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Adverse events associated with un-blinded, but not with blinded, statin therapy in the Anglo-Scandinavian Cardiac Outcomes Trial

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43 **Background**

44 Large-scale evidence from randomised placebo-controlled trials has shown that statin therapy
45 reduces the incidence of major vascular events (i.e., coronary deaths or myocardial infarctions,
46 ischaemic strokes and coronary revascularisation procedures) by about one quarter for each 1
47 mmol/L LDL-cholesterol reduction during each year (after the first) that it continues to be taken.¹
48 The proportional reductions in risk were similar in secondary and primary prevention, and were
49 somewhat greater among lower-risk individuals (although the absolute benefits were smaller).
50 These findings have resulted in guidelines recommending that statin therapy be considered for all
51 patients who have experienced an atherosclerotic event and, in primary prevention, for individuals
52 who have a 10 year risk of having a cardiovascular event (defined as coronary death, myocardial
53 infarction, angina stroke, or transient ischaemic attack) of at least 10%, as well as for those with
54 high LDL-cholesterol levels or relevant co-morbidity (such as diabetes).^{2,3}

55
56 Concerns have been expressed about the expansion in statin use produced by lowering risk
57 thresholds for offering statin therapy to patients.^{4,5} In making the argument against so-called
58 “over-medicalization” of the population, it has been claimed that statin therapy causes increased
59 rates of adverse events and symptomatic side-effects (chiefly muscle pain and weakness) that
60 prevent as many as one fifth of patients from continuing to take statin therapy long-term.^{5,6} These
61 claims have usually derived from observational studies using health-care databases which, since
62 they are neither randomised nor blinded, are subject to potential biases in the assessment of
63 causation.⁷ By contrast, in double-blind randomised trials of statin therapy, the reported rates of
64 different types of adverse event have generally been similar among patients receiving statin or
65 placebo treatment (except for reductions in atherosclerotic events), with no differences between
66 the groups in the rates of treatment cessation in association with adverse events^{7,8,9,10}.

67
68 It has been suggested that the lack of an excess of AEs in randomised controlled trials of statin
69 therapy might be due to their ascertainment not being sufficiently specific or sensitive.^{5,11} The
70 Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT)¹² provides a unique opportunity to assess the
71 impact of blinded and un-blinded ascertainment of AEs identified using the same approach during
72 blinded randomised statin therapy in the Lipid-lowering arm (LLA) of the trial¹³ (i.e., the “blinded
73 randomised” phase) and during the subsequent follow-up period when a proportion of patients
74 were taking open-label statin (the “non-blinded non-randomised” phase).¹⁴ Four AEs of interest
75 (AEOI) were pre-specified due to the public health impact of widespread claims about muscle-
76 related side-effects and the addition to the drug label of erectile dysfunction, sleep disturbance
77 and cognitive impairment as possible side-effects based on reviews by MHRA and FDA.^{15,16}

78
79 **Methods**

80 Details of the ASCOT protocol, including study design, organization, clinical measurements, power
81 calculations, recruitment rates, and baseline characteristics have been published¹² and further
82 information is available on the trial website (www.ascotstudy.org). ASCOT was an independent,
83 investigator-led, multicentre study. Men and women aged between 40 and 79 years were eligible
84 if they had ≥ 3 risk factors for CV disease but had no history of myocardial infarction and were not
85 being treated for angina. They were randomly assigned in an open-label comparison between two
86 antihypertensive treatment regimens and, by using a 2 X 2 factorial design, between atorvastatin
87 10 mg daily versus placebo in the blinded LLA comparison.

88
89 The study conformed to good clinical practice guidelines and the Declaration of Helsinki. The
90 protocol and all subsequent amendments were reviewed and ratified by central and regional

91 ethics review boards in the UK and by national ethics and statutory bodies in Ireland and the
92 Nordic countries (Sweden, Denmark, Iceland, Norway, and Finland).

93

94 ***ASCOT-LLA and LLA-extension phases***

95 Patients included in the ASCOT blood pressure-lowering comparison (BPLA) were also eligible for
96 inclusion in the LLA comparison if they had a total cholesterol concentration of 6.5 mmol/L or less
97 and were not taking a statin or a fibrate. There was no formal run-in period to test for tolerance to
98 statins and few, if any, patients had any prior exposure to statin treatment. 10,305 patients were
99 randomised in the LLA between 1998 and 2000, but 65 were withdrawn soon after randomisation
100 due to concerns about source documentation validation. For the remaining 10,240 patients, the
101 randomly assigned atorvastatin or placebo was stopped for efficacy (at the recommendation of
102 the Data Safety and Monitoring Board) in 2002, after a median of 3.3 years of active follow-up,
103 (the period hitherto referred as the “blinded randomised phase” of the ASCOT-LLA).¹³ The patients
104 were then told whether they had been assigned atorvastatin or placebo, but they continued to be
105 actively followed in the same way until 2004, for a median of 2.2 years, while the ASCOT-BPLA
106 comparison continued.¹⁴ During that period they were offered open-label atorvastatin (the “non-
107 blinded non-randomised phase”), approximately two thirds of the patients opted to commence or
108 continue open-label statin therapy (“users”) while one third did not (“non-users”); see figure 1.

109

110 ***Adverse Event recording, classification and adjudication***

111 Following randomisation, study participants were scheduled to be seen at six weeks, three months
112 and, thereafter, at six monthly intervals during both the blinded randomised and the non-blinded
113 non-randomised phase of the ASCOT-LLA (until the ASCOT-BPLA completed). At each study visit,
114 all AEs reported by participants were recorded by the study team in the case report form (CRF).
115 Specific questions relating to any putative AEs were not asked at these visits. During total follow-
116 up for a median of 5.5 years among 10,240 randomised patients in the LLA, there were 60,612
117 distinct AEs (i.e., after removing multiple reports from the database of the same AE occurrence).

118

119 Reports of AEs by study participants were initially recorded verbatim and subsequently classified
120 using the Medical Dictionary for Regulatory Activities (MedDRA)¹⁷ into 26 separate system organ
121 classification (SOC) groups, 2,288 unique preferred terms, and 5,109 separate lower level terms.
122 For the present report, two physicians (AW and DT) adjudicated the four AEs of interest (AEOI):
123 muscle-related, erectile dysfunction, sleep disturbance and cognitive impairment. Each of the
124 adjudicators reviewed (blind to baseline characteristics, randomised treatment, non-study statin
125 use, and trial phase) all reported AEs for the presence of any of the four AEOIs and, based on the
126 description in the CRF, classified their degree of certainty (definite, probable or possible) according
127 to pre-specified definitions. Further details are given in supplementary table 4. Any disagreements
128 between the two adjudicators were independently resolved by a third physician (AG), who was
129 similarly blinded.

130

131 ***Statistical analysis***

132 Cox proportional hazard models were used to compare time to first AE in the blinded phase
133 between patients randomly assigned atorvastatin versus those randomly assigned placebo, and in
134 the non-blinded non-randomised phase between patients who were exposed to statin therapy
135 during that phase (“users”) versus those who were not exposed (“non-users”). Patients were
136 considered to be non-users in the non-blinded non-randomised phase until statin treatment was
137 given for at least two consecutive days (i.e., events occurring beforehand were included in the
138 non-user group, whereas events occurring after statin use had started were included in the “user”
139 group even if the treatment had been stopped). Consequently, time-updated Cox-models were

140 used for the comparisons of time to first AE between statin users and non-users. Hazard ratios
141 (HRs) and 95% confidence intervals (95% CIs) were calculated for the pre-specified primary
142 outcome for each AEOI of the combination of definite and probable events, with subsidiary
143 sensitivity analyses of definite AEOIs only and of all AEOIs (i.e., including those considered to be
144 only possible AEOIs). Primary analyses did not involve adjustment for baseline characteristics at
145 the time of randomisation, but subsidiary analyses were conducted of the non-blinded
146 comparisons with adjustment for baseline characteristics. All of the reported AEs not classified as
147 one of the four AEOIs were also analysed grouped by SOC. Incident rates where applicable were
148 reported as percentage per annum (% pa).

149

150 **Results**

151 The blinded randomised phase of the LLA was conducted from 1998 to 2002, and the non-blinded
152 non-randomised phase from 2002 to 2004. Of the 10,240 eligible randomised patients, 60 (33
153 atorvastatin; 27 placebo) were excluded from these analyses as they were missing end dates for
154 the blinded phase. A further 281 patients (129 atorvastatin; 152 placebo) had either died or been
155 censored (i.e., those who stopped routine follow-up prior to the end of LLA), and were therefore
156 only included in the blinded analyses. Among 9,899 patients in the non-blinded non-randomised
157 phase, 6,409 (64.7%) were users of statin therapy (most commonly atorvastatin 10mg) at some
158 time during that period, with 52% using it immediately after the end of the blinded randomised
159 phase.

160

161 Table 1 describes the baseline characteristics at the time of randomisation among patients who
162 were randomly assigned atorvastatin or placebo in the blinded randomised phase, and among
163 those who were users and non-users of statin therapy in the non-blinded non-randomised phase.
164 The patients were predominantly male, with an average age of 63 years at baseline. No material
165 differences in baseline characteristics were observed between the randomised treatment groups.
166 However, in the non-randomised phase, users of statin therapy were less likely than non-users to
167 be women or to have been smokers, and more likely to have had diabetes at baseline. Patients
168 who had reported AEOIs during the blinded phase were slightly less likely to use a statin during the
169 open phase. (supplementary table 1).

170

171 **Adverse events in the blinded randomised phase**

172 **Adverse events of interests (AEOI):** During the blinded randomised phase of ASCOT-LLA, the rate
173 of reporting of definite or probable muscle-related AEOIs was similar among patients randomly
174 assigned atorvastatin or placebo (298 [2.03%pa] vs 283 [2.00%pa]; HR 1.03 [95%CI 0.88-1.21]:
175 table 2). Compared with placebo, the rate of reports of erectile dysfunction was slightly, but non-
176 significantly, lower among the patients assigned atorvastatin (272 [1.86%pa] vs 302 [2.14%pa]; HR
177 0.88 [0.75-1.04]). Patients assigned to receive atorvastatin reported sleep disturbance significantly
178 less often than did those assigned placebo (149 [1.00%pa] vs 210 [1.46%pa]; HR 0.69 [0.56-0.85];
179 $p=0.0005$ before any adjustment for multiple comparisons). However, too few cases of cognitive
180 impairment were reported (31 [0.20%pa] vs 32 [0.22%pa]) for a statistically reliable analysis (HR
181 0.94 [0.57-1.54]). There were similar findings in sensitivity analyses based on definite AEOIs alone
182 or when the larger number of possible AEOIs were included (figure 2).

183

184 **Other adverse events:** Compared with patients assigned placebo, the rates of reports of all other
185 AEs grouped by SOC categories were similar among patients assigned atorvastatin (table 3), with
186 the exception of a small excess of AEs attributed to renal and urinary disorders (481 [1.87%pa] vs
187 392 [1.51%pa]; HR 1.23 [1.08 to 1.41]; $p=0.0021$: table 3). Subdivision of that SOC, indicates the
188 excess was chiefly due to reports of nocturia and urinary frequency (supplementary table 2).

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There were no differences between the treatment groups in the rates of serious AEs (except for reductions in atherosclerotic events)¹³ or treatment cessation in association with adverse events (supplementary table 3; www.ascotstudy.org). In particular, there was no excess of serious AEs that had been attributed to musculoskeletal or connective tissue disorders. However, one case of non-fatal rhabdomyolysis was reported in a man receiving atorvastatin who had had a very high alcohol intake and a recent febrile illness.

Adverse events in the non-blinded non-randomised phase

Adverse events of interest: During the non-blinded non-randomised extension phase of ASCOT-LLA, overall reporting rates for AEOIs were lower than in the blinded phase of the trial. However, muscle-related AEOIs were reported at a higher rate by statin users than by those who were not (161 [1.26%pa] vs 124 [0.90%pa]; HR 1.41 [1.10-1.79]; p=0.0059: table 2). The proportional excess was similar among patients who had been assigned atorvastatin (HR 1.49 [1.05-2.11]) or placebo (HR 1.33 [0.96-1.84]) during the blinded randomised phase (interaction p=0.63).

There were no significant differences between statin users and non-users in the reported rates of erectile dysfunction (88 [0.68%pa] vs 99 [0.80%pa]; HR 0.89 [0.66 to 1.20]), sleep disturbance (72 [0.56%pa] vs 82 [0.66%pa]; HR 0.87 [0.63 to 1.20]) or cognitive impairment (22 [0.17%pa] vs 36 [0.29%pa]; HR 0.59 [0.34-1.02]: table 2).

There were similar findings in the sensitivity analyses based on definite AEOIs alone or when the larger number of possible AEOIs were included (figure 2). A subsidiary analysis of the non-blinded comparisons adjusted for baseline characteristics (age, sex, race, smoking, diabetes, left ventricular hypertrophy, total cholesterol and systolic blood pressure), had minimal effect on the HRs. For muscle-related AEs, the adjusted HR was 1.43 [1.12-1.83]

Other adverse events: The rates of reports of all other AEs grouped by SOC categories, were similar among the patients who were using and not using statin therapy (table 4), with the exception of an excess among statin users of AEs attributed to musculoskeletal and connective tissue disorders (992 [8.69%pa] vs 831 [7.45%pa]; HR 1.17 [1.06-1.29]; p=0.0012). There were no differences in the rates of serious AEs between users and non-users (supplementary table 5).

Discussion

The ASCOT-LLA trial provides a unique opportunity to compare the rate of reporting of AEs using an identical follow-up procedure and AE ascertainment process in the same individuals during blinded randomised and non-blinded non-randomised statin therapy. There was no excess of reports of muscle-related AEs among patients assigned statin therapy during the blinded randomised phase, but there was a significant excess when patients knew that they were taking a statin during the subsequent non-blinded phase. This observation is consistent with a “nocebo” effect, whereby subjective AEs (e.g., symptoms reported by patients) may be more likely to be attributed to a treatment thought to cause some particular side-effect.¹⁸

Statin therapy has been shown to cause myopathy (i.e., muscle pain or weakness combined with large increases in blood concentrations of creatine kinase) in about 1 per 10,000 patients per year of treatment.¹⁹ However, in double-blind randomised trials of statin therapy, muscle-related symptoms have generally been reported with similar frequency by patients assigned statin or placebo treatment.

238 Although muscle-related problems were not sought systematically in all such trials, sufficiently
239 large numbers of cases have been reported to detect or rule out small excesses.⁷ For example, a
240 meta-analysis of 26 blinded randomised trials found little difference in the rates of muscle
241 problems reported during an average treatment duration of three years: 7,544 cases (12.7%)
242 among 59,237 participants assigned statin versus 6,735 (12.4%) among 54,458 assigned placebo.²⁰
243 Combination of the reported results in the large placebo-controlled trials eligible for the
244 Cholesterol Treatment Trialists' Collaborative meta-analyses¹ yielded similar results: 5,162 (11.7%)
245 cases allocated statin therapy versus 5,015 (11.4%) allocated placebo during an average of five
246 years of treatment (p=0.10).⁷ The numbers of cases of muscle-related problems that led to the
247 randomised study treatment being stopped were also found to be similar. Consequently, it has
248 been estimated that any excess of symptomatic muscle pain or other muscle-related problems
249 that is actually caused by statin therapy is likely to be no more than about 0.1-0.2% per year of
250 treatment.⁷

251
252 Despite these results from blinded randomised trials, the increasingly widespread use of statins
253 has been associated with increasingly common reports of so-called "statin intolerance"^{6,21} chiefly
254 attributed to muscle pain or weakness.⁶ Indeed, based on non-randomised observational studies
255 of statin use in routine care, it has been claimed that as many as one-fifth of patients are not able
256 to tolerate statin therapy.^{5,22} However, patients who are taking a treatment as part of their
257 routine care know they are doing so (as do their doctors) and they may also be specifically told
258 that the treatment has particular side-effects (e.g. patients given statin therapy are typically
259 advised that serious muscle problems can arise rarely). This inherent lack of blinding in
260 observational studies may introduce substantial ascertainment bias, particularly for the
261 assessment of the effects of a treatment on substantive outcomes.^{7,18} The contrast between the
262 similarity of the rates of muscle-related symptoms reported during the blinded randomised phase
263 of ASCOT-LLA and the excess associated with statin use during the non-blinded non-randomised
264 phase illustrates this problem. Moreover, the present analyses may well under-estimate the
265 impact of the nocebo effect because ASCOT-LLA was conducted during 1998-2004, before claims
266 that statin therapy causes high rates of side-effects had become as common as they are now.

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269 We selected three other categories of AE for scrutiny because the regulatory authorities had
270 added them to the drug label as possible statin side-effects^{16,17} based largely on associations in
271 observational studies (and despite a general lack of support for such associations in randomised
272 trials).⁷ Unexpectedly, and by contrast with the regulatory concerns, the rate of reports of sleep
273 disturbances was reduced by about one third among patients assigned atorvastatin during the
274 blinded randomised phase of ASCOT-LLA (but not with statin use during the non-blinded non-
275 randomised phase).. A beneficial effect of statin use on sleep disturbance has not previously been
276 reported,^{7,23} and it may be that this difference was due to chance (although it is conventionally
277 significant after adjustment for multiple comparisons). There were also fewer reports of erectile
278 dysfunction in ASCOT-LLA among patients assigned atorvastatin during the blinded randomised
279 phase, but that difference did not achieve statistical significance (irrespective of whether the
280 analyses were restricted to definite cases or included all reported cases).

281
282 There were too few reported cases of cognitive impairment during ASCOT-LLA to assess the effects
283 of statin therapy reliably. However, specific assessment of this outcome among large numbers of
284 older people in the PROSPER and HPS randomised placebo-controlled trials,^{24,25} as well as in trials
285 among people who already had pre-existing cognitive impairment, provides good evidence that
286 statin therapy has little effect on memory loss or other measures of cognitive function.^{7,13} Most

287 recently, it has been reported that there was no effect of statin therapy on cognitive decline or
288 memory loss among the 12,000 patients in the randomised blinded HOPE-3 trial.²⁶ In exploratory
289 analyses of all other AE reports grouped according to SOC, we did not find significant differences
290 during the blinded randomised phase, with the exception of a small excess of reports of renal and
291 urinary disorders in the atorvastatin group which appeared to be related to increased frequency of
292 micturition and nocturia. As far as we are aware, such an excess has not previously been reported.
293 Given the small number of events on which it is based, the large number of separate comparisons
294 made, and their exploratory nature, it may well be that this apparent difference is due to chance.

295
296 Our findings were not materially altered when the analyses were based on reports of only those
297 AEs that were considered to be definite, or when the larger numbers of probable and possible AEs
298 were included (which tend to increase statistical power to detect an effect of a particular size, but
299 might decrease sensitivity due to dilution of the treatment effect by including events that are not
300 actually the AE of interest).

301
302 The ASCOT trial was conducted in a hypertensive population in the UK, Ireland and the Nordic
303 countries among patients who were predominately aged over 60 years, male and of European
304 ancestry. It seems likely that the findings would be generalisable to younger and older patients,
305 (particularly given the results from other blinded randomised trials in such individuals), but it may
306 not be generalisable to people from other ethnic groups. Atorvastatin at a daily dose of 10mg
307 was studied specifically only in the blinded phase of the trial, but most of the patients in the open
308 phase who took a statin used the same dose of atorvastatin, with only a few using simvastatin.
309 Atorvastatin 10mg daily would now be considered a relatively low dose, but randomised trials of
310 higher doses have also not found differences in muscle-related AEs, other than the very small
311 excess of myopathy (as described above).

312
313 The widespread media coverage that has been engendered by claims that statin therapy causes
314 side effects in up to one fifth of patients,^{5,27} and the failure to correct such misleading claims
315 rapidly and properly has led to high risk patients with established cardiovascular disease stopping
316 their statin therapy.^{28,29} It has been estimated that such reductions in statin use may result in
317 thousands of fatal and disabling heart attacks and strokes occurring, that would otherwise have
318 been avoided. Seldom in the history of modern therapeutics have the substantial proven benefits
319 of a treatment been compromised to such an extent by serious misrepresentations of the
320 evidence about its safety. We hope that the demonstration in ASCOT-LLA of not only the lack of
321 adverse effects of statin therapy on muscle-related and other AEs, but also the impact of
322 ascertainment bias in non-blinding studies (which have been the basis of many of the misleading
323 claims) will help to counter the adverse effect on public health of exaggerated claims about statin
324 side-effects.

325 326 **Role of the funding source**

327 ASCOT was conceived, designed and coordinated by an investigator-led independent Steering
328 Committee with two non-voting members from the principal funding source (Pfizer Inc). Data
329 analyses and preparation of all reports were conducted independently of the funding sources.

330 331 **Contributors**

332 PS and AG designed the study, planned the analyses and wrote the manuscript with the assistance
333 of TC and RC.

334 DT, AW and AG carried out the review and classification of adverse events.

335 AG and TC conducted the statistical analyses. All authors reviewed and approved the final
336 manuscript.

337

338 **Acknowledgements**

339 PS and NP are recipients of NIHR Senior Investigator Awards and are supported by the Biomedical
340 Research Centre Award to Imperial College Healthcare NHS Trust. The authors wish to
341 acknowledge statistical assistance from Tom Godec.

342

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Table 1. Baseline characteristics among those allocated to atorvastatin and placebo in the blinded phase of the LLA of the ASCOT trial, and among users and non-users in the non-blinded non-randomized phase of LLA-extension

	Blinded randomized (LLA) phase		Non-blinded non-randomized (LLA-extension) phase*	
	Placebo	Atorvastatin	Non-user	User
	(n = 5079)	(n = 5101)	(n = 3490)	(n = 6409)
Patients characteristics				
Woman	949 (18.7%)	955 (18.7%)	760 (21.8%)	1097 (17.1%)
Age (years)				
≤ 60.0	1821 (35.9%)	1842 (36.1%)	1204 (34.5%)	2405 (37.5%)
> 60.0	3258 (64.2%)	3259 (63.9%)	2286 (65.5%)	4004 (62.5%)
White Ethnicity	4805 (94.6%)	4822 (94.5%)	3367 (96.5%)	5996 (93.6%)
Current smoker	1644 (32.4%)	1697 (33.3%)	1250 (35.8%)	1987 (31.0%)
Alcohol consumption per week				
≤ 14.0 units	4149 (81.7%)	4170 (81.8%)	2916 (83.6%)	5175 (80.8%)
> 14.0 units	929 (18.3%)	929 (18.2%)	574 (16.4%)	1231 (19.2%)
Systolic blood pressure, mm Hg	164.2 (18.0)	164.2 (17.7)	166.0 (18.2)	163.2 (17.6)
Diastolic blood pressure, mm Hg	95.0 (10.3)	94.9 (10.3)	95.8 (10.6)	94.6 (10.0)
Heart rate, beats/min	71.8 (12.6)	71.2 (12.7)	71.6 (12.4)	71.4 (12.8)
BMI, kg/m²	28.7 (4.6)	28.6 (4.7)	28.5 (4.7)	28.8 (4.6)
Total cholesterol, mmol/L	5.5 (0.8)	5.5 (0.8)	5.4 (0.8)	5.5 (0.8)
LDL- cholesterol, mmol/L	3.4 (0.7)	3.4 (0.7)	3.4 (0.7)	3.5 (0.7)
HDL- cholesterol, mmol/L	1.3 (0.4)	1.3 (0.4)	1.3 (0.4)	1.3 (0.4)
Triglycerides, mmol/L	1.6 (0.9)	1.7 (0.9)	1.6 (0.8)	1.7 (0.9)
Glucose, mmol/L	6.2 (2.1)	6.2 (2.1)	6.1 (2.0)	6.2 (2.1)
Creatinine, mmol/L	98.9 (16.4)	99.1 (16.6)	98.6 (17.1)	99.1 (15.9)
Medical History				
Previous stroke or TIA	524 (10.3%)	493 (9.7%)	350 (10.0%)	630 (9.8%)
Diabetes (T2DM)	1267 (25.0%)	1254 (24.6%)	792 (22.7%)	1660 (25.9%)
LVH (on ECG or ECHO)	721 (14.2%)	735 (14.4%)	478 (13.6%)	927 (14.5%)
ECG abnormalities other than LVH	721 (14.2%)	731 (14.3%)	483 (13.8%)	908 (14.2%)
Peripheral vascular disease	251 (4.9%)	259 (5.1%)	166 (4.8%)	318 (5.0%)
Other relevant cardiovascular disease	204 (4.0%)	184 (3.6%)	135 (3.9%)	234 (3.7%)
Mean (SD) number of risk factors	3.7 (0.9)	3.7 (0.9)	3.6 (0.8)	3.7 (0.9)
Previous antihypertensive treatments				

None	977 (19.2%)	1000 (19.6%)	769 (22.0%)	1163 (18.2%)
1	2252 (44.3%)	2286 (44.8%)	1571 (45.0%)	2842 (44.3%)
> 1	1850 (36.4%)	1815 (35.6%)	1150 (33.0%)	2404 (37.5%)
Previous lipid-lowering treatment	44 (0.9%)	34 (0.7%)	31 (0.9%)	46 (0.7%)
Aspirin use	881 (17.4%)	900 (17.6%)	527 (15.1%)	1188 (18.5%)

Data not shown as n (%) are mean (SD). BMI = body mass index. TIA = transient ischaemic attack. LVH = left-ventricular hypertrophy. ECG = echocardiogram. ECHO = echocardiogram.

*Note. 281 patients were included in the analysis of the blind period only, and hence are not included in this phase.

Table 2. Risk (hazards ratio) for the adverse events of interest in the blinded randomised and un-blinded non-randomised phase of the ASCOT-LLA

ASCOT-LLA phase		Blinded Randomized Phase (3.3 years)		Open Non-Randomized Phase (2.2 years)	
Adverse Event of Interest*		Placebo (n = 5,079)	Atorvastatin (n = 5,101)	Non-user (n = 3,490)	Statin-user (n = 6,409)
Muscle related*	Nos. of patients	283	298	124	161
	Rate (% pa)	2.00	2.03	1.00	1.26
	HR (95% CI)	1.03 (0.88, 1.21), p=0.7229		1.41 (1.10, 1.79), p=0.0059	
Erectile dysfunction*	Nos. of patients	302	272	99	88
	Rate (% pa)	2.14	1.86	0.80	0.68
	HR (95% CI)	0.88 (0.75, 1.04) , p=0.1260		0.89 (0.66, 1.20), p=0.4447	
Sleep disturbance*	Nos. of patients	210	149	82	72
	Rate (% pa)	1.46	1.00	0.66	0.56
	HR (95% CI)	0.69 (0.56, 0.85), p=0.0005		0.87 (0.63, 1.20), p=0.3992	
Cognitive impairment*	Nos. of patients	32	31	36	22
	Rate (% pa)	0.22	0.20	0.29	0.17
	HR (95% CI)	0.94 (0.57, 1.54), p=0.8098		0.59 (0.34, 1.02), p=0.0576	

* First event only in each phase, definite and probable AEs; number of patients with at least one event reported.

Table 3. Incident rates of all adverse events, stratified by system organ classification, among those allocated to either statin or placebo in the blinded randomized phase of the ASCOT-LLA (median follow-up, 3.3 years)

System Organ Class	Rate [% per annum]		Hazard ratio (95% CI)		P-value
	Placebo	Atorvastatin			
Blood and lymphatic system disorders	0.33	0.25	0.78	(0.57, 1.07)	0.1179
Cardiac disorders	1.89	1.92	1.02	(0.90, 1.15)	0.7801
Congenital, familial and genetic disorders	0.05	0.05	0.99	(0.47, 2.08)	0.9840
Ear and labyrinth disorders	1.38	1.30	0.95	(0.82, 1.10)	0.4569
Endocrine disorders	0.09	0.09	1.03	(0.59, 1.81)	0.9065
Eye disorders	1.37	1.36	0.99	(0.86, 1.15)	0.9299
Gastrointestinal disorders	5.70	5.72	1.01	(0.93, 1.09)	0.8668
General disorders and administration site conditions	4.81	4.91	1.02	(0.94, 1.11)	0.6104
Hepatobiliary disorders	0.17	0.15	0.88	(0.58, 1.35)	0.5675
Immune system disorders	0.13	0.13	0.97	(0.61, 1.53)	0.8830
Infections and infestations	7.72	7.53	0.98	(0.92, 1.05)	0.6060
Injury, poisoning and procedural complications	1.90	1.80	0.95	(0.84, 1.08)	0.4319
Investigations	1.07	1.00	0.94	(0.79, 1.11)	0.4322
Metabolism and nutrition disorders	0.96	0.85	0.89	(0.75, 1.07)	0.2054
Musculoskeletal and connective tissue disorders	6.91	7.19	1.04	(0.96, 1.11)	0.3270
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1.01	0.98	0.97	(0.82, 1.15)	0.7287
Nervous system disorders	5.97	6.18	1.03	(0.96, 1.12)	0.3950
Psychiatric disorders	0.12	0.07	0.59	(0.33, 1.04)	0.0678
Renal and urinary disorders	1.51	1.87	1.23	(1.08, 1.41)	0.0021
Reproductive system and breast disorders	0.83	0.82	1.00	(0.83, 1.20)	0.9776
Respiratory, thoracic and mediastinal disorders	4.83	4.76	0.98	(0.91, 1.07)	0.7225
Skin and subcutaneous tissue disorders	2.70	2.53	0.94	(0.84, 1.05)	0.2752
Social circumstances	0.02	0.01	0.66	(0.19, 2.35)	0.5232
Surgical and medical procedures	0.52	0.53	1.03	(0.82, 1.30)	0.8018
Vascular disorders	1.96	1.73	0.89	(0.78, 1.01)	0.0699
Uncoded	0.18	0.16	0.87	(0.58, 1.31)	0.5091

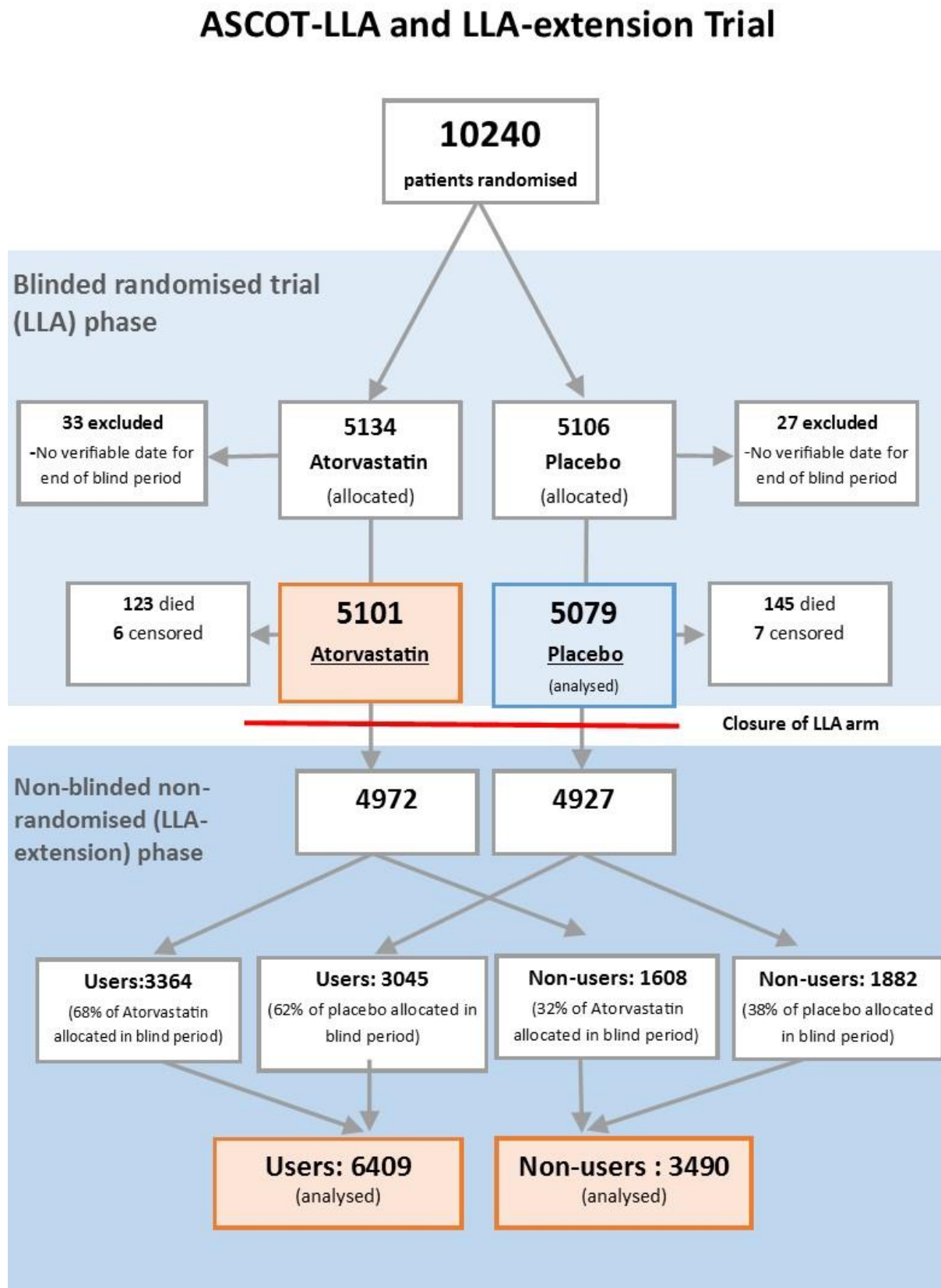
Rate in percentage per annum (equivalent to rate per 100 patient years); hazard ratio from Cox PH model

Table 4. Incident rates of all adverse events, stratified by system organ classification, among statin-users and non-users in the non-blinded non-randomized phase of the LLA-extension (median follow-up, 2.2 years)

System Organ Class	Rate (% per annum)		Hazard Ratio (95% CI)		P-value
	Non-User	Statin-User			
Blood and lymphatic system disorders	0.64	0.88	1.40	(1.04, 1.88)	0.0278
Cardiac disorders	2.46	2.41	0.96	(0.82, 1.14)	0.6639
Congenital, familial and genetic disorders	0.14	0.17	0.97	(0.51, 1.83)	0.9156
Ear and labyrinth disorders	1.35	1.42	1.04	(0.84, 1.30)	0.7062
Endocrine disorders	0.18	0.17	0.92	(0.50, 1.68)	0.7828
Eye disorders	1.88	1.92	1.00	(0.83, 1.20)	0.9887
Gastrointestinal disorders	6.32	6.19	1.01	(0.90, 1.12)	0.9076
General disorders and administration site conditions	3.91	4.05	1.10	(0.97, 1.26)	0.1419
Hepatobiliary disorders	0.36	0.25	0.70	(0.44, 1.12)	0.1378
Immune system disorders	0.22	0.15	0.63	(0.35, 1.13)	0.1223
Infections and infestations	9.62	9.42	0.96	(0.88, 1.05)	0.3663
Injury, poisoning and procedural complications	2.58	2.76	1.07	(0.91, 1.25)	0.4037
Investigations	1.49	1.51	0.98	(0.79, 1.21)	0.8419
Metabolism and nutrition disorders	1.64	1.30	0.81	(0.65, 1.00)	0.0494
Musculoskeletal and connective tissue disorders	7.45	8.69	1.17	(1.06, 1.29)	0.0012
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1.93	1.95	1.02	(0.85, 1.23)	0.8339
Nervous system disorders	5.23	4.79	0.94	(0.84, 1.06)	0.3197
Psychiatric disorders	0.14	0.12	0.84	(0.41, 1.72)	0.6416
Renal and urinary disorders	2.20	2.41	1.11	(0.94, 1.31)	0.2330
Reproductive system and breast disorders	1.45	1.41	0.92	(0.74, 1.13)	0.4169
Respiratory, thoracic and mediastinal disorders	4.50	4.30	0.98	(0.87, 1.12)	0.8046
Skin and subcutaneous tissue disorders	2.98	2.94	0.98	(0.84, 1.14)	0.7971
Social circumstances	0.02	0.02	0.51	(0.08, 3.09)	0.4638
Surgical and medical procedures	0.75	0.92	1.20	(0.91, 1.60)	0.1965
Vascular disorders	1.73	1.51	0.89	(0.73, 1.09)	0.2638
Uncoded	0.18	0.31	1.80	(1.05, 3.08)	0.0332

Incident rates in percentage per annum (equivalent to incident rate per 100 patient years); hazard ratio from time-updated Cox PH model.

Figure 1: Patient flow in the ASCOT-LLA and LLA-extension

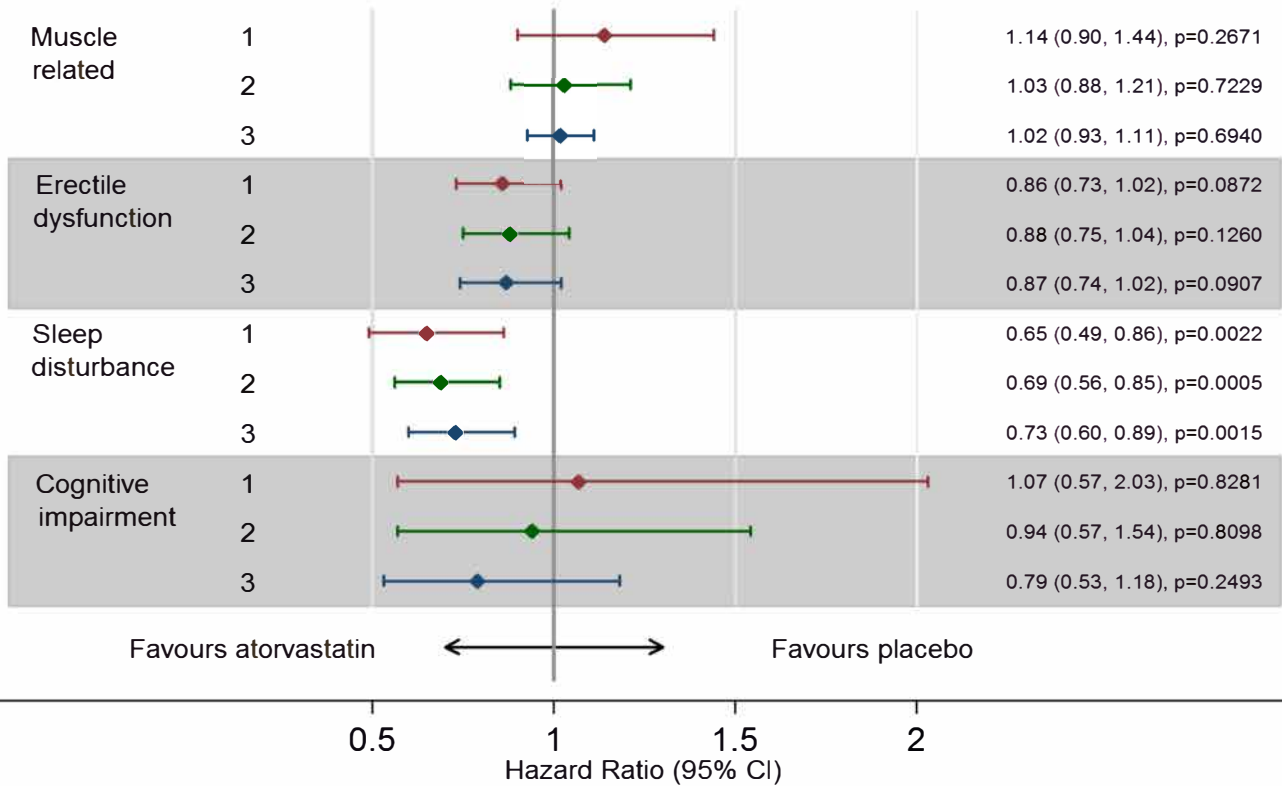


* Censored: due to lost follow-up prior to completion of LLA

Adverse events

Related (1 = definite, 2 = definite/probable, 3 = all including possible)

Hazard Ratio (95% CI)

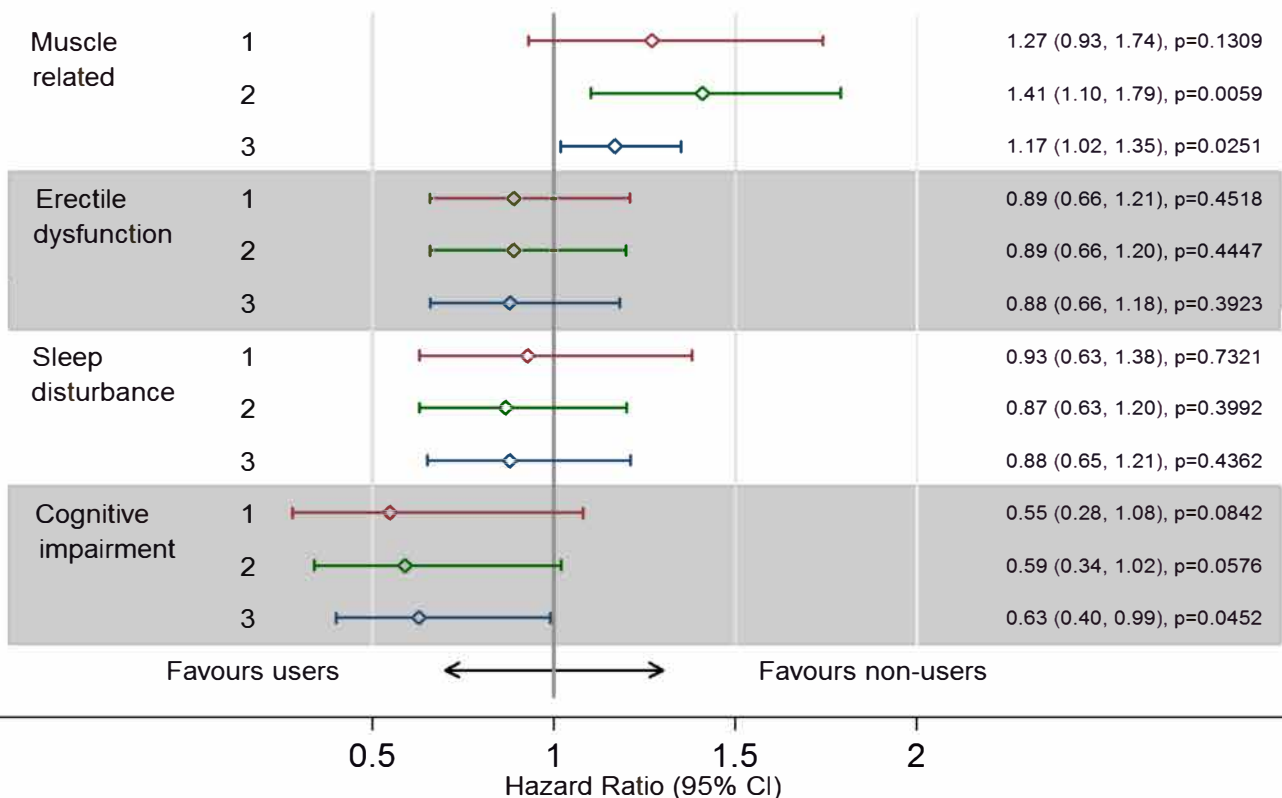


B: Non-Blinded Non-Randomized Phase

Adverse events

Related (1 = definite, 2 = definite/probable, 3 = all including possible)

Hazard Ratio (95% CI)



Supplementary Table 1

Table showing percentage of “users” in the open period stratified by whether or not they experienced each of the 4 AEOI’s (definite/probable) during the blind period

AEOI Blind Period (definite/probable)	User in Open period	P-value	User in Open period		Interaction p- value
			Placebo	Statin	
Muscle related					
No	65.0%		61.9%	68.1%	
Yes	60.5%	0.0299	59.9%	61.1%	0.2087
Cognitive impairment					
No	64.8%		61.8%	67.7%	
Yes	62.9%	0.7609	64.5%	61.3%	0.4511
Insomnia					
No	64.9%		61.9%	67.8%	
Yes	61.4%	0.1765	59.0%	64.6%	0.9354
Erectile dysfunction					
No	64.9%		62.0%	67.7%	
Yes	62.9%	0.3311	58.6%	67.5%	0.4489

Supplementary Table 2.

Incident rate of renal and bladder complaints according to preferred terms, among those on either placebo or statin and categorised in the system organ classification for renal and urinary disorders in the blinded randomized phase of the LLA

		Blinded Randomized Period of LLA							
Serious and non-serious events	Number of patients experiencing event (%)				Rate % per annum		Hazard ratio*		
	Placebo		Statin		Placebo	Statin	Hazard Ratio	(95% CI)	P-value
	n	%	n	%					
Albuminuria	6	0.12	1	0.02	0.04	0.01	0.16	(0.02, 1.36)	0.094
Anuria	2	0.04	1	0.02	0.01	0.01	-	-	-
Bilateral hydronephrosis	0	0.00	1	0.02	0.00	0.01	-	-	-
Bilirubinuria	0	0.00	1	0.02	0.00	0.01	-	-	-
Bladder discomfort	1	0.02	1	0.02	0.01	0.01	-	-	-
Bladder disorder	3	0.06	2	0.04	0.02	0.01	-	-	-
Bladder obstruction	2	0.04	0	0.00	0.02	0.00	-	-	-
Bladder pain	1	0.02	2	0.04	0.01	0.01	-	-	-
Bladder prolapse	0	0.00	1	0.02	0.00	0.01	-	-	-
Bladder spasm	0	0.00	1	0.02	0.00	0.01	-	-	-
Bladder stenosis	1	0.02	1	0.02	0.01	0.01	-	-	-
Calculus bladder	0	0.00	3	0.06	0.00	0.02	-	-	-
Calculus ureteric	4	0.08	2	0.04	0.03	0.01	-	-	-
Calculus urethral	0	0.00	1	0.02	0.00	0.01	-	-	-
Calculus urinary	10	0.20	8	0.16	0.07	0.05	0.78	(0.31, 1.97)	0.594
Chromaturia	3	0.06	1	0.02	0.02	0.01	-	-	-
Costovertebral angle tenderness	1	0.02	0	0.00	0.01	0.00	-	-	-
Cystocele	3	0.06	1	0.02	0.02	0.01	-	-	-
Dysuria	40	0.79	34	0.67	0.29	0.32	0.88	(0.55, 1.39)	0.577
Enuresis	1	0.02	0	0.00	0.01	0.00	-	-	-
Glomerulonephritis proliferative	1	0.02	0	0.00	0.01	0.00	-	-	-
Glycosuria	3	0.06	1	0.02	0.02	0.01	-	-	-
Haematuria	75	1.48	98	1.92	0.53	0.68	1.27	(0.94, 1.73)	0.122
Hydronephrosis	1	0.02	1	0.02	0.01	0.01	-	-	-
Hypertonic bladder	1	0.02	2	0.04	0.01	0.01	-	-	-
Incontinence	21	0.41	22	0.43	0.14	0.14	1.08	(0.59, 1.97)	0.812
Leukocyturia	0	0.00	1	0.02	0.00	0.01	-	-	-
Microalbuminuria	0	0.00	6	0.12	0.00	0.05	-	-	-
Micturition disorder	10	0.20	6	0.12	0.07	0.04	0.65	(0.23, 1.82)	0.410
Micturition urgency	17	0.33	29	0.57	0.11	0.21	1.61	(0.88, 2.94)	0.121
Nephritis	0	0.00	1	0.02	0.00	0.01	-	-	-
Nephrolithiasis	16	0.32	22	0.43	0.11	0.15	1.53	(0.78, 3.00)	0.211
Nephropathy	1	0.02	1	0.02	0.01	0.01	-	-	-
Nocturia	57	1.12	84	1.65	0.40	0.55	1.43	(1.01, 2.02)	0.041
Oliguria	1	0.02	1	0.02	0.01	0.01	-	-	-
Pollakiuria	83	1.63	116	2.27	0.59	0.79	1.47	(1.10, 1.97)	0.008
Polyuria	15	0.30	19	0.37	0.11	0.13	1.19	(0.60, 2.35)	0.627
Proteinuria	18	0.35	12	0.24	0.13	0.09	0.65	(0.31, 1.35)	0.251
Pyuria	0	0.00	1	0.02	0.00	0.01	-	-	-
Renal artery embolism	1	0.02	0	0.00	0.01	0.00	-	-	-
Renal artery stenosis	2	0.04	2	0.04	0.01	0.01	-	-	-
Renal colic	3	0.06	1	0.02	0.02	0.01	-	-	-
Renal cyst	3	0.06	3	0.06	0.02	0.02	-	-	-
Renal disorder	3	0.06	1	0.02	0.02	0.01	-	-	-
Renal failure acute	0	0.00	1	0.02	0.00	0.01	-	-	-
Renal failure chronic	0	0.00	1	0.02	0.00	0.01	-	-	-
Renal impairment	3	0.06	8	0.16	0.02	0.05	2.27	(0.59, 8.79)	0.234
Renal insufficiency	1	0.02	5	0.10	0.01	0.03	4.9	(0.57, 41.94)	0.147
Renal pain	6	0.12	2	0.04	0.04	0.01	0.32	(0.07, 1.61)	0.168
Residual urine	0	0.00	3	0.06	0.00	0.02	-	-	-
Strangury	0	0.00	1	0.02	0.00	0.01	-	-	-
Stress incontinence	2	0.04	5	0.10	0.01	0.03	2.44	(0.47, 12.60)	0.285
Urethral disorder	1	0.02	0	0.00	0.01	0.00	-	-	-
Urethral haemorrhage	0	0.00	1	0.02	0.00	0.01	-	-	-
Urethral obstruction	0	0.00	1	0.02	0.00	0.01	-	-	-
Urethral stricture	1	0.02	1	0.02	0.01	0.01	-	-	-
Urge incontinence	3	0.06	1	0.02	0.02	0.01	-	-	-
Urinary bladder polyp	1	0.02	0	0.00	0.01	0.00	-	-	-
Urinary hesitation	1	0.02	0	0.00	0.01	0.00	-	-	-
Urinary incontinence	22	0.43	20	0.39	0.15	0.15	0.84	(0.46, 1.55)	0.580
Urinary retention	27	0.53	17	0.33	0.19	0.11	0.61	(0.33, 1.12)	0.112

Urinary tract disorder	10	0.20	14	0.27	0.07	0.09	1.36	(0.61, 3.07)	0.455
Urinary tract obstruction	0	0.00	2	0.04	0.00	0.01	-	-	-
Urinary tract pain	2	0.04	2	0.04	0.01	0.01	-	-	-
Urine abnormality	0	0.00	1	0.02	0.00	0.01	-	-	-
Urine flow decreased	3	0.06	3	0.06	0.02	0.02	-	-	-
Urine odour abnormal	1	0.02	1	0.02	0.01	0.01	-	-	-
Urinoma	1	0.02	0	0.00	0.01	0.00	-	-	-

Rate percentage per annum (% pa), which is equivalent to rate 100 patient years

* Hazard ratios were only estimated for those with events in both arm, and with cumulative incidence >1%

Supplementary Table 3.

Risk (hazard ratio) of serious adverse events, stratified by system organ classification, among those allocated to either statin or placebo in the blinded randomized phase of the ASCOT-LLA (median follow-up, 3.3 years).

System Organ Class	Placebo	Atorva-statin	Hazard Ratio	(95% CI)	P-value
	Rate % pa	Rate % pa			P-value
Blood and lymphatic system disorders	0.05	0.05	0.93	(0.45, 1.92)	0.836
Cardiac disorders	0.20	0.23	1.16	(0.81, 1.67)	0.424
Congenital, familial and genetic disorders	0.00	0.00	0.99	(0.06, 15.88)	0.996
Ear and labyrinth disorders	0.05	0.06	1.06	(0.52, 2.14)	0.871
Endocrine disorders	0.01	0.01	0.99	(0.20, 4.92)	0.993
Eye disorders	0.05	0.04	0.71	(0.32, 1.60)	0.407
Gastrointestinal disorders	0.55	0.57	1.04	(0.83, 1.30)	0.732
General disorders and administration site conditions	0.31	0.22	0.69	(0.50, 0.96)	0.028
Hepatobiliary disorders	0.11	0.07	0.68	(0.39, 1.21)	0.191
Immune system disorders	0.00	0.00	0.99	(0.06, 15.89)	0.997
Infections and infestations	0.43	0.43	0.99	(0.77, 1.28)	0.945
Injury, poisoning and procedural complications	0.28	0.23	0.84	(0.60, 1.16)	0.288
Investigations	0.09	0.08	0.80	(0.45, 1.42)	0.451
Metabolism and nutrition disorders	0.07	0.03	0.45	(0.20, 0.98)	0.045
Musculoskeletal and connective tissue disorders	0.38	0.37	0.97	(0.74, 1.28)	0.843
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0.42	0.37	0.87	(0.67, 1.14)	0.313
Nervous system disorders	0.33	0.26	0.79	(0.58, 1.07)	0.126
Psychiatric disorders	0.01	0.01	0.66	(0.11, 3.97)	0.652
Renal and urinary disorders	0.18	0.17	0.97	(0.65, 1.45)	0.889
Reproductive system and breast disorders	0.09	0.15	1.65	(1.01, 2.68)	0.045
Respiratory, thoracic and mediastinal disorders	0.26	0.22	0.85	(0.61, 1.20)	0.359
Skin and subcutaneous tissue disorders	0.04	0.02	0.45	(0.16, 1.30)	0.140
Social circumstances	0.02	0.01	0.66	(0.19, 2.35)	0.523
Surgical and medical procedures	0.26	0.28	1.09	(0.79, 1.51)	0.593
Vascular disorders	0.19	0.14	0.74	(0.49, 1.13)	0.163
Uncoded	0.02	0.01	0.50	(0.12, 1.99)	0.322

Incident rate percentage (%) per annum (% pa) (which is equivalent to rate per 100 person years).

Supplementary Table 4.

Adjudication Definitions			
Myalgia	1: Possible	2: Probable	3: Definite
	<ul style="list-style-type: none"> - Poorly localised complaints suspicious for potential myalgia (incl. tiredness, fatigue, lassitude, weakness, loss of power or physical strength) - Also included are areas such as shoulder, unilateral limb symptoms, descriptions affecting small individual muscles or muscle groups e.g. suprascapularis, or descriptions affecting unlikely areas e.g. groin. - Exclusions: chest pain, non cardiac chest pain, 'musculoskeletal chest pain', thoracic pain, abdominal pain, headache, lower back pain, neck pain, hand and foot pain, claudication and claudication-equivalent descriptions 	<ul style="list-style-type: none"> - Complaints well-localised to a large, muscular area that are reasonably likely to represent pain but have not specifically used pain or pain-equivalent terms, or are present with bilaterality, or affect large continuous body regions. - Muscular areas include: bilateral limbs, bilateral shoulders, large continuous areas of torso and/or limbs. - Terminology includes: muscle fatigue, muscle tiredness, muscle weakness - Exclusions: chest pain, non cardiac chest pain, 'musculoskeletal chest pain', thoracic pain, abdominal pain, headache, lower back pain, neck pain, hand and foot pain, claudication and claudication-equivalent descriptions 	<ul style="list-style-type: none"> - Pain or pain-equivalent term described as muscular or referring to a specified muscle. If the AE specifically mentions 'myalgia' this is included automatically, but excludes back, neck, hands, feet. - Pain equivalent terms: ache, spasm, cramp, dolor, myositis - Examples: myalgia, muscle pain, muscle cramp, calf ache, thigh pain, polymyalgia, polymyalgia rheumatica, fibromyalgia. - Exclusions: chest pain, non cardiac chest pain, 'musculoskeletal chest pain', thoracic pain, abdominal pain, headache, lower back pain, neck pain, hand and foot pain, claudication and claudication-equivalent descriptions
Cognitive Impairment	1: Possible	2: Probable	3: Definitive
<p>Symptoms or events reported that are concerning for potential cognitive decline</p> <p>e.g. delirium, confusion</p> <p>Depression and low mood excluded</p>	<p>Clear reporting of symptoms or behavioural patterns likely suggestive of cognitive impairment</p> <p>e.g. Memory trouble, forgetfulness, difficulty with tasks such as reading, slowness of thought</p> <p>Depression and low mood excluded</p>	<p>Clear medical or diagnostic terminology reporting confirmed deficits in memory, concentration, planning, decision making</p> <p>e.g. Memory disorder, dementia</p> <p>Depression and low mood excluded</p>	<p>Symptoms or events reported that are concerning for potential cognitive decline</p> <p>e.g. delirium, confusion</p> <p>Depression and low mood excluded</p>
Erectile Dysfunction	1: Possible	2: Probable	3: Definitive
	<p>Complaints of sexual disturbance</p> <p>E.g. sexual dysfunction</p>	<p>Symptoms more clearly suggestive of ED</p> <p>E.g. Loss of libido</p>	<p>Impotence, erectile dysfunction</p>

Supplementary Table 5.

Incident rates of serious adverse events, stratified by system organ classification, among statin users and non-users in the non-blinded non-randomized phase of the LLA-extension (median follow-up, 2.2 years)

System Organ Class	Non-user	Statin-user	Hazard ratio	(95% ci)	P-value
	Rate per 100 pyr				
Blood and lymphatic system disorders	0.08	0.12	1.42	(0.63, 3.18)	0.394
Cardiac disorders	0.67	0.50	0.77	(0.55, 1.07)	0.120
Congenital, familial and genetic disorders	0.01	0.00	0.00	(0.00, .)	1.000
Ear and labyrinth disorders	0.07	0.05	0.69	(0.24, 2.03)	0.503
Endocrine disorders	0.02	0.00	0.00	(0.00, .)	1.000
Eye disorders	0.12	0.10	0.95	(0.44, 2.04)	0.886
Gastrointestinal disorders	1.10	0.97	0.85	(0.66, 1.09)	0.208
General disorders and administration site conditions	0.63	0.55	0.94	(0.67, 1.31)	0.701
Hepatobiliary disorders	0.21	0.17	0.83	(0.46, 1.50)	0.545
Immune system disorders	0.04	0.02	0.35	(0.07, 1.84)	0.213
Infections and infestations	1.00	0.93	0.88	(0.68, 1.14)	0.345
Injury, poisoning and procedural complications	0.65	0.63	0.94	(0.68, 1.30)	0.712
Investigations	0.14	0.25	1.95	(1.06, 3.59)	0.033
metabolism and nutrition disorders	0.19	0.12	0.60	(0.31, 1.17)	0.137
Musculoskeletal and connective tissue disorders	0.52	0.51	1.01	(0.71, 1.44)	0.965
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0.90	0.83	0.90	(0.69, 1.19)	0.470
Nervous system disorders	0.74	0.56	0.73	(0.53, 1.01)	0.055
Psychiatric disorders	0.02	0.05	1.72	(0.41, 7.18)	0.457
Renal and urinary disorders	0.42	0.40	1.04	(0.69, 1.55)	0.861
Reproductive system and breast disorders	0.26	0.23	0.93	(0.56, 1.55)	0.779
Respiratory, thoracic and mediastinal disorders	0.54	0.41	0.81	(0.56, 1.18)	0.281
Skin and subcutaneous tissue disorders	0.04	0.09	2.05	(0.70, 5.99)	0.188
Social circumstances	0.02	0.02	0.51	(0.08, 3.09)	0.464
Surgical and medical procedures	0.50	0.38	0.79	(0.54, 1.17)	0.235
Vascular disorders	0.42	0.37	0.92	(0.61, 1.37)	0.669
Uncoded	0.02	0.06	2.69	(0.67, 10.82)	0.162

Rate per 100 patient years; hazard ratio from time-updated Cox PH model