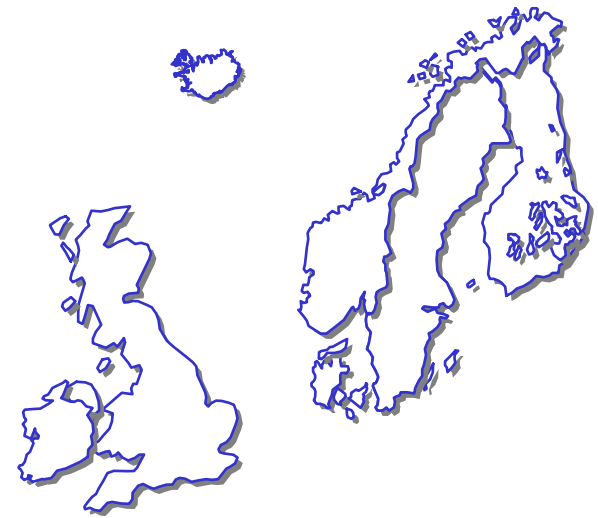


Anglo-Scandinavian
ascot
Cardiac Outcomes Trial



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**

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ASCOT- BPLA: Rationale

- Insufficient outcome data on newer types of BP-lowering agents, especially in specific combination treatment regimens
- Less-than-expected CHD prevention using standard therapy

ASCOT- BPLA

Primary Objective

To compare the effect on non-fatal myocardial infarction (MI) and fatal CHD of the standard antihypertensive regimen (β -blocker \pm diuretic) with a more contemporary regimen (CCB \pm ACE inhibitor)

Additional objectives include:

Secondary end points

- Total stroke
- All coronary events
- Primary end point minus silent MI
- Total cardiovascular (CV) events and procedures
- CV mortality
- All-cause mortality
- Heart failure

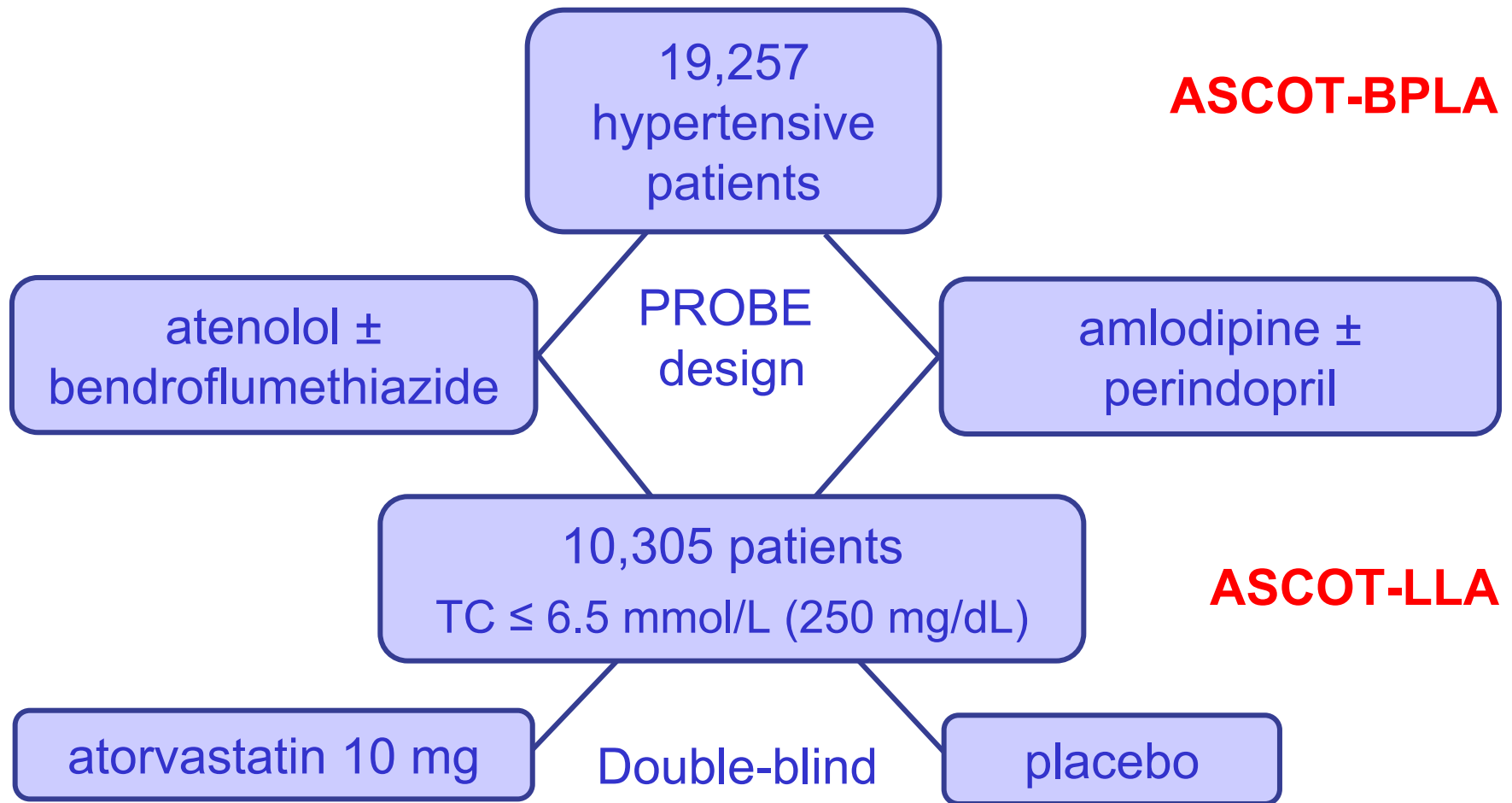
Tertiary end points

- Development of diabetes
- Impairment of renal function
- Pre-specified end points in pre-specified subgroups
- Life-threatening arrhythmias

Other objectives

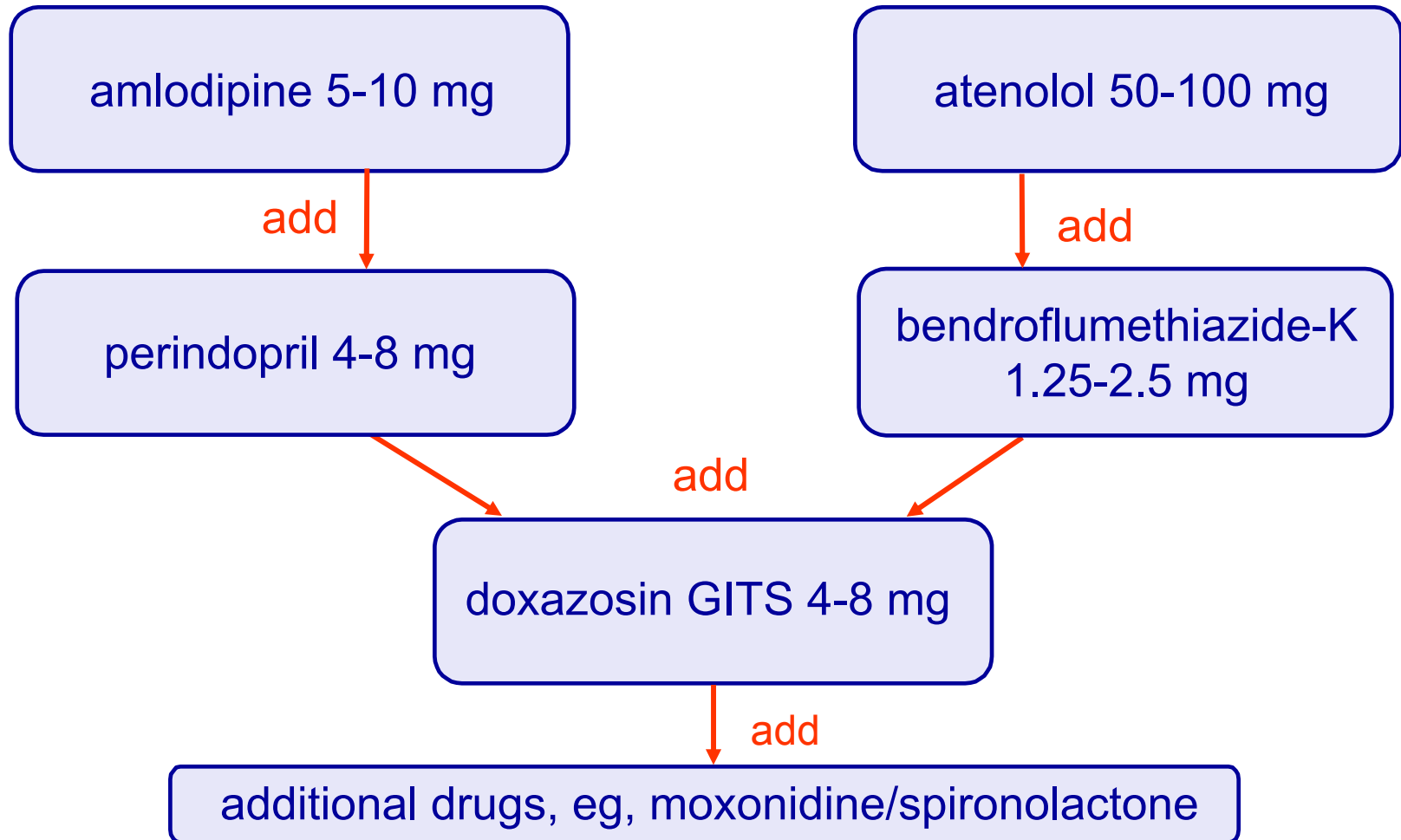
- Interaction between statins and antihypertensive treatment
- Health economic analyses

Study design



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

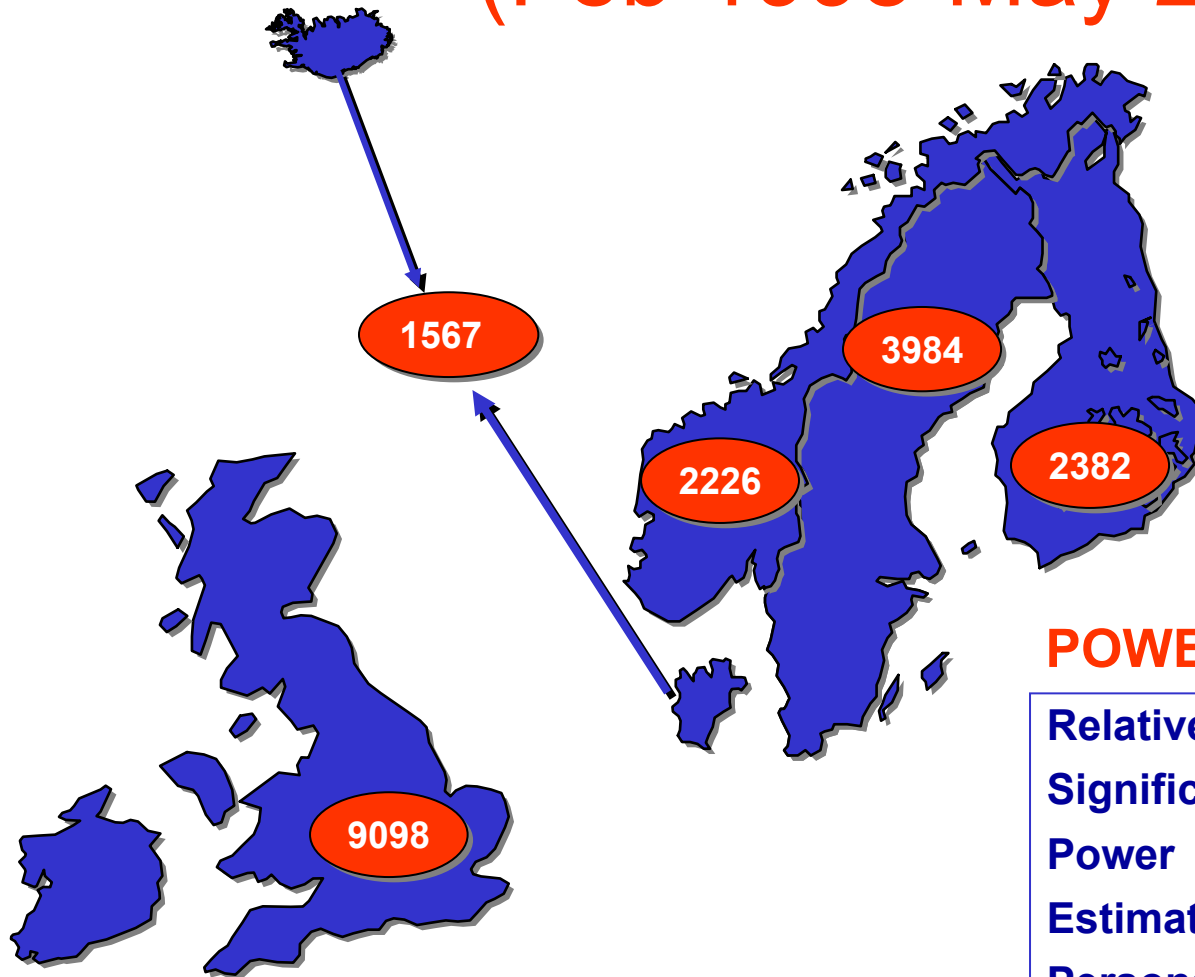
Treatment algorithm to BP targets < 140/90 mm Hg or < 130/80 mm Hg in patients with diabetes



Patient inclusion criteria

- Screening and baseline BP
 - $\geq 160/100$ mm Hg untreated
 - $\geq 140/90$ mm Hg following treatment with 1 or more drugs
- Age 40-79 years
- ***No previous MI or current clinical CHD***
- 3 or more CV risk factors

Study power and recruitment (Feb 1998-May 2000)



TOTAL RECRUITED 19,257

POWER: PRIMARY END POINT

Relative additional benefit (ITT)	16%
Significance level	5%
Power	80%
Estimated sample size	18,000
Persons with events	1150

Baseline characteristics

amlodipine ± perindopril atenolol ± thiazide

Demographics and clinical characteristics

	n = 9639	n = 9618
Woman	2258 (23.4%)	2257 (23.5%)
White	9187 (95.3%)	9170 (95.3%)
Current smoker	3168 (32.9%)	3110 (32.3%)
Age (years)	63.0 (8.5)	63.0 (8.5)
SBP (mm Hg)	164.1 (18.1)	163.9 (18.0)
DBP (mm Hg)	94.8 (10.4)	94.5 (10.4)
Heart rate (bpm)	71.9 (12.7)	71.8 (12.6)
BMI (kg/m ²)	28.7 (4.6)	28.7 (4.5)

Drug therapy

Previous antihypertensive treatments		
0	1841 (19.1%)	1825 (19.0%)
1	4280 (44.4%)	4283 (44.5%)
≥ 2	3518 (36.5%)	3510 (36.5%)
Lipid-lowering therapy	1046 (10.9%)	1004 (10.4%)
Aspirin	1851 (19.2%)	1837 (19.1%)

Values are number of patients, (%) or mean (SD)

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 \pm thiazide would continue to be disadvantaged compared with the comparator group

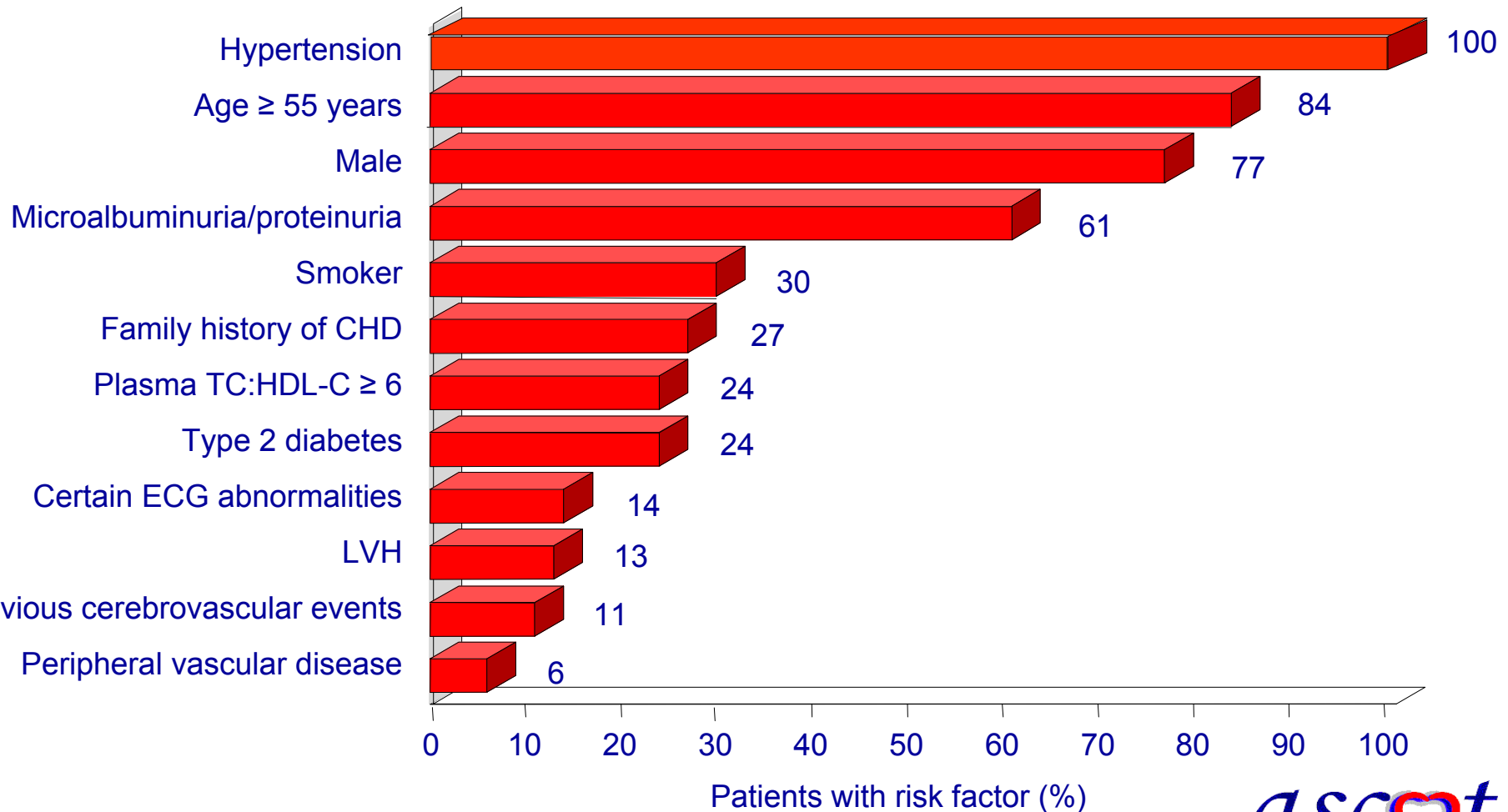
The Steering Committee endorsed the recommendation of the DSMB, and trial closure began Dec, 2004 and ended June 2005.

Statistical methods

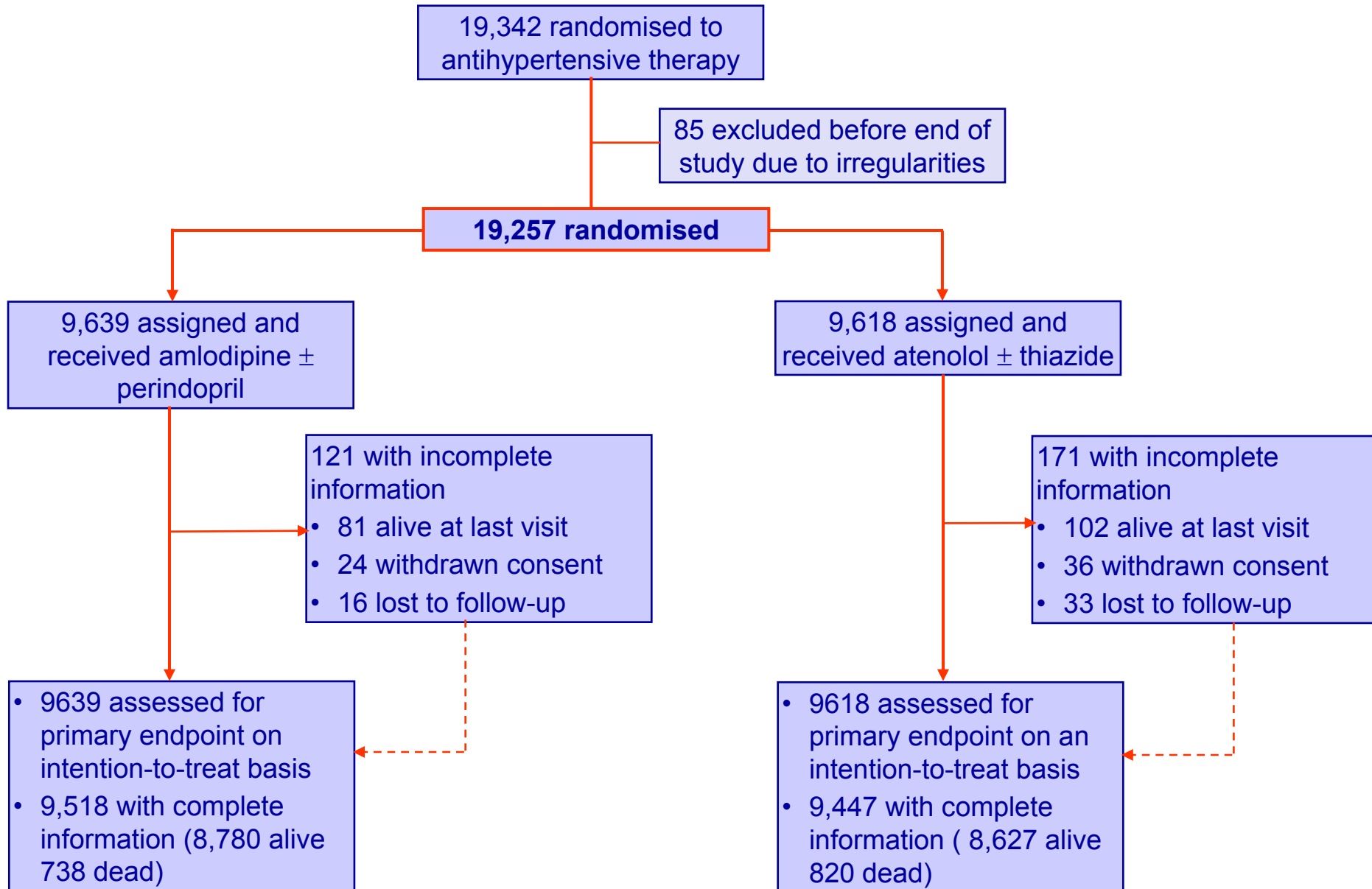
- Based on an intention-to-treat analysis
- Time to first primary event
- Log-rank procedure and Cox's Proportional Hazards were used to calculate confidence intervals
- Cumulative incidence curves were generated using the Kaplan-Meier method

ASCOT patient population risk factor profile

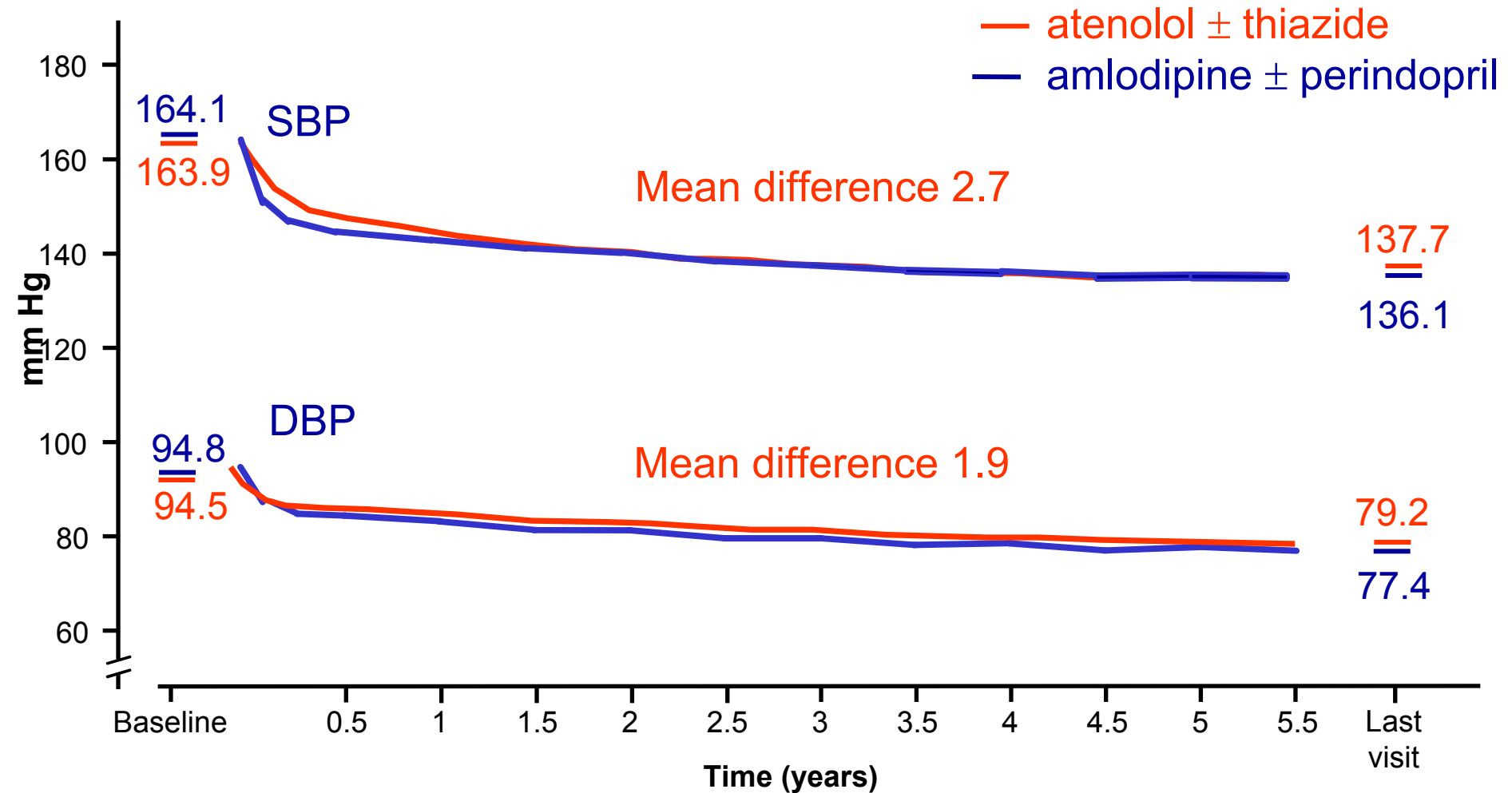
All patients in ASCOT have hypertension plus ≥ 3 risk factors for CHD



ascot trial design



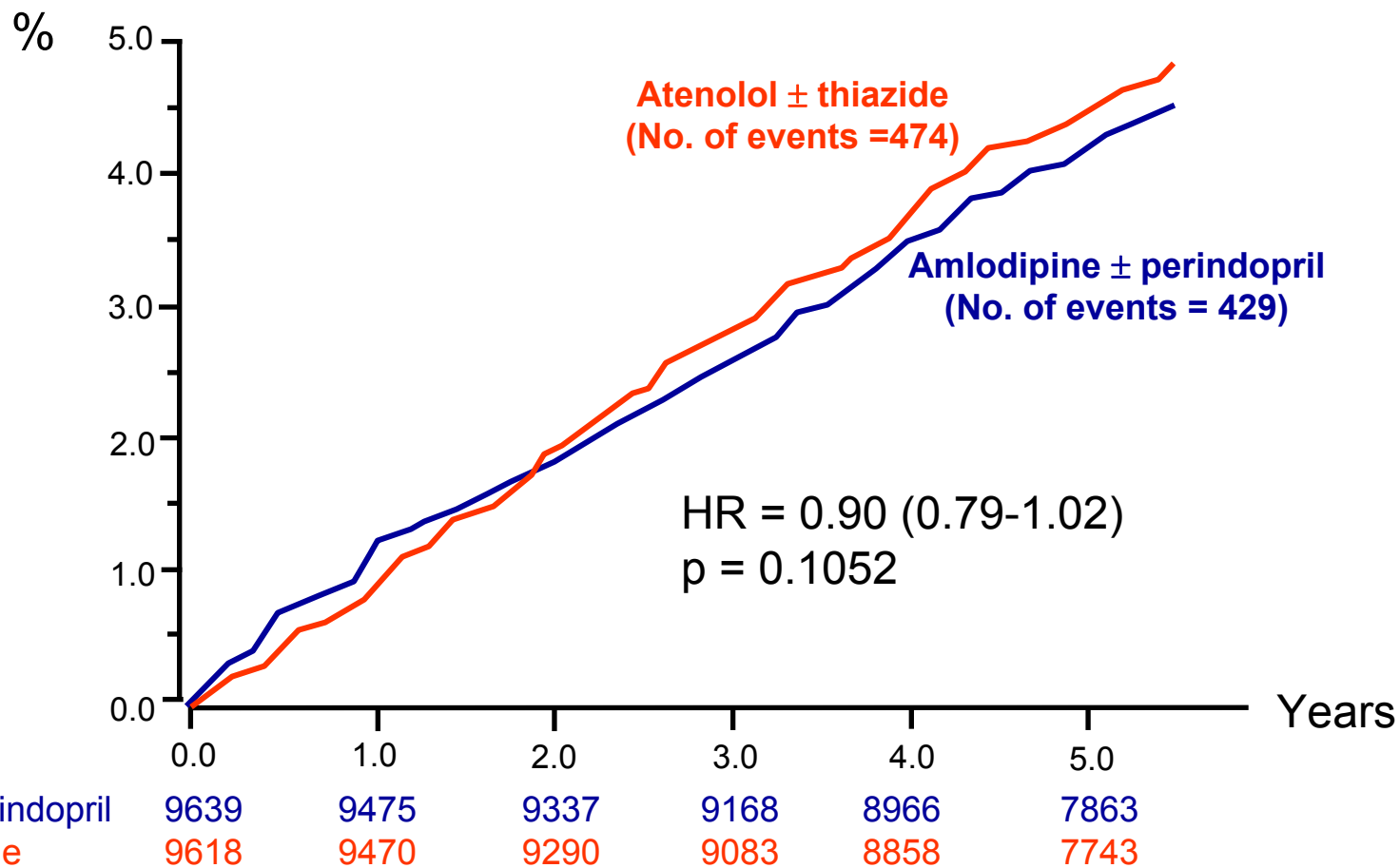
Systolic and diastolic blood pressure



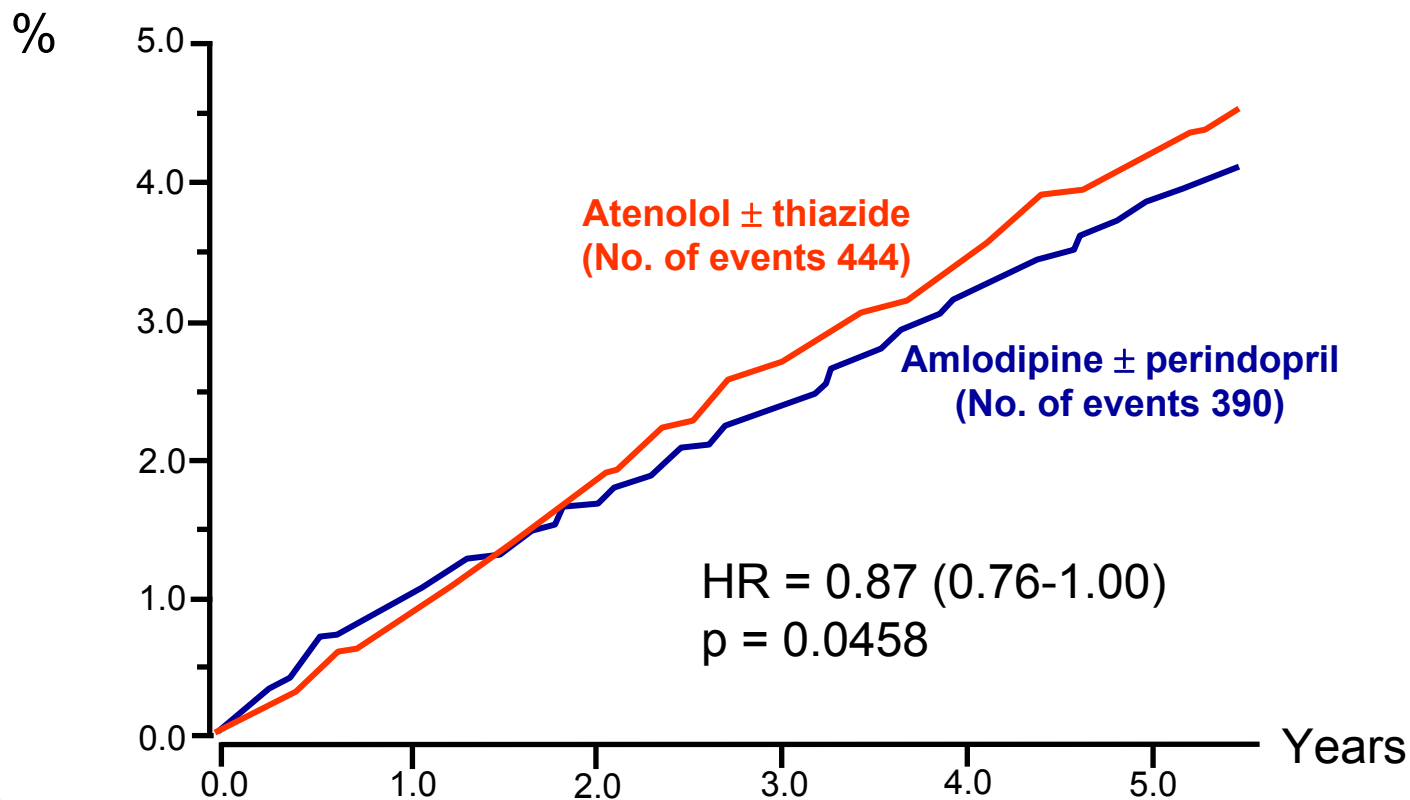
Mean proportion of time on antihypertensive medication by treatment group

	Year 1	All Study
Randomised to Amlodipine		
Amlodipine	88.2	82.5
Perindopril	46.2	58.5
Amlodipine + perindopril	39.1	49.5
Randomised to atenolol		
Atenolol	87.4	79.4
Bendroflumethiazide	56.6	65.7
Atenolol + bendroflumethiazide	49.1	54.9

Primary end point: Non-fatal MI, fatal CHD



Endpoints: Non-fatal MI (excl silent) + fatal CHD



Number at risk

Amlodipine ± perindopril

Atenolol ± thiazide

9639

9485

9354

9193

8998

7895

9618

9475

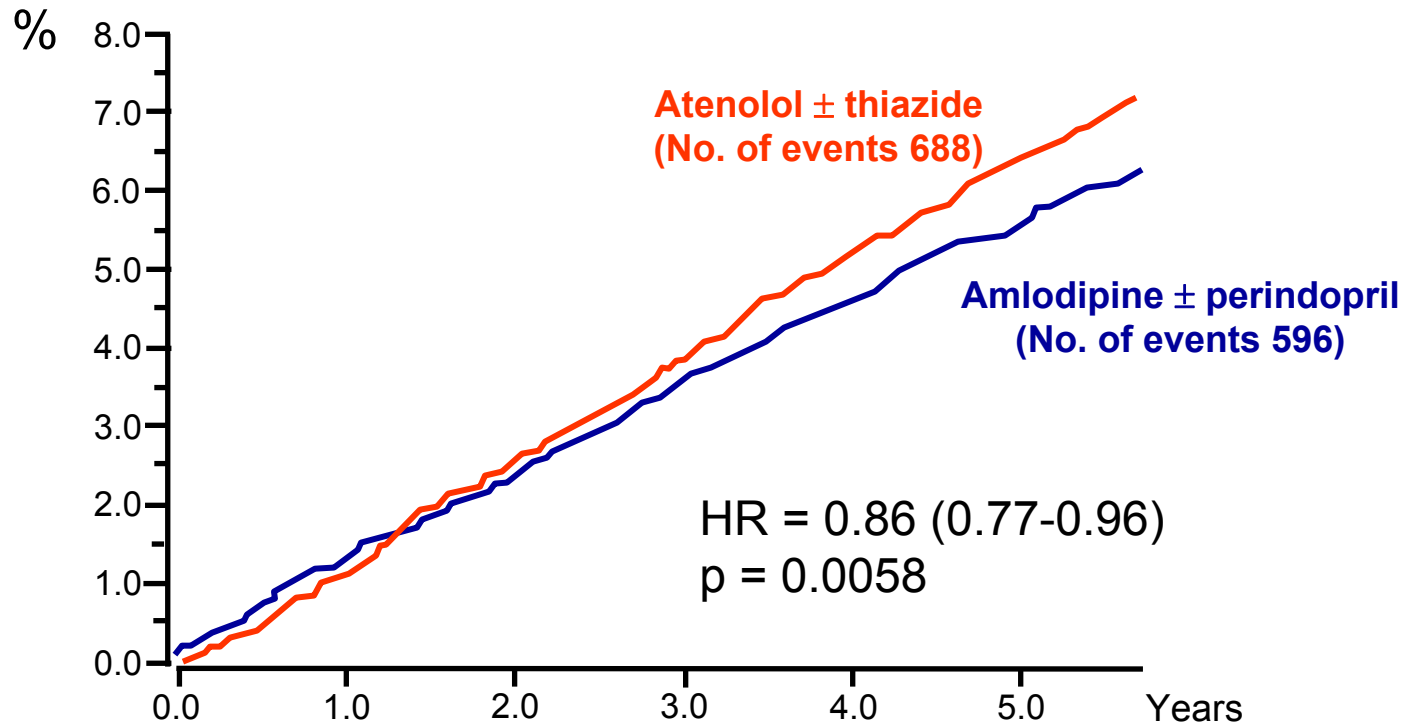
9302

9099

8881

7768

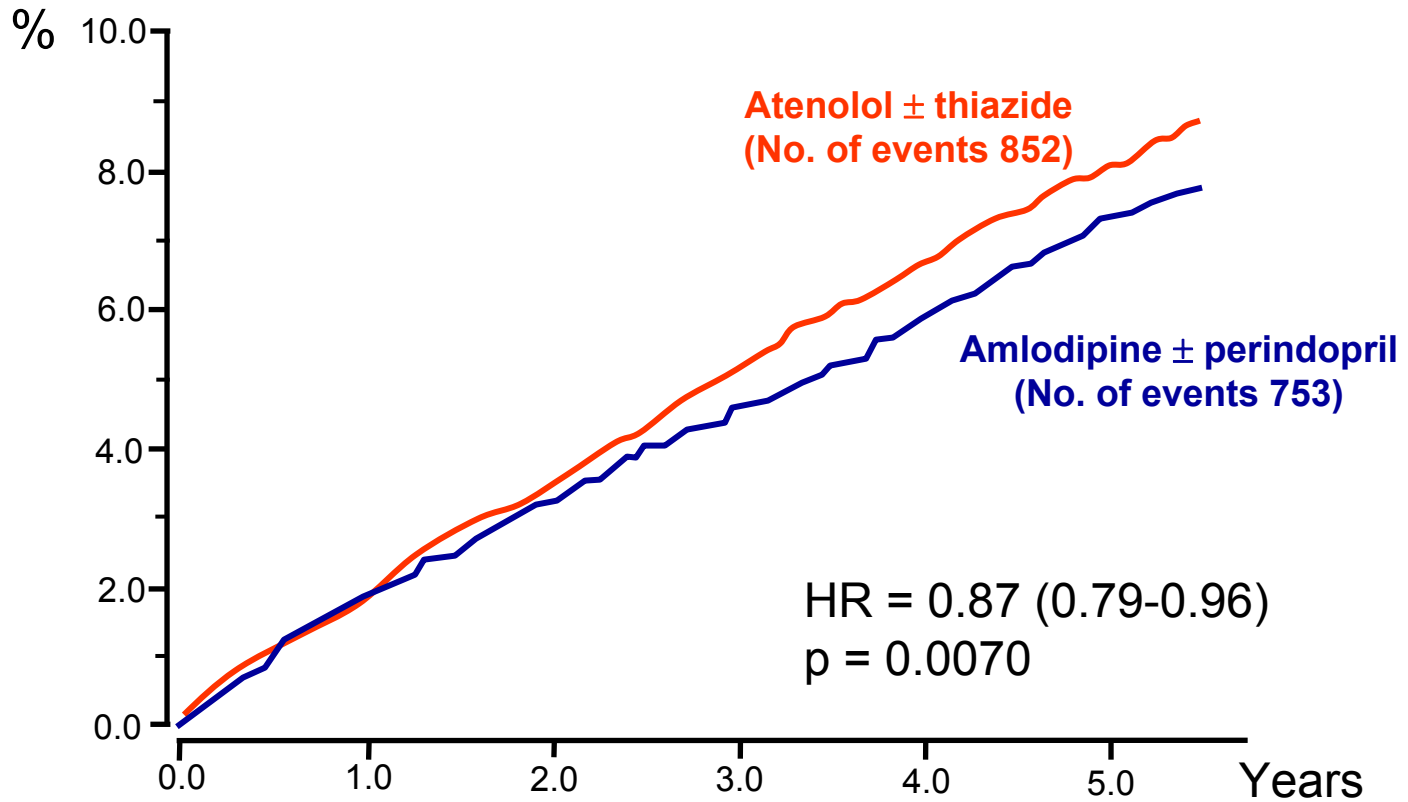
Primary end point + coronary revascularisation procedures



Number at risk

Amlodipine ± perindopril	9639	9458	9288	9086	8857	7732
Atenolol ± thiazide	9618	9447	9236	8986	8719	7590

Total coronary end point

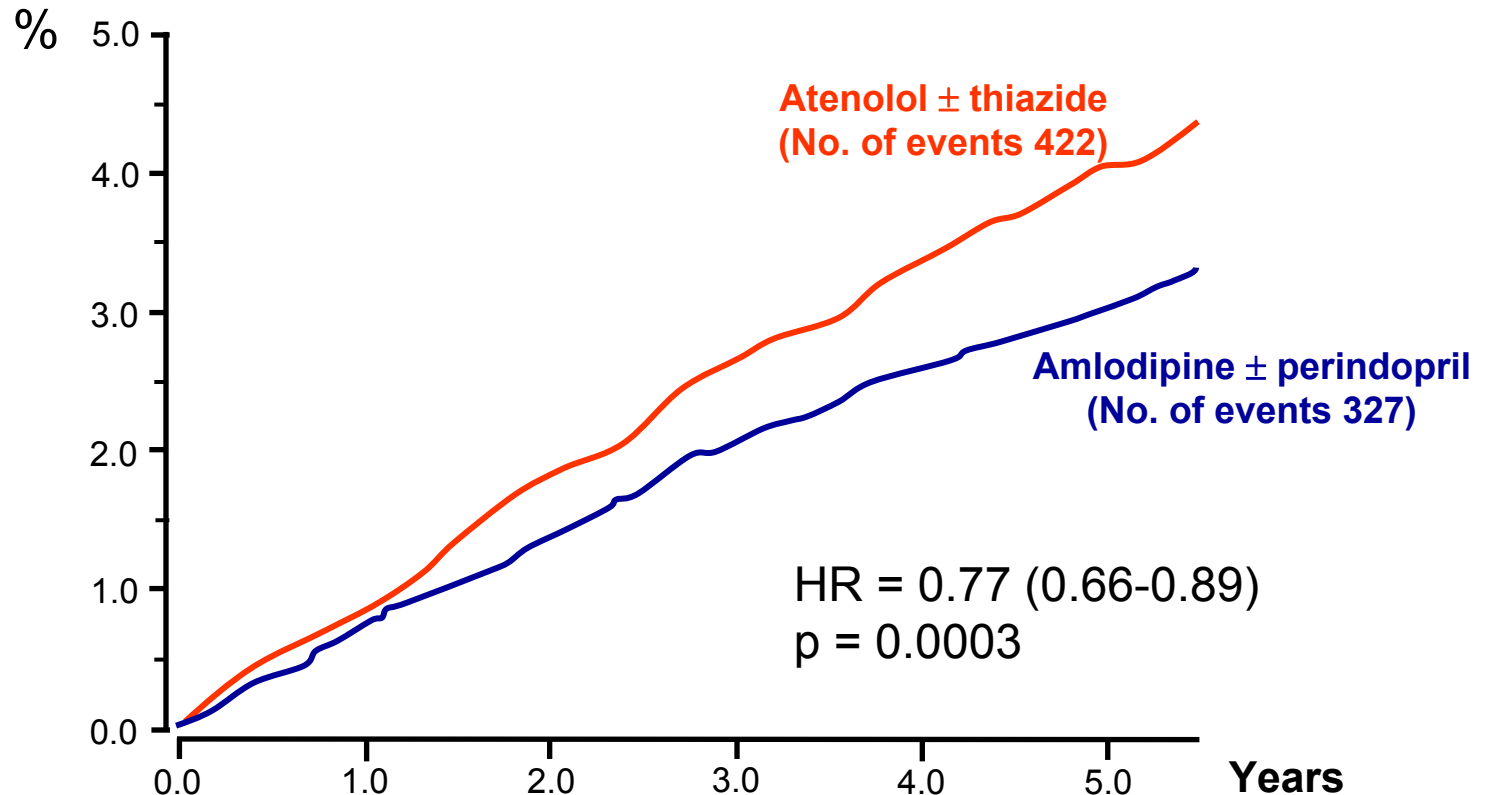


Number at risk

Amlodipine ± perindopril
Atenolol ± thiazide

9639	9400	9204	8984	8744	7614
9618	9373	9136	8864	8591	7470

Fatal and non-fatal stroke

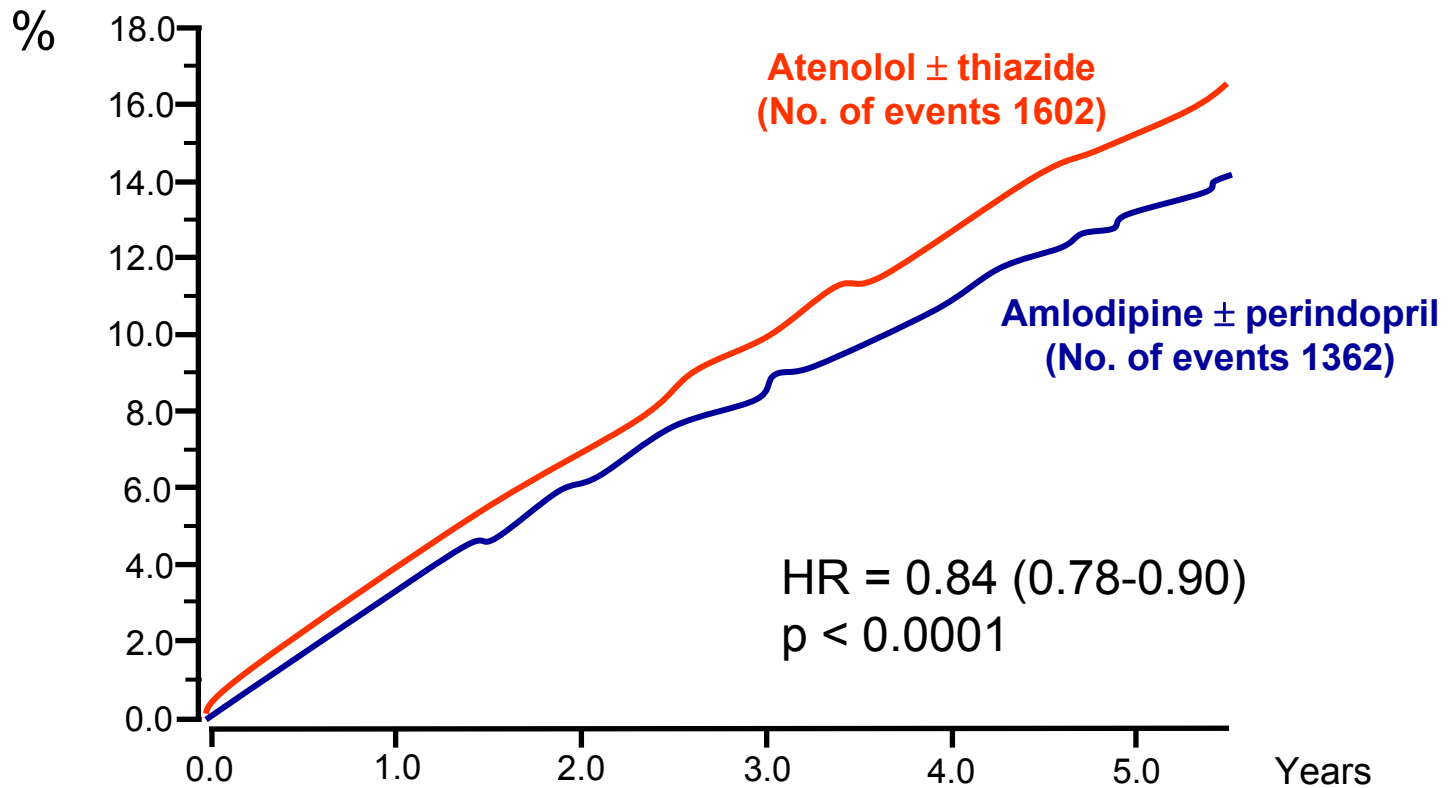


Number at risk

Amlodipine ± perindopril
Atenolol ± thiazide

Years	0.0	1.0	2.0	3.0	4.0	5.0
Amlodipine ± perindopril	9639	9483	9331	9156	8972	7863
Atenolol ± thiazide	9618	9461	9274	9059	8843	7720

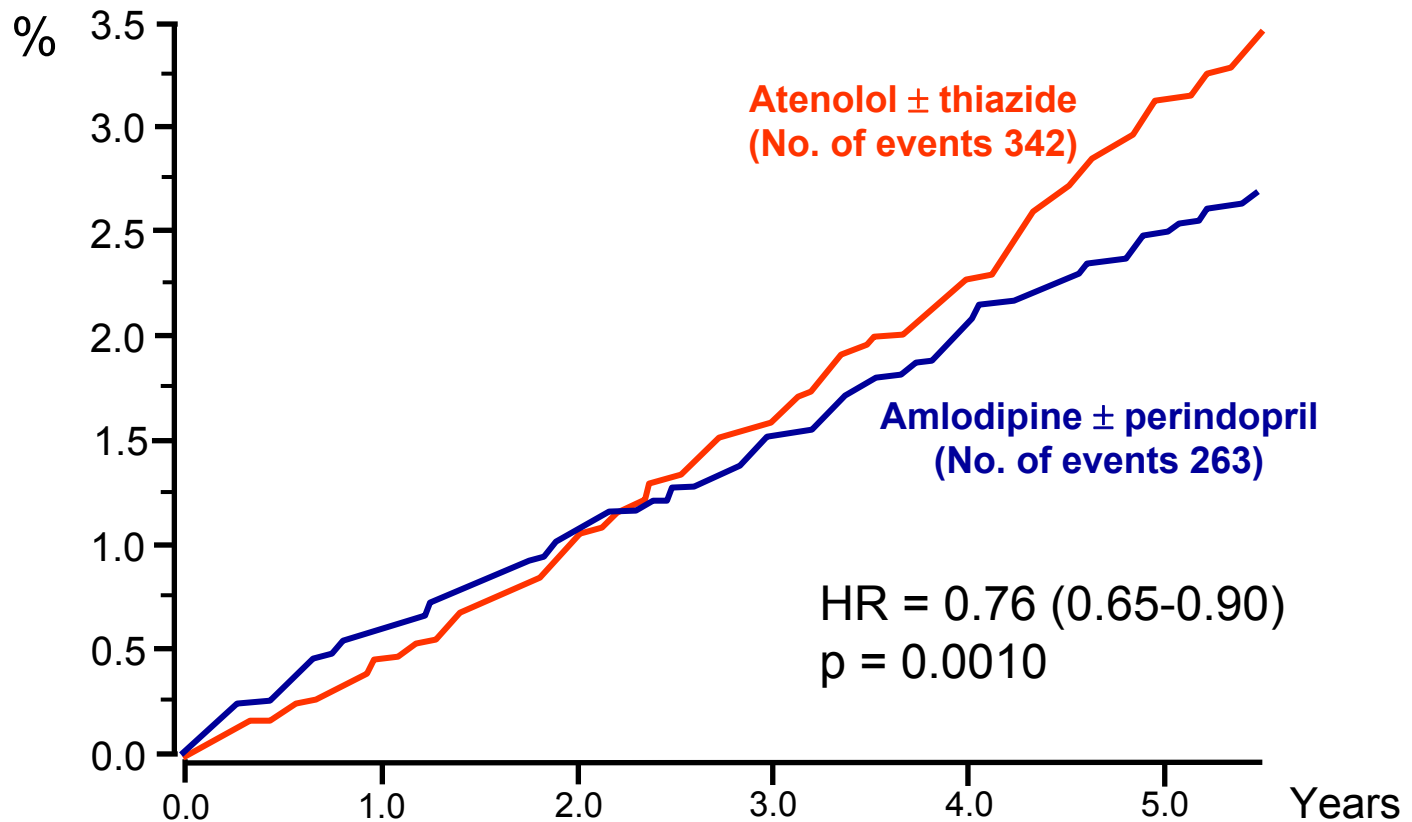
Total CV events and procedures



Number at risk

Amlodipine ± perindopril	9639	9277	8957	8646	8353	7207
Atenolol ± thiazide	9618	9210	8848	8465	8121	6977

CV mortality



Number at risk

Amlodipine ± perindopril
Atenolol ± thiazide

9639
9618

9544
9532

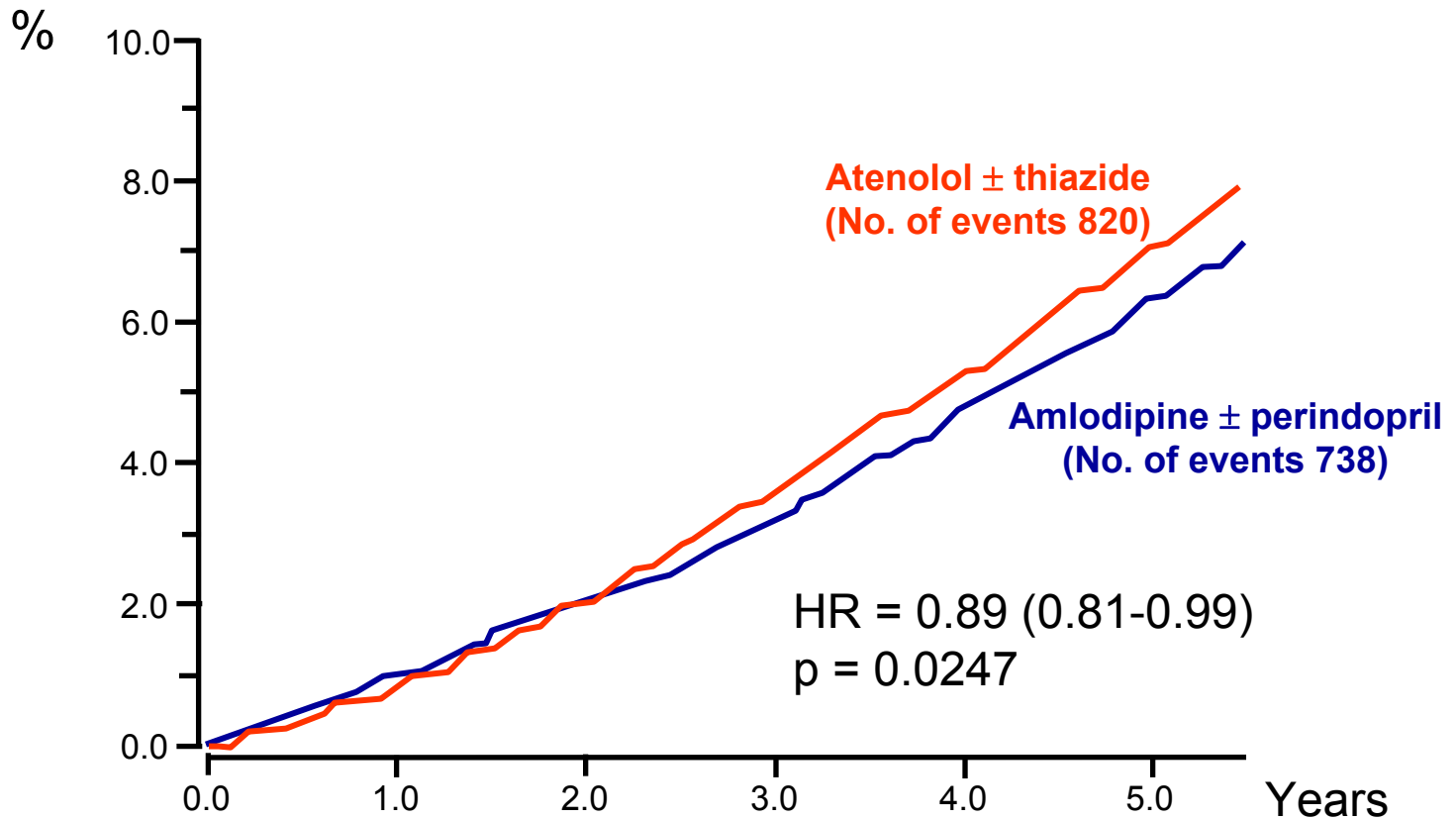
9441
9415

9322
9261

9167
9085

8078
7975

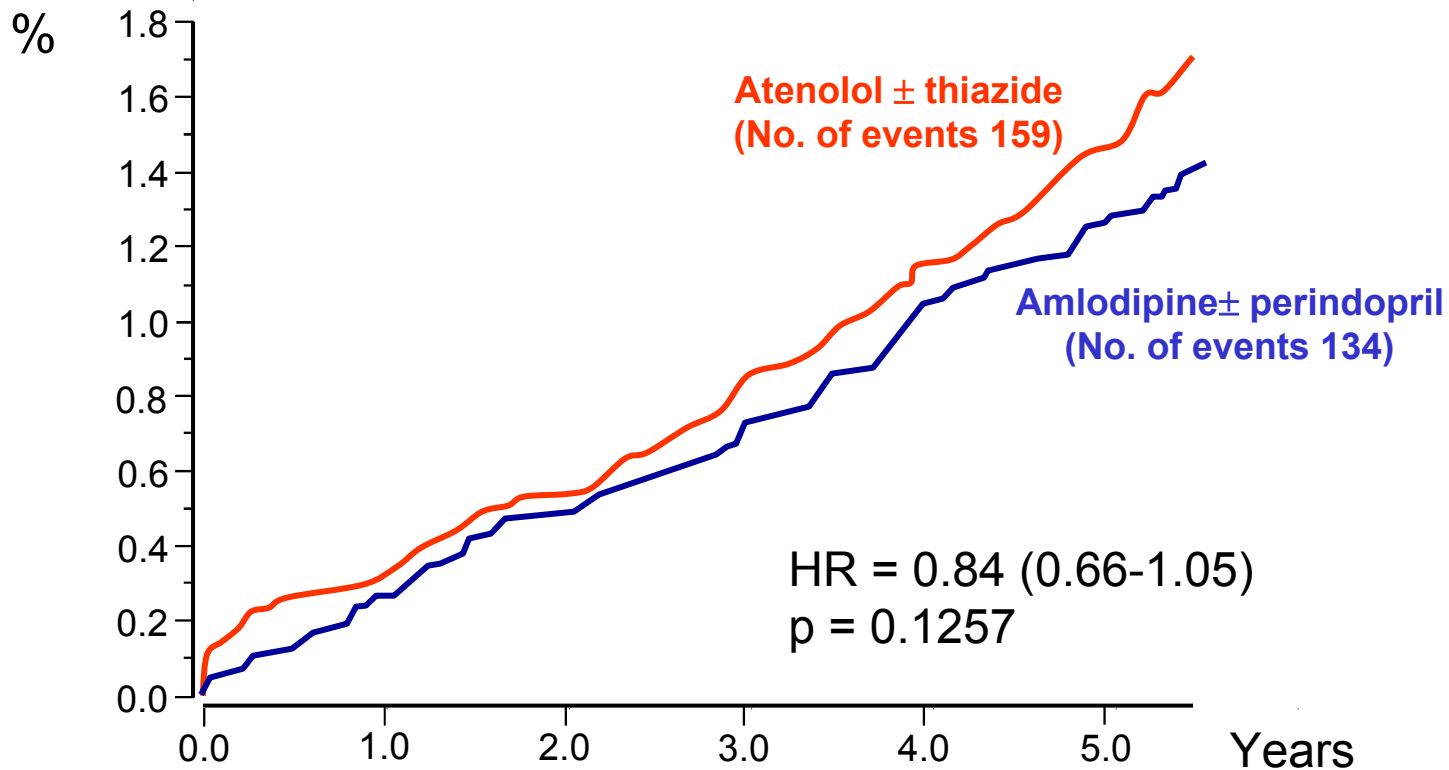
All-cause mortality



Number at risk

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

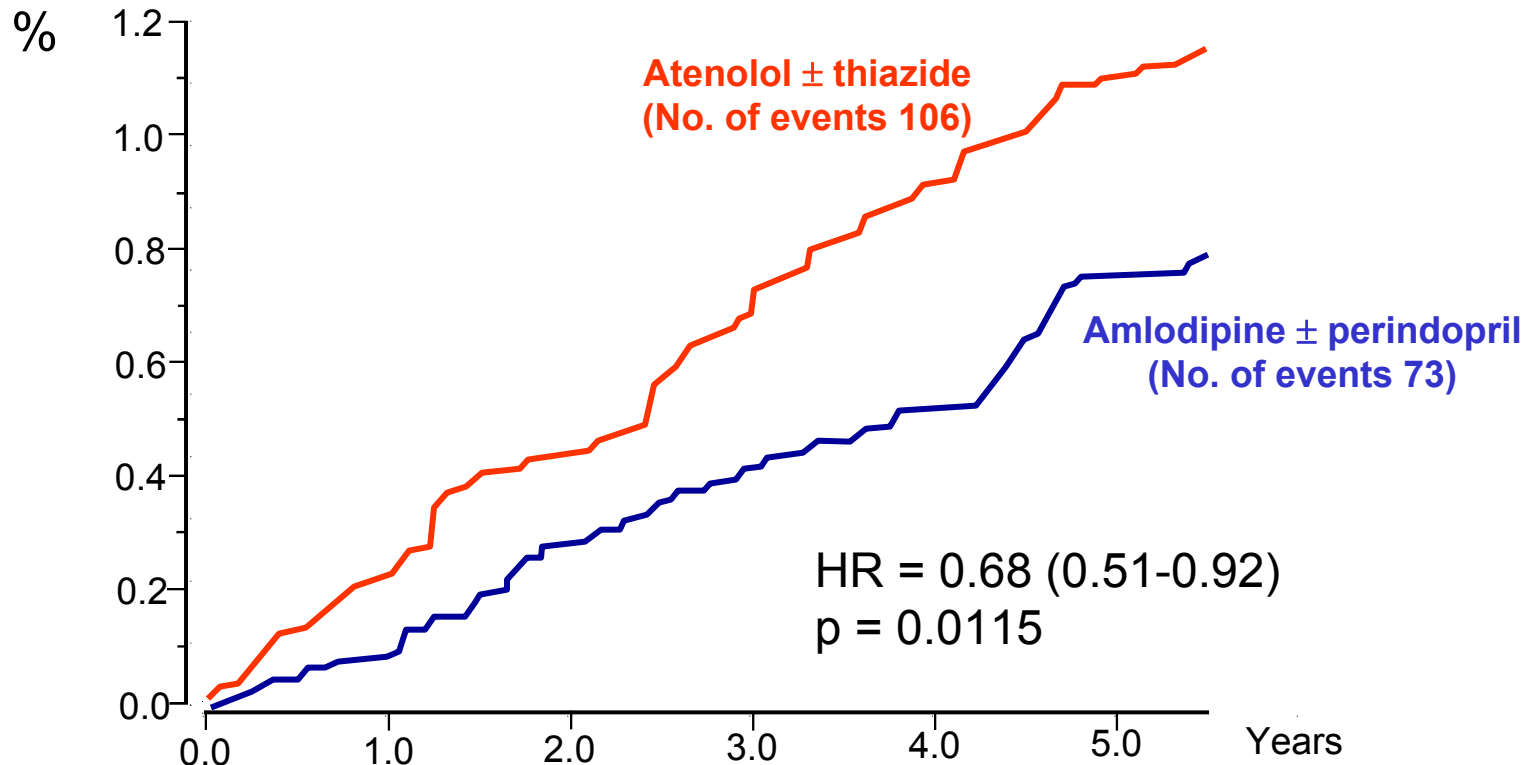
Fatal and non-fatal heart failure



Number at risk

	0.0	1.0	2.0	3.0	4.0	5.0
Amlodipine ± perindopril	9639	9524	9409	9275	9101	8004
Atenolol ± thiazide	9618	9501	9369	9195	9011	7901

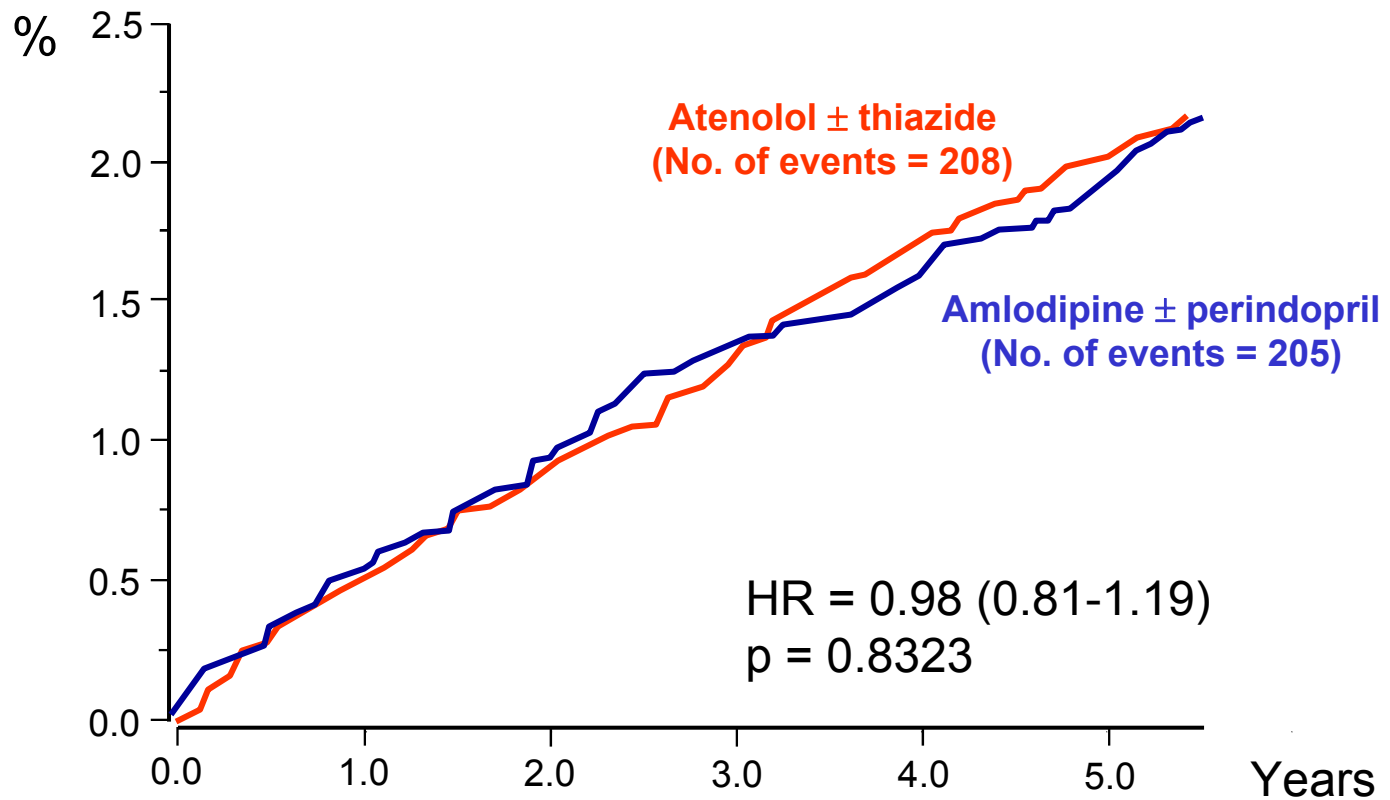
Unstable angina



Number at risk

Amlodipine ± perindopril	9639	9536	9416	9285	9123	8021
Atenolol ± thiazide	9618	9510	9374	9198	9007	7888

Chronic stable angina



Number at risk

Amlodipine ± perindopril
Atenolol ± thiazide

9639
9618

9493
9482

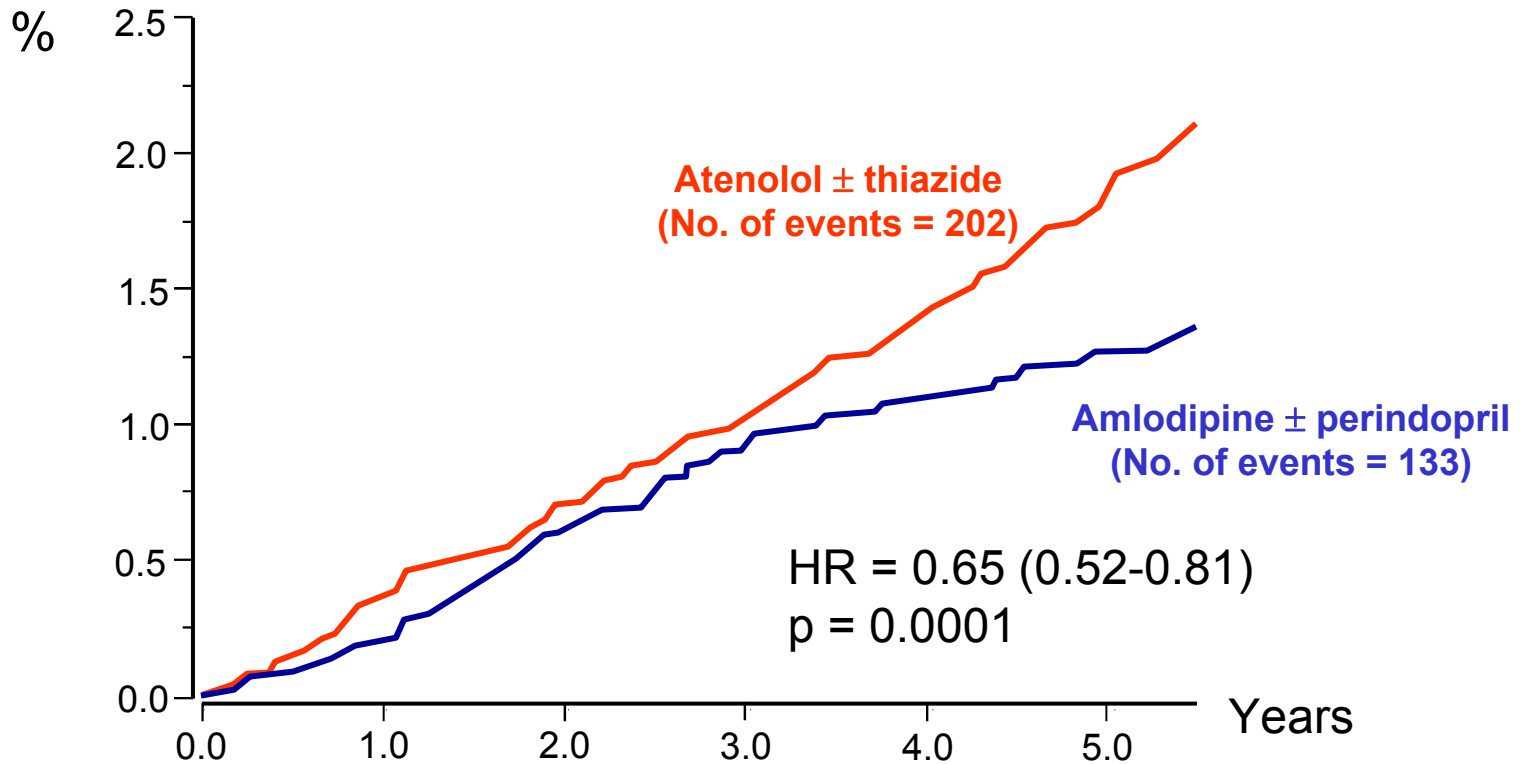
9350
9327

9198
9135

9017
8924

7917
7817

Peripheral arterial disease



Number at risk

Amlodipine ± perindopril

9639

9523

9382

9237

9070

7958

Atenolol ± thiazide

9618

9495

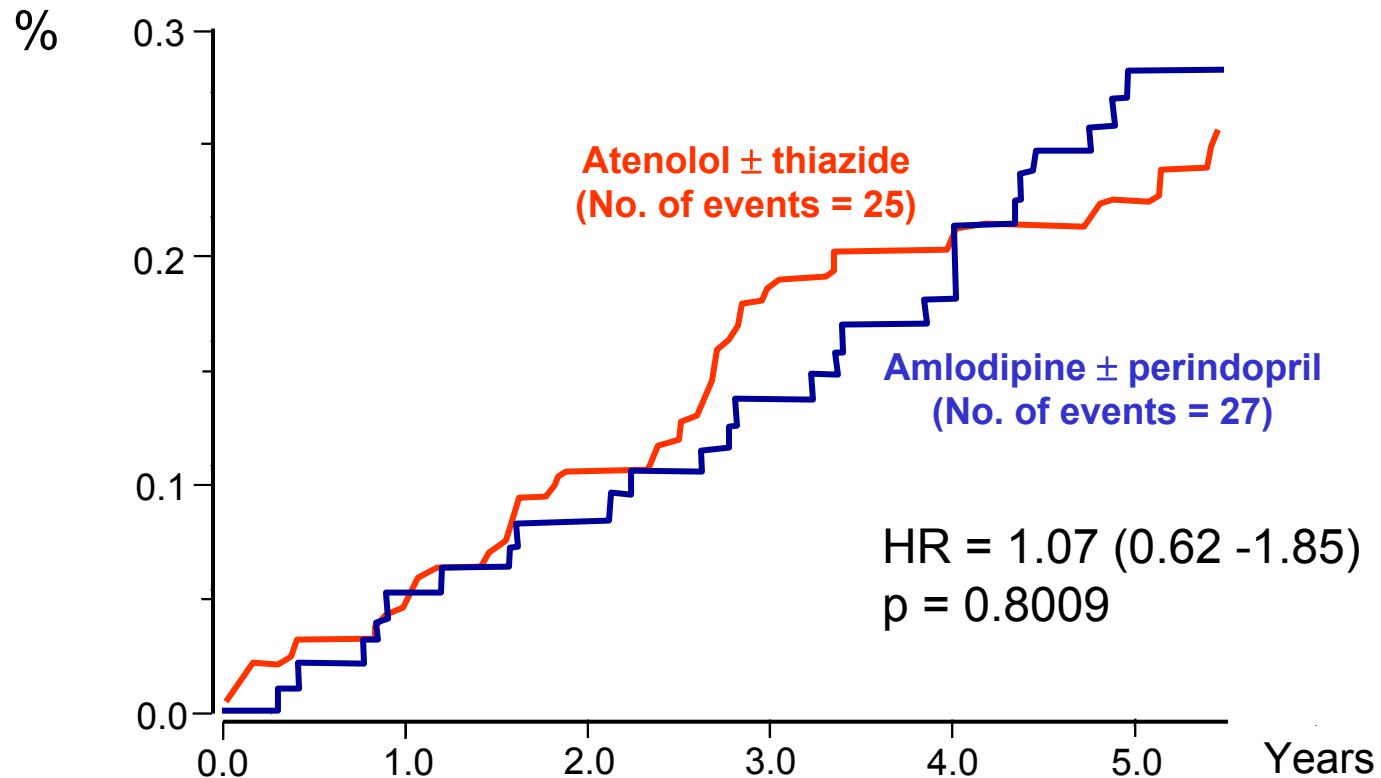
9348

9163

8958

7828

Life-threatening arrhythmias

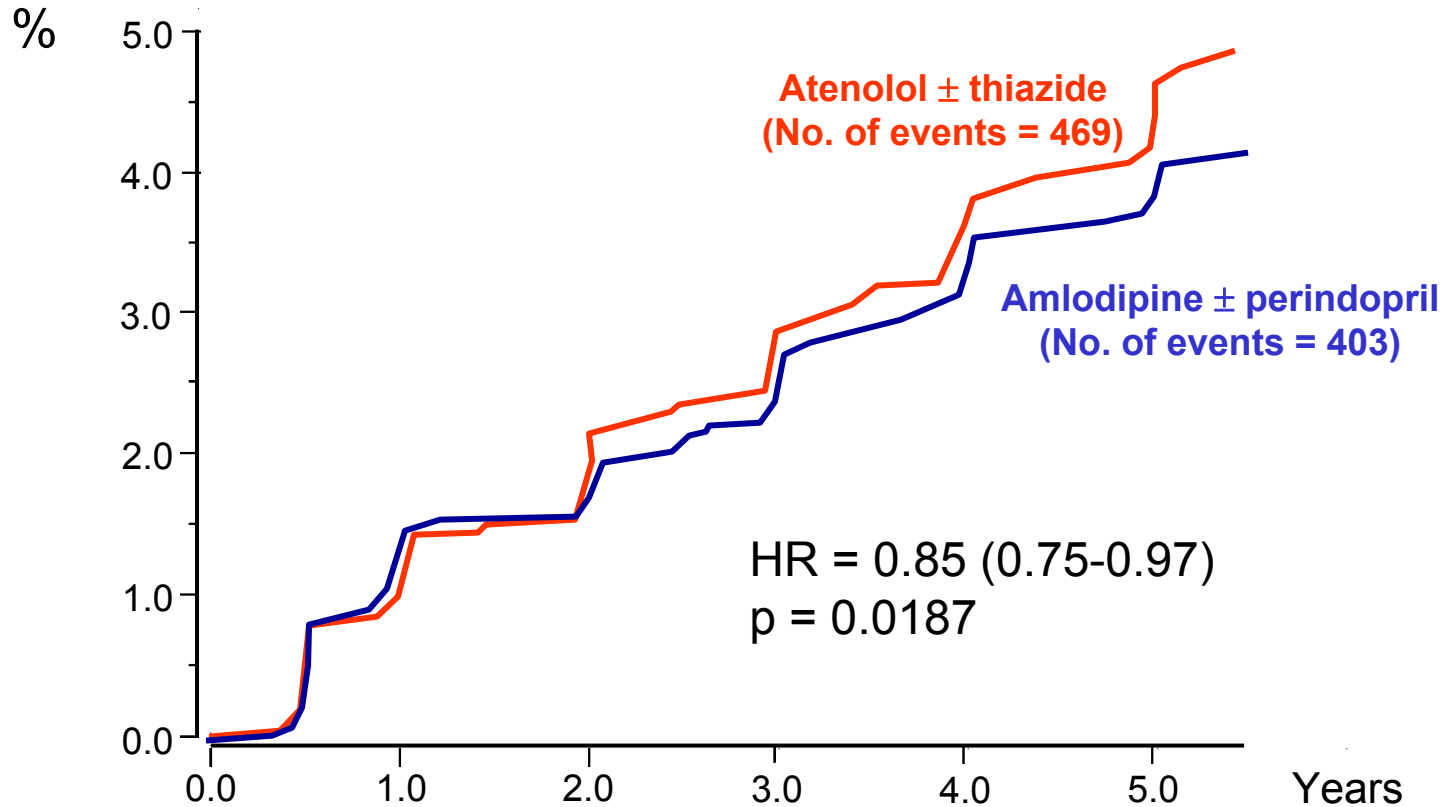


Number at risk

Amlodipine ± perindopril	9639	9539	9433	9310	9153	8060
Atenolol ± thiazide	9618	9527	9405	9243	9069	7961

9639	9539	9433	9310	9153	8060
9618	9527	9405	9243	9069	7961

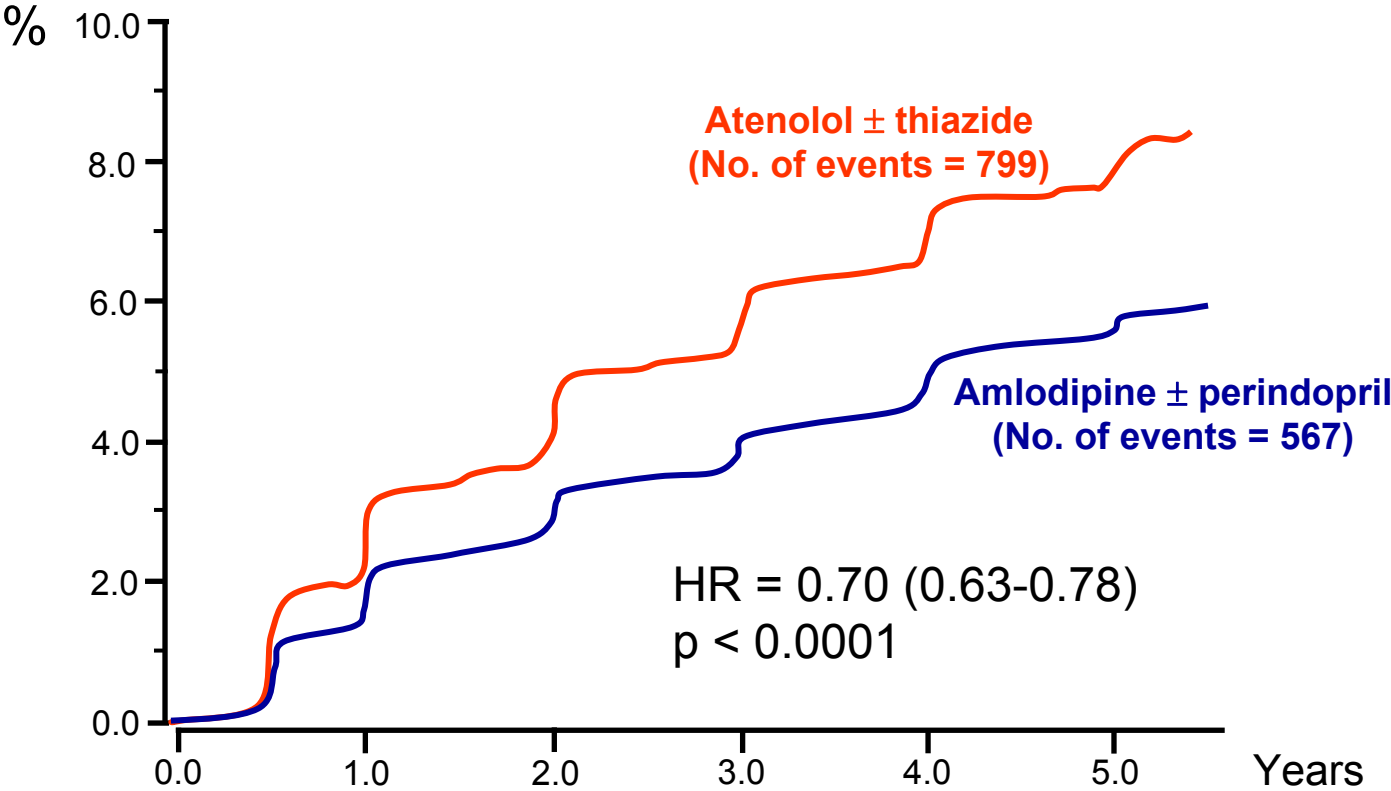
New-onset renal impairment



Number at risk

Amlodipine ± perindopril	9639	9426	9277	9093	8877	7775
Atenolol ± thiazide	9618	9431	9247	9021	8782	7640

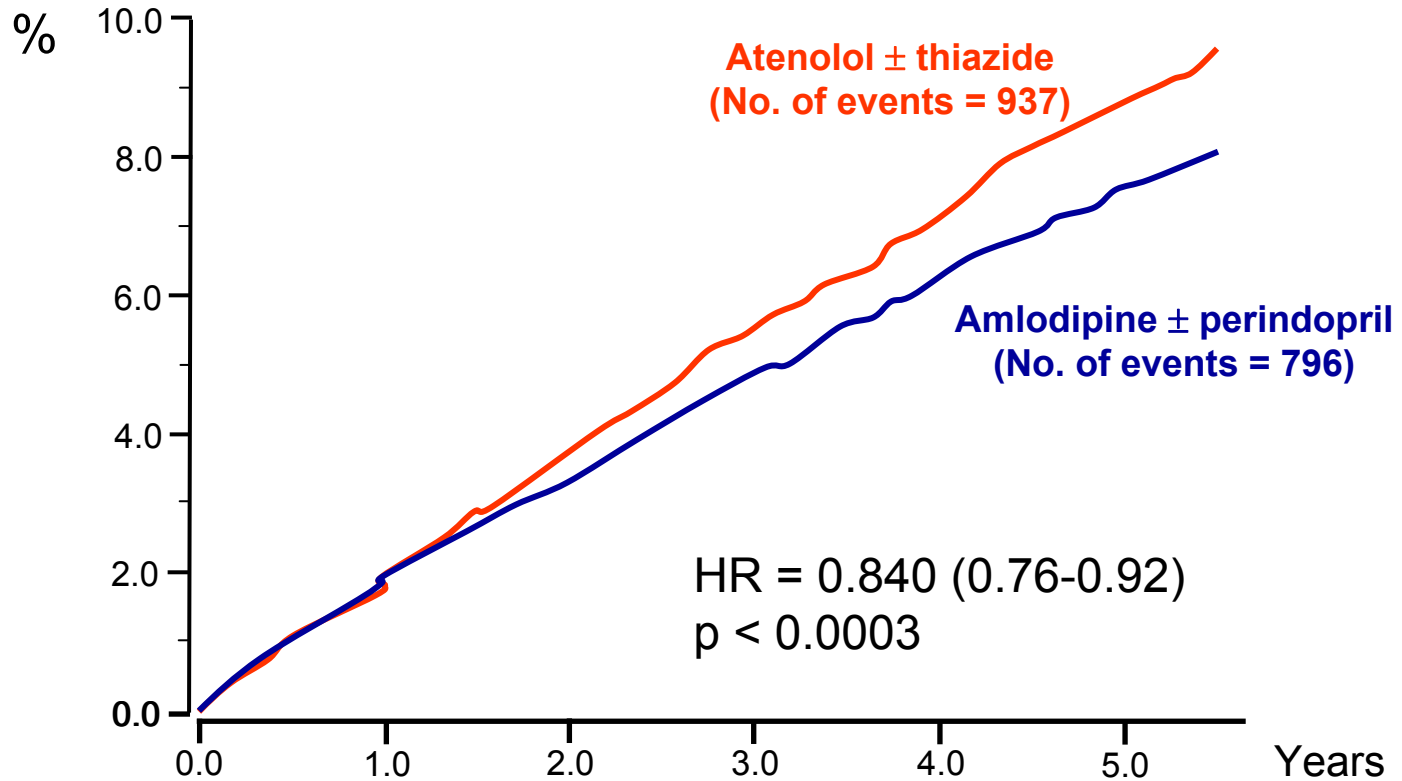
New-onset diabetes mellitus



Number at risk

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

CV death + MI + stroke



Number at risk

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

Summary of all end points

Primary

Non-fatal MI (incl silent) + fatal CHD

Secondary

Non-fatal MI (exc. Silent) +fatal CHD

Total coronary end point

Total CV event and procedures

All-cause mortality

Cardiovascular mortality

Fatal and non-fatal stroke

Fatal and non-fatal heart failure

Tertiary

Silent MI

Unstable angina

Chronic stable angina

Peripheral arterial disease

Life-threatening arrhythmias

New-onset diabetes mellitus

New-onset renal impairment

Post hoc

Primary end point + coronary revasc procs

CV death + MI + stroke

Unadjusted Hazard
ratio (95% CI)

0.90 (0.79-1.02)

0.87 (0.76-1.00)

0.87 (0.79-0.96)

0.84 (0.78-0.90)

0.89 (0.81-0.99)

0.76 (0.65-0.90)

0.77 (0.66-0.89)

0.84 (0.66-1.05)

1.27 (0.80-2.00)

0.68 (0.51-0.92)

0.98 (0.81-1.19)

0.65 (0.52-0.81)

1.07 (0.62-1.85)

0.70 (0.63-0.78)

0.85 (0.75-0.97)

0.86 (0.77-0.96)

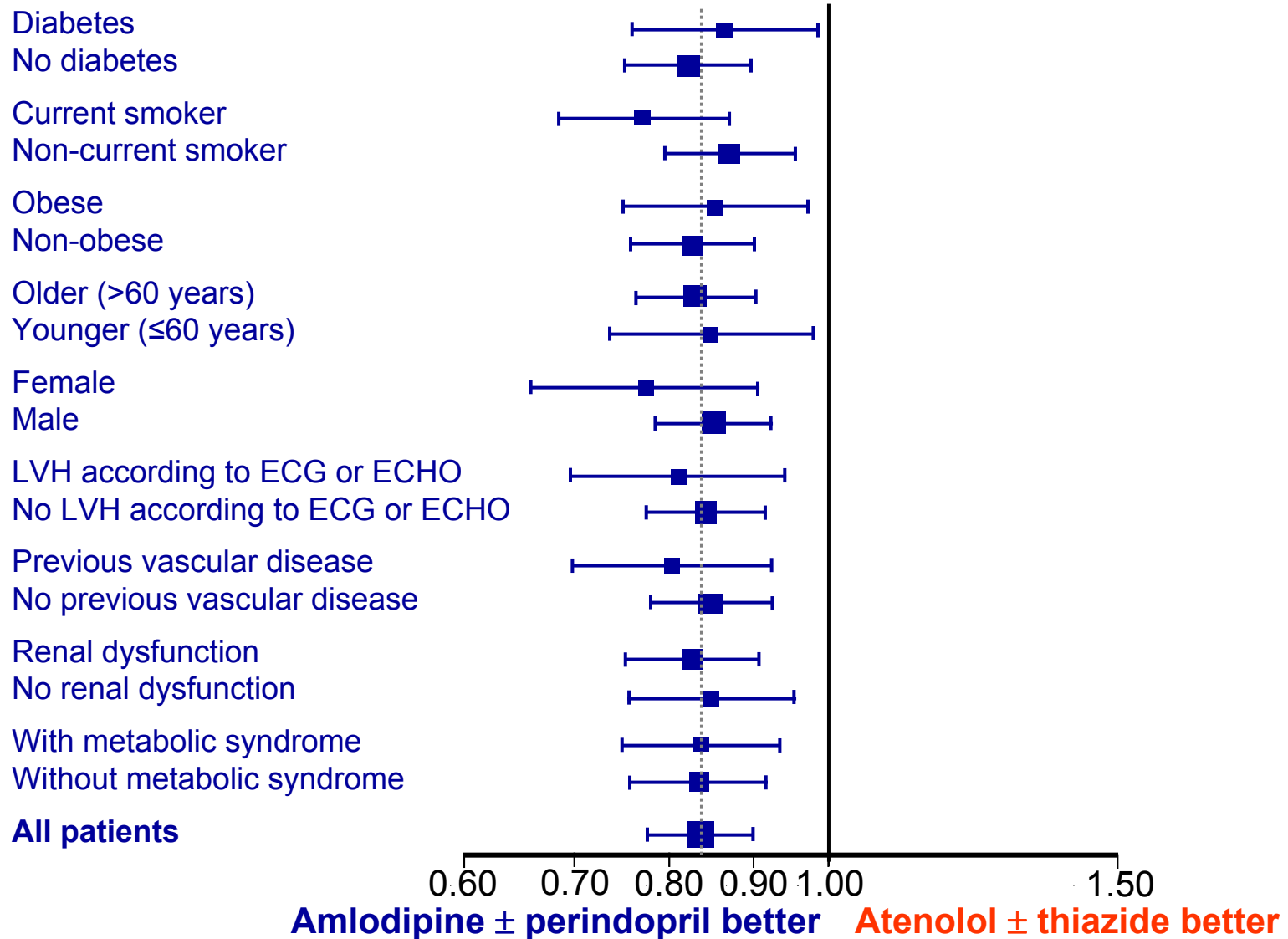
0.84 (0.76-0.92)

0.50 0.70 1.00 1.45 2.00
Amlodipine ± perindopril better Atenolol ± thiazide better

The area of the blue square is proportional to the amount of statistical information

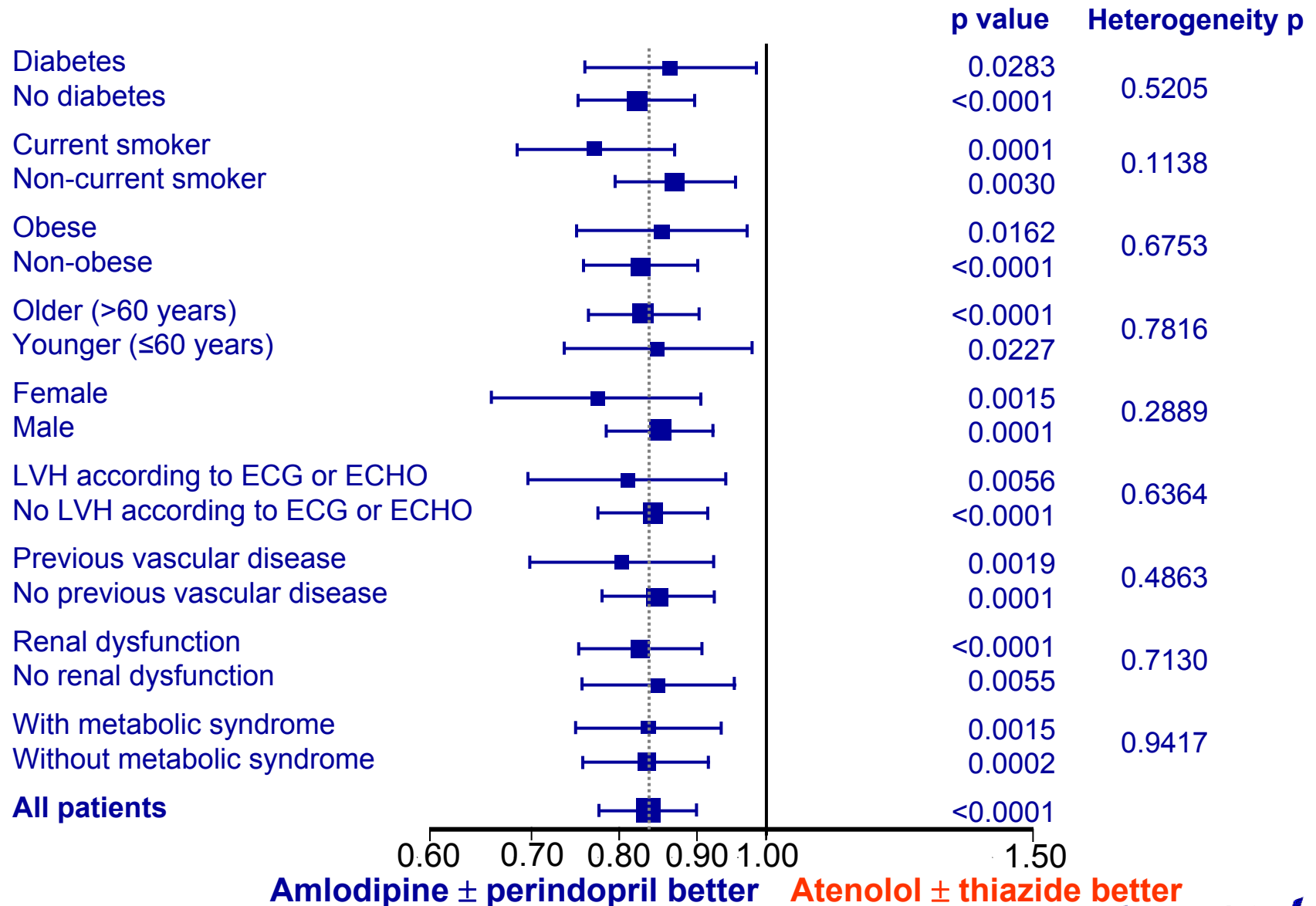
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Total CV events and procedures among subgroups



The area of the black square is proportional to the amount of statistical information

Total CV events and procedures among subgroups



The area of the black square is proportional to the amount of statistical information

Adverse events leading to treatment discontinuation

Adverse event	Amlodipine ± perindopril (%)	Atenolol ± thiazide (%)
Total	2358 (24.5)	2402 (25.0)
Serious	162 (1.7)	254 (2.6)*

* p<0.0001

Adverse events

Adverse event*	Amlodipine ± perindopril n (%)	Atenolol ± thiazide n (%)	p-value
Bradycardia	34 (0.4)	536 (6)	<0.0001
Chest pain	740 (8)	849 (9)	0.0040
Cough	1859 (19)	782 (8)	<0.0001
Diarrhoea	377 (4)	548 (6)	<0.0001
Dizziness	1183 (12)	1555 (16)	<0.0001
Dyspnoea	599 (6)	987 (10)	<0.0001
Eczema	493 (5)	383 (4)	0.0002
Erectile dysfunction	556 (6)	707 (7)	<0.0001
Fatigue	782 (8)	1556 (16)	<0.0001
Joint swelling	1371 (14)	308 (3)	<0.0001
Lethargy	202 (2)	525 (6)	<0.0001
Oedema peripheral	2188 (23)	588 (6)	<0.0001
Peripheral coldness	81 (1)	579 (6)	<0.0001
Vertigo	642 (7)	745 (8)	0.0039

* Adverse events with incidence >5% and difference of more than 1%

ASCOT Committees

Executive and Writing Committee

B Dahlöf, Co-Chairman, Gothenburg, P Sever, Co-Chairman, London, N Poulter, Secretary, London, H Wedel, Statistician, Gothenburg.

Steering Committee

A Adderkin, London, DG Beevers, Birmingham, J Buch, New York (non-voting), M Caulfield, London, R Collins, Oxford, B Dahlöf, Gothenburg, A Jarl, Stockholm (non-voting), SE Kjeldsen, Oslo, A Kristinsson, Reykjavik, J Mehlsen, Copenhagen, G McInnes, Glasgow, M Nieminen, Helsinki, N Poulter, London, E O'Brien, Dublin, P Sever, London, H Wedel, Gothenburg, J Östergren, Stockholm, Servier representative, Paris (non-voting).

Working Group

A Adderkin, London, J Buch, New York, S Cavanaugh (up to 2003), New York, R Chamberlain, New York, B Dahlöf, Gothenburg, S Gee, London, A Holmner, Gothenburg, A Jarl, Stockholm, N Poulter, London, P Sever, London, H Wedel, Gothenburg.

Data Safety Monitoring Board

J Cohn, Minneapolis, L Erhardt, Malmö, K Fox, London, A Oden, Gothenburg, S Pocock, London, J Tuomilehto, Helsinki.

Endpoint Committee

U Dahlström, Linköping, F Fyhrquist, Helsinki, H Hemingway, London, K Midtbo, Oslo.

Substudy Committee

M Caulfield, London, B Dahlöf, Gothenburg, T Kahan, Stockholm, J Mehlsen, Copenhagen, M Nieminen, Helsinki, E O'Brien, Dublin, I Os, Oslo, N Poulter, London, P Sever, London, S Thom, London.

Possible explanations for the observed differences in outcomes

- Better BP lowering with amlodipine \pm perindopril
- Non-BP-lowering benefits of amlodipine \pm perindopril
- Non-BP-related disadvantages of atenolol \pm thiazide
- Adverse interaction between atenolol \pm thiazide and statin
- Beneficial interaction between amlodipine \pm perindopril and statin

Variables which differed significantly (baseline - final visit) between treatment regimens

	Mean differences (Amlodipine \pm perindopril - Atenolol \pm thiazide)	Changes baseline to final visit p-value
Systolic BP (mm Hg)	-1.78	<0.0001
Diastolic BP (mm Hg)	-2.05	<0.0001
Heart rate (bpm)	11.12	<0.0001
Weight (kg)	-0.79	<0.0001
HDL-cholesterol (mmol/L)	0.11	<0.0001
Triglycerides (mmol/L)	-0.23	<0.0001
Glucose (mmol/L)	-0.20	<0.0001
Creatinine (μ mol/L)	-5.06	<0.0001
Potassium (mmol/L)	0.05	<0.0001

Endpoints evaluated

1. Primary endpoint + coronary revascularisation (coronary events)
2. Non-fatal and fatal stroke

Rationale

- Significantly different rates
- Potentially different mechanisms
- Sufficient power

The role of BP differences?

Methods

- Temporal association
- Serial mean matching
- Updated Cox regression adjustment

Which BP measure?

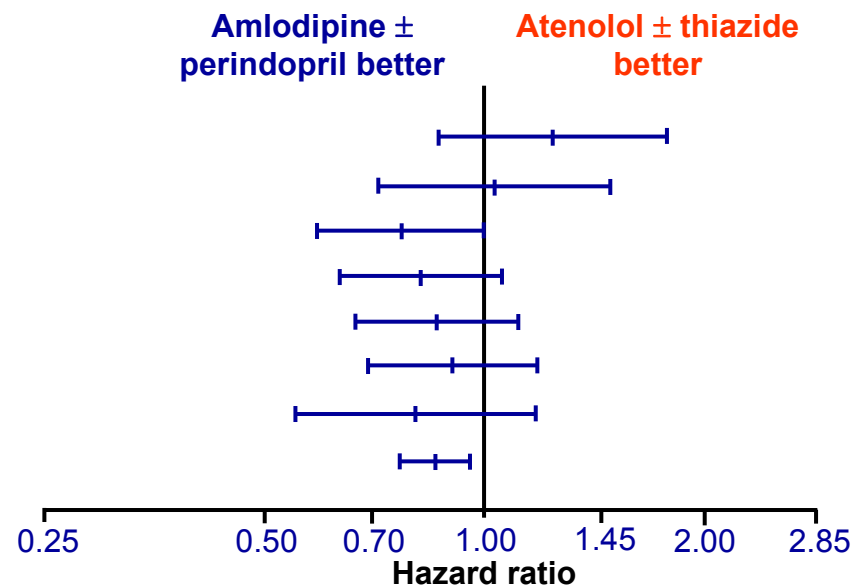
- SBP
- DBP
- MBP - $[(SBP + DBP) / 2]$
- Pulse pressure

When?

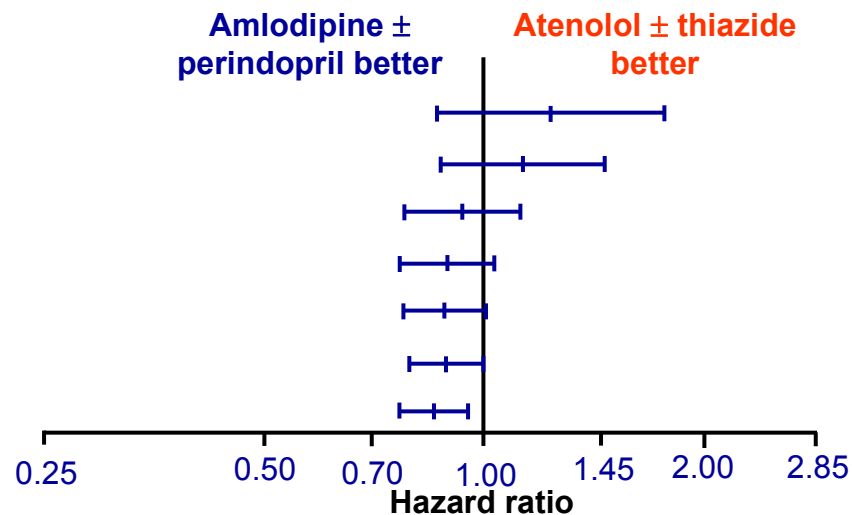
- Latest
- One year recurrent average
- Accumulated mean

Differences in coronary event rates and in BP over time

Time interval	Accumulated differences (mmHg) Atenolol ± thiazide - Amlodipine ± perindopril	
	SBP	DBP
0-6 months	4.95	1.72
0.5 - 1 year	4.03	1.99
1 - 2 years	2.62	1.89
2 - 3 years	2.02	1.76
3 - 4 years	1.85	1.88
4 - 5 years	1.62	1.88
> 5 years	1.55	1.78
All study	2.76	1.91



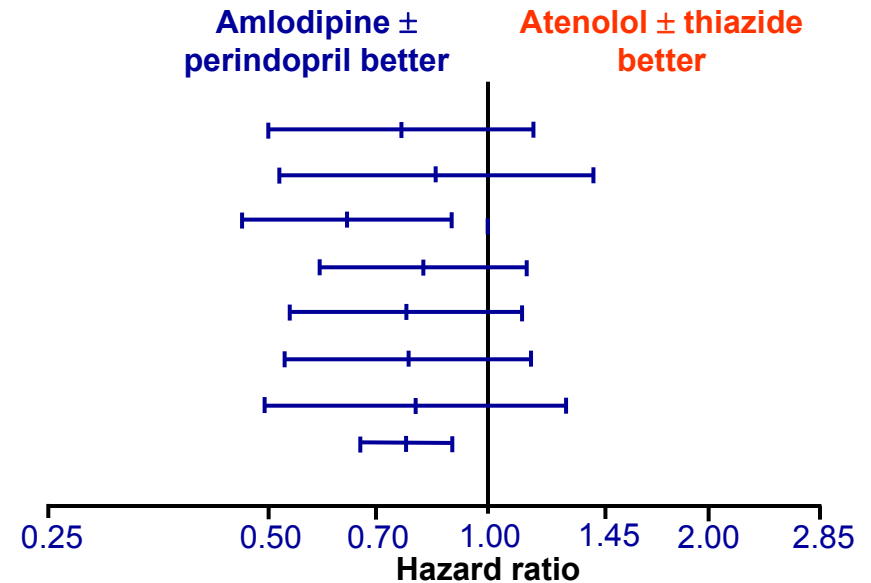
Time interval	Accumulated differences (mmHg) Atenolol ± thiazide - Amlodipine ± perindopril	
	SBP	DBP
0-6 months	4.95	1.72
0 - 1 year	4.51	1.86
0 - 2 years	3.67	1.89
0 - 3 years	3.24	1.87
0 - 4 years	3.01	1.89
0 - 5 years	2.85	1.91
All study	2.76	1.91



Differences in stroke event rates and in BP over time

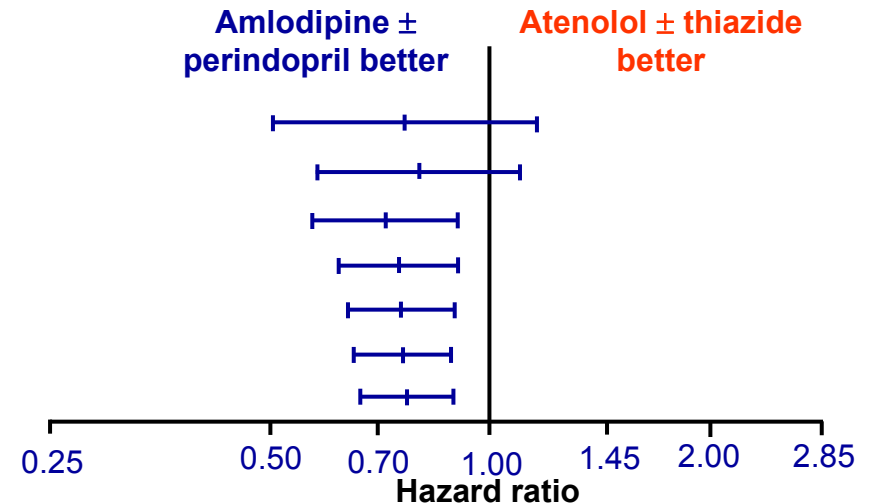
Time interval **Accumulated differences (mmHg)**
Atenolol ± thiazide - Amlodipine ± perindopril

	SBP	DBP
0-6 months	4.95	1.72
0.5 - 1 year	4.03	1.99
1 - 2 years	2.62	1.89
2 - 3 years	2.02	1.76
3 - 4 years	1.85	1.88
4 - 5 years	1.62	1.88
> 5 years	1.55	1.77
All study	2.76	1.91



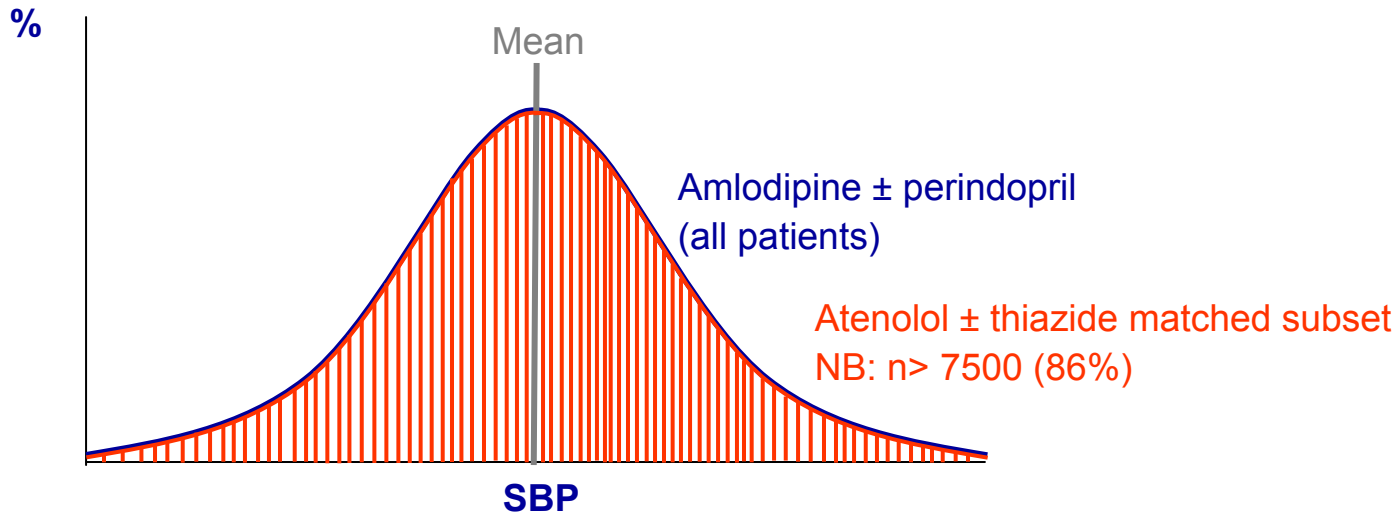
Time interval **Accumulated differences (mmHg)**
Atenolol ± thiazide - Amlodipine ± perindopril

	SBP	DBP
0-6 months	4.95	1.72
0 - 1 year	4.51	1.86
0 - 2 years	3.67	1.89
0 - 3 years	3.24	1.87
0 - 4 years	3.01	1.89
0 - 5 years	2.85	1.91
All study	2.76	1.91



Serial mean matching: Methods

- Take Amlodipine \pm perindopril cohort at each of five time points plus baseline



- Select “atenolol \pm thiazide” person closest to mean after randomisation
- Add others sequentially to maintain group SBP matching
- Maximum mean SBP group difference = 0.02 mm Hg
- 9% of coronary events and 14% of stroke events excluded
- Multiple Cox regression - adjusted HR in 6 periods
- Further adjustment for age and number of risk factors

Serial mean matching: Results

	Hazard ratio unadjusted	Pooled hazard ratio SMM adjusted	p-value for adjusted HR
Primary endpoint + Coronary revascularisation	0.86 (0.77 - 0.96)	0.87 (0.78 - 0.98)	0.0177
Fatal and non-fatal stroke	0.77 (0.66 - 0.89)	0.83 (0.71 - 0.96)	0.0147

Hazard ratios for treatment effect on coronary events adjusted for accumulated mean levels of variables that differed

Coronary events		
	HR	p-value
Unadjusted	0.86	0.0058
Systolic BP	0.88	0.0258
Diastolic BP	0.86	0.0065
Mean BP*	0.88	0.0205
Pulse pressure	0.87	0.0170
Heart rate	0.85	0.0201
Glucose	0.85	0.0041
HDL cholesterol	0.90	0.0610
Triglycerides	0.85	0.0043
Creatinine	0.86	0.0091
Potassium	0.85	0.0045
Weight	0.86	0.0053

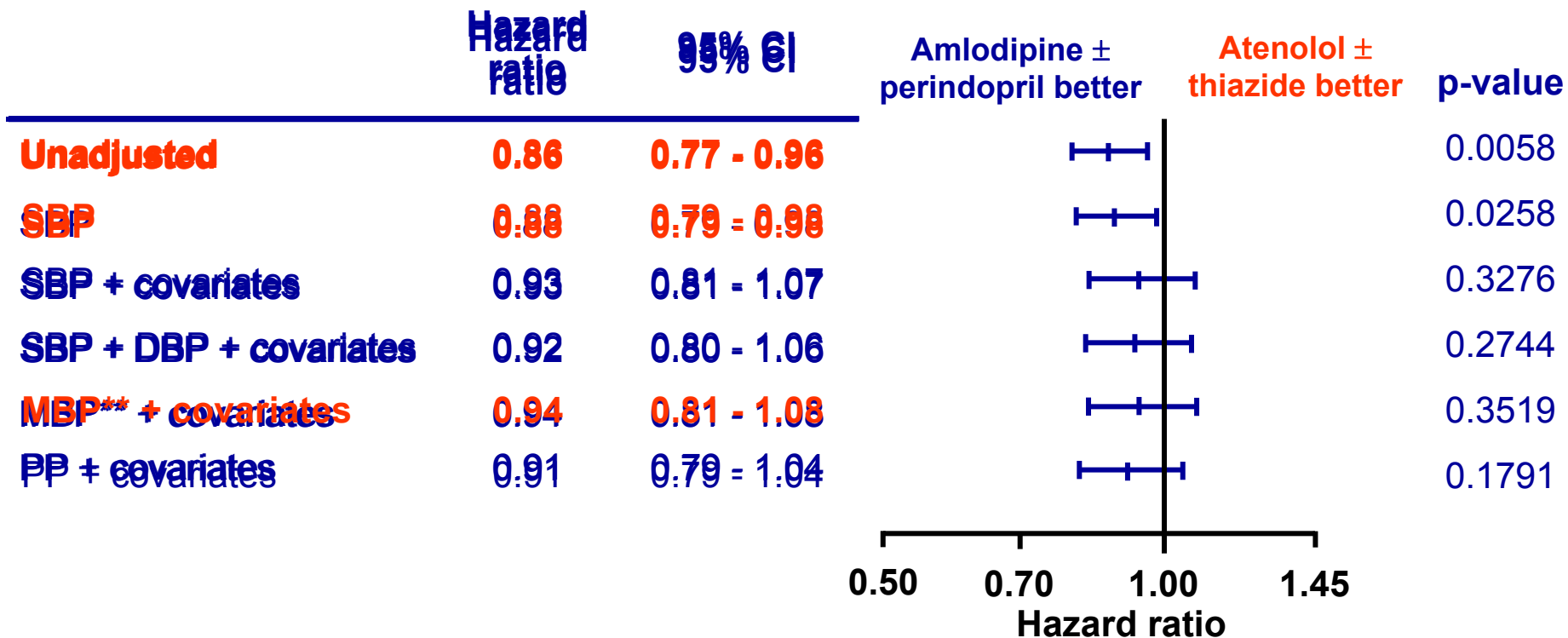
* Mean BP = (SBP/DBP)/2

Hazard ratios for treatment effect on stroke events adjusted for accumulated mean levels of variables that differed

	Fatal and non-fatal stroke	
	HR	p-value
Unadjusted	0.77	0.0003
Systolic BP	0.83	0.0144
Diastolic BP	0.80	0.0033
Mean BP*	0.84	0.0170
Pulse pressure	0.80	0.0026
Heart rate	0.74	0.0007
Glucose	0.78	0.0007
HDL cholesterol	0.76	0.0002
Triglycerides	0.78	0.0008
Creatinine	0.79	0.0014
Potassium	0.76	0.0002
Weight	0.76	0.0002

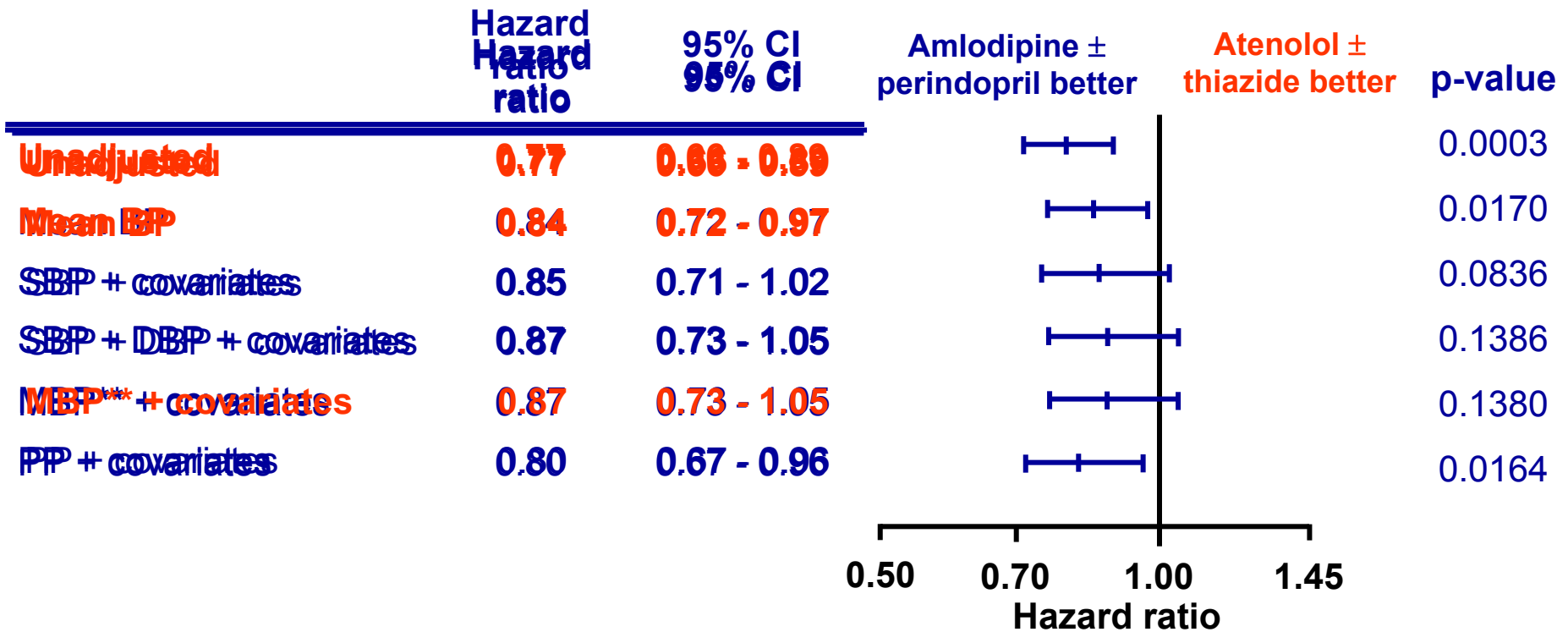
* Mean BP = (SBP/DBP)/2

Impact on the treatment effect on coronary events after adjustment for BP and all variables that differed



** MBP = (SBP+DBP)/2

Impact on the treatment effect on stroke events after adjustment for BP and all variables that differed



** MBP = (SBP+DBP)/2

Summary

- Several potentially important variables including BP differed post-randomisation between 2 treatment groups
- No temporal association between BP differences and event rate differences
- SMM for SBP and updated Cox regression analyses suggested BP accounted for about 15% of coronary differences and 30% of stroke differences
- Full multivariate adjustment accounted for about 50% of coronary differences (mainly HDL-C differences) and 40% of strokes
- Residual differences are large for stroke but non-significant for coronary and stroke events

Conclusions

- These analyses are compatible with the possibility that CV event differences were explained by the variables considered
- BP differences unlikely single explanation
- Residual differences, albeit non-significant, are large especially for stroke
- ASCOT provides implications for optimal CV prevention independent of these analyses

ASCOT: BPLA and LLA combined: Insight into optimal CV prevention (2)

Rates / 1000 patient years

Endpoint	Amlodipine ± perindopril + atorvastatin	Atenolol ± thiazide + placebo	Relative risk reduction
Non-fatal MI and fatal CHD	4.8	9.2	48%
Fatal and non-fatal stroke	4.6	8.2	44%

Final conclusions

- **Amlodipine ± perindopril based therapy confers an advantage over atenolol ± thiazide based therapy on all major CV end points, all-cause mortality and new-onset diabetes**
- Irrespective of the reasons for benefit, the standard regimen of beta-blocker ± thiazide should not be preferred to the amlodipine ± perindopril regimen for most patients
- Compared with standard antihypertensive therapy without statin therapy, the amlodipine ± perindopril regimen plus atorvastatin reduced coronary and stroke events by almost 50%