Multiple risk factor management

Benefits seen in recent trials

Interaction of antihypertensive and lipid lowering therapy

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Outline

- Large-scale epidemiological studies
  - Blood pressure
  - Cholesterol
  - Joint effects
- Large-scale clinical trials
  - Antihypertensive
  - Lipid lowering
  - Joint effects

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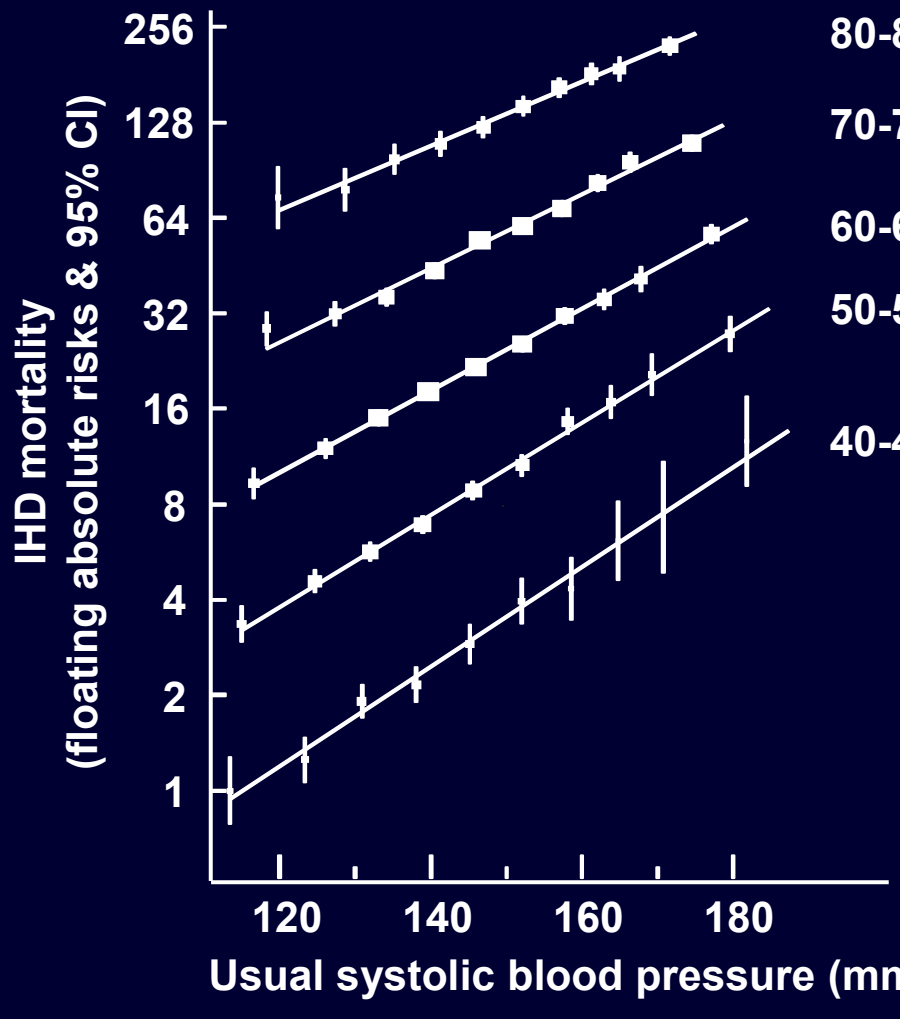
Fatal ischemic heart disease
by usual SBP and age

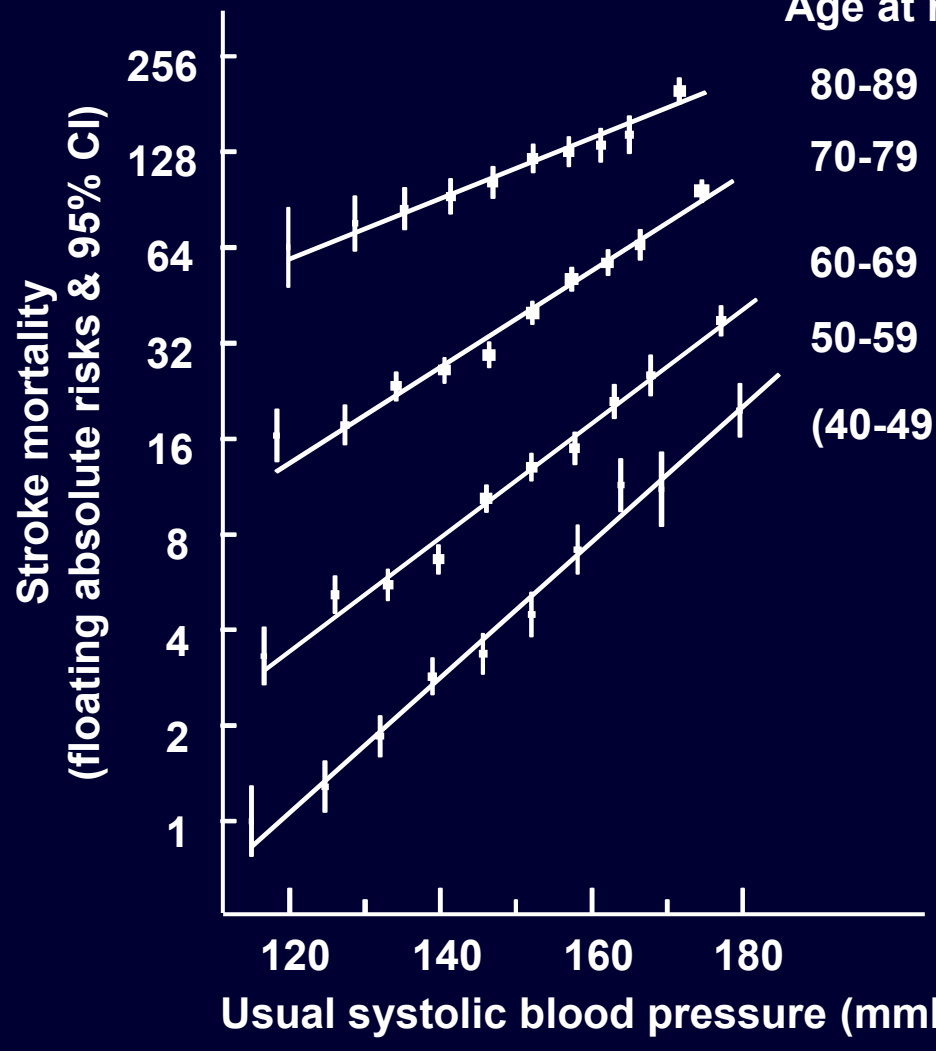
33 867 deaths at ages 40 - 89



Age at risk	20 mmHg ↓ SBP
80-89	31% ↓ risk
70-79	40% ↓ risk
60-69	46% ↓ risk
50-59	50% ↓ risk
40-49	51% ↓ risk

Fatal stroke
by usual SBP and age

11 274 deaths at ages 50 - 89

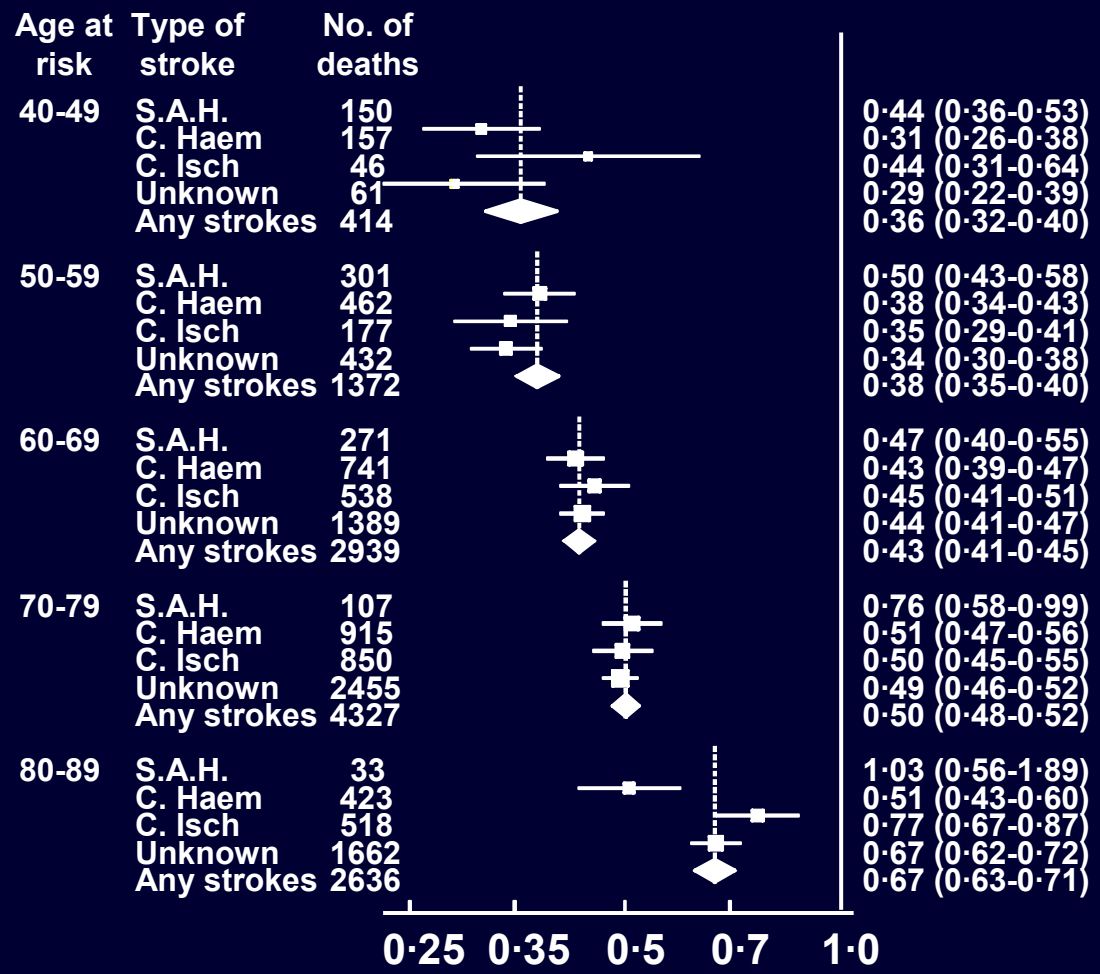


Age at risk:	20 mmHg ↓ SBP
80-89	33% ↓ risk
70-79	50% ↓ risk
60-69	57% ↓ risk
50-59	62% ↓ risk
(40-49	64% ↓ risk)

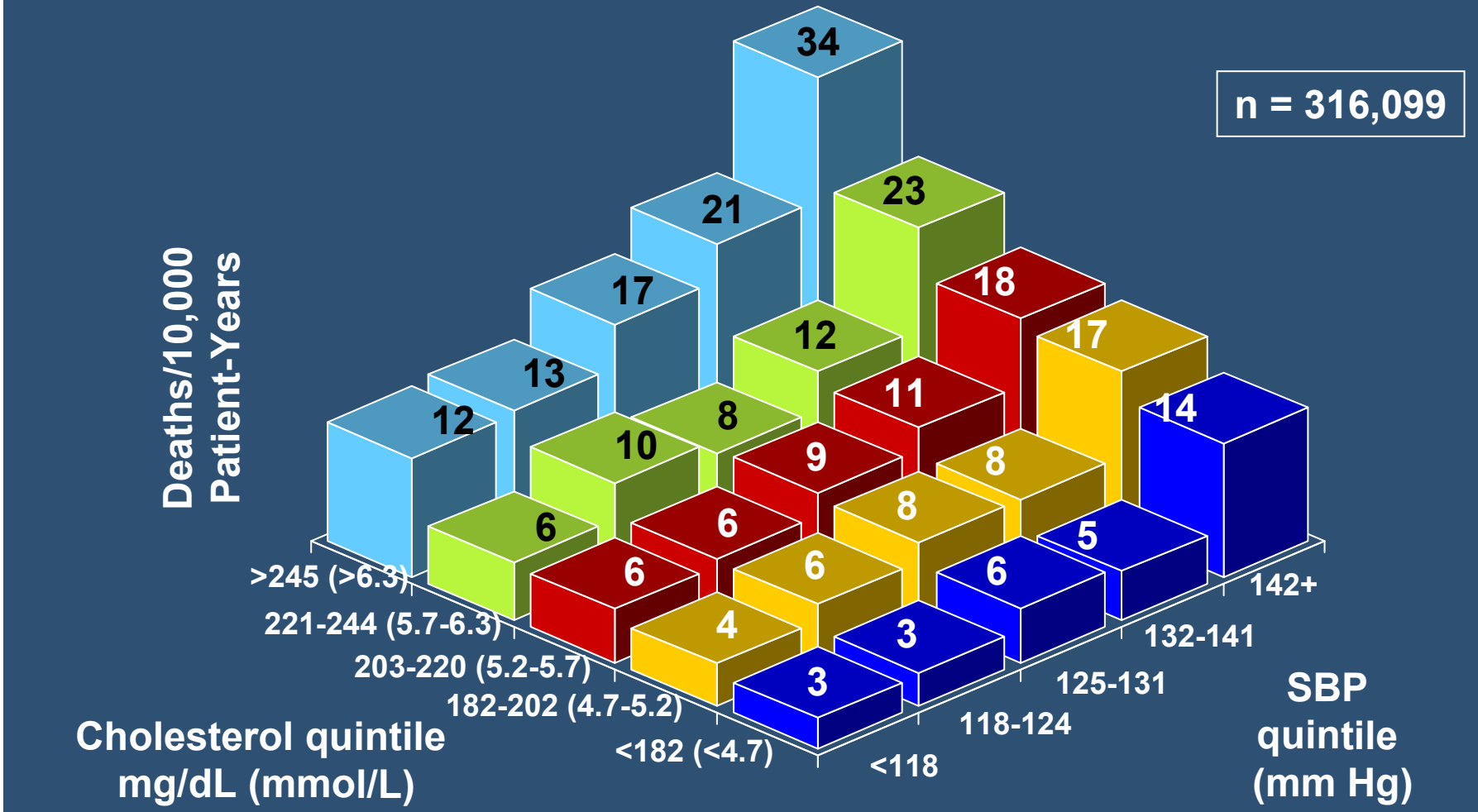
Fatal stroke (by sub-type):

hazard ratios for 20 mmHg lower usual SBP

11 688 deaths at ages 40-89

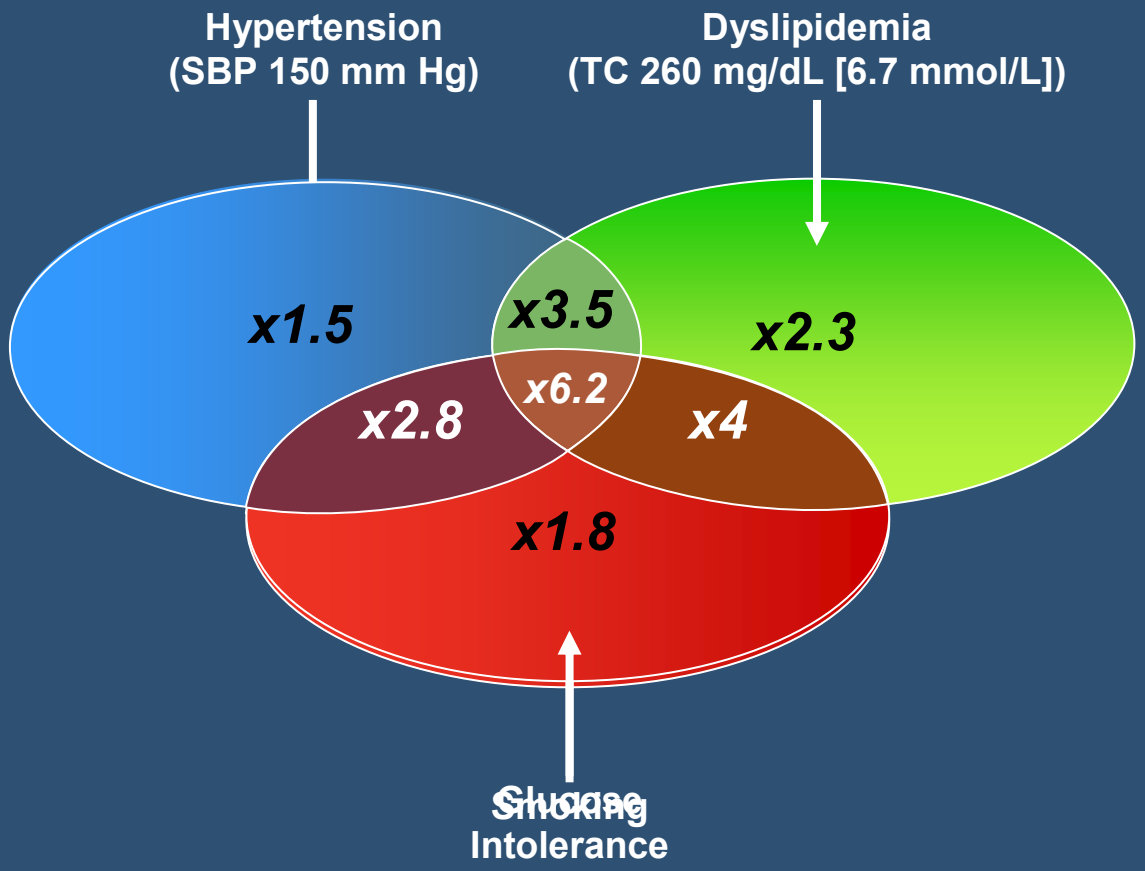


Combined Effects of Systolic Blood Pressure and Cholesterol on Fatal CHD



Neaton JD, et al, for the Multiple Risk Factor Intervention Trial Research Group. *Arch Intern Med*. 1992;152:56-64.

Incremental Risk of Fatal CHD Associated With Multiple Risk Factors



Risk shown is compared with the baseline risk for a 40-year-old male nonsmoker with SBP 120 mm Hg, TC of 185 mg/dL (4.8 mmol/L), no glucose intolerance, who is electrocardiographic left ventricular hypertrophy (ECG-LVH) negative, and has a probability of developing CVD of 15/1000 (or 1.5%) in 8 years. Clustering of risk factors in US men aged 40 to 74 years.

Kannel WB. In: Genest J et al, eds. *Hypertension: Physiopathology and Treatment*. New York, NY: McGraw Hill, Inc; 1977:888-910.

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Blood Pressure Lowering
Treatment Trialists' Collaboration

1995-2006

Secretariat:
The George Institute, University of Sydney Faculty of Medicine &
The Royal Prince Alfred Hospital, Sydney

Principal sponsor:
National Health & Medical Research Council of Australia

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BLOOD
PRESSURE
LOWERING
TREATMENT
TRIALISTS'
COLLABORATION

Analysis cycles

- 1st cycle main report *Lancet* 2000; 355:1955-64
- 2nd cycle main report *Lancet* 2003; 362:1527-35
  - 2nd cycle diabetes paper *Arch Intern Med* 2005 27;165:1410-9
- RAAS inhibitor analysis 2005-2006
- 3rd cycle 2006-2008

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2nd cycle
Contributing studies

First Cycle (N = 74,696)

- ABCD (H)
- CAPPP
- HOPE
- HOT
- INSIGHT
- NICS-EH
- NORDIL
- PART-2
- PREVENT
- QUIET
- SCAT
- STOP-2
- SYST-EUR
- UKPDS-HDS
- VHAS

Second Cycle (N = 87,669)

- AASK
- ABCD (N)
- ALLHAT
- ANBP2
- CONVINCE
- ELSA
- IDNT
- JMIC-B
- LIFE
- NICOLE
- PROGRESS
- RENAAL
- SCOPE
- SHELL

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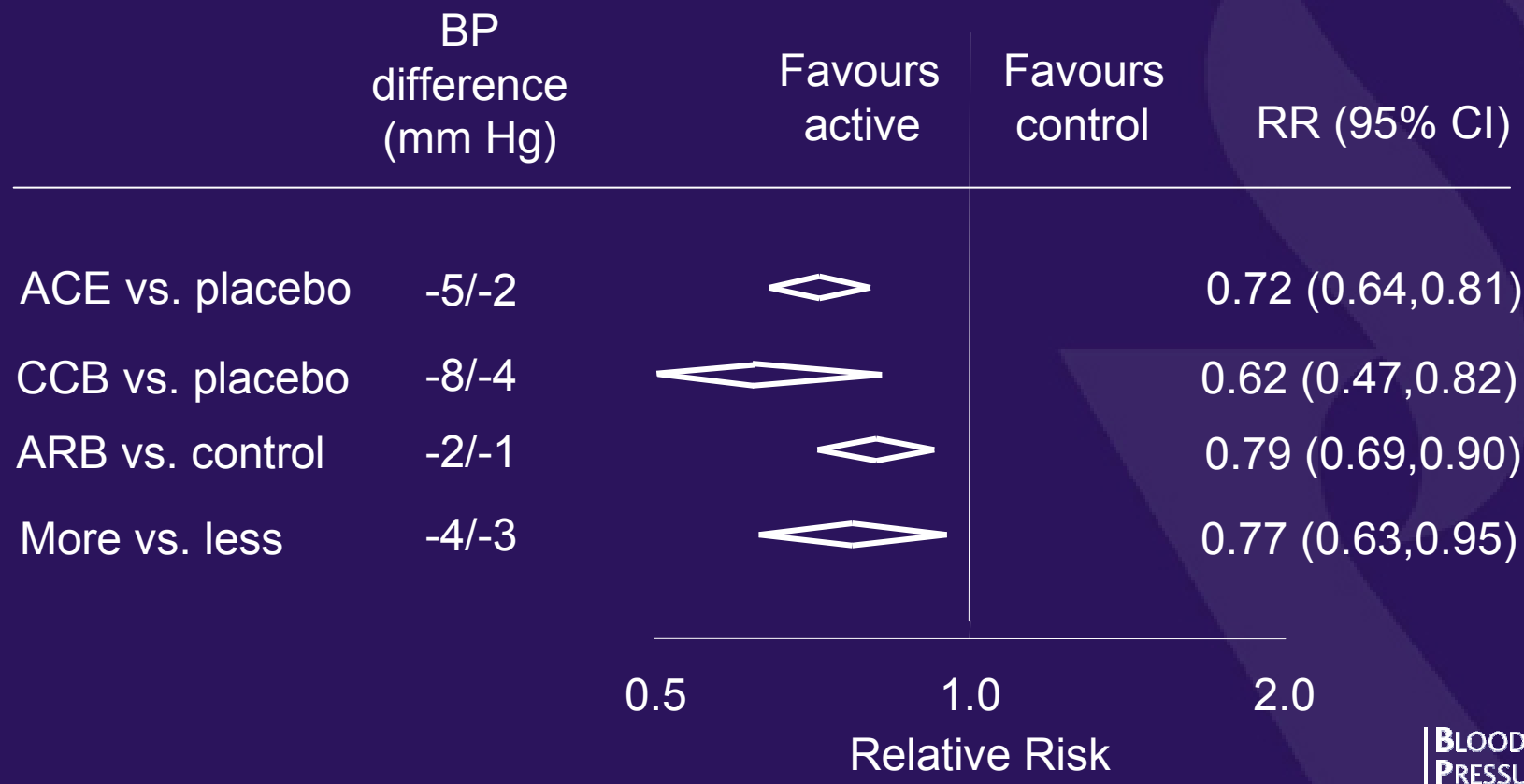
Lancet 2003; 362:1527-35

Active *vs.* control
Stroke



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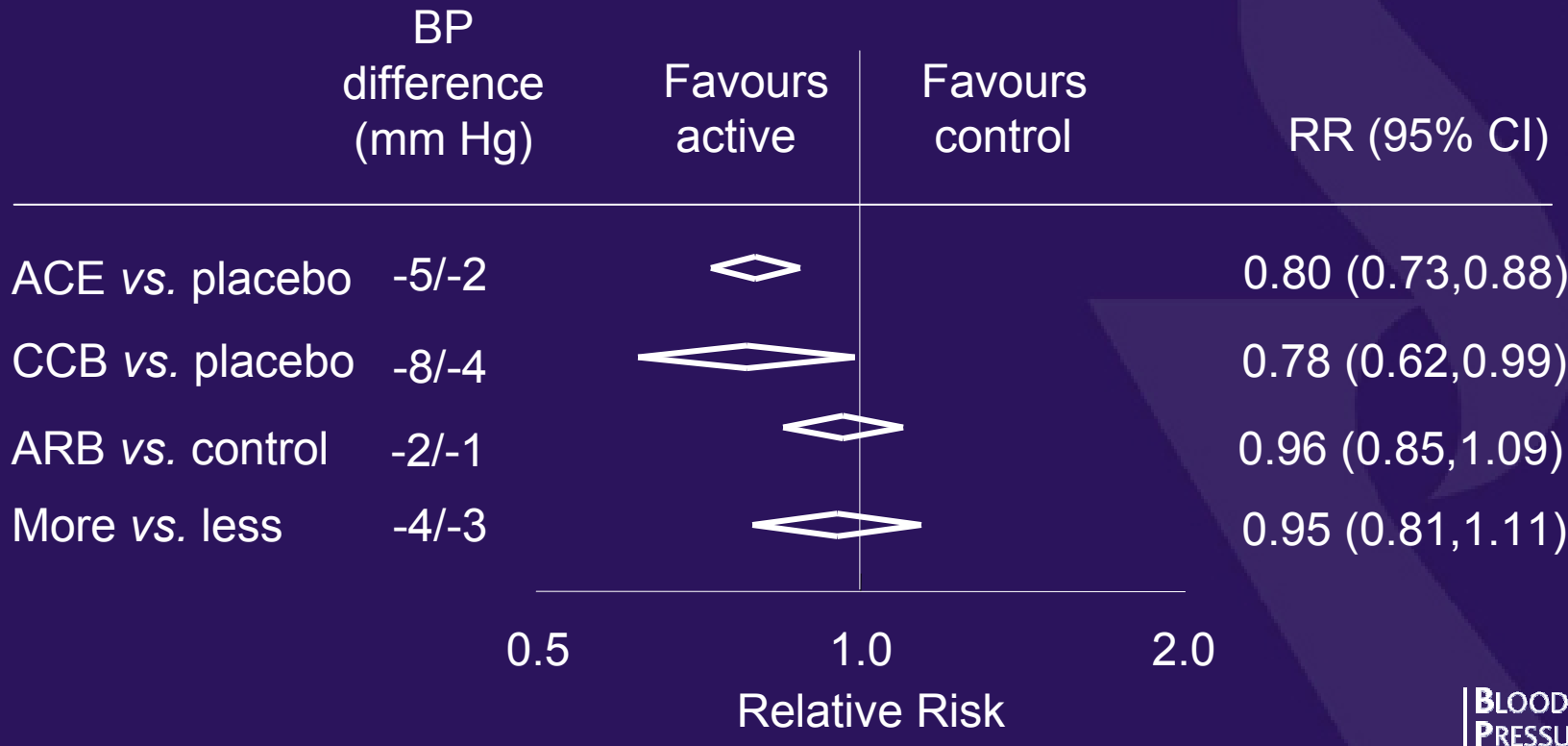
Active *vs.* control
Coronary heart disease



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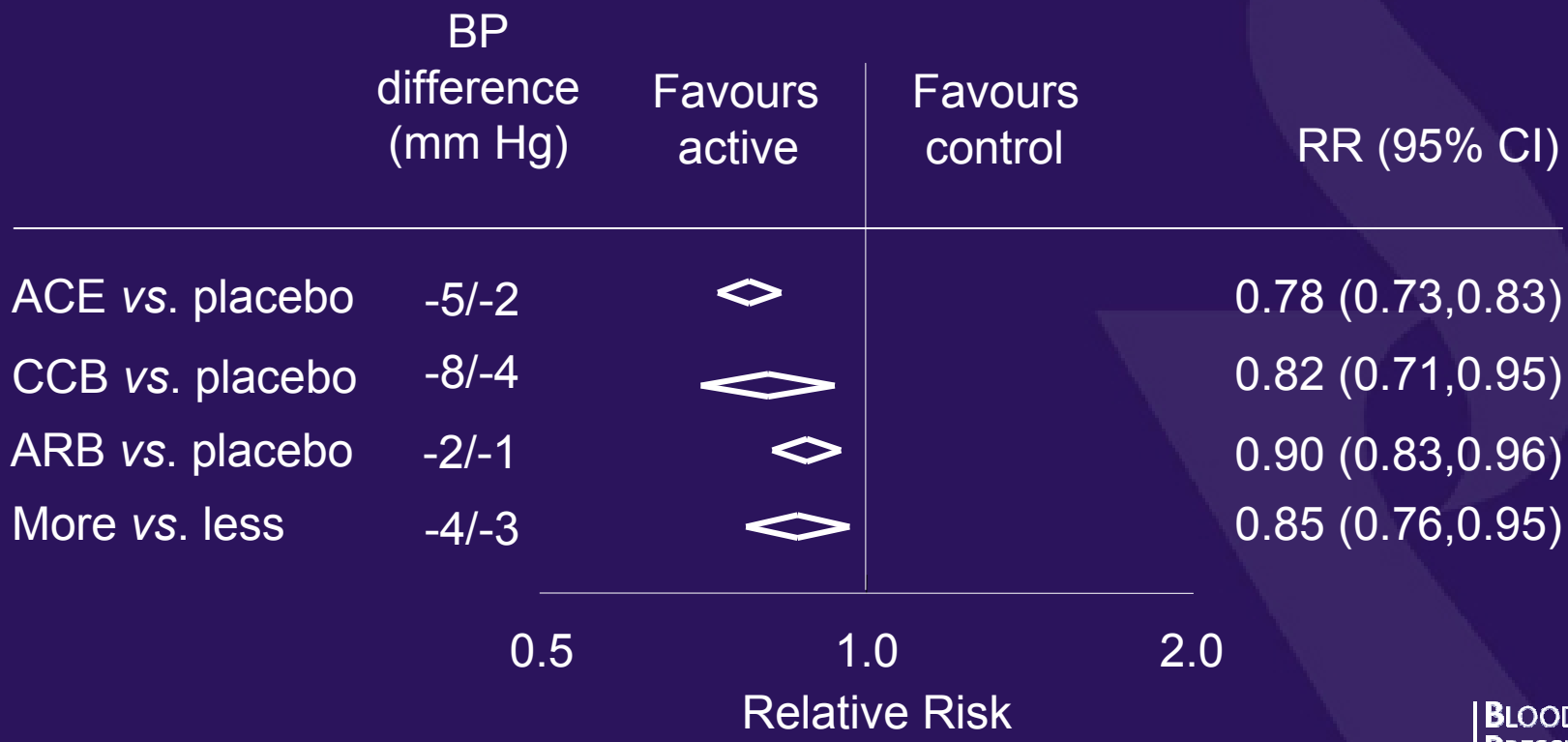
Active *vs.* control
Composite major CVD events



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BLOOD PRESSURE LOWERING TREATMENT TRIALISTS' COLLABORATION

ASCOT–BPLA and LLA

Primary Objectives

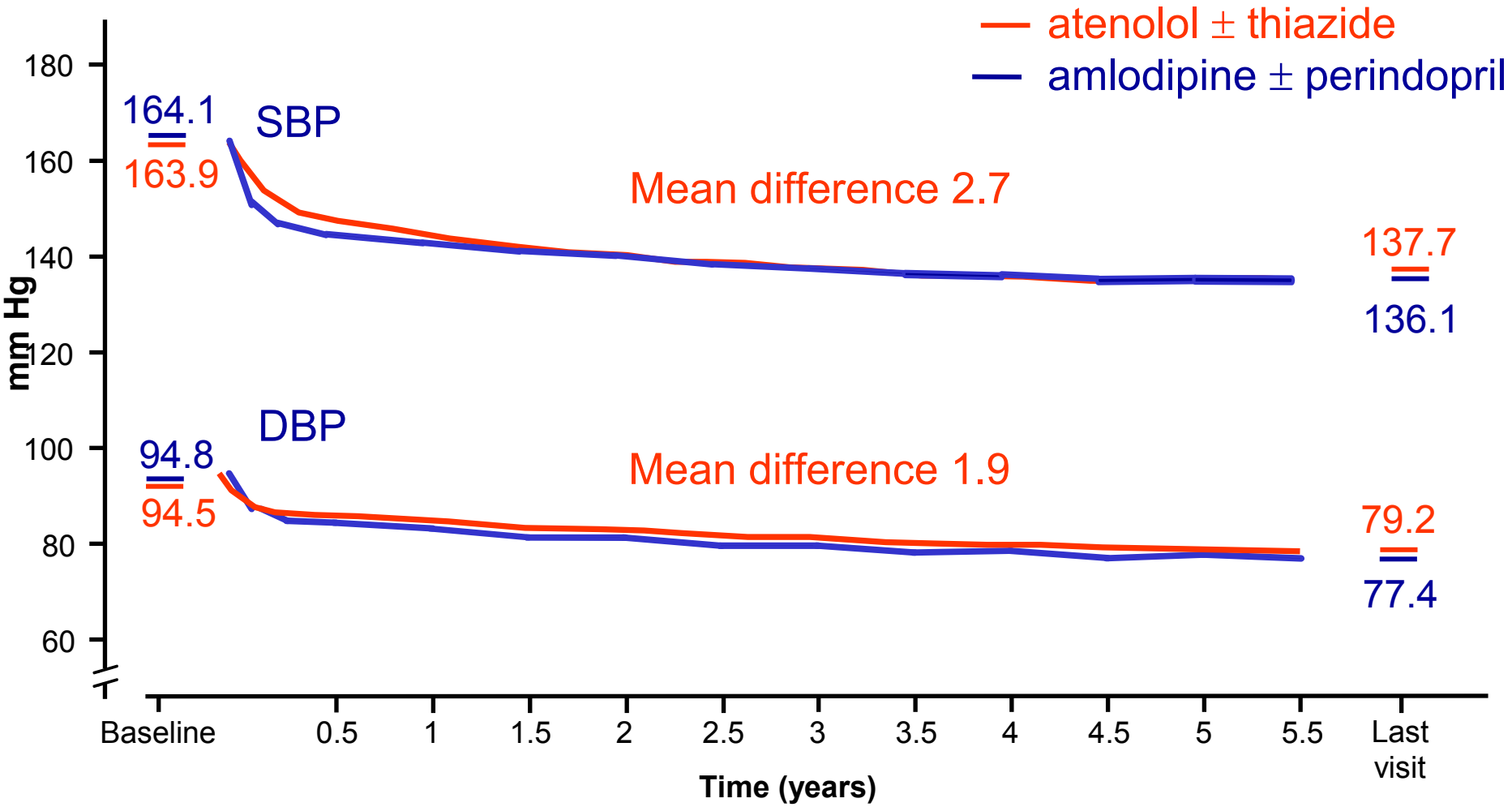
To compare the effect on non-fatal myocardial infarction (MI) and fatal
CHD of :

a standard antihypertensive regimen (β-blocker +/- diuretic) with a more contemporary regimen (CCB +/- ACE inhibitor)

and

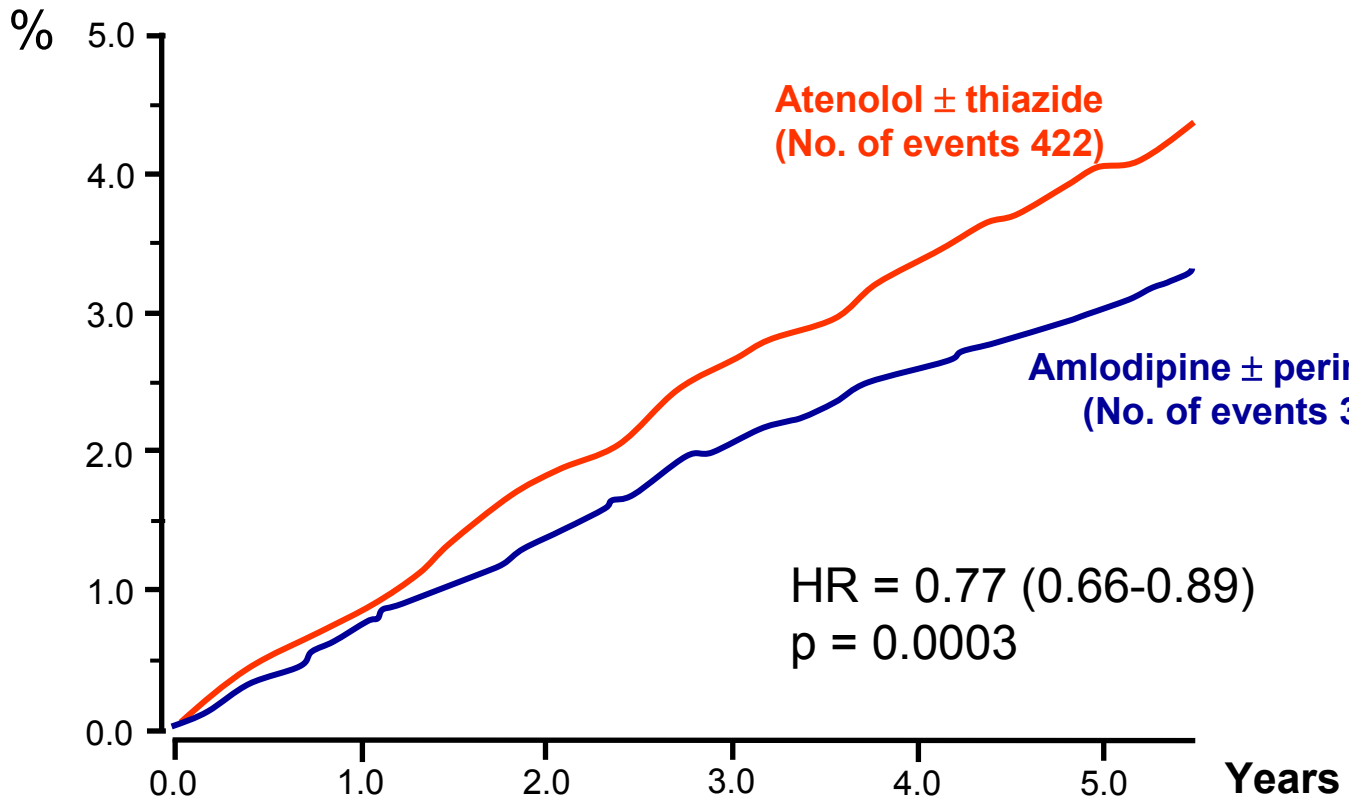
atorvastatin with placebo in those with total cholesterol <250mg/dl

Effects of amlodipine-based regimen on systolic and diastolic blood pressure



ascot

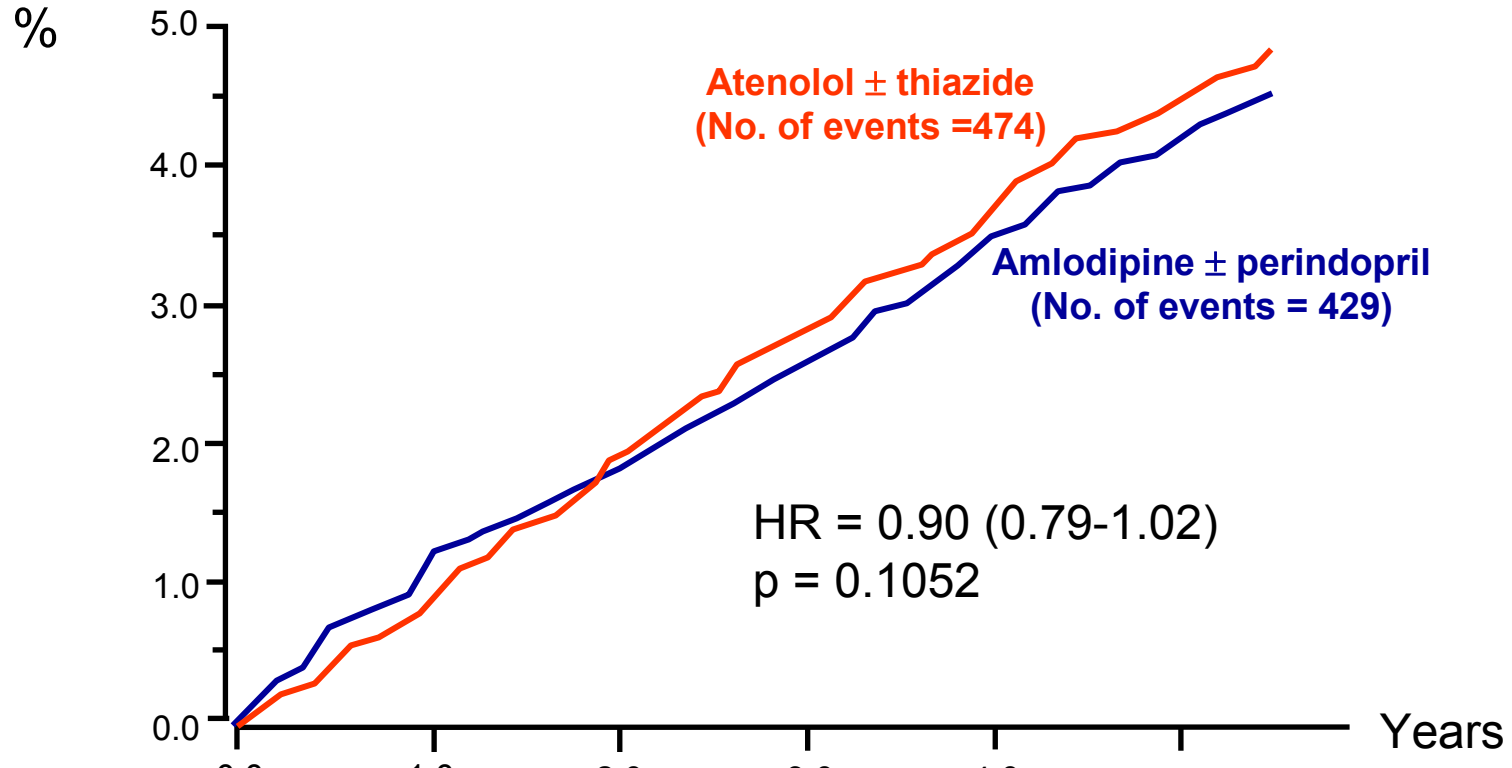
Effects of amlodipine-based regimen among hypertensive individuals: total stroke



Number at risk						
Amlodipine ± perindopril	9639	9483	9331	9156	8972	7863
Atenolol ± thiazide	9618	9461	9274	9059	8843	7720

ascot

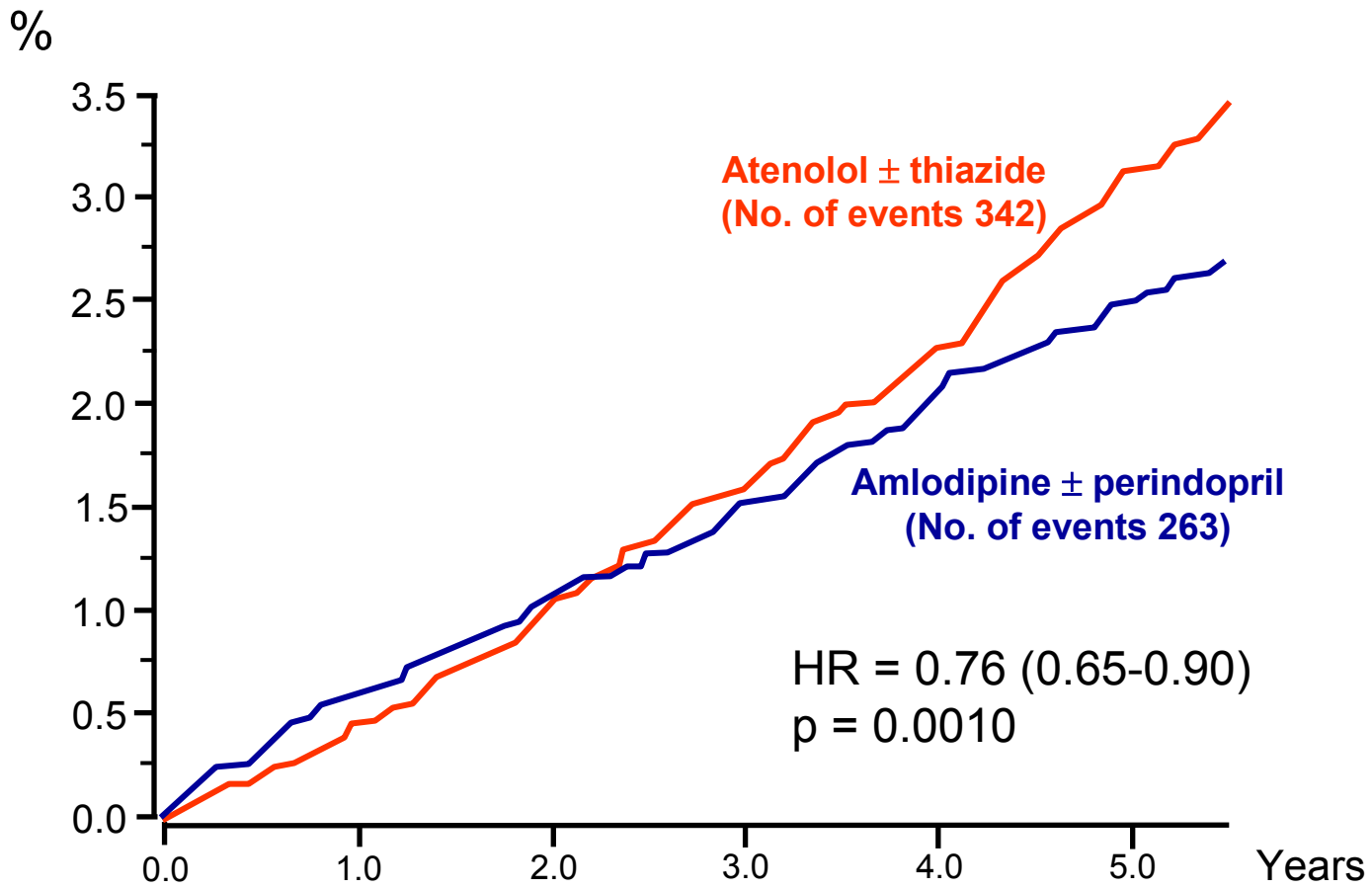
Effects of amlodipine-based regimen among hypertensive individuals: i*schemic heart disease*



Number at risk	0.0	1.0	2.0	3.0	4.0	5.0
Amlodipine ± perindopril	9639	9475	9337	9168	8966	7863
Atenolol ± thiazide	9618	9470	9290	9083	8858	7743

ascot

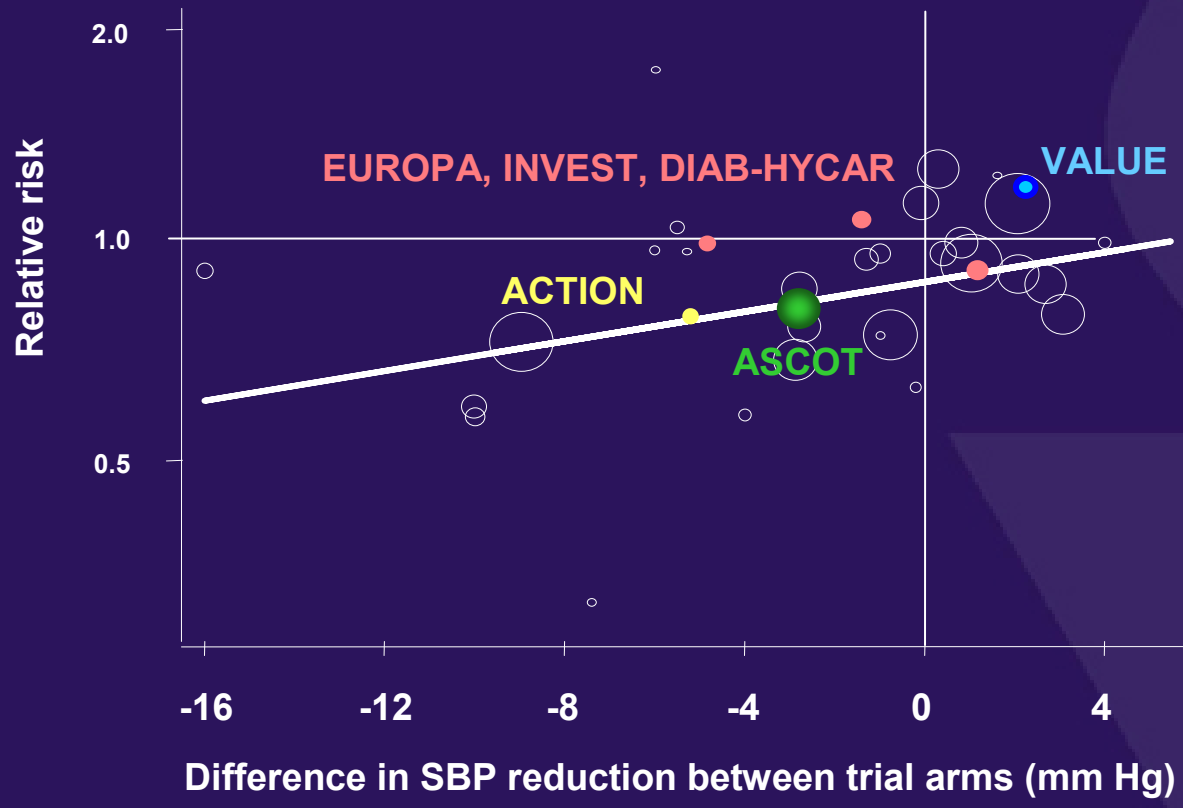
Effects of amlodipine-based regimen among hypertensive individuals: total CV death



Number at risk						
Amlodipine ± perindopril	9639	9544	9441	9322	9167	8078
Atenolol ± thiazide	9618	9532	9415	9261	9085	7975

ascot

Reduction in stroke risk by SBP reduction



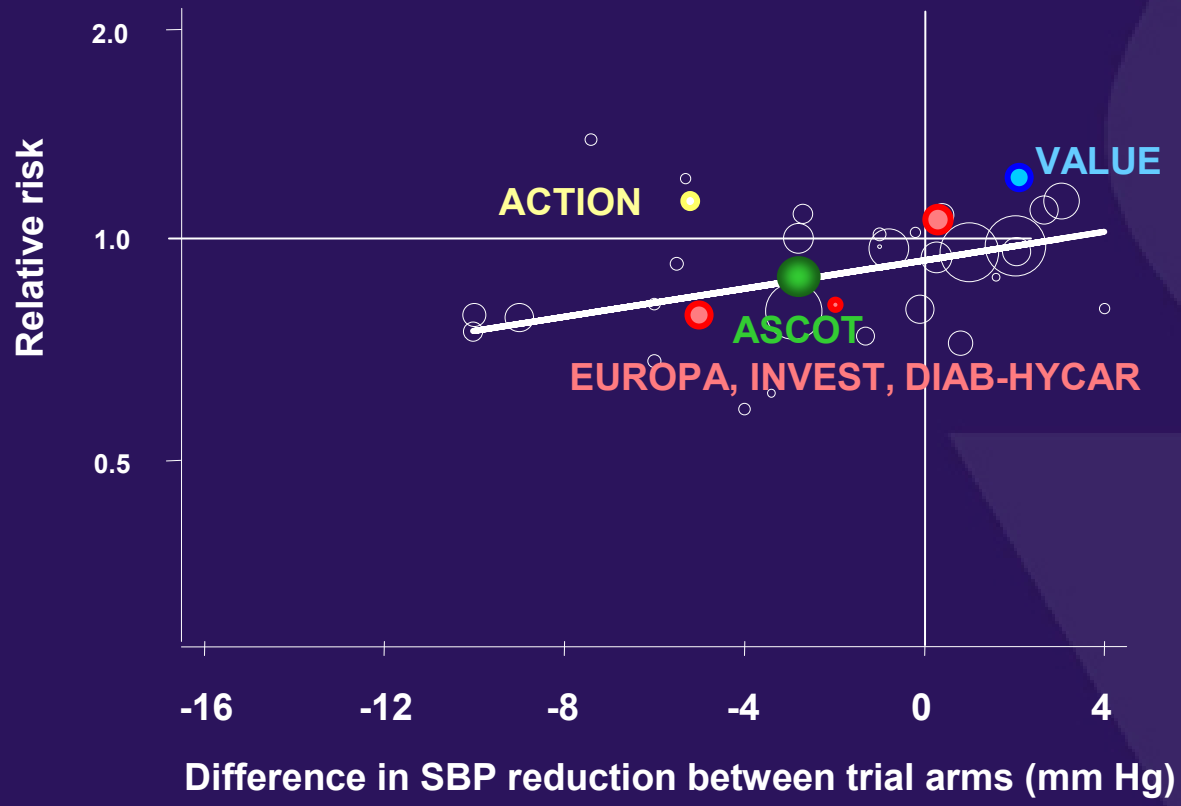
slope = 22% risk reduction per 10 mm decrease in SBP p<0.01

intercept = 9% risk reduction at 0 mm difference in SBP p=0.02

○ 2003 BPLTTC trials ——— regression line for BPLTTC trials

BLOOD PRESSURE LOWERING TREATMENT TRIALISTS' COLLABORATION

Reduction in coronary disease risk by SBP reduction



slope = 20% risk reduction per 10 mm decrease in SBP p<0.001

intercept = 5% risk reduction at 0 mm difference in SBP p=0.03

○ 2003 BPLTTC trials

—— regression line for BPLTTC trials

BLOOD PRESSURE LOWERING TREATMENT TRIALISTS' COLLABORATION

Effects of cholesterol lowering for the primary prevention of coronary disease

Effect of treatment on coronary heart disease events

Study	Treatment (No of events/ No of subjects)	Control (No of events/ No of subjects)	Odds ratio (95% CI)	Weight (%)	Odds ratio (95% CI)	Year
LRC	155/1906	187/1900		29.5	0.81 (0.65 to 1.01)	1984
HHS	56/2051	84/2030		14.1	0.65 (0.46 to 0.92)	1987
WOSCOPS	174/3302	248/3293		40.3	0.68 (0.56 to 0.83)	1995
AFCAPS/TexCAPS	56/3304	96/3301		16.2	0.58 (0.41 to 0.80)	1998
Total	441/10 563	615/10 524		100.0	0.70 (0.62 to 0.79)	

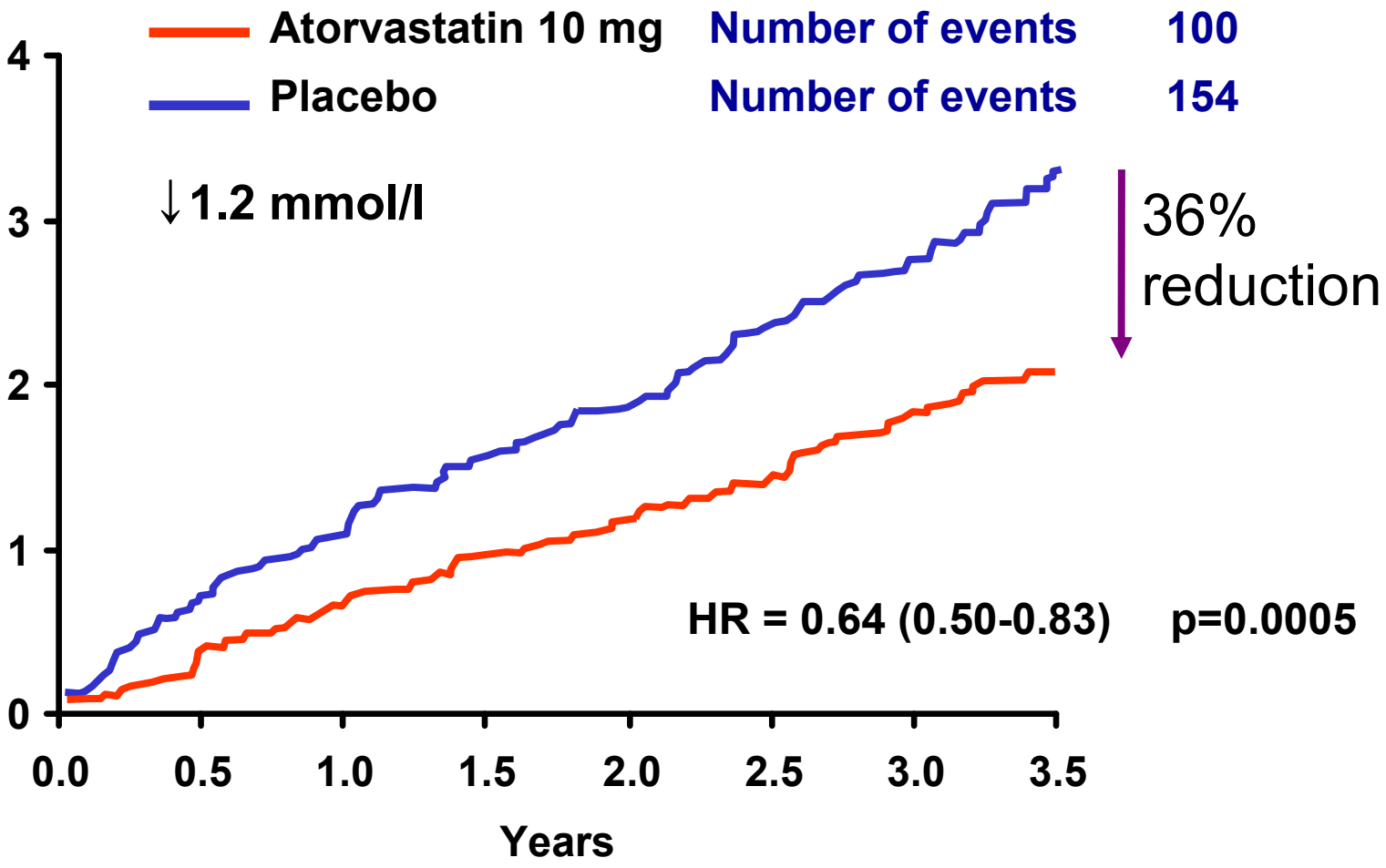
χ^2 test for heterogeneity = 3.23 (df=3;P=0.36)

Effect of treatment on coronary heart disease mortality

LRC	30/1906	38/1900		24.4	0.78 (0.48 to 1.27)	1984
HHS	14/2051	19/2030		12.4	0.73 (0.36 to 1.45)	1987
WOSCOPS	50/3302	73/3293		47.0	0.68 (0.47 to 0.98)	1995
AFCAPS/TexCAPS	17/3304	25/3301		16.2	0.68 (0.37 to 1.26)	1998
Total	111/10 563	155/10 524		100.0	0.71 (0.56 to 0.91)	

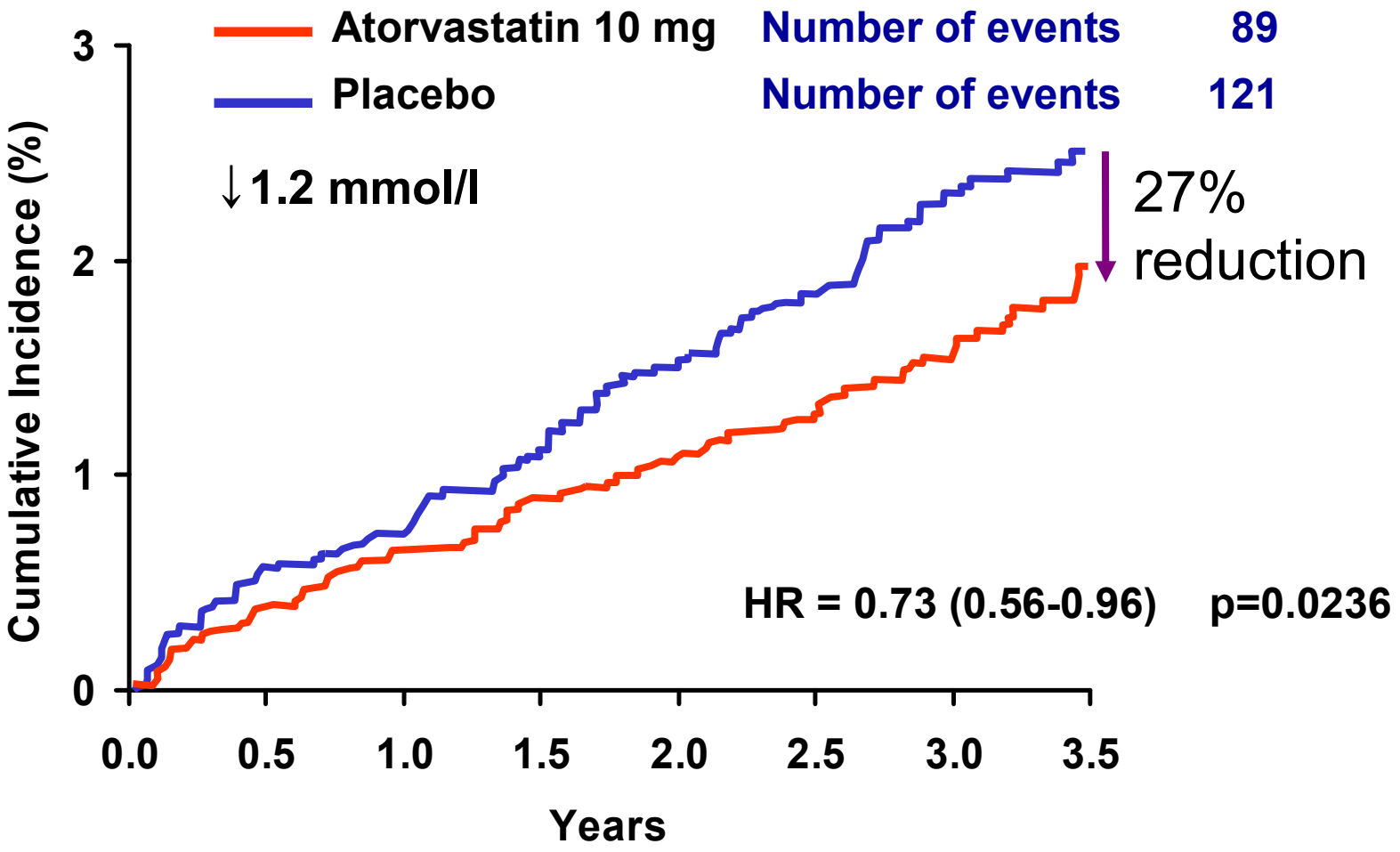
χ^2 test for heterogeneity = 0.25 (df=3;P=0.97)

Effects of atorvastatin among hypertensive individuals: ischemic heart disease



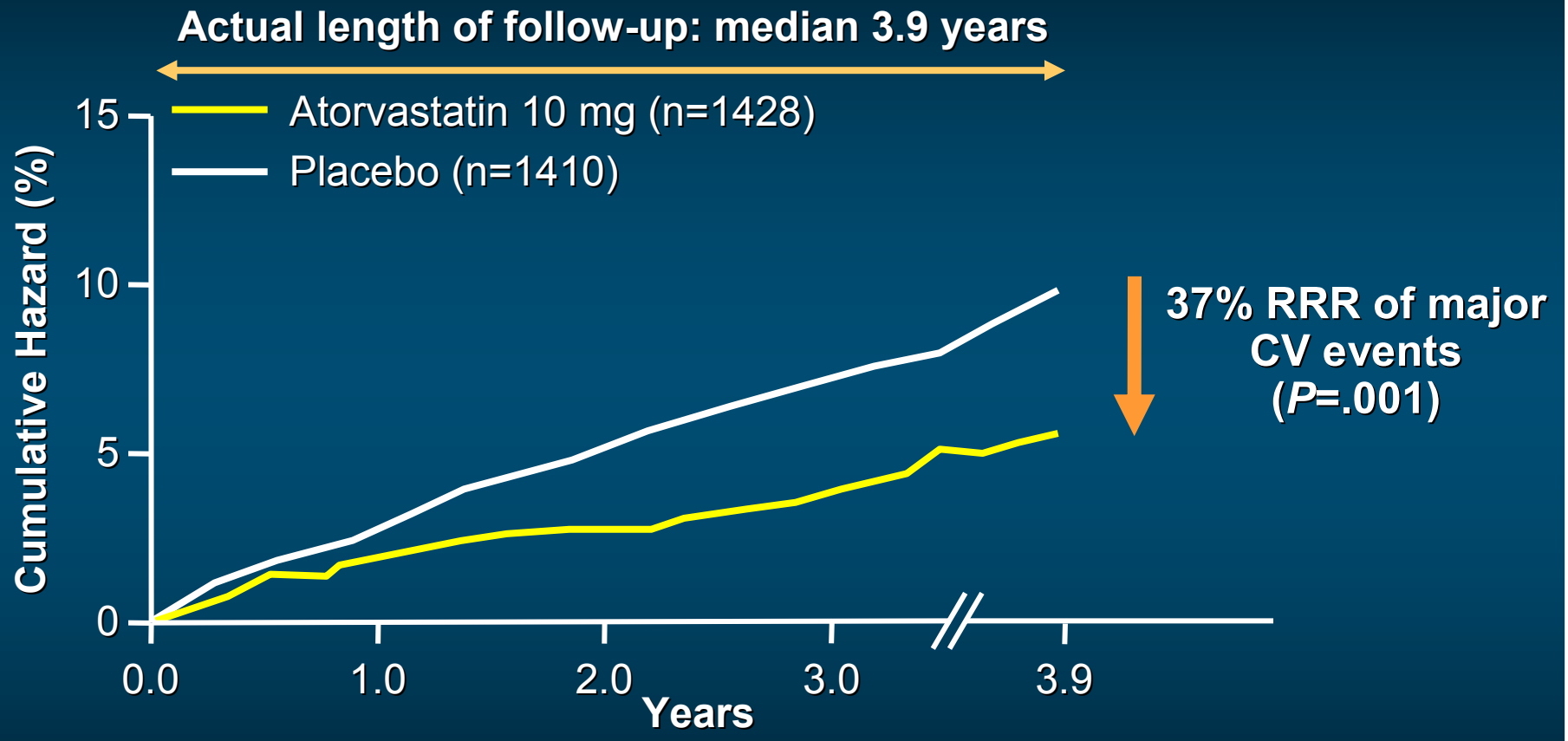
ascot

Effects of atorvastatin among hypertensive individuals: total stroke



ascot

CARDS: Effects of Atorvastatin on Major Cardiovascular Events in Patients With Diabetes



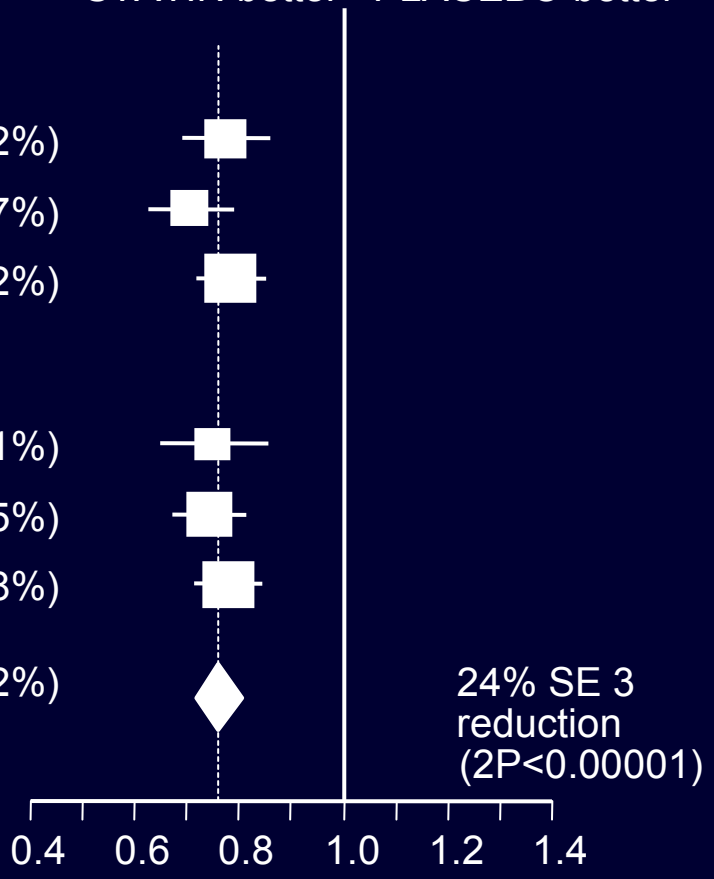
Patients had no history of CVD and slightly elevated LDL-C levels

*Primary end point=time to first occurrence of the following: acute CHD events, coronary revascularization, or stroke.

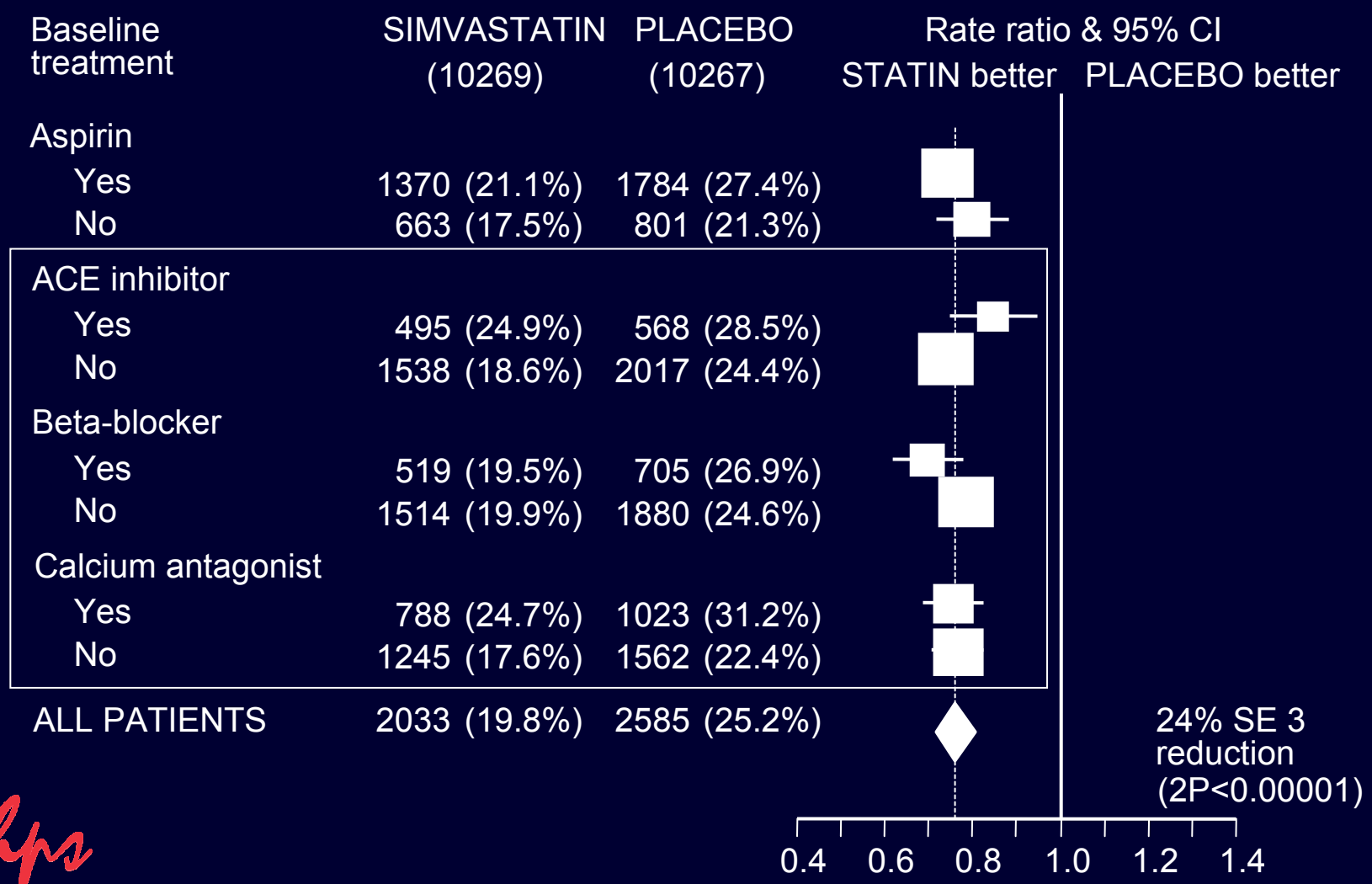
Colhoun et al. *Diabet Med*. 2002;19:201-211.
Colhoun et al. *Lancet*. 2004;364:685-696.

Effects on major cardiovascular events
by baseline cholesterol

Lipid levels at entry	SIMVASTATIN (10269)	PLACEBO (10267)
LDL cholesterol (mmol/l)		
< 3.0 (116 mg/dl)	598 (17.6%)	756 (22.2%)
≥ 3.0 < 3.5	484 (19.0%)	646 (25.7%)
≥ 3.5 (135 mg/dl)	951 (22.0%)	1183 (27.2%)
Total cholesterol (mmol/l)		
< 5.0 (193 mg/dl)	360 (17.7%)	472 (23.1%)
≥ 5.0 < 6.0	744 (18.9%)	964 (24.5%)
> 6.0 (323 mg/dl)	929 (21.6%)	1149 (26.8%)
ALL PATIENTS	2033 (19.8%)	2585 (25.2%)

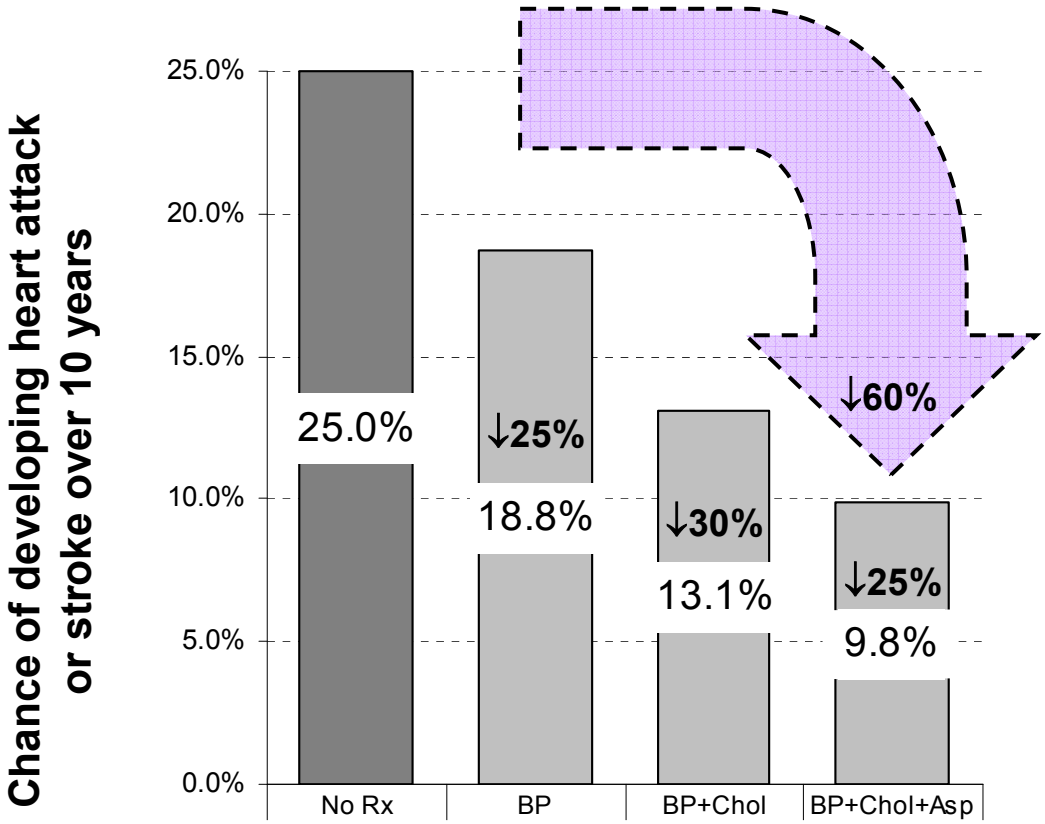


Effects on major cardiovascular events
by ancillary treatment

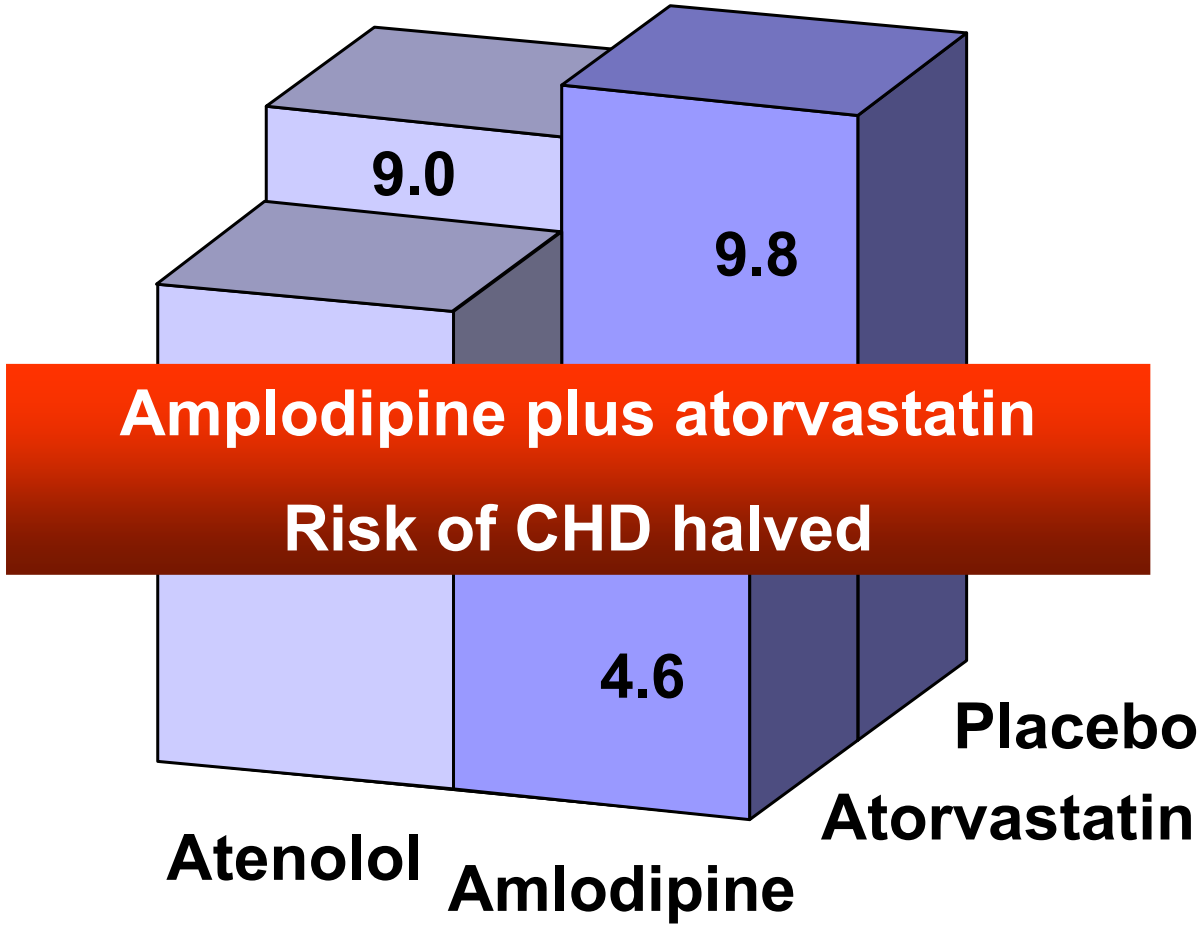


Rationale for multi-factorial intervention

10 mmHg reduction in SBP reduces risk by about 25%,
1 mmol/l reduction in cholesterol reduces risk by 30%
Low dose aspirin reduces risk by by 25%
these effects are *independent* of one other



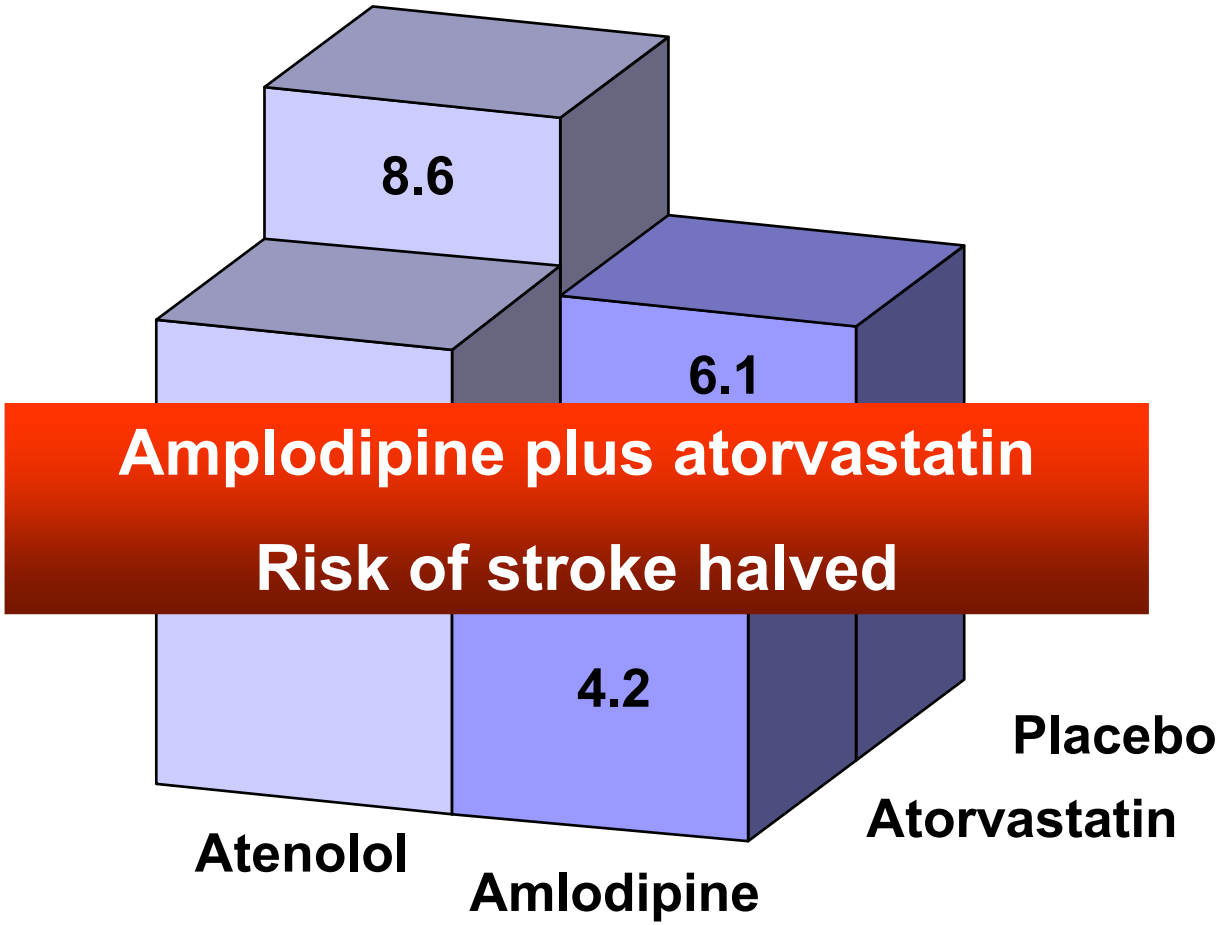
Total major coronary events



Interaction p=0.025

Sever *Circ* 2005;112:134A

Total stroke

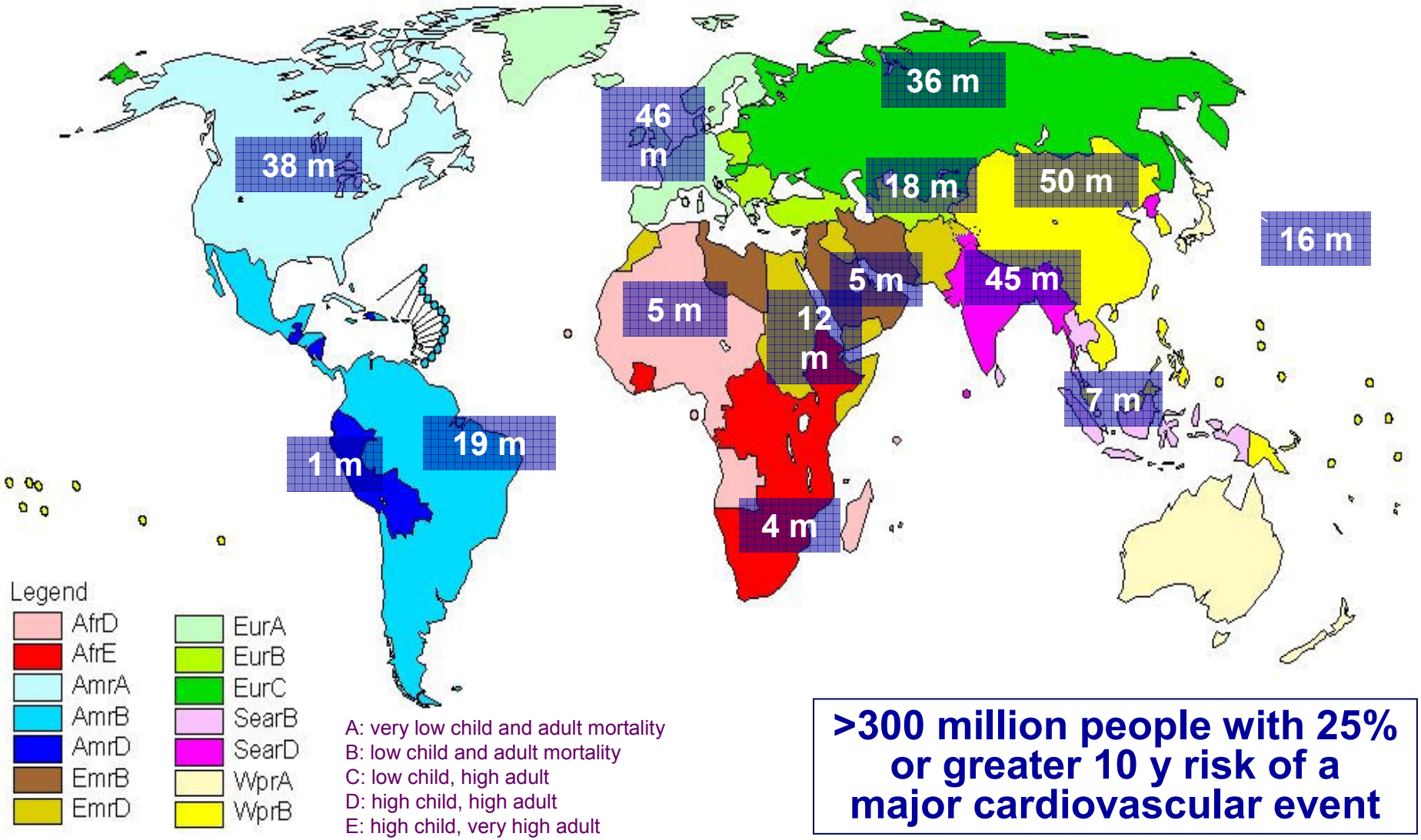


Interaction p=0.73

Sever *Circ* 2005;112:134A

ascot

Number of people worldwide at high cardiovascular risk in 2000



A: very low child and adult mortality
B: low child and adult mortality
C: low child, high adult
D: high child, high adult
E: high child, very high adult

>300 million people with 25% or greater 10 y risk of a major cardiovascular event

Conclusions (I)

- Large-scale epidemiological studies
  - Blood pressure continuously associated with stroke and coronary disease risks (from SBP 110 mmHg)
  - Cholesterol continuously associated with stroke and coronary disease risks (from TC 4 mmol/l))
  - Effects of these two risk factors are multiplicative
  - At age 40y, modest elevations in SBP (150 mmHg) and total cholesterol (6.7 mmol/l) increase coronary disease risks 3-4 fold

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Equivalent to risks associated with diabetes

Conclusions (II)

- Large-scale clinical trials
  - Blood pressure lowering with diuretic, ACEI, CCB or ARB-based therapy reduces risks of major cardiovascular events
  - Cholesterol lowering with statins reduces risks of major cardiovascular events
  - Effects are directly related to size of risk factor reduction
  - Effects of two treatments are multiplicative
  - 10 mmHg reduction in SBP and 1 mmol/l reduction in total cholesterol will lower cardiovascular risks by about half