Long-term mortality after the blood pressure and lipid-lowering treatment in hypertensive patients: 16-year follow-up of the ASCOT Legacy study

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ASCOT Legacy

Queen Mary University of London

Declaration of interests

- In last 3 years, I have received travel support from Servier and Pfizer to cover for the expenses incurred when attending conferences.

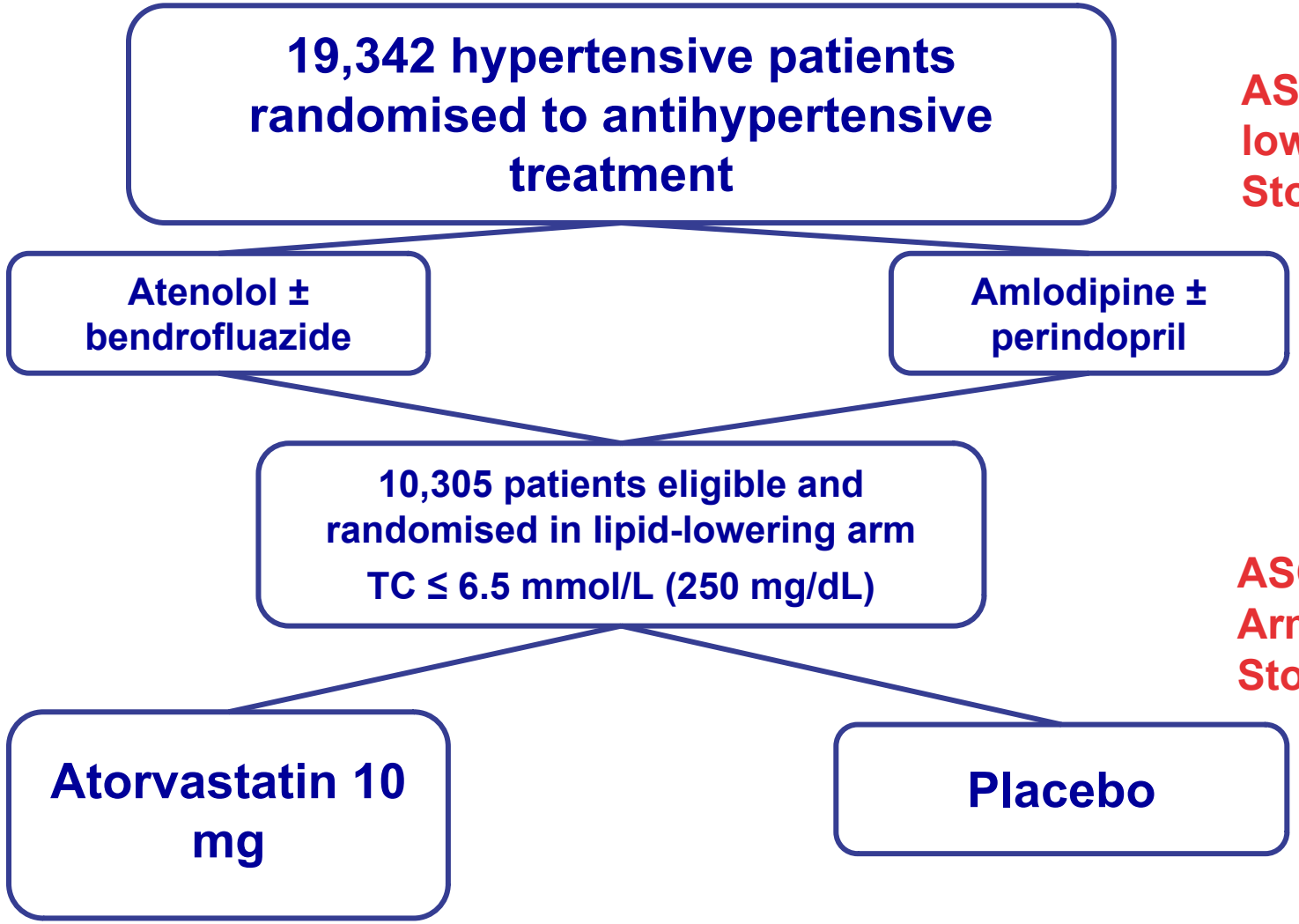
Background

- Previously, hypertension trials comparing active drug treatment compared with placebo, with substantial in-trial blood pressure (BP) differences, have reported some long-term cardiovascular (CV) benefits in those on active treatment.

- It is uncertain whether more recent trials, which compared two active treatment regimens and demonstrated the benefits of a regimen, have long-lasting beneficial effects on CV and all-cause mortality.

- A few long-term follow-up studies of placebo-controlled statin trials have reported persistent legacy benefits in those assigned to statin group, but none was specifically designed for hypertensive patients

The original ASCOT Study Design



ASCOT-Blood pressure lowering arm (BPLA)
Stopped at 5.5 yrs

ASCOT-Lipid Lowering Arm (LLA)
Stopped at 3.3 yrs

Investigator lead trial of hypertensive subjects aged 40-79 yrs , no history of CHD, but with 3 additional CV risk factors

The ASCOT Legacy cohort

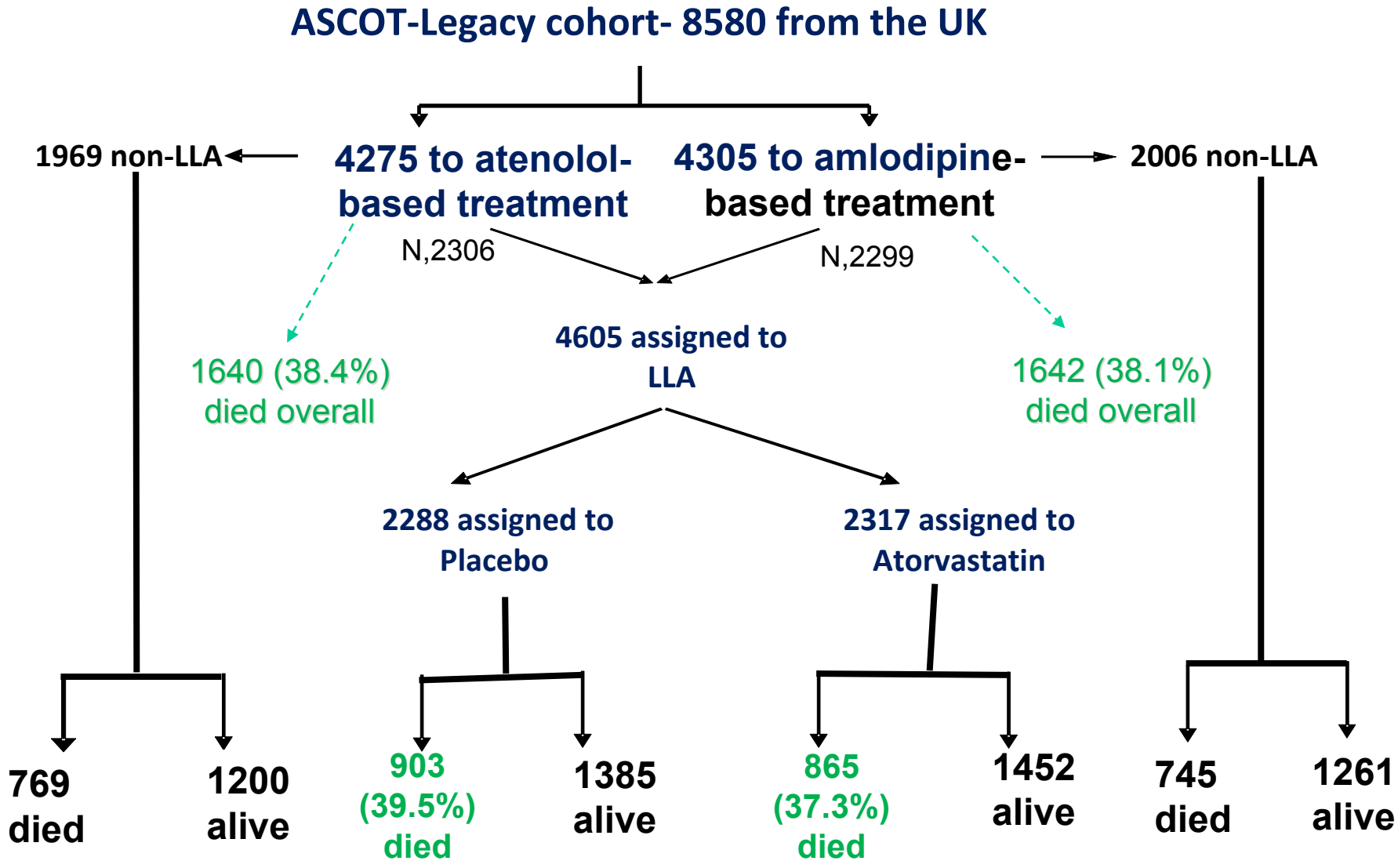
The ASCOT Legacy cohort

- 8580 hypertensive patients, who were randomized in the ASCOT study from the UK
- Post-trial mortality data were collected every 2-3 months from the Office of National Statistics, and General Register Office for Scotland.
- All death reports were independently adjudicated, and cause of death categorised using pre-specified criteria consistent with the definitions used during the trial.
- For current analyses, we report on all-cause mortality, and deaths from CV causes. All CV deaths were further adjudicated to report on deaths due to CHD or stroke.

Statistical Methods

- All analyses were performed using the intention-to-treat principle.
- For each death outcome, separate Cox models were developed in each treatment arm: BPLA and LLA.
- Analyses were adjusted for pre-specified covariates, including age, sex, ethnicity, socio-economic status, body-mass index, systolic BP, total cholesterol, the presence of diabetes, smoking history, and the other treatment comparison
- Tests for interactions were performed:
  - between the two treatment arms
  - to determine whether the impact of the two BP- lowering treatments differed between subgroups such as allocation to the LLA or not.

Study profile: ASCOT legacy BPLA and LLA



ASCOT Legacy cohort: baseline characteristics stratified by 2 arms

Baseline characteristics ASCOT -legacy	BPLA (n, 8580)		LLA (n, 4605)	
	Amlodipine-based (n, 4305)	Atenolol-based (n, 4275)	Atorvastatin (n, 2317)	Placebo (n, 2288)
	% or mean/median		% or mean/median	
Age (years)	64	64	64	64
Male gender (%)	81·1%	81·1%	87·0%	87·6%
White/Europids (%)	89·7%	89·8%	88·3%	88·2%
Body mass index (kg/m2)	28·9	28·9	28·8	28·8
Current Smokers (%)	24·0%	23·5%	23·6%	23·6%
Systolic blood pressure (mmHg)	162	162	162	162
Diastolic blood pressure (mmHg)	92	92	92	93
Total cholesterol (mmol/L)	5·9	5·9	5·5	5·5
HDL-cholesterol (mmol/L)	1·3	1·3	1·3	1·3
LDL-cholesterol (mmol/L)	3.8	3.8	3.5	3.5
Fasting plasma glucose (mmol/L)	5·6	5·6	5·6	5·6
Serum creatinine (umol/L)	99	98	99	99
Presence of diabetes mellitus (%)	26·5%	26·.8%	26·8%	27·5%
H/o peripheral vascular disease (%)	8·3%	9·0%	6·9%	6·6%
Presence of atrial fibrillation	1·4%	1·4%	1·6%	1·4%

ASCOT-Legacy

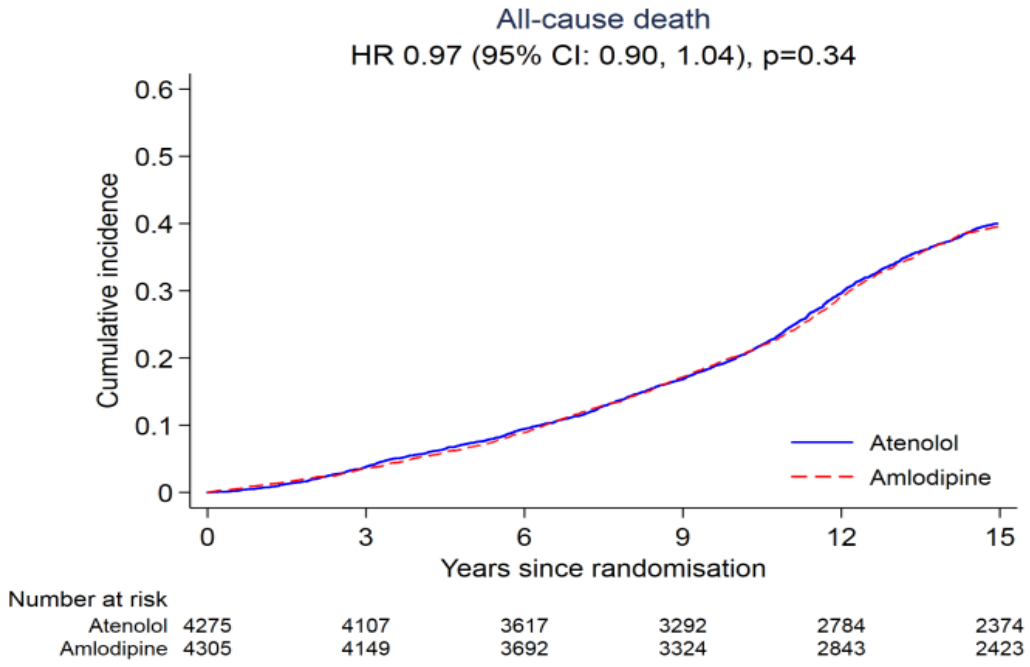
The Blood Pressure Lowering Arm results

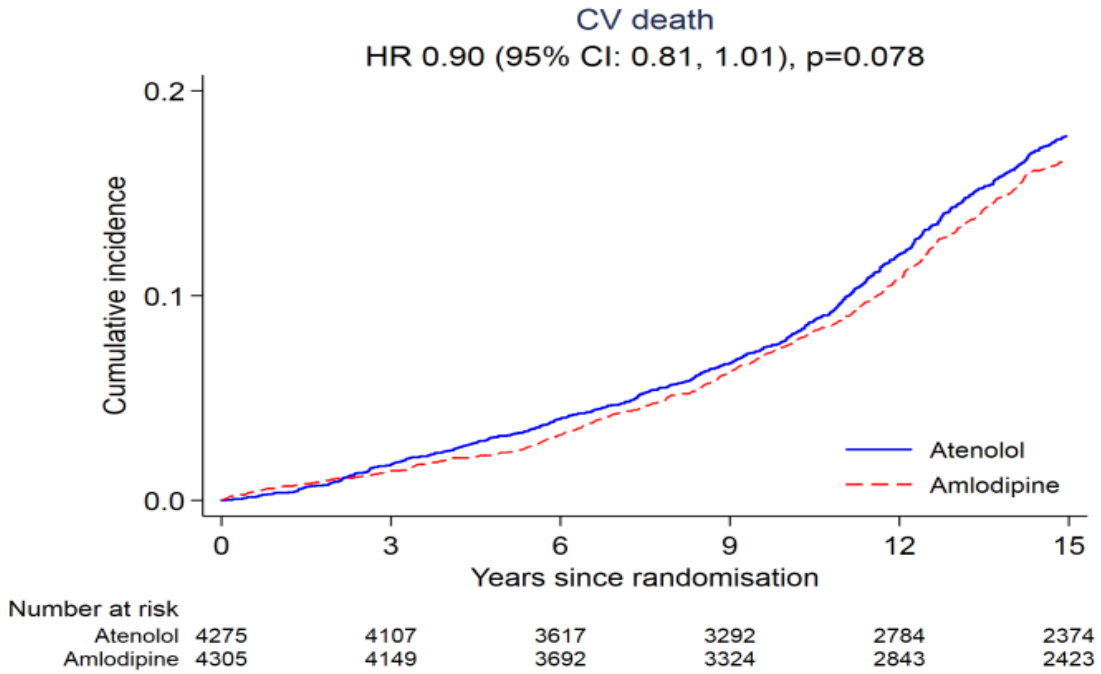
Incidence rates for cause specific mortality amongst those assigned to the two BP- lowering treatments

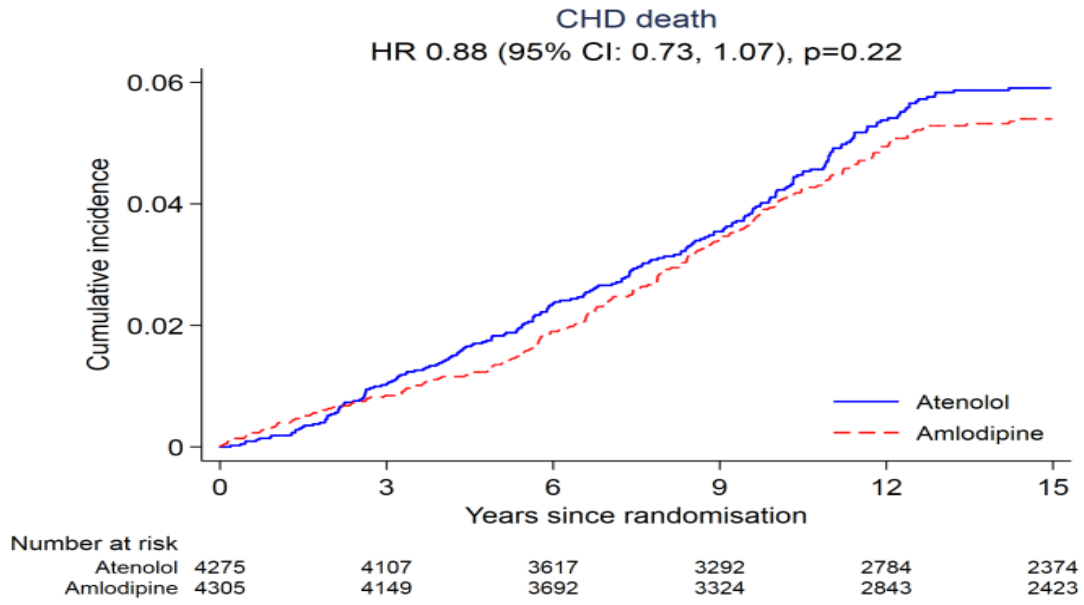
Cause of death	In trial (median follow-up, 5·5 year)				Total follow-up (median follow-up, 15·7 years)			
	Atenolol-based (N=4275)		Amlodipine-based (N=4305)		Atenolol-based (N=4275)		Amlodipine-based (N=4305)	
	n	Rate*	n	Rate*	n	Rate*	n	Rate*
All-cause	370	**1·62**	347	**1·50**	1640	**2·99**	1642	**2·95**
CV	149	**0·65**	115	**0·50**	623	**1·13**	587	**1·05**
CHD	86	**0·38**	66	**0·29**	213	**0·39**	198	**0·36**
Stroke	30	**0·13**	21	**0·09**	99	**0·18**	72	**0·13**
Non-CV	221	**0·97**	232	**1.00**	1017	**1·85**	1055	**1·90**

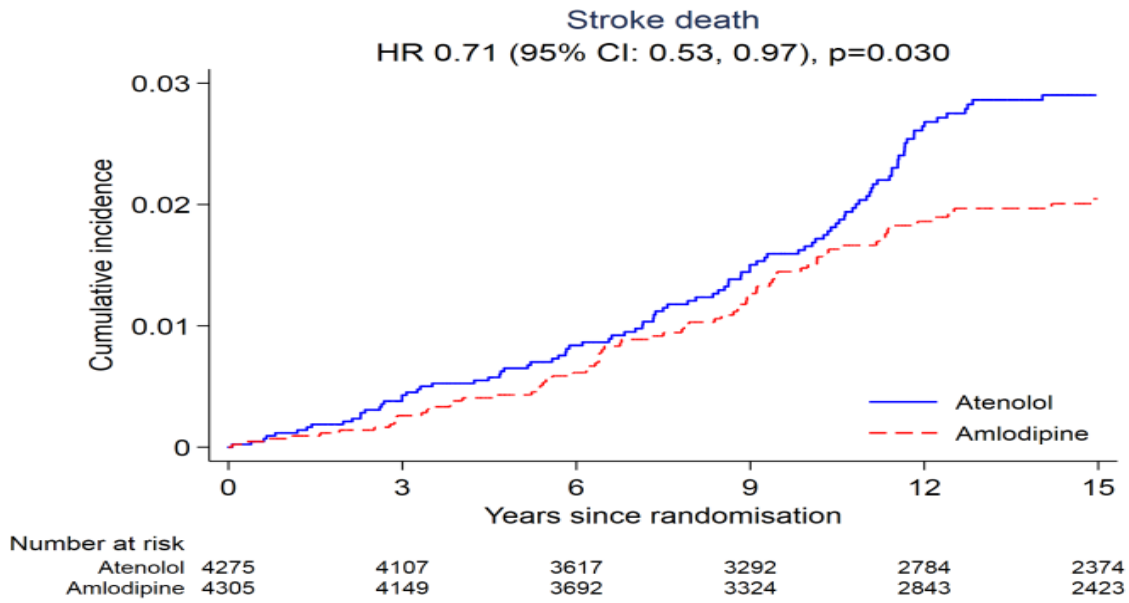
*** Rate: per 100 person years**
Atenolol-based regimen: atenolol adding thiazide diuretic as required; Amlodipine-based regimen: amlodipine adding perindopril as required
CV: cardiovascular ; CHD: coronary heart disease; BP: blood pressure

Kaplan Meier plots for cause-specific mortality in the BPLA









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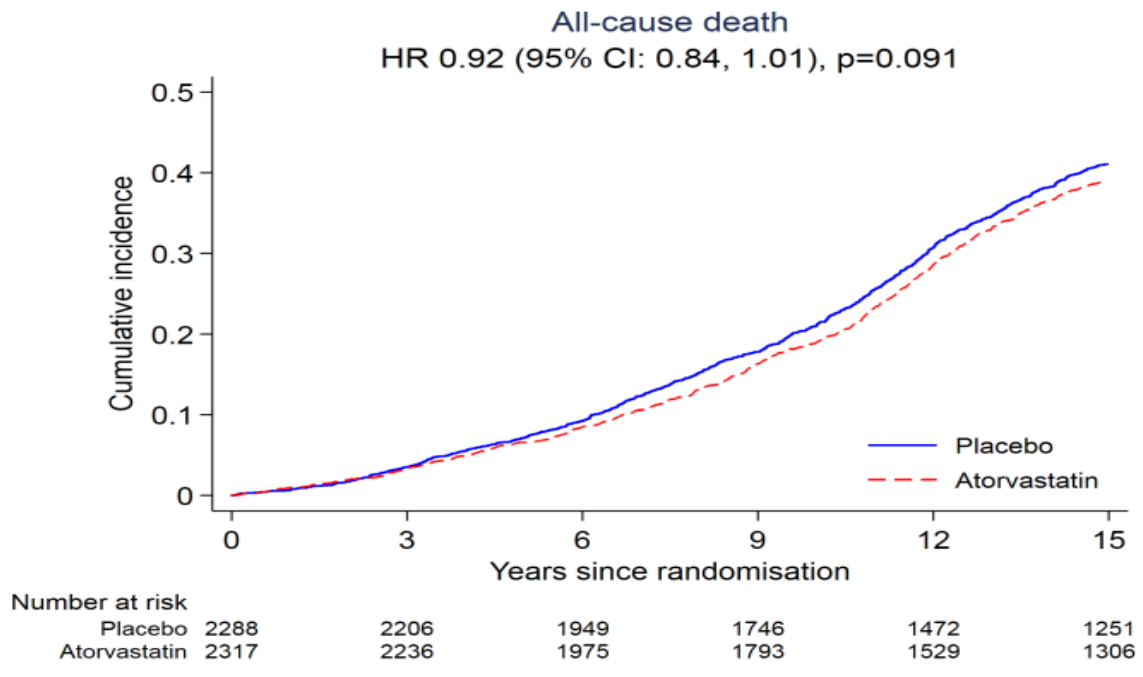
The Lipid Lowering Arm results

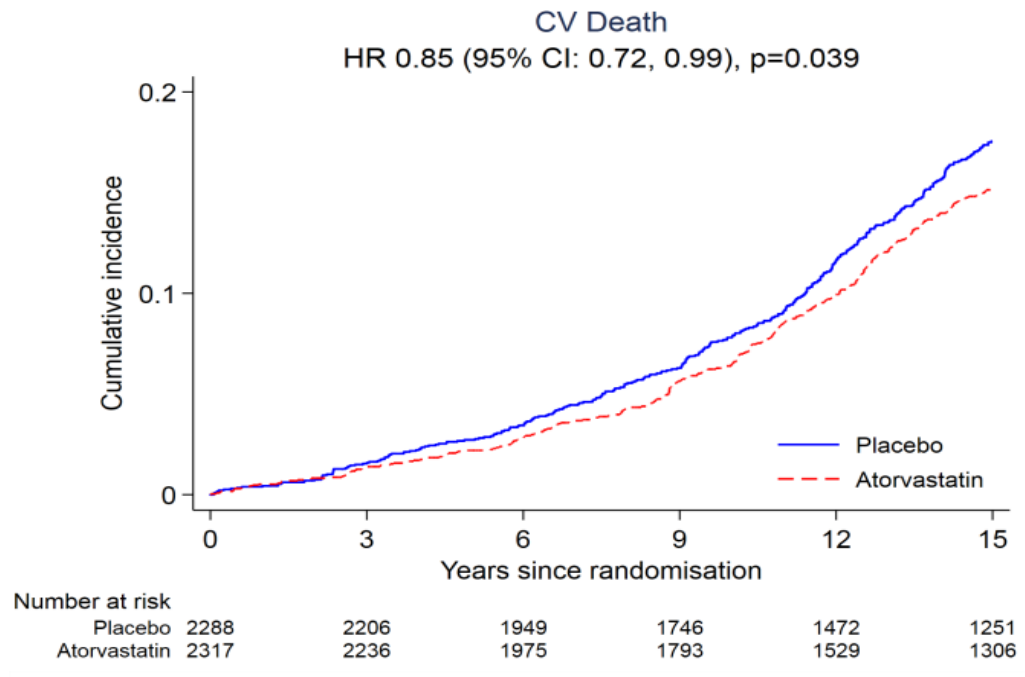
Incidence rates for cause specific mortality amongst those assigned to a placebo or atorvastatin in the LLA

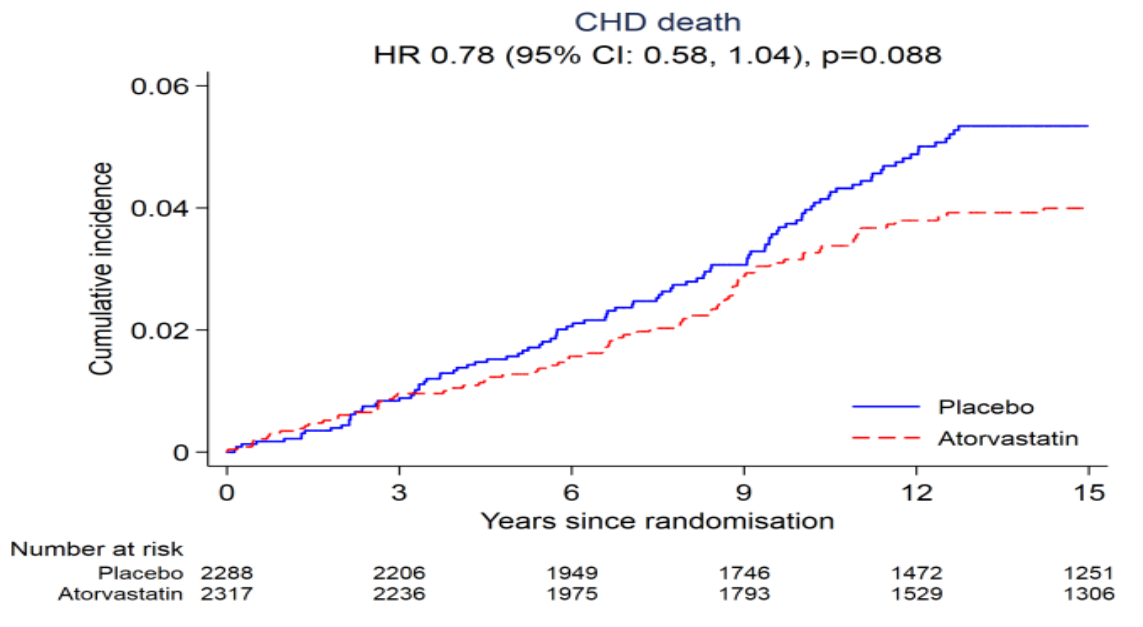
Cause of death	In trial (median follow-up, 3.3 year)				Total follow-up (median follow-up, 15·7 years)			
	Placebo (N=2288)		Atorvastatin (N=2317)		Placebo (N=2288)		Atorvastatin (N=2317)	
	n	Rate*	n	Rate*	n	Rate*	n	Rate*
All-cause	90	**1.28**	83	**1·18**	903	**3·09**	865	**2·89**
CV	36	**0.51**	30	**0·43**	325	**1·11**	285	**0·95**
CHD	19	**0.27**	19	**0·27**	103	**0·35**	81	**0·27**
Stroke	8	**0.11**	6	**0.09**	43	**0·15**	45	**0·15**
Non-CV	54	**0.77**	53	**0·75**	578	**1·98**	580	**1·94**

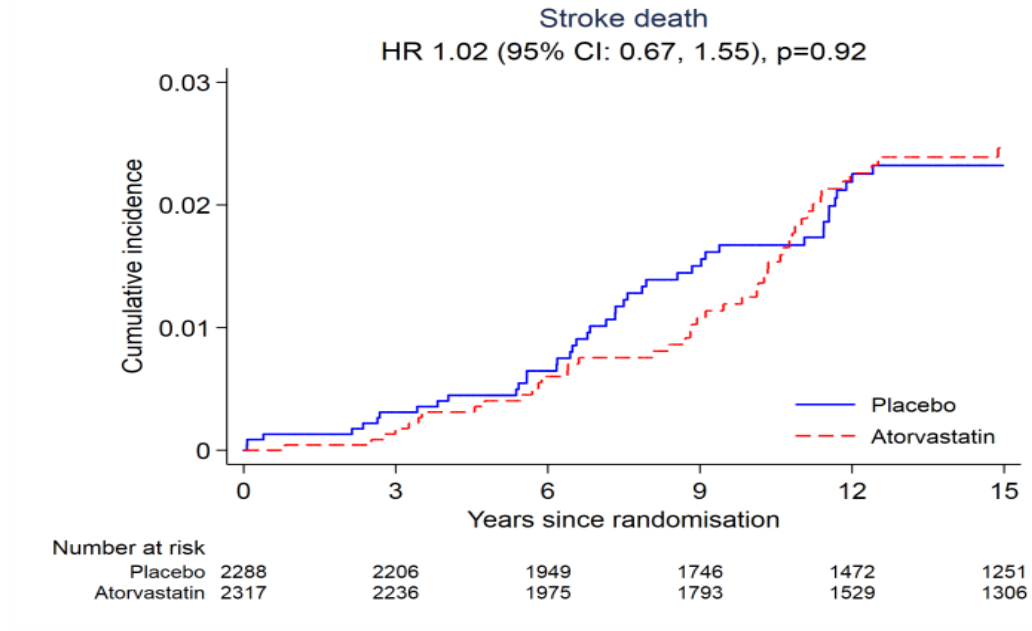
*** Rate: per 100 person years**
Atenolol-based regimen: atenolol adding thiazide diuretic as required; Amlodipine-based regimen: amlodipine adding perindopril as required
CV: cardiovascular ; CHD: coronary heart disease; BP: blood pressure

Kaplan Meier plots for cause-specific mortality in the LLA









ASCOT-Legacy

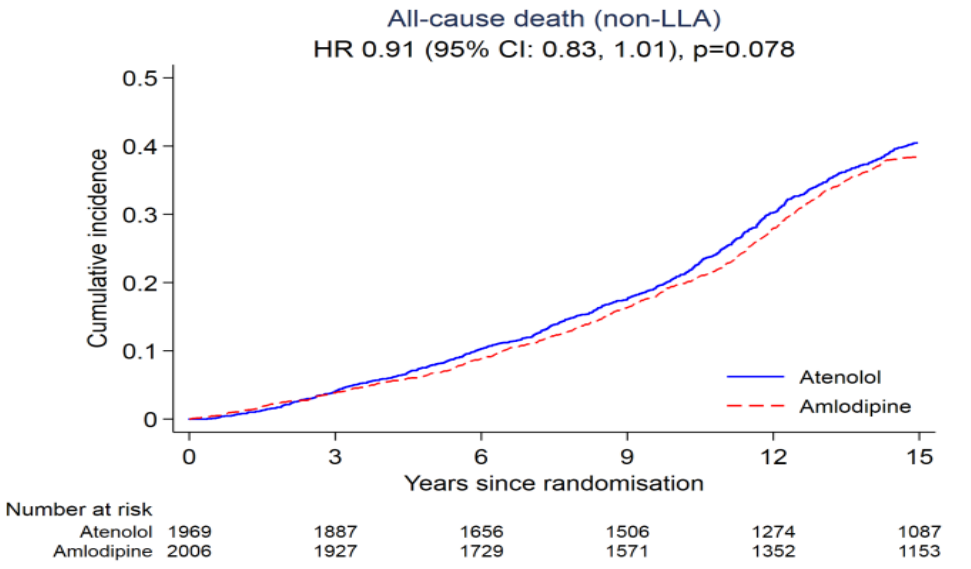
The non-LLA group

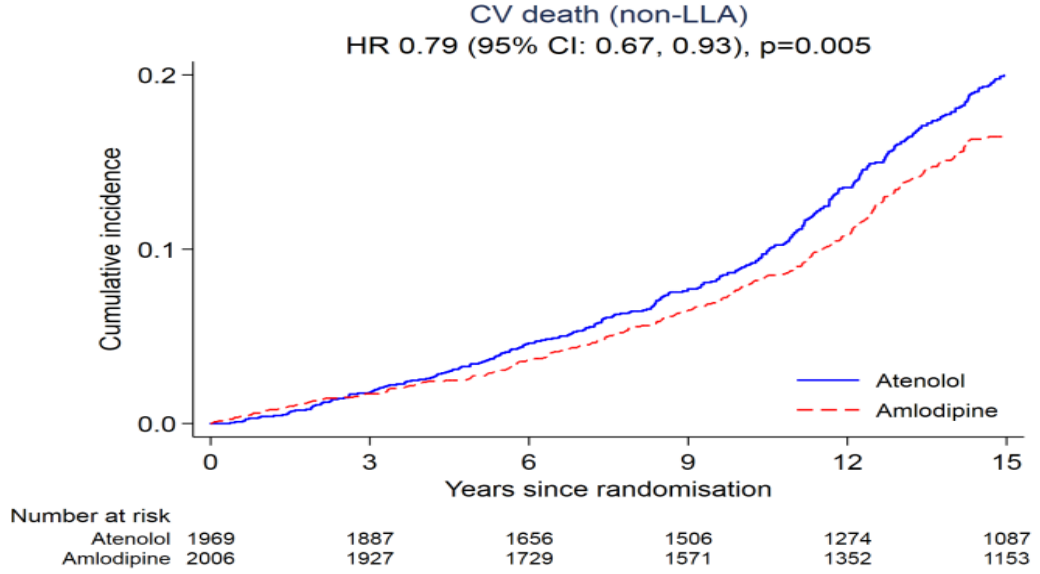
Incident rates and the risk of the cause specific deaths amongst those assigned to two BP treatment regimens, stratified by the allocation to LLA or not (the non-LLA group)

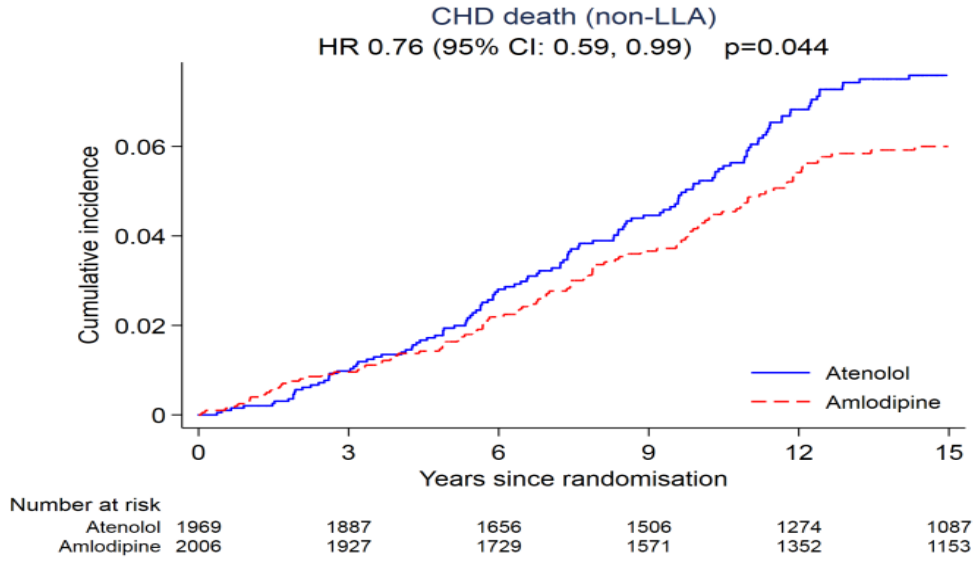
Cause of death		Atenolol-based	Amlodipine-based	Risk		Test
	LLA or not	Rate*	Rate*	Adjusted HR (95% CI)**	P-value	Interaction p-value#
All-cause	Non-LLA	3·05	2·84	0·91 (0·83, 1·01)	p=0·078	p=0·122
	LLA	2·93	3·05	1·02 (0·93, 1·12)	p=0·709	
Cardiovascular	Non-LLA	1·29	1·05	0·79 (0·67, 0·93)	p=0·005	p=0·0.022
	LLA	1·00	1·06	1·03 (0·88, 1·21)	p=0·670	
CHD	Non-LLA	0·50	0·39	0·76 (0·59, 0·99)	p=0·044	p=0·095
	LLA	0·30	0·33	1·06 (0·80, 1·42)	p=0·671	
Stroke	Non-LLA	0·19	0·13	0·67 (0·43, 1·04)	p=0·075	p=0·698
	LLA	0·17	0·13	0·76 (0·50, 1·16)	p=0·198	

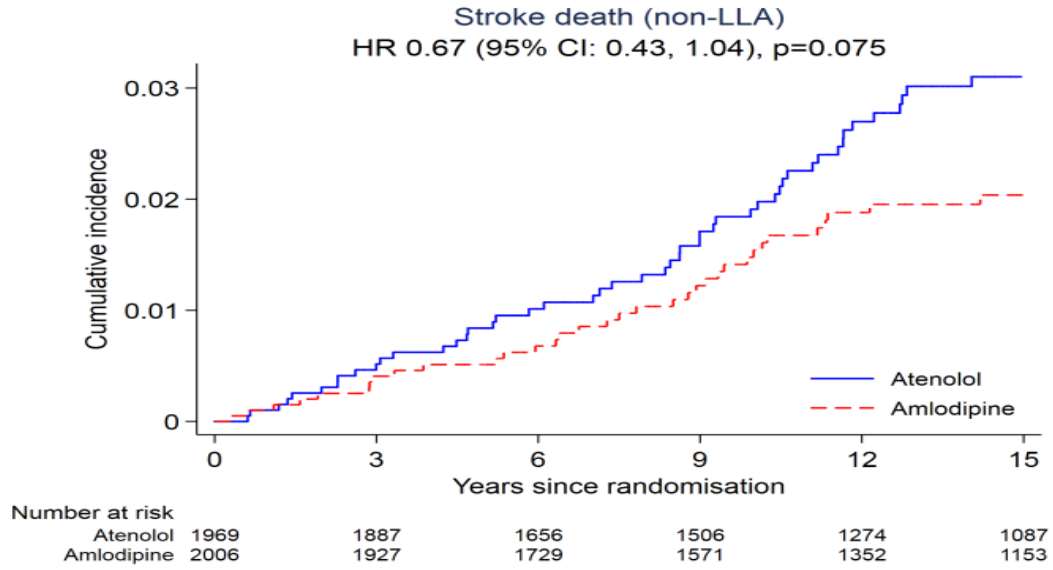
* rate per 100 person years
**Adjusted for age, sex, ethnicity, socio-economic status, body-mass index, systolic BP, total cholesterol, the presence of diabetes, & smoking history.
#P-value from test on interaction from adjusted models

Risk of cause-specific deaths among those allocated to the two BP treatment regimen in the non- LLA sub-group









HR: hazard ratio; CV: cardiovascular

Summary of results- BPLA and LLA

- This study is the first to report that both blood pressure- and lipid-lowering treatments confer long-term cardiovascular mortality benefits.
- Assignment to amlodipine-based treatment (vs. atenolol-based treatment) was associated with significant, 29% reduction in the stroke deaths, and numerically fewer CV deaths over a 16 year period.
- We also confirm the long-term benefits of statin therapy in reducing the risk of CV deaths. In our analyses, there was a significant, 15% reduction in the CV deaths amongst those on atorvastatin (vs. placebo), even after 13 years of trial closure.
- Furthermore, findings from the higher baseline risk group — the non-LLA sub-group – confirms the long-term benefits of blood pressure lowering therapies in such patients.

Acknowledgements and Thanks

- All patients who participated in the ASCOT trial

- Colleagues at Imperial College London and William Harvey Research Institute

Thank you for your attention

Overall mean BPs throughout the follow-up period in the BPLA period, stratified by the BP treatment allocation, and by ASCOT legacy and non-LLA population

	ASCOT Legacy-BPLA		Non-LLA	
Cumulative mean, over all	Atenolol-based (N=3154)	Amlodipine-based (N=3188)	Atenolol-based (N=1438)	Amlodipine-based (N=1502)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
mean SBP, mmHg	134·88 (13·39)	133·70 (12·00)	134·78 (13·15)	133·69 (12·42)
mean DBP, mmHg	77·94 (8·27)	76·32 (8·19)	77·57 (8·29)	76·08 (8·15)
mean PP, mmHg	56·94 (12·12)	57·38 (11·01)	57·21 (11·99)	57·61 (11·33)