Anglo-Scandinavian ascot-11 Cardiac Outcomes Trial

The Anglo-Scandinavian Cardiac Outcomes Trial Lipid-Lowering Arm (ASCOT-LLA): 11 Year Mortality Follow-up in the UK

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on behalf of the ASCOT Investigators

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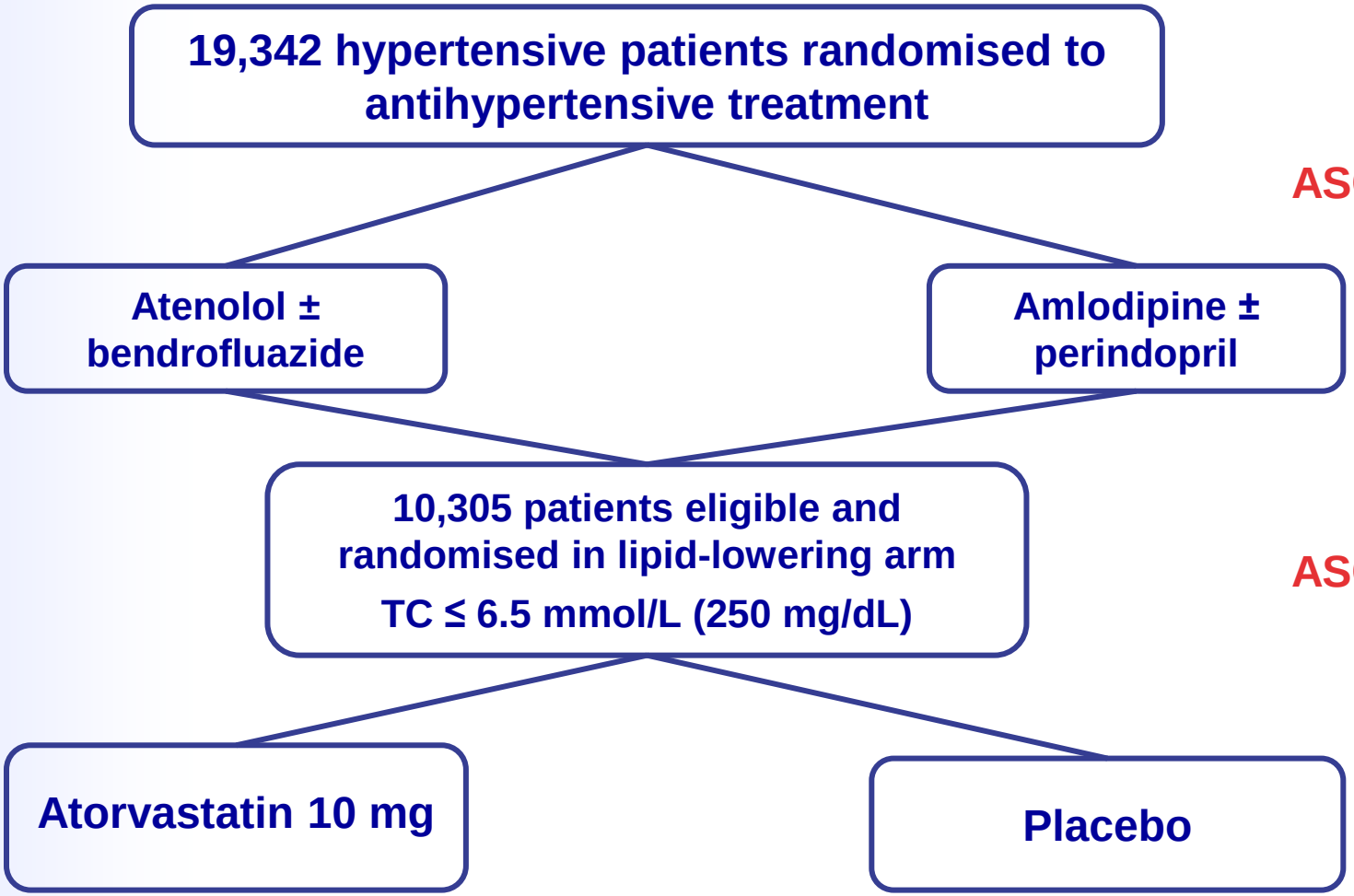
Presenter Disclosure Information

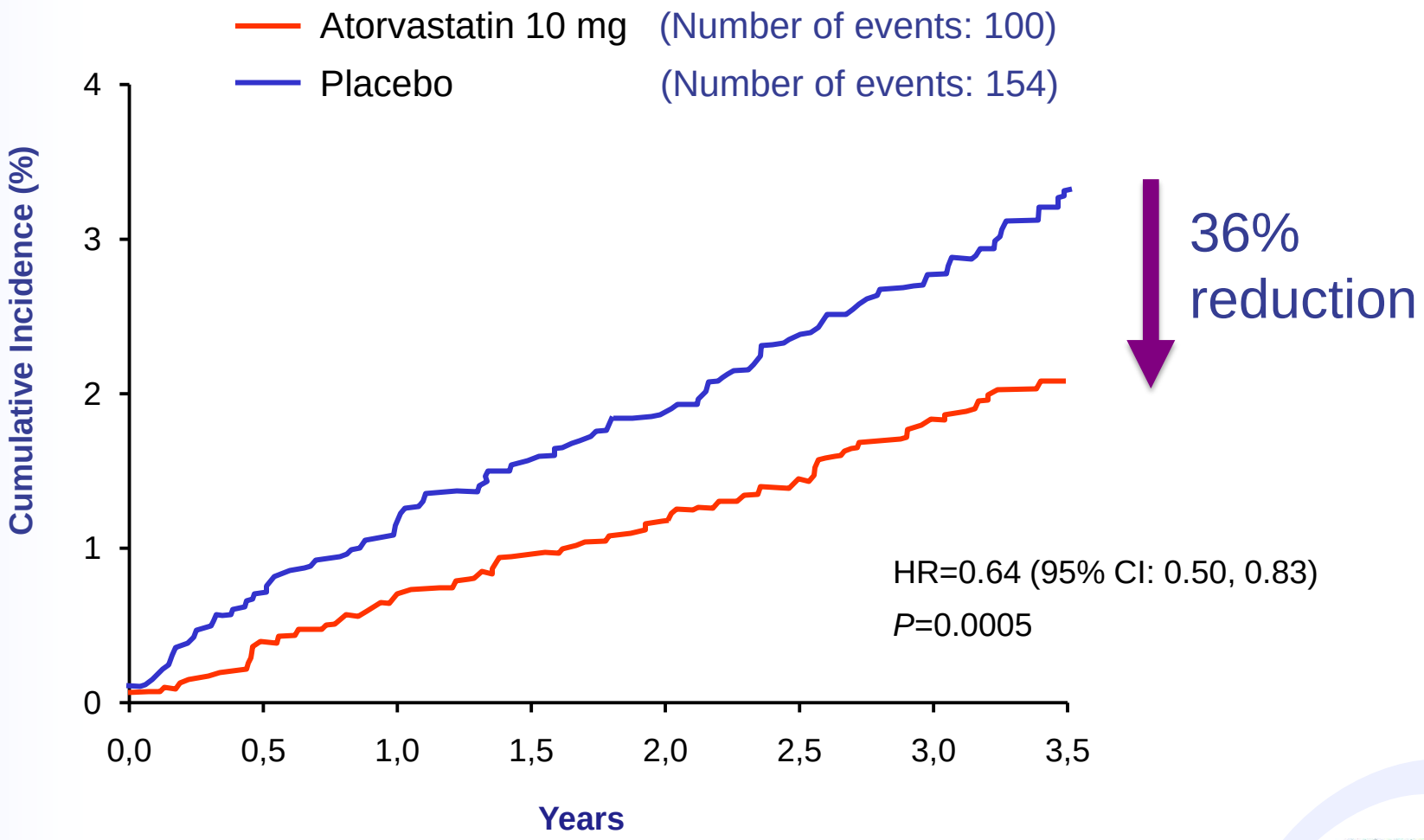
ASCOT-LLA: ***11 year mortality follow-up in the UK***

- P. S. Sever and N. R. Poulter have served as consultants or received travel expenses, or payment for speaking at meetings, or funding for research from one or more pharmaceutical companies that market blood-pressure lowering or lipid-lowering drugs, including Pfizer for ASCOT

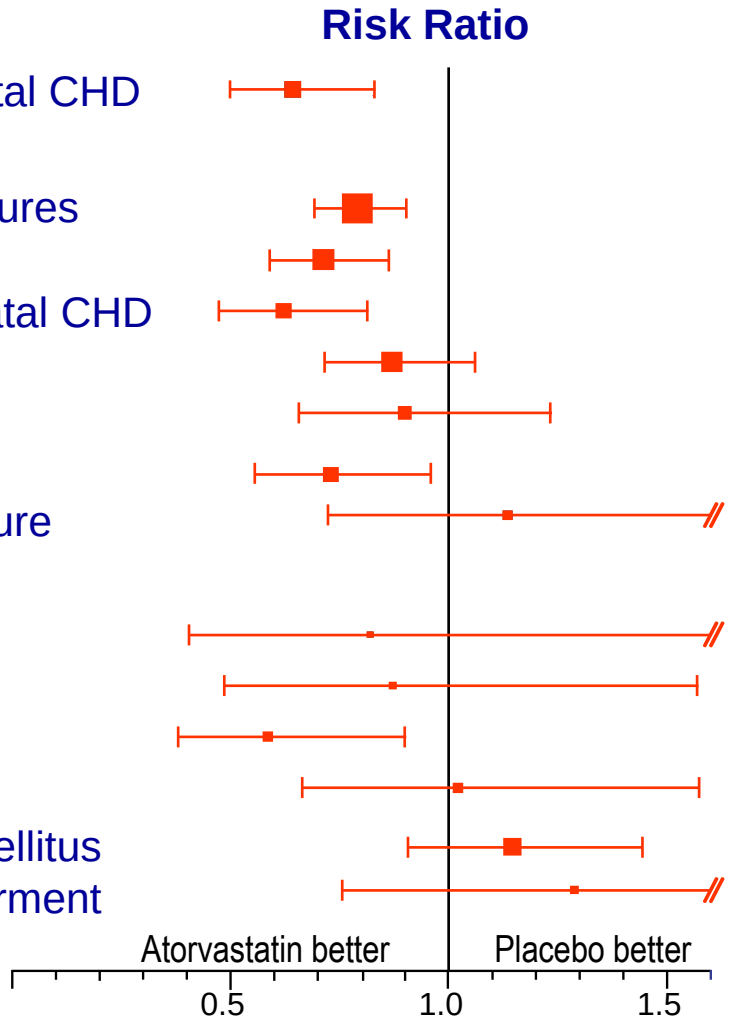
ASCOT Study Design



ASCOT-LLA Primary End Point: Nonfatal MI and Fatal CHD



ASCOT-LLA: Effects of Atorvastatin and Placebo on End Points



	HR (95% CI)
Primary End Points	
Nonfatal MI (incl silent) + fatal CHD	0.64 (0.50, 0.83)
Secondary End Points	
Total CV events and procedures	0.79 (0.69, 0.90)
Total coronary events	0.71 (0.59, 0.86)
Nonfatal MI (excl silent) + fatal CHD	0.62 (0.47, 0.81)
All-cause mortality	0.87 (0.71, 1.06)
Cardiovascular mortality	0.90 (0.66, 1.23)
Fatal and nonfatal stroke	0.73 (0.56, 0.96)
Fatal and nonfatal heart failure	1.13 (0.73, 1.78)
Tertiary End Points	
Silent MI	0.82 (0.40, 1.66)
Unstable angina	0.87 (0.49, 1.57)
Chronic stable angina	0.59 (0.38, 0.90)
Peripheral arterial disease	1.02 (0.66, 1.57)
Development of diabetes mellitus	1.15 (0.91, 1.44)
Development of renal impairment	1.29 (0.76, 2.19)

Area of squares is proportional to the amount of statistical information

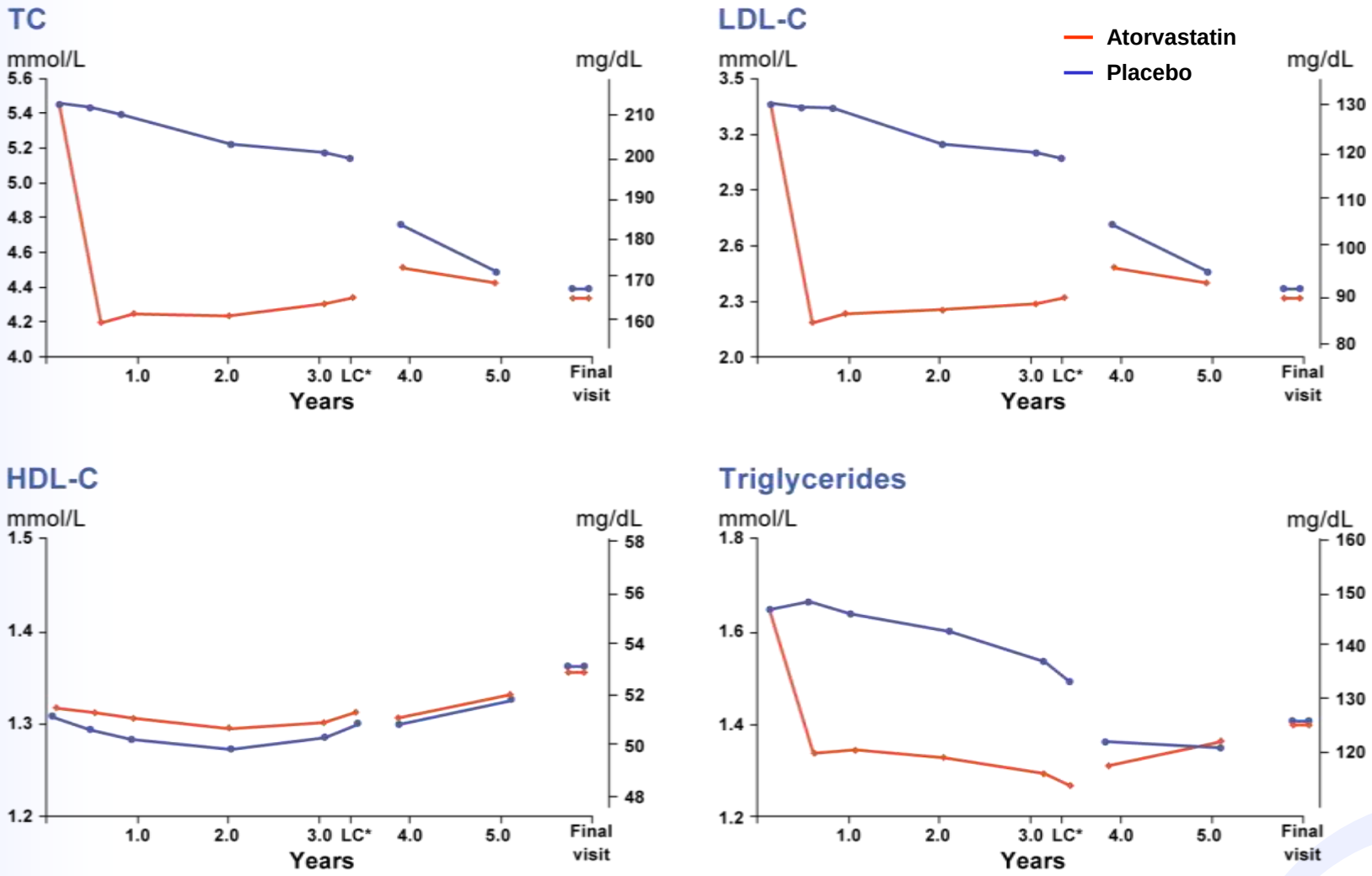
ASCOT-LLA-Extension

- Early closure of ASCOT-LLA
  - Median follow-up 3.3 years
  - Atorvastatin versus placebo:
    - 36% reduction in the primary endpoint
    - 27% reduction in stroke
- ASCOT-LLA-extension
  - Offering atorvastatin 10 mg daily to all patients in LLA
  - Continued for a further 2.2 years until the closure of ASCOT-BPLA
- Statin usage

	Atorvastatin (n=4978)		Placebo (n=4916)	
	Atorvastatin	Other statins	Atorvastatin	Other satins
End of ASCOT-LLA	4113 (82.6)	54 (1.1)	415 (8.4)	220 (4.5)
End of ASCOT-BPLA*	3122 (62.7)	200 (4.0)	2752 (56.0)	337 (6.9)

Values are n (%)
*Also the end of LLA-extension

Lipids Levels During ASCOT-LLA and LLA-Extension



*Lipid closeout visit (end of ASCOT-LLA)

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ASCOT-LLA endpoints at the end of the trial (3.3 yrs) and at the end of BPLA (5.5 yrs)

Primary endpoints

Non-fatal MI (incl silent) + fatal CHD

Secondary endpoints

Total CV events and procedures

Total coronary events

Non-fatal MI (excl silent) + fatal CHD

All-cause mortality

Cardiovascular mortality

Fatal and non-fatal stroke

Fatal and non-fatal heart failure

Tertiary endpoints

Silent MI

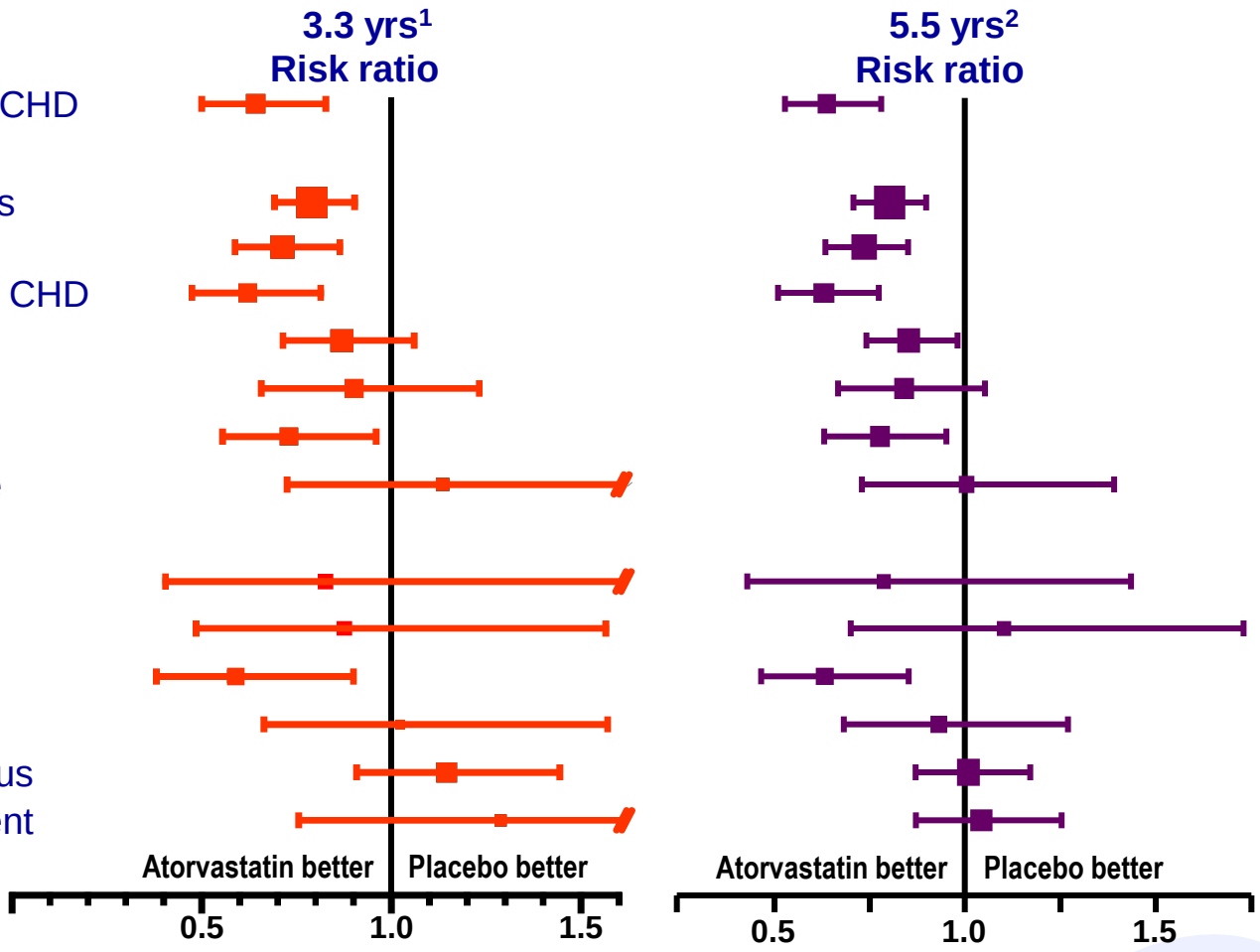
Unstable angina

Chronic stable angina

Peripheral arterial disease

Development of diabetes mellitus

Development of renal impairment



Area of each square is proportional to the amount of statistical information

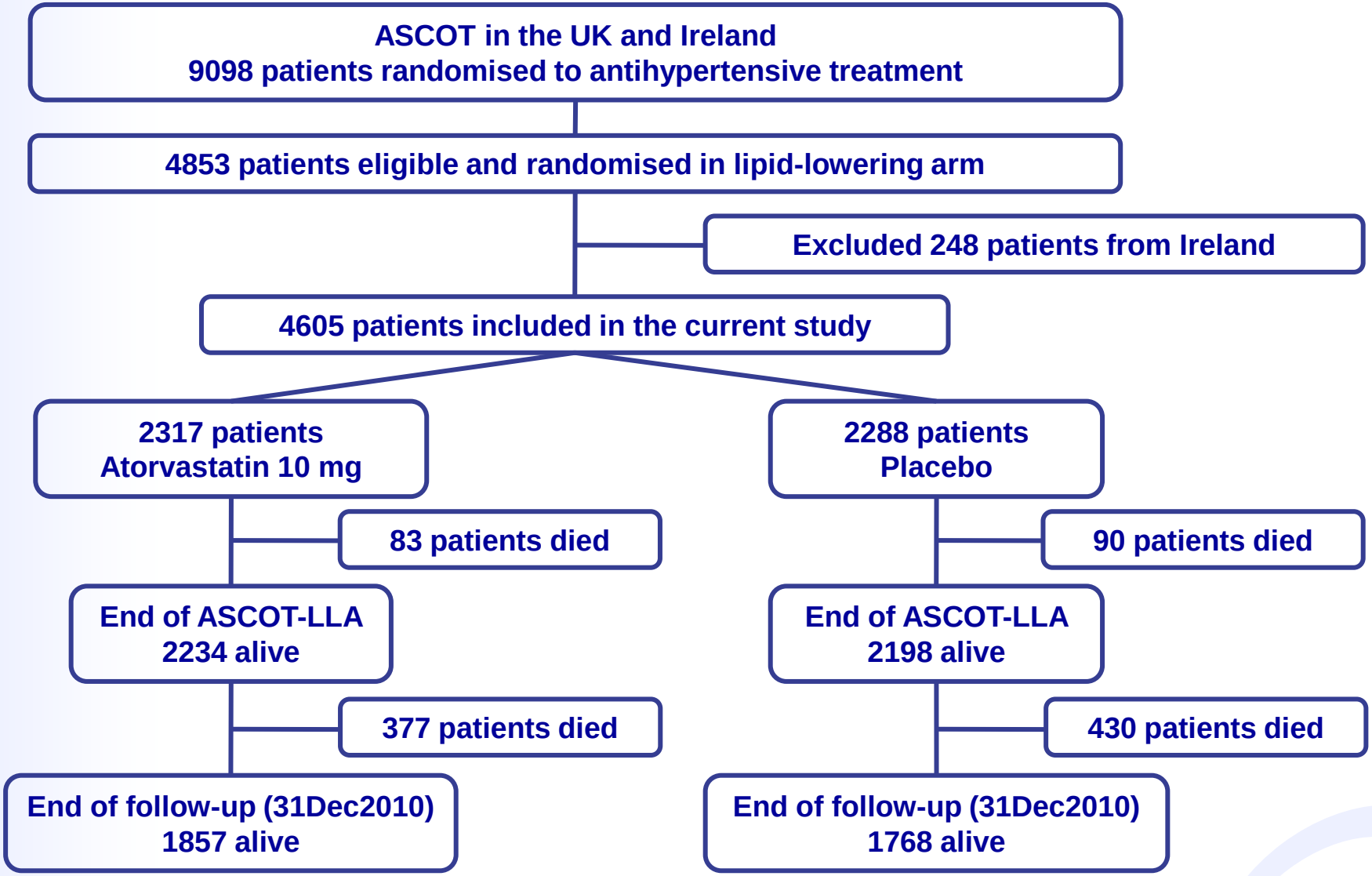
ASCOT-LLA: 11 Year Mortality Follow-up

- Post-trial mortality data were collected every 2-3 months in the UK
- For the current analysis:
  - The primary causes of death were defined as death from:
    - Any cause
    - Cardiovascular (CV) or non-CV disease
    - Cancer
  - Additional post-hoc outcomes included are death from:
    - Infection (infectious or parasitic diseases)
    - Respiratory illness (disease of the respiratory system including pneumonia, chronic obstructive pulmonary disease and acute respiratory diseases)
    - Infection/respiratory combined
- The cut-off date was 31st December 2010 (inclusive)

Statistical Methods

- Patients
  - All patients in the intention-to-treat population who were alive at the end of ASCOT-BPLA (also the end of LLA-extension)
- Cox regression analysis
  - Two randomised treatment groups, i.e., atorvastatin and placebo, were compared for each mortality outcome
  - Analyses were unadjusted and adjusted for prespecified baseline risk factors including age, sex, systolic blood pressure, body mass index, total cholesterol, diabetes, current smokers, ethnicity, randomised blood pressure treatment and age at completion of education; hazard ratios (HR) were estimated
  - The assumption of proportionality was tested using Schoenfeld residuals
  - Tests for interactions were performed for:
    - Atorvastatin treatment and trial period (in- or post-trial)
    - Atorvastatin and randomised blood pressure treatment
    - Whether the atorvastatin effects differed between subgroups such as age, sex, ethnic or diabetes status
- Statistical tests were 2-sided and a *P* value of <0.05 was considered to be of statistical significance

ASCOT-LLA 11 Year Mortality: Study Profile



Effect of Atorvastatin on Mortality and Causes of Death – 1

Cause of Death	LLA						Total Follow-up					
	Placebo		Atorvastatin		HR (95% CI)†	*P* value	Placebo		Atorvastatin		HR (95% CI)†	*P* value
	N (%)	Rate*	N (%)	Rate*			N (%)	Rate*	N (%)	Rate*		
All-cause	90 (3.9)	1.28	83 (3.6)	1.18	0.92 (0.68, 1.24)	0.60	520 (22.7)	2.24	460 (19.9)	1.94	0.86 (0.76, 0.98)	0.02
CV	36 (1.6)	0.51	30 (1.3)	0.43	0.83 (0.51, 1.35)	0.45	167 (7.3)	0.73	154 (6.6)	0.65	0.89 (0.72, 1.11)	0.32
Non-CV	54 (2.4)	0.77	53 (2.3)	0.75	0.99 (0.67, 1.44)	0.94	353 (15.4)	1.52	306 (13.2)	1.29	0.85 (0.73, 0.99)	0.03

*Per 100 person-years

†Unadjusted hazard ratios (HR) (95% confidence interval [CI]) of atorvastatin effect on mortality and causes of death during ASCOT-LLA and total follow-up period

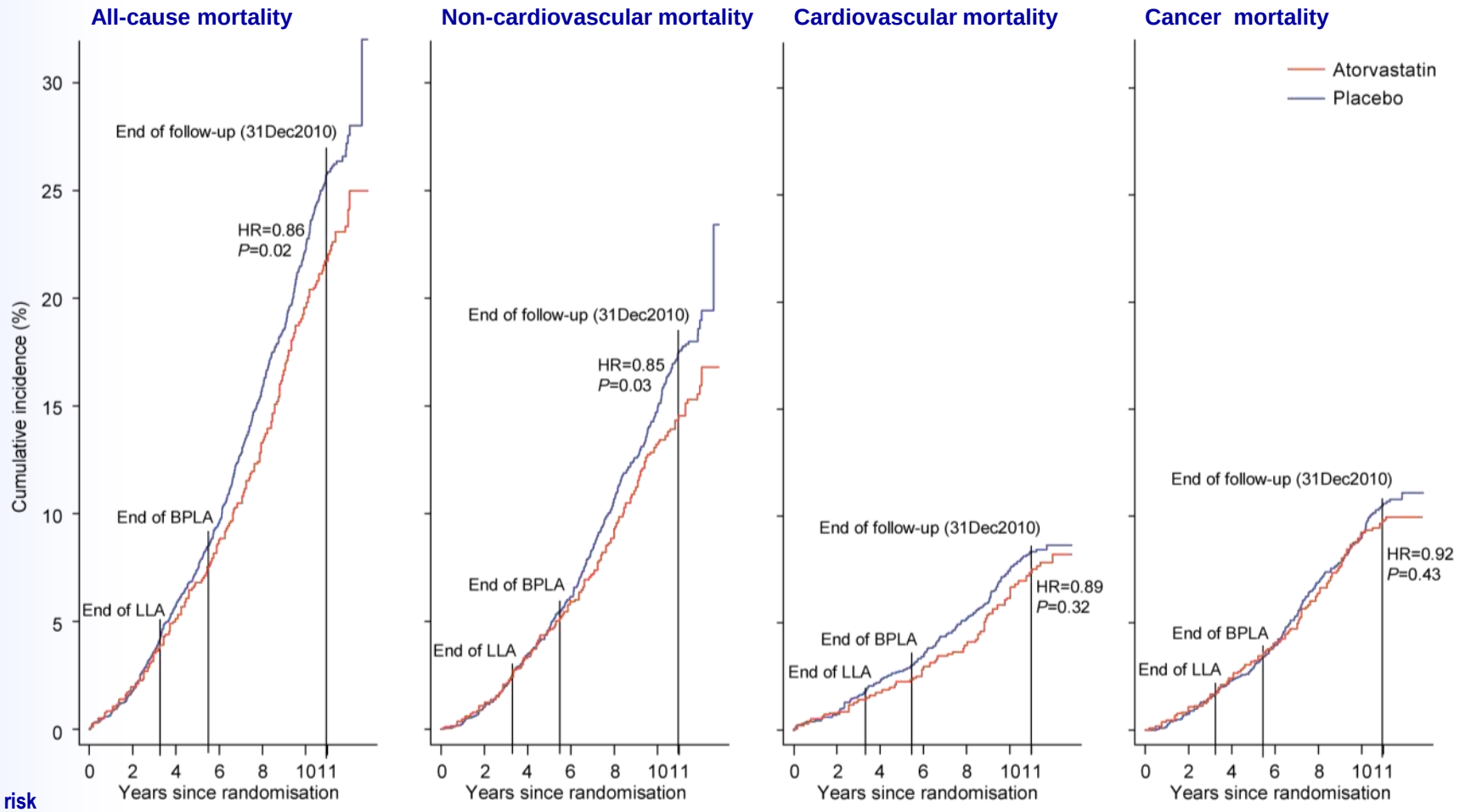
Effect of Atorvastatin on Mortality and Causes of Death – 2

Cause of Death	LLA						Total Follow-up					
	Placebo		Atorvastatin		HR (95% CI)†	*P* value	Placebo		Atorvastatin		HR (95% CI)†	*P* value
	N (%)	Rate*	N (%)	Rate*			N (%)	Rate*	N (%)	Rate*		
Cancer	37 (1.6)	0.53	39 (1.7)	0.55	1.05 (0.67, 1.65)	0.82	212 (9.3)	0.92	201 (8.7)	0.85	0.92 (0.76, 1.12)	0.43
Infection/ Respiratory	6 (11.1)	0.09	3 (5.7)	0.04	0.51 (0.13, 2.04)	0.34	56 (15.9)	0.24	37 (12.1)	0.16	0.64 (0.42, 0.97)	0.04
Infection	3 (5.6)	0.04	1 (1.9)	0.01	0.34 (0.04, 3.26)	0.35	37 (10.5)	0.16	23 (7.5)	0.10	0.60 (0.36, 1.02)	0.06
Respiratory	3 (5.6)	0.04	2 (3.8)	0.03	0.68 (0.11, 4.07)	0.67	19 (5.4)	0.08	14 (4.6)	0.06	0.72 (0.36, 1.44)	0.35

*Per 100 person-years;

†Unadjusted hazard ratios (HR) (95% confidence interval [CI]) of atorvastatin effect on mortality and causes of death during ASCOT-LLA and total follow-up period

Cumulative Incidence by Cause of Death – 1



Number at risk

Placebo	2288	2191	2052	1208	2288	2191	2052	1208	2288	2191	2052	1208	2288	2191	2052	1208
Atorvastatin	2317	2228	2091	1226	2317	2228	2091	1226	2317	2228	2091	1226	2317	2228	2091	1226

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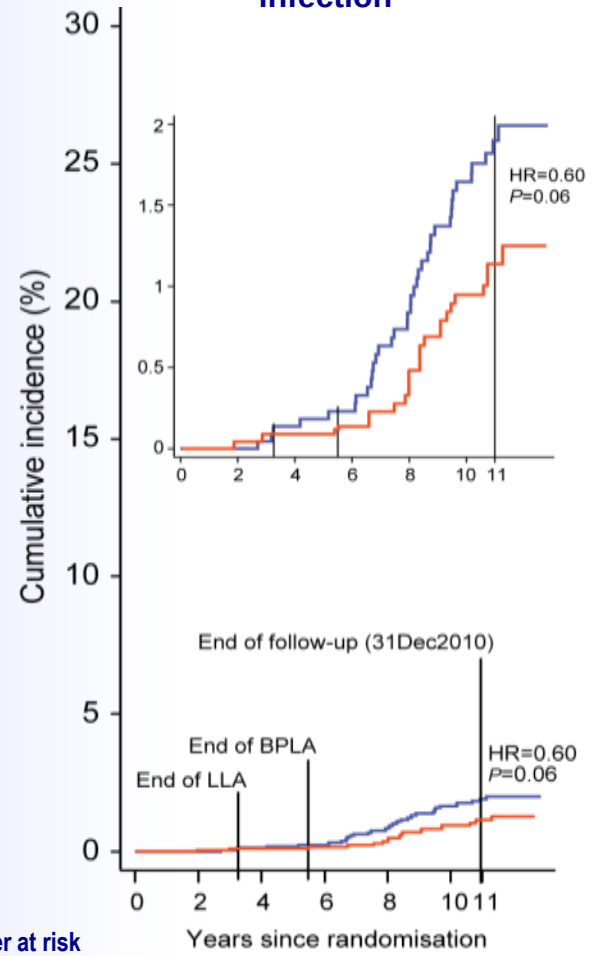
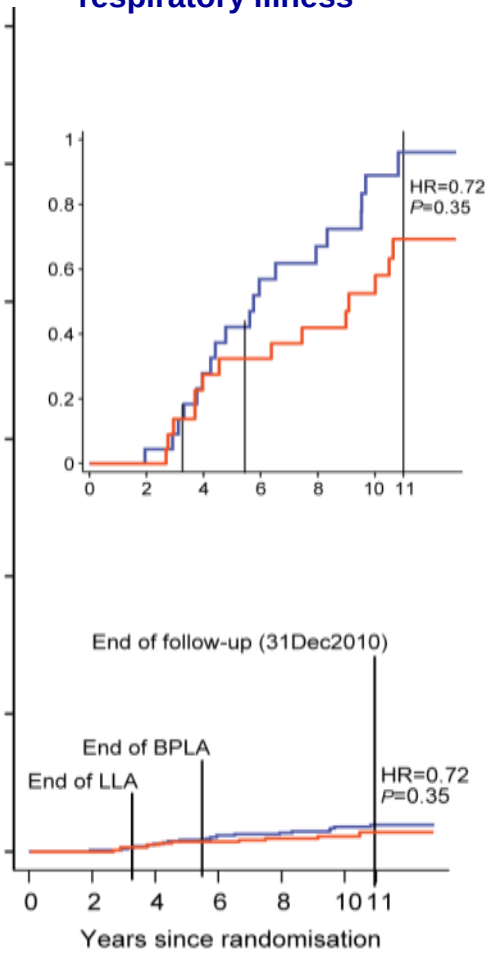
Cumulative Incidence by Cause of Death – 2

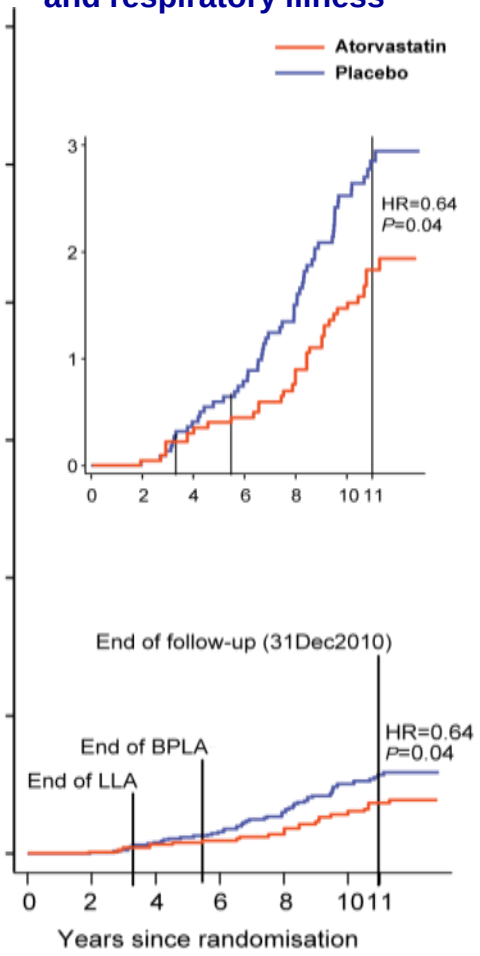
Mortality due to infection



Mortality due to respiratory illness



Mortality due to infection and respiratory illness



Number at risk						
Placebo	2288	2191	2052	1208	2288	2191	2052	1208	2288	2191	2052	1208
Atorvastatin	2317	2228	2091	1226	2317	2228	2091	1226	2317	2228	2091	1226

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Adjusted Effect of Atorvastatin on Mortality and Causes of Death

Cause of death	LLA		Post-LLA*		Total Follow-up	
	HR (95% CI)†	*P* value	HR (95% CI)†	*P* value	HR (95% CI)†	*P* value
All-cause	0.93 (0.69, 1.25)	0.64	0.85 (0.74, 0.98)	0.02	0.86 (0.76, 0.98)	0.02
CV	0.85 (0.52, 1.38)	0.51	0.91 (0.72, 1.17)	0.47	0.90 (0.72, 1.12)	0.35
Non-CV	0.99 (0.68, 1.44)	0.94	0.82 (0.69, 0.97)	0.02	0.84 (0.72, 0.98)	0.03
Cancer	1.05 (0.67, 1.64)	0.84	0.89 (0.72, 1.10)	0.28	0.92 (0.75, 1.11)	0.37
Infection/Respiratory	0.51 (0.13, 2.05)	0.35	0.65 (0.42, 1.01)	0.06	0.64 (0.42, 0.97)	0.04
Infection	0.33 (0.03, 3.16)	0.33	0.61 (0.36, 1.05)	0.07	0.59 (0.35, 0.99)	0.046
Respiratory	0.73 (0.12, 4.39)	0.73	0.75 (0.36, 1.60)	0.46	0.75 (0.37, 1.50)	0.42

*Participants who died during LLA period were excluded

†Adjusted for age, sex, body mass index, systolic blood pressure, total cholesterol, diabetes, current smokers, ethnicity, randomised blood pressure treatment and completion educational age

Summary

- A median 11 years after the initial randomisation for ASCOT, and approximately 8 years after the closure of the LLA, all-cause mortality remained significantly lower in those originally assigned atorvastatin
- Among the UK participants of ASCOT-LLA who were initially randomised to atorvastatin 10 mg therapy:
  - CV deaths were fewer, but the difference was not significant
  - Non-CV deaths were significantly fewer, attributed to a reduction in deaths caused by infection and respiratory illness

Statins on Infection

- Experimental studies[1] show statins:
  - Modulate neutrophil function
  - Reduce pro-inflammatory cytokine release
  - Improve vascular function
  - Are anti-thrombotic and
  - Improve outcome from pneumonia and sepsis
- Observational studies have shown prior statin use reduces mortality from sepsis and community acquired pneumonia[1]
- A review and meta-analysis[2] of randomised trials and cohort studies found that:
  - In 9 cohorts addressing the role of statins in treating infection, the pooled effect estimate was 0.55 (95% CI: 0.36, 0.83) in favour of statin
  - In cohort studies investigating the prevention of infection in patients with vascular disease, the pooled effect estimate was 0.57 (95% CI: 0.43, 0.75) in favour of statin use
- A recent editorial[3]
  - Urged caution in their interpretation, on account of the fact that observational, retrospective and meta-analytical studies cannot eliminate the possibility of confounding bias
  - highlighted the need for formal prospective randomized controlled trials to be conducted

1. Chalmers JD, et al. *Resp Med.* 2010;104:1081-1091.
2. Tleyjeh IM, et al. *Arch Intern Med.* 2009;169:1658-1667.
3. Chopra V and Flanders SA. *BMJ.* 2011;342:d1907

Conclusions

- Long-term benefits on all-cause mortality were observed among the UK participants of ASCOT-LLA who were originally assigned atorvastatin

- No definitive explanation has been established for the hypothesised legacy effects of atorvastatin therapy on non-CV death reduction

Back up

Characteristics of Surviving Patients at the End of UK-ASCOT-LLA

	Placebo (n=2198)	Atorvastatin (n=2234)	*P* value
Male, n (%)	1923 (87.5)	1946 (87.1)	0.70
Age (Years)	64.30 (8.21)	64.31 (8.10)	0.99
Age >60 years	1534 (69.8)	1560 (69.8)	0.98
White, n (%)	1939 (88.2)	1974 (88.4)	0.95
Current Smokers, n (%)	559 (25.4)	585 (26.2)	0.57
Alcohol (units/week)	11.17 (14.44)	10.82 (13.41)	0.41
SBP (mmHg)	162.18 (17.84)	162.00 (17.32)	0.74
DBP (mmHg)	92.75 (9.51)	92.41 (9.85)	0.24
BMI (Kg/m^2)	28.86 (4.60)	28.87 (4.85)	0.92
Total Cholesterol (mmol/L)	5.49 (0.81)	5.48 (0.81)	0.66
LDL-C (mmol/L)	3.46 (0.75)	3.45 (0.74)	0.65
HDL-C (mmol/L)	1.29 (0.35)	1.30 (0.35)	0.50
Triglycerides (mmol/L)	1.66 (0.88)	1.64 (0.91)	0.32
Glucose (mmol/L)	6.34 (2.30)	6.22 (2.15)	0.08
Creatinine (mmol/L)	100.49 (16.86)	100.26 (17.12)	0.65
Stroke/TIA, n (%)	224 (10.2)	226 (10.1)	0.93
Diabetes, n (%)	641 (29.2)	632 (28.3)	0.52
LVH, n (%)	500 (22.7)	505 (22.6)	0.91
Peripheral vascular disease, n (%)	140 (6.4)	154 (6.9)	0.48
Other CV disease, n (%)	55 (2.5)	63 (2.8)	0.51
Number of risk factors	3.72 (0.89)	3.69 (0.90)	0.31
Amlodipine, n (%)	1107 (50.4)	1106 (49.5)	0.57
Previous Lipid-lowering drug, n (%)	21 (1.0)	28 (1.3)	0.34
Aspirin use, n (%)	490 (22.3)	511 (22.9)	0.64
Previous anti-BP drugs, n (%)			
None	177 (8.1)	194 (8.7)	
≥ 1	2021 (91.9)	2040 (91.3)	

Values are mean (SD) or n (%)