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

Ajay Gupta[1,2]MRCP, David Thompson[1]MRCPI, Andrew Whitehouse[1]MBBS, Tim Collier[3] MSc , Bjorn Dahlof[4]MD , Neil Poulter[5], FMedSci, Rory Collins[6] FRS, and Peter Sever[1,] FRCP; on behalf of the ASCOT Investigators

1. Imperial College London, Translational & Experimental Medicine Building, NHLI, 3rd Floor Du Cane Road, London, W12 0NN, UK
2. The Royal London Hospital, Barts Health NHS Trust, Whitechapel, London E1 1BB, UK
3. Department of Medical Statistics, London School of Hygiene & Tropical Medicine, Keppel Street, London, WC1E 7HT, UK
4. Institute of Medicine, Department of Molecular and Clinical Medicine, Sahlgrenska Academy, University of Gothenburg, SE 405 30 Gothenburg, Sweden
5. Imperial Clinical Trials Unit, Stadium House, 68 Wood Lane, London W12 7RH, UK
6. Clinical Trial Service Unit & Epidemiological Studies Unit, Nuffield Department of Population Health, University of Oxford, Oxford OX3 7LF, UK

Corresponding author:-
Professor Peter Sever
Imperial College London – Hammersmith Campus
Translational & Experimental Medicine Building
NHLI, 3rd Floor
Du Cane Road
London W12 0NN, UK

Email: p.sever@imperial.ac.uk
Telephone: 0207 594 1100

Background

Large-scale evidence from randomised placebo-controlled trials has shown that statin therapy reduces the incidence of major vascular events (i.e., coronary deaths or myocardial infarctions, ischaemic strokes and coronary revascularisation procedures) by about one quarter for each 1 mmol/L LDL-cholesterol reduction during each year (after the first) that it continues to be taken.[1] The proportional reductions in risk were similar in secondary and primary prevention, and were somewhat greater among lower-risk individuals (although the absolute benefits were smaller). These findings have resulted in guidelines recommending that statin therapy be considered for all patients who have experienced an atherosclerotic event and, in primary prevention, for individuals 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 levels or relevant co-morbidity (such as diabetes).[2,3]

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

It has been suggested that the lack of an excess of AEs in randomised controlled trials of statin therapy might 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 impact of blinded and un-blinded ascertainment of AEs identified using the same approach during blinded randomised statin therapy in the Lipid-lowering arm (LLA) of the trial[13] (i.e., the "blinded randomised" phase) and during the subsequent follow-up period when a proportion of patients were taking open-label statin (the "non-blinded non-randomised" phase).[14] Four AEs of interest (AEOI) were pre-specified due to the public health impact of widespread claims about muscle-related side-effects and the addition to the drug label of erectile dysfunction, sleep disturbance and cognitive impairment as possible side-effects based on reviews by MHRA and FDA.[15,16]

Methods

Details of the ASCOT protocol, including study design, organization, clinical measurements, power calculations, recruitment rates, and baseline characteristics have been published[12] and further information is available on the trial website (www.ascotstudy.org). ASCOT was an independent, investigator-led, multicentre study. Men and women aged between 40 and 79 years were eligible if they had $\geq$ 3 risk factors for CV 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 antihypertensive treatment regimens and, by using a 2 X 2 factorial design, between atorvastatin 10 mg daily versus placebo in the blinded LLA comparison.

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

ASCOT-LLA and LLA-extension phases

Patients included in the ASCOT blood pressure-lowering comparison (BPLA) were also eligible for inclusion in the LLA comparison if they had a total cholesterol concentration of 6·5 mmol/L or less and were not taking a statin or a fibrate. There was no formal run in period to test for tolerance to statins and few, if any, patients had any prior exposure to statin treatment. 10,305 patients were randomised in the LLA between 1998 and 2000, but 65 were withdrawn soon after randomisation due to concerns about source documentation validation. For the remaining 10,240 patients, the randomly assigned atorvastatin or placebo was stopped for efficacy (at the recommendation of the Data Safety and Monitoring Board) in 2002, after a median of 3·3 years of active follow-up, (the period hitherto referred as the "blinded randomised phase" of the ASCOT-LLA).[13] The patients were then told whether they had been assigned atorvastatin or placebo, but they continued to be actively followed in the same way until 2004, for a median of 2·2 years, while the ASCOT-BPLA comparison continued.[14] During that period they were offered open-label atorvastatin (the "non-blinded non-randomised phase"), approximately two thirds of the patients opted to commence or continue open-label statin therapy ("users") while one third did not ("non-users"); see figure 1.

Adverse Event recording, classification and adjudication

Following randomisation, study participants were scheduled to be seen at six weeks, three months and, thereafter, at six monthly intervals during both the blinded randomised and the non-blinded non-randomised phase 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 (CRF). Specific questions relating to any putative AEs were not asked at these visits. During total follow-up for a median of 5·5 years among 10,240 randomised patients in the LLA, there were 60,612 distinct AEs (i.e., after removing multiple reports from the database of the same AE occurrence).

Reports of AEs by study participants were initially recorded verbatim and subsequently classified using the Medical Dictionary for Regulatory Activities (MedDRA)[17] into 26 separate system organ classification (SOC) groups, 2,288 unique preferred terms, and 5,109 separate lower level terms. For the present report, two physicians (AW and DT) adjudicated the four AEs of interest (AEOI): muscle-related, erectile dysfunction, sleep disturbance and cognitive impairment. Each of the adjudicators reviewed (blind 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, based on the description in the CRF, classified their degree of certainty (definite, probable or possible) according to pre-specified definitions. Further details are given in supplementary table 4. Any disagreements between the two adjudicators were independently resolved by a third physician (AG), who was similarly blinded.

Statistical analysis

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

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

Results

The blinded randomised phase of the LLA was conducted from 1998 to 2002, and the non-blinded non-randomised phase from 2002 to 2004. Of the 10,240 eligible randomised patients, 60 (33 atorvastatin; 27 placebo) were excluded from these analyses as they were missing end dates for the blinded phase. A further 281 patients (129 atorvastatin; 152 placebo) had either died or been censored (i.e., those who stopped routine follow-up prior to the end of LLA), and were therefore only included in the blinded analyses. Among 9,899 patients in the non-blinded non-randomised phase, 6,409 (64·7%) were users of statin therapy (most commonly atorvastatin 10mg) at some time during that period, with 52% using it immediately after the end of the blinded randomised phase.

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

Adverse events in the blinded randomised phase

Adverse events of interests (AEOI)*:* During the blinded randomised phase of ASCOT-LLA, the rate of reporting of definite or probable muscle-related AEOIs was similar among patients randomly assigned atorvastatin or placebo (298 [2·03%pa] vs 283 [2·00%pa]; HR 1·03 [95%CI 0·88-1·21]: table 2). Compared with placebo, the rate of reports of erectile dysfunction was slightly, but non-significantly, lower among the patients assigned atorvastatin (272 [1·86%pa] vs 302 [2·14%pa]; HR 0·88 [0·75-1·04]). Patients assigned to receive atorvastatin reported sleep disturbance significantly less often than did those assigned placebo (149 [1·00%pa] vs 210 [1·46%pa]; HR 0·69 [0·56-0·85]; p=0.0005 before any adjustment for multiple comparisons). However, too few cases of cognitive impairment were reported (31 [0·20%pa] vs 32 [0·22%pa]) for a statistically reliable analysis (HR 0·94 [0·57-1·54]). There were similar findings in sensitivity analyses based on definite AEOIs alone or when the larger number of possible AEOIs were included (figure 2).

Other adverse events*:* Compared with patients assigned placebo, the rates of reports of all other AEs grouped by SOC categories were similar among patients assigned atorvastatin (table 3), with the exception of a small excess of AEs attributed to renal and urinary disorders (481 [1·87%pa] vs 392 [1·51%pa]; HR 1·23 [1·08 to 1·41]; p=0.0021: table 3). Subdivision of that SOC, indicates the excess was chiefly due to reports of nocturia and urinary frequency (supplementary table 2).

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.

Although muscle-related problems were not sought systematically in all such trials, sufficiently large numbers of cases have been reported to detect or rule out small excesses.[7] For example, a meta-analysis of 26 blinded randomised trials found little difference in the rates of muscle problems reported during an average treatment duration of three years: 7,544 cases (12·7%) among 59,237 participants assigned statin versus 6,735 (12·4%) among 54,458 assigned placebo.[20] Combination of the reported results in the large placebo-controlled trials eligible for the Cholesterol Treatment Trialists' Collaborative meta-analyses[1] yielded similar results: 5,162 (11·7%) cases allocated statin therapy versus 5,015 (11·4%) allocated placebo during an average of five 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, it has been estimated that any excess of symptomatic muscle pain or other muscle-related problems that is actually caused by statin therapy is likely to be no more than about 0·1-0·2% 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 so-called "statin intolerance"[6,21] chiefly attributed to muscle pain or weakness.[6] Indeed, based on non-randomised observational studies of statin use in routine care, it has been claimed that as many as one-fifth of patients are not able to tolerate statin therapy.[5,22] However, patients who are taking a treatment as part of their routine care know they are doing so (as do their doctors) and they may also be specifically told that the treatment has particular side-effects (e.g. patients given statin therapy are typically advised that serious muscle problems can arise rarely). This inherent lack of blinding in observational studies may introduce substantial ascertainment bias, particularly for the 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 ASCOT-LLA and the excess associated with statin use during the non-blinded non-randomised phase illustrates this problem. Moreover, the present analyses may well under-estimate the impact of the nocebo effect because ASCOT-LLA was conducted during 1998-2004, 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] based largely on associations in observational studies (and despite a general lack 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 of ASCOT-LLA (but not with statin use during the non-blinded non-randomised phase).. A beneficial effect of statin use on sleep disturbance has not previously been reported,[7,23] and it may be that this difference was due to chance (although it is conventionally significant after adjustment for multiple comparisons). There were also fewer reports of erectile dysfunction in ASCOT-LLA among patients assigned atorvastatin during the blinded randomised phase, but that difference did not achieve statistical significance (irrespective of whether the analyses were restricted to definite cases or included all reported cases).

There were too few reported cases of cognitive impairment during ASCOT-LLA to assess the effects of statin therapy reliably. However, specific assessment of this outcome among large numbers of older people in the PROSPER and HPS randomised placebo-controlled trials,[24,25] as well as in trials among 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.[7,13] Most

recently, it has been reported that there was no effect of statin therapy on cognitive decline or memory loss among the 12,000 patients in the randomised blinded HOPE-3 trial.[26] In exploratory analyses of all other AE reports grouped according to SOC, we did not find significant differences during the blinded randomised 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 micturition and nocturia. As far as we are aware, such an excess has not previously been reported. Given the small number of events on which it is based, the large number of separate comparisons made, and their exploratory nature, it may well be that this apparent difference is due to chance.

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

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

The widespread media coverage that has been engendered by claims that statin therapy causes side effects in up to one fifth of patients,[5,27] and the failure to correct such misleading claims rapidly and properly has led to high risk patients with established cardiovascular disease stopping their statin therapy.[28,29] It has been estimated that such reductions in statin use may result in thousands of fatal and disabling heart attacks and strokes occurring, that 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 about its safety. We hope that the demonstration in ASCOT-LLA of not only the lack of adverse effects of statin therapy on muscle-related and other AEs, but also the impact 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.

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 Inc). Data analyses and preparation of all reports were conducted independently of the funding sources.

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 conducted the statistical analyses. All authors reviewed and approved the final manuscript.

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

References

1. Cholesterol Treatment Trialists' (CTT) Collaboration. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. *Lancet* 2012; **380**: 581-90.

2. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 2014; **129** (25 Suppl 2): S1-45.

3. National Institute for Health and Care Excellence. Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. NICE guideline CG181 2014. https://www.nice.org.uk/guidance/cg181 (accessed 02 May 2016).

4. Thompson R GC, Haslam D, Gerada C et al,. Concerns about the latest NICE draft guidance on statins. http://www.nice.org.uk/Media/Default/News/NICE-statin-letter.pdf (accessed 14 March 2016). 2014.

5. Abramson JD, Rosenberg HG, Jewell N, Wright JM. Should people at low risk of cardiovascular disease take a statin? *BMJ* 2013; **347**: f6123.

6. Stroes ES, Thompson PD, Corsini A, et al. Statin-associated muscle symptoms: impact on statin therapy-European Atherosclerosis Society Consensus Panel Statement on Assessment, Aetiology and Management. *European Heart Journal* 2015; **36**: 1012-22.

7. Collins R, Reith C, Emberson J, et al. Interpretation of the evidence for the efficacy and safety of statin therapy. *Lancet* 2016; **388**: 2532-61.

8. Kashani A, Phillips CO, Foody JM, et al. Risks associated with statin therapy: a systematic overview of randomized clinical trials. *Circulation* 2006; **114**: 2788–97.

9. Desai CS, Martin SS, Blumenthal RS. Non-cardiovascular effects associated with statins. *BMJ* 2014; **349:** g3743.

10. Naci H, Brugts J, Ades T. Comparative tolerability and harms of individual statins: a study-level network meta-analysis of 246 955 participants from 135 randomized, controlled trials. *Circ Cardiovasc Qual Outcomes* 2013; **6**: 390–99.

11. Parker BA, Capizzi JA, Grimaldi AS, et al. Effect of statins on skeletal muscle function. *Circulation* 2013; **127**: 96-103.

12. Sever PS, Dahlof B, Poulter NR, et al. Rationale, design, methods and baseline demography of participants of the Anglo-Scandinavian Cardiac Outcomes Trial. ASCOT investigators. *J Hypertens* 2001; **19:** 1139-47.

13. Sever PS, Dahlof B, Poulter NR, et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial--Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. *Lancet* 2003; **361**: 1149-58.

14. Sever PS, Poulter NR, Dahlof B, et al. The Anglo-Scandinavian Cardiac Outcomes Trial lipid lowering arm: extended observations 2 years after trial closure. *European Heart Journal* 2008; **29**: 499-508.

15. . Medicines and Healthcare products Regulatory Agency. Statins: updates to product safety information November 2009. Public Assessment Report. http://www.mhra.gov.uk/home/groups/s-par/documents/websiteresources/con079339.pdf (accessed 19 Oct 2016).

16. The U.S. Food and Drug Administration. FDA Drug Safety Communication 2012: Important safety label changes to cholesterol-lowering statin drugs. http://www.fda.gov/Drugs/DrugSafety/ucm293101.htm (accessed 20th Oct 2016).

17. MedDRA. Introductory guide MedDRA version 17.1. 18th Jan 2015 2014. http://www.meddra.org/sites/default/files/guidance/file/intguide_17_1_english.pdf.

18. Tobert JA, Newman CB. The nocebo effect in the context of statin intolerance. *Journal Clin Lipidology* 2016; **10**: 739-47.

19. Armitage J. The safety of statins in clinical practice. *Lancet* 2007; **370**: 1781-90.

20. Ganga HV, Slim HB, Thompson PD. A systematic review of statin-induced muscle problems in clinical trials. *Am Heart Journal* 2014; **168**: 6-15.

21. Guyton JR, Bays HE, Grundy SM, Jacobson TA. An assessment by the Statin Intolerance Panel: 2014 update. *Journal Clin Lipidology* 2014; **8**(3, Supplement): S72-S81.

22. Redberg RF, Katz MH. Healthy men should not take statins. *JAMA 2012; **307**: 1491-92*.

23. Tuccori M, Montagnani S, Mantarro S, et al. Neuropsychiatric adverse events associated with statins: epidemiology, pathophysiology, prevention and management. *CNS Drugs* 2014; **28**: 249-72.

24. Shepherd J, Blauw GJ, Murphy MB, et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. *Lancet* 2002; **360**: 1623-30.

25. Heart Protection Study Collaborative G. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002; **360**: 7-22.

26. Yusuf S, Bosch J, Dagenais G, et al. Cholesterol Lowering in Intermediate-Risk Persons without Cardiovascular Disease. *N Engl J Med* 2016; **374**: 2021-31.

27. Catalyst ABC1 2013. Heart of the Matter. The Cholesterol Myth: Dietary Villains and Cholesterol Drug War. http://www.abc.net.au/catalyst/stories/4002580.htm; http://about.abc.net.au/press-releases/statement-from-abc-managing-director-on-catalyst-ruling/ (accessed 02 May 2016).

28. Matthews A, Herrett E, Gasparrini A, et al. Impact of statin related media coverage on use of statins: interrupted time series analysis with UK primary care data. *BMJ* 2016; **353**: i3283.

29. Nielsen SF, Nordestgaard BG. Negative statin-related news stories decrease statin persistence and increase myocardial infarction and cardiovascular mortality: a nationwide prospective cohort study. *European Heart Journal* 2016; **37**: 908-16.

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/m^2	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 <u>all</u> 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

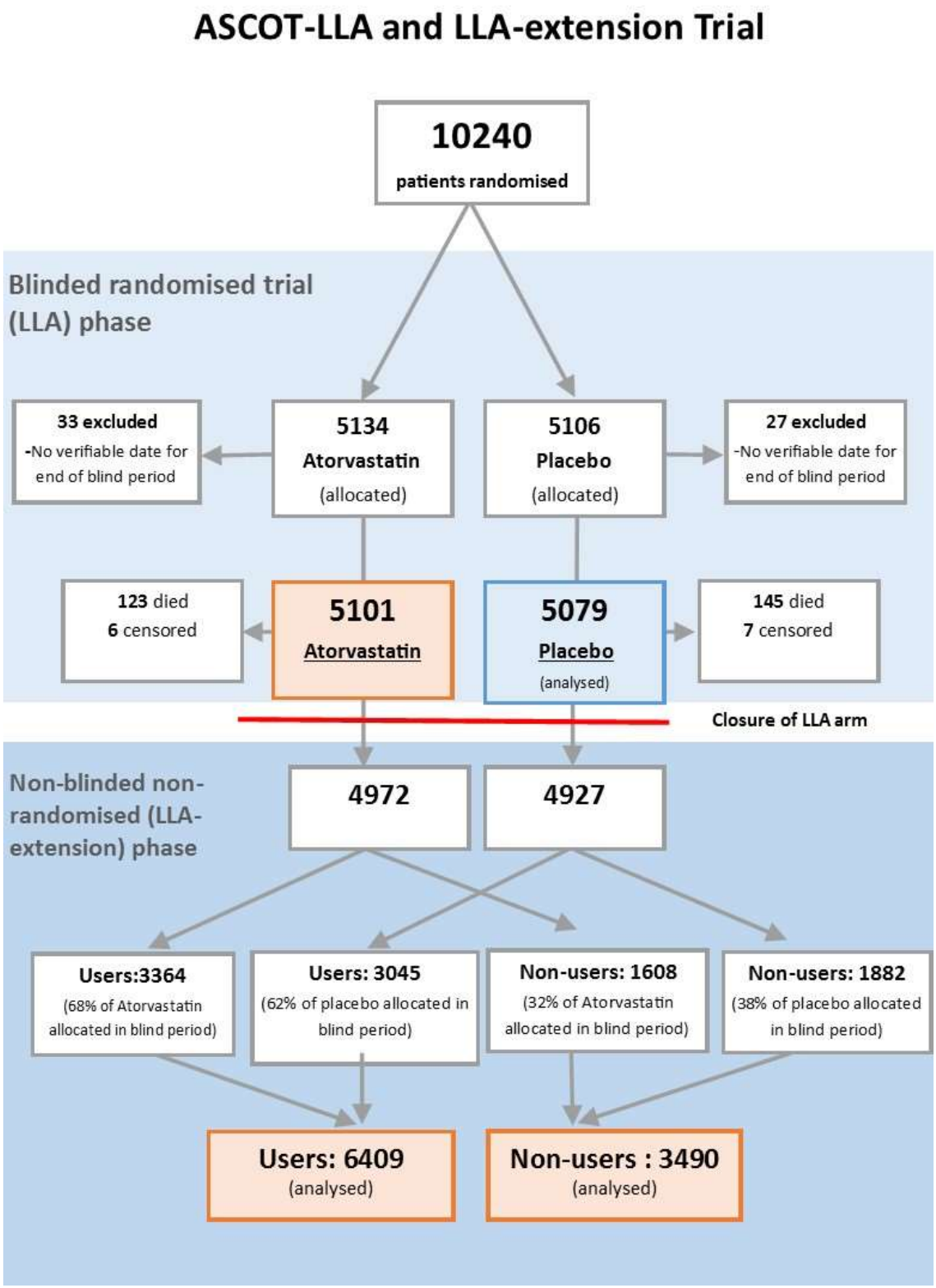
Rate in percentage per annum (equivalent to rate per 100 patient years); hazard ratio from Cox PH model

Table 4. Incident rates of <u>all</u> 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