Protocol for analyses of adverse event data from randomized controlled trials of statin therapy

Cholesterol Treatment Trialists' (CTT) Collaboration

The Cholesterol Treatment Trialists' (CTT) Collaboration was originally established to conduct individual participant data meta-analyses of major vascular events, cause-specific mortality, and site-specific cancers in large, long-term, randomized trials of statin therapy (and other cholesterol-modifying treatments). The results of the trials of statin therapy and their associated meta-analyses have shown that statins significantly reduce the risk of major vascular events without any increase in the risk of nonvascular causes of death or of site-specific cancer, but do produce small increases in the incidence of myopathy, diabetes, and, probably, hemorrhagic stroke. The CTT Collaboration has not previously sought data on other outcomes, and so a comprehensive meta-analysis of all adverse events recorded in each of the eligible trials has not been conducted. This protocol prospectively describes plans to extend the CTT meta-analysis data set so as to provide a more complete understanding of the nature and magnitude of any other effects of statin therapy. (Am Heart J 2016;176:63-9.)

Reprint requests: Cholesterol Treatment Trialists' Collaboration, Clinical Trial Service Unit and Epidemiological Studies Unit (CTSU), Nuffield Department of Population Health, University of Oxford, Oxford, OX3 7LF, UK. Submitted November 3, 2015; accepted January 16, 2016. 0002-8703 © 2016 Elsevier Inc. All rights reserved. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/). http://dx.doi.org/10.1016/j.ahj.2016.01.016

Clinical Investigation
associations in nonrandomized observational studies could be due to differences between the people who do and do not take statins in their underlying risks of having particular health outcomes or in the reporting and detection of health outcomes.31-34

Compared with observational studies, the most important methodological strength of randomized controlled trials is that the process of randomization results in groups of patients who differ from each other only by the play of chance with respect to their risks of experiencing all types of health outcome.31-33,35 In addition, in contrast to observational studies, the ascertainment and definition of health outcomes in the controlled circumstances of a randomized trial are usually systematic and consistent. Furthermore, blinding study treatments through the use of a matching placebo helps to ensure nondifferential assessment of outcomes in the different randomized treatment groups within a randomized trial. Consequently, subject to tests of statistical significance, differences in the rates of health outcomes between the study treatment groups can be attributed causally to the randomly assigned treatment (by contrast with the situation in observational studies).

The previous randomized trials of statin therapy typically collected extensive information on adverse events, which will have been carefully reviewed not only by the trial investigators but also by regulatory authorities (although not necessarily published in its entirety). Many of the larger trials (eg, those recruiting several thousand individuals or more) have had sufficient statistical power on their own to detect any large adverse effects of a statin on particular adverse events (eg, an absolute excess of approximately 10-20 per 1,000 person-years), so it is unlikely that any effects of such magnitude are yet to be identified. However, it is possible that smaller increases or reductions in the risks of adverse events could have been missed by individual trials that would be detectable in a meta-analysis of these trials. For example, despite apparently contradictory36,37 but mostly nonsignificant findings in individual randomized trials, recent meta-analyses of the available data have shown that statin therapy is associated with approximately a 10% to 20% proportional increase in the risk for developing diabetes,9,10 equating to approximately 1 to 3 additional cases per 1,000 person-years of statin treatment in those trials.

The CTT Collaboration involves the principal investigators and sponsors responsible for conducting around 30 large randomized trials of statin therapy in approximately 200,000 people. For its previous analyses, the outcome data obtained on individual participants in these trials were limited to major vascular events, site-specific cancers, and cause-specific mortality.1 As no comprehensive summary of the effects of statins on all recorded adverse events is currently available to prescribers and patients, the present protocol describes plans to seek individual participant data on all of the other adverse events recorded in eligible trials for detailed analyses.

Methods

Study eligibility

Randomized trials of statin therapy will be included in the present analyses if they fulfill the original criteria for the CTT Collaboration analyses,1 in particular: (i) no confounding with respect to the statin comparisons (ie, no other intended differences in risk factor modification between the randomized treatment groups) and (ii) recruitment of at least 1,000 participants with scheduled study treatment duration of at least 2 years. Table I lists published trials that were eligible and for which there was agreement in principle for data provision at the time this protocol was finalised.

Data collection

For each eligible trial, the CTT secretariat will seek:

(i) The methods used for ascertaining all adverse events:
(a) high-level documentation describing the way in which adverse events were sought and recorded (eg, trial protocols);
(b) blank copies of the case report forms (and any supplementary forms) on which adverse events were to be recorded and detailed descriptions of how information was elicited (eg, by direct questioning for particular symptoms, or unprompted reports) and what was recorded (eg, whether it included symptom severity);
(c) details of any coding systems used for adverse events (eg, Medical Dictionary for Regulatory Activities [MedDRA], including version number) and of any trial-specific event definitions (eg, for myopathy or diabetes);
(d) details of any special assessments of particular health outcomes (eg, cognitive function questionnaires, ophthalmic examinations); and
(e) statistical methods used in assessing adverse events (eg, statistical analysis plan).

(ii) Any tabulations in published articles or available elsewhere (eg, clinical study reports provided to regulatory authorities or previously unpublished analyses held by trialists) of:
(a) all types of adverse events that were recorded;
(b) study drug discontinuations and the attributed reasons; and
(c) any other trial-specific safety outcomes (eg, incidence of raised blood levels of CK or liver transaminases).

The principal investigators and/or sponsors of each trial will also be asked to provide individual participant data (or, where applicable, provide access to such data, and
(i) participant identifiers: individual participants in each trial are to be coded with a unique anonymized identifier (ideally one which allows linkage with any data provided for the previous CTT meta-analyses);

(ii) baseline variables: additional baseline variables (eg, glycated hemoglobin [HbA1c], glucose) will be...
sought in assessing the effects on particular adverse events (eg, onset of diabetes);

(iii) adverse events: each recorded occurrence (ie, not just the first) of all adverse events, and the time since randomization for each adverse event;

(iv) study treatment adherence: the occurrence and timing of, and attributed reasons for, discontinuing study statin/placebo or starting a nonstudy statin;

(v) comedication: information will be sought on the use of drugs at baseline and during trial follow-up that are relevant for particular adverse events (eg, hypoglycemic drugs that may indicate diabetes mellitus; medications that may interfere with statin metabolism);

(vi) laboratory variables: results will be sought for assays that are relevant for particular adverse events (eg, CK for muscle symptoms; liver transaminases for hepatic function; blood glucose or Hba1c for diabetes development or worsening creatinine for renal function); and

(vii) physical parameters: results will be sought for physical measurements that are relevant for particular adverse events (eg, weight in relation to diabetes).

Analysis plan

The main objective is to assess the proportional and absolute effects of statin therapy on particular adverse events of interest, so that the balance of benefits and harms in specific types of individuals can be determined.

Outcomes to be assessed

Several types of outcome will be considered, based on current knowledge of the effects of statin therapy in the following hierarchical order:

(i) adverse events that are definitely or probably increased by statin therapy (ie, myopathy, diabetes, and hemorrhagic stroke): analyses of these events will examine the magnitude, timing, and duration of the excess risks both overall and in particular subgroups (eg, diabetes according to baseline Hba1c, hemorrhagic stroke with or without prior stroke) and will also explore how the magnitude of the risks varies according to how an adverse event is defined (eg, biochemical vs clinical diagnosis of diabetes mellitus);

(ii) muscle-related symptoms: analyses of these events will consider muscle pain (ie, myalgia) and weakness separately from myopathy (as defined above) and will explore whether statins increase reported rates of muscle pain of different levels of severity (including, for example, muscle symptoms given as a reason for stopping study treatment);

(iii) other possible effects of statin therapy: this will include adverse events which have been added to some statin drug labels on the basis that there may be a class effect for such events (including cognitive impairment, depression, sleep disturbance, sexual dysfunction, and interstitial lung disease), as well as adverse events for which it has been suggested there may be a reduction with statin therapy (eg, pancreatitis); and

(iv) all other adverse events recorded in these trials.

Main and subsidiary analyses

Preliminary information obtained about trial methodological details and tabular data will be used to construct more detailed plans for the combination of adverse event data from each of the trials. Because there will be some heterogeneity between trials with respect to recorded event categories (eg, adverse events, serious adverse events, drug-related adverse events, etc) as well as the type of event coding system (eg, MedDRA, International Classification of Diseases [ICD], etc), it is intended to create analogous event categories and definitions prior to combining trial event data by grouping adverse events into categories based on body systems (eg, as defined by MedDRA “system organ classes” or “high level group terms”), with more detailed examination in other subcategories (eg, using MedDRA “preferred terms” or “standardized medical queries”) in order to create a single analyzable database. This recoding process will be performed prior to unblinding treatment allocation.

The primary analyses will be conducted among blinded trials that examined a statin versus placebo. Subsidiary analyses will be conducted (i) among blinded trials of more versus less intensive statin regimens; and (ii) among trials that assessed statin therapy without a blinded control group (allowing assessment of any reporting biases in unblinded studies).

Statistical methods

The primary analyses will include all participants who were randomly assigned to the different study treatment groups, irrespective of whether they remained compliant with their allocated study treatment. Such “intention-to-treat” comparisons are used to provide unbiased assessment of moderate effects of a treatment on relatively common outcomes. However, due to noncompliance with the allocated study treatment, they may underestimate the magnitude of the effect of actually taking it, so estimates of compliance will be used to evaluate the likely effects of full compliance. In addition, for rare outcomes on which statin therapy may be exerting a large relative effect (as is the case with myopathy), “on-treatment” analyses (ie, excluding those known not to be taking their allocated study treatment) will be performed to help increase sensitivity.
Table II. Approximate statistical power (2-sided $\alpha = 0.01$) among 100,000 participants randomized between statin and placebo to detect relative risks of 1.05, 1.1, 1.2, or 1.3 with absolute 5-year control rates of 2%, 5%, 10%, or 20%

| Event rate | Power at 2-sided $\alpha = 0.01$ |
|------------|---------------------------------|
| 2%         | 7% 36% 96% >99%                 |
| 5%         | 22% 83% >99% >99%              |
| 10%        | 51% >99% >99% >99%            |
| 20%        | 91% >99% >99% >99%           |

The above power estimates are based on a test of the observed odds ratio under each scenario, which will be slightly larger than the relative risks but will correspond exactly to the relative risks given the control event rate in each case. Odds ratios and relative risks are similar when outcomes are rare but become more different as outcome rates increase (eg, when the 5-year control event rate is 20%, the relative risks of 1.05, 1.1, 1.2, and 1.3 correspond to odd ratios of 1.06, 1.13, 1.26, and 1.41, respectively).

Table III. Five-year absolute excess risk under hypothetical relative risks shown in Table II

| Relative risk | 1.05 | 1.1 | 1.2 | 1.3 |
|-------------|-----|-----|-----|-----|
| Event rate |  |  |  |  |
| 2%         | 0.1% | 0.2% | 0.4% | 0.6% |
| 5%         | 0.25% | 0.5% | 1.0% | 1.5% |
| 10%        | 0.5% | 1.0% | 2.0% | 3.0% |
| 20%        | 1.0% | 2.0% | 4.0% | 6.0% |

In view of the large number of adverse events that will be examined, both uncorrected $P$ values and false discovery rate-corrected $P$ values will be presented. The above power estimates are based on a test of the observed odds ratio under each scenario, which will be slightly larger than the relative risks but will correspond exactly to the relative risks given the control event rate in each case. In previous reports, the meta-analyses were performed with these $(o−e)$ and $v$ values weighted by the absolute LDL cholesterol difference in each trial at 1 year but, since the main purpose of the present analyses is to assess the effects of statin therapy (rather than of lowering LDL cholesterol), the emphasis of the present meta-analyses will be on unweighted results. When the primary analyses indicate differences between the treatment groups in the rates of first occurrences of some particular adverse event, exploratory analyses will assess whether there is an effect on the subsequent events. SAS (SAS Institute, Cary, NC) and R (www.R-project.org) will be used for analyses.

Analyses of adverse events recorded in approximately 100,000 participants randomized to statin therapy versus placebo would provide excellent statistical power for detecting small absolute differences in the rates of events that are recorded in more than a few percent of participants. For example, with a 5-year adverse event rate among control-allocated participants of 2% (ie, 0.4% per year), the meta-analysis would have >95% power at 2-sided $P = 0.01$ to detect a relative risk of $\geq 1.2$ (Table II), which translates into an absolute 5-year excess of as little as 0.4% (Table III). Moreover, if the 5-year control rate is 10%, then the meta-analysis would have >99% power at 2-sided $P = 0.01$ to detect a relative risk of 1.1 or more (Table II) or an absolute 5-year excess of 1.0% (Table III).
the pharmaceutical industry. Although most of the trials that will contribute to these analyses were supported (at least in part) by research grants from the pharmaceutical industry, most of them were conducted, analyzed, interpreted, and reported independently of all funding sources by academic investigators.

Data handling and publication policy

The CTT Collaboration is coordinated jointly by the CTT Secretariat in the Clinical Trial Service Unit & Epidemiological Studies Unit in Oxford and the National Health and Medical Research Council Clinical Trials Centre in Sydney. The CTT Secretariat is responsible for collecting and analyzing the data from participating trials on behalf of the CTT Collaboration. The CTT Secretariat was responsible for the design, drafting and editing of this protocol, with members of the CTT Collaboration being given an opportunity to review and comment on its wording before submission. All members of the CTT Collaboration will have an opportunity to contribute to analyses of the data, interpretation of the results, and drafting of future reports resulting from this project as members of a Writing Committee. As before, these reports will be published in the name of the CTT Collaborative group. Further details of the CTT Secretariat and Collaborators can be found at www.cttcollaboration.org.

Writing committee

Reith C., Blackwell L., Emberson J., Mihaylova B., Armitage J., Fulcher J., Keech A., Simes J., Baigent C., Collins R.

References

1. Cholesterol Treatment Trialists' (CTT) Collaboration. Protocol for a prospective collaborative overview of all current and planned randomized trials of cholesterol treatment regimens. Am J Cardiol 1995;75(16):1130-4.
2. Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90 056 participants in 14 randomised trials of statins. Lancet 2005;366(9493):1267-78.
3. Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy of cholesterol-lowering therapy in 18 686 people with diabetes in 14 randomised trials of statins: a meta-analysis. Lancet 2008;371(9607):117-25.
4. Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials. Lancet 2010;376(9753):1670-81.
5. 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(9841):581-90.
6. Cholesterol Treatment Trialists' (CTT) Collaboration. Lack of effect of lowering LDL cholesterol on cancer: meta-analysis of individual data from 175,000 people in 27 randomised trials of statin therapy. PLoS ONE 2012;7(11):e52949, http://dx.doi.org/10.1371/journal.pone.0029849.
7. Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy and safety of LDL-lowering therapy among men and women: meta-analysis of individual data from 174,000 participants in 27 randomised trials. Lancet 2015;385(9976):1397-405.
8. Armitage J. The safety of statins in clinical practice. Lancet 2007;370(9601):1781-90.
9. Sattar N, Preiss D, Murray HM, et al. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. Lancet 2010;375(9716):735-42.
10. Preiss D, Seshasai SR, Welsh P, et al. Risk of incident diabetes with intensive-dose compared with moderate-dose statin therapy: a meta-analysis. JAMA 2011;305(24):2556-64.
11. The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Investigators. High-dose atorvastatin after stroke or transient ischemic attack. N Engl J Med 2006;355(6):549-59.
12. 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].
13. 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. J Am Coll Cardiol 2014;63(25 Pt B):2899-303.
14. Abramson JD, Rosenberg HG, Jewell N, et al. Should people at low risk of cardiovascular disease take a statin? BMJ 2013;347:f6123.
15. Bruckert E, Hayem G, Dejager S, et al. Mild to moderate muscular symptoms with high-dosage statin therapy in hyperlipidemic patients—the PRIMO study. Cardiovasc Drugs Ther 2005;19(6):403-14.
16. Buechner C, Davis RB, Lewille SG, et al. Prevalence of musculoskeletal pain and statin use. J Gen Intern Med 2008;23(8):1182-6.
17. Hippisley-Cox J, Coupland C. Unintended effects of statins in men and women in England and Wales: population based cohort study using the QResearch database. BMJ 2010;340:c2197.
18. Björnsson E, Jacobsen EI, Kalaitzakis E. Hepatotoxicity associated with statins: reports of idiosyncratic liver injury post-marketing. J Hepatol 2012;56(2):374-80.
19. Leuschl J, Mortensen EM, Frei CR, et al. Association of statin use with cataracts: a propensity score–matched analysis. JAMA Ophthalmol 2013;131(11):1427-34.
20. Kang JH, Kao LT, Lin HC, et al. Statin use increases the risk of depressive disorder in stroke patients: a population-based study. J Neurol Sci 2015;348(1-2):89-93.
21. Evans MA, Golomb BA. Statin-associated adverse cognitive effects: survey results from 171 patients. Pharmacotherapy 2009;29(7):800-11.
22. Takada M, Fujimoto M, Yamazaki K, et al. Association of statin use with sleep disturbances: data mining of a spontaneous reporting database and a prescription database. Drug Saf 2014;37(6):421-31.
23. Dormuth CR, Hemmelgarn BR, Paterson JM, et al. Use of high potency statins and rates of admission for acute kidney injury: multicenter, retrospective observational analysis of administrative databases. BMJ 2013;346:f880.

24. Nielsen SF, Nordestgaard BG, Bojesen SE. Statin use and reduced cancer-related mortality. N Engl J Med 2012;367(19):1792-802.

25. van de Garde EM, Hak E, Souverein PC, et al. Statin treatment and reduced risk of pneumonia in patients with diabetes. Thorax 2006;61(11):957-61.

26. Khan AR, Riaz M, Bin Abdulhak AA, et al. The role of statins in prevention and treatment of community acquired pneumonia: a systematic review and meta-analysis. PLoS ONE 2013;8(1):e52929, http://dx.doi.org/10.1371/journal.pone.0052929.

27. Frost FJ, Petersen H, Tollestrup K, et al. Influenza and COPD mortality protection as pleiotropic, dose-dependent effects of statins. Chest 2007;131(4):1006-12.

28. Chan KA, Andrade SE, Boles M, et al. Inhibitors of hydroxymethyl-glutaryl-coenzyme A reductase and risk of fracture among older women. Lancet 2000;355(9222):2185-8.

29. Wahnner AD, Bronstein JM, Bordelon YM, et al. Statin use and the risk of Parkinson disease. Neurology 2008;70(16 Pt 2):1418-22.

30. Lee YC, Lin CH, Wu RM, et al. Discontinuation of statin therapy associates with Parkinson disease: a population-based study. Neurology 2013;81(5):410-6.

31. Temple R. Meta-analysis and epidemiologic studies in drug development and postmarketing surveillance. JAMA 1999;281(9):841-4.

32. Pocock SJ, Elbourne DR. Randomized trials or observational tribulations? N Engl J Med 2000;342(25):1907-9.

33. MacMahon S, Collins R. Reliable assessment of the effects of treatment on mortality and major morbidity, II: observational studies. Lancet 2001;357(9254):455-62.

34. Tapert JA, Newman CB. Statin tolerability: In defence of placebo-controlled trials. Eur J Prev Cardiol 2015, http://dx.doi.org/10.1177/2047487315602861.

35. Collins R, MacMahon S. Reliable assessment of the effects of treatment on mortality and major morbidity, I: clinical trials. Lancet 2001;357(9253):373-80.

36. Freeman DJ, Norrie J, Sattar N, et al. Pravastatin and the development of diabetes mellitus: evidence for a protective treatment effect in the West of Scotland Coronary Prevention Study. Circulation 2001;103(3):357-62.

37. Ridker PM, Danielson E, Fonseca FA, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med 2008;359(21):2195-207.

38. Medicines and Healthcare products Regulatory Agency. Statins: updates to product safety information. Public Assessment Report. 2009. [http://www.mhra.gov.uk/home/groups/s-par/documents/websitesources/con079339.pdf, accessed 19 Oct 2015].

39. U.S. Food and Drug Administration. Drug safety communication: important safety label changes to cholesterol-lowering statin drugs. http://www.fda.gov/Drugs/DrugSafety/ucm293101.htm 2012. [accessed 19 Oct 2015].

40. Preiss D, Tikkanen MJ, Welsh P, et al. Lipid-modifying therapies and risk of pancreatitis: a meta-analysis. JAMA 2012;308(8):804-11.

41. Mehrtra D, Heyse JF. Use of the false discovery rate for evaluating clinical safety data. Stat Methods Med Res 2004;13(3):227-38.

42. Antiplatelet Trialists’ Collaboration. Collaborative overview of randomised trials of antiplatelet therapy-I: prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. BMJ 1994;308(6921):81-106.