

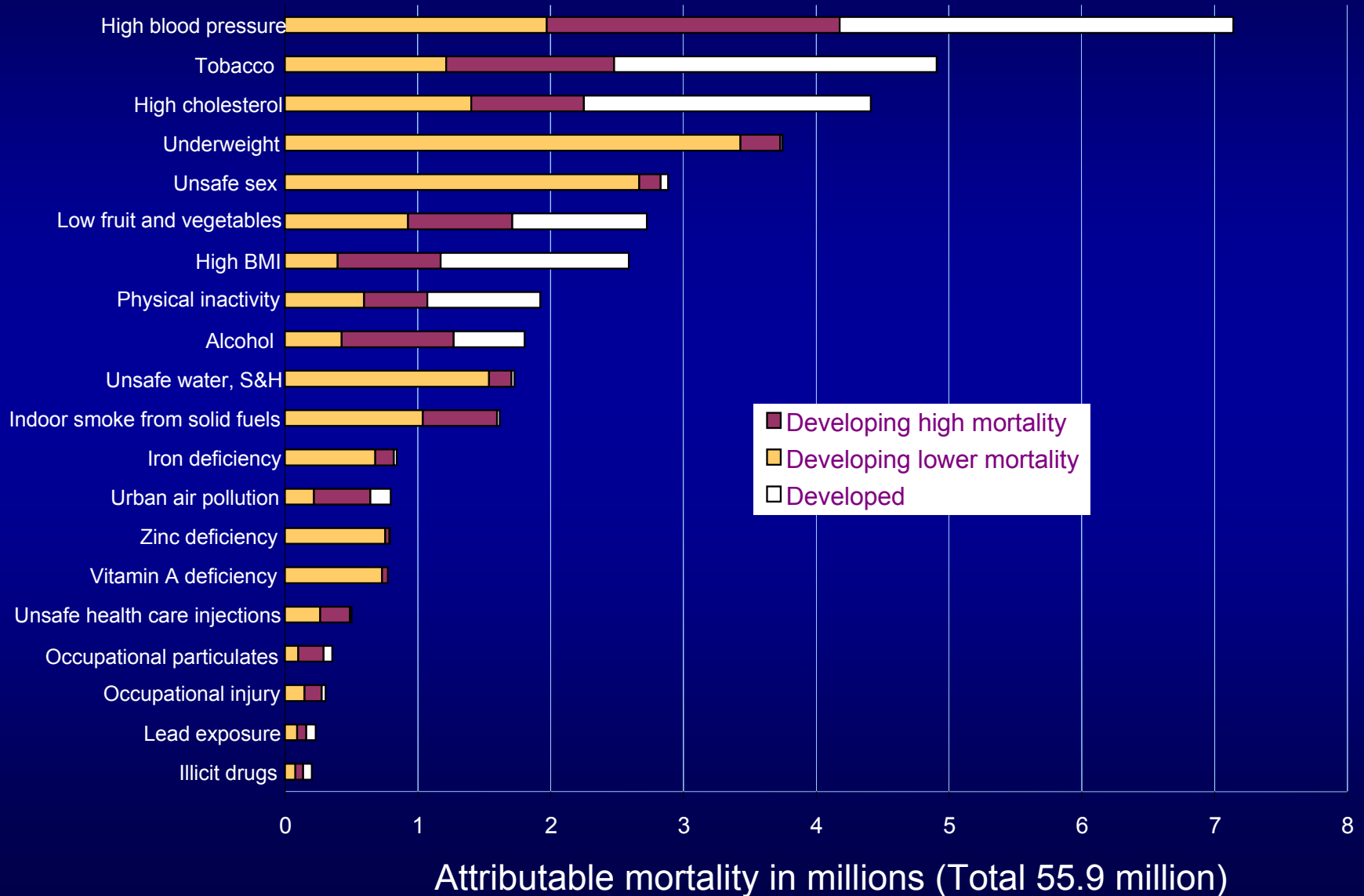
Is there a mechanism of interaction between hypertension and dyslipidaemia?

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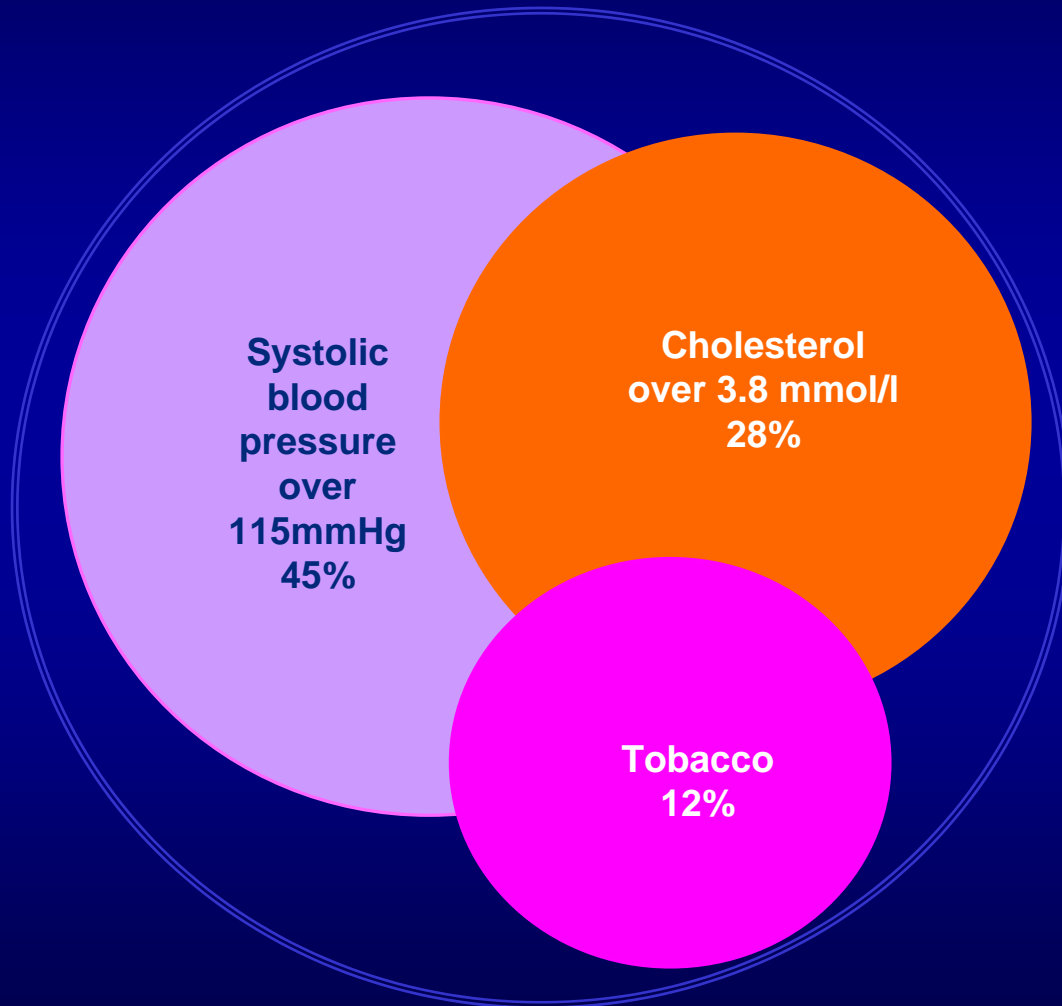
Daegu, Korea
April 2005

Observational data

Global distribution of mortality attributable to 20 leading selected risk factors



Global cardiovascular disease burden due to 6 major risk factors



Systolic pressure > 115mmHg	45%
Cholesterol > 3.8 mmol/l	28%
Fruit & vegetable < 600g/day	16%
Body mass index > 21 kg/m²	15%
Tobacco	12%
Physical inactivity	11%

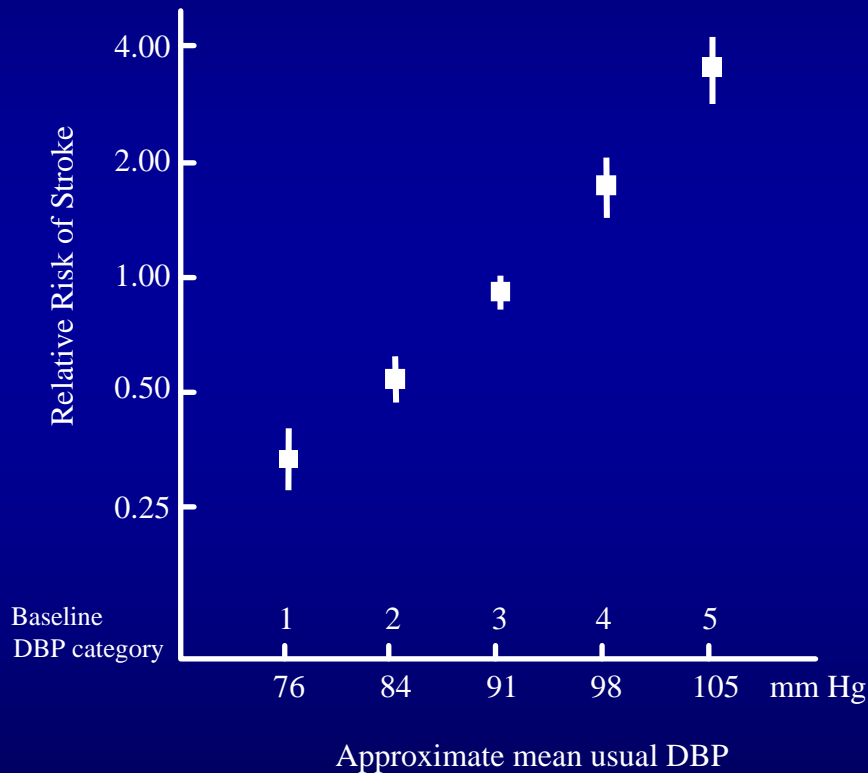
Area proportional to population attributable fraction for global DALYs, overlap approx. proportional to joint effects

Relative risk of stroke and of CHD increases with increasing DBP

Stroke and usual DBP

(in 5 categories defined by baseline DBP)

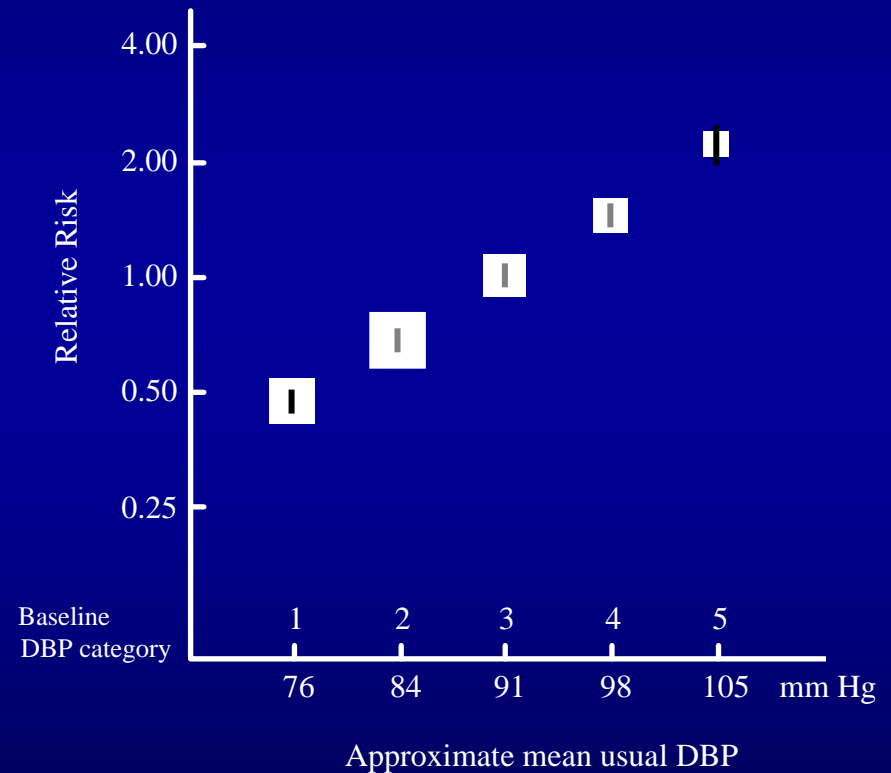
7 prospective observational studies: 843 events



Coronary Heart Disease and usual DBP

(in 5 categories defined by baseline DBP)

9 prospective observational studies: 4856 events



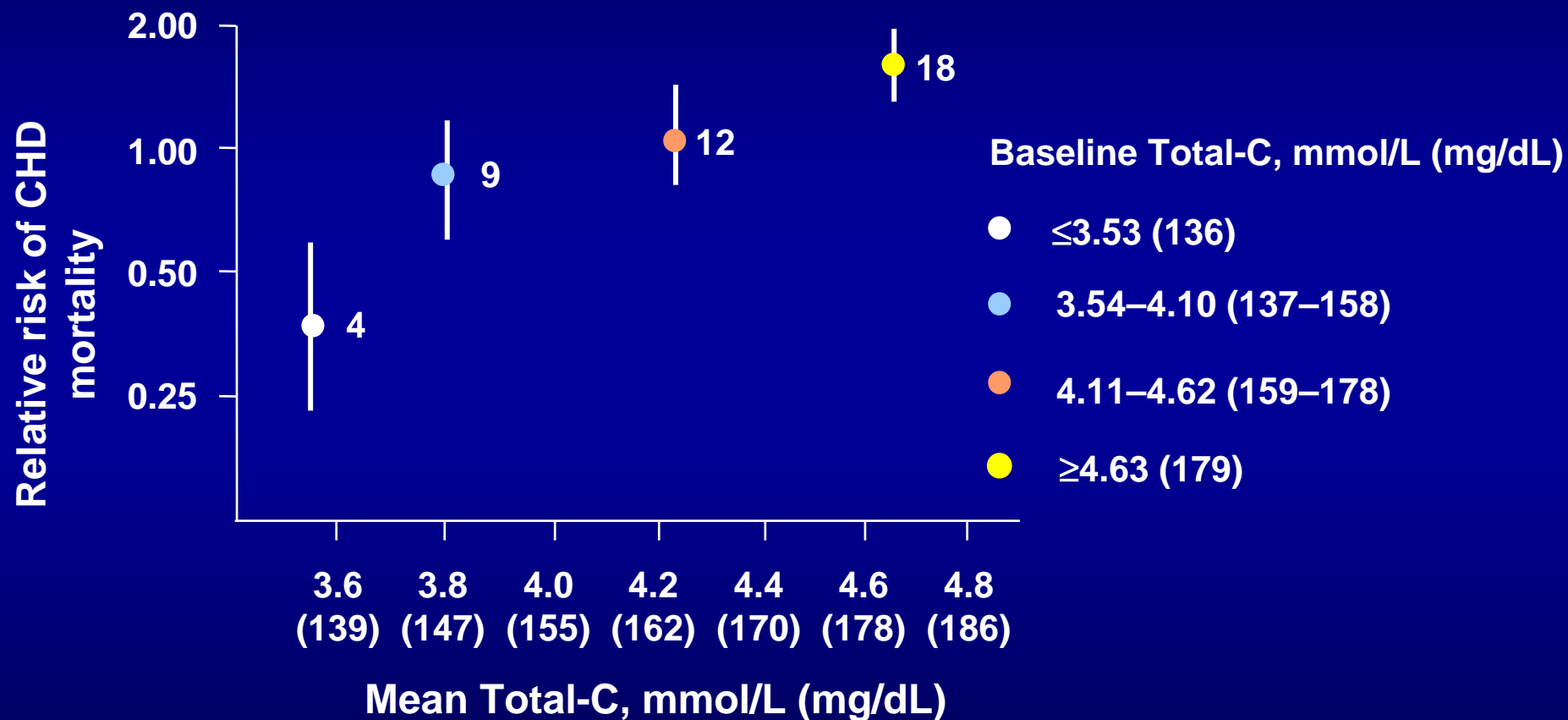
Blood pressure and stroke risk*

Korea 1986-2000

BP range (mmHg)	Stroke type	
	Ischaemic n = 5326	Haemorrhagic n = 2695
<140 / <90	1	1
140-159 / 90-99	2.76	4.90
169-179 / 100-109	4.83	11.55
≥180 / 110	9.56	28.83

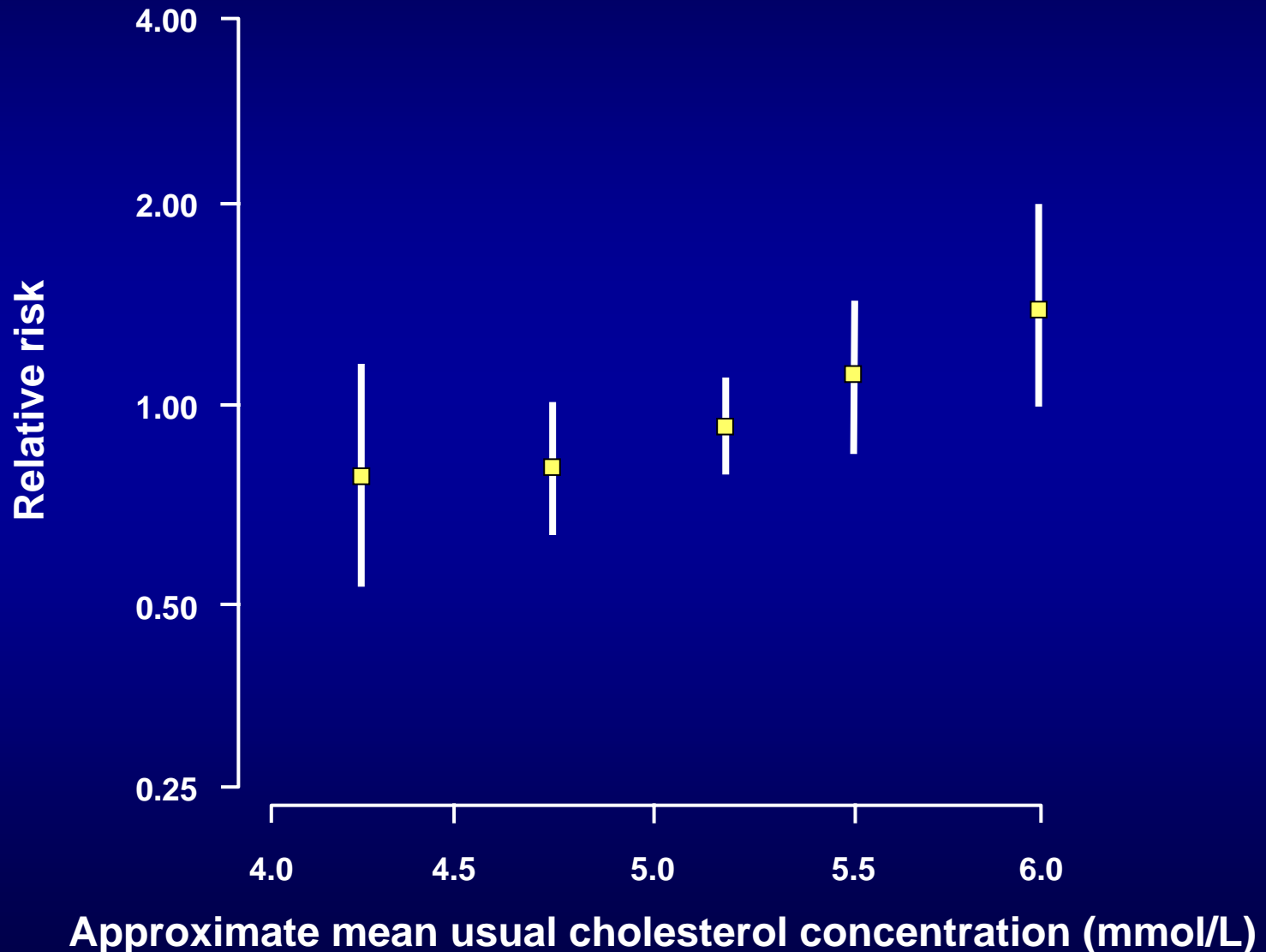
* *Adjusted for multiple risk factors*

Lower cholesterol levels may be associated with lower mortality rates



Data from the Shanghai study, conducted in 9021 Chinese people with 8–13 years' follow up. Numbers of deaths from CHD in each baseline cholesterol group are shown with vertical lines that represent one standard deviation.

Non-haemorrhagic stroke (11 studies, 60,750 participants, 494 events)

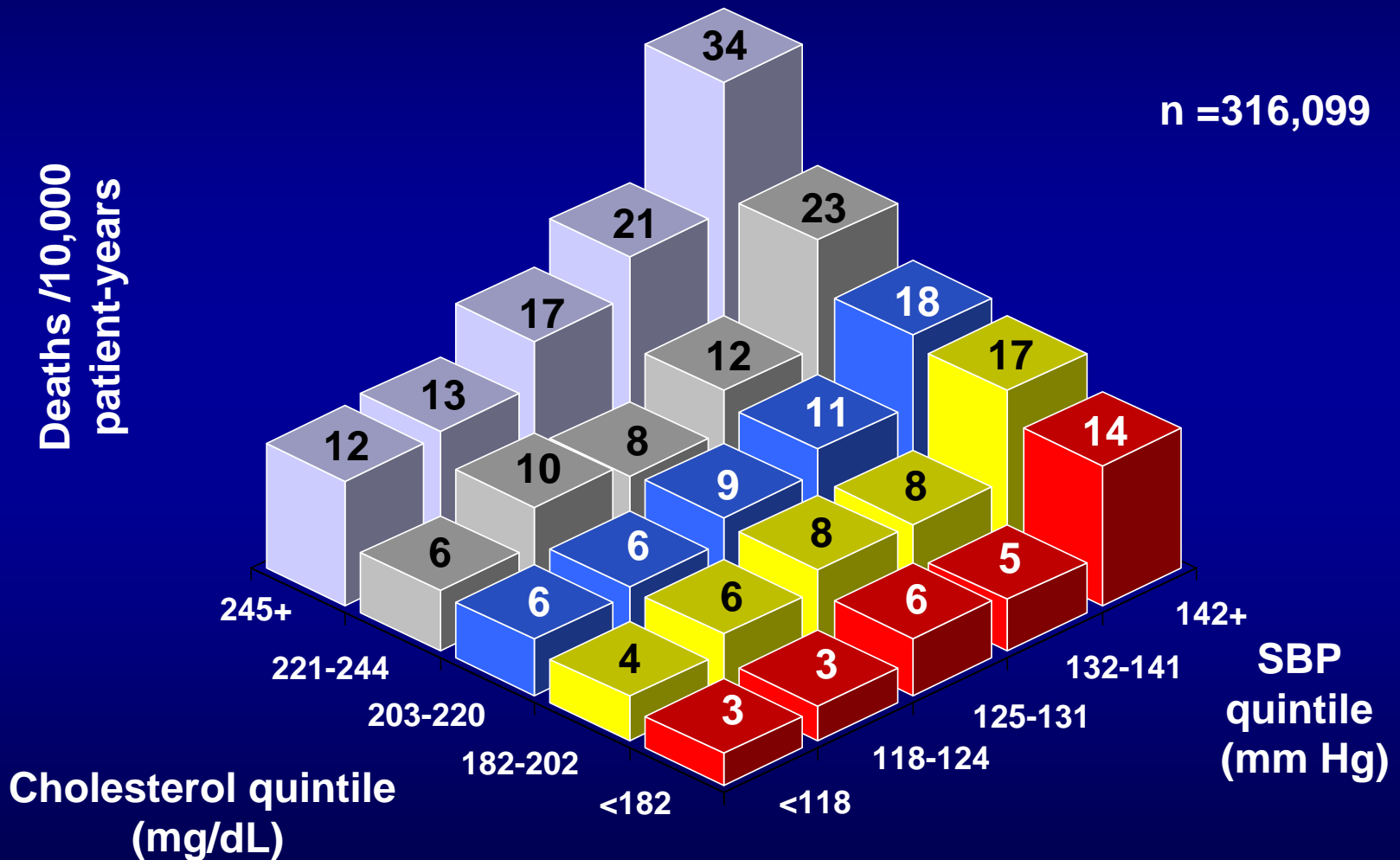


Total cholesterol and risk of CHD and stroke death in 482,472 Korean men aged 30-65: 1990-1996

TC range	Stroke (n = 744)		CHD (n = 394)	
	RR*	95% CI	RR*	95% CI
<135	1.42	0.99-2.03	1.44	0.87-2.38
135-164	1.07	0.84-1.36	0.98	0.69-1.39
165-185	1.00	-	1.00	-
186-210	1.14	0.93-1.41	1.17	0.87-1.57
211-251	1.06	0.85-1.32	1.33	0.99-1.79
≥252	1.20	0.89-1.63	2.42	1.69-3.48

* adjusted

Additive effect of cholesterol and systolic BP on risk of CHD death



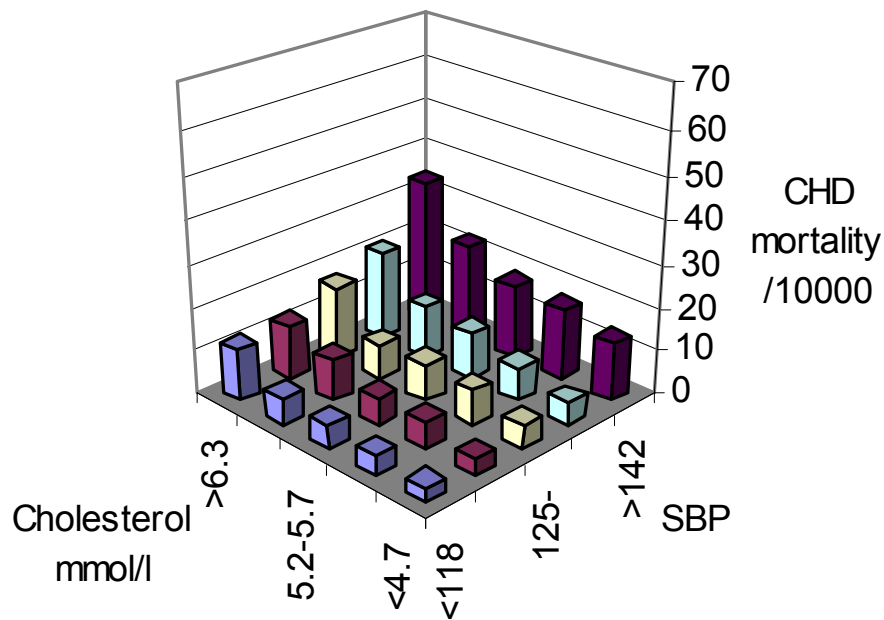
Cholesterol and blood pressure: coexistence

Korean men aged 30-65: 1990-1996

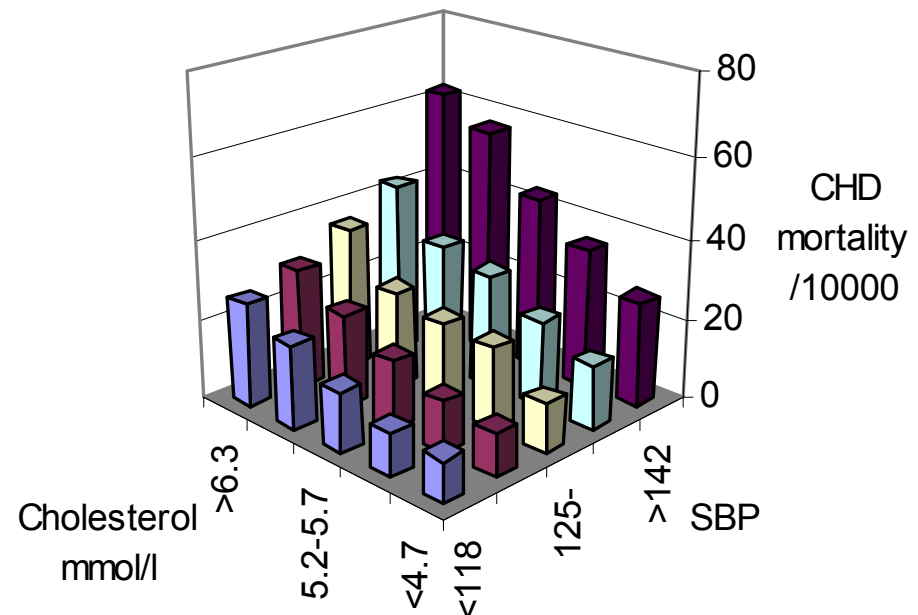
n	Total chol mg/100mL	SBP mmHg	DBP mmHg	% BMI >25Kg/m ²
23890	<135	121.0	79.0	13.9
95060	135-164	121.7	79.5	16.2
118283	165-185	122.7	80.2	19.6
123745	186-210	123.8	81.0	22.9
96511	211-251	125.4	82.3	27.4
24974	≥252	127.7	83.7	32.0

12 year coronary heart disease mortality by blood pressure, cholesterol and smoking status in men 35-64 years

Non smokers



Smokers

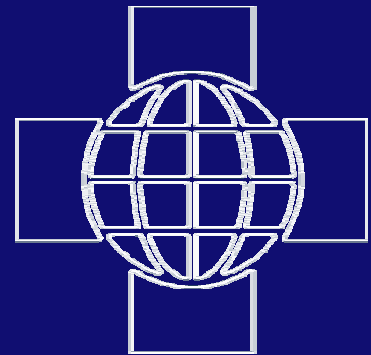


Reversibility of risk

Blood Pressure Lowering Treatment Trialists' Collaboration

Second cycle of overview analyses

**BLOOD
PRESSURE
LOWERING
TREATMENT
TRIALISTS'
COLLABORATION**



Institute
for
International
Health

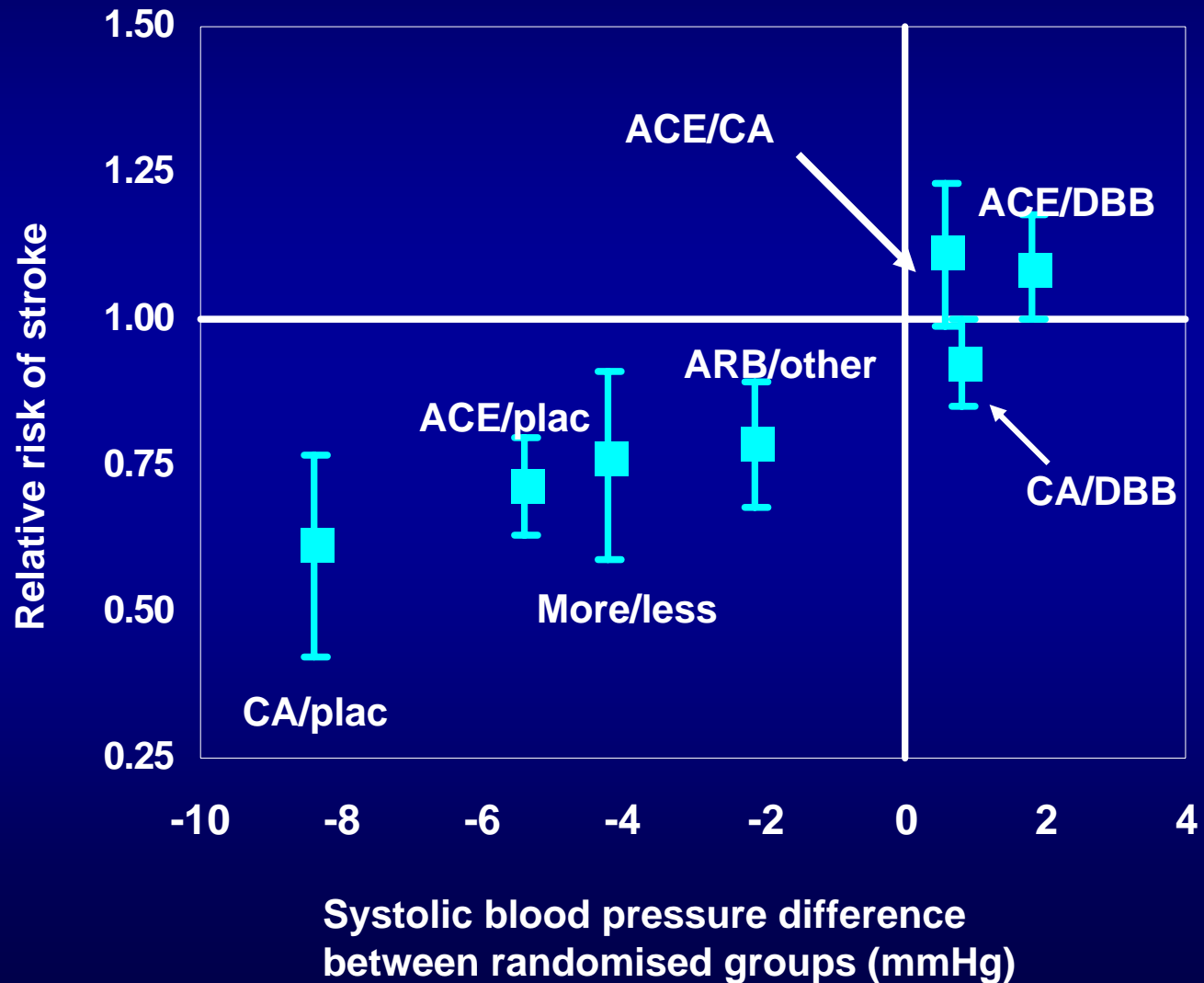
Conclusions I

- Similar net effects on total cardiovascular events of:
 - ACE inhibitors
 - Calcium antagonists
 - Diuretics/beta-blockers
- ARBs also effective in reducing total cardiovascular events

Conclusions III

- Size of blood pressure difference between randomised groups closely associated with reduction in risk (except for heart failure)
- Size of blood pressure reduction appears to be a more important determinant of outcome than drug choice

Stroke



Lipid lowering in hypertension

Randomised clinical trials of statins

Trial	1°/2°	Treated Hypertension		Not Hypertensive	
		n	End-point	n	End-point
4S*	2°	1154	-37%	4444	-34%
Care*	2°	1774	-23%	4159	-24%
LIPID*	2°	3758	-15%	9014	-24%
GREACE*	2°	686	-48%	1600	-51%
HPS †	1° +2°	10594	-20%	20536	-24%
PROSPER †	1° +2°	2212	-15%	5804	-15%
WOSCOPS*	1°	1037	?	6595	-31%
AFCAPS/TexCAPS*	1°	1445	-39%	6605	-37%

End-point* CHD †CHD + Stroke



Randomised design

High-risk
hypertensive
patients



Consent /
Randomize
(N = 42,418)



Amlodipine
Chlorthalidone
Doxazosin
Lisinopril

Eligible for lipid-
lowering

Not eligible for
lipid-lowering

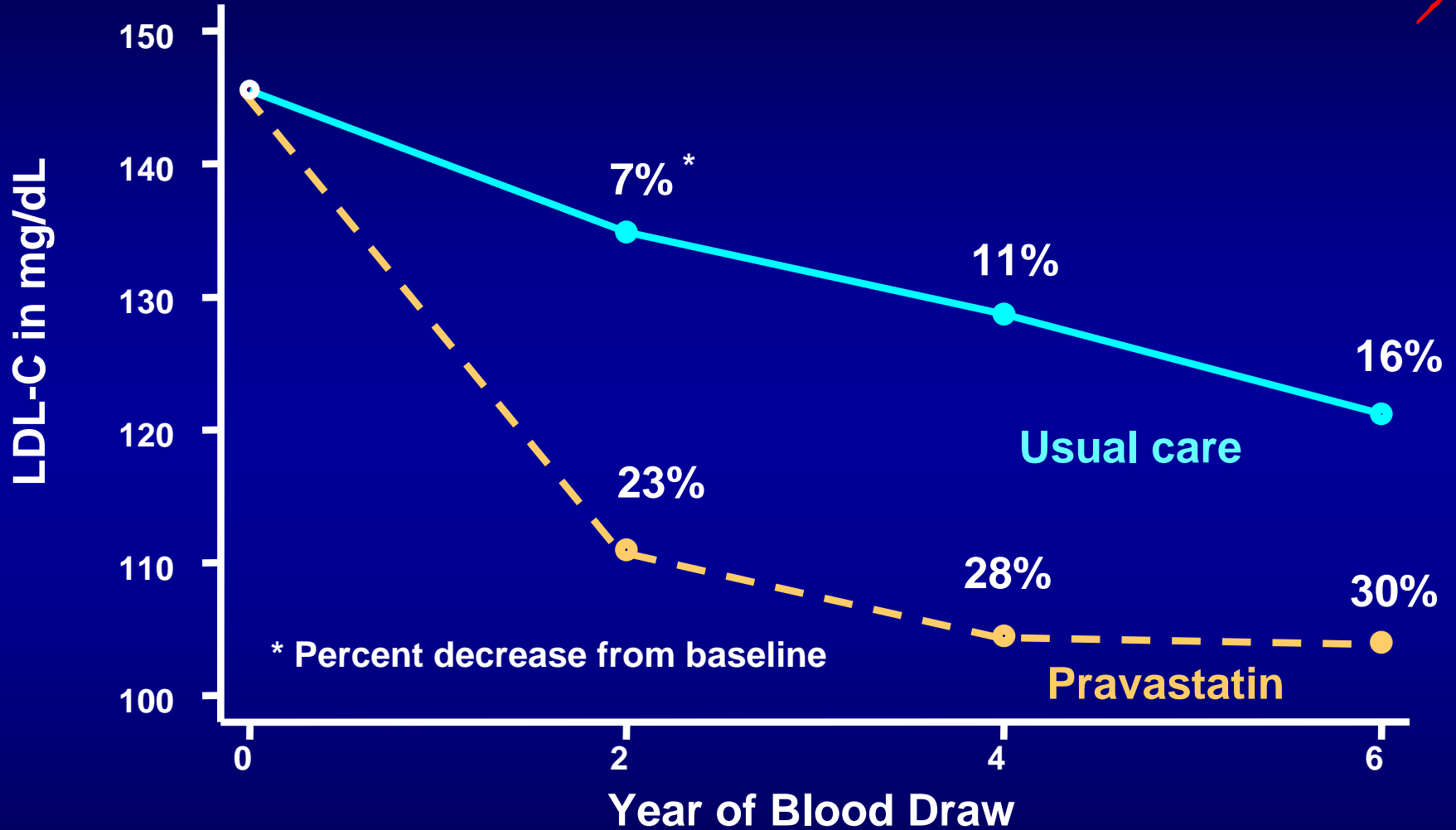
Consent / Randomize (N = 10,355)

Pravastatin

Usual care

Follow until death or end of study (max 7.8 yr, average 4.8 yr).

LDL-C



No. of Participants

Pravastatin	5129	850	572	157
Usual Care	5131	508	330	75

Lipid lowering results: ALLHAT

Pravastatin vs usual care
Non significant reductions (9%) in

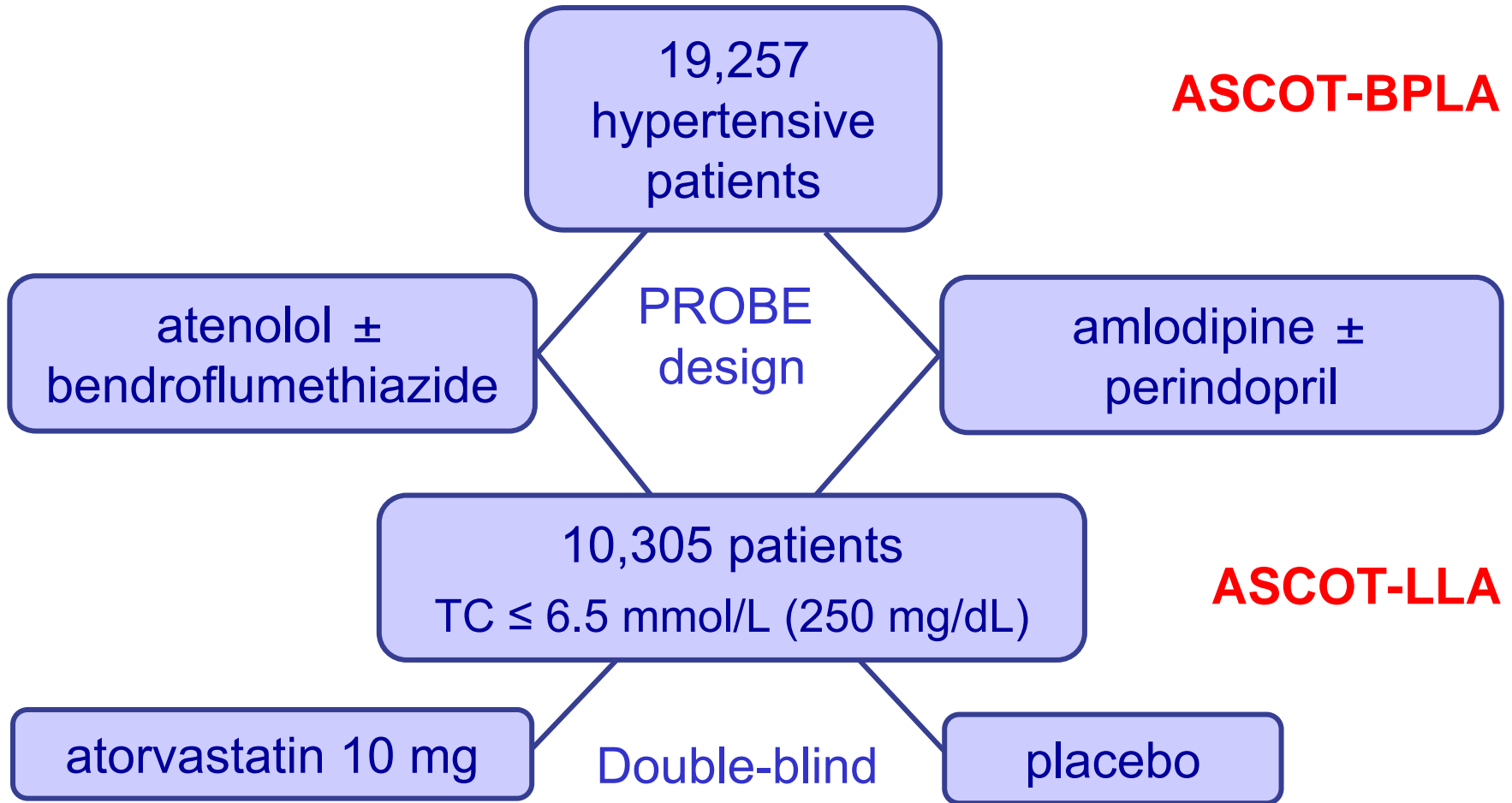
- CHD
- Stroke

“Less is less”



Anglo-Scandinavian
ascot
Cardiac Outcomes Trial

ASCOT Study Design

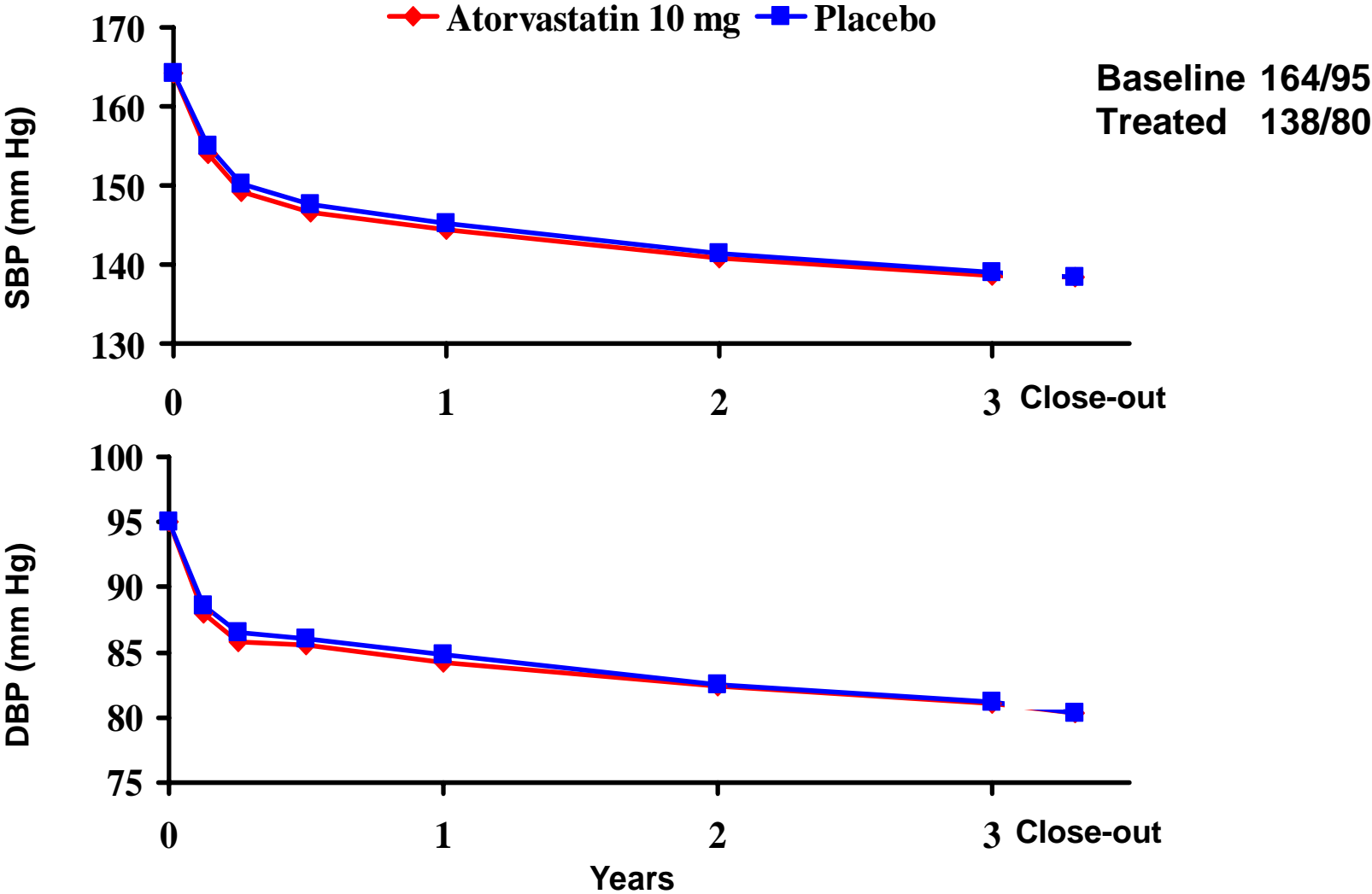


**Investigator-led, multinational
randomized controlled trial**

Patient inclusion criteria

- Screening and baseline BP \geq 160/100 mm Hg untreated, or baseline BP \geq 140/90 mm Hg following treatment with 1 or more drugs
- Age 40-79 years
- ***No previous MI or current clinical CHD***
- 3 or more risk factors for a future CV event
- Total chol \leq 6.5 mmol/l (250mg%) [LLA only]

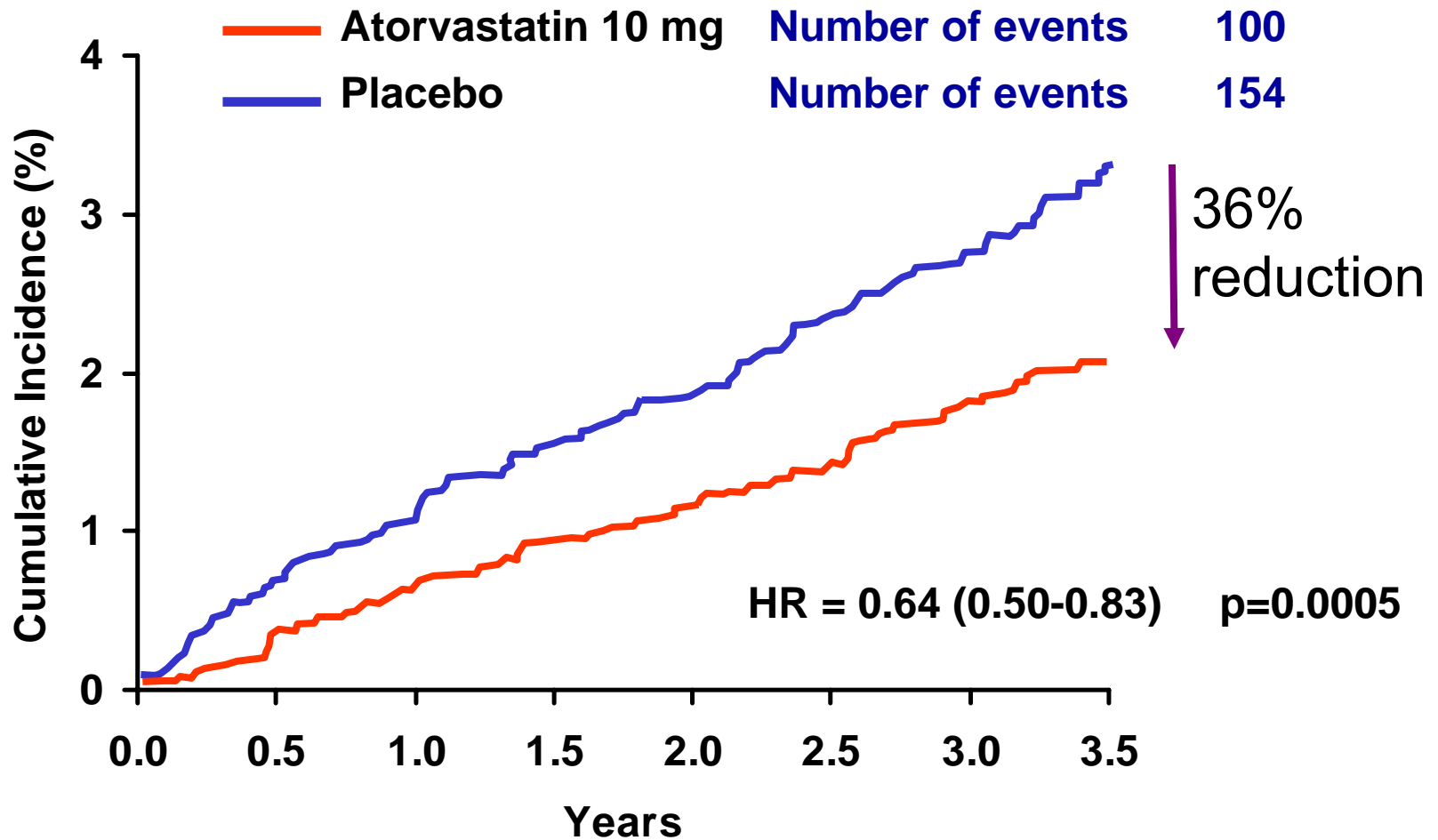
Blood Pressure Changes



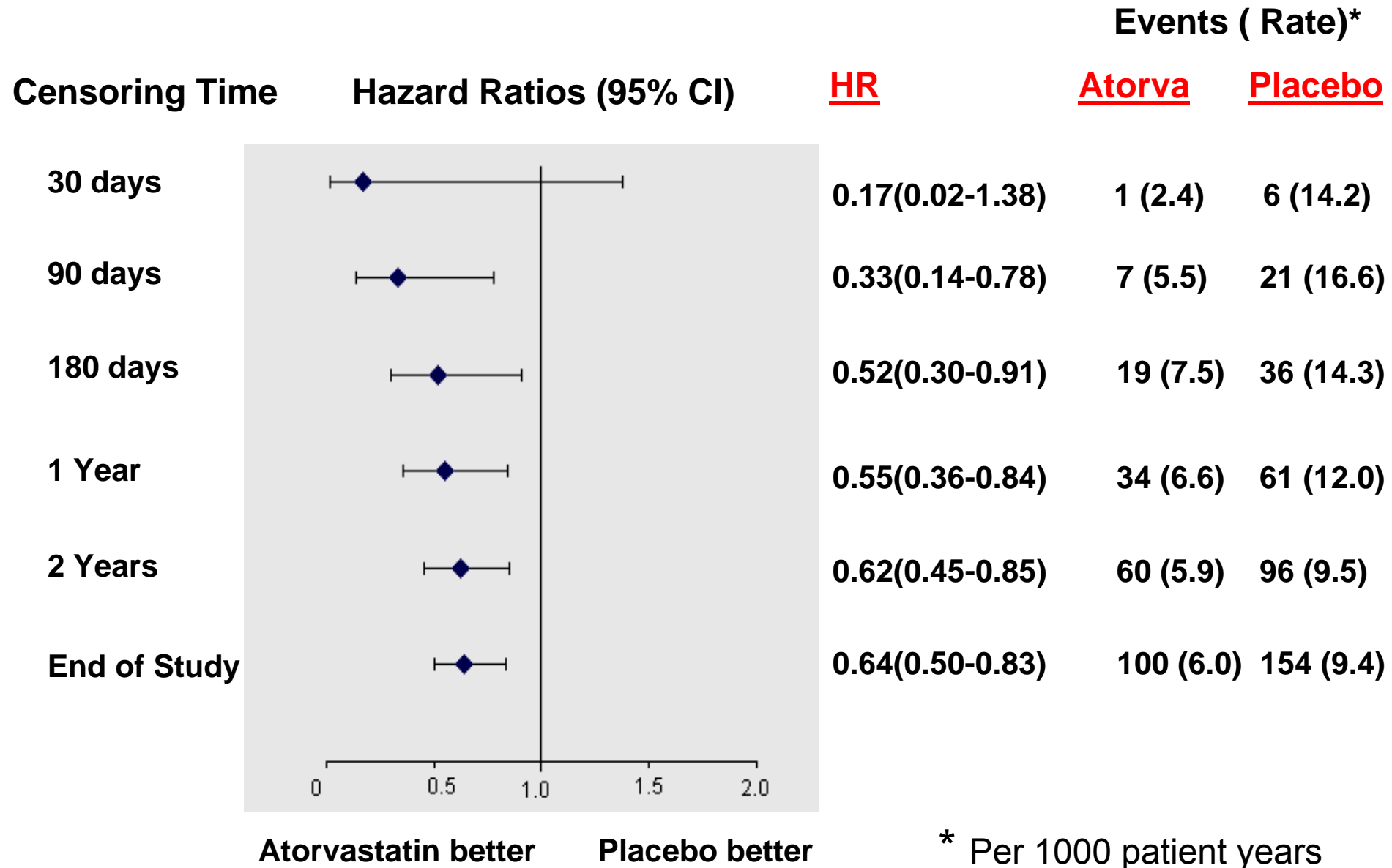
ASCOT LLA: DSMB Recommendation

- The DSMB, in September 2002, reported that in the lipid arm of ASCOT there was a highly significant reduction in the primary end point as well as a significant reduction in stroke.
- The DSMB recommended that the double-blind, cholesterol-lowering study treatment arm be terminated since the results were outside of the stopping rules of the trial.
- The Steering Committee endorsed the recommendation of the DSMB, and the lipid arm was closed after a median follow-up period of 3.3 years; the overall BPLA study is continuing.

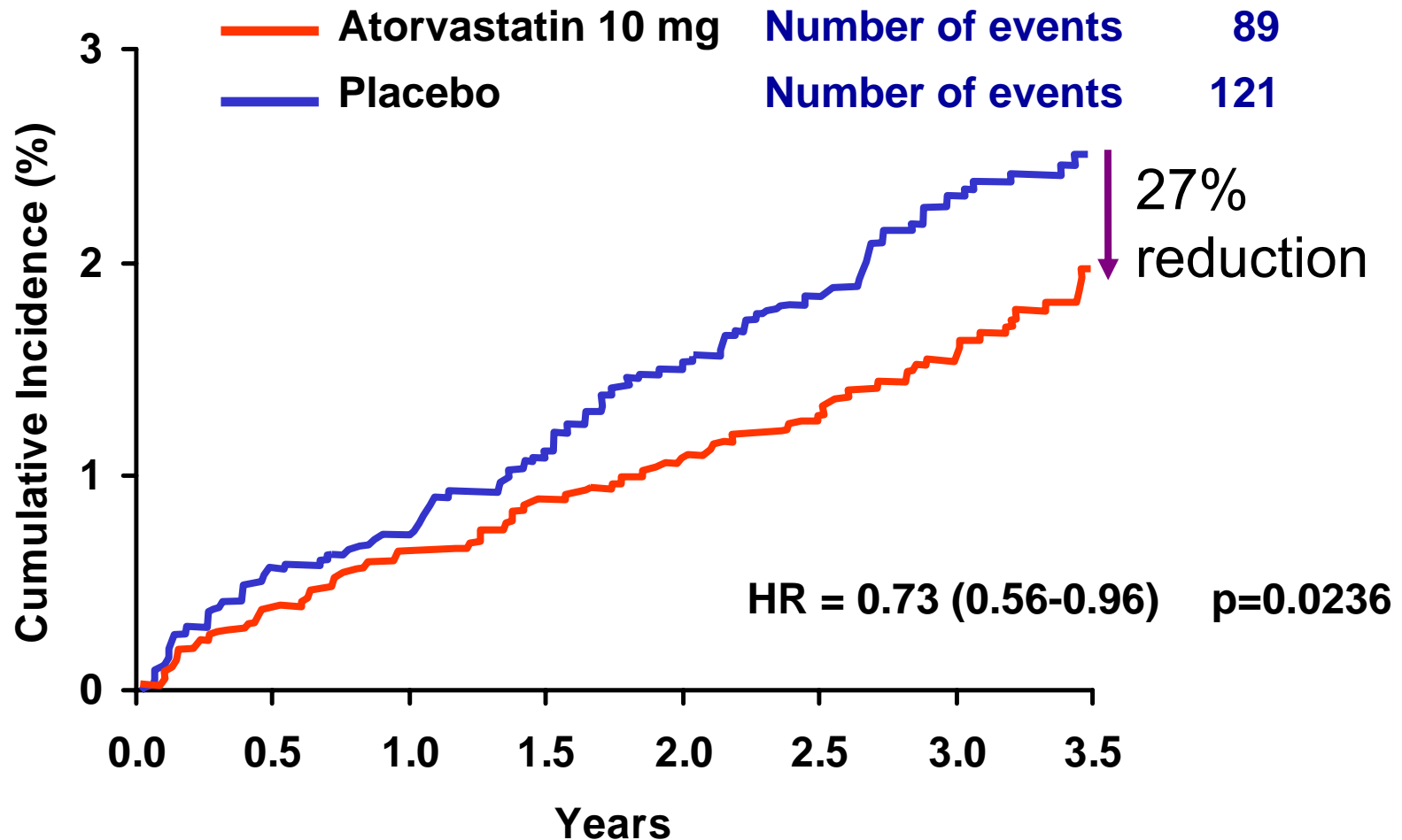
Primary End Point: Nonfatal MI and Fatal CHD



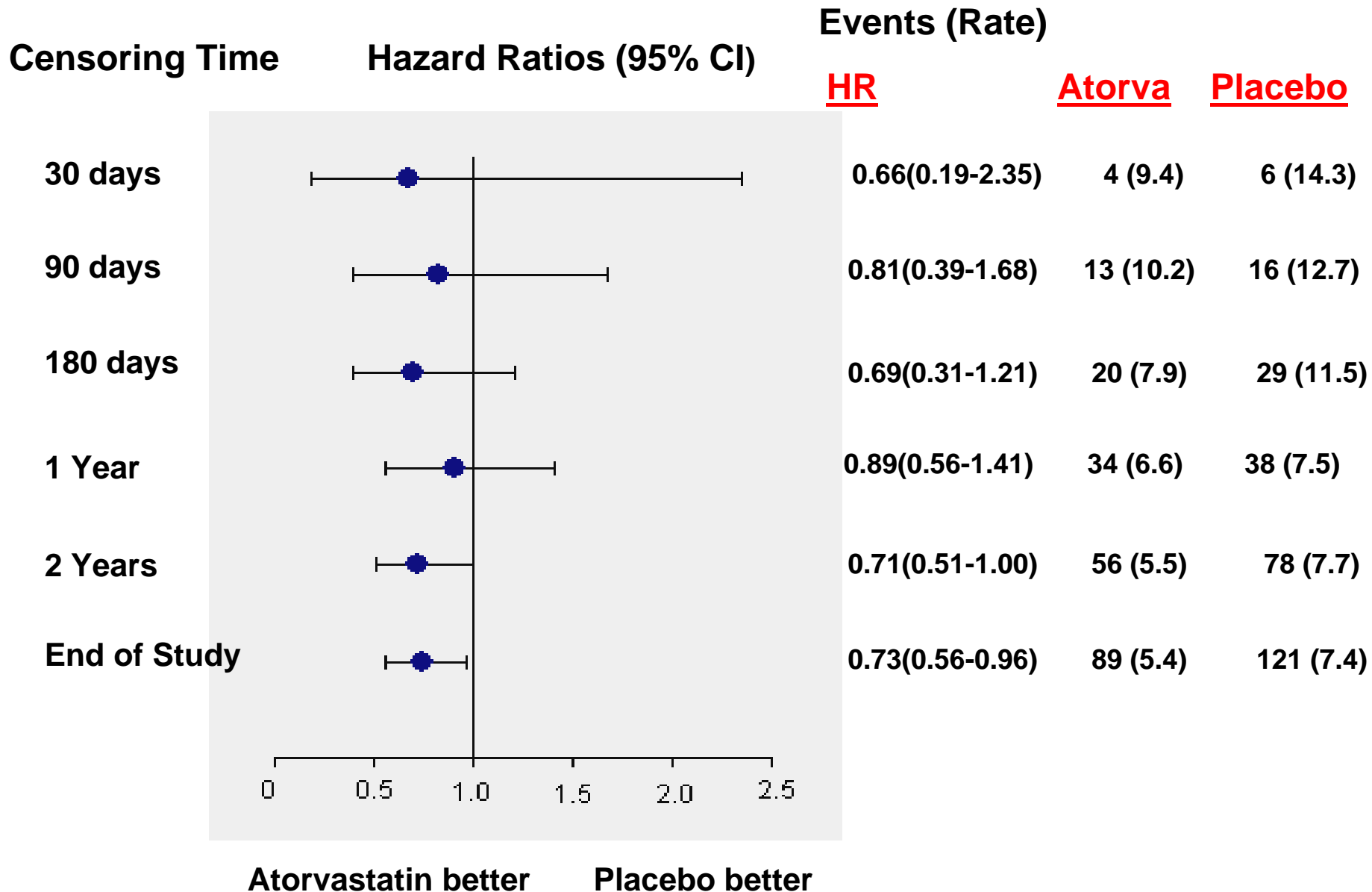
CHD events



Secondary End Point: Fatal and Nonfatal Stroke



Stroke Events



ASCOT: Post hoc analysis of benefit across the cholesterol range

Primary end point (nonfatal MI + fatal CHD):

TC Range mmol/L (mg/dL)	Hazard Ratio	P Value
<5.0 (<193)	0.628	0.098
5.0-5.99 (193-230)	0.615	0.011
6.0-6.5 (231-250)	0.689	0.084

BHS IV: Other medications for hypertensive patients

Primary prevention

(1) Aspirin: use 75mg daily if patient is aged ≥ 50 years with blood pressure controlled to $< 150/90$ mm Hg and either; target organ damage, diabetes mellitus, or 10 year risk of cardiovascular disease of $\geq 20\%$ (measured by using the new Joint British Societies' cardiovascular disease risk chart)

(2) Statin: use sufficient doses to reach targets if patient is aged up to at least 80 years, with a 10 year risk of cardiovascular disease of $\geq 20\%$ (measured by using the new Joint British Societies' cardiovascular disease risk chart) and with total cholesterol concentration ≥ 3.5 mmol/l

(3) Vitamins—no benefit shown, do not prescribe

Recent guidelines for lipid lowering in patients with hypertension: 'Targets' in 1° and 2° prevention

Total cholesterol (TC) <4 mmol/l

LDL cholesterol <2 mmol/l

OR 25% ↓ in TC

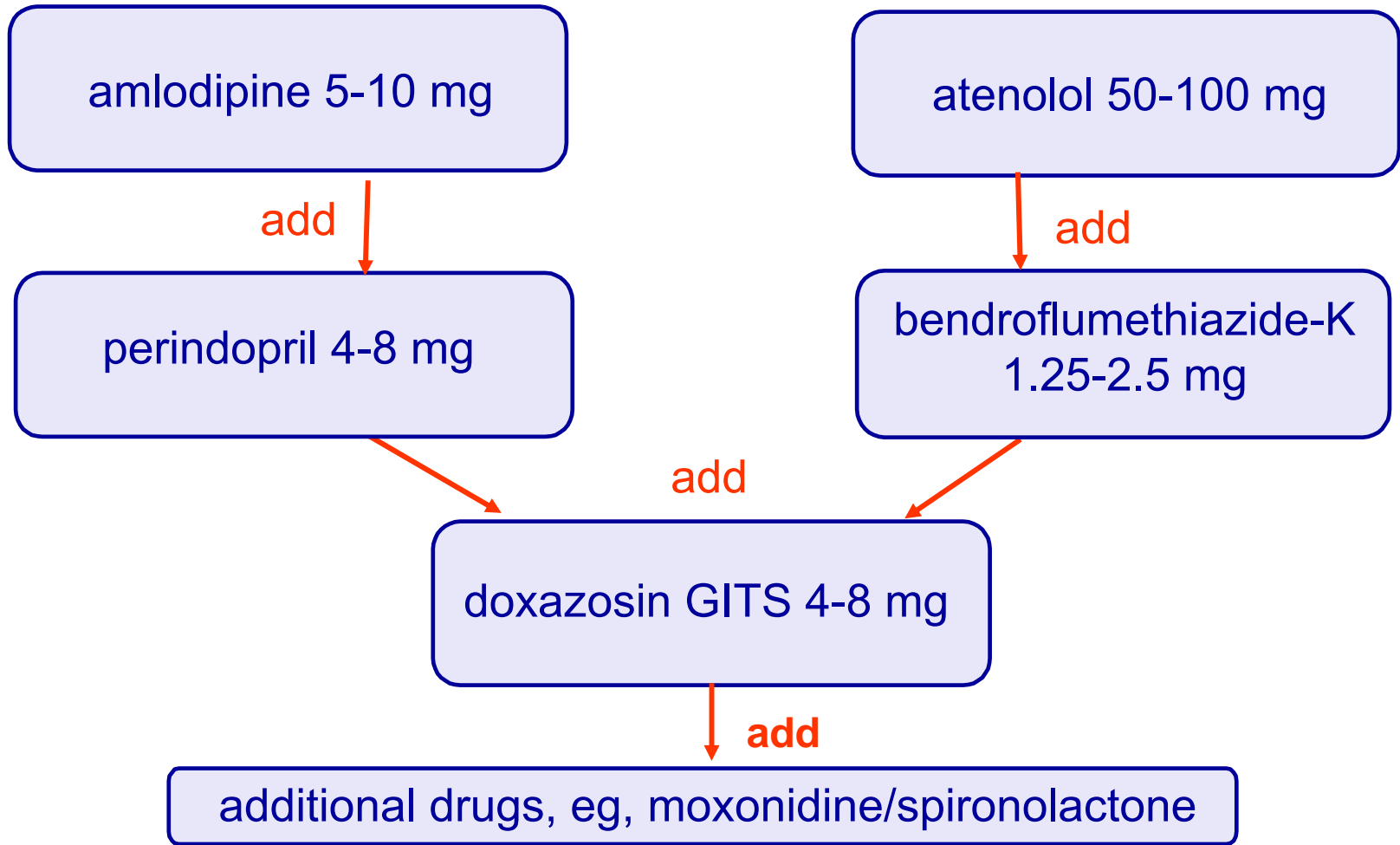
OR 30% ↓ in LDL-C

- whichever is the greater

BHS IV (2004)

ESC-ESH (2003)

Treatment Algorithm to BP Targets < 140/90 mm Hg or < 130/80 mm Hg in Patients with Diabetes



Data Safety Monitoring Board (DSMB)

In October 2004 the DSMB recommended that the BP arm of ASCOT should be stopped on account of concerns that those patients receiving atenolol/thiazide would continue to be disadvantaged compared with the comparator group.

The Steering Committee endorsed the recommendation of the DSMB, and trial closure began December 2004 after a median follow-up period of 5.4 years.

Last ASCOT-BPLA close-out visit anticipated May, 2005

Preliminary results are presented including adjudicated events only, as censored at November 30, 2004

Final results anticipated September, 2005

Number of Adjudicated Events (censored at November 30, 2004)

Primary events	869*
Secondary events	3192
Tertiary events	2581

*In 803 patients (study powered for 1150 patients with primary events)

Compared with Atenolol/thiazide, Amlodipine/perindopril resulted in:

1. For all-cause mortality, a significant reduction of about 15% ($p \leq 0.005$)
2. For the primary endpoint of non-fatal MI and fatal CHD, a non-significant reduction of about 10%
3. For all coronary events, a significant reduction of about 15% ($p \leq 0.005$)
4. For all fatal and non-fatal stroke, a significant reduction of about 25% ($p \leq 0.001$)

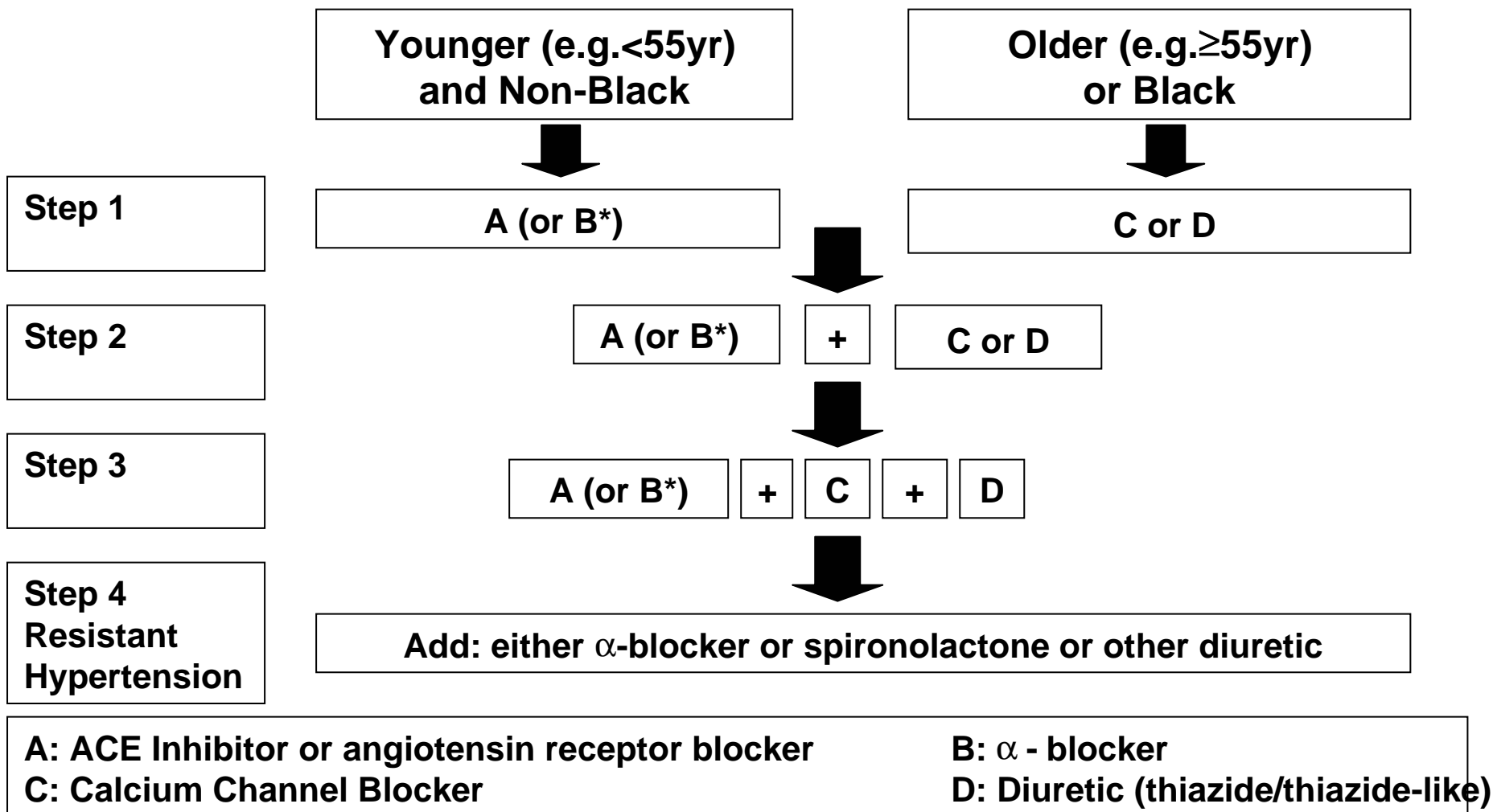
Compared with Atenolol/thiazide, Amlodipine/perindopril resulted in: (cont'd)

5. For all CV events and procedures a significant reduction of about 15% ($p \leq 0.001$)
6. For CV mortality, a significant reduction of about 25% ($p \leq 0.005$)
7. For new-onset diabetes, a significant reduction of about 30% ($p \leq 0.001$)

First line therapy

JNC VII	ESH-ESC	WHO-ISH	BHS IV 2004
Thiazide-type Di	Any of 5 (A,A,B,C,D)	Low dose Di	AB/CD
2 drug combo	2 drug combo	---	---
Compelling indication for others	Compelling indication for others	Compelling indication for others	Compelling indication for others

The British Hypertension Society recommendations for combining Blood Pressure Lowering drugs



* Combination therapy involving B and D may induce more new onset diabetes compared with other combination therapies

Recent guidelines for lipid lowering in patients with hypertension

'Thresholds' in 1° prevention

“In view of the results of the ASCOT trial and other currently available trial data, it seems reasonable, in the interests of simplicity, to treat with a statin, all those patients at least up to the age of 80 years with a total cholesterol $>3.5\text{mmol/l}$ who have an estimated 10 year CVD risk of 20% or more. In reality, this would mean considering statin therapy in most hypertensive patients (especially men) over the age of 50 years. As resources allow, a rationale for lowering this threshold could be made on the basis of trial evidence.”

BHS IV (2004)
ESC-ESH (2003)