Hypertension Highlights: The New British Hypertension Society- NICE Guideline 2006

Seoul, 12th October 2006

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Boehringer Ingelheim, Merck, Schering Plough, Servier

EUROPEAN SOCIETY OF CARDIOLOGY®

BHS


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North Sea
Glasgow
Edinburgh
UNITED KINGDOM
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IRELAND
ENGLAND
WALES
London
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Ocean
I. of Lewis
Stornoway
North Sea
Shetland Is.
The Minch
Loch Shin
Dornoch Firth
Moray Firth
Hebrides Is.
HIGHLANDS
Fraserburgh
Inverness
Peterhead
I. of Skye
Loch Ness
Aberdeen
SCOTLAND
GRAMPIAN MTS.
Dee
Ben Nevis
Loch Tay
Tay
Dundee
Loch Lomond
Perth
Firth of Tay
I. of Mull
Firth of Lorne
Glenrothes
St. Andrews
Forth
Kirkcaldy
Stirling
Firth of Forth
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Glasgow
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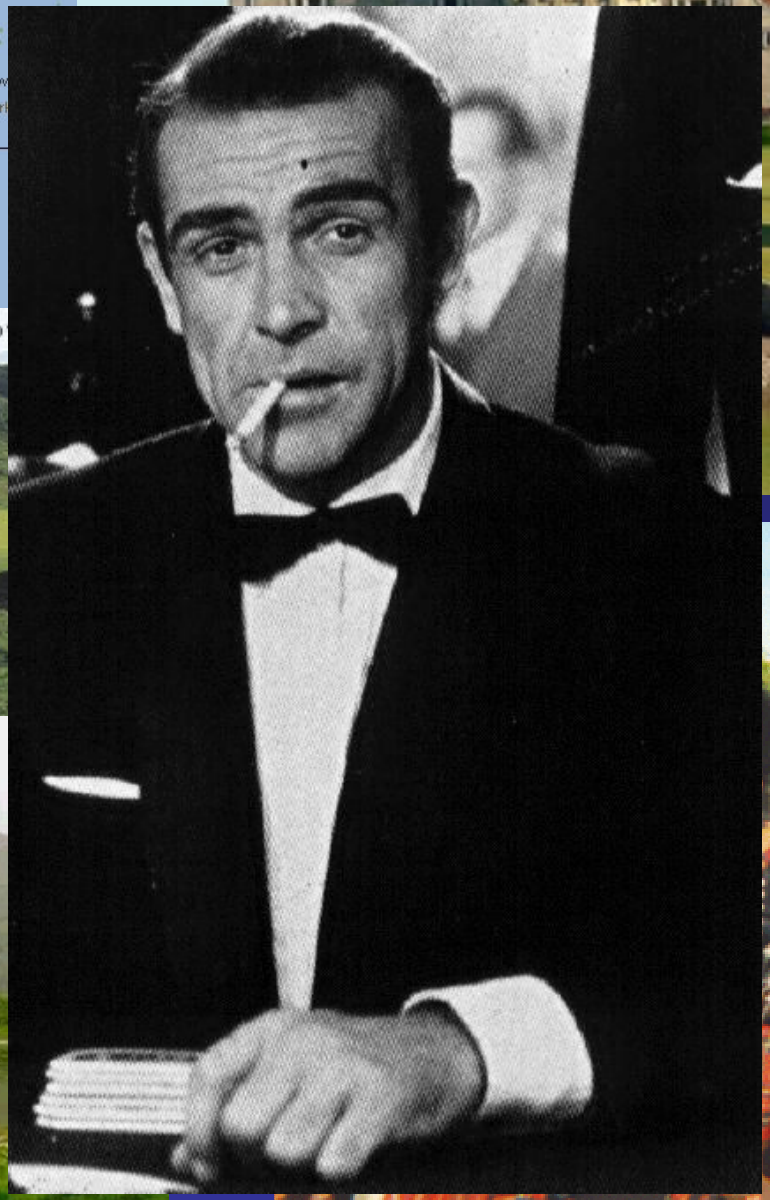
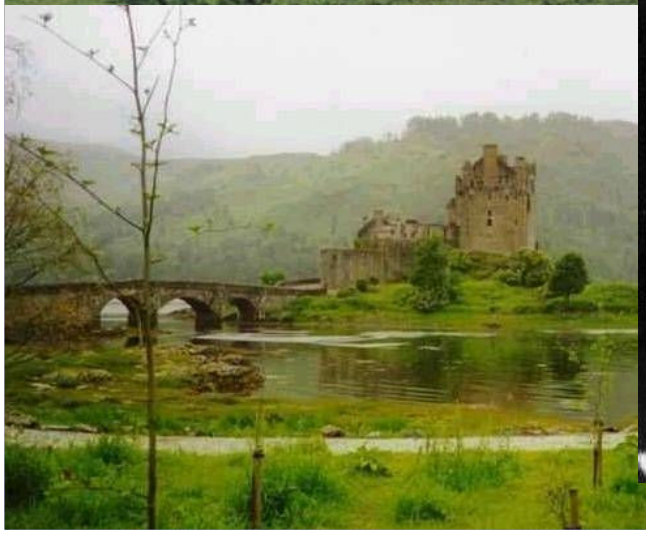
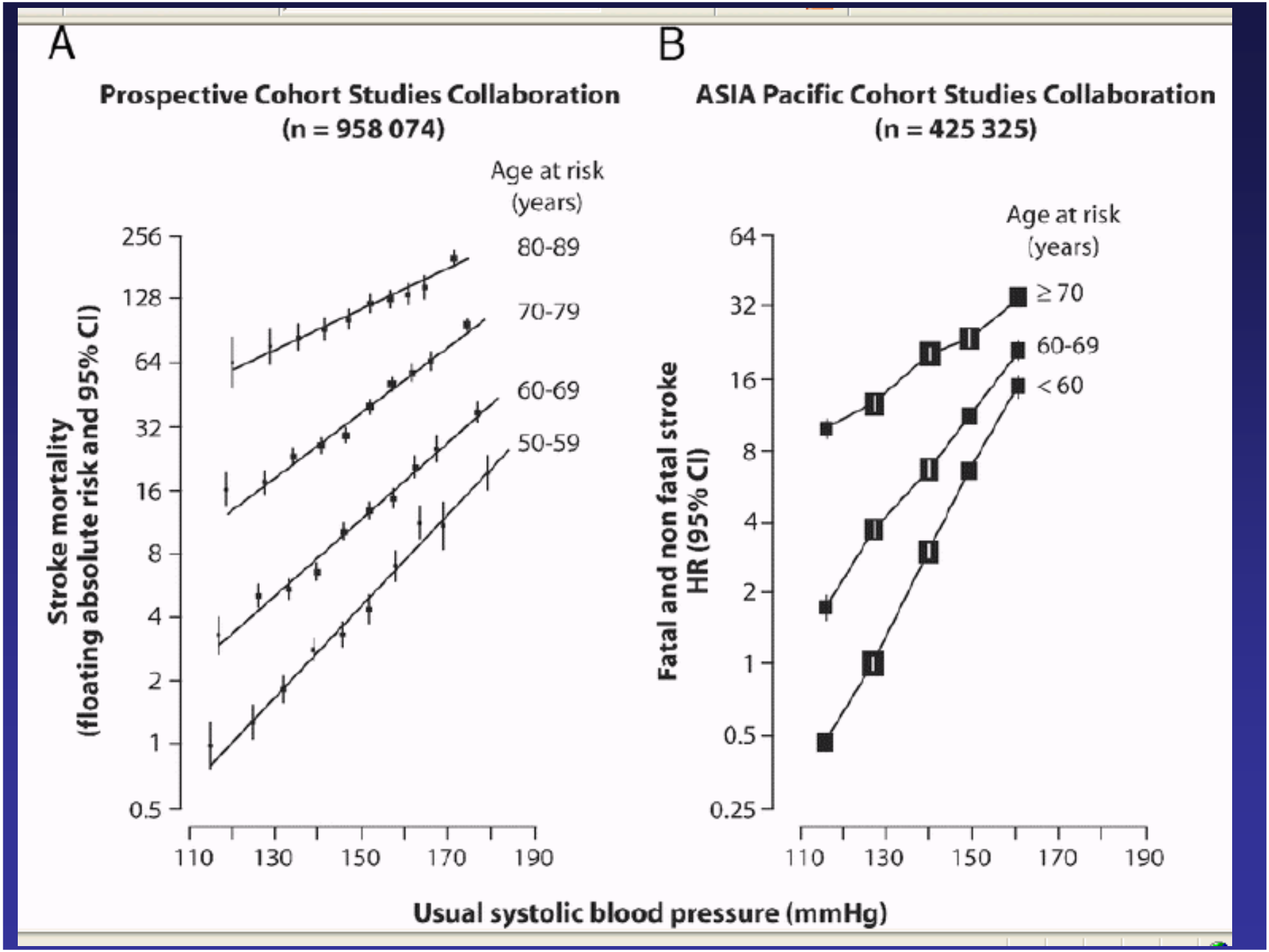
CENTRAL LOWLANDS
Kilmarnock
Clyde
Tweed
Newtown St. Boswells
IRELAND
Firth of Clyde
Ayr
SOUTHERN UPLANDS
CHEVIOT HILLS


GLENMORANGIE
SINGLE HIGHLAND
MALT SCOTCH WHISKY
18



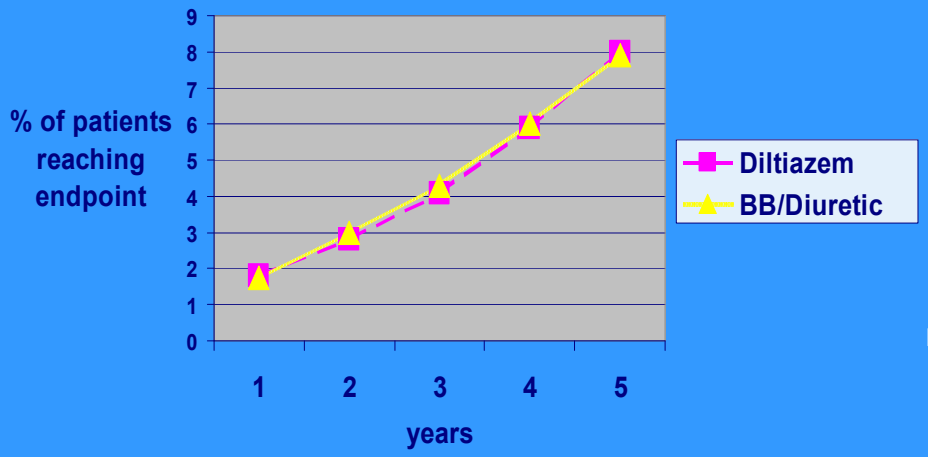



A
Prospective Cohort Studies Collaboration
(n = 958 074)
Age at risk
(years)
80-89
70-79
60-69
50-59
Stroke mortality
(floating absolute risk and 95% CI)
256
128
64
32
16
8
4
2
1
0.5
110
130
150
170
190
B
ASIA Pacific Cohort Studies Collaboration
(n = 425 325)
Age at risk
(years)
≥ 70
60-69
< 60
Fatal and non fatal stroke
HR (95% CI)
64
32
16
8
4
2
1
0.5
0.25
110
130
150
170
190
Usual systolic blood pressure (mmHg)

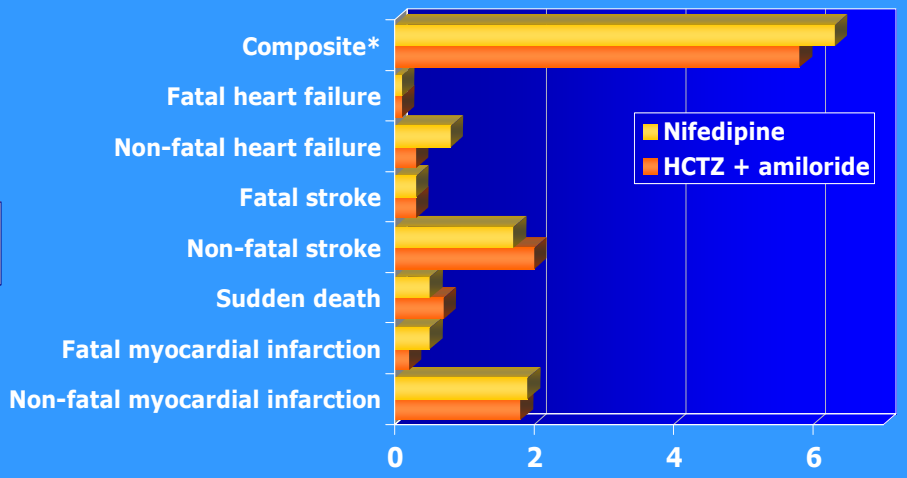
Evolution of trials in Hypertension 1991- 2005

Active Rx vs. Placebo - superior	Active vs. active - comparable	Active vs. active - superior
▪ SHEP (4,736 elderly ISH; chlorthalidone) 1991 ▪ STOP (1,627 elderly; BB/ HCTZ) 1991 ▪ SYST-EUR (4,695 ISH ; nitrendipine) 1997 ▪ [HOPE (9,297 high risk; ramipril] 1999	▪ HOT (18,000; felodipine) 1998 ▪ STOP2 (6,614 elderly; ACEI/CCB vs.DU/BB) 2000 ▪ CAPPP (10,985 25-66y; captopril vs. DU/BB) 1999 ▪ NORDIL (10,881 50-69y; diltiazem vs. DU/BB) 2000 ▪ INSIGHT (6,321 high risk, nifedipine vs DU) 2000 ▪ ALLHAT (42,418 moderate risk; chlorthalidone vs. amlodipine vs. lisinopril vs. doxazosin) Dec 2002	**LIFE (9193 high risk; Losartan vs. atenolol) 2002** **ASCOT 2005**

Nordil study:
Kaplan-Meier curves of proportion of patients in each group who reached primary endpoint



INSIGHT TRIAL



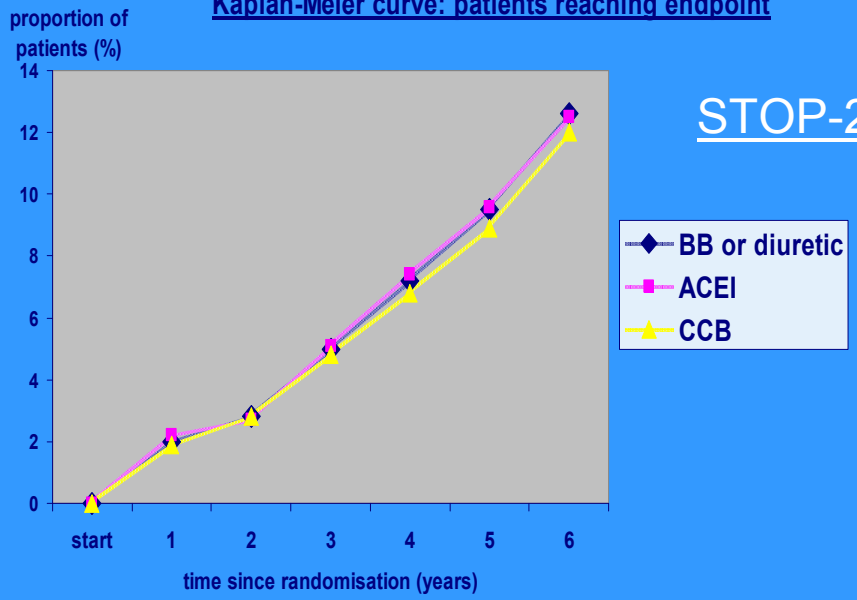
CAPP TRIAL

10,985 patients

Captopril v Thiazide±B blocker

No difference in outcome

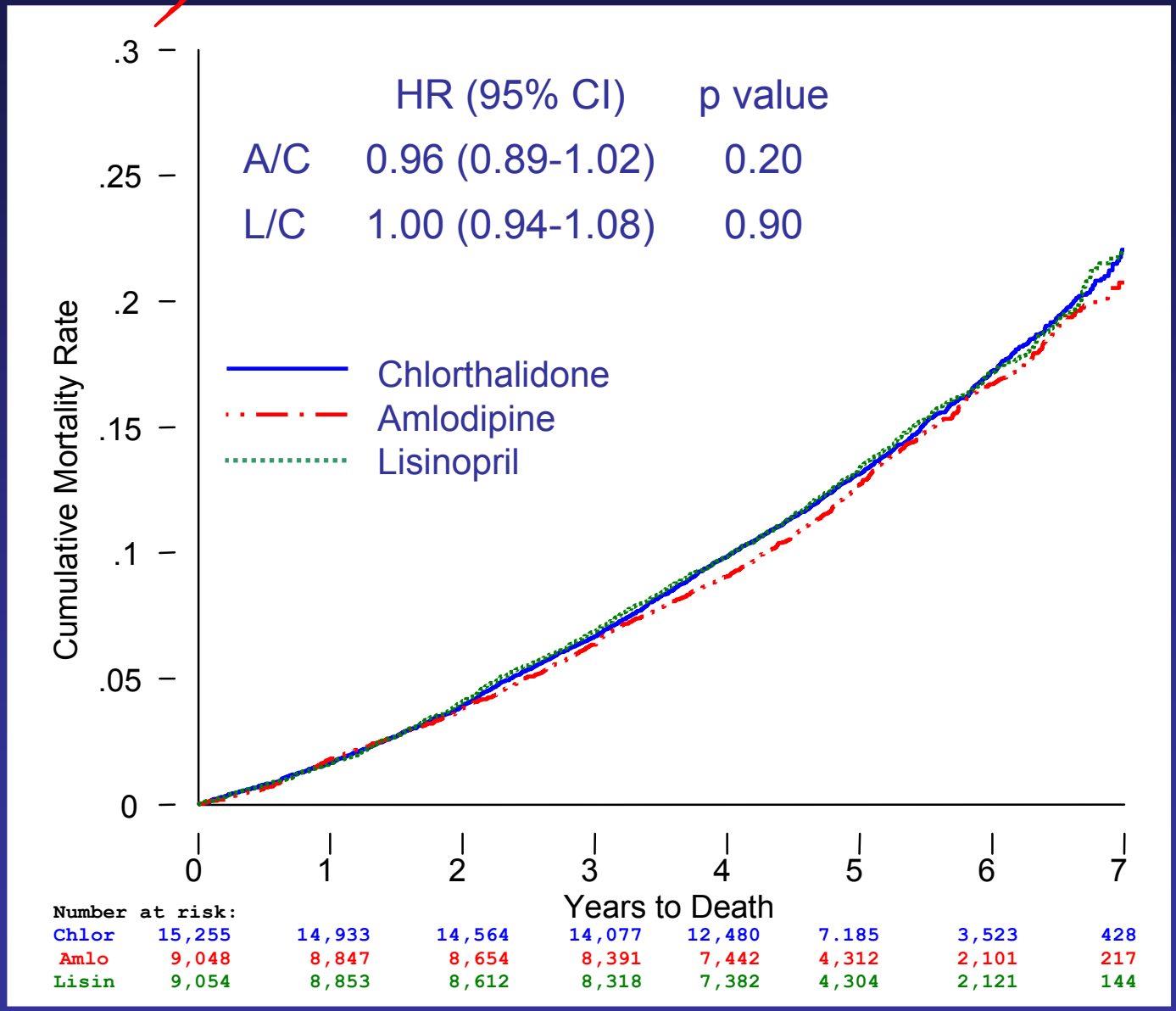
Kaplan-Meier curve: patients reaching endpoint



STOP-2

Hansson L, et al. *Lancet* 1999; **354:** 1751-56

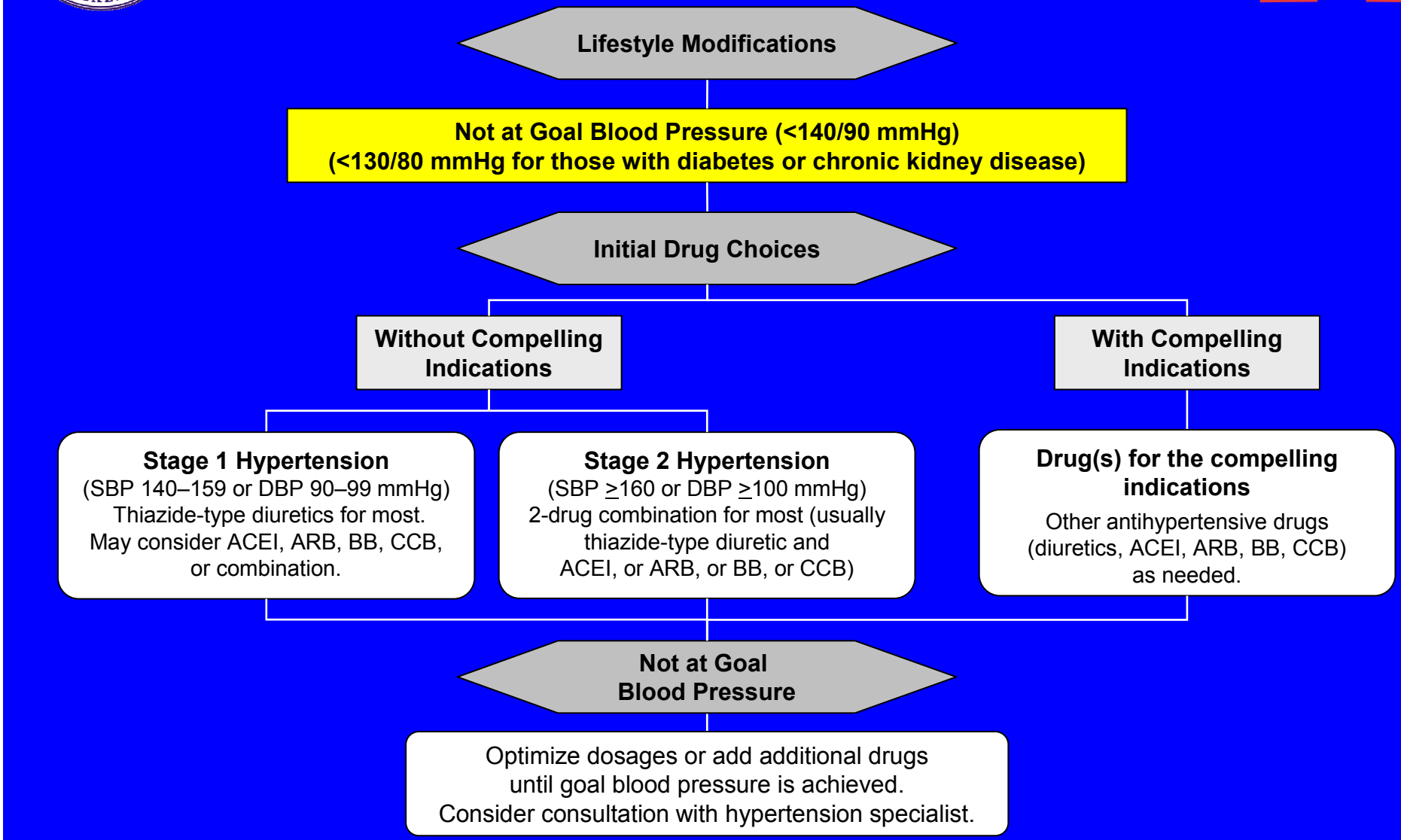
Cumulative Event Rates for All-Cause Mortality by ALLHAT Treatment Group



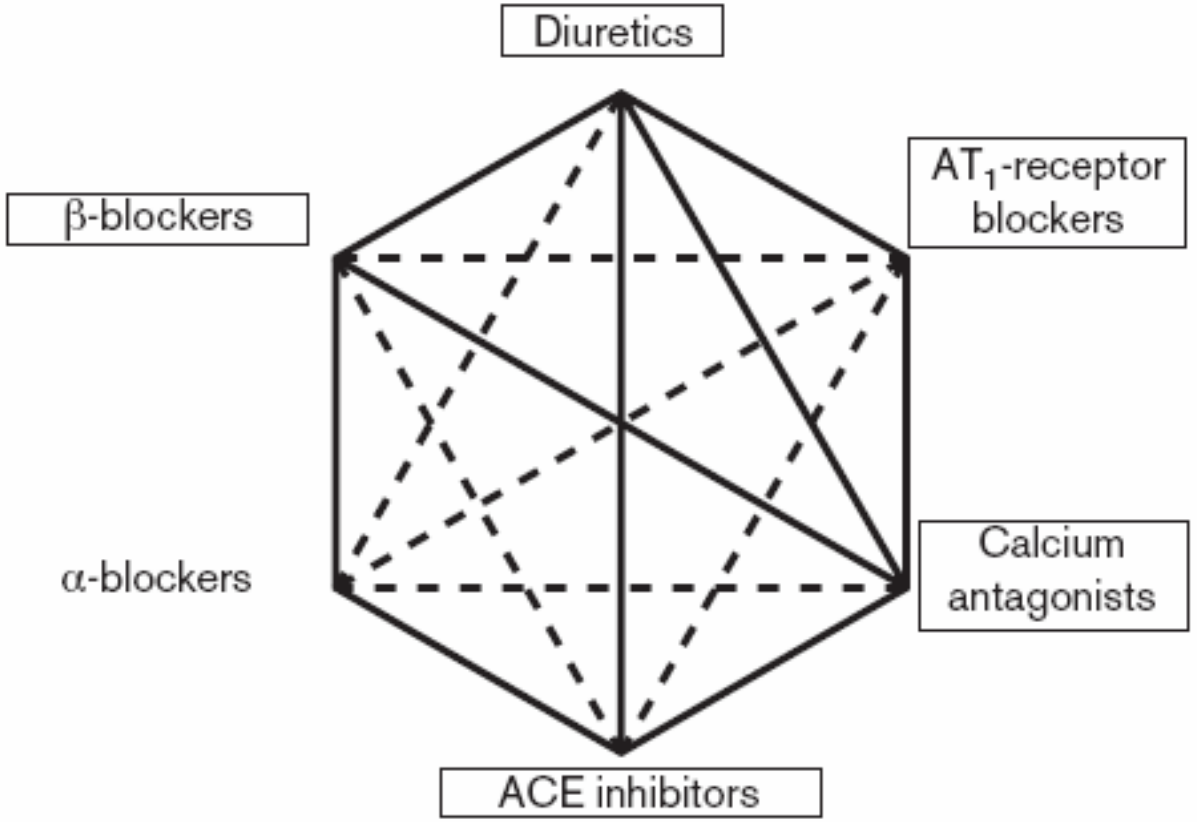
Target Organ Damage and total cardiovascular risk in hypertensive patients (ESH - ESC 2003)

Other risk factors and disease history	Grade I SBP 140-159 or DBP 90-99	Grade II SBP 160-179 or DBP 100-109	Grade III SBP ≥ 180 or DBP ≥ 110
I no other risk factors	**LOW added RISK**	**MODERATE added RISK**	**HIGH added RISK**
II 1-2 risk factors	**MODERATE added RISK**	**MODERATE added RISK**	**Very HIGH added RISK**
III 3 or more RF or **Target Organ Damage** or diabetes	**HIGH added RISK**	**HIGH added RISK**	**Very HIGH added RISK**
IV Associated clinical conditions	**Very HIGH added RISK**	**Very HIGH added RISK**	**Very HIGH added RISK**

Algorithm for Treatment of Hypertension



ESC-ESH 2003 Hypertension guideline



Possible combinations of different classes of antihypertensive agents. The most rational combinations are represented as thick lines. ACE, angiotensin-converting enzyme. The frames indicate classes of antihypertensive agents proven to be beneficial in controlled interventional trials.

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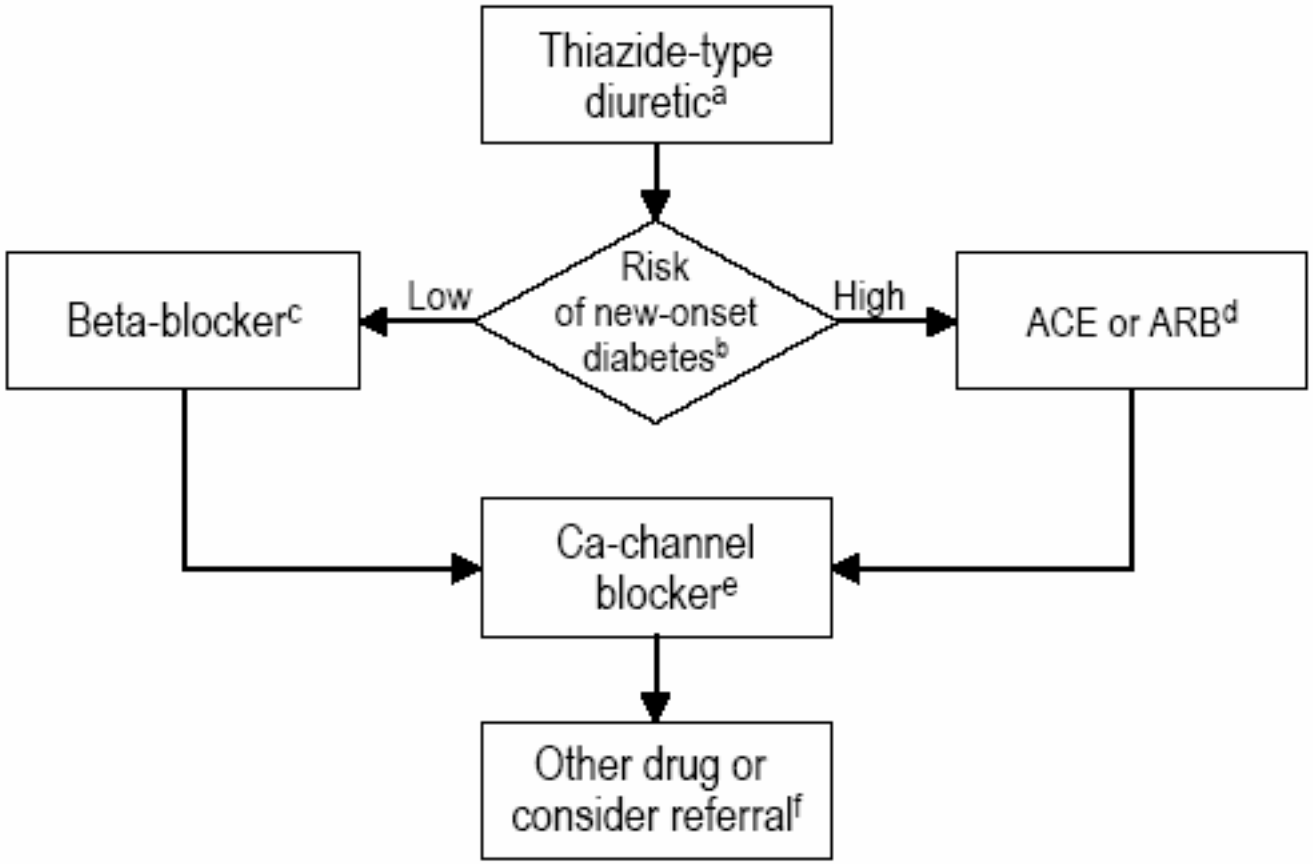
UK National Institute of Clinical Excellence 2003 Algorithm for treatment of Hypertension

Figure 26: Drug sequencing algorithm for essential hypertension



The British Hypertension Society 2003 recommendations for combining Blood Pressure Lowering drugs: BHS IV

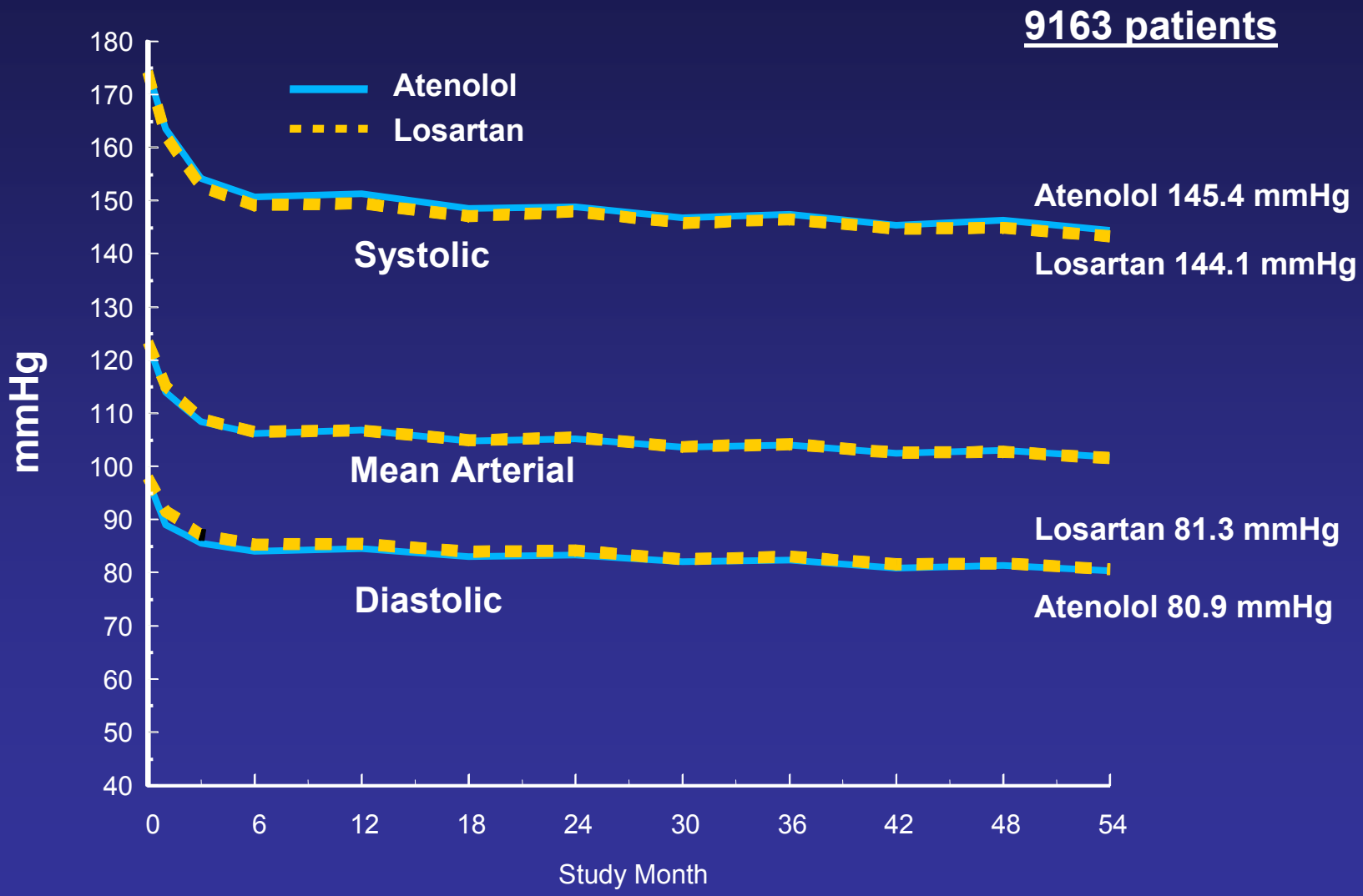
BHS

	Younger (e.g.<55yr) and Non-Black	Older (e.g.≥55yr) or Black
Step 1	A or B	C or D
Step 2	A (or B) + C or D	
Step 3	A + C + D	
Step 4 Resistant Hypertension	Add: either α-blocker or spironolactone or other diuretic	

A: ACE Inhibitor or angiotensin receptor blocker
B: β - blocker
C: Calcium Channel Blocker
D: Diuretic (thiazide)

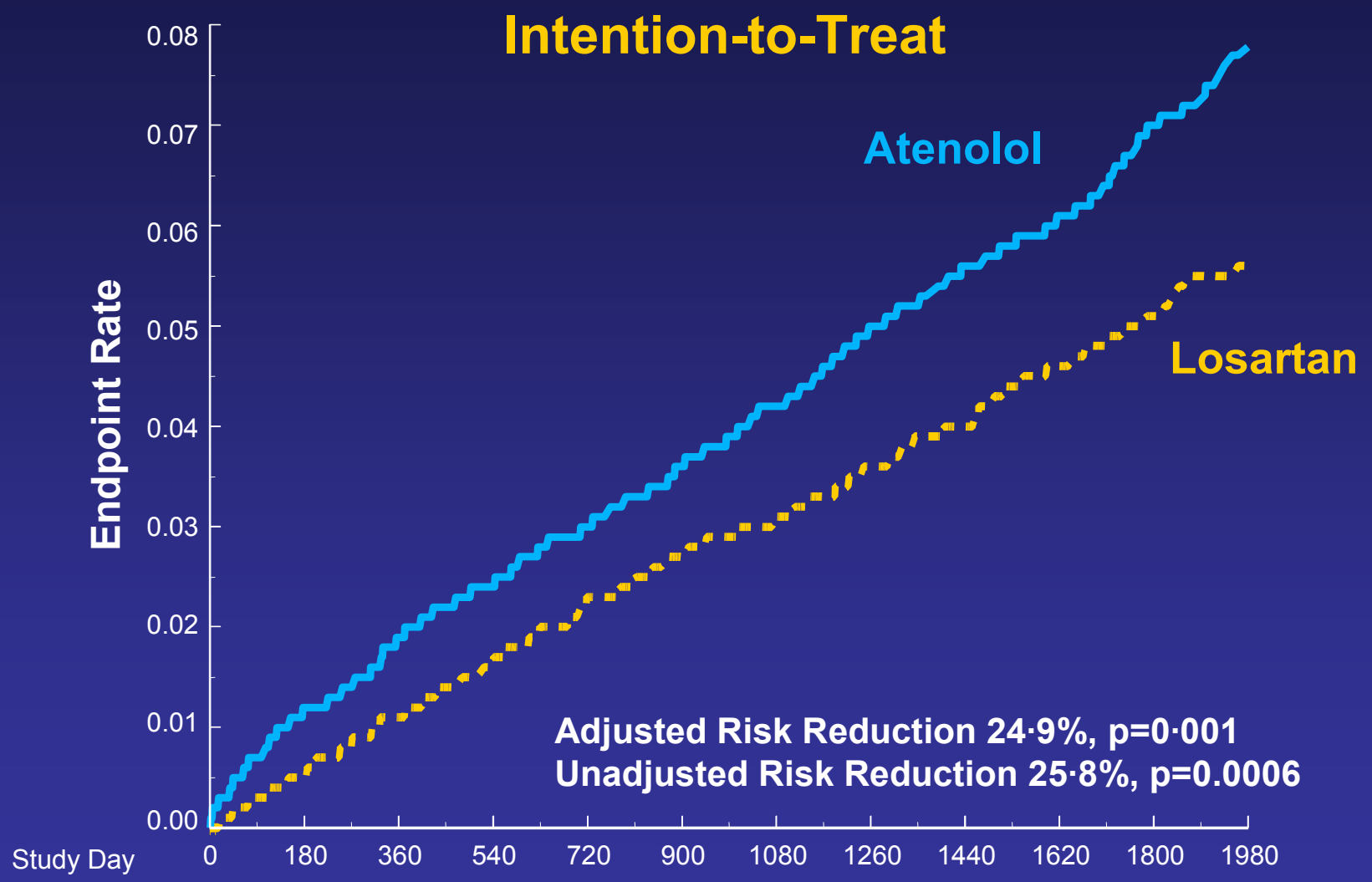
Adapted from : 'Better blood pressure control: how to combine drugs'
Journal of Human Hypertension (2003) 17, 81-86

LIFE: Blood Pressure Results



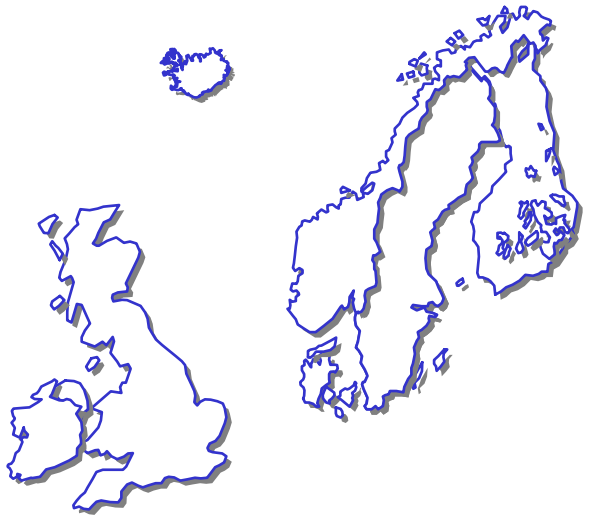
B Dahlof et al. Lancet 2002;359:995-1003

LIFE: Fatal/Nonfatal Stroke



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

Anglo-Scandinavian ascot Cardiac Outcomes Trial

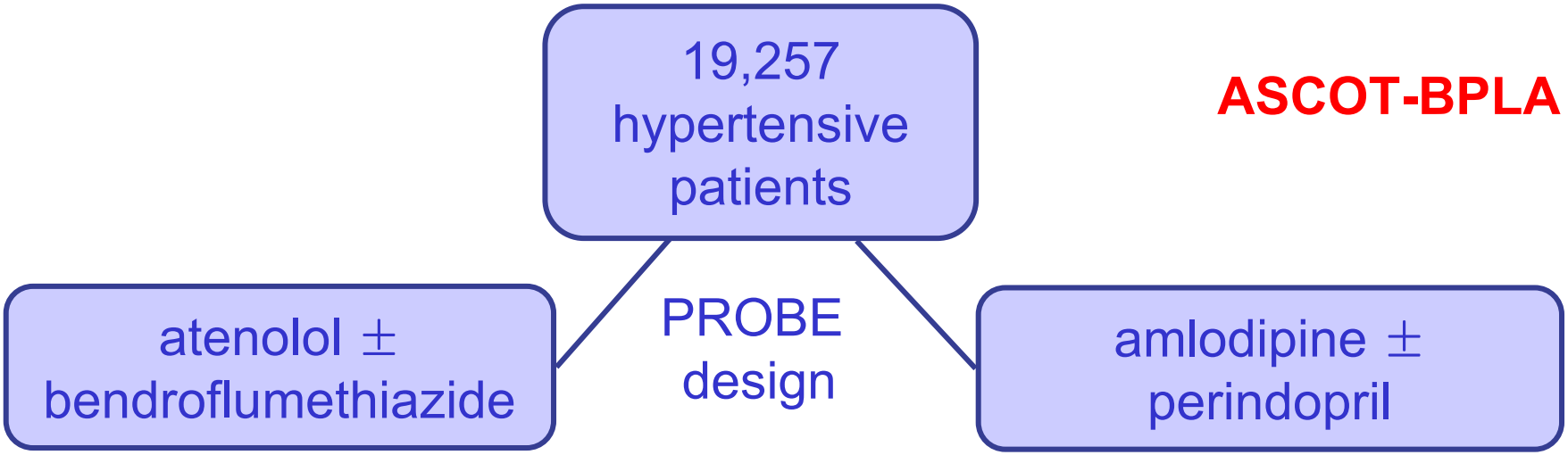


A randomised controlled trial of the prevention of CHD and other vascular events by BP and cholesterol lowering in a factorial study design

B.Dahlof (Co-chair), P.Sever (Co-chair), N. Poulter (Secretary)
H. Wedel (Statistician), G. Beevers, M. Caulfield, R. Collins
S. Kjeldsen, A. Kristinsson, J. Mehlsen, G. McInnes, M. Nieminen
E. O'Brien, J. Östergren, on behalf of the ASCOT Investigators

ascot

Study design



ASCOT-BPLA

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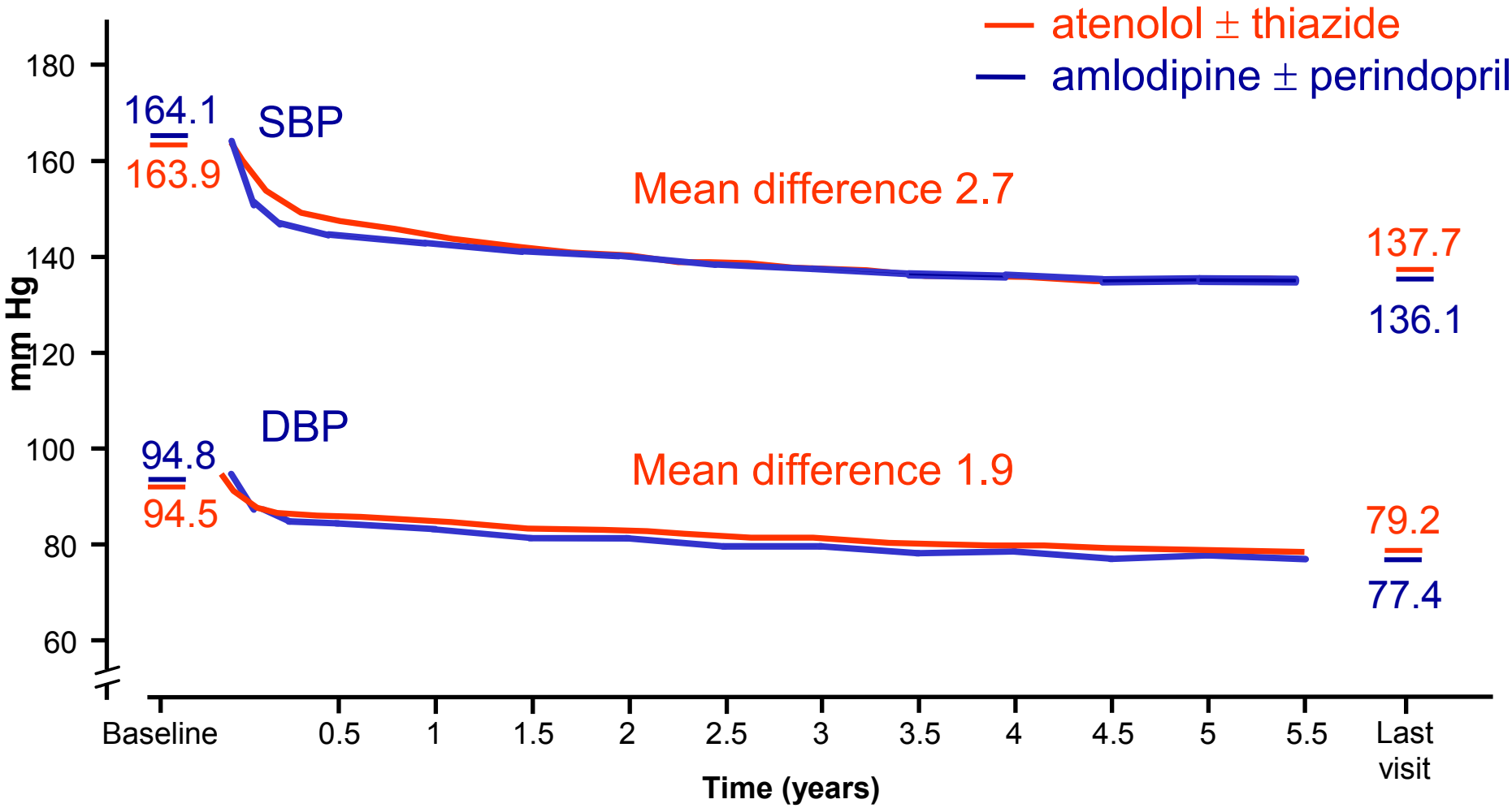
Systolic and diastolic blood pressure



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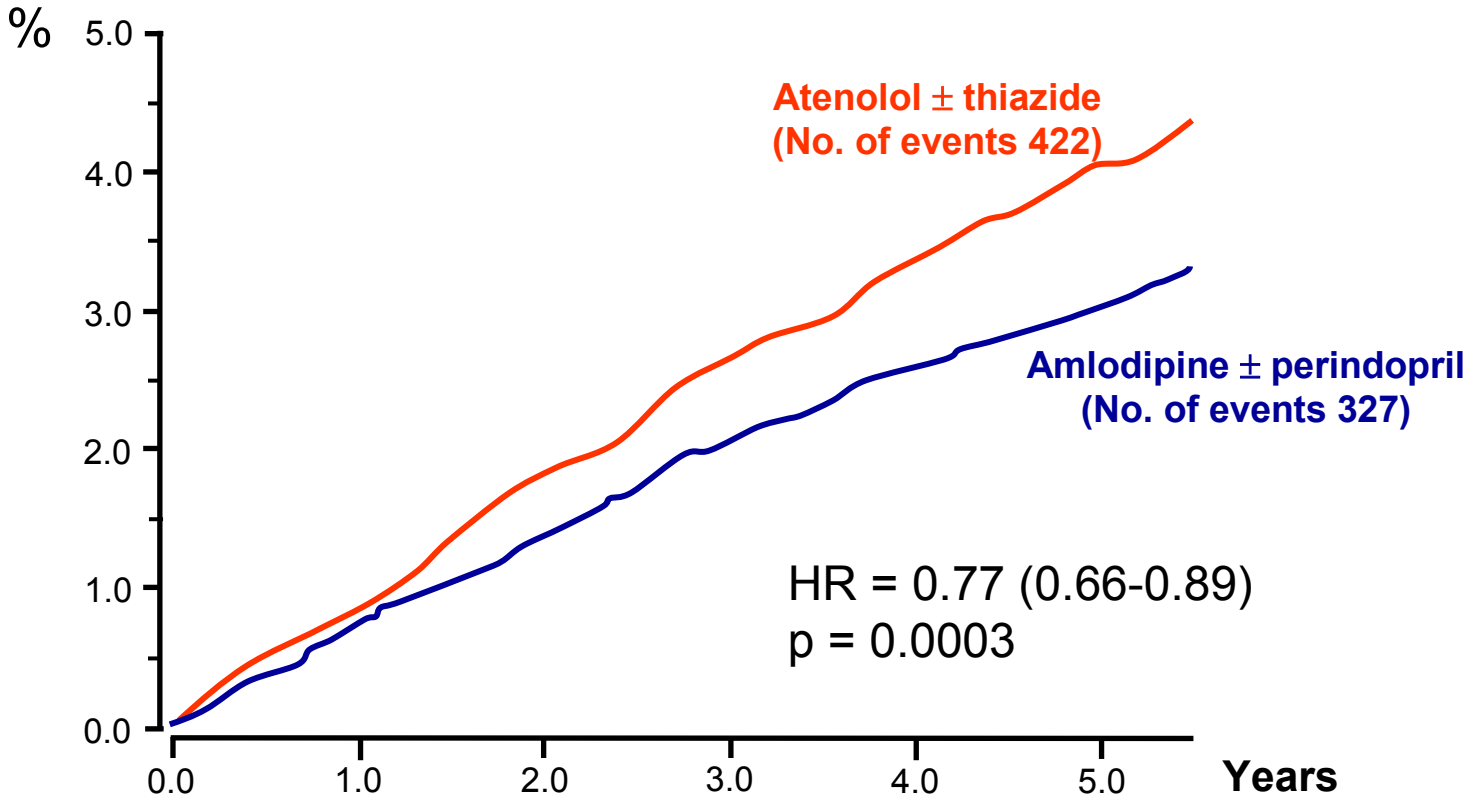
Fatal and non-fatal stroke



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

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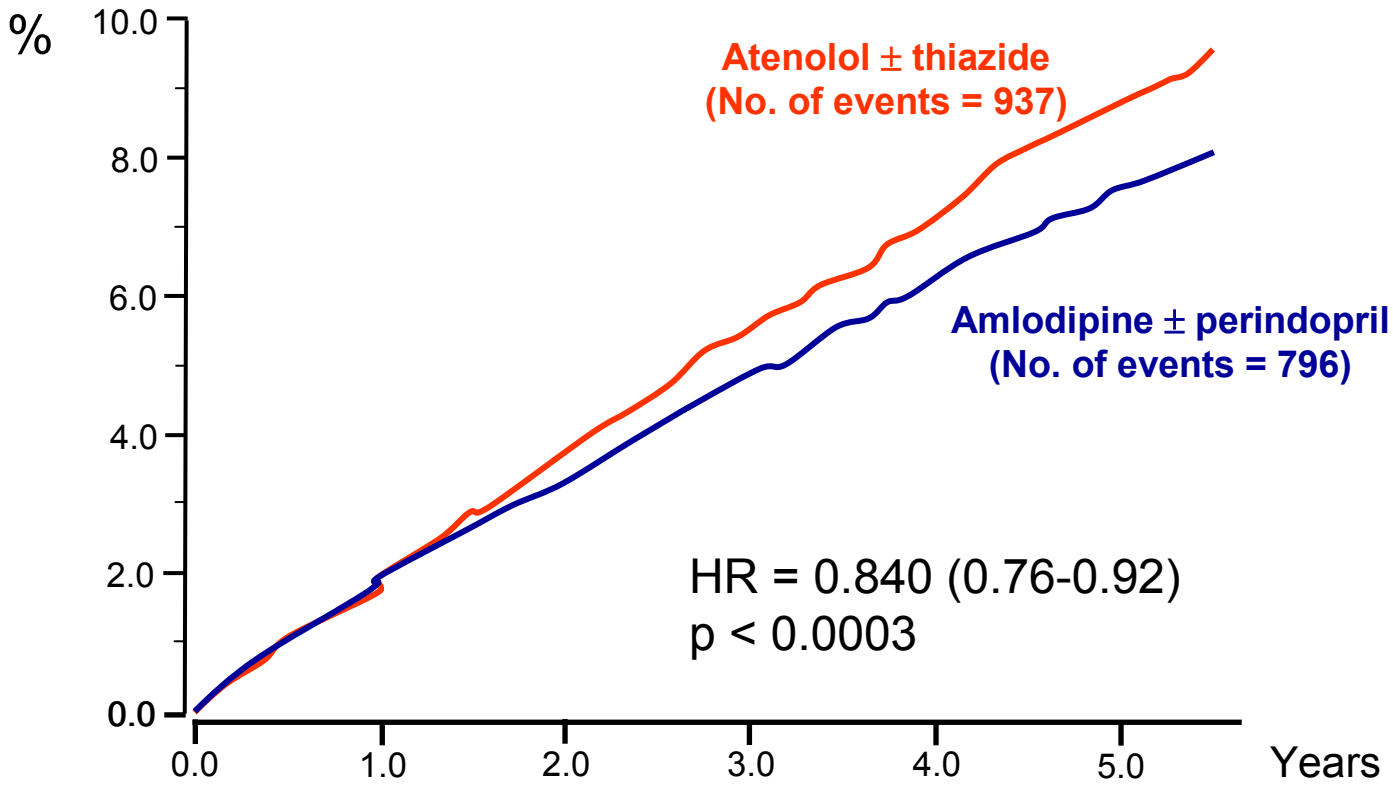
CV death + MI + stroke



Number at risk						
Amlodipine ± perindopril	9639	9415	9228	9007	8778	7655
Atenolol ± thiazide	9618	9400	9152	8891	8629	7500

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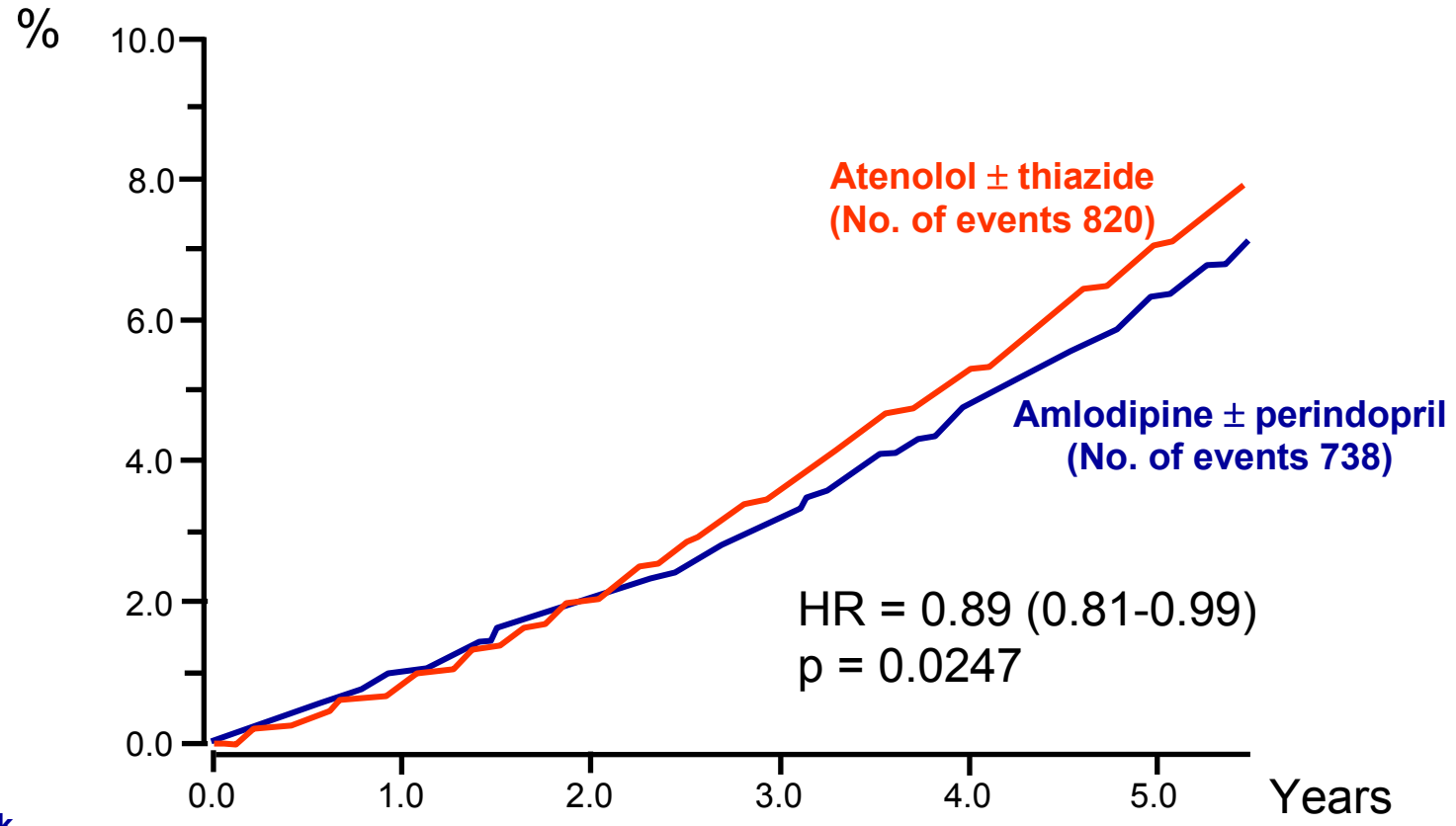
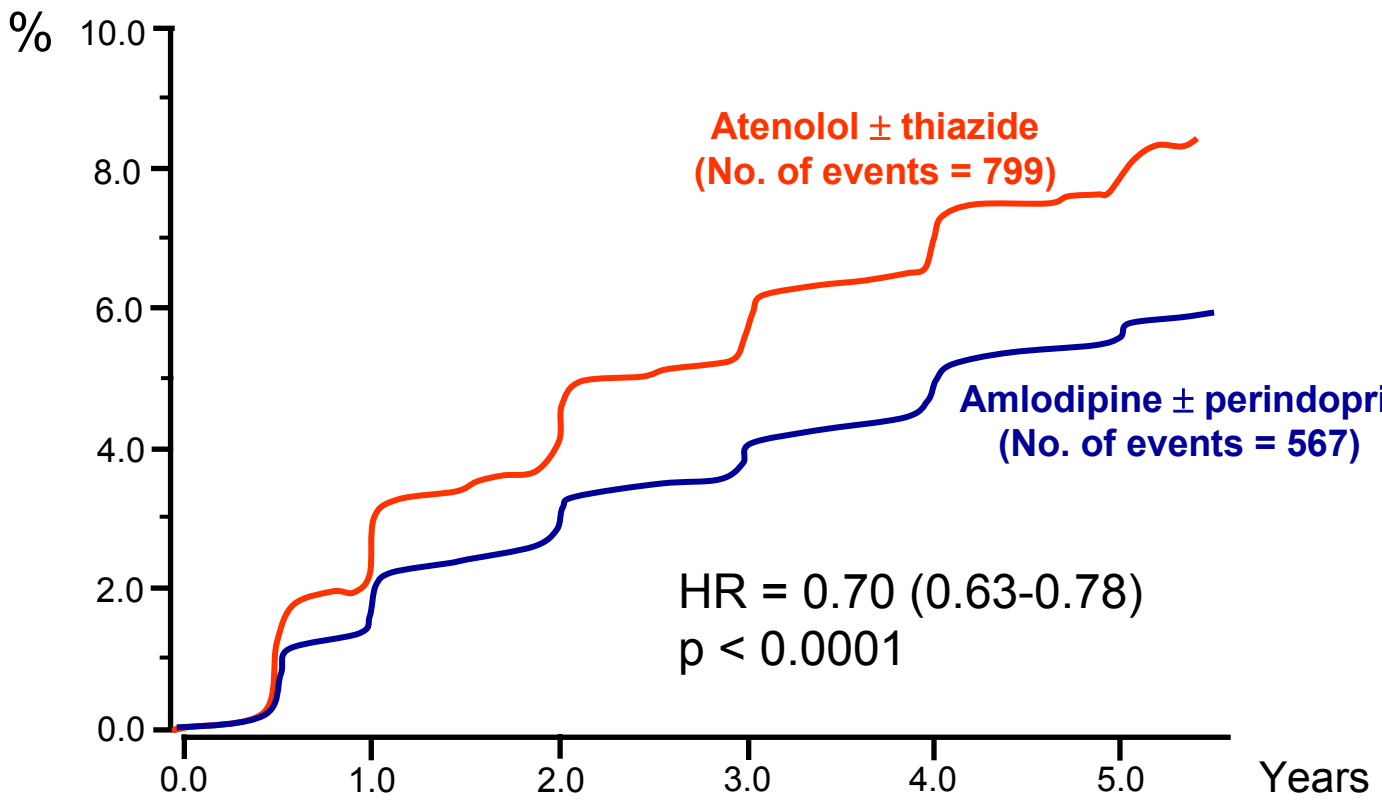
All-cause mortality



Number at risk						
Amlodipine ± perindopril	9639	9544	9441	9332	9167	8078
Atenolol ± thiazide	9618	9532	9415	9261	9085	7975

New-onset diabetes mellitus



Number at risk						
Amlodipine ± perindopril	9639	9383	9165	8966	8726	7618
Atenolol ± thiazide	9618	9295	9014	8735	8455	7319

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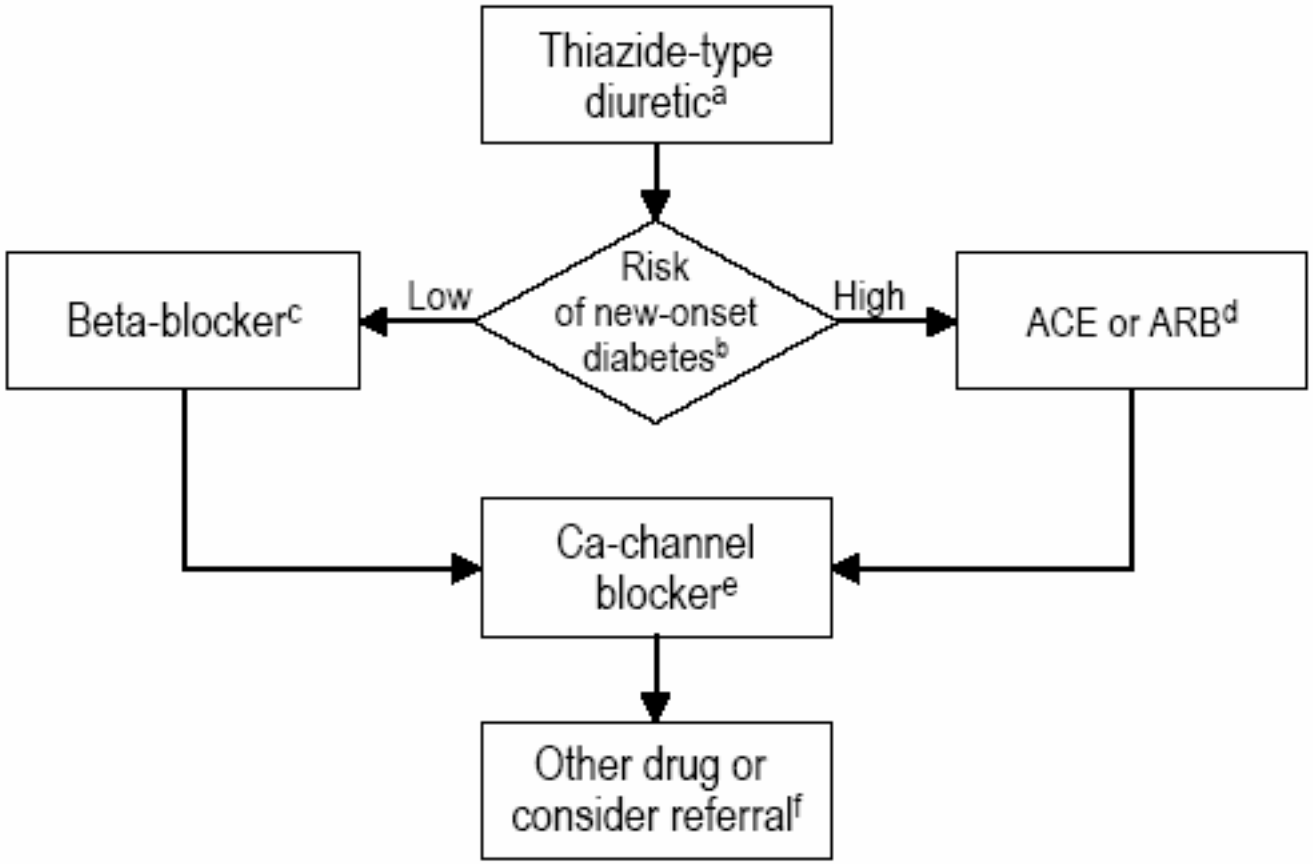
UK National Institute of Clinical Excellence 2003 Algorithm for treatment of Hypertension

Figure 26: Drug sequencing algorithm for essential hypertension



The British Hypertension Society 2003 recommendations for combining Blood Pressure Lowering drugs: BHS IV

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Step 2	A (or B) + C or D	
Step 3	A + C + D	
Step 4 Resistant Hypertension	Add: either α-blocker or spironolactone or other diuretic	

A: ACE Inhibitor or angiotensin receptor blocker
B: β - blocker
C: Calcium Channel Blocker
D: Diuretic (thiazide)

Adapted from : 'Better blood pressure control: how to combine drugs'
Journal of Human Hypertension (2003) 17, 81-86

Atenolol meta-analysis. Carlberg, Lancet 2004

Atenolol better | Placebo better

All cause mortality

Cardiovascular mortality

Myocardial infarction

Stroke

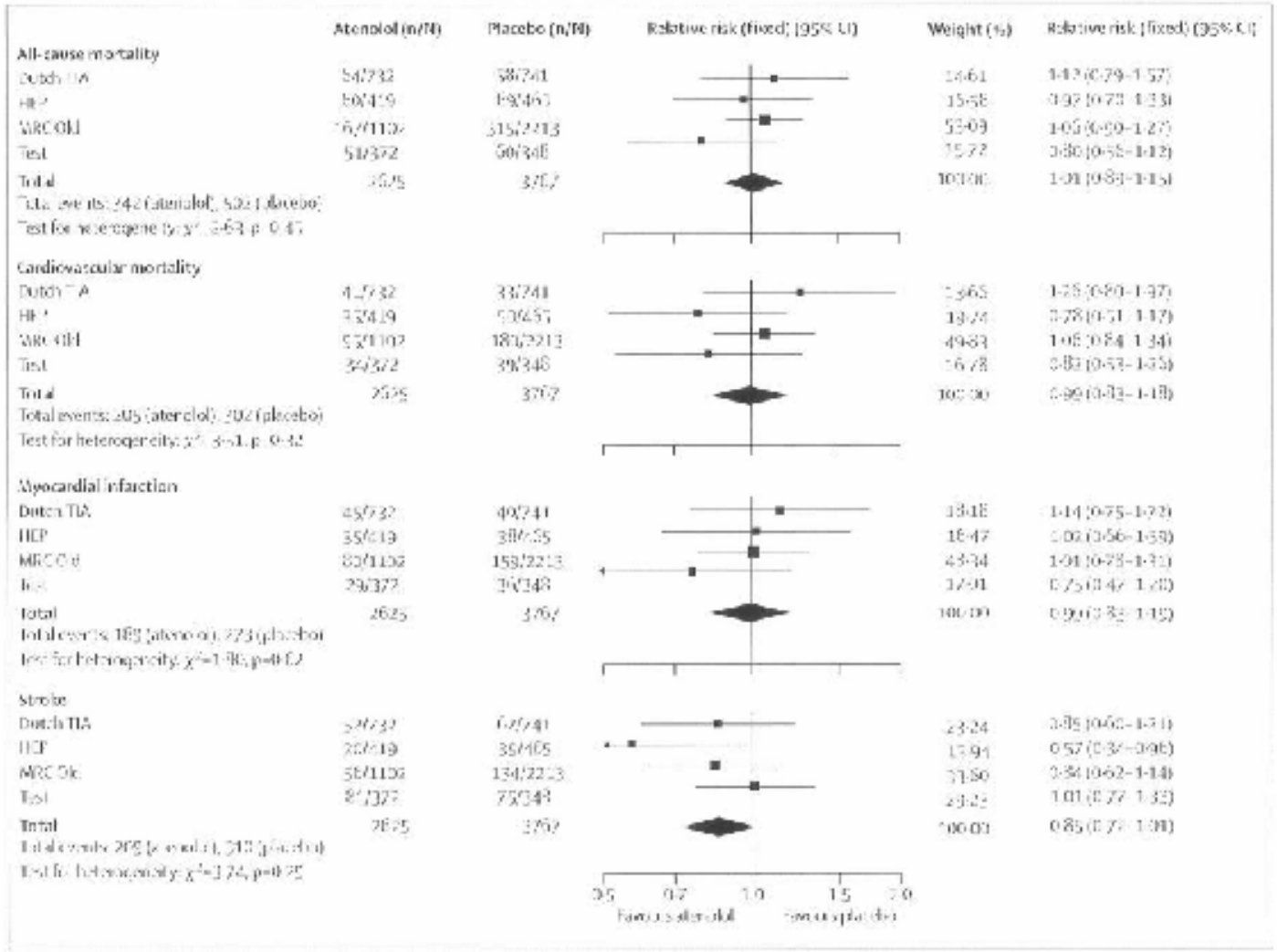

Figure 2: Outcome data for atenolol versus placebo or no treatment
*=number of patients with events. N=total number of patients. In the TIST study,† myocardial infarction was calculated as non-fatal myocardial infarction plus cardiac death.

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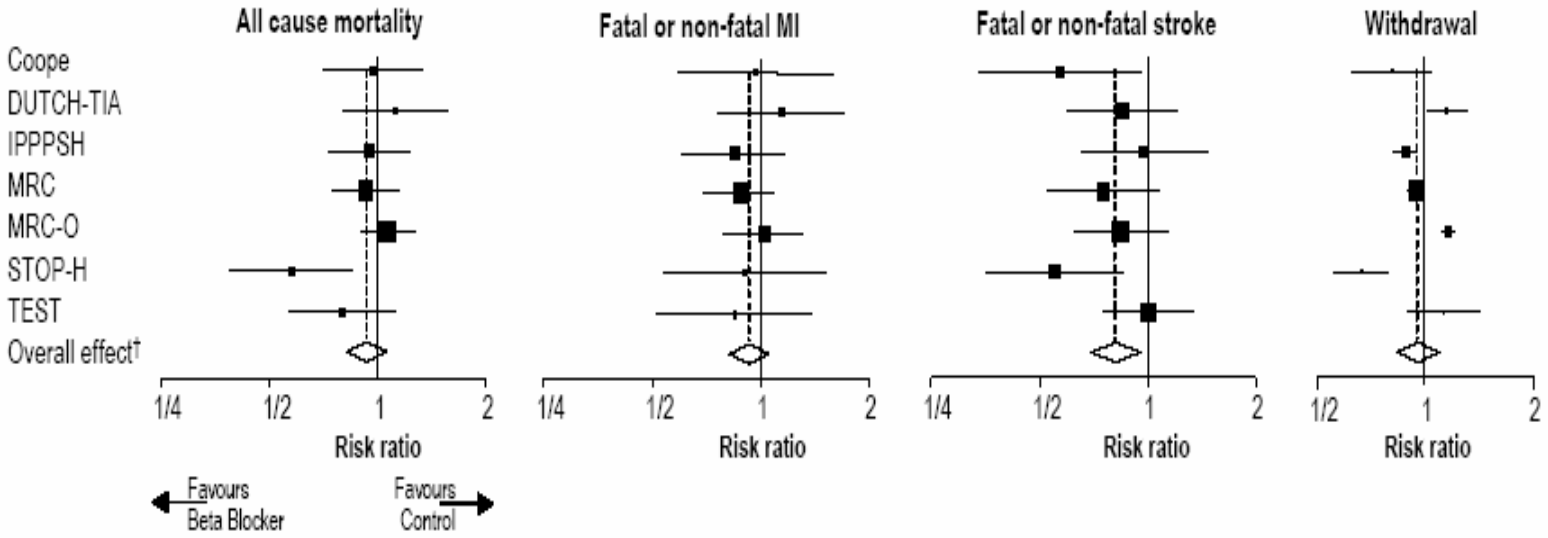
NICE meta-analysis 2005

Figure 20: Meta-analysis of placebo-controlled randomised controlled trials of beta-blockers



† DerSimonian-Laird risk ratio (RR)

	All cause mortality				Fatal or non-fatal MI				Fatal or non-fatal stroke				Withdrawal			
	RR	95% CI	Q, p	Size, p	RR	95%CI	Q, p	Size, p	RR	95%CI	Q, p	Size, p	RR	95%CI	Q, p	Size, p
Beta Blocker	0.94	(0.83 to 1.06)	0.21	0.16	0.92	(0.81 to 1.05)	0.90	0.76	0.81	(0.69 to 0.95)	0.25	0.08	0.95	(0.83 to 1.09)	<0.001	0.59

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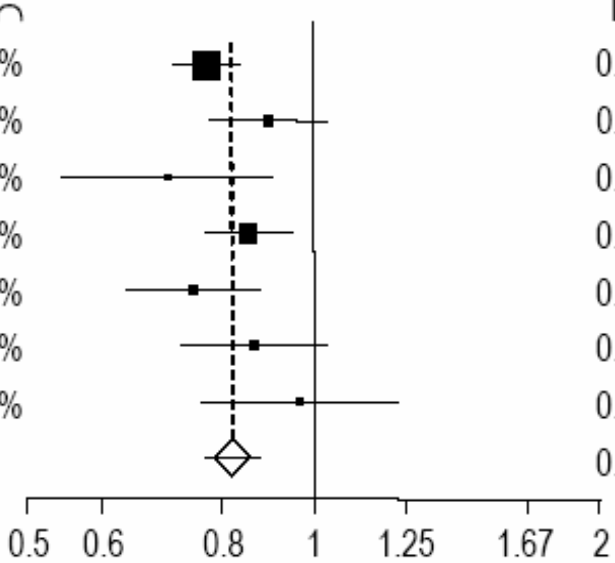
NICE meta-analysis 2005: Newer drugs versus older drugs

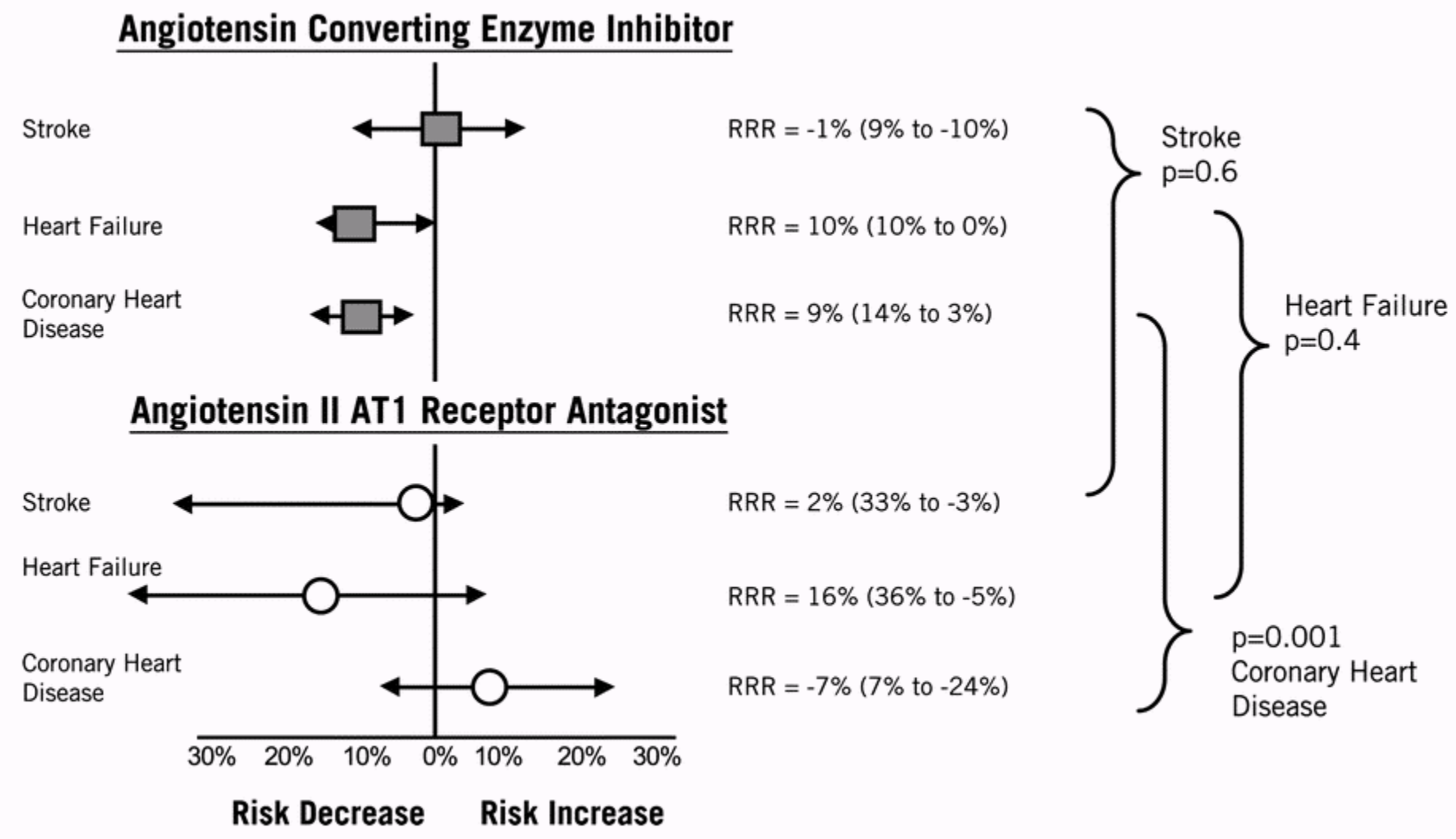
Figure 25: Meta analysis of trials comparing thiazide and beta-blocker combination therapy with other combinations and reporting new onset diabetes mellitus.

Trial	PbY	N	FU	Age	Risk	T/B	∩	RR	(95% CI)
ALLHAT	2002	21,294	4.9	67	29	T	41%	0.77	(0.71 to 0.84)
CAPPP	1999	10,413	6.1	53	6	T or B	?%	0.89	(0.78 to 1.03)
INSIGHT	2000	5,019	3.5	65	14	T	40%	0.70	(0.54 to 0.90)
INVEST	2003	16,176	2.7	66	29	B	60%	0.85	(0.77 to 0.95)
LIFE	2002	7,998	4.8	67	18	B	58%	0.75	(0.64 to 0.88)
NORDIL	2000	10,154	4.5	60	9	T or B	48%	0.87	(0.73 to 1.03)
STOP-H2	1999	5,895	5.0	76	33	T or B	29%	0.97	(0.76 to 1.23)
Overall effect †								0.81	(0.77 to 0.86)



PbY Publication year.
N Total number of patients enrolled without diabetes at baseline.
FU Average trial follow-up in years.
Age Average age of patients at enrolment
Risk Risk of all-cause mortality per 1000 patient years for all patients enrolled.
T/B Drug sequence in Thiazide diuretic (T)/Beta blocker (B) arm.
T (T, then B if necessary), B (B, then T if necessary), T or B (either, then both if necessary)
∩ Approximate percentage (T/B) receiving second drug;
† Heterogeneity, Q=9.04; p=0.17
Normalized effect vs. precision (Egger et al.), p=0.56

BPLTTC regression meta-analysis for ACEIs or comparator [AASK, ABCD(H), ABCD(N), ALLHAT, ANBP2, CAPPP, DIAB-HYCAR, EUROPA, HOPE, JMIC-B, PART-2, PEACE, PROGRESS, SCAT, STOP-2, and UKPDS-HDS) or for ARB or comparator (IDNT, LIFE, RENAAL, SCOPE, and VALUE).



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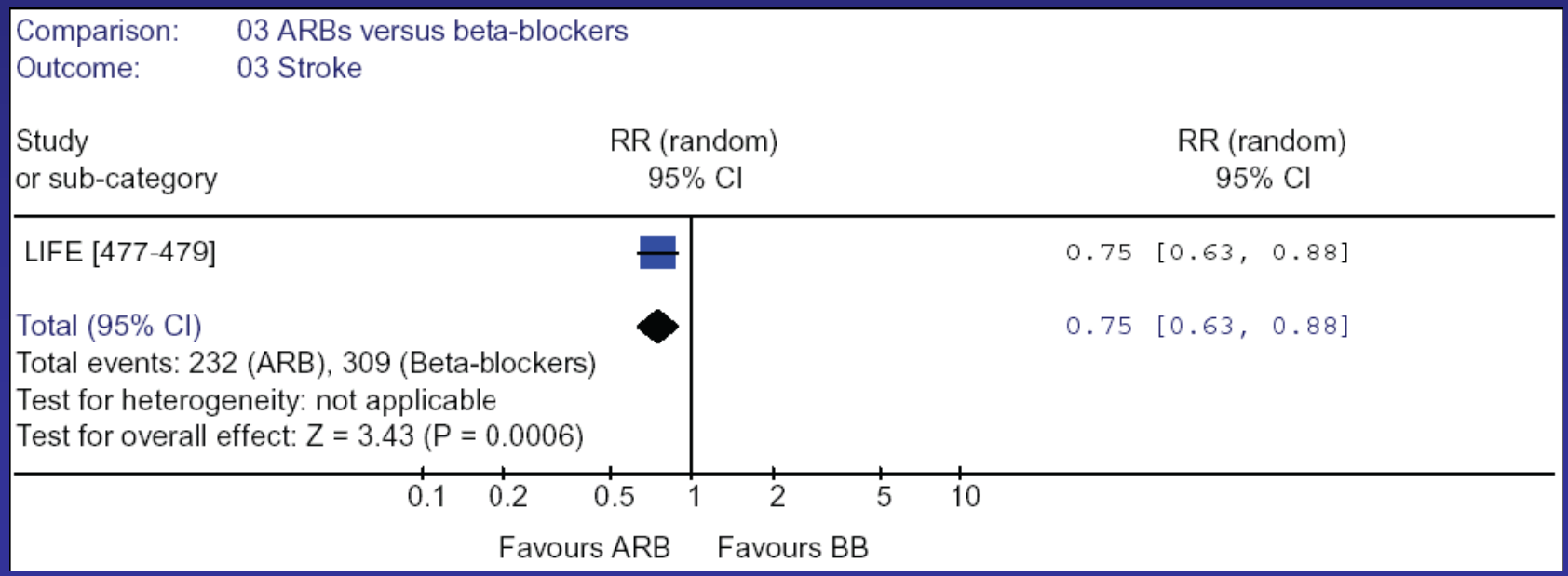
2006 partial update of *NICE Clinical Guideline* 18

BHS

Comparison	Studies	Total N	Effect Size (RR)
03 **ARBs versus beta-blockers**			
01 Mortality	1	9103	0.89 [0.78, 1.01]
02 Myocardial Infarction	1	9103	1.05 [0.86, 1.28] N/A
03 Stroke	1	9103	0.75 [0.63, 0.88] N/A
05 Diabetes	1	7998	0.75 [0.64, 0.88] N/A



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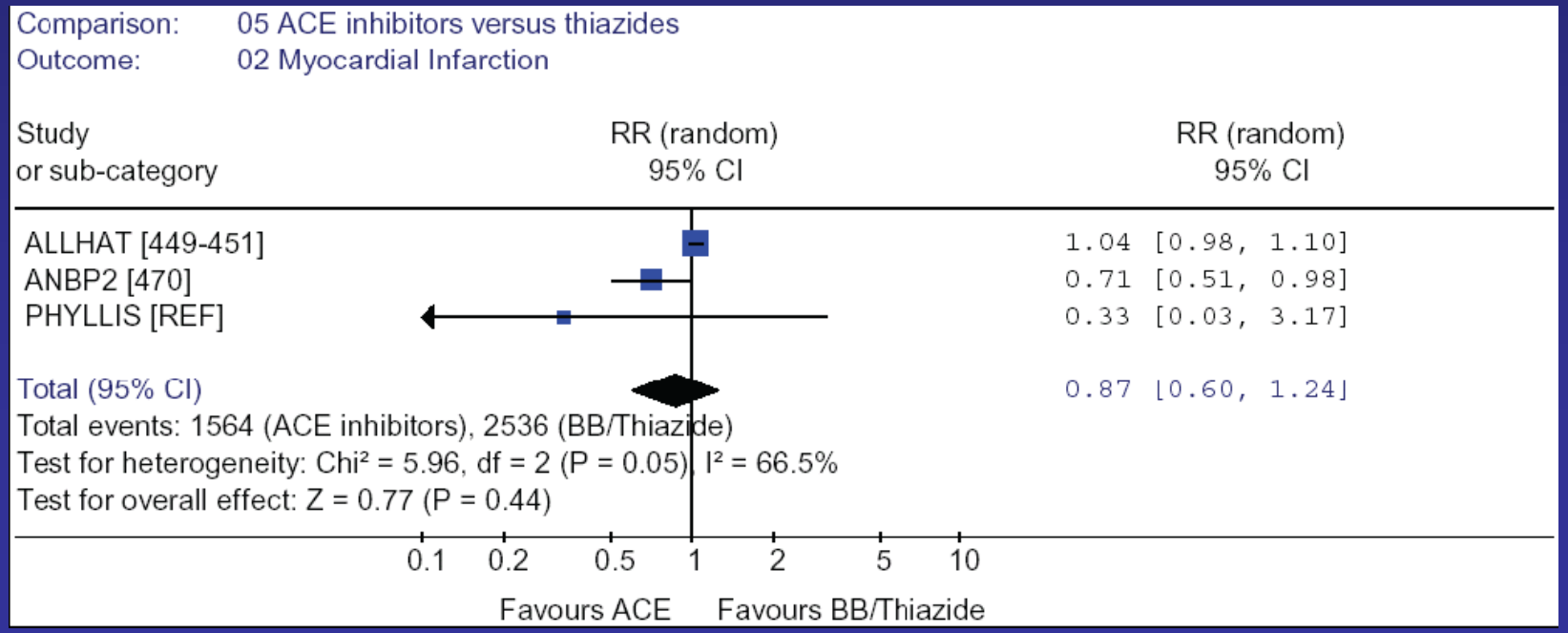
BHS

Comparison	Studies	Total N	Effect Size (RR)
05 **ACE inhibitors versus thiazides**			
01 Mortality	2	29697	1.00 [0.94, 1.06] 0%
02 Myocardial Infarction	3	30204	0.87 [0.60, 1.24] 66.5%
03 Stroke	3	30204	1.13 [1.02, 1.25] 0%



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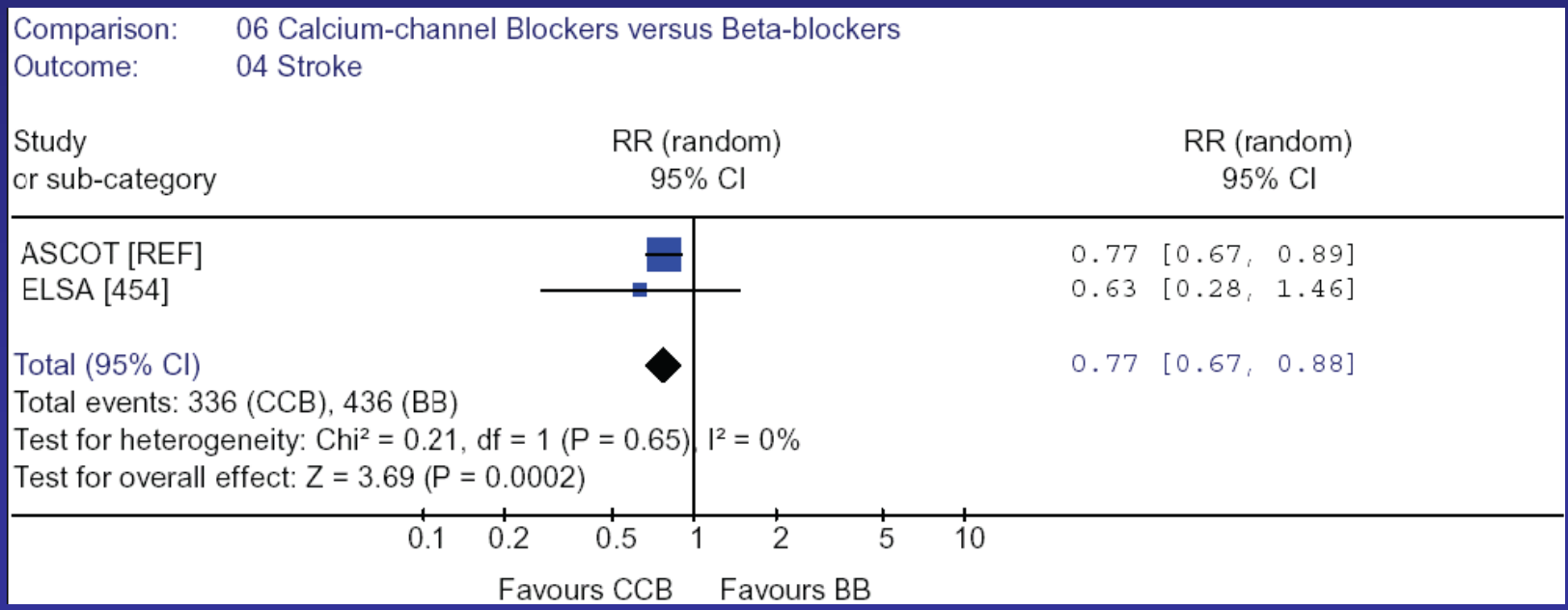
BHS

Comparison	Studies	Total N	Effect Size (RR)
06 **Calcium-channel Blockers versus Beta-blockers**			
01 Mortality	3	44075	0.94 [0.88, 1.01] 5.7%
02 Myocardial Infarction (Inc. Silent MI)	3	44075	0.93 [0.83, 1.03] 0%
03 Myocardial Infarction (Exc. Silent MI)	3	44075	0.91 [0.81, 1.02] 0%
04 Stroke	2	21499	0.77 [0.67, 0.88] 0%
06 Diabetes	1	14112	0.71 [0.64, 0.78] N/



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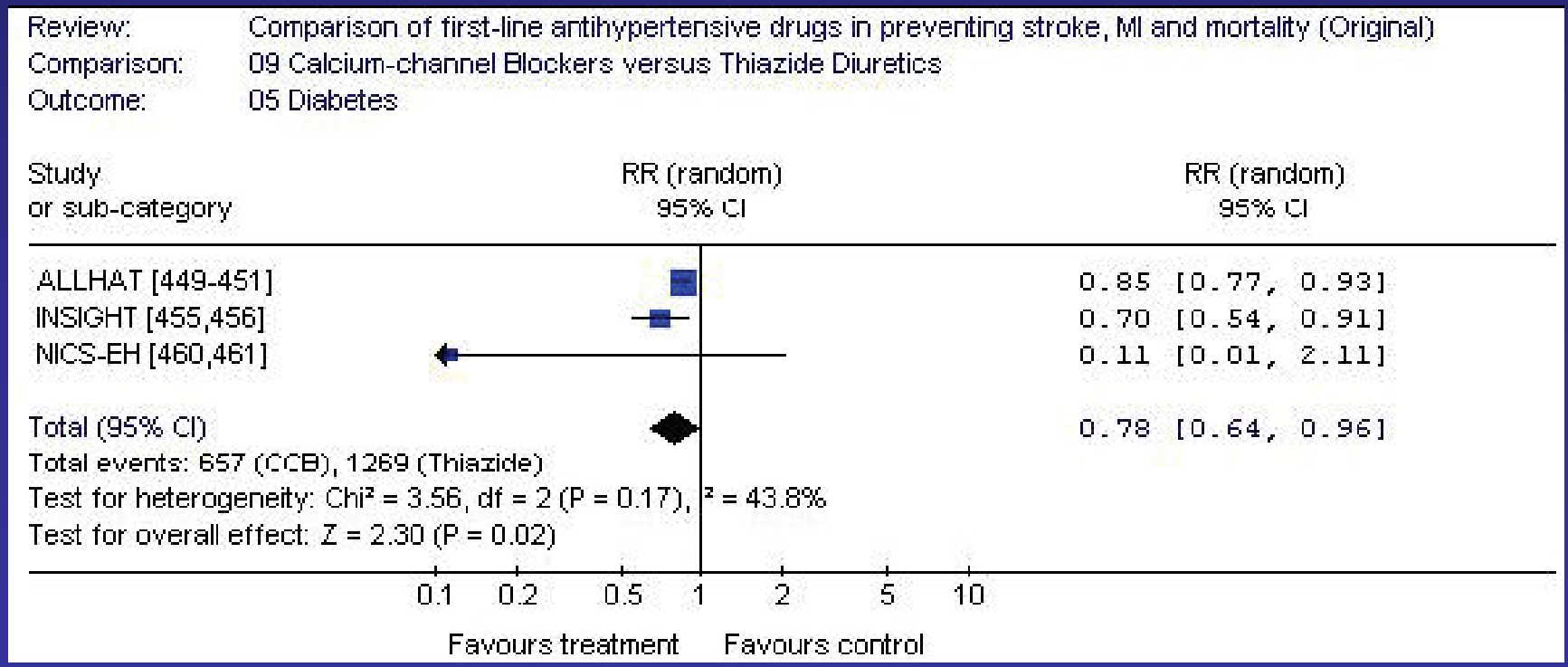
Comparison	Studies	Total N	Effect Size (RR)
07 **Calcium-channel Blockers versus Thiazide Diuretics**			
01 Mortality	6	54771	0.97 [0.92, 1.02] 0%
02 Myocardial Infarction	6	54771	1.02 [0.96, 1.07] 0%
03 Stroke	6	54771	0.93 [0.84, 1.04] 0%
05 Diabetes	3	20885	0.78 [0.64, 0.96]



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Markov model of lifetime treatment

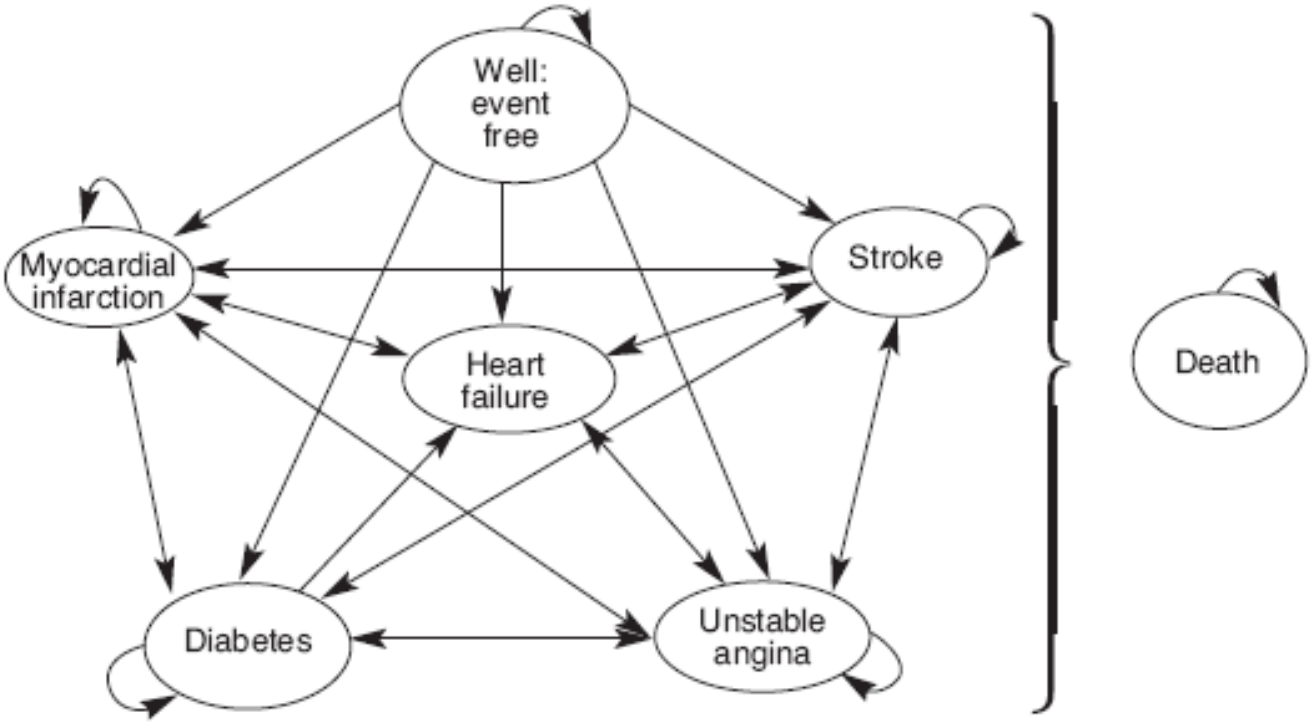
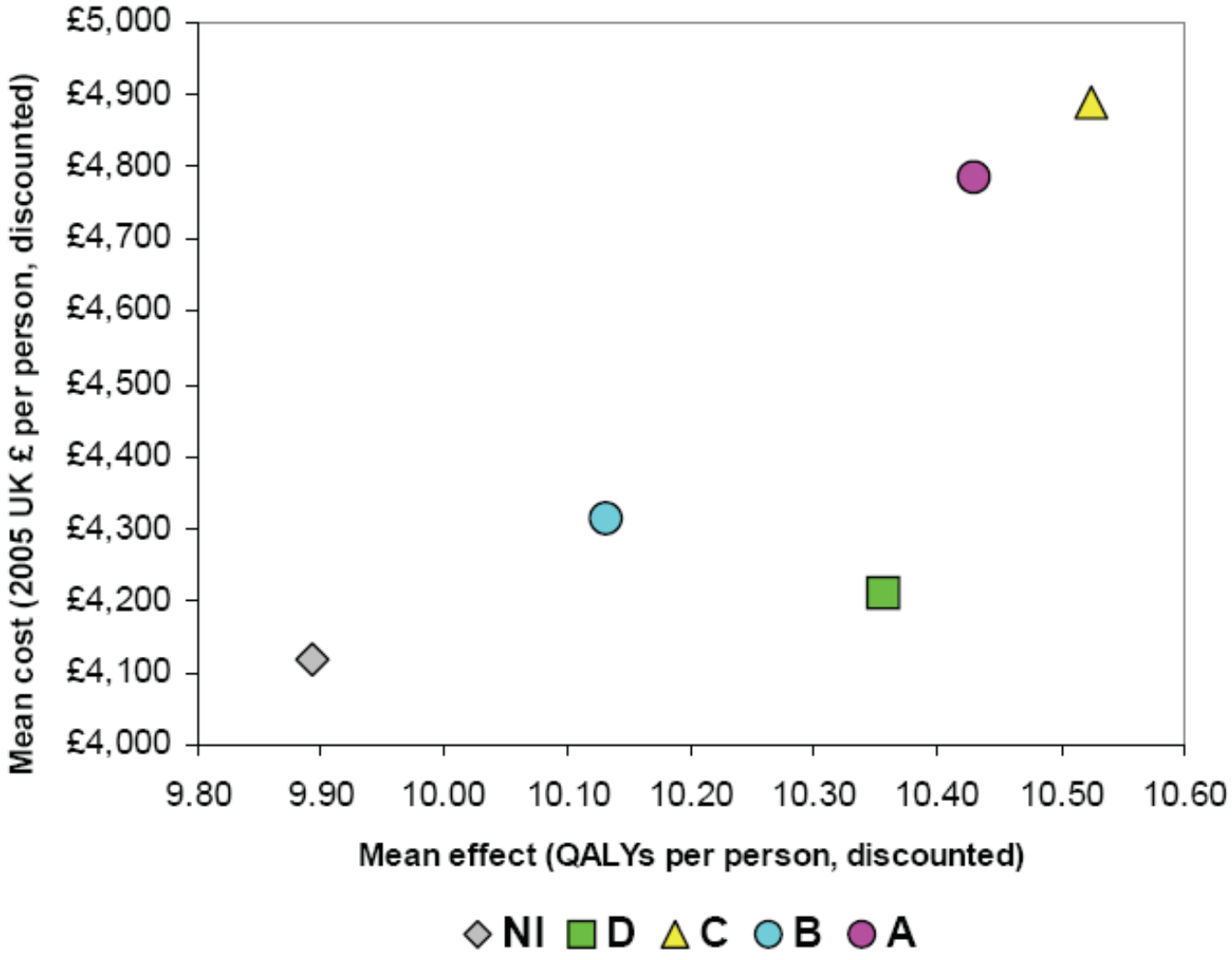


Figure C1 Model structure for hypertension

Figure 2, Base case results 65-year-old male 2% annual CVD risk, Cost effectiveness plane



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Beta-blockers versus dihydropyridine calcium-channel blockers

Meta-analysis of three studies (ASCOT6, ELSA, INVEST) compared beta-blockers with dihydropyridine calcium-channel blockers (CCBs) when used as first-line antihypertensive therapy.

Nonsignificant results that appeared to favour CCBs for the outcomes of myocardial infarction (RR 0.93, 95% CI 0.83 to 1.03) and mortality (RR 0.94, 95% CI 0.88 to 1.01.

On the results of two studies (ASCOT, ELSA), CCBs are associated with a reduced incidence of stroke (RR 0.77, 95% CI 0.67 to 0.88).

Based on the results of one study (ASCOT), CCBs are associated with a reduced incidence of new-onset diabetes (RR 0.71, 95% CI 0.64 to 0.78).

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partial update of *NICE Clinical Guideline* 18

BHS

1.5.1.6.

Beta-blockers are no longer preferred as a routine initial therapy for hypertension.

Beta-blockers may be considered in:

- younger women of child-bearing potential
- patients with hypertension and evidence of increased sympathetic drive
- intolerance / contra-indication to ACE inhibitors and ARBs.

In these circumstances, if initial therapy is with a beta-blocker and a second drug is required, add a dihydropyridine calcium-channel blocker rather than a thiazide-type diuretic to reduce the risk of developing diabetes. **[B]**

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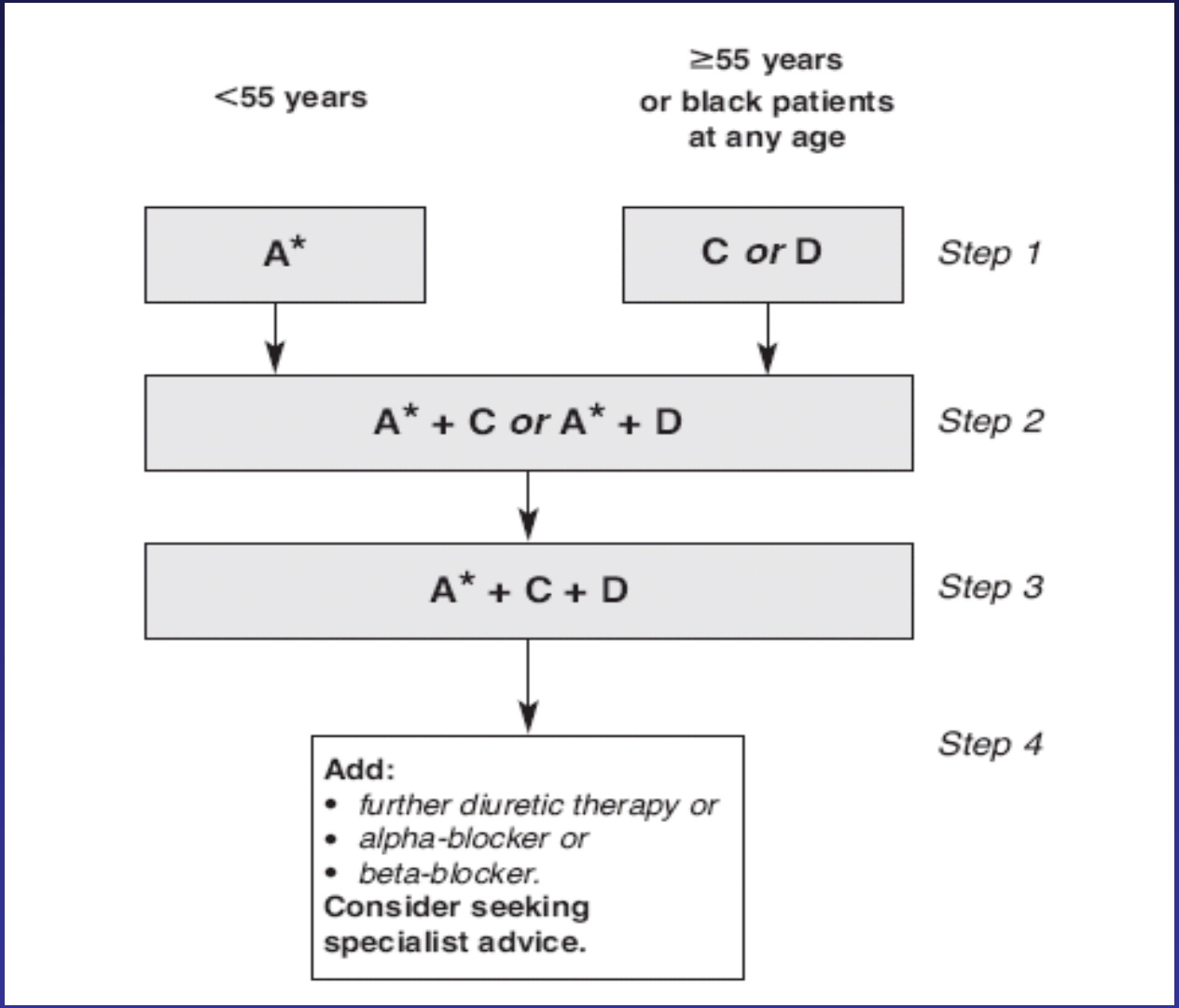
In individuals with an existing diagnosis of hypertension, whose blood pressure is controlled with a regimen which includes a betablocker, there is no urgent need to replace the beta-blocker with an alternative agent.

In patients whose blood pressure is not controlled despite a treatment regimen including a beta-blocker, treatment should be revised according to the treatment algorithm. **[D]**

2006 UK guideline for treatment of hypertension



A = ACE inhibitor (* or ARB if ACEi-intolerant); C = calcium-channel blocker;
D = thiazide-type diuretic. Beta-blockers are not a preferred initial therapy for hypertension but are an alternative to A in patients <55 years in whom A is not tolerated, or contraindicated (includes women of childbearing potential). Black patients = African or Caribbean descent.

Unpublished data from ASCOT

BP lowering effects:	SBP	DBP
Amlodipine 5 mg	15.5	9
Amlodipine 10 mg	25.9	15.2
Perindopril data not yet available		
Doxazosin 7 mg	11.7	6.9
Spironolactone 41 mg	21.9	9.5

ascot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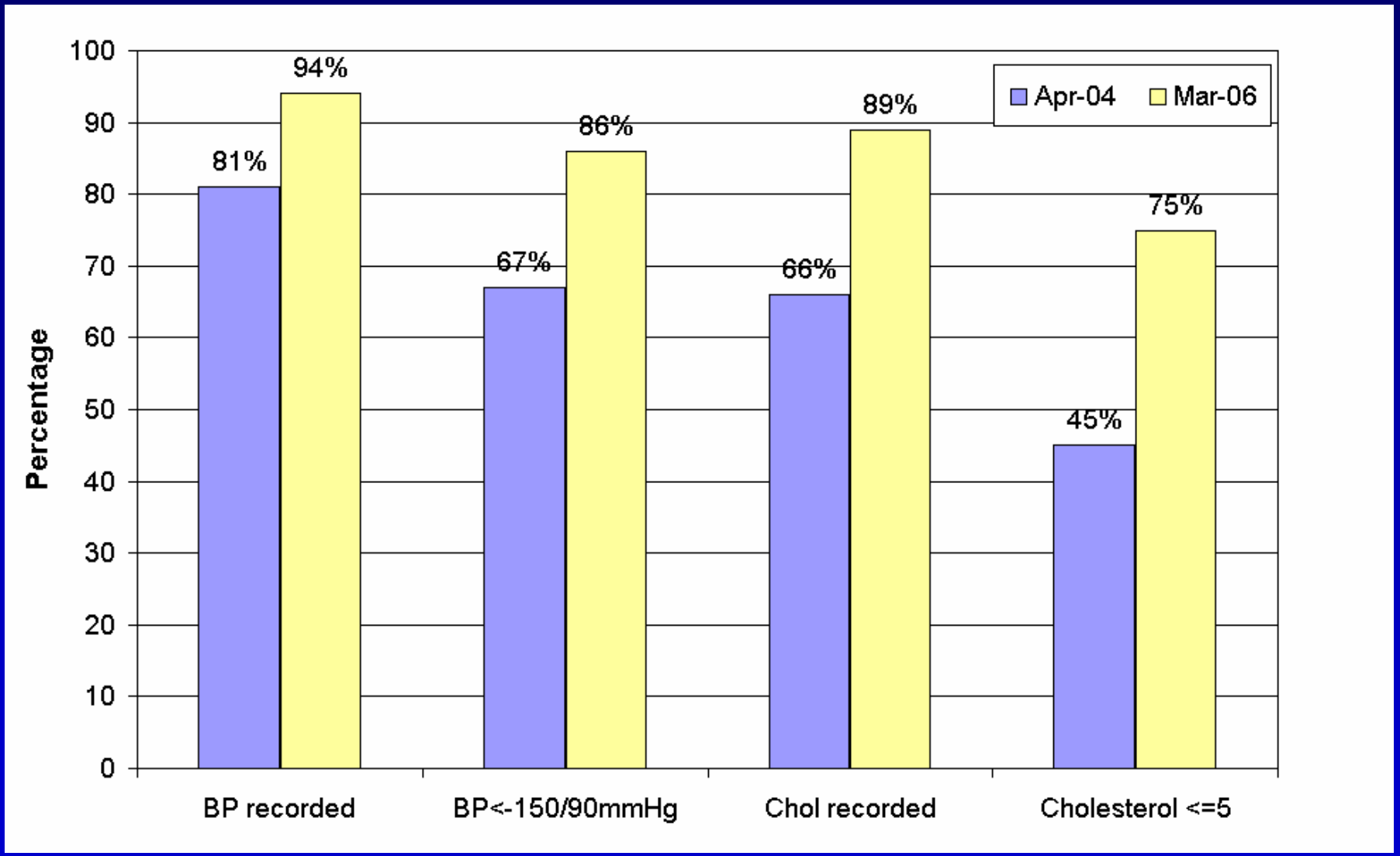
Hypertension

UK approach to HT improvement

All minimum thresholds are 25%

Indicator	Points	Maximum threshold
Records		
BP 1. The practice can produce a register of patients with established hypertension	9	
Diagnosis and initial management		
BP 2.The percentage of patients with hypertension whose notes record smoking status at least once	10	90%
BP 3.The percentage of patients with hypertension who smoke, whose notes contain a record that smoking cessation advice has been offered at least once	10	90%
Ongoing Management		
BP 4.The percentage of patients with hypertension in which there is a record of the blood pressure in the past 9 months	20	90%
BP 5. The percentage of patients with hypertension in whom the last blood pressure (measured in last 9 months) is 150/90 or less	56	70%

BP and Cholesterol Monitoring, all Coronary Heart Disease Patients (April 2004 and March 2006) Ayrshire and Arran, Scotland. 19,164 patients with CHD (prevalence 5.54%)



New British Hypertension Society-NICE Guideline 2006 - Conclusions

- Newer drugs are better than older drugs, especially in combination
- ACE inhibitors have additional protective effects against myocardial infarction
- Payment of doctors by results - works!

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