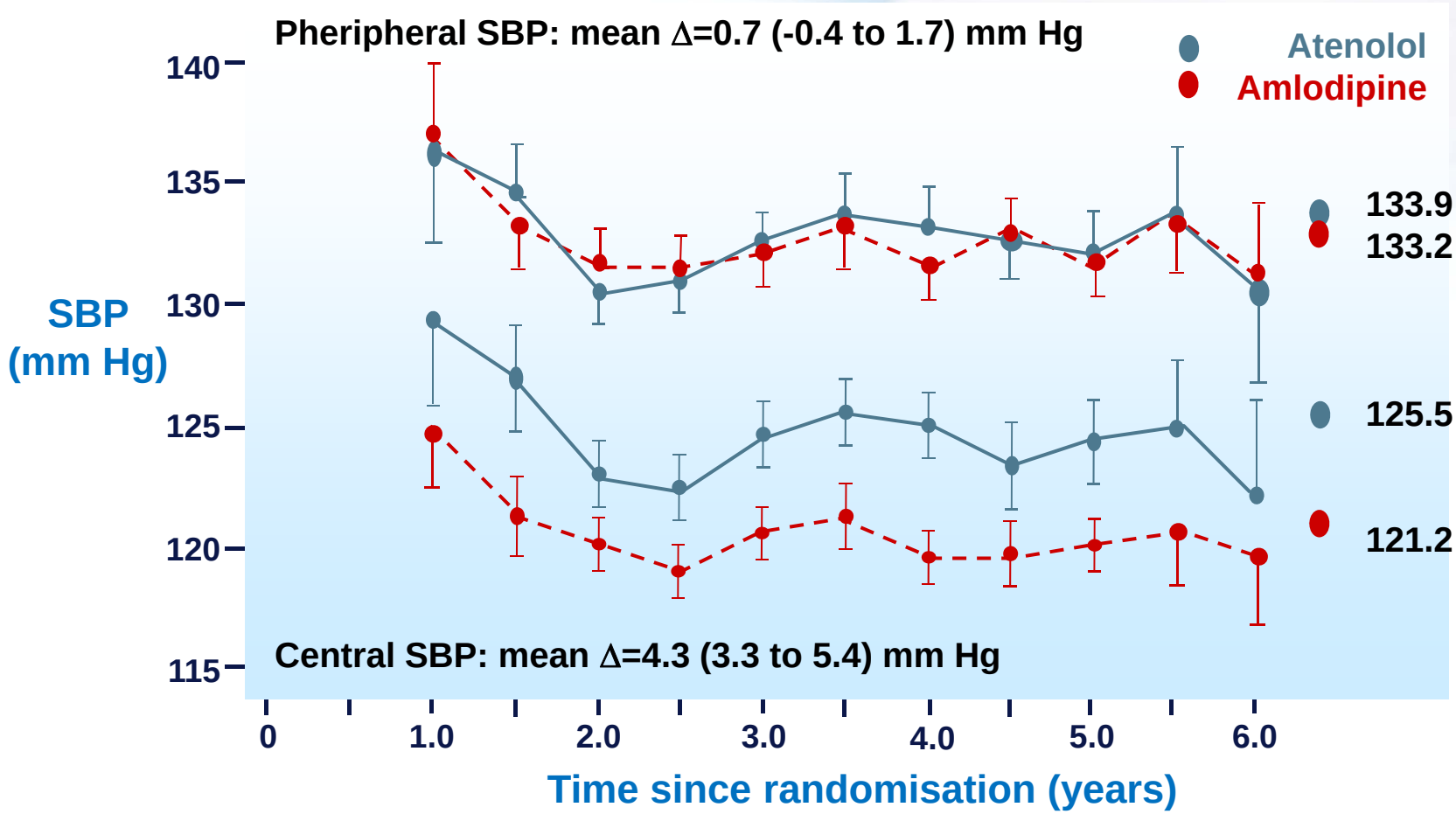
Pedersen et al. J Hypertens 2007;25:707-712.

Augmentation Index (AIx)



$$AIx = AP / PP$$

ASCOT-CAFE: Peripheral and central pressure



Williams B, et al. Circulation 2006;113:1213-1225.

Associations between SBP variability and stroke risk

(hazard ratios per 20 mm Hg increase in SBP)

	UK trial	Dutch trial	Pooled*
Patients with low visit-to-visit variability†			
Unadjusted baseline SBP	1·58 (1·25–2·00)	1·35 (0·99–1·85)	1·50 (1·24–1·80)
Estimated usual SBP‡	1·93 (1·38–2·70)	1·60 (0·98–2·61)	1·82 (1·38–2·40)
Actual mean SBP§	1·72 (1·25–2·35)	1·68 (1·18–2·39)	1·70 (1·35–2·15)
Patients with high visit-to-visit variability‡			
Unadjusted baseline SBP	1·30 (1·11–1·52)	1·15 (0·95–1·40)	1·24 (1·09–1·40)
Estimated usual SBP‡	2·83 (1·51–5·30)	4·06 (0·57–28·8)	2·93 (1·61–5·32)¶
Actual mean SBP§	1·27 (1·00–1·61)	1·08 (0·76–1·54)	1·21 (1·00–1·47)¶

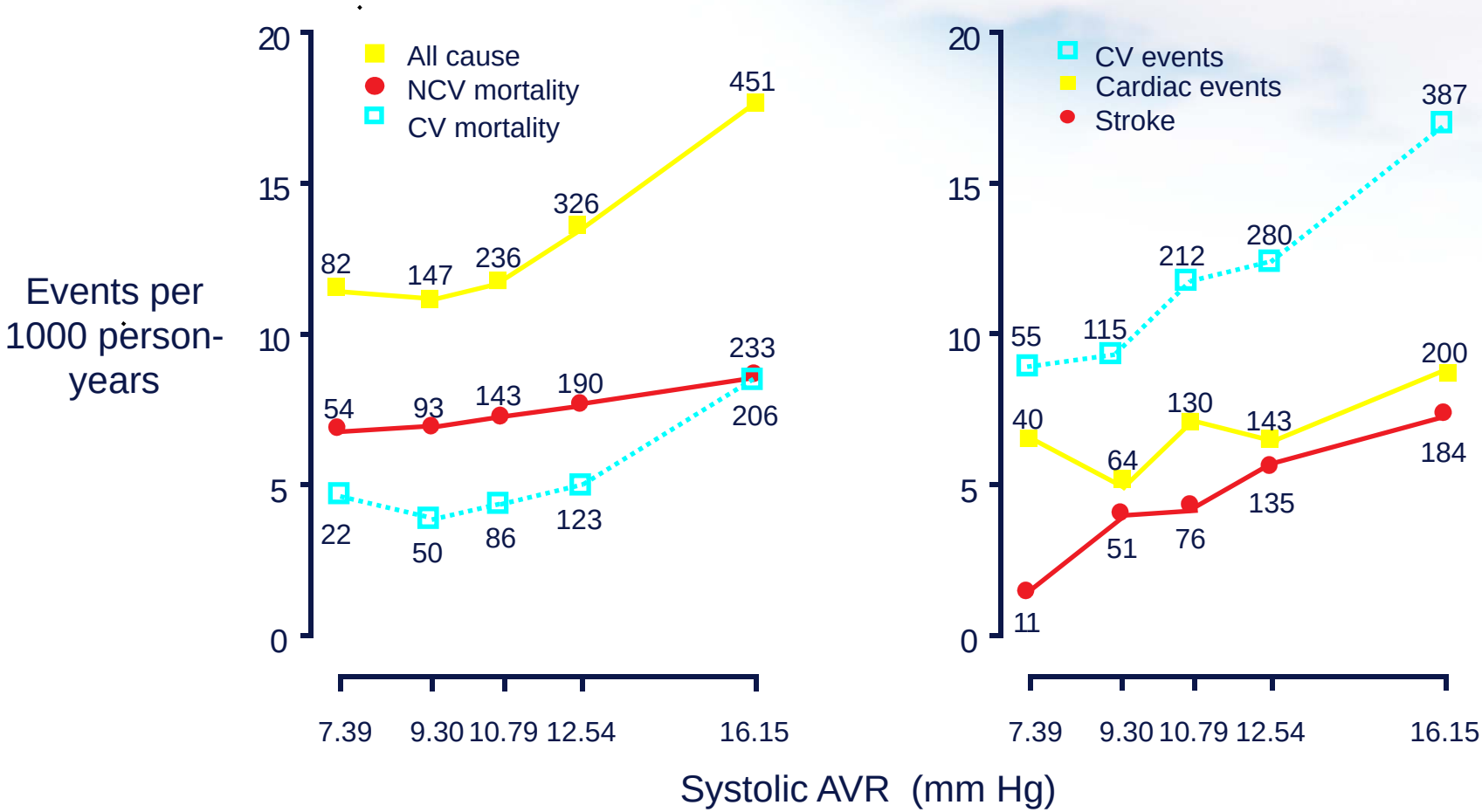
¶ p value=0.006

UK and Dutch TIA trials

Mean (SD) SBP at baseline and during follow-up in the ALLHAT trial

	Treatment group			p value for difference in SD SBP	
	Amlodipine	Chlorthalidone	Lisinopril	Amlodipine vs lisinopril	Chlorthalidone vs lisinopril
Baseline	146·2 (15·7)	146·2 (15·7)	146·4 (15·7)	0·5	0·5
1-year follow up	138·5 (14·9)	136·9 (15·8)	140·0 (18·5)	9×10^{-79}	7×10^{-55}
2-year follow up	137·1 (15·0)	135·9 (15·9)	138·4 (17·9)	3×10^{-48}	1×10^{-28}
3-year follow up	135·6 (15·2)	134·8 (15·4)	136·7 (17·3)	9×10^{-25}	2×10^{-25}
4-year follow up	134·8 (15·0)	133·9 (15·7)	135·5 (17·2)	1×10^{-24}	2×10^{-14}
5-year follow up	134·7 (14·9)	133·9 (15·2)	135·9 (17·9)	1×10^{-24}	8×10^{-25}

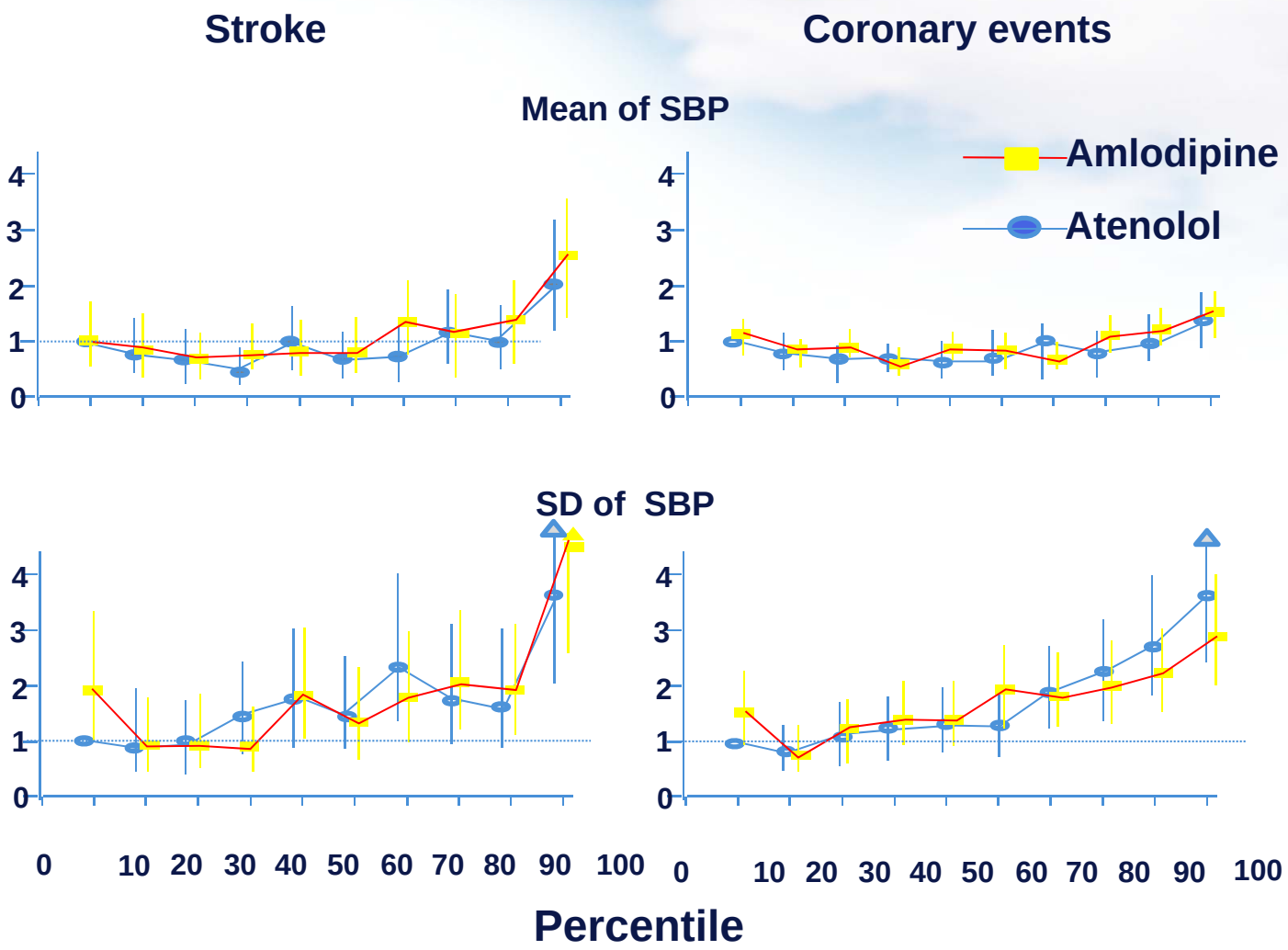
IDACO*: Reading-to-reading BP variability



*IDACO; International Database of Ambulatory Blood Pressure in relation to Cardiovascular Outcome

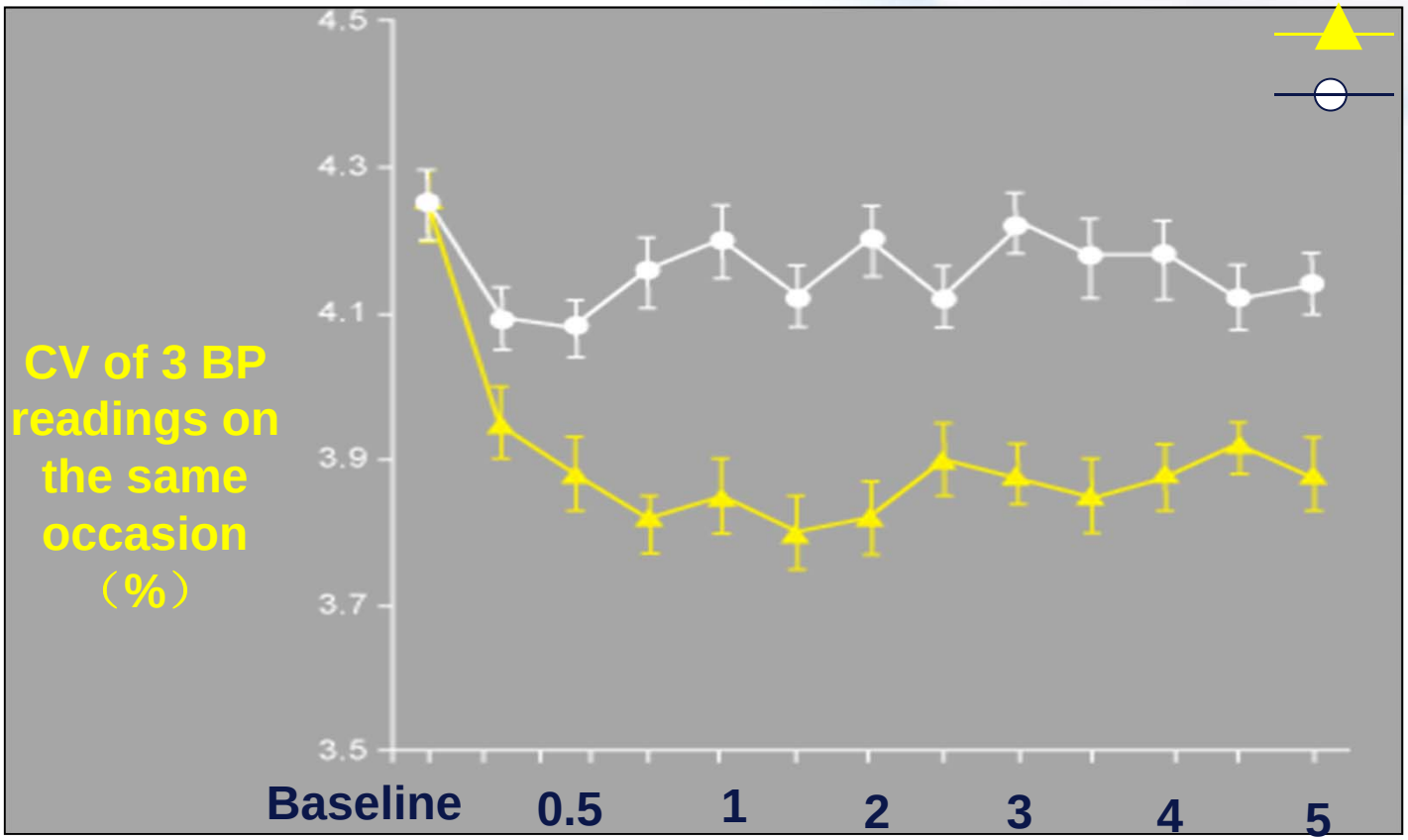
Hansen TW, et al. Hypertension. 2010;55:1049-57.

ASCOT：Long-term BP variability



Rothwell PM et al. Lancet 2010; 375: 895–905.

ASCOT: Coefficient of variation for SBP



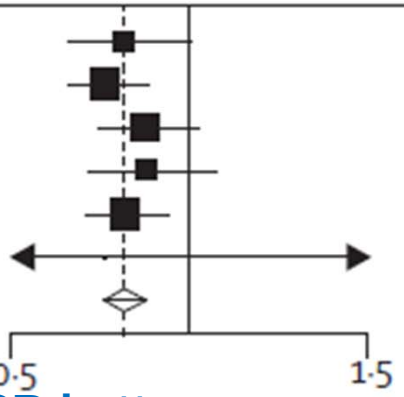
Rothwell PM et al. Lancet Neurol 2010; 9: 469–80.

Mean and SD SBP during F/U

All large randomised trials of CCBs versus β blockers or ACEIs

A Stroke risk

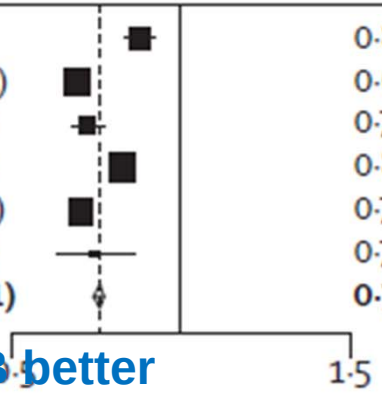
	Events/patients		Odds ratio (95% CI)
	CCB	Drug B	
NORDIL (*vs* BB/D)[77]	159/5410	196/5471	0·81 (0·66 to 1·01)
ASCOT (*vs* BB)[47]	327/9639	422/9618	0·77 (0·66 to 0·89)
VALUE (*vs* ARB)[78]	281/7596	322/7649	0·87 (0·74 to 1·03)
INVEST (*vs* BB)[76]	176/11267	201/11309	0·88 (0·72 to 1·08)
ALLHAT (*vs* ACE)[74]	377/9048	457/9054	0·82 (0·71 to 0·94)
CAMELOT (*vs* ACE)[46]	6/663	8/673	0·76 (0·26 to 2·20)
Total	**1326/43623**	**1606/43774**	**0·82 (0·76 to 0·88)**



CCB better

B SBP at follow-up

	Mean (SD)		Mean SBP difference (95% CI)	Variance ratio (95% CI)
	CCB	Drug B		
NORDIL (*vs* BB/D)[77]	155·2 (16·3)	151·5 (17·4)	3·70 (3·07 to 4·33)	0·88 (0·83 to 0·93)
ASCOT (*vs* BB)[47]	138·4 (14·8)	140·3 (17·8)	−1·90 (−2·36 to −1·44)	0·69 (0·67 to 0·72)
VALUE (*vs* ARB)[78]	138·2 (13·8)	140·0 (16·2)	−1·80 (−4·92 to 1·32)	0·73 (0·68 to 0·77)
INVEST (*vs* BB)[76]	131·0 (11·0)	131·0 (10·0)	0·00 (−0·27 to 0·27)	0·83 (0·80 to 0·86)
ALLHAT (*vs* ACE)[74]	137·1 (15·0)	138·4 (17·9)	−1·30 (−1·78 to −0·82)	0·70 (0·67 to 0·73)
CAMELOT (*vs* ACE)[46]	124·2 (15·5)	123·6 (18·0)	0·60 (−1·20 to 2·40)	0·74 (0·64 to 0·86)
Total			**−0·21 (−0·41 to −0·01)**	**0·76 (0·74 to 0·77)**



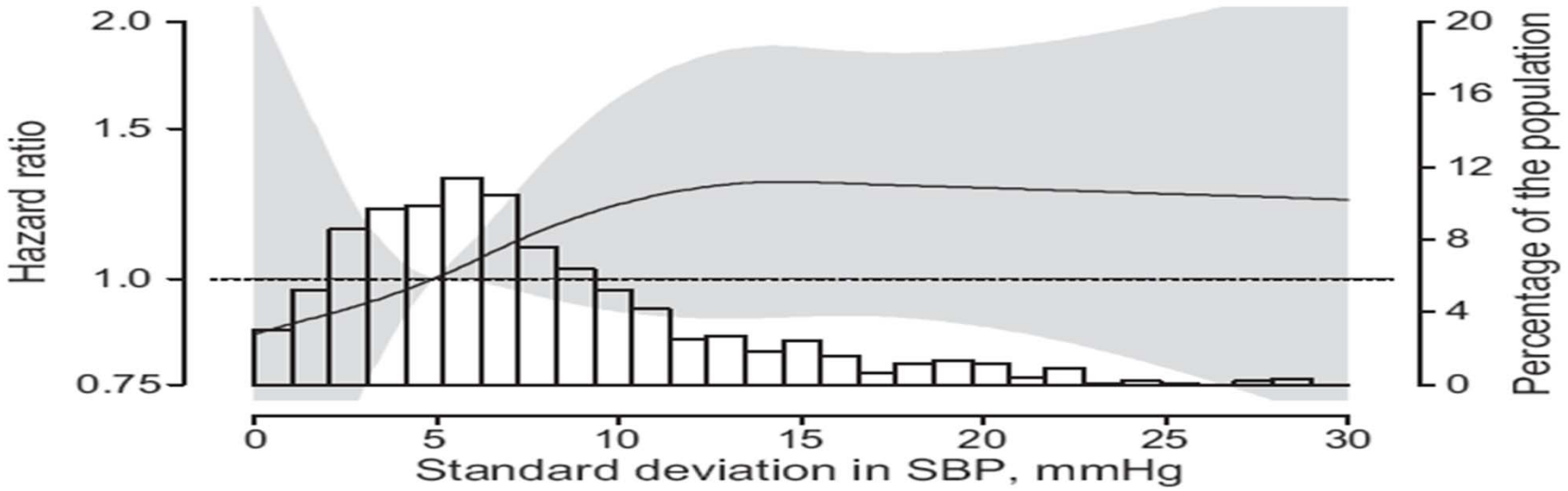
CCB better

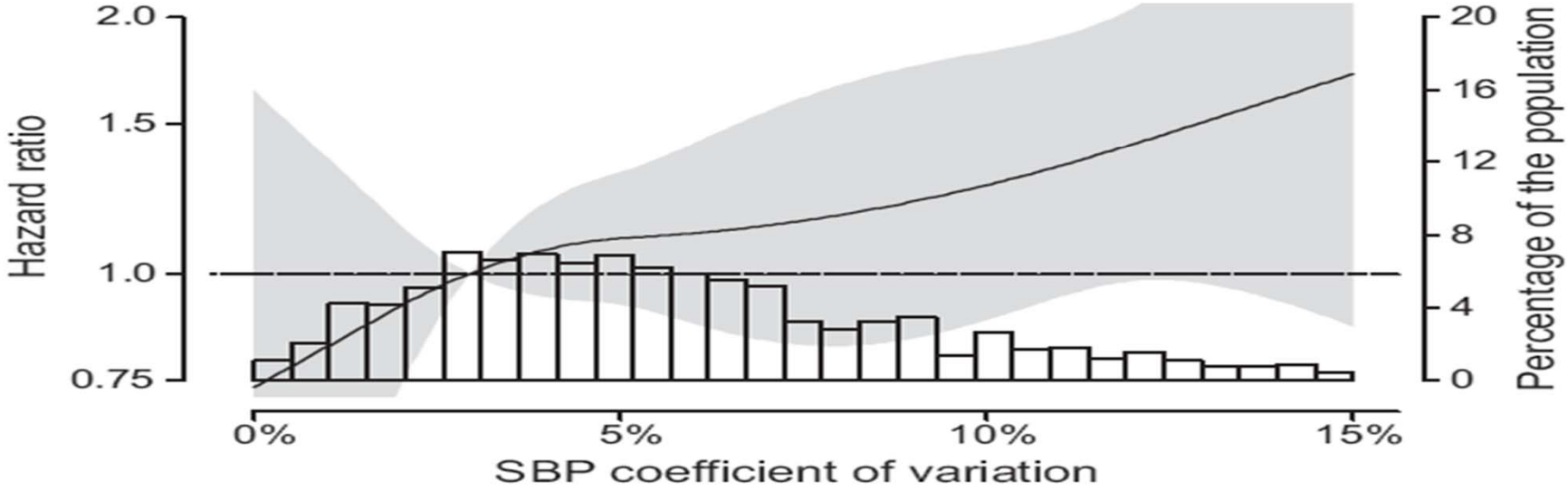
The Relationship Between Visit-to-Visit Variability in SBP and All-Cause Mortality in the General Population

Findings From NHANES III, 1988 to 1994

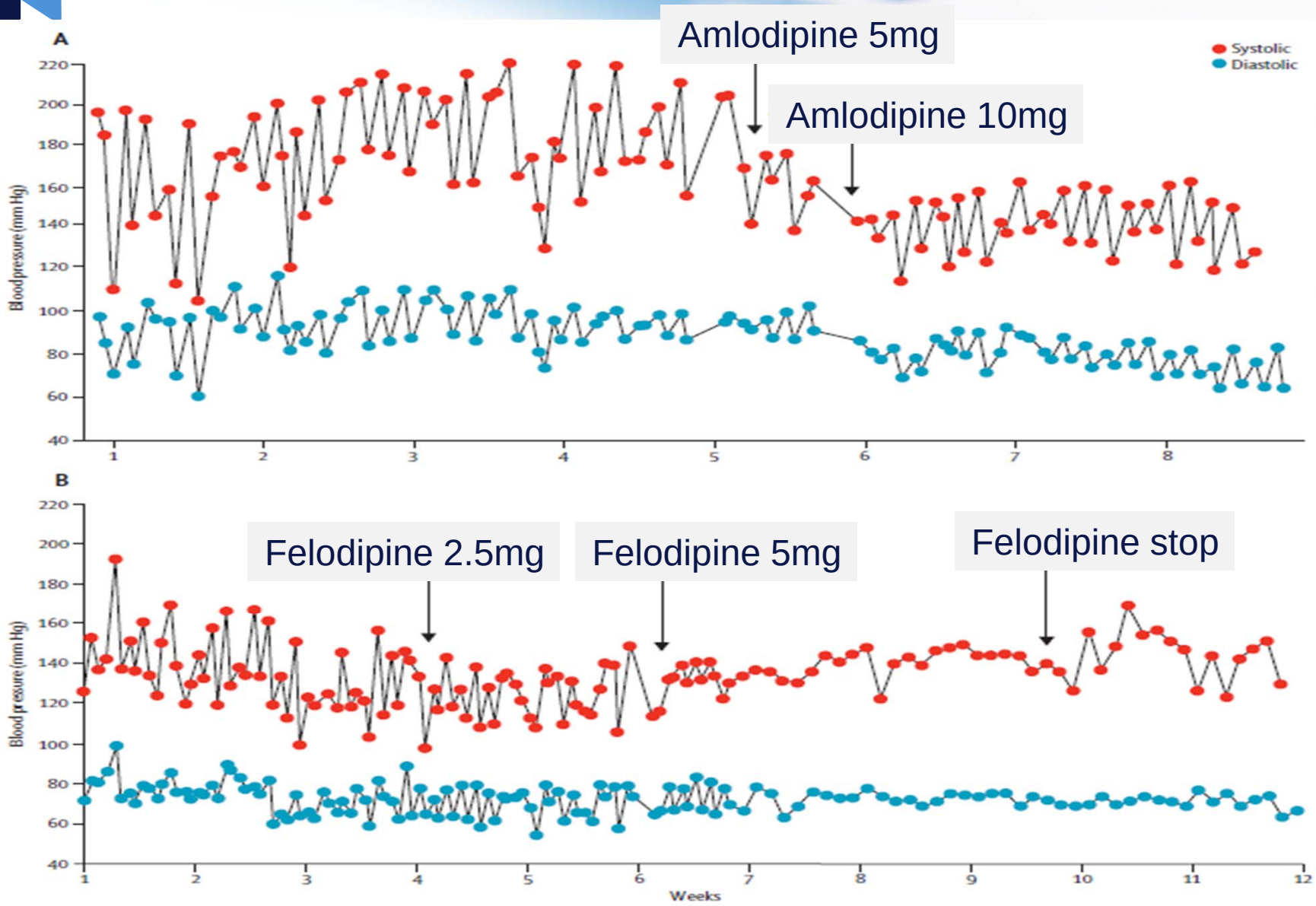
Hypertension. 2011;57:160-166

All-Cause Mortality over a median of 14 years of follow-up

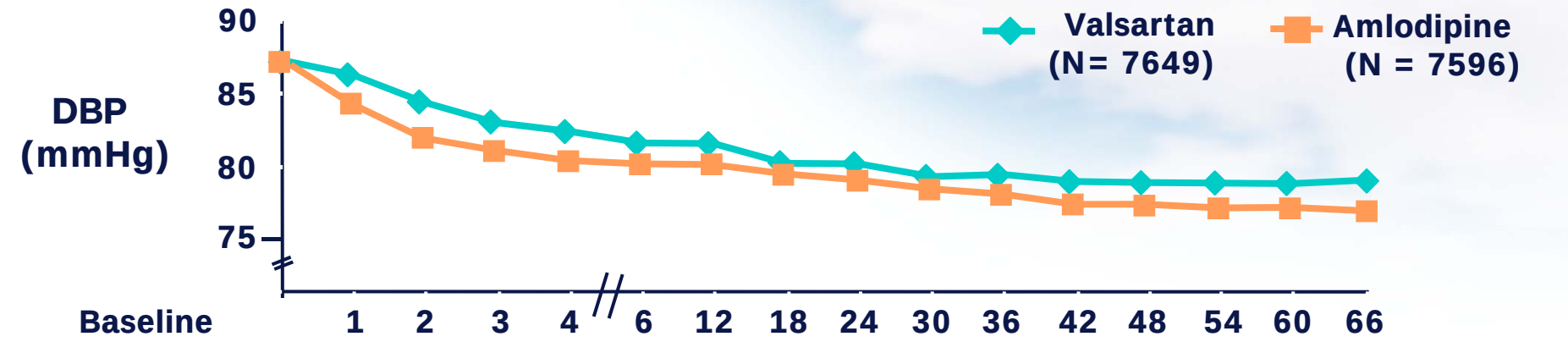


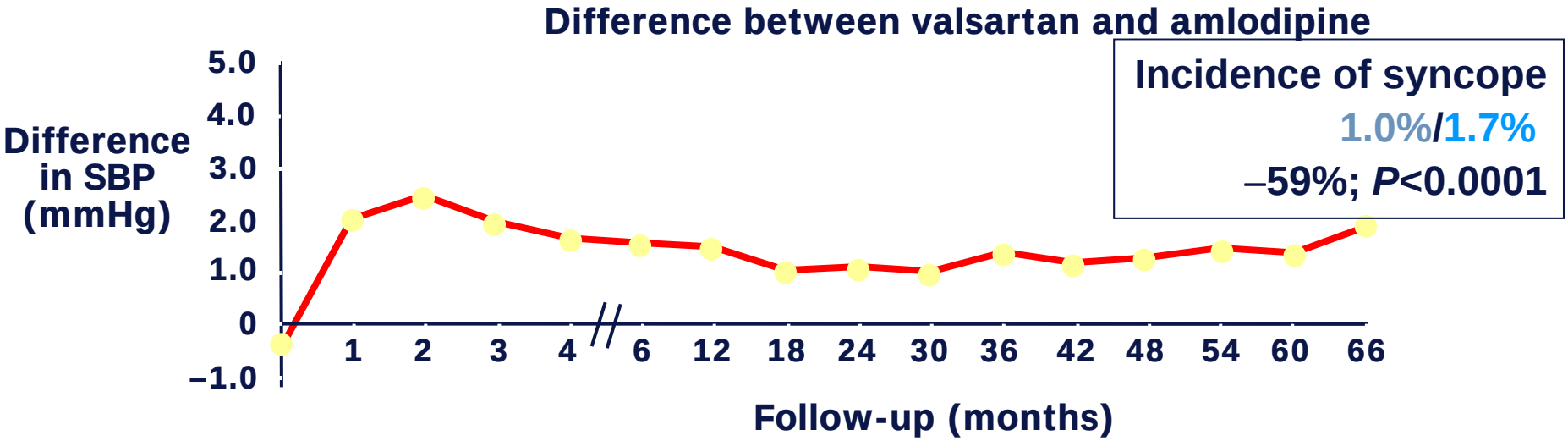


Effects of initiation and increase in dose of CCBs on within-individual variability in BP



VALUE: Blood pressure

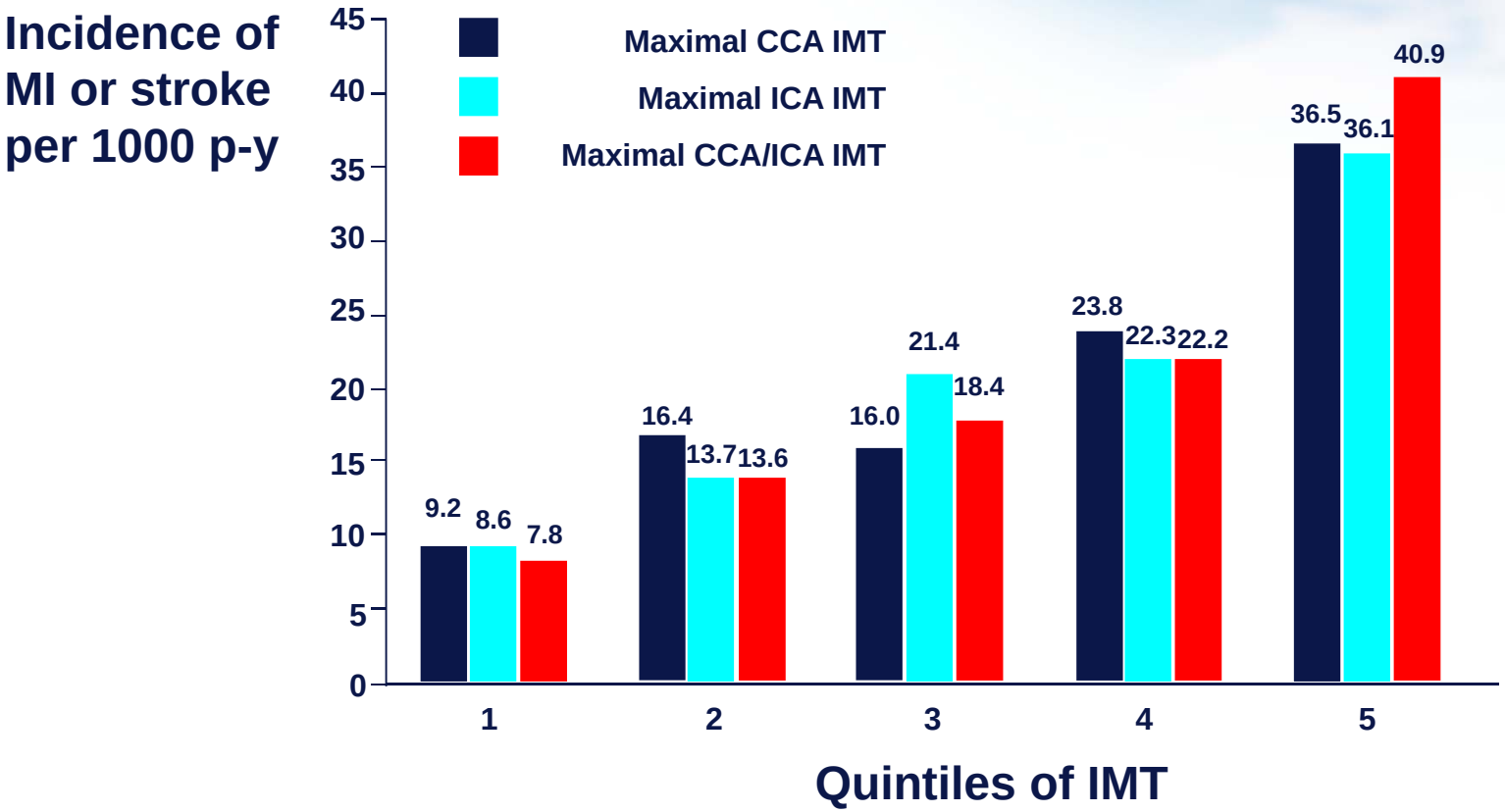




Incidence of syncope
1.0%/1.7%
–59%; *P*<0.0001

Julius S et al. *Lancet*. June 2004;363.

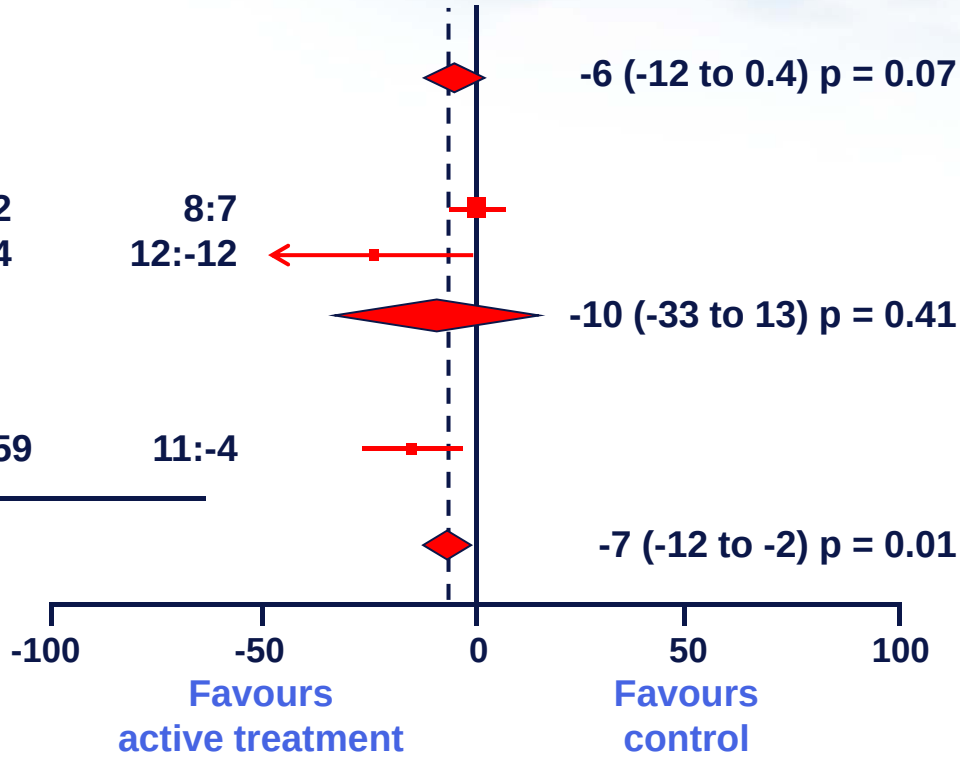
IMT and CV events



O'Leary DH, et al. N Engl J Med 1999;340:14.

Active treatment *vs* placebo/no treatment on IMT

Trial	n*	Baseline IMT (μm)*	Change/y (μm)*	Difference (μm/y, 95% CI)
All ACEIs	929:1161			-6 (-12 to 0.4) p = 0.07
Heterogeneity χ^2 = 18.1 *P* = 0.003				
BCAPS	390:393	893:912	8:7	
ELVA	44:35	897:894	12:-12	
All βBs	434:428			-10 (-33 to 13) p = 0.41
Heterogeneity χ^2 = 3.7				
PREVENT	186:191	1258:1259	11:-4	
All trials	1549:1780			-7 (-12 to -2) p = 0.01
Heterogeneity χ^2 = 25.9 *P* = 0.001				



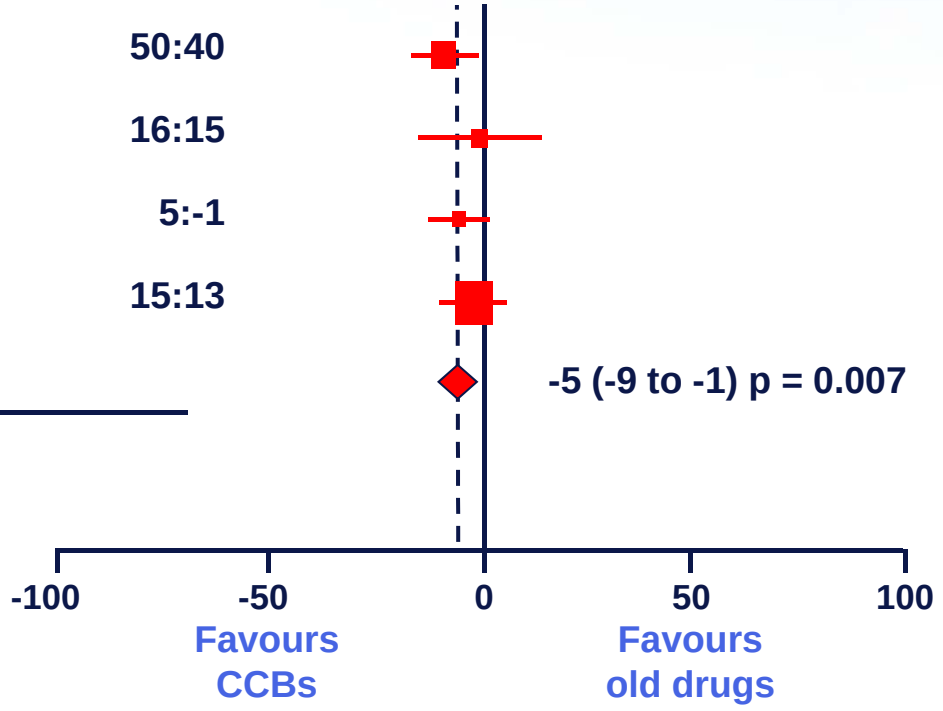
*Control:Active

Wang JG, et al. Stroke 2006;37:1933.

CCBs *vs* diuretics/β-blockers

Trial	n*	Baseline IMT (μm)*	Change/y (μm)*
MIDAS	441:442	1170:1170	50:40
VHAS	191:186	908:902	16:15
INSIGHT	164:160	660:668	5:-1
ELSA	1012:1023	1162:1159	15:13
All CCBs	1808:1811		

Heterogeneity $\chi^2 = 2.1$ $P = 0.55$



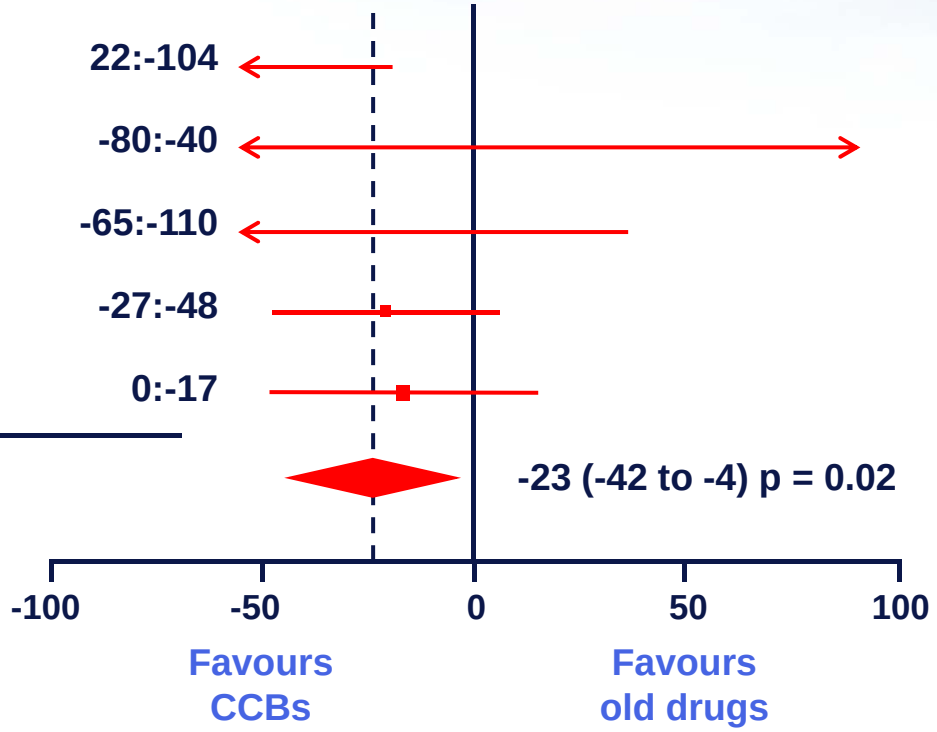
*Old:CCB

Wang JG et al. Stroke 2006;37:1933-40.

IMT: CCBs *vs.* ACEIs

Trial	n*	Baseline IMT (μm)*	Change/y (μm)*
Koshiyama	11:11	– : –	22:-104
Topouchian	18:21	680:720	-80:-40
Pontremoli	16:15	820:840	-65:-110
Stanton	34:35	792:763	-27:-48
ELVERA	63:63	1057:1019	0:-17
All trials	142:145		

Heterogeneity $\chi^2 = 4.5$ $P = 0.34$

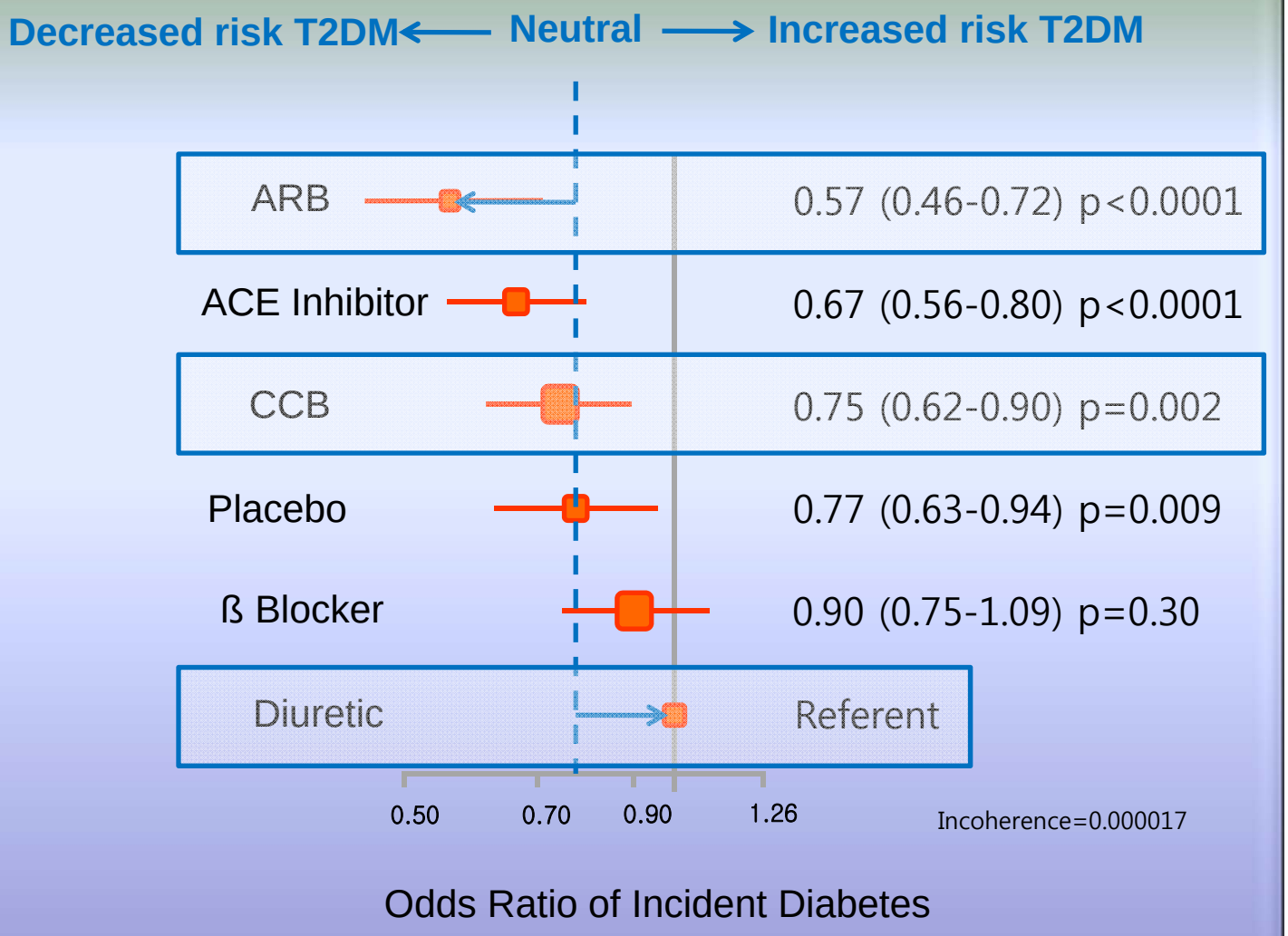


*ACEIs:CCBs

Wang JG, et al. Stroke 2006;37:1933.

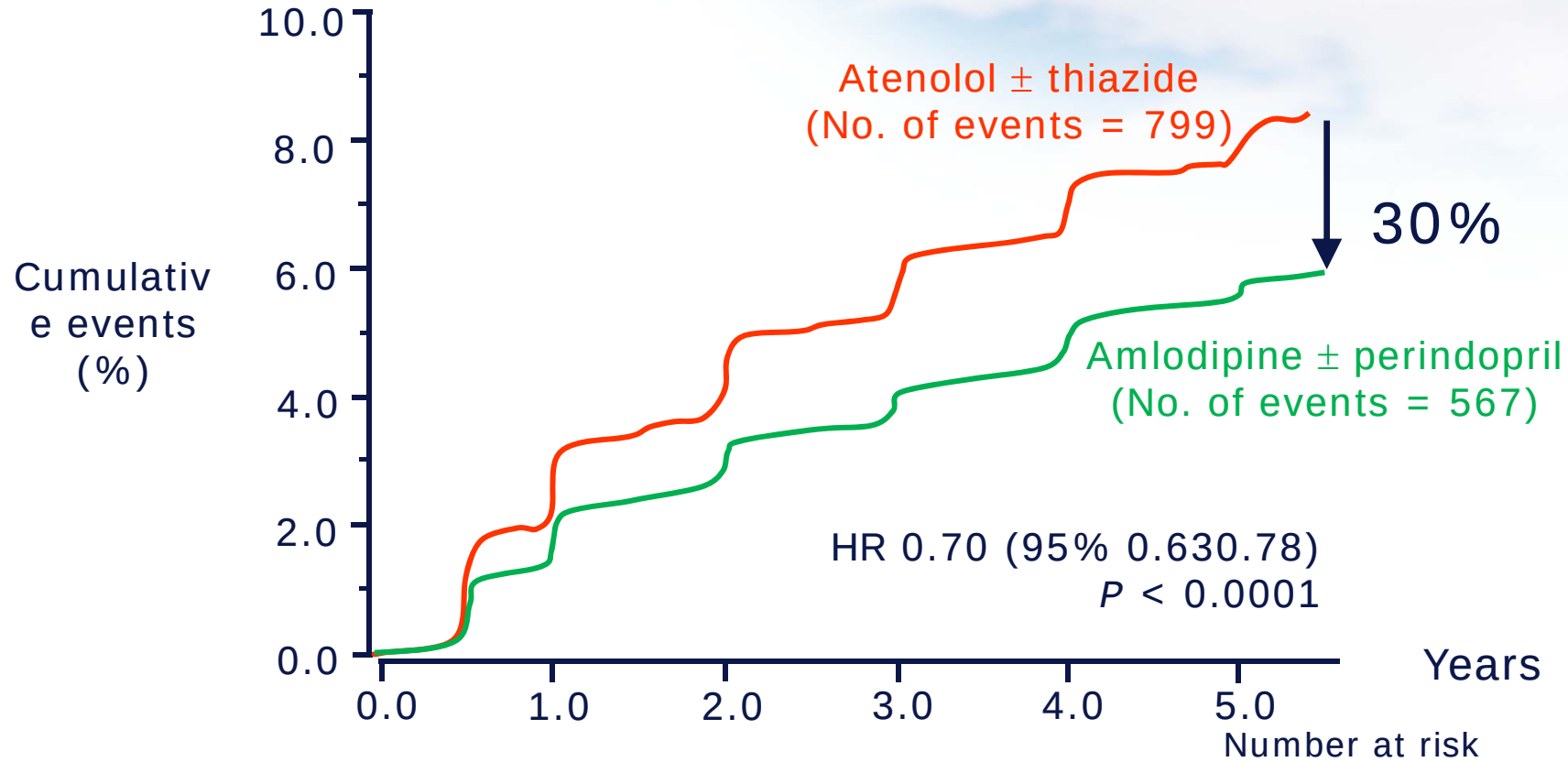
Impact on the risk of development of T2DM based on treatment choice

AASK
ALLHAT
ALPINE
ANBP-2
ASCOT
CAPPP
CHARM
DREAM
EWPHE
FEVER
HAPPHY
HOPE
HOPE-TOO-HOPE
INSIGHT
INVEST LIFE
MRC-E
NORDIL
PEACE
SCOPE
SHEP
SHEP-2
SOLVD
STAR
STOP-2
TROPHY
VALUE



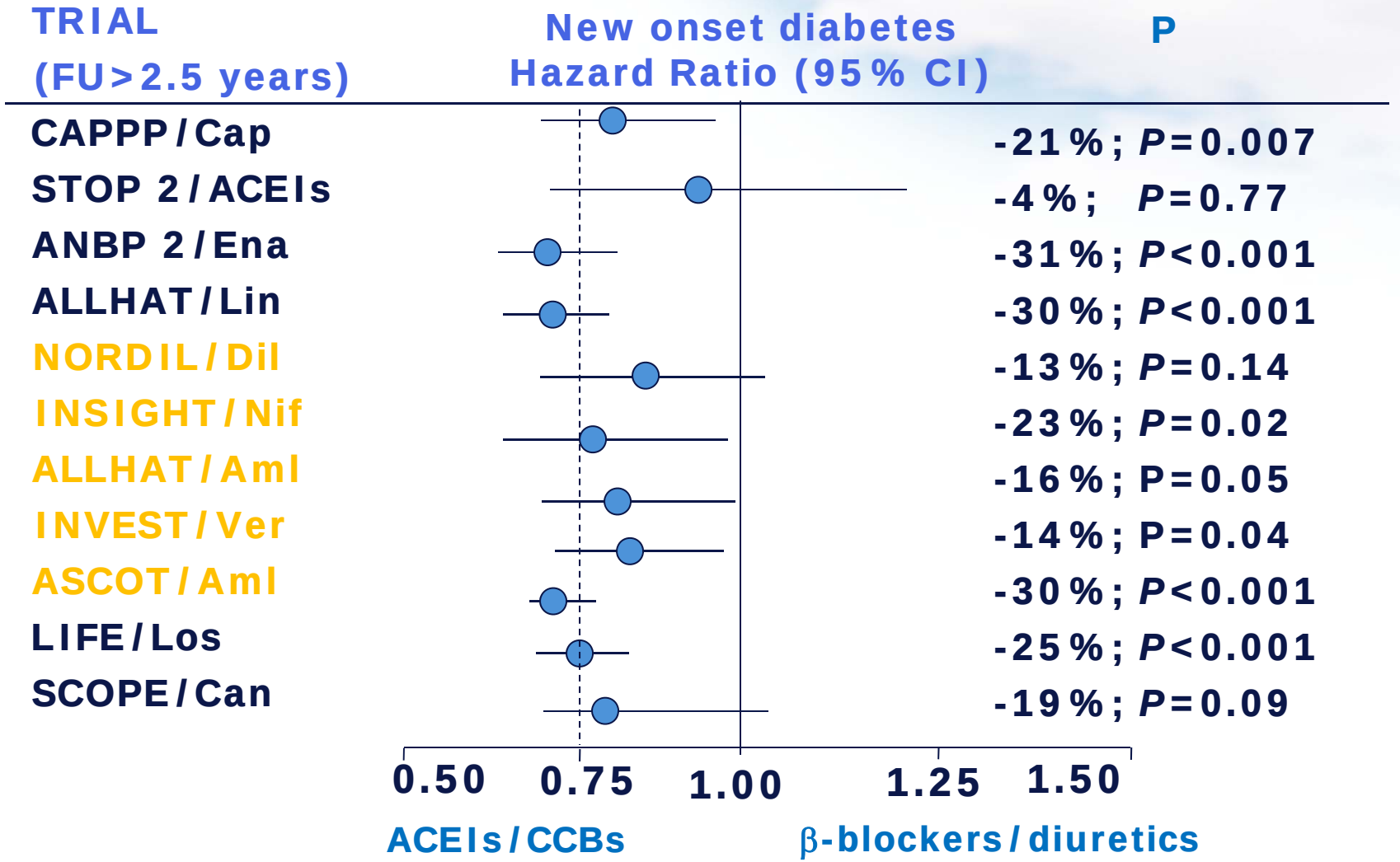
Adapted from Elliott et al. Lancet.2007;369(9557):201-7

ASCOT-BPLA: New-onset diabetes mellitus



Dahlöf B et al. Lancet 2005:366;895-906.

Clinical trials：New onset diabetes



Mancia G, et al. J Hypertens 2006;24:3-10.

Take Home Message (1)

- CCBs are more beneficial in stroke prevention compared with diuretics, β-blockers, ACEIs and ARBs.

Take Home Message (2)

- Among various DHP-CCBs, amlodipine has the best evidence in the prevention of MI.
- Amlodipine is efficacious as diuretics, β-blockers, and ACEIs, and more than ARBs.

Take Home Message (3)

- **The better outcome of CCB over other class of antihypertensive drugs is largely due to**
  - Better 24 h and central BP control
  - Less SBP variability
  - Prevention of thickening of arterial wall

Thanks for your attention !