강압제의 선택-표적장기보호 특정약제가 더 효과적이다

박 창 규

고려대학교 의과대학 순환기내과

To prevent CVD
in hypertensive patient

BP control is the most important

However,

JNC 7: Compelling Indications for Individual Drug Classes

Compelling Indication	Initial Therapy Options	Clinical Trial Basis
Heart failure	Diuretic, BB, ACE inhibitor, ARB, ALDO ANT	ACC/AHA Heart Failure Guideline, MERIT-HF, COPERNICUS, CIBIS, SOLVD, AIRE, TRACE, ValHEFT, RALES, CHARM
Post-MI	BB, ACE inhibitor, ALDO ANT	ACC/AHA Post-MI Guideline, BHAT, SAVE, Capricorn, EPHESUS
High CAD risk	Diuretic, BB, ACE inhibitor, CCB	ALLHAT, HOPE, ANBP2, LIFE, CONVINCE, EUROPA, INVEST

ALDO ANT=aldosterone antagonist.

Chobanian et al, and the National High Blood Pressure Education Program Coordinating Committee. *Hypertension.* 2003;42:1206-1252.

JNC 7: Compelling Indications for Individual Drug Classes

Compelling Indication	Initial Therapy Options	Clinical Trial Basis
Diabetes	Diuretic, BB, ACE inhibitor, ARB, CCB	NKF-ADA Guideline, UKPDS, ALLHAT
Chronic kidney disease	ACE inhibitor, ARB	NKF Guideline, Captopril Trial, RENAAL, IDNT, REIN, AASK
Recurrent stroke prevention	Diuretic, ACE inhibitor	PROGRESS

Chobanian et al, and the National High Blood Pressure Education Program Coordinating Committee. *Hypertension.* 2003;42:1206-1252.

WHO/ISH: ESC/ESH BHS Compelling Indications for Specific Antihypertensive Drugs

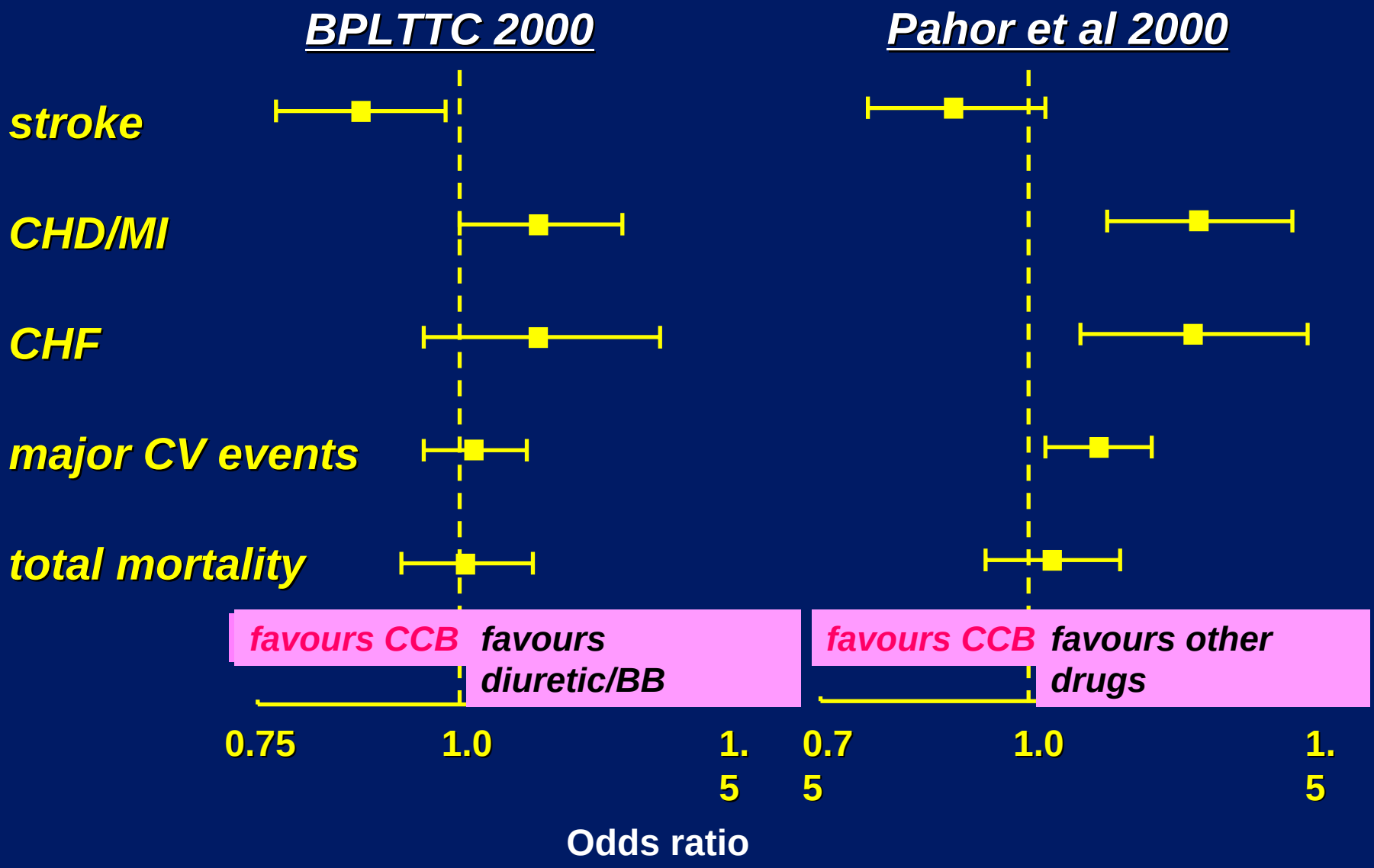
Compelling Indications	Preferred Drug	Primary End Point
Elderly with isolated systolic hypertension	Diuretic DHP CCB	Stroke Stroke
Renal disease		
Diabetic nephropathy type 1	ACE inhibitor	Progression of renal failure
Diabetic nephropathy type 2	ARB	Progression of renal failure
Nondiabetic nephropathy	ACE inhibitor	Progression of renal failure
Cardiac disease		
Post-MI	ACE inhibitor β-blocker	Mortality Mortality
LV dysfunction	ACE inhibitor ACE inhibitor	Heart failure Mortality
CHF (diuretics almost always included)	β-blocker Spironolactone	Mortality Mortality
LV hypertrophy	ARB	CV morbidity and mortality
Cerebrovascular disease	ACE inhibitor + diurectic Diuretic	Recurrent stroke Recurrent Stroke

WHO/ISH Writing Group. *J Hypertens.* 2003;21:1983-1992.

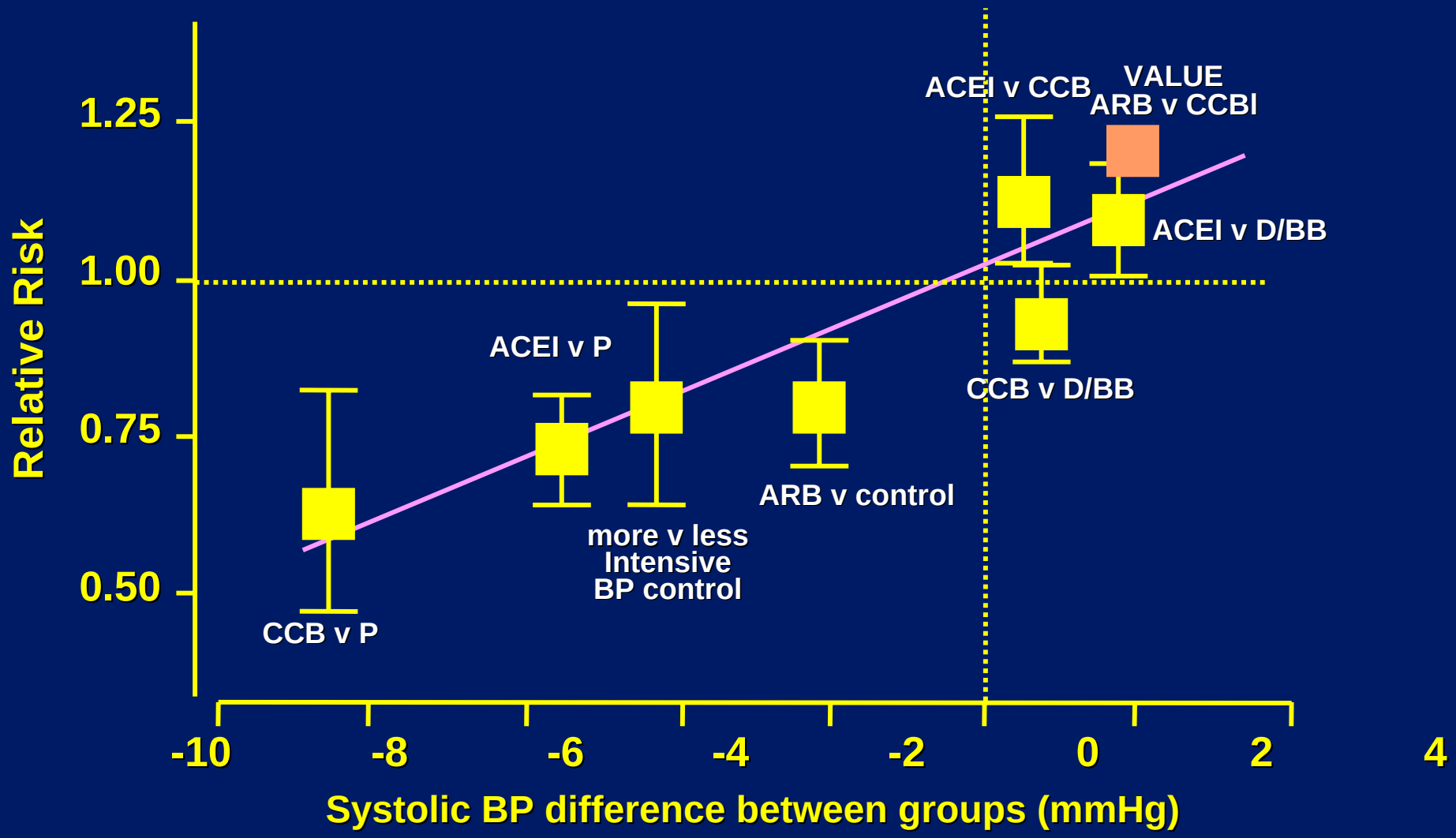
Are there suitable antihypertensive drugs for specific disease ?

- Stroke
- MI and CHF
- LVH and Atherosclerosis
- DM and CKD

META-ANALYSES OF TRIALS IN HYPERTENSION: CALCIUM ANTAGONISTS COMPARED WITH OTHERs

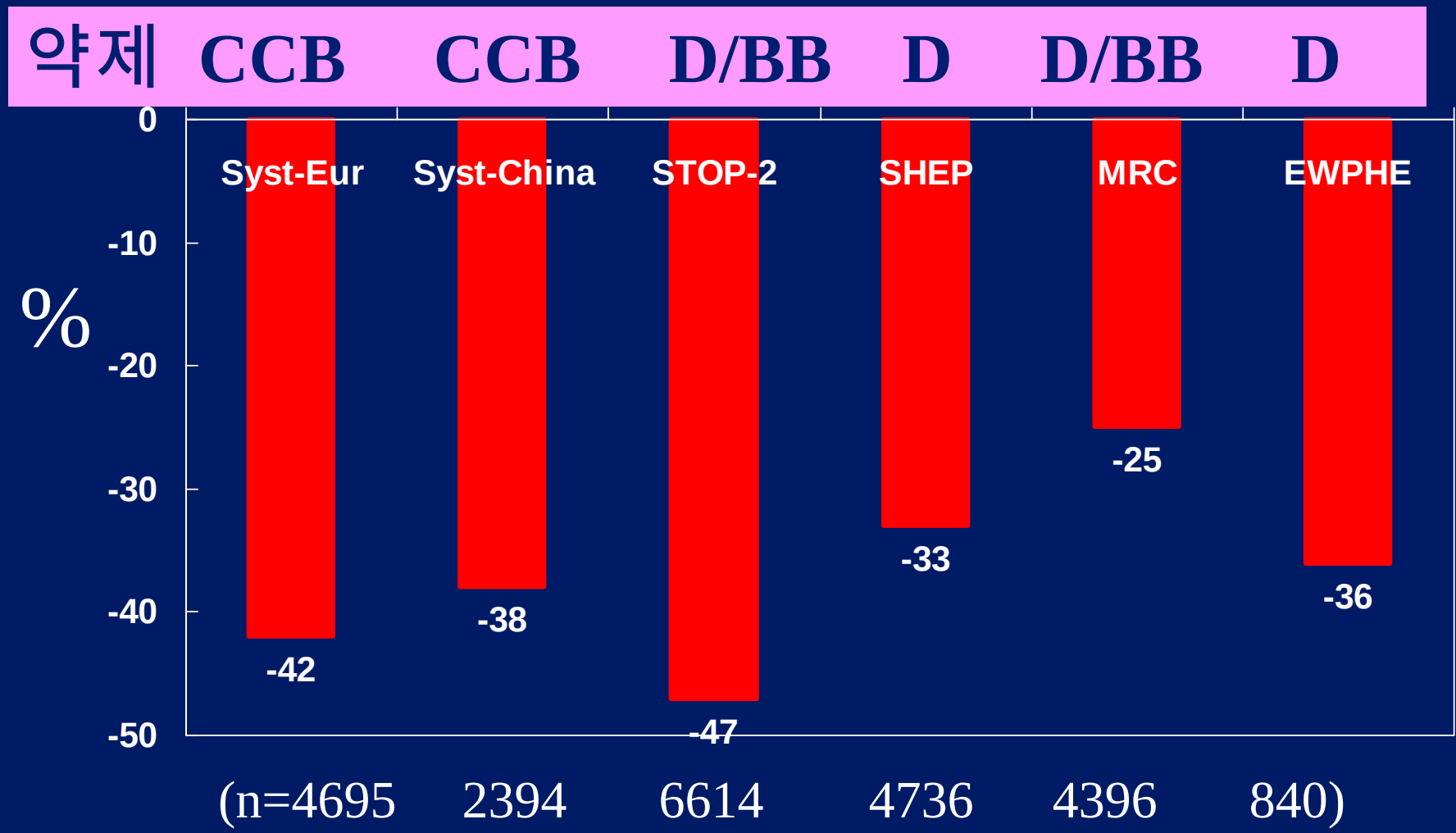


ASSOCIATIONS OF BP DIFFERENCES BETWEEN GROUPS FOR RISK OF STROKE



BPLTTC 2003

고혈압치료와 뇌졸증 위험 감소도



CCB:calcium channel blocker, D:diuretic, BB:beta-blocker

RAAS의 차단이 fatal & nonfatal stroke 예방효과를 나타내는 연구들

Study	Therpy	SBP/DBP 차이(mmHg)	RRR	P value
HOPE (n=9297)	Ramipril placebo	**3.8/2.8**	**32%**	<0.001
LIFE (n=9193)	Losartan atenolol	**1.1/0.0**	**25%**	0.001
SCOPE (n=4937)	Candesartan placebo	**3.2/1.6**	**28%**	<0.05
ANBP2 (n=6083)	ACEI diuretic	**NA**	**RR 1.02**	**NS**

Antihypertensive for Stroke Prevention

CCB > Diuretic > ARB > ACEI > B-blocker

Are there suitable antihypertensive drugs for specific disease ?

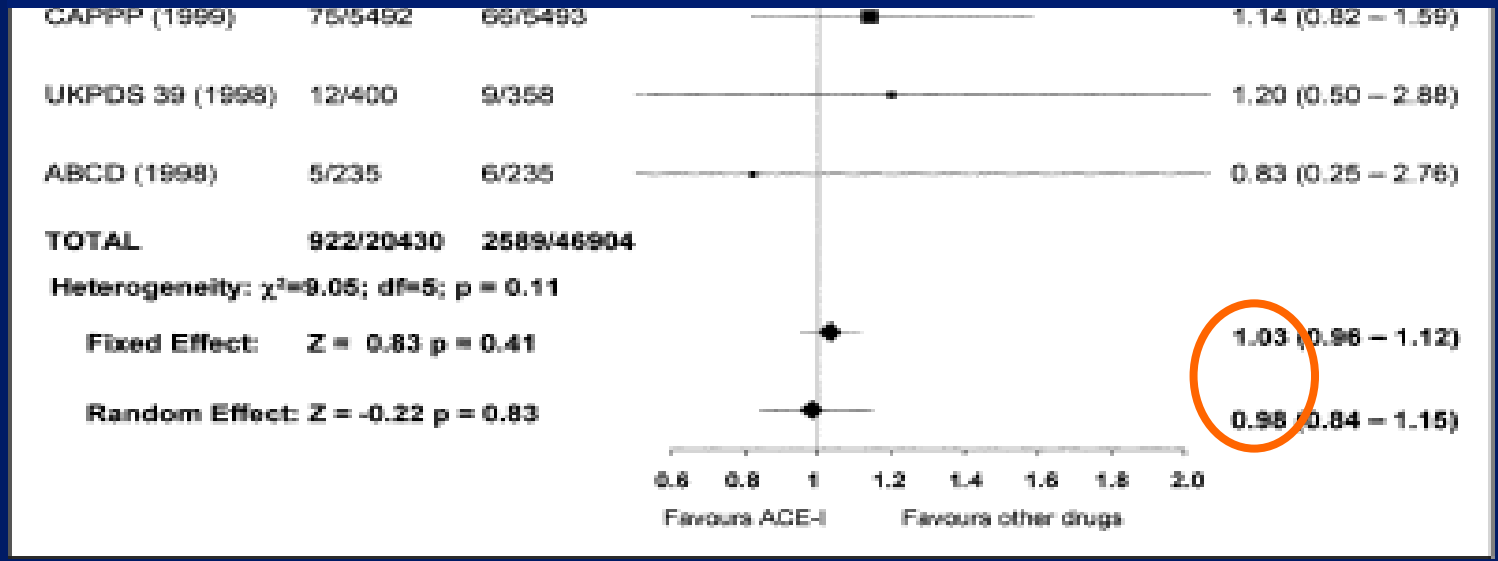
- Stroke
- MI and CHF
- LVH and Atherosclerosis
- DM and CKD

Meta-Analysis of Effectiveness or Lack Thereof of Angiotensin-Converting Enzyme Inhibitors for Prevention of Heart Failure in Patients With Systemic Hypertension

Fabio Angeli, MD, Paolo Verdecchia, MD, Gian Paolo Reboldi, MD, PhD, MSc, Roberto Gattobigio, MD, Maurizio Bentivoglio, MD, Jan A. Staessen, MD, PhD, and Carlo Porcellati, MD

(Am J Cardiol 2004;93:240–243)

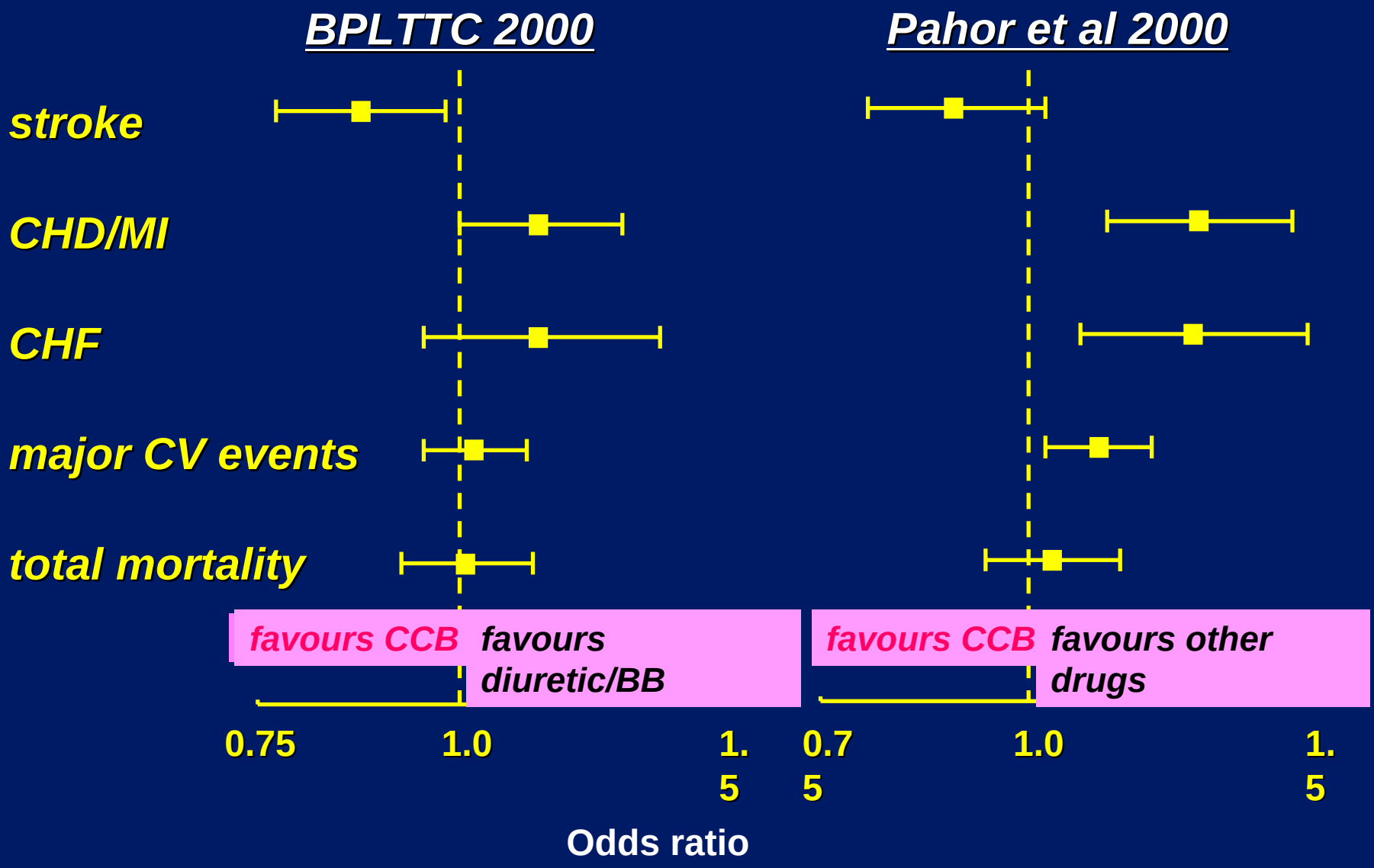
Superiority of ACE Inhibitors for Primary Prevention of CHF in Hypertension "Unproven"



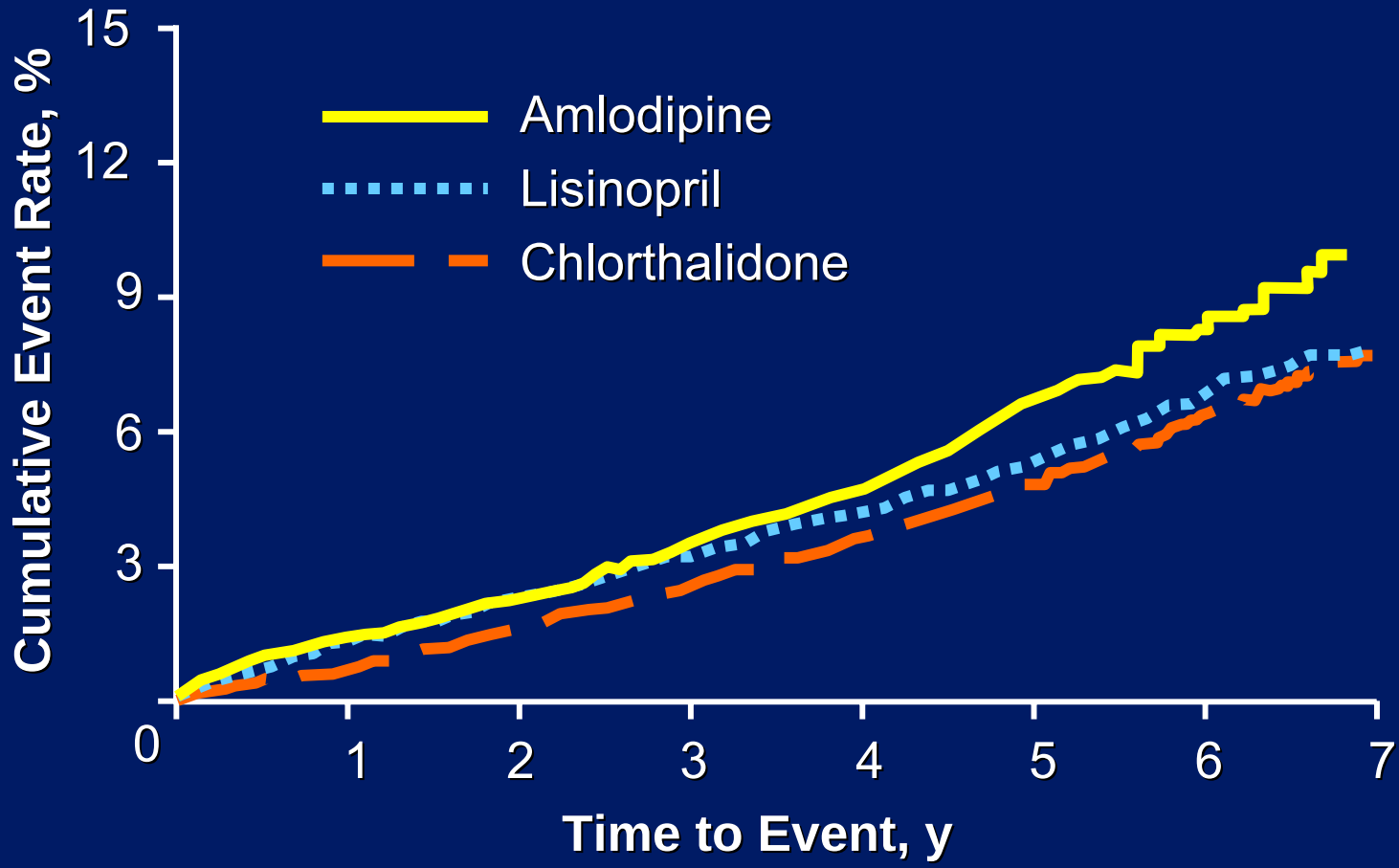
Effect of ACE Inhibitors on Mortality in Patients With Heart Failure (Stage B,C)

Trial	Mortality		
	ACEI	Controls	RR (95% CI)
Chronic CHF			
Consensus I	39%	54%	0.56 (0.34–0.91)
SOLVD (Treatment)	35%	40%	0.82 (0.70–0.97)
SOLVD (Prevention)	15%	16%	0.92 (0.79–1.08)
Post MI			
SAVE	20%	25%	0.81 (0.68–0.97)
AIRE	17%	23%	0.73 (0.60–0.89)
TRACE	35%	42%	0.78 (0.67–0.91)
SMILE	5%	6.5%	0.75 (0.40–1.11)
Totals	21%	25%	

META-ANALYSES OF TRIALS IN HYPERTENSION: CALCIUM ANTAGONISTS COMPARED WITH OTHERs



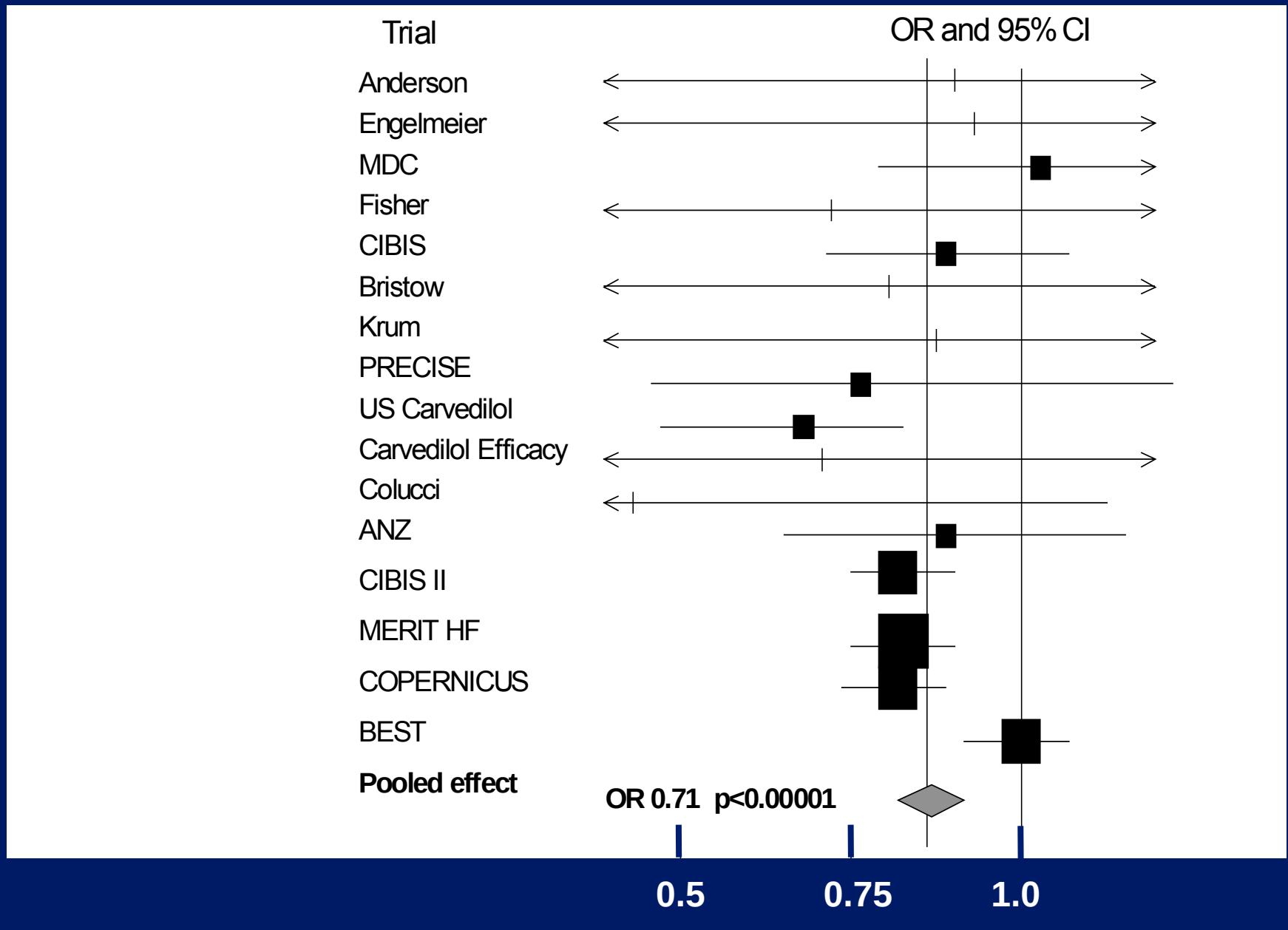
ALLHAT: Hospitalized Plus Fatal Heart Failure



*Heart failure was not a prespecified endpoint.

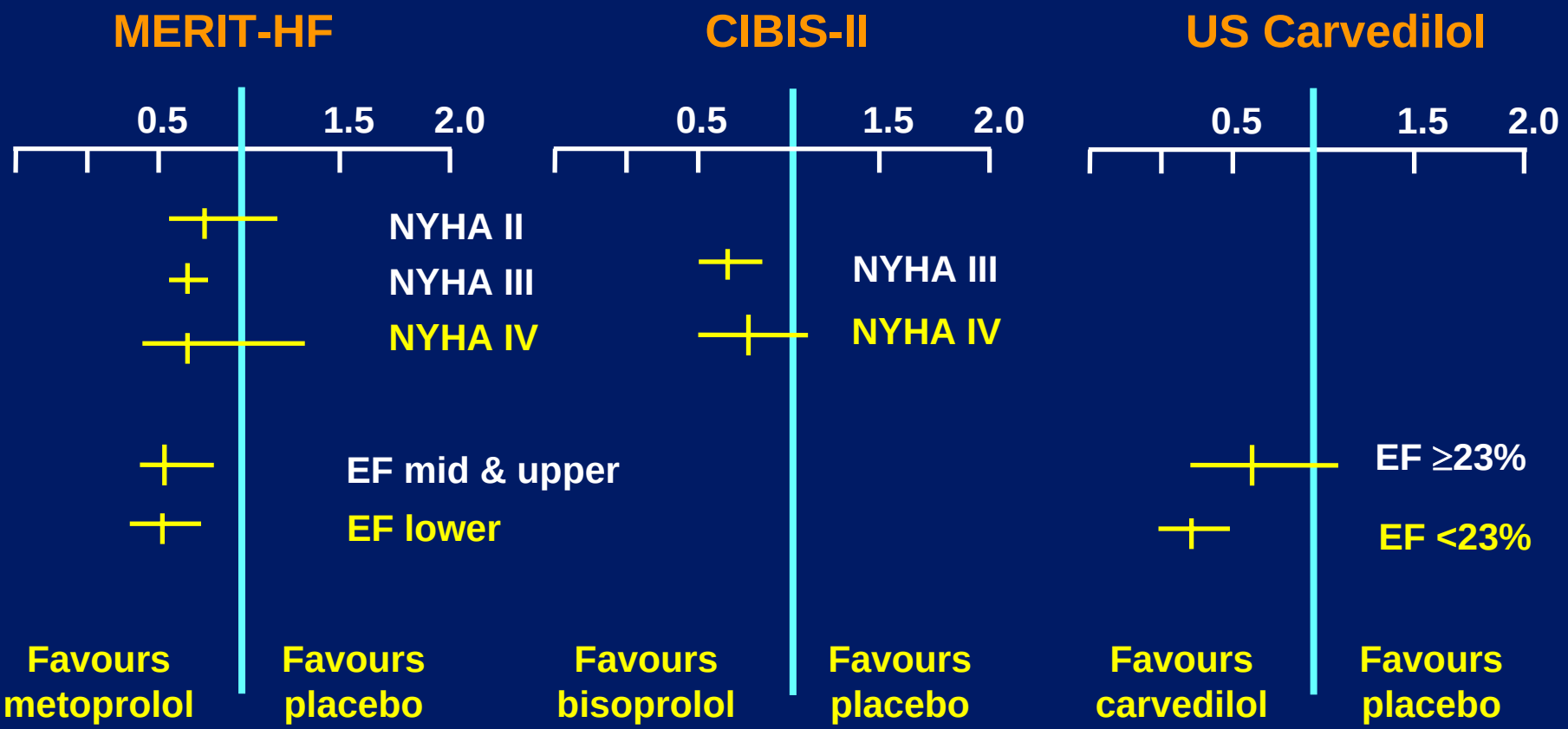
ALLHAT Collaborative Research Group. *JAMA*. 2002;288:2981-2997.

Effects of beta blockers on mortality in CHF



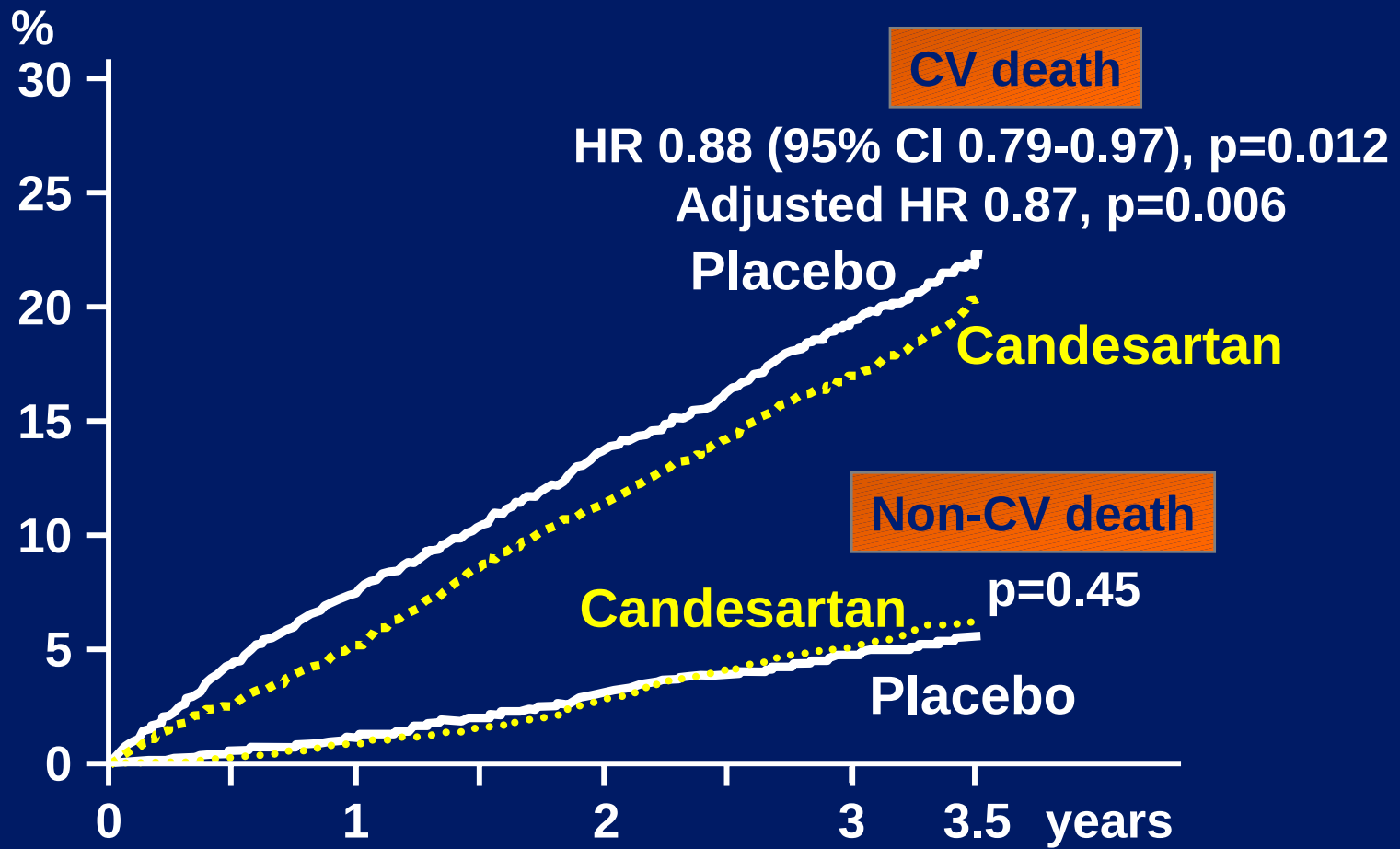
Mortality in severe heart failure

Subgroup analysis of major trials



CHARM-Overall

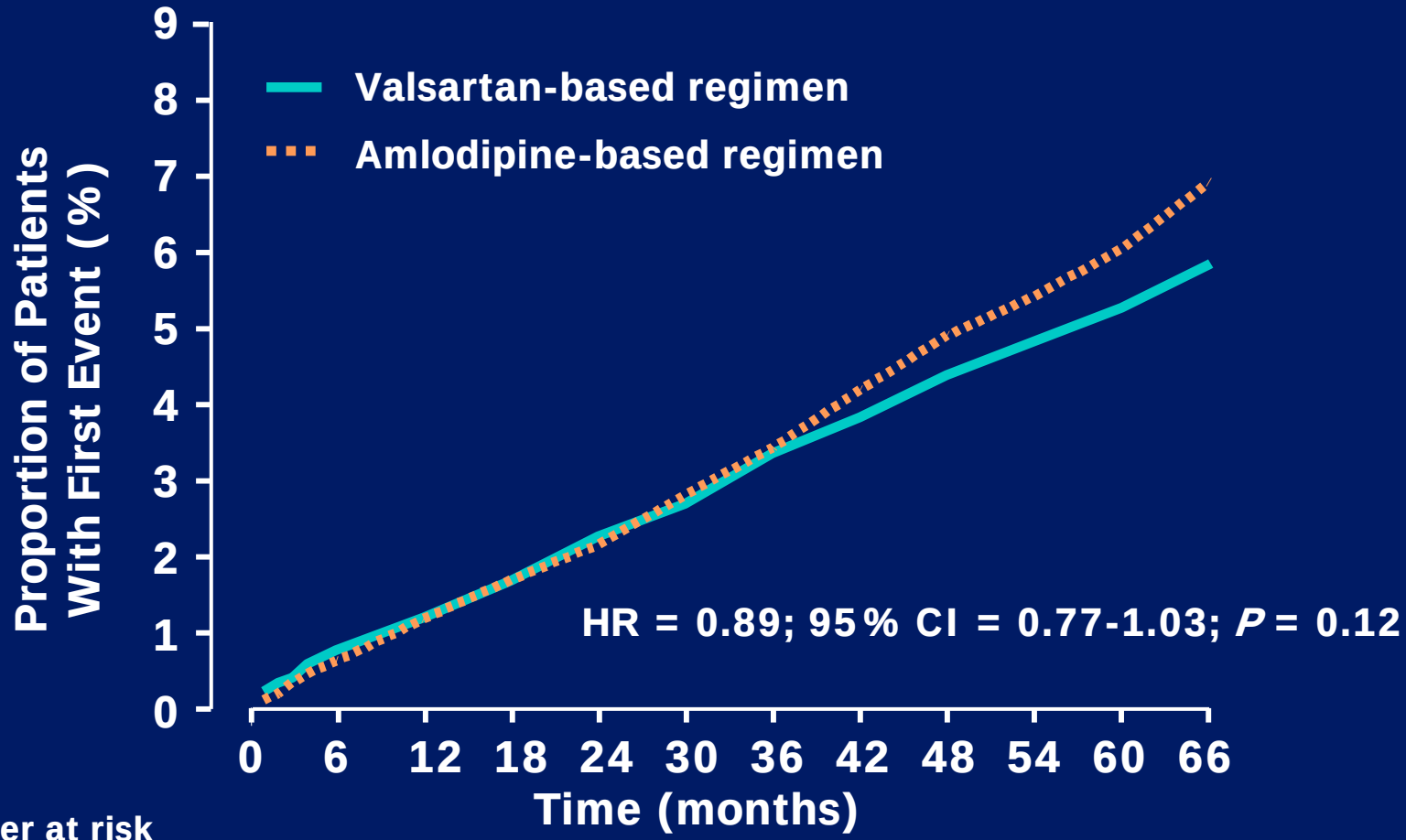
CV death and non-CV death



Pfeffer et al, Lancet 2003

VALUE: Heart Failure

Hospitalisation for HF or death from HF

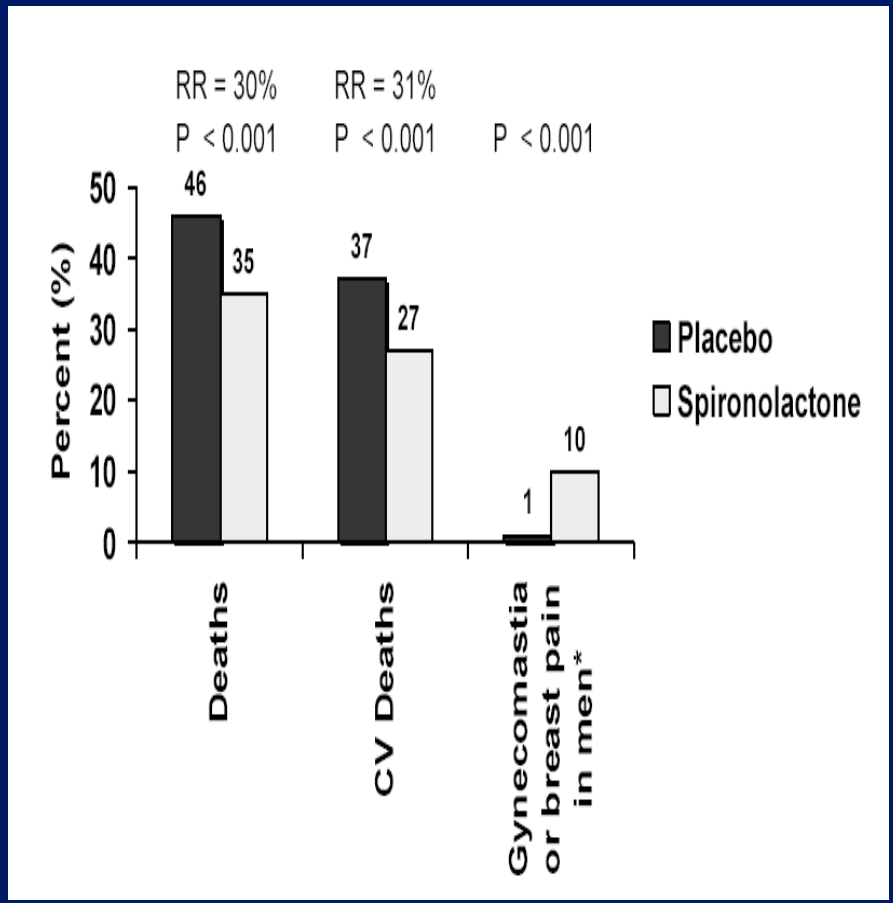


Number at risk											
Valsartan	7649	7485	7444	7312	7169	7012	6852	6671	6498	6072	3860	1513
Amlodipine	7596	7486	7444	7312	7176	7033	6874	6702	6534	6100	3823	1511

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

RALES:(CHF Stage C)

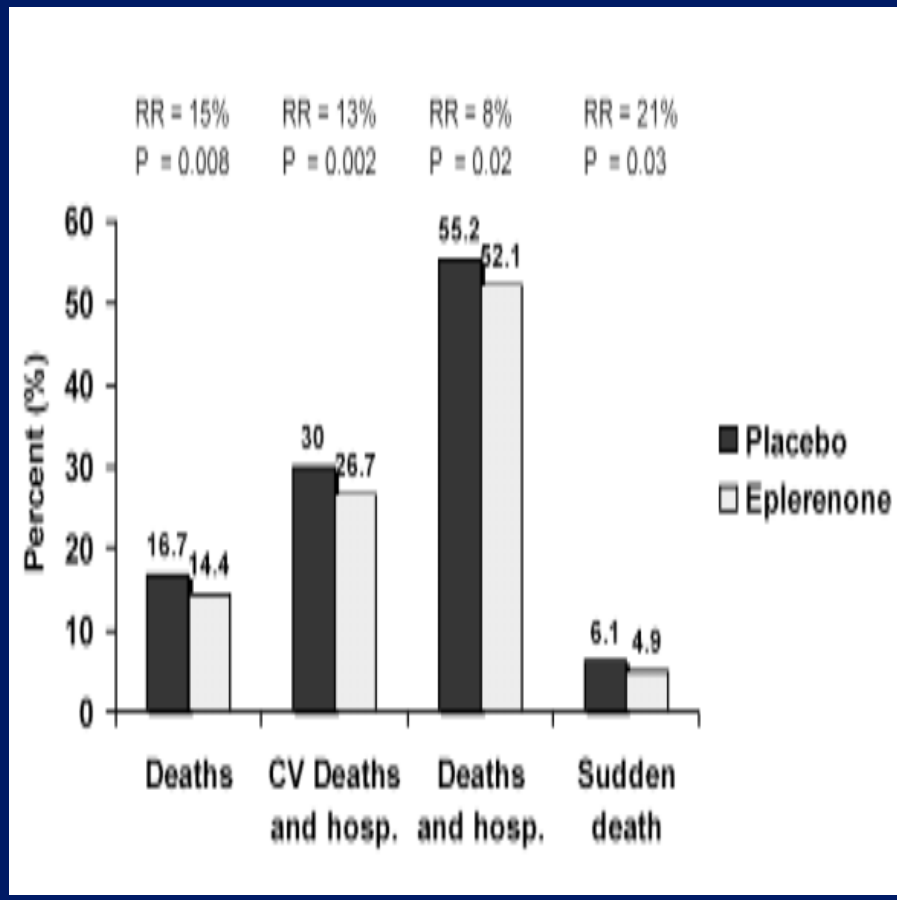
- 1,663 NYHA III-IV, EF ≤ 35%
- Tx: 25 mg/day vs. placebo,
- average f/u 24 months (stopped early)



NEJM 1999;341:709-717

EPHESUS(postMI-HF)

- 6,642, 3-14 days after AMI, EF ≤ 40%
- Tx: 25 mg- 50 mg/day vs placebo
- average f/u 16 months



NEJM 2003;348:1309-1321

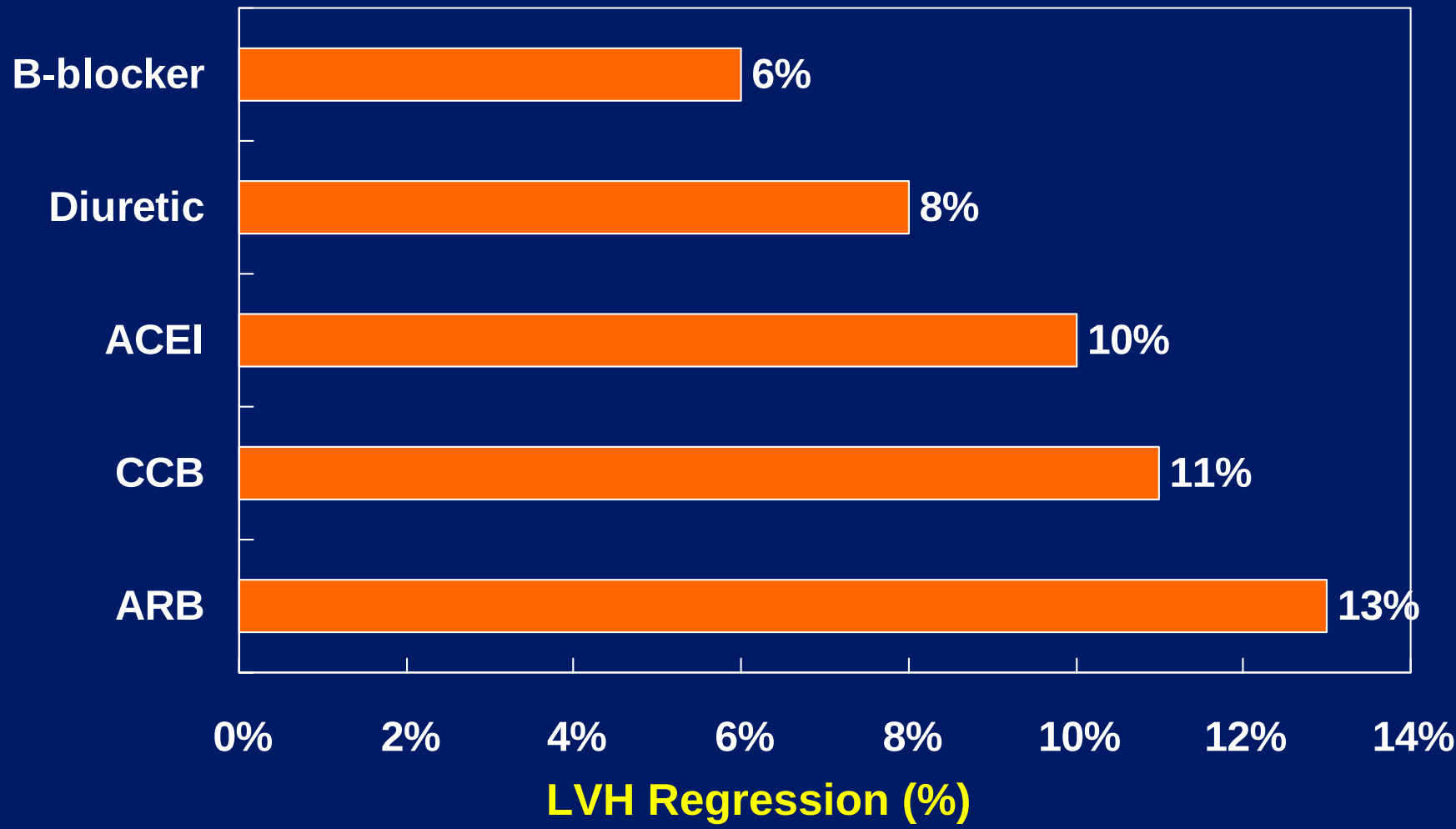
JNC 7: Compelling Indications for Individual Drug Classes

Compelling Indication	Initial Therapy Options
Heart failure	Diuretic, BB, ACE inhibitor, ARB, ALDO ANT
Post-MI	BB, ACE inhibitor, ALDO ANT

Are there suitable antihypertensive drugs for specific disease ?

- Stroke
- MI and CHF
- LVH and Atherosclerosis
- DM and CKD

A meta-analysis of the effects of treatment on left ventricular mass in essential hypertension



Eighty trials with 146 active treatment arms (n = 3767) and 17 placebo arms (n = 346)

Am J Med. 2003;115:41-6

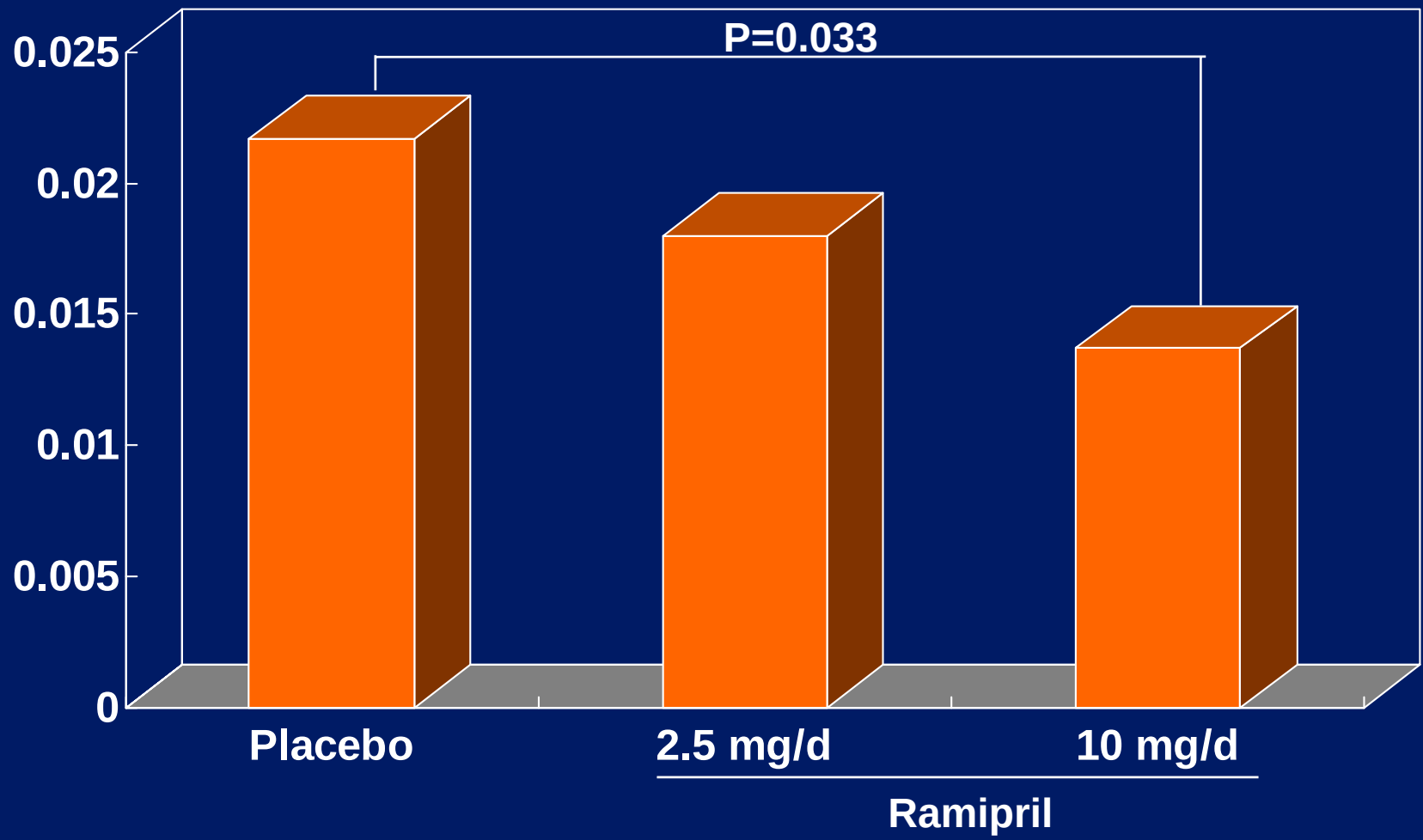
Carotid IMT Regression – Clinical trials with Calcium Antagonists

Study name	No of patients	Treatment duration	Comparative drugs	Results
ELSA (*Zanchetti et al, 1998*)	2259	4 years	Lacidipine vs atenolol	Significantly less carotid IMT progression in lacidipine group
MIDAS (*Borhani,et al 1996*)	883	3 years	Isradipine vs hydrochlorothiazide	No difference in rate of carotid IMT progression between treatment groups
VHAS (*Zanchetti et al, 1998*)	498	4 years	Verapamil vs chlorthalidone	Regression of larger lesions significantly greater in verapamil group
PREVENT (*Pitt et al, 2000*)	825	3 years	Amlodipine vs placebo	Less carotid IMT progression in amlodipine group

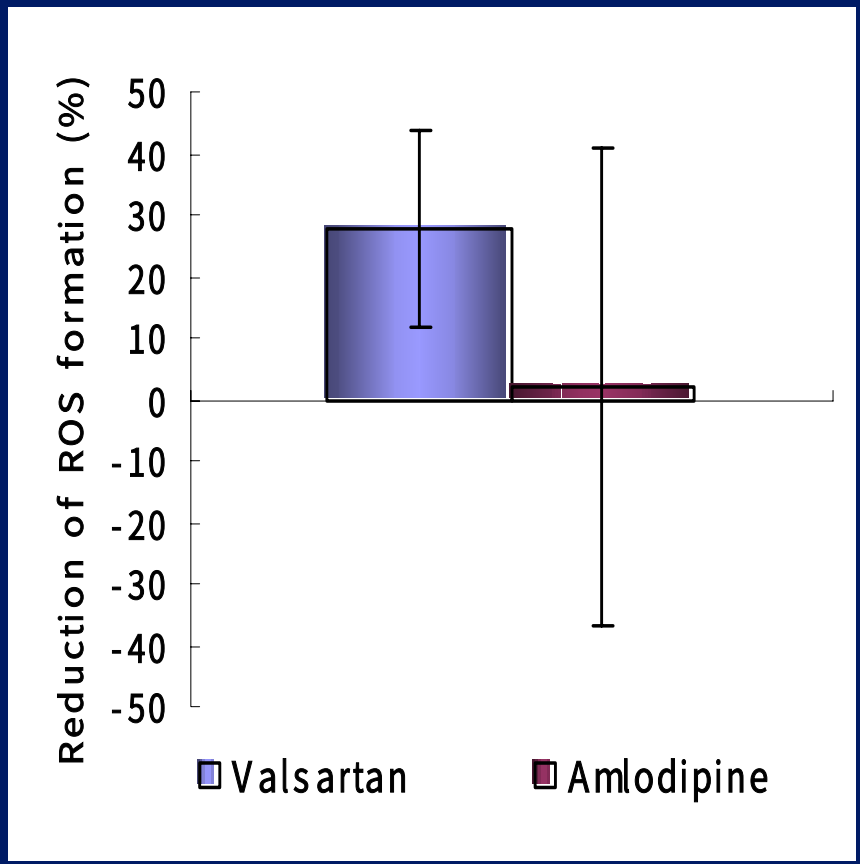
Effects of Ramipril and Vitamin E on Atherosclerosis

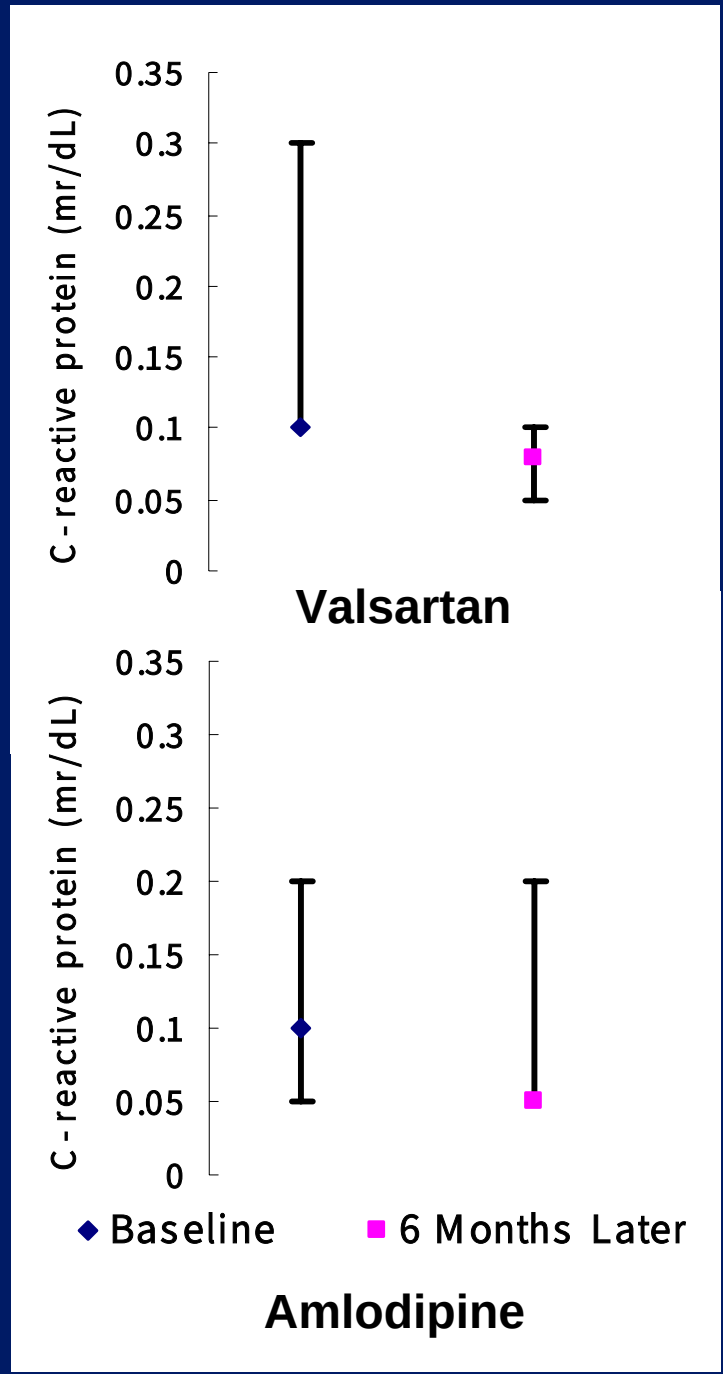
The Study to Evaluate Carotid Ultrasound Changes in Patients Treated With Ramipril and Vitamin E (SECURE)

Circulation. 2001;103:919-925



Reduction of ROS and CRP





Yasunari et al. J Am Coll Cardiol 2004: 43:2116-23

LVH regression

ACEI
ARB **>= CCB > Diuretic > B-blocker**

Carotid atherosclerosis

Are there suitable antihypertensive drugs for specific disease ?

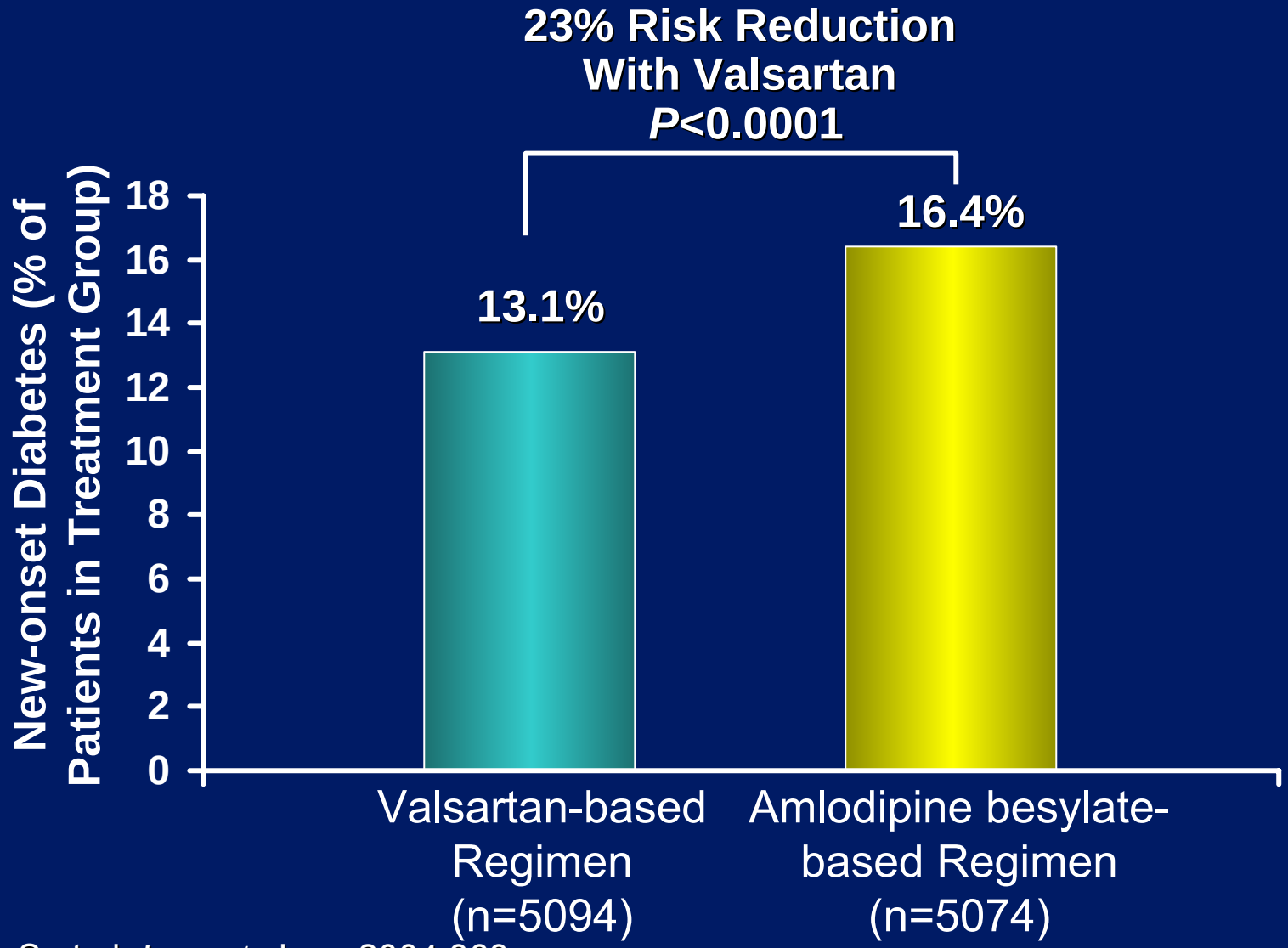
- Stroke
- MI and CHF
- LVH and Atherosclerosis
- DM and CKD

JNC 7: Compelling Indications for Individual Drug Classes

Compelling Indication	Initial Therapy Options
Diabetes	Diuretic, BB, ACE inhibitor, ARB, CCB
Chronic kidney disease	ACE inhibitor, ARB

Chobanian et al, and the National High Blood Pressure Education Program Coordinating Committee. *Hypertension.* 2003;42:1206-1252.

VALUE: Incidence of New-onset Diabetes (Not Prespecified in Design Paper)



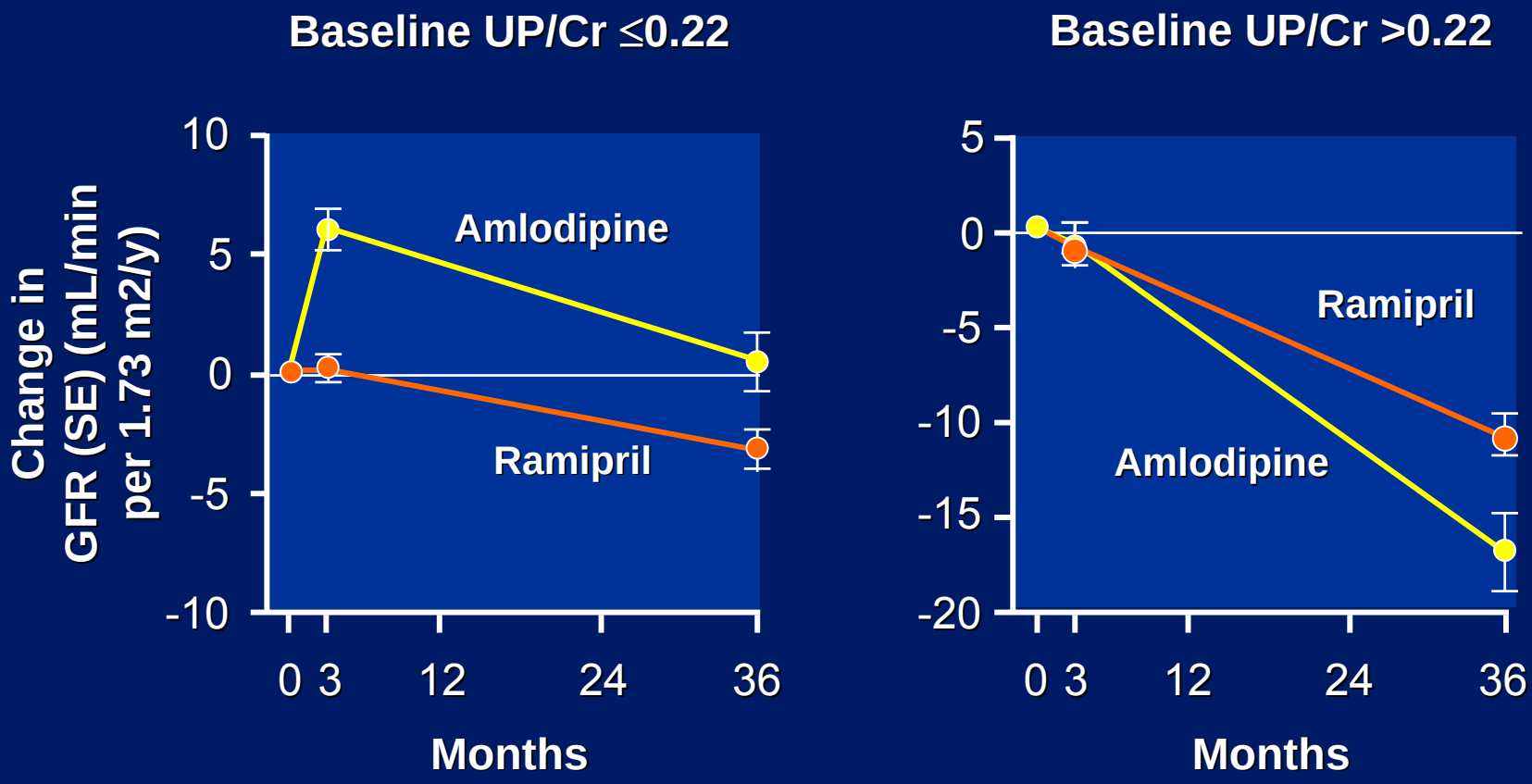
Julius S et al. *Lancet*. June 2004;363.

Summary for Diabetes Prevention Results of RAS inhibition

	VALUE valsartan	HOPE ramipril	LIFE losartan	ALLHAT lisinopril
Subjects	≥ 50 yo with high risk factor	≥ 55 yo CVD or DM	≥ 55 yo LVH	≥ 55 yo with high risk factor
Comparator	Amlodipine + diuretic	Add on	B-blocker + diuretic	Diuretic / Amlodipine
Results (reduction)	23%	34%	25%	44% / 18%

Hypertensive nephrosclerosis

AASK: Changes in GFR According to Baseline UP/Cr (3-Year Data)

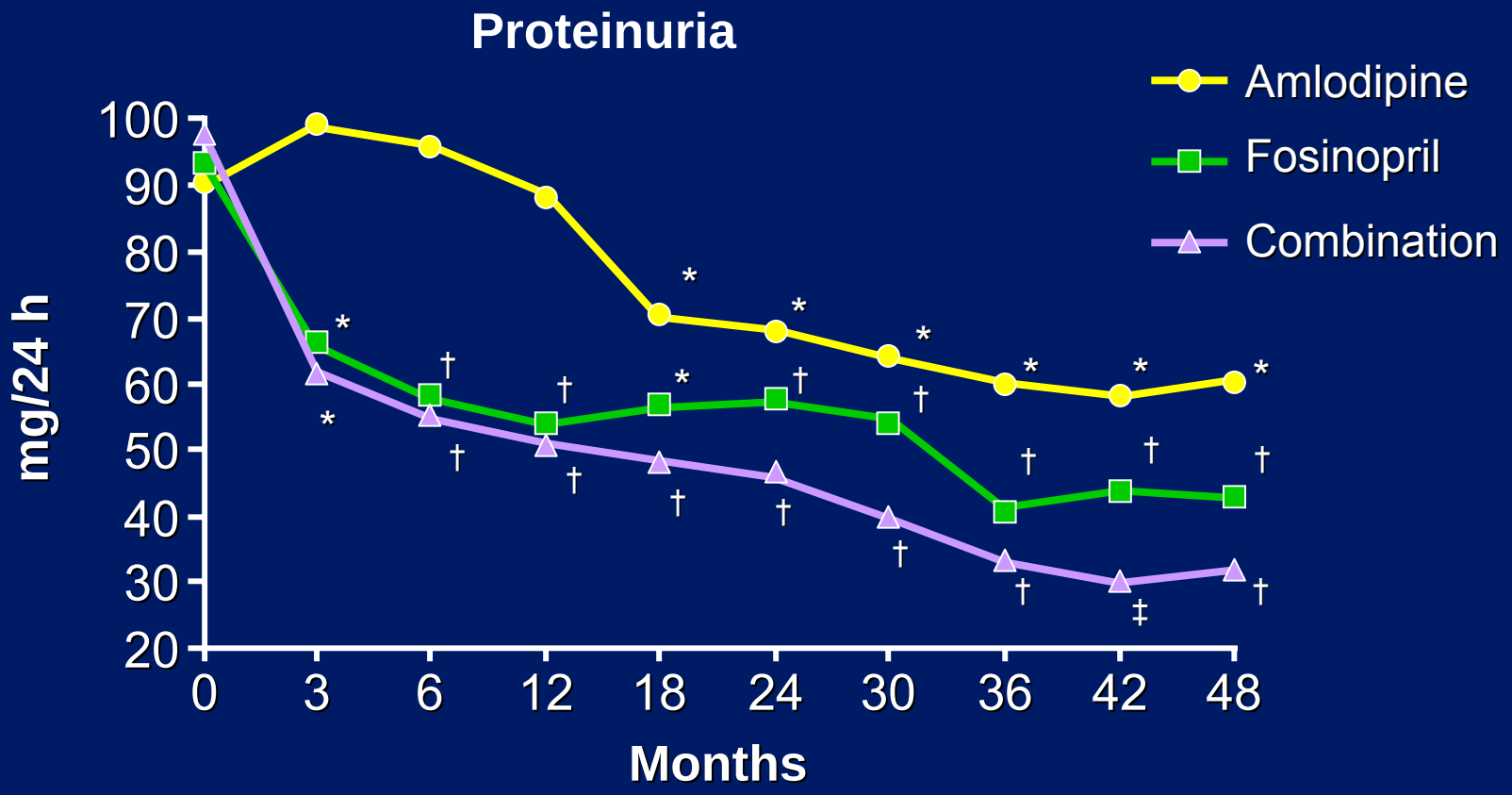


UP/Cr = urinary protein to creatinine ratio.

Baseline UP/Cr of 0.22 corresponds approximately to proteinuria of 300 mg/d.

Agodoa et al. *JAMA*. 2001;285:2719-2728.

FACET; Amlodipine, Fosinopril, or Combination in Patients With NIDDM and Microalbuminuria

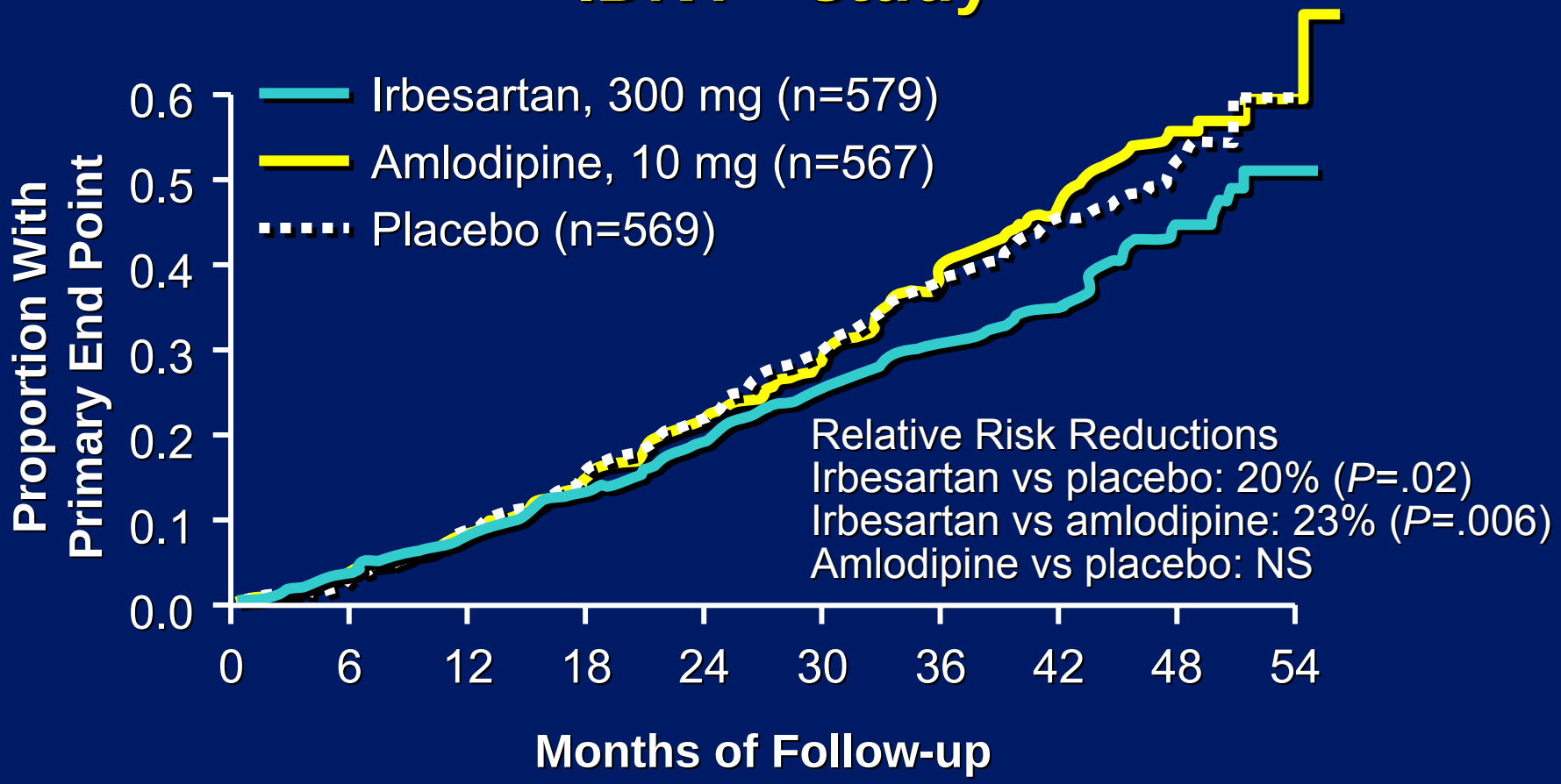


- **Combination significantly better than amlodipine at all visits**
- **Combination significantly better than fosinopril from 18 months**

*P<.05; †P<.01; ‡P<.001 from baseline.

Fogari et al. *Am J Hypertens*. 2002;15:1042-1049.

Diabetic nephropathy type 2
IDNT * study



*Composite of the doubling of baseline SCr, onset of ESRD, or death from any cause. The end point difference was driven by differences in doubling of SCr and ESRD; there was no difference in mortality.

Lewis et al. *N Engl J Med*. 2001;345:851-860.

WHO/ISH: Compelling Indications for Specific Antihypertensive Drugs

Compelling Indications	Preferred Drug	Primary End Point
Elderly with isolated systolic hypertension	Diuretic DHP CCB	Stroke Stroke
Renal disease		
Diabetic nephropathy type 1	ACE inhibitor	Progression of renal failure
Diabetic nephropathy type 2	ARB	Progression of renal failure
Nondiabetic nephropathy	ACE inhibitor	Progression of renal failure
Cardiac disease		
Post-MI	ACE inhibitor β-blocker	Mortality Mortality
LV dysfunction	ACE inhibitor ACE inhibitor	Heart failure Mortality
CHF (diuretics almost always included)	β-blocker Spironolactone	Mortality Mortality
LV hypertrophy	ARB	CV morbidity and mortality
Cerebrovascular disease	ACE inhibitor + diurectic Diuretic	Recurrent stroke Recurrent Stroke

WHO/ISH Writing Group. *J Hypertens.* 2003;21:1983-1992.

결론

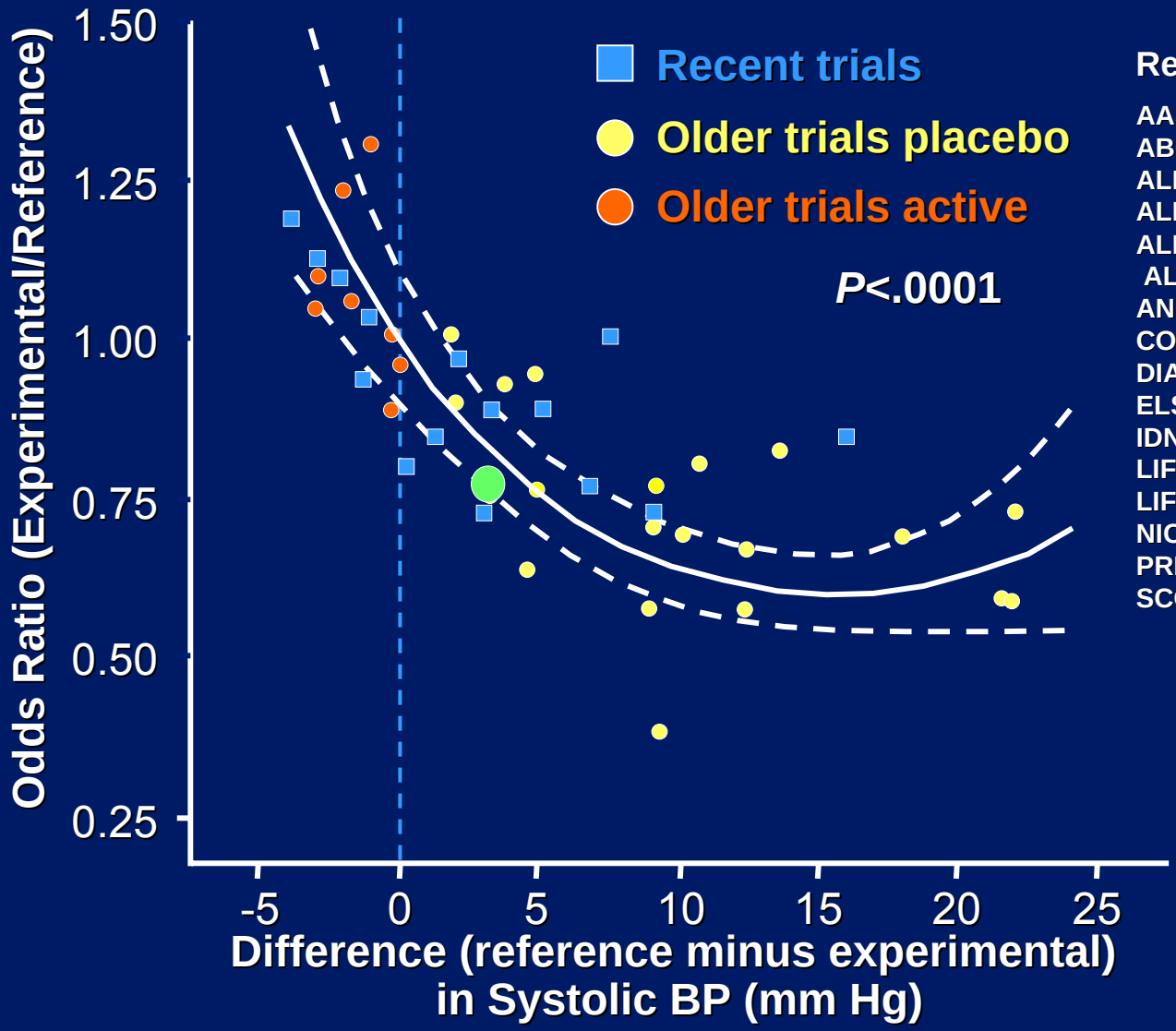
강압제의 선택- 특정표적장기보호

특정약제가 더 효과적이다


Thank you for your attention !

BACKUP SLIDES

Odds Ratio for CV Events and Systolic BP Difference: Recent and Older Trials



Recent	Older
AASK L vs H	ALLHAT/Dox
ABCD/NT L vs H	ATMH
ALLHAT/Aml	EWPHE
ALLHAT/Lis	HEP
ALLHAT/Lis ≥65	HOPE
ALLHAT/Lis Blcks	HOT
ANBP2	HOT M vs H
CONVINCE	INSIGHT
DIABHYCAR	MIDAS/NICS/VHAS
ELSA	L vs H
IDNT2	MRC
LIFE/ALL	MRC2
LIFE/DM	PART2/SCAT
NICOLE	PATS
PREVENT	PROGRESS/Per
SCOPE	PROGRESSION/Com
	RCT70-80
	RENAAL
	SHEP
	STONE
	STOP 1
	STOP2/CCBs
	STOP2/ACEIs
	Syst-China
	Syst-Eur
	UKPDS C vs A
	UKPDS L vs H

Staessen et al. *J Hypertens*. 2003;21:1055-1076.

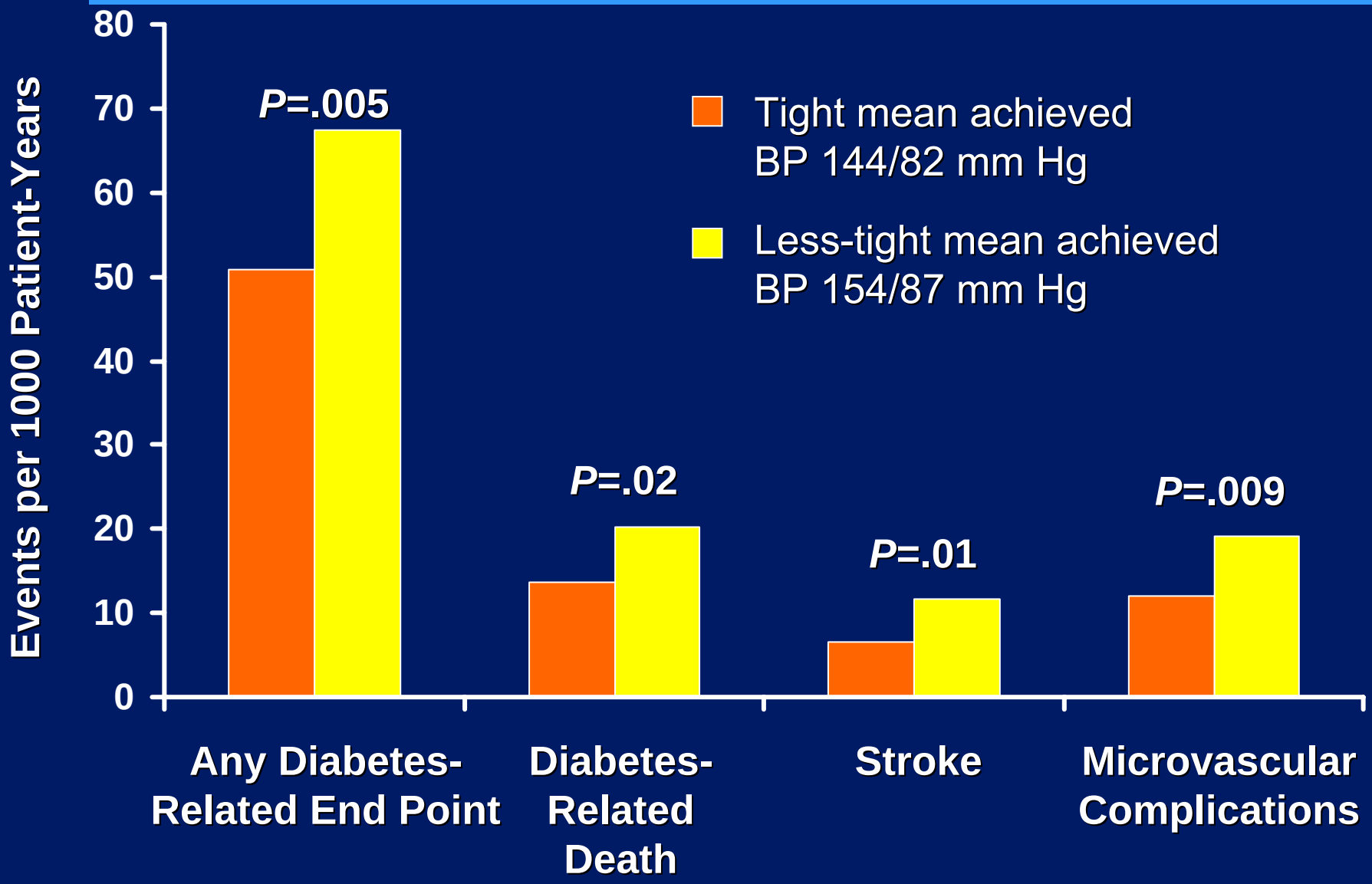
Summary of Major Findings

In older non-black vs black hypertensives

	Blacks	Non-Blacks
Syst. BP control		
– DHP	+ 1 mmHg *	0 mmHg
– ACE-inh.	+ 4-5 mmHg **	0.5 mmHg
Coronary events		
– DHP	- 3 %	- 1 %
– ACE-inhibitor	+ 15 %*	+ 1 %
Strokes		
– DHP	- 7 %	- 7 %
– ACE-inhibitor	+ 40 %*	0
All cardiovascular events		
– DHP	+ 6 %	+ 4 %
– ACE-inhibitor	+ 19 %*	+ 6 %*

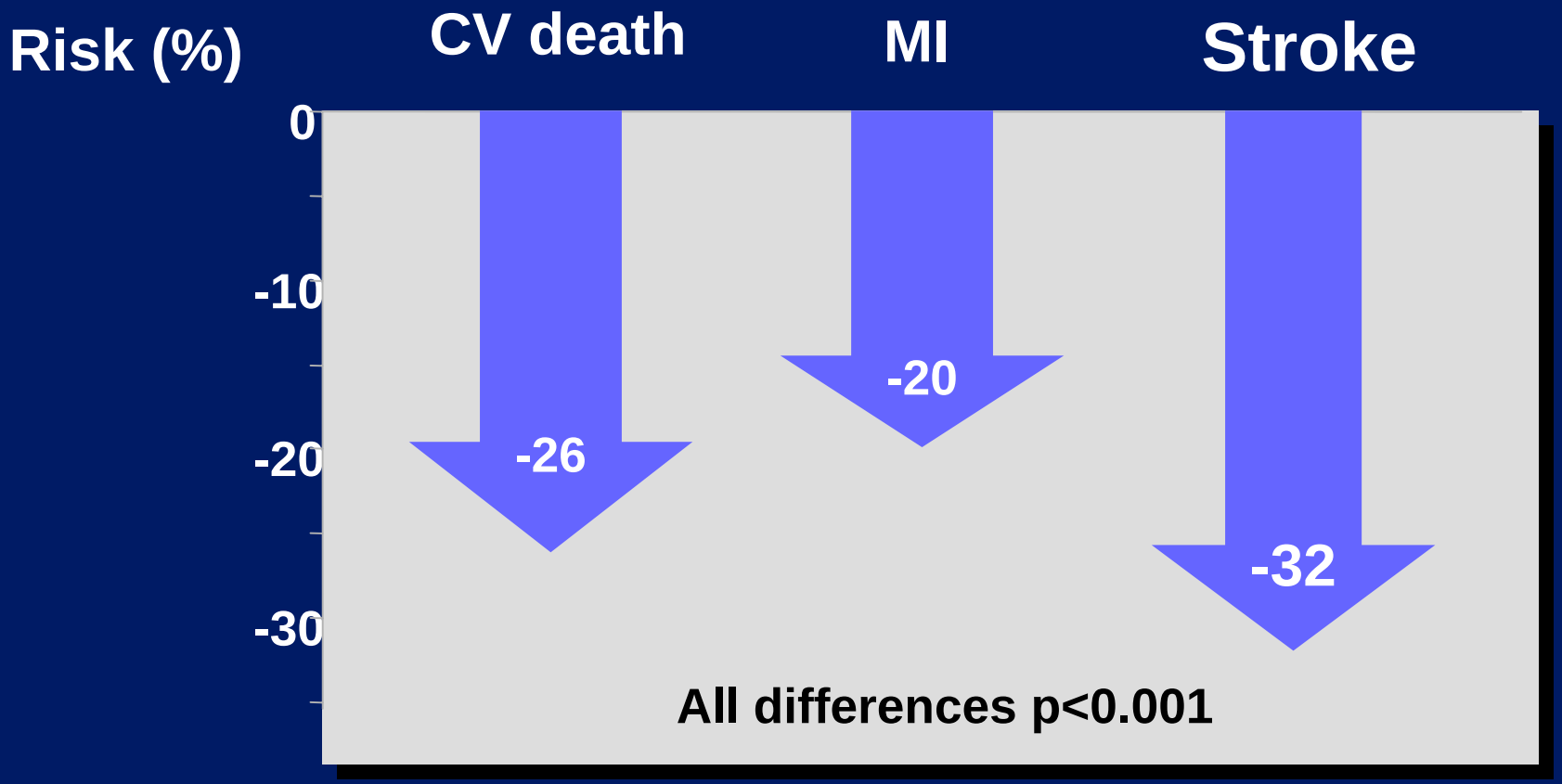
*p<0.05 vs chlorthiazide

UKPDS Event Rates for Select End Points With Tight vs Less-Tight BP Control



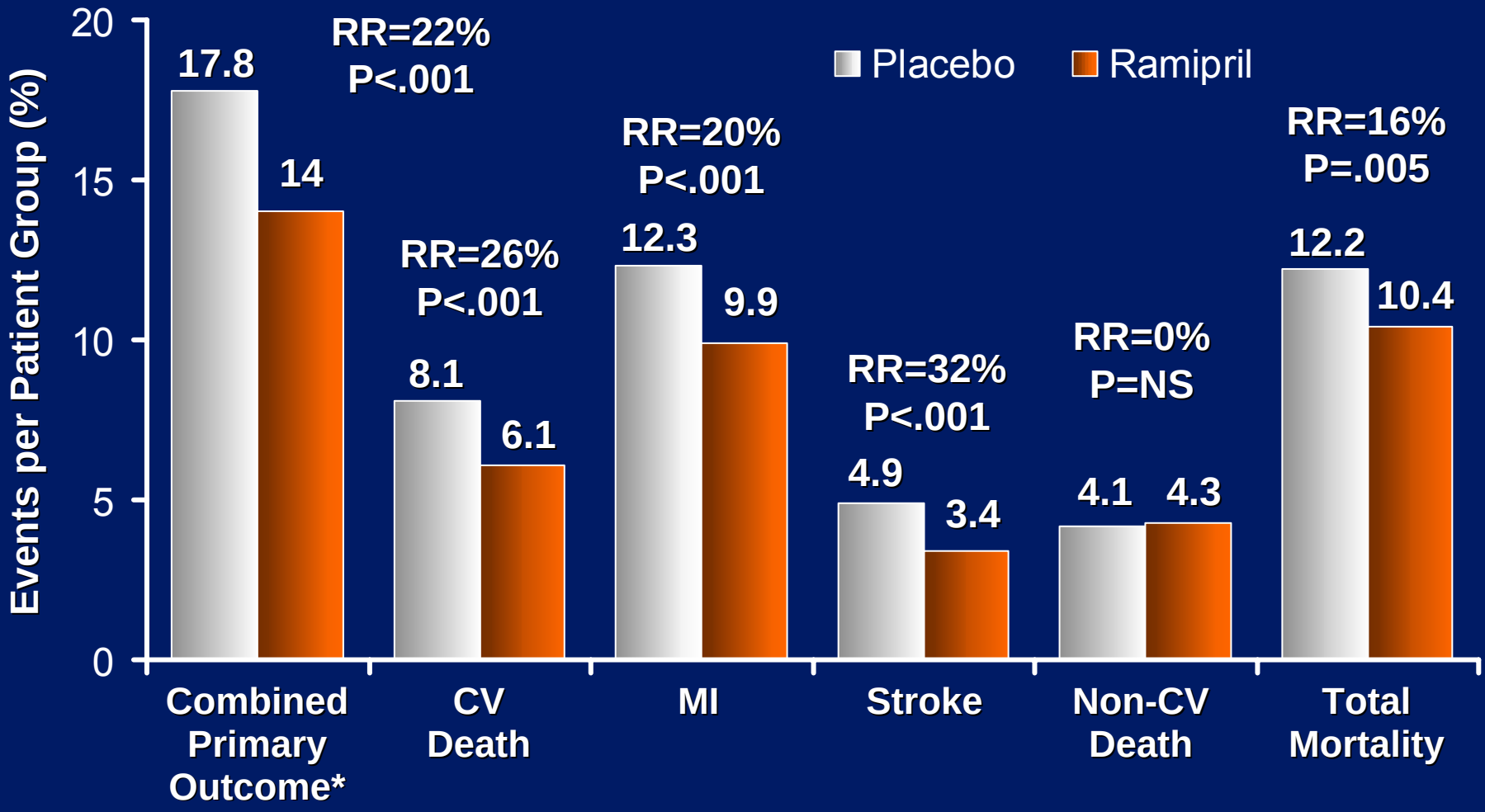
UK Prospective Diabetes Study Group. *BMJ*. 1998;317:703-713.

HOPE - Primary outcome (ramipril vs placebo)



HOPE Study Investigators. New Engl J Med 342:145-153, 2000

HOPE Outcomes



*MI, stroke, or CV death

Yusuf et al. N Engl J Med. 2000;342:145-153.

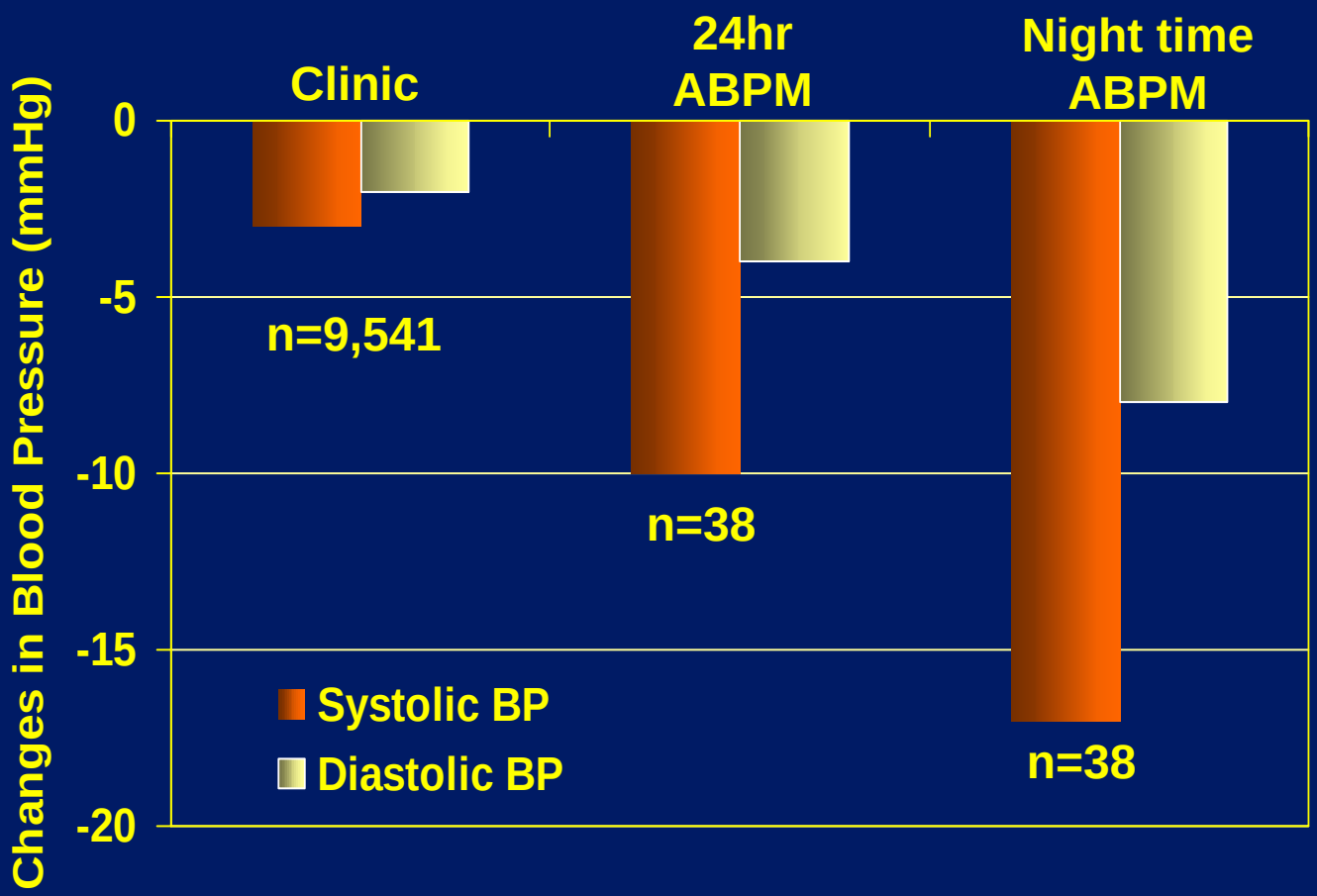
HOPE – BP change

	SBP/DBP (mm Hg)			
	Baseline	1 month	2 years	final
Ramipril	139/79	133/76	135/76	136/76
Placebo	139/79	137/78	138/78	139/77

⇒ **Extremely small decrease in BP in the ramipril group (3/3 mmHg) and even less in the placebo group (0/2 mmHg)**

HOPE Study Investigators New Engl J Med 2000;342:145-153.

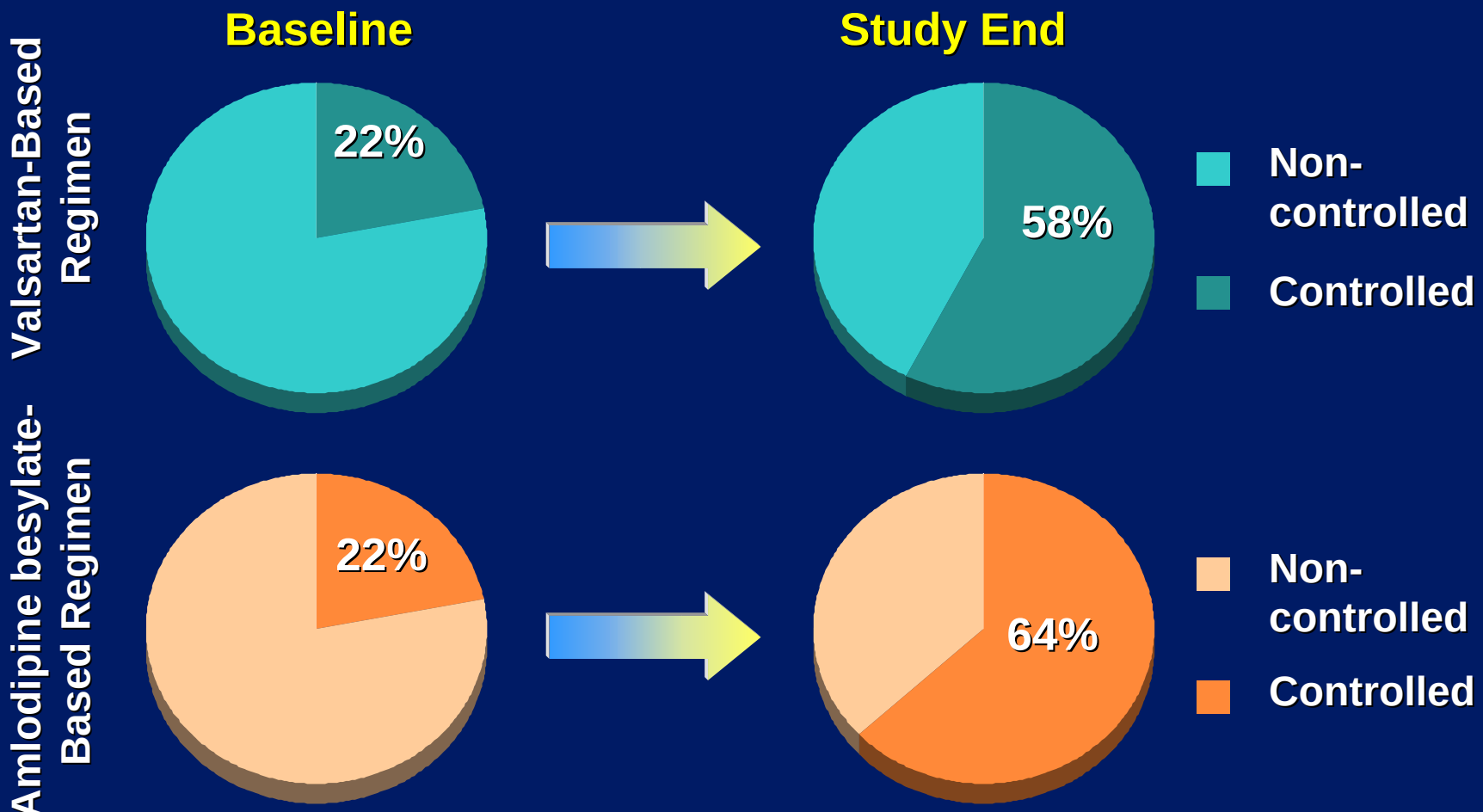
HOPE
Changes in Blood Pressure



JACC 40:2201-3, 2002

VALUE: SBP Control (<140 mmHg)

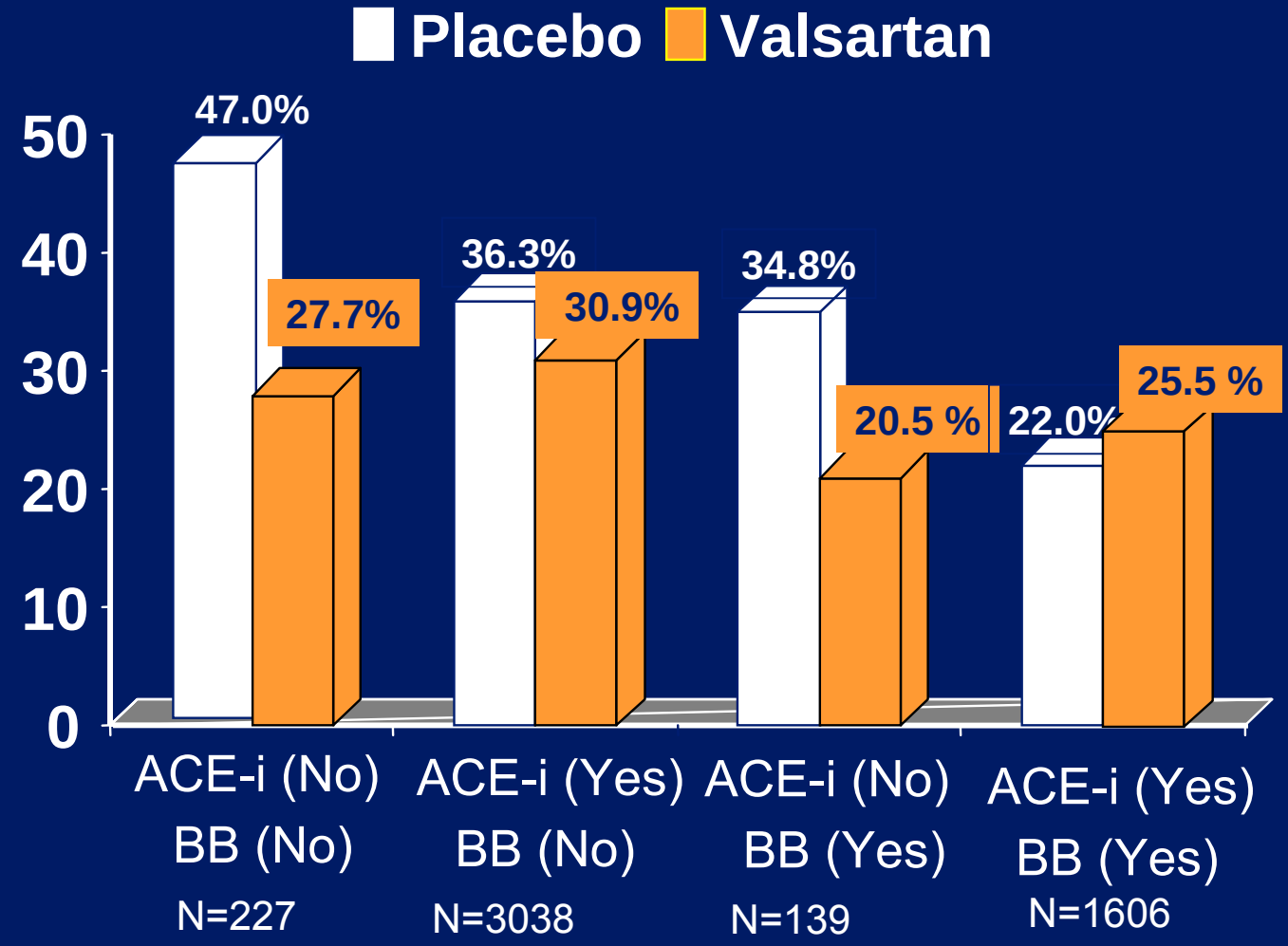
- 92% of patients were previously treated with antihypertensive medication(s) at time of entry
- BP control was better with amlodipine despite more use of add-on medications in valsartan-based regimen



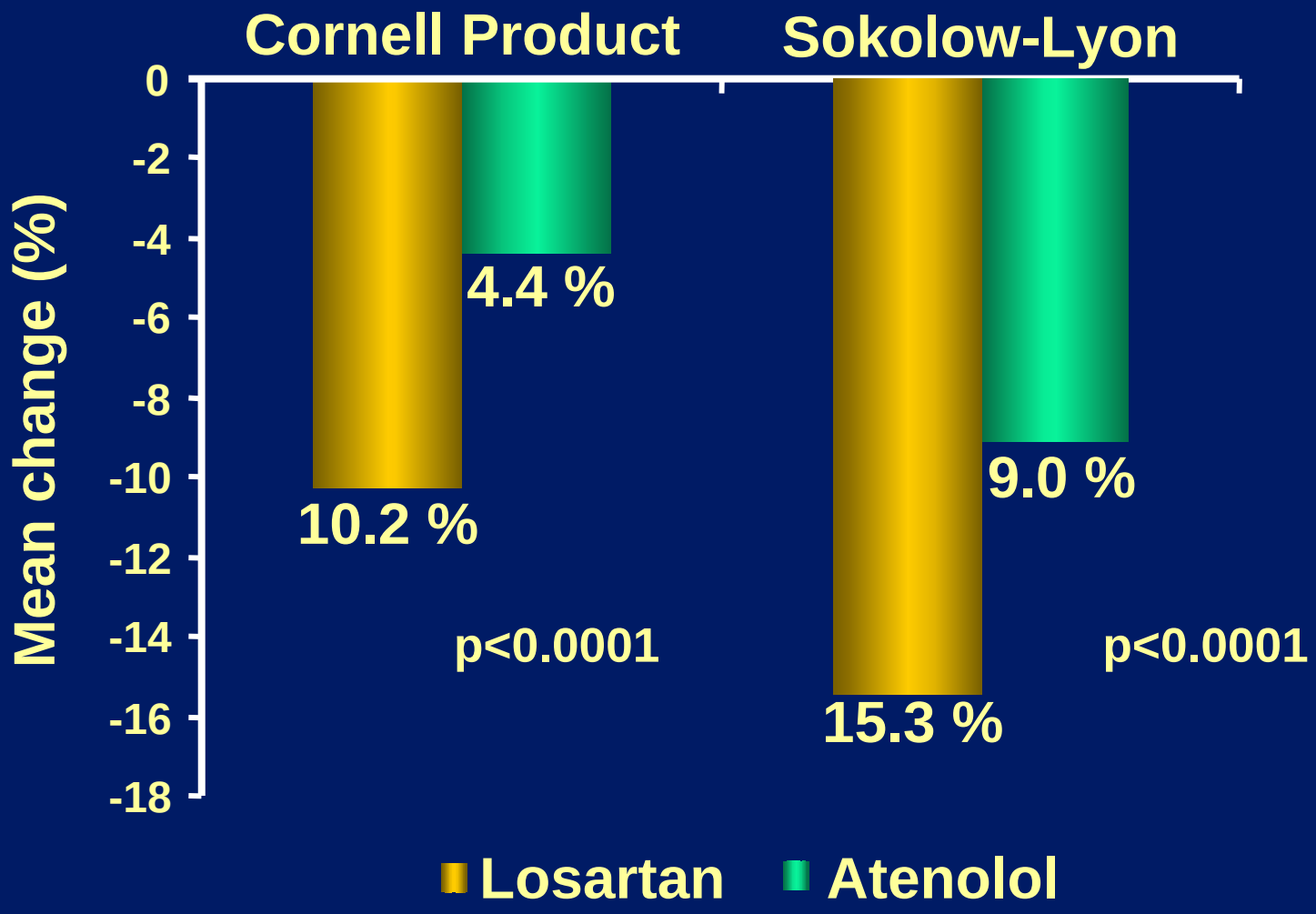
Julius S et al. *Lancet*. June 2004;363.

Val-HeFT

Combined All-Cause Mortality and Morbidity
ACE Inhibitor/Beta Blocker Subgroups



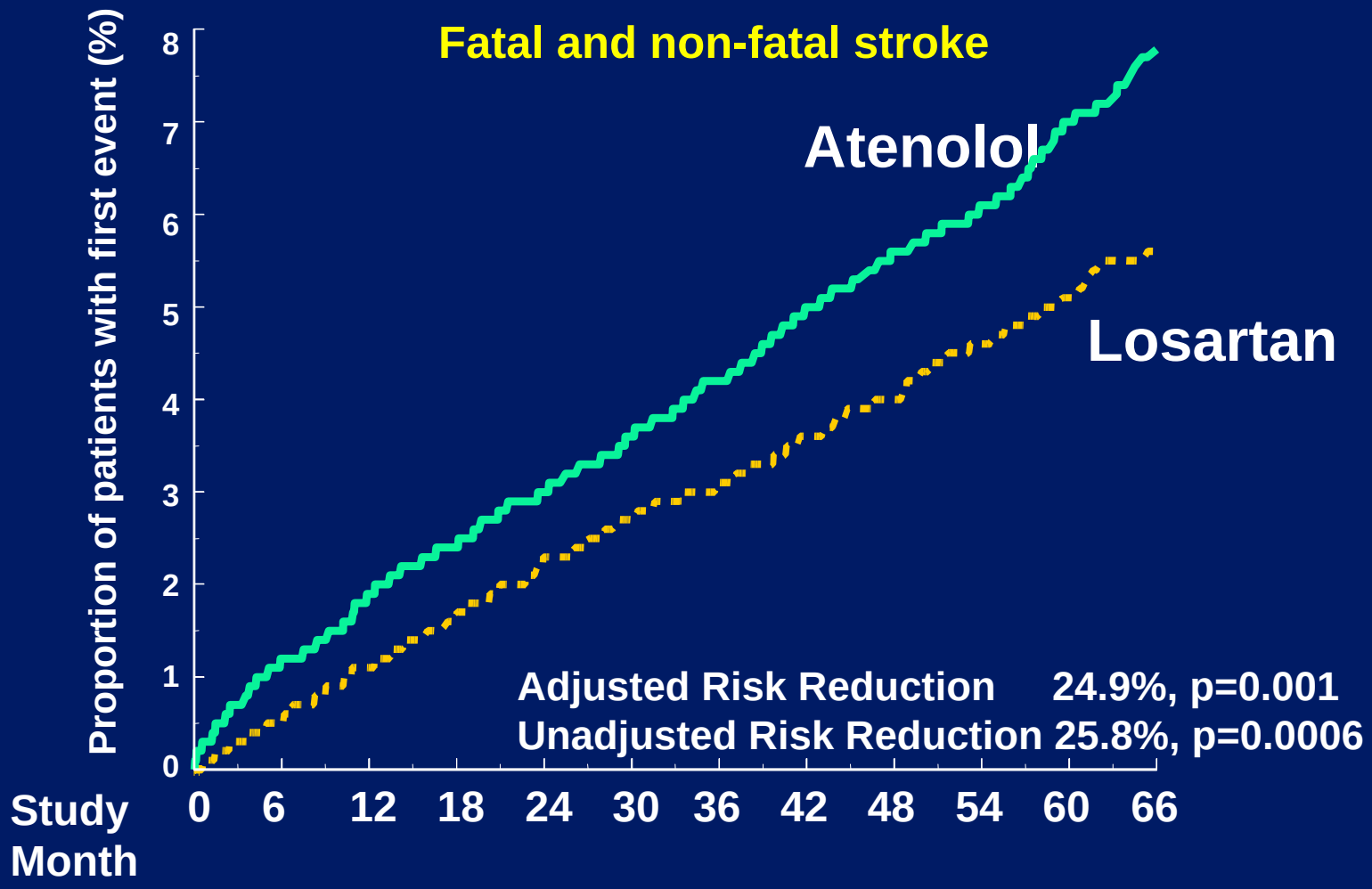
LIFE: LVH Regression after Treatment



Dahlöf B et al Lancet 2002;359:995-1003.

ARB와 B-blocker 비교연구

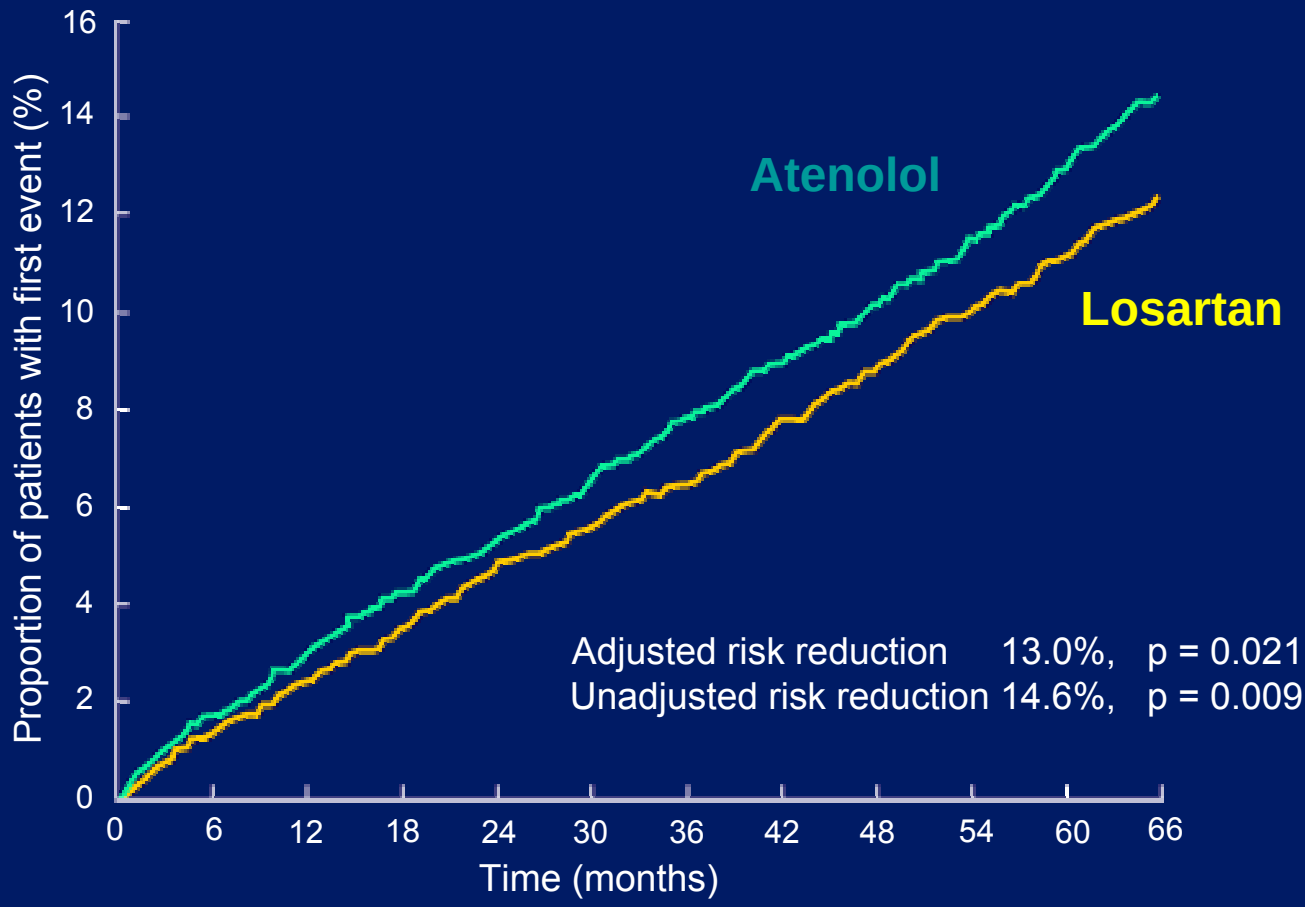
LIFE: Stroke



Dahlöf B et al Lancet 2002;359:995-1003.

Hypertension with ECG- LVH

LIFE: stroke, CV death, and MI

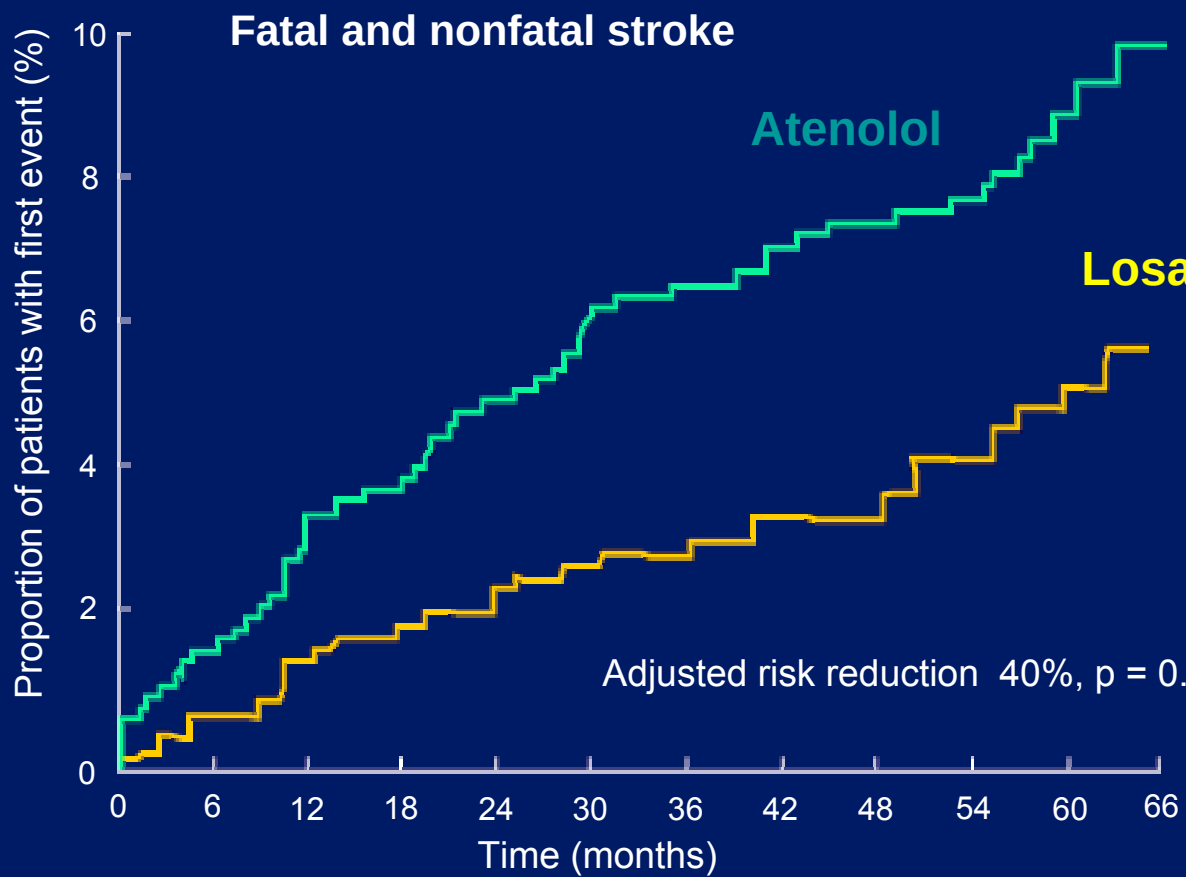


Number at risk												
	Losartan (n)	4605	4524	4460	4392	4312	4247	4189	4112	4047	3897	1889	901
	Atenolol (n)	4588	4494	4414	4349	4289	4205	4135	4066	3992	3821	1854	876

Risk reduction = relative risk vs. atenolol.
No significant difference in CV death and MI vs. atenolol.

Hypertension with ISH

LIFE: Reduction in Risk of Stroke

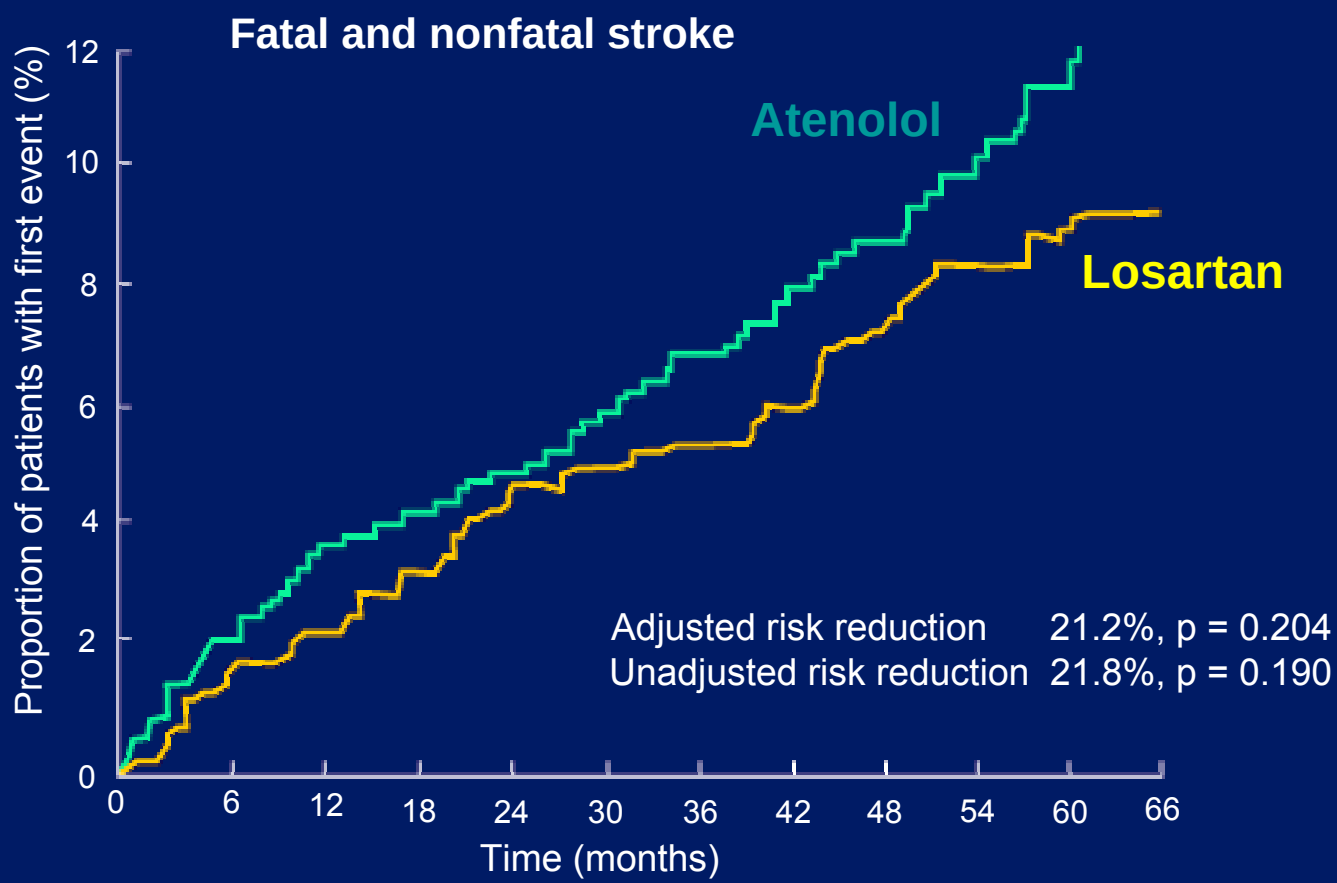


No significant difference in MI vs. atenolol.

Kjeldsen SE et al. *JAMA* 2002;288:1491-1498.

Hypertension with Diabetes

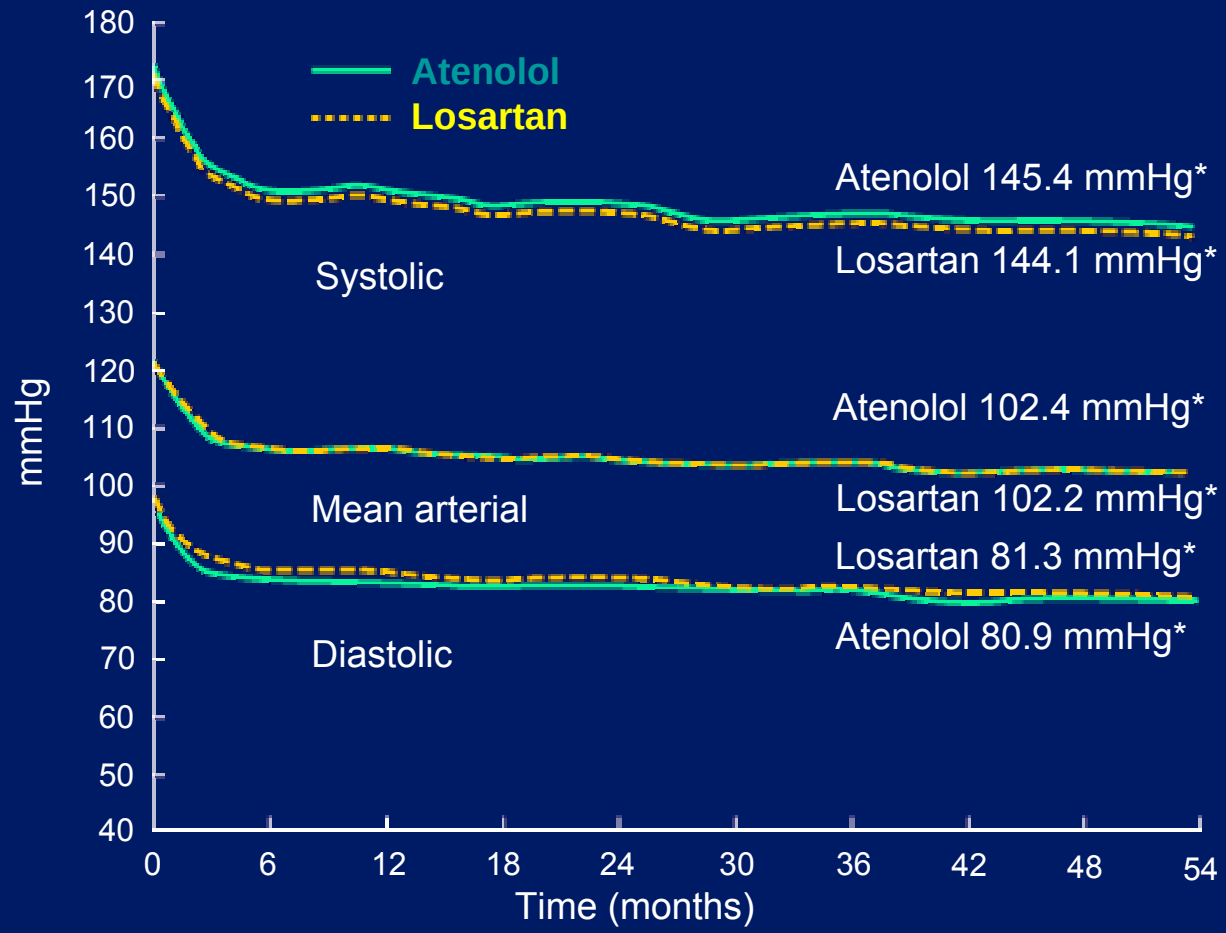
LIFE: Reduction in Risk of Stroke



Number at risk											
Losartan (n)	586	570	560	554	540	530	524	519	500	477	248
Atenolol (n)	609	590	572	561	549	537	521	515	494	456	211

Lindholm LH et al. *Lancet* 2002;359:1004-1010.

Comparable Blood-Pressure Reductions



*Mean BP at last visit.

ACEI or ARB vs placebo

Study	Treatments	Duration(yr)	NODM %	RR	P
HOPE	ACEI vs placebo	5.0	2.2 vs 3.3	0.659	<0.001
CHARM-OVERALL	ARB vs placebo	3.5	4.3 vs 5.3	0.809	<0.036
Total			3.1 vs 4.2	0.742	0.0002

RR; Relative risk

ACEI or ARB vs conventional therapy

Study	Treatments	Duration(yr)	NODM %	RR	P
CAPPP	ACEI vs BB/diuretic	6.1	6.5 vs 7.3	0.895	0.131
LIFE	ARB vs BB	4.8	6.0 vs 8.0	0.748	<0.001
ALLHAT	ACEI vs diuretic	4.9	8.1 vs 11.6	0.701	<0.001
Total			6.5 vs 8.5	0.798	<0.001

NODM; new onset DM, RR; Relative risk

CCB vs conventional therapy

Study	Treatments	Duration(yr)	NODM %	RR	P
NORDIL	CCB vs BB/diuretic	4.5	4.3 vs 4.9	0.867	0.118
INSIGHT	CCB vs diuretic	3.5	5.4 vs 7.0	0.774	0.023
ALLHAT	CCB vs diuretic	4.9	9.8 vs 11.6	0.848	0.082
INVEST	CCB vs BB	4.0	6.2 vs 7.3	0.845	0.004
Total			5.8 vs 7.2	0.798	<0.001