Adverse events associated with unblinded, but not with blinded, statin therapy in the Anglo-Scandinavian Cardiac Outcomes Trial—Lipid-Lowering Arm (ASCOT-LLA): a randomised double-blind placebo-controlled trial and its non-randomised non-blind extension phase

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Summary

Background In blinded randomised controlled trials, statin therapy has been associated with few adverse events (AEs). By contrast, in observational studies, larger increases in many different AEs have been reported than in blinded trials.

Methods In the Lipid-Lowering Arm of the Anglo-Scandinavian Cardiac Outcomes Trial, patients aged 40–79 years with hypertension, at least three other cardiovascular risk factors, and fasting total cholesterol concentrations of 6·5 mmol/L or lower, and who were not taking a statin or fibrate, had no history of myocardial infarction, and were not being treated for angina were randomly assigned to atorvastatin 10 mg daily or matching placebo in a randomised double-blind placebo-controlled phase. In a subsequent non-randomised non-blind extension phase (initiated because of early termination of the trial because efficacy of atorvastatin was shown), all patients were offered atorvastatin 10 mg daily open label. We classified AEs using the Medical Dictionary for Regulatory Activities. We blindly adjudicated all reports of four prespecified AEs of interest—muscle-related, erectile dysfunction, sleep disturbance, and cognitive impairment—and analysed all remaining AEs grouped by system organ class. Rates of AEs are given as percentages per annum.

Results The blinded randomised phase was done between February, 1998, and December, 2002; we included 10180 patients in this analysis (5101 [50%] in the atorvastatin group and 5079 [50%] in the placebo group), with a median follow-up of 3·3 years (IQR 2·7–3·7). The non-blinded non-randomised phase was done between December, 2002, and June, 2005; we included 9899 patients in this analysis (6409 [65%] atorvastatin users and 3490 [35%] non-users), with a median follow-up of 2·3 years (2·2–2·4). During the blinded phase, muscle-related AEs (298 [2·03% per annum] *vs* 283 [2·00% per annum]; hazard ratio 1·03 [95% CI 0·88–1·21]; p=0·72) and erectile dysfunction (272 [1·86% per annum] *vs* 302 [2·14% per annum]; 0·88 [0·75–1·04]; p=0·13) were reported at a similar rate by participants randomly assigned to atorvastatin or placebo. The rate of reports of sleep disturbance was significantly lower among participants assigned atorvastatin than assigned placebo (149 [1·00% per annum] *vs* 210 [1·46% per annum]; 0·69 [0·56–0·85]; p=0·0005). Too few cases of cognitive impairment were reported for a statistically reliable analysis (31 [0·20% per annum] *vs* 32 [0·22% per annum]; 0·94 [0·57–1·54]; p=0·81). We observed no significant differences in the rates of all other reported AEs, with the exception of an excess of renal and urinary AEs among patients assigned atorvastatin (481 [1·87%] per annum *vs* 392 [1·51%] per annum; 1·23 [1·08–1·41]; p=0·002). By contrast, during the non-blinded non-randomised phase, muscle-related AEs were reported at a significantly higher rate by participants taking statins than by those who were not (161 [1·26% per annum] *vs* 124 [1·00% per annum]; 1·41 [1·10–1·79]; p=0·006). We noted no significant differences between statin users and non-users in the rates of other AEs, with the exception of musculoskeletal and connective tissue disorders (992 [8·69% per annum] *vs* 831 [7·45% per annum]; 1·17 [1·06–1·29]; p=0·001) and blood and lymphatic system disorders (114 [0·88% per annum] *vs* 80 [0·64% per annum]; 1·40 [1·04–1·88]; p=0·03), which were reported more commonly by statin users than by non-users.

Interpretation These analyses illustrate the so-called nocebo effect, with an excess rate of muscle-related AE reports only when patients and their doctors were aware that statin therapy was being used and not when its use was blinded. These results will help assure both physicians and patients that most AEs associated with statins are not causally related to use of the drug and should help counter the adverse effect on public health of exaggerated claims about statin-related side-effects.

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Research in context

Evidence before this study

We reviewed evidence from trials of the effect of statins on major cardiovascular outcomes identified in a 2012 meta-analysis by the Cholesterol Treatment Trialists' Collaboration and from observational studies reporting statin-associated adverse events identified in a 2016 review. In randomised blinded controlled trials of statins, drug-related adverse events were rare in comparison with observational studies in which adverse events were reported in as many as 20% of drug recipients.

Added value of this study

This report of putative statin-related adverse events is derived from a unique analysis of information obtained in the Anglo-Scandinavian Cardiac Outcomes Trial—Lipid-Lowering Arm, in which, in a blinded randomised phase, atorvastatin was compared with placebo and, in a non-randomised non-blinded phase, users of statins were compared with non-users. Assessment of adverse events was systematic throughout the trial and done by observers who were blinded to treatment allocation and phases of the trial. We observed an excess of muscle-related adverse events only in the non-blinded phase of the trial when patients were aware that they were taking a statin.

Implications of all the available evidence

This report provides further support for the evidence that statin use is not causally associated with adverse events, which have been reported from observational studies by contrast with randomised blinded trials, in which the incidence of adverse events is similar in those assigned placebo and statins. These observations should help assure physicians and patients that most statin-associated adverse events are not causally related to use of the statins and that the benefits of statins in reducing cardiovascular events should override concerns about reports of side-effects, which are not substantiated by findings from this study.

Introduction

Large-scale evidence from randomised placebo-controlled trials has shown that statin therapy reduces the incidence of major vascular events (ie, coronary deaths or myocardial infarctions, ischaemic strokes, and coronary revascularisation procedures) by about one quarter for each 1 mmol/L LDL cholesterol concentration reduction during each year (after the first) that it continues to be taken.[1] The proportional reductions in risk have been shown to be similar in secondary and primary prevention and somewhat greater among individuals at a lower risk (although the absolute benefits are smaller). These findings have resulted in guidelines recommending that statin therapy be considered for all patients who have had an atherosclerotic event and, in primary prevention, for those who have a 10 year risk of having a cardiovascular event (defined as coronary death, myocardial infarction, angina, stroke, or transient ischaemic attack) of at least 10%, as well as for those with high LDL cholesterol concentrations or relevant comorbidities (such as diabetes).[2,3]

Concerns have been expressed about the expansion in statin use produced by lowering of risk thresholds for offering of statin therapy to patients.[4,5] In making the argument against so-called over-medicalisation of the population, statin therapy has been claimed to cause increased rates of adverse events (AEs) and symptomatic side-effects (chiefly muscle pain and weakness); claims that prevent as many as one fifth of patients from continuing to take statin therapy in the long term.[5,6] These claims are usually derived from observational studies using health-care databases which, since they are neither randomised nor blinded, are subject to potential biases in assessment of causation.[7] By contrast, in double-blind randomised controlled trials of statin therapy, the reported rates of different types of AE have generally been similar between patients receiving statin or placebo treatment (except for reductions in atherosclerotic events), with no differences between groups in the rates of treatment cessation in association with advere events.[7–10]

The absence of a difference in AEs in randomised controlled trials of statin therapy has been suggested to be due to their ascertainment not being sufficiently specific or sensitive.[5,11] The Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT)[12] provides a unique opportunity to assess the effect of blinded and unblinded ascertainment of AEs identified with the same approach during blinded randomised statin therapy in the Lipid-Lowering Arm (LLA) of the trial[13] and the subsequent follow-up period when a proportion of patients were taking open-label statins.[14] We prespecifed four AEs of interest (AEOIs) because of the public health effect of widespread claims about muscle-related side-effects and the additions to the drug label of erectile dysfunction, sleep disturbance, and cognitive impairment as possible side-effects on the basis of reviews by the Medicines and Healthcare Products Regulatory Agency[15] and US Food and Drug Administration.[16]

For the **ASCOT website** see www.ascotstudy.org

Methods

Study design and patients

Details of the ASCOT protocol, including study design, organisation, clinical measurements, power calculations, recruitment rates, and baseline characteristics, have been previously published.[12] Men and women aged between 40 years and 79 years were eligible if they had three or

more risk factors for cardiovascular disease but had no history of myocardial infarction and were not being treated for angina. They were randomly assigned in an open-label comparison between two blood pressure-lowering treatment regimens (amlodipine-based regimen or atenolol-based regimen) in the ASCOT Blood Pressure-Lowering Arm (BPLA)[17] and, with use of a 2×2 factorial design, between atorvastatin 10 mg daily and matching placebo in the LLA comparison, forming the randomised double-blind placebo-controlled phase for this study.

Patients included in the BPLA were also eligible for inclusion in the LLA comparison if they had a total cholesterol concentration of 6·5 mmol/L or lower and were not taking a statin or fibrate. No formal run-in period to test for tolerance to statins was used and few, if any, patients had any previous exposure to statin treatment. In the LLA, the randomly assigned atorvastatin or placebo was stopped for efficacy (at the recommendation of the data safety and monitoring board) between October and December, 2002. Patients were then told whether they had been assigned atorvastatin or placebo, but they continued to be actively followed up in the same way until June, 2005, while the ASCOT-BPLA comparison continued.[14] During that period they were offered open-label atorvastatin, forming the non-randomised non-blind extension phase for this report.

The study conformed to good clinical practice guidelines and the Declaration of Helsinki. The protocol and all subsequent amendments were reviewed and ratified by central and regional ethics review boards in the UK and national ethics and statutory bodies in Ireland and the Nordic countries (Sweden, Denmark, Iceland, Norway, and Finland). All participants provided written informed consent.

Procedures

After randomisation, study participants were scheduled to be seen at 6 weeks and 3 months and then at 6-monthly intervals thereafter during both the blinded randomised and non-blinded non-randomised phases of the ASCOT-LLA (until the ASCOT-BPLA completed). At each study visit, all AEs reported by participants were recorded by the study team in the case report form. Specific questions relating to any putative AEs were not asked at these visits.

Reports of AEs by study participants were initially recorded verbatim and subsequently classified with use of the Medical Dictionary for Regulatory Activities[18] into 26 separate system organ class (SOC) groups, 2288 unique preferred terms, and 5109 separate low-level terms. For this report, two physicians (AW and DT) adjudicated the four AEOIs: muscle-related, erectile

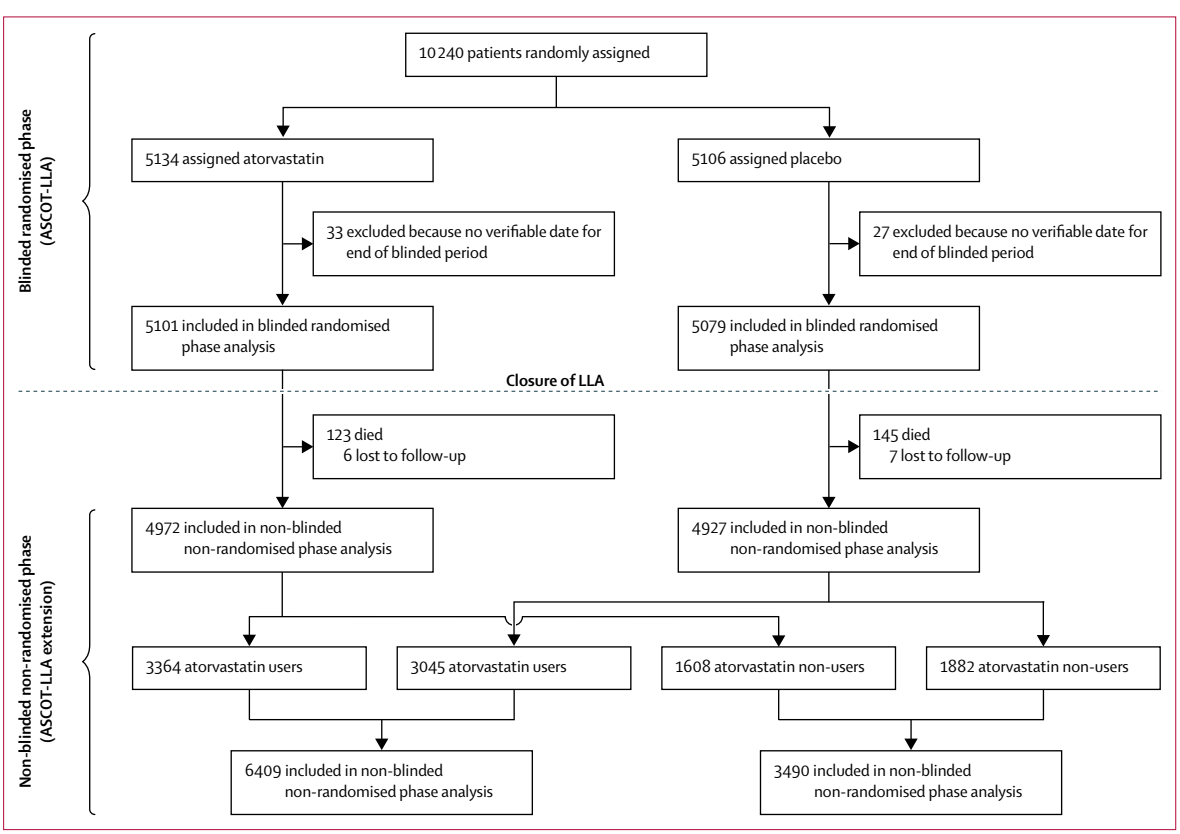

Figure 1: **Trial profile**
ASCOT=Anglo-Scandinavian Cardiac Outcomes Trial. LLA=Lipid-Lowering Arm.

	Blinded randomised phase (ASCOT-LLA)		Non-blinded non-randomised phase (ASCOT-LLA extension)	
	Placebo (n=5079)	Atorvastatin (n=5101)	Atorvastatin non-user (n=3490)	Atorvastatin user (n=6409)
Patient characteristics				
Woman	949 (19%)	955 (19%)	760 (22%)	1097 (17%)
Age (years)				
≤60	1821 (36%)	1842 (36%)	1204 (34%)	2405 (38%)
>60	3258 (64%)	3259 (64%)	2286 (66%)	4004 (62%)
White ethnicity	4805 (95%)	4822 (95%)	3367 (96%)	5996 (94%)
Current smoker	1644 (32%)	1697 (33%)	1250 (36%)	1987 (31%)
Alcohol consumption per week				
≤14 units	4149/5078 (82%)	4170/5099 (82%)	2916 (84%)	5175/6406 (81%)
>14 units	929/5078 (18%)	929/5099 (18%)	574 (16%)	1231/6406 (19%)
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 per min)	71·8 (12·6)	71·2 (12·7)	71·6 (12·4)	71·4 (12·8)
BMI (kg/m^2)	28·7 (4·6)	28·6 (4·7)	28·5 (4·7)	28·8 (4·6)
Total cholesterol concentration (mmol/L)	5·5 (0·8)	5·5 (0·8)	5·4 (0·8)	5·5 (0·8)
LDL cholesterol concentration (mmol/L)	3·4 (0·7)	3·4 (0·7)	3·4 (0·7)	3·5 (0·7)
HDL cholesterol concentration (mmol/L)	1·3 (0·4)	1·3 (0·4)	1·3 (0·4)	1·3 (0·4)
Triglyceride concentration (mmol/L)	1·6 (0·9)	1·7 (0·9)	1·6 (0·8)	1·7 (0·9)
Glucose concentration (mmol/L)	6·2 (2·1)	6·2 (2·1)	6·1 (2·0)	6·2 (2·1)
Creatinine concentration (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%)	493 (10%)	350 (10%)	630 (10%)
Type 2 diabetes	1267 (25%)	1254 (25%)	792 (23%)	1660 (26%)
LVH (according to ECG or ECHO)	721 (14%)	735 (14%)	478 (14%)	927 (14%)
ECG abnormalities other than LVH	721 (14%)	731 (14%)	483 (14%)	908 (14%)
Peripheral vascular disease	251 (5%)	259 (5%)	166 (5%)	318 (5%)
Other relevant cardiovascular disease	204 (4%)	184 (4%)	135 (4%)	234 (4%)
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%)	1000 (20%)	769 (22%)	1163 (18%)
One	2252 (44%)	2286 (45%)	1571 (45%)	2842 (44%)
More than one	1850 (36%)	1815 (36%)	1150 (33%)	2404 (38%)
Previous lipid-lowering treatment	44 (1%)	34 (1%)	31 (1%)	46 (1%)
Aspirin use	881 (17%)	900 (18%)	527 (15%)	1188 (19%)

Data are n (%) or mean (SD). BMI=body-mass index. TIA=transient ischaemic attack. LVH=left-ventricular hypertrophy. ECG=electrocardiogram. ECHO=echocardiogram.

***Table 1*: Baseline characteristics**

See Online for appendix

dysfunction, sleep disturbance, and cognitive impairment. Each of the adjudicators reviewed (blinded to baseline characteristics, randomised treatment, non-study statin use, and trial phase) all reported AEs for the presence of any of the four AEOIs and, on the basis of the description in the case report form, classified their degree of certainty (definite, probable, or possible) according to prespecified definitions. Further details are given in the appendix. Any disagreements between the two adjudicators were independently resolved by a third physician (AG), who was similarly blinded.

Statistical analysis

We used Cox proportional hazard models to compare time to first AE in the blinded randomised phase between patients randomly assigned to atorvastatin and those randomly assigned to placebo, and in the non-blinded non-randomised phase between those who were exposed to statin therapy during that phase and those who were not. We considered patients to be non-users in the non-blinded non-randomised phase until statin treatment was given for at least 2 consecutive days (ie, we included events occurring beforehand in the non-user group, whereas we included those occurring after statin use had started in the user group, even if treatment had been stopped). Consequently, we used time-updated Cox models for the comparisons of time to first AE between statin users and non-users. We calculated hazard ratios (HRs) and 95% CIs for each AEOI of the combination of definite and probable events, with subsidiary sensitivity analyses of definite AEOIs only, and of all AEOIs (ie, including those considered to be only possible AEOIs). Main analyses did not involve adjustment for baseline characteristics at the time of randomisation, but we did subsidiary analyses of the non-blinded non-randomised comparisons with adjustment for baseline characteristics. We also analysed all the reported AEs not classified as one of the four AEOIs grouped by SOC. We reported incident rates as percentages per annum. We did all statistical analyses using Stata version 14.2.

Role of the funding source

ASCOT was conceived, designed, and coordinated by an investigator-led independent Steering Committee with two non-voting members from the principal funding source (Pfizer). Data collection, analysis, and interpretation and preparation of all reports were done independently of the funding sources. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

The blinded randomised phase was done between February, 1998, and December, 2002; 10 305 patients were randomly allocated in the LLA (5168 [50%] to atorvastatin and 5137 [50%] to placebo), but 65 were withdrawn soon after randomisation because of concerns about source documentation validation. Of the remaining 10 240 (99%) eligible randomised patients, 60 (1%) patients (33 [55%] in the atorvastatin group *vs* 27 [45%] in the placebo group) were excluded from these analyses as they were missing end dates for the blinded phase (figure 1). 10 180 (99%) patients were therefore included in the blinded

randomised phase analysis (5101 [50%] in the atorvastatin group and 5079 [50%] in the placebo group). The randomly assigned atorvastatin or placebo was stopped for efficacy between October and December, 2002, after a median of 3·3 years (IQR 2·7–3·7) of active follow-up. The non-blinded non-randomised phase was done between December, 2002, and June, 2005; 281 (3%) patients (129 [46%] in the atorvastatin group *vs* 152 [64%] in the placebo group) had either died or been censored (ie, those who stopped routine follow-up before the end of the LLA) and were excluded from the non-blinded non-randomised phase analysis. We therefore included 9899 (97%) patients in this analysis, with a median follow-up of 2·3 years (IQR 2·2–2·4). 6409 (65%) patients were users of statin therapy (most commonly atorvastatin 10 mg) at some time during the non-blinded non-randomised phase, with 3341 (52%) using it immediately after the end of the blinded randomised phase compared with 3490 (35%) non-users.

Table 1 describes baseline characteristics. Patients were predominantly male, with a mean age of 63·2 years (SD 8·5) at baseline. We did not observe any differences in baseline characteristics between the randomised treatment groups. However, in the non-randomised phase, users of statin therapy were less likely than were non-users to be women or smokers and more likely to have diabetes at baseline. Patients who had reported muscle-related AEOIs during the blinded randomised phase were less likely to use a statin during the non-blinded non-randomised phase than were those who had not reported these AEs (appendix).

60 612 distinct AEs (ie, after removing multiple reports from the database of the same AE occurrence) occurred in total. During the blinded randomised phase, the rate of reporting of definite or probable muscle-related AEOIs (298 [2·03% per annum] *vs* 283 [2·00% per annum]; HR 1·03 [95% CI 0·88–1·21]; p=0·72) and of erectile dysfunction (272 [1·86% per annum] *vs* 302 [2·14% per annum]; 0·88 [0·75–1·04]; p=0·13) was similar among patients randomly assigned to atorvastatin or placebo (table 2). Patients assigned to receive atorvastatin reported sleep disturbance significantly less often than did those assigned placebo (149 [1·00% per annum] *vs* 210 [1·46% per annum]; 0·69 [0·56–0·85]; p=0·0005). However, too few cases of cognitive impairment were reported for a statistically reliable analysis (31 [0·20% per annum] *vs* 32 [0·22% per annum]); 0·94 [0·57–1·54]; p=0·81). We observed similar findings in sensitivity analyses based on definite AEOIs alone or when we included the larger number of possible AEOIs (figure 2).

The rates of reports of all other AEs grouped by SOC categories were similar between patients assigned atorvastatin and placebo, with the exception of an excess of AEs attributed to renal and urinary disorders among patients assigned atorvastatin (481 [1·87% per annum] *vs* 392 [1·51% per annum]; HR 1·23 [95% CI 1·08–1·41]; p=0·002; table 3). Subdivision of that SOC indicates that the excess was chiefly due to reports of nocturia and frequent urination (appendix).

	Blinded randomised phase (ASCOT-LLA)		Non-blinded non-randomised phase	
	Placebo (n=5079)	Atorvastatin (n=5101)	Atorvastatin non-user (n=3490)	Atorvastatin user (n=6409)
Muscle related				
Patients (n)	283	298	124	161
AE rate (% per annum)	2·00%	2·03%	1·00%	1·26%
HR (95% CI)	1	1·03 (0·88–1·21)	1	1·41 (1·10–1·79)
p value	..	0·72	..	0·006
Erectile dysfunction				
Patients (n)	302	272	99	88
AE rate (% per annum)	2·14%	1·86%	0·80%	0·68%
HR (95% CI)	1	0·88 (0·75–1·04)	1	0·89 (0·66–1·20)
p value	..	0·13	..	0·44
Sleep disturbance				
Patients (n)	210	149	82	72
AE rate (% per annum)	1·46%	1·00%	0·66%	0·56%
HR (95% CI)	1	0·69 (0·56–0·85)	1	0·87 (0·63–1·20)
p value	..	0·0005	..	0·40
Cognitive impairment				
Patients (n)	32	31	36	22
AE rate (% per annum)	0·22%	0·20%	0·29%	0·17%
HR (95% CI)	1	0·94 (0·57–1·54)	1	0·59 (0·34–1·02)
p value	..	0·81	..	0·06

First event only in each phase reported; definite and probable AEs reported; number of patients with at least one event reported. AE=adverse event. HR=hazard ratio.

Table 2: **Risk of adverse events of interest**

During the non-blinded non-randomised extension phase, overall reporting rates for AEOIs were lower than those in the blinded randomised phase of the trial (table 2). However, muscle-related AEOIs were reported at a higher rate by statin users than by non-users (161 [1·26% per annum] *vs* 124 [1·00% per annum]; HR 1·41 [95% CI 1·10–1·79]; p=0·006). The proportional excess was similar between patients who had been assigned atorvastatin (HR 1·49 [95% CI 1·05–2·11]) or placebo (1·33 [0·96–1·84]) during the blinded randomised phase (interaction p=0·63). We noted no significant differences between statin users and non-users in the reported rates of erectile dysfunction (88 [0·68% per annum] *vs* 99 [0·80% per annum]; HR 0·89 [95% CI 0·66–1·20]; p=0·44), sleep disturbance (72 [0·56% per annum] *vs* 82 [0·66% per annum]; 0·87 [0·63–1·20]; p=0·40), or cognitive impairment (22 [0·17% per annum] *vs* 36 [0·29% per annum]; 0·59 [0·34–1·02]; p=0·06; table 2).

We noted 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 concentration, and systolic blood pressure) had minimal effect on the

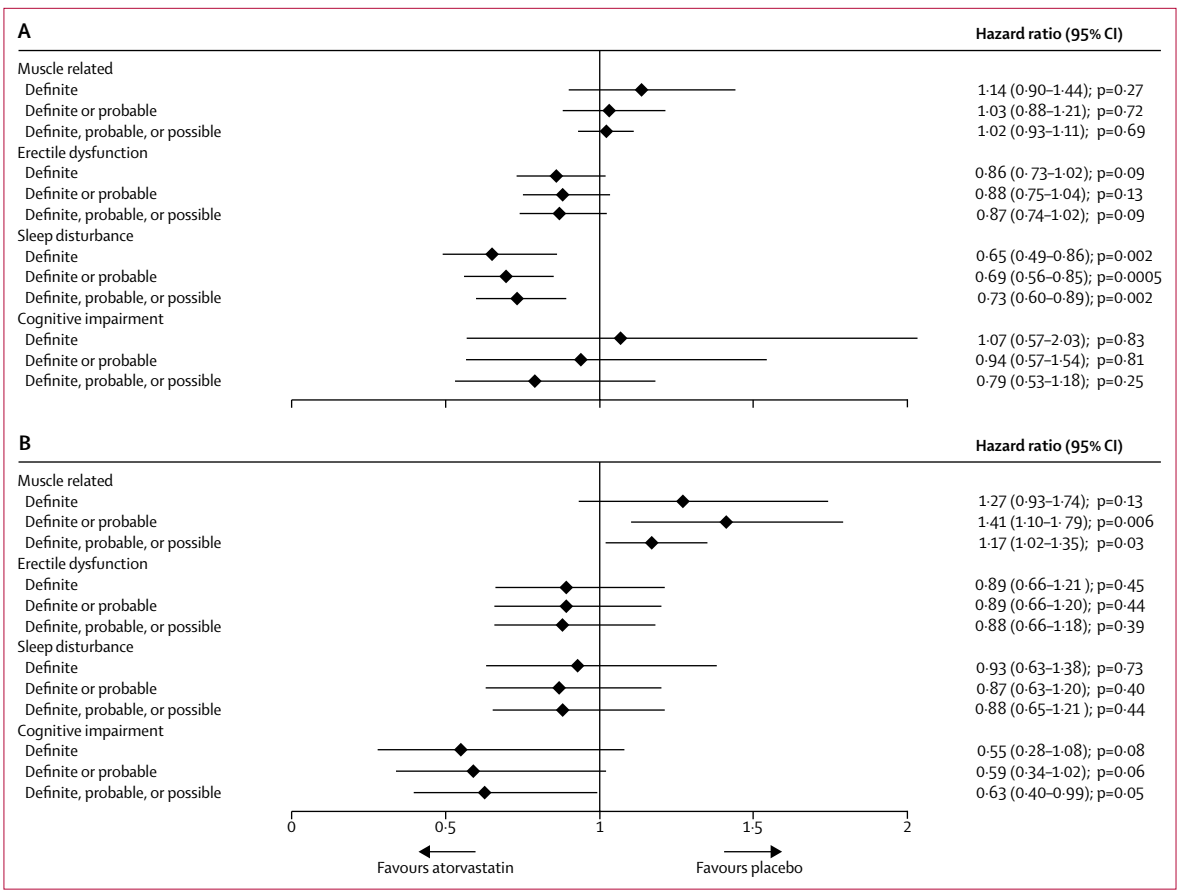

Figure 2: **Risk of adverse events of interest in the (A) blinded randomised phase and (B) non-blinded non-randomised phase, grouped according to adjudication certainty**

HRs (appendix). For muscle-related AEs, the adjusted HR was 1·43 (95% CI 1·12–1·83).

The rates of reports of all other AEs grouped by SOC categories were similar among patients who were using and not using statin therapy, with the exception of an excess among statin users of AEs attributed to musculoskeletal and connective tissue disorders (992 [8·69% per annum] *vs* 831 [7·45% per annum]; HR 1·17 [95% CI 1·06–1·29]; p=0·001) and blood and lymphatic system disorders (114 [0·88% per annum] *vs* 80 [0·64% per annum]; 1·40 [1·04–1·88]; p=0·03; table 4). We noted no differences in the rates of serious AEs between users and non-users (appendix).

Discussion

The ASCOT-LLA provides a unique opportunity to compare the rate of reporting of AEs with use of an identical follow-up procedure and AE ascertainment process in the same individuals during blinded randomised and non-blinded non-randomised statin therapy. We noted no excess of reports of muscle-related AEs among patients assigned statin therapy during the blinded randomised phase, but we noted a significant excess when patients knew that they were taking a statin during the subsequent non-blinded non-randomised phase. This observation is consistent with a nocebo effect, whereby subjective AEs (eg, symptoms reported by patients) can be more likely to be attributed to a treatment thought to cause some particular side-effect.[19]

We noted no differences between treatment groups in the previously reported rates of serious AEs (appendix) or treatment cessation in association with AEs.[20] In particular, we observed no excess of serious AEs 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.

Statin therapy has been shown to cause myopathy (ie, muscle pain or weakness combined with large increases in blood concentrations of creatine kinase) in about one per 10 000 patients per year of treatment.[21] However, in double-blind randomised controlled trials of statin therapy, muscle-related symptoms have generally been reported with similar frequency by patients assigned statin or placebo treatment. Although muscle-related problems were not systematically sought in all such trials, sufficiently large numbers of cases have been reported to detect or rule out small excesses.[7] For

example, authors of a meta-analysis[22] of 26 blinded randomised trials found little difference in the proportions of muscle problems reported during an average treatment duration of 3 years: 7544 cases (12·7%) among 59 237 participants assigned statins versus 6735 (12·4%) among 54 458 assigned placebo. Combination of the reported results in the large placebo-controlled trials eligible for the Cholesterol Treatment Trialists' Collaborative meta-analyses[1] yielded similar results: 5162 (11·7%) cases allocated statin therapy versus 5015 (11·4%) allocated placebo during an average of 5 years of treatment (p=0·10).[7] The numbers of cases of muscle-related problems that led to the randomised study treatment being stopped were also found to be similar. Consequently, any excess of symptomatic muscle pain or other muscle-related problems that is actually caused by statin therapy has been estimated to be likely to be no more than about 0·1–0·2% of patients taking statins per year of treatment.[7]

Despite these results from blinded randomised trials, the increasingly widespread use of statins has been associated with increasingly common reports of statin intolerance,[6,23] chiefly attributed to muscle pain or weakness.[6] Indeed, on the basis of non-randomised observational studies of statin use in routine care, as many as one fifth of patients have claimed to not be able to tolerate statin therapy.[5,24] However, patients who are taking a treatment as part of their routine care know that they are doing so (as do their doctors) and they might also be specifically told that the treatment has particular side-effects (eg, patients given statin therapy are typically advised that serious muscle problems can arise rarely). This inherent absence of blinding in observational studies can introduce substantial ascertainment bias, particularly for assessment of the effects of a treatment on substantive outcomes.[7,18] The contrast between the similarity of the rates of muscle-related symptoms reported during the blinded randomised phase of the ASCOT-LLA and the excess associated with statin use during the non-blinded non-randomised phase illustrates this problem. Moreover, these analyses could well underestimate the effect of the nocebo effect because the ASCOT-LLA was done during 1998–2005, before claims that statin therapy causes high rates of side-effects had become as common as they are now.

We selected three other categories of AE for scrutiny because the regulatory authorities had added them to the drug label as possible statin side-effects[16,17] largely on the basis of associations in observational studies (and despite a general absence of support for such associations in randomised trials).[7] Unexpectedly, and by contrast with the regulatory concerns, the rate of reports of sleep disturbances was reduced by about one third among patients assigned atorvastatin during the blinded randomised phase (but not during the non-blinded non-randomised phase). A beneficial effect of statin use on sleep disturbance has not been previously reported,[7,25] and this difference could have been due to chance (although it is conventionally significant after adjustment for multiple comparisons). No significant differences occurred in erectile dysfunction among patients assigned atorvastatin or placebo during the blinded randomised phase.

Too few reported cases of cognitive impairment occurred to assess the effects of statin therapy reliably. However, specific assessment of this outcome among large numbers of older people in the PROSPER[26] and Heart Protection Study[27] randomised double-blind placebo-controlled trials, as well as in trials[7] of people who already had pre-existing cognitive impairment, provides good evidence that statin therapy has little effect on memory loss or other measurers of cognitive function. Most recently, statin therapy has been reported to have no effect on cognitive decline or memory loss among the 12 000 patients in the randomised double-blind placebo-controlled Heart Outcomes Prevention Evaluation 3 trial.[28] In exploratory analyses of all other AE reports grouped according to SOC, we did not find significant differences during the blinded randomised

	Rate (% per annum)		HR (95% CI)	p value
	Placebo	Atorvastatin		
Blood and lymphatic system disorders	0·33%	0·25%	0·78 (0·57–1·07)	0·12
Cardiac disorders	1·89%	1·92%	1·02 (0·90–1·15)	0·78
Congenital, familial, and genetic disorders	0·05%	0·05%	0·99 (0·47–2·08)	0·98
Ear and labyrinth disorders	1·38%	1·30%	0·95 (0·82–1·10)	0·46
Endocrine disorders	0·09%	0·09%	1·03 (0·59–1·81)	0·91
Eye disorders	1·37%	1·36%	0·99 (0·86–1·15)	0·93
Gastrointestinal disorders	5·70%	5·72%	1·01 (0·93–1·09)	0·87
General disorders and administration site conditions	4·81%	4·91%	1·02 (0·94–1·11)	0·61
Hepatobiliary disorders	0·17%	0·15%	0·88 (0·58–1·35)	0·57
Immune system disorders	0·13%	0·13%	0·97 (0·61–1·53)	0·88
Infections and infestations	7·72%	7·53%	0·98 (0·92–1·05)	0·61
Injury, poisoning, and procedural complications	1·90%	1·80%	0·95 (0·84–1·08)	0·43
Investigations	1·07%	1·00%	0·94 (0·79–1·11)	0·43
Metabolism and nutrition disorders	0·96%	0·85%	0·89 (0·75–1·07)	0·21
Musculoskeletal and connective tissue disorders	6·91%	7·19%	1·04 (0·96–1·11)	0·33
Neoplasms: benign, malignant, and unspecified (including cysts and polyps)	1·01%	0·98%	0·97 (0·82–1·15)	0·73
Nervous system disorders	5·97%	6·18%	1·03 (0·96–1·12)	0·40
Psychiatric disorders	0·12%	0·07%	0·59 (0·33–1·04)	0·07
Renal and urinary disorders	1·51%	1·87%	1·23 (1·08–1·41)	0·002
Reproductive system and breast disorders	0·83%	0·82%	1·00 (0·83–1·20)	0·98
Respiratory, thoracic, and mediastinal disorders	4·83%	4·76%	0·98 (0·91–1·07)	0·72
Skin and subcutaneous tissue disorders	2·70%	2·53%	0·94 (0·84–1·05)	0·28
Social circumstances	0·02%	0·01%	0·66 (0·19–2·35)	0·52
Surgical and medical procedure-related complications	0·52%	0·53%	1·03 (0·82–1·30)	0·80
Vascular disorders	1·96%	1·73%	0·89 (0·78–1·01)	0·070
Uncoded	0·18%	0·16%	0·87 (0·58–1·31)	0·51

HR=hazard ratio.

Table 3: **Rates of all adverse events, stratified by system organ classification, in the blinded randomised phase**

	Rate (% per annum)		HR (95% CI)	p value
	Atorvastatin non-user	Atorvastatin user		
Blood and lymphatic system disorders	0·64%	0·88%	1·40 (1·04–1·88)	0·03
Cardiac disorders	2·46%	2·41%	0·96 (0·82–1·14)	0·66
Congenital, familial, and genetic disorders	0·14%	0·17%	0·97 (0·51–1·83)	0·92
Ear and labyrinth disorders	1·35%	1·42%	1·04 (0·84–1·30)	0·71
Endocrine disorders	0·18%	0·17%	0·92 (0·50–1·68)	0·78
Eye disorders	1·88%	1·92%	1·00 (0·83–1·20)	0·99
Gastrointestinal disorders	6·32%	6·19%	1·01 (0·90–1·12)	0·91
General disorders and administration site conditions	3·91%	4·05%	1·10 (0·97–1·26)	0·14
Hepatobiliary disorders	0·36%	0·25%	0·70 (0·44–1·12)	0·14
Immune system disorders	0·22%	0·15%	0·63 (0·35–1·13)	0·12
Infections and infestations	9·62%	9·42%	0·96 (0·88–1·05)	0·37
Injury, poisoning, and procedural complications	2·58%	2·76%	1·07 (0·91–1·25)	0·40
Investigations	1·49%	1·51%	0·98 (0·79–1·21)	0·84
Metabolism and nutrition disorders	1·64%	1·30%	0·81 (0·65–1·00)	0·05
Musculoskeletal and connective tissue disorders	7·45%	8·69%	1·17 (1·06–1·29)	0·001
Neoplasms: benign, malignant, and unspecified (including cysts and polyps)	1·93%	1·95%	1·02 (0·85–1·23)	0·83
Nervous system disorders	5·23%	4·79%	0·94 (0·84–1·06)	0·32
Psychiatric disorders	0·14%	0·12%	0·84 (0·41–1·72)	0·64
Renal and urinary disorders	2·20%	2·41%	1·11 (0·94–1·31)	0·23
Reproductive system and breast disorders	1·45%	1·41%	0·92 (0·74–1·13)	0·42
Respiratory, thoracic, and mediastinal disorders	4·50%	4·30%	0·98 (0·87–1·12)	0·80
Skin and subcutaneous tissue disorders	2·98%	2·94%	0·98 (0·84–1·14)	0·80
Social circumstances	0·02%	0·02%	0·51 (0·08–3·09)	0·46
Surgical and medical procedure-related complications	0·75%	0·92%	1·20 (0·91–1·60)	0·20
Vascular disorders	1·73%	1·51%	0·89 (0·73–1·09)	0·26
Uncoded	0·18%	0·31%	1·80 (1·05–3·08)	0·03

HR=hazard ratio.

Table 4: **Rates of all adverse events, stratified by system organ classification, in the non-blinded non-randomised phase**

phase, with the exception of a small excess of reports of renal and urinary disorders in the atorvastatin group, which appeared to be related to increased frequency of urination and nocturia. As far as we are aware, such an excess has not been previously reported. Given the small number of events on which it is based, the large number of separate comparisons made, and their exploratory nature, this apparent difference could well be due to chance.

None of our findings were materially altered when the analyses were based on reports of only AEs considered to be definite, or when we included the larger numbers of possible AEs (which tend to increase statistical power to detect an effect of a particular size, but might decrease sensitivity because of dilution of the treatment effect by including events that are not actually the AE of interest).

The ASCOT trial was done in a hypertensive population in the UK, Ireland, and the Nordic countries, consisting of patients who were predominately aged older than 60 years, men, and of European ancestry. The findings are likely to be generalisable to younger and older patients (given the results from other blinded randomised trials in such individuals),[7] but they may not be generalisable to people from other ethnic groups. Atorvastatin at a daily dose of 10 mg was studied specifically only in the blinded phase of the trial, but most of the patients in the non-blinded phase who took a statin used the same dose of atorvastatin, with only a few using simvastatin. Atorvastatin 10 mg daily would now be considered a low dose, but investigators of randomised trials of higher doses have also not found differences in muscle-related AEs, other than the very small excess of myopathy.[7]

The widespread media coverage that has arisen from claims that statin therapy causes side-effects in up to one fifth of patients,[5,29] and the failure to correct such misleading claims rapidly and fully, has led to patients at high risk of major vascular events with established cardiovascular disease stopping their statin therapy.[30,31] Such reductions in statin use have been estimated to result in thousands of fatal and disabling heart attacks and strokes, which would otherwise have been avoided. Seldom in the history of modern therapeutics have the substantial proven benefits of a treatment been compromised to such an extent by serious misrepresentations of the evidence for its safety. We hope that the demonstration in the ASCOT-LLA of not only the absence of adverse effects of statin therapy on muscle-related and other AEs, but also the effect of ascertainment bias in non-blinding studies (which have been the basis of many of the misleading claims), will help to counter the adverse effect on public health of exaggerated claims about statin side-effects.

Contributors

PS and AG designed the study, planned the analyses, and wrote the manuscript, with the assistance of TC and RC. DT, AW, and AG carried out the review and classification of adverse events. AG and TC did the statistical analyses. All authors reviewed and approved the final manuscript.

Declaration of interests

AG was given support from the Foundation for Circulatory Health for expenses incurred while working on this project. BD has received personal fees from Novartis, Vicore Pharma, Cereno Scientific, and Merck Sharp & Dohme outside the submitted work. NP's institution (Imperial College London) held a grant for the conduct of the Anglo-Scandinavian Cardiac Outcomes Trial in the UK and Ireland and he has also received speaker's honoraria from Pfizer outside the submitted work. He is also a recipient of the National Institute for Health Research Senior Investigator Award and is supported by the Biomedical Research Centre Award to Imperial College Healthcare NHS Trust. RC was supported by the University of Oxford and British Heart Foundation in the writing of this paper, drawing on expertise developed during research funded by both commercial and academic funders. He reports grants to the University of Oxford from Abbott/Solvay/Mylan, AstraZeneca, Bayer Germany, Cancer Research UK, Merck, the Medical Research Council, and the Wellcome Trust, grants and salary from the British Heart Foundation and UK Biobank, and a prize to his institution (the University of Oxford) from Pfizer, all for independent research outside the submitted work. He has a patent for a statin-related myopathy genetic test, with royalties paid to the University of Oxford from Boston Heart Diagnostics (but he has waived any personal reward). He sought retraction of papers published by the *British Medical Journal* in October, 2013, about the rate of side-effects with statin therapy and other information about its effects, but they have not been retracted. PS' institution (Imperial College London) held a grant for the conduct of the Anglo-Scandinavian Cardiac

Outcomes Trial in the UK and Ireland and he has also received speaker's honoraria from Pfizer and Amgen. He is also a recipient of the National Institute for Health Research Senior Investigator Award and supported by the BioMedical Research Centre Award to the Imperial College Healthcare National Health Service Trust. All other authors declare no competing interests.

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