Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials


Summary

Background Trials of statin therapy have had conflicting findings on the risk of development of diabetes mellitus in patients given statins. We aimed to establish by a meta-analysis of published and unpublished data whether any relation exists between statin use and development of diabetes.

Methods We searched Medline, Embase, and the Cochrane Central Register of Controlled Trials from 1994 to 2009, for randomised controlled endpoint trials of statins. We included only trials with more than 1000 patients, with identical follow-up in both groups and duration of more than 1 year. We excluded trials of patients with organ transplants or who needed haemodialysis. We used the P statistic to measure heterogeneity between trials and calculated risk estimates for incident diabetes with random-effect meta-analysis.

Findings We identified 13 statin trials with 91 140 participants, of whom 4278 (2226 assigned statins and 2052 assigned control treatment) developed diabetes during a mean of 4 years. Statin therapy was associated with a 9% increased risk for incident diabetes (odds ratio [OR] 1·09; 95% CI 1·02–1·17), with little heterogeneity (P=11%) between trials. Meta-regression showed that risk of diabetes with statins was highest in trials with older participants, but neither baseline body-mass index nor change in LDL-cholesterol concentrations accounted for residual variation in risk. Treatment of 255 (95% CI 150–852) patients with statins for 4 years resulted in one extra case of diabetes.

Interpretation Statin therapy is associated with a slightly increased risk of development of diabetes, but the risk is low both in absolute terms and when compared with the reduction in coronary events. Clinical practice in patients with moderate or high cardiovascular risk or existing cardiovascular disease should not change.

Funding None.

Introduction Statin therapy is effective for reduction of cardiovascular events and is generally recognised as being safe and well tolerated. However, researchers of six large randomised placebo-control trials have reported conflicting results about the development of diabetes in patients taking such drugs. In the JUPITER trial, 17 802 adults with no clinical or biochemical diagnosis of diabetes based on fasting glucose concentrations were assigned rosuvastatin or placebo for a median of 1·9 years. Significantly more individuals in the statin group than in the placebo group developed diabetes.

By contrast, results from the WOSCOPS study suggested that pravastatin therapy might reduce the frequency of diabetes. These findings have raised questions about the safety of long-term use of statins, and led to calls for a systematic exploration of the possible effect of statin therapy on incident diabetes. Over-estimation of clinical benefit or underestimation of risk is potentially of major public health importance. To resolve this uncertainty, we investigated this effect by undertaking a meta-analysis of all available published and unpublished data from large placebo-controlled and standard-care-controlled statin trials.

Methods Search strategy and selection criteria We gathered data from large placebo and standard-care-controlled endpoint trials of statins that were designed to assess the effect of statin treatment on cardiovascular endpoints in stable individuals—ie, no patients with organ transplants or receiving haemodialysis. We excluded trials comparing statins (either different statins or doses of the same statin), those in patients with diabetes, trials assessing change in surrogate markers of cardiovascular disease, and those that had recruited 1000 or fewer participants. To be consistent with other large meta-analysis protocols, we excluded trials with a mean follow-up of 1 year or less. We also stipulated that any trials comparing statin therapy with usual care needed to follow up patients in both treatment groups identically to avoid systematic error and resultant bias in diagnosis of incident diabetes.

We searched Medline, Embase, and the Cochrane Central Register of Controlled Trials, from 1994 to 2009, for randomised placebo and standard care-controlled endpoint trials of statins with the term “statin” as a title word and keyword, and with names of individual statins to identify reports of trials of adult patients. We restricted the search to English-language publications. We excluded trials of patients with organ transplants or who needed haemodialysis. In some cases, we obtained unpublished data from trial investigators; we did not consider unpublished data to be at increased risk of bias relative to published data.

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Funding None.
our search to reports that were published in English between 1994 and 2009. We undertook our search on Jan 8, 2009, and identified 2841 reports that were reviewed by two independent readers (DP and PW), with a third reviewer (NS) to settle any discrepancies.

Data sources
We contacted investigators from nine trials about unpublished data for incident diabetes, and received and included data from six of these trials, leading to the final inclusion of 13 trials, for which six4–9 had previously published data for incident diabetes and seven10–18 had not. For those seven trials, incident diabetes data had not been analysed until our request for this collaboration.

For all published trials, information about the number of non-diabetic patients at baseline and cases of incident diabetes were independently abstracted, and were tabulated according to the randomisation group by two authors (DP and PW). Because the effect estimates for incident diabetes were directly reported as hazard ratios (HRs) in only three of the six published trials, we adopted a standard approach across all trials, in which we calculated odds ratios (ORs) and their 95% CIs from the abstracted data for the number of patients who did not have diabetes at baseline and those developing incident diabetes. A previous WOSCOPS report1 gave lower numbers of incident diabetes cases than we include here; the discrepancy is attributable to the use of different criteria to diagnose diabetes. We used standard diabetes diagnostic criteria, whereas rigorous and non-standard criteria (such as the requirement for glucose to rise ≥2·0 mmol/L above baseline) were used in the previous report.

For trials with unpublished information, we requested and received data according to a formal question sheet (webappendix p I). Questions were about the number of participants who did not have diabetes at baseline, the number developing diabetes, and change in LDL-cholesterol concentration over time by randomisation group, plus baseline body-mass index (BMI), baseline age, and the methods used to diagnose diabetes. The diagnostic criteria used differed slightly, according to the data available in the trials. At least one fasting glucose result per patient was available for all seven trials with unpublished data. To approach expected rates of incident diabetes, we used the diagnostic criterion of two glucose concentrations of ≥7·0 mmol/L or higher in trials that measured fasting glucose roughly every 6 months, but only one glucose value of ≥7·0 mmol/L or higher in trials that measured fasting glucose less frequently than 6 monthly. We also calculated ORs for these trials.

Statistical analysis
To identify potential effects of statin therapy on incident diabetes, we calculated an overall OR with a random-effects model meta-analysis, which assumes that the true underlying effect varies between trials. We assessed statistical heterogeneity between trials with $I^2$ statistic (with 95% CIs), which is derived from Cochran’s Q [100×(Q−df)/Q]$^{19}$ and provides a measure of the proportion of overall variation that is attributable to between-trial heterogeneity. We used risk estimates obtained with random-effects meta-analysis instead of fixed-effects models, because this approach provides a more conservative assessment (ie, wide CIs) of the average effect size. We used meta-regression analyses to investigate potential sources of heterogeneity between trials. Factors that we investigated were baseline age, baseline BMI, and percentage change in LDL-cholesterol concentrations, and these factors were decided before the meta-analysis was undertaken. We analysed data with Stata version 10.1.

To test for publication bias, we formed a funnel plot and undertook the Egger test.20 Although five different statins were used in the 13 trials, combination of results from all trials in the meta-analysis was deemed to be appropriate on the basis of homogeneity of effect21 and results obtained. However, we assessed effects of individual statins separately in a sensitivity analysis. Additionally, we undertook meta-analyses restricted to the trials that had fasting glucose concentrations (CORONA,22 and HPS2 excluded); placebo-control trials only (ie, those without a standard-care-control group; ALLHAT-LTT,23 MEGA,24 GISSI Prevenzione25 excluded); all trials apart from JUPITER; all trials apart from

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**Figure 1: Flow diagram of literature search to identify randomised placebo-controlled and standard care-controlled statin trials**

- **2841 reports identified with Medline, Embase, and Cochrane Central**
  - 2800 reports excluded
    - not randomised controlled trials (RCT)
    - high-dose vs low-dose statin trials
    - RCT of a non-statin intervention
    - trial examining surrogate markers
    - trial investigating patients with diabetes
- **41 articles identified from 19 potentially relevant trials, six with published data**
- **3 trials excluded**
  - -Greace21 and ALLIANCE22 had different follow-up procedures for each group, with possibility of bias for incident diabetes endpoint
  - -POST-CABG23 compared different statin doses
- **Trial investigators contacted for nine unpublished trials (PROSPER already available to authors)**
- **13 studies fulfilled criteria and included in meta-analysis**

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**Webappendix**

- Section I describes the search strategy and the selection criteria for the meta-analysis.
- Section II describes the data abstraction process.
- Section III describes the statistical methods used.
- Section IV presents the results of the meta-analysis, including the effect estimates and the statistical tests for heterogeneity.
- Section V discusses the potential sources of heterogeneity between trials.
- Section VI presents the sensitivity analysis and the publication bias analysis.
- Section VII concludes with a discussion of the implications of the findings for clinical practice and future research.
Figure 2: Association between statin therapy and incident diabetes in 13 major cardiovascular trials†

*Events per 1000 patient-years. †Weights are from random-effects analysis.
MEGA (in which all the participants were Japanese); and a comparison of trials with hydrophilic (pravastatin, and rosuvastatin) and lipophilic (atorvastatin, simvastatin, and lovastatin) statins.

Role of the funding source

There was no funding source for this study. The corresponding authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

We identified 13 clinical trials providing data for 91140 non-diabetic participants of whom 4278 developed incident diabetes (figure I). The mean study follow-up was about 4 years (weighted average; table). Rate of diabetes in individual trials varied substantially (figure 2). Of the 13 trials, two (JUPITER and PROSPER) individually showed positive associations between statin therapy and incident diabetes (figure 2). For combined data (table), we identified 174 more cases of incident diabetes in the groups assigned to statin treatment than in the placebo or standard-care groups, representing a 9% increase in the likelihood of development of diabetes during follow-up (figure 2).

For the combined study cohort, the extra 174 cases in the statin group can also be expressed in absolute terms as one additional case of diabetes per 255 (95% CI 150–852) patients taking statin therapy for 4 years (12·23 cases per 1000 patient-years with statin treatment and 11·25 cases per 1000 patient-years with control therapy). We undertook a funnel plot and Egger test of the original six published trials, with results showing no underlying publication bias (webappendix p 2).

As in the main analysis, risk of incident diabetes with statin therapy remained higher with statin therapy than with control in analyses restricted to the placebo-control trials (OR 1·10, 95% CI 1·01–1·20, P=0·021; n=75 507). The association weakened slightly (OR 1·07, 0·97–1·17, P=0·32;
75033) when we analysed only trials that used fasting glucose measurements—possibly because of a loss of statistical power. Further analyses for individual statins yielded overlapping CIs, suggesting that combination of all trials in the primary analysis was appropriate (figure 3).

Analyses also showed no clear difference between statins in terms of diabetes risk. Lipophilic (OR 1·10, 0·99–1·22, $I^2=0\%$) and hydrophilic (OR 1·08, 0·98–1·20, $I^2=36\%$) statins were associated with very similar risks. Results of analyses without JUPITER (OR 1·08, 1·01–1·15, $I^2=1·5\%$) or MEGA (1·09, 1·01–1·18, $I^2=18·4\%$) were similar to the overall analysis.

Heterogeneity between trials in the overall analysis was low, suggesting that most variation was attributable to chance alone (figure 2). In an exploratory attempt to identify other sources of the residual slight difference between trials, we undertook meta-regression analyses of baseline age, baseline BMI, and change in LDL-cholesterol during treatment (figure 4). Of these variables, the association between statin therapy and risk of incident diabetes was stronger in trials with older participants, but baseline BMI (analysed both with and without MEGA data) and percentage change in LDL-cholesterol concentration did not seem to be important factors.

**Discussion**

The results of this meta-analysis show that individuals assigned statins were at slightly increased risk of diabetes compared with those assigned placebo or standard care. This risk seemed higher in trials with older participants. Results from only those trials that used fasting glucose measurements and were placebo-controlled were consistent with this finding. We identified no apparent difference between hydrophilic and lipophilic statins in the association with diabetes risk. These results do not prove that statin therapy raises diabetes risk via a molecular mechanism, although this possibility should be considered. In one study of the effects of various statins on the glucose-transporter-4, atorvastatin but not other statins seemed to have a detrimental effect on glucose metabolism via this mechanism. Conversely, as far as we are aware, genome-wide scans of type 2 diabetes have not identified an association with genes regulating LDL-cholesterol metabolism or 3-hydroxy-3-methylglutaryl-Co-A reductase.

Another potential explanation is that the association between statin therapy and incident diabetes is due to residual confounding factors. Possible factors are improved survival with statin treatment, or a change to a healthy lifestyle (ie, weight loss with resultant lowered risk for incident diabetes) after cardiovascular events, which are more likely in placebo than in statin treatment groups. However, overall survival with statins is very similar to survival with control therapy (about 1·4% absolute difference), suggesting that survival bias does not explain the variation.

In some short-term studies investigating the effect of statins on insulin resistance in animals and people, a benefit has been detected, but few have identified a...
deterioration in glucose homoeostasis. Therefore, a raised risk of incident diabetes with statins could represent a chance finding, although the low heterogeneity of results suggests otherwise. However, such short-term studies are not necessarily informative about long-term risk.

The additional 174 cases of diabetes in the combined statin groups equate only to a slight increase of diabetes in absolute terms. The risk is also small in relation to the reduction in vascular events. With data from the Cholesterol Treatment Trialists’ (CTT) meta-analysis of statin trials in 71370 non-diabetic participants, we calculate that statin therapy was associated with a reduction in major coronary events (coronary heart disease death and non-fatal myocardial infarction) of 5.4 events per 255 patients treated for 4 years compared with control therapy for a 1 mmol/L reduction in LDL-cholesterol concentration. This benefit would be expected to be even greater when accounting for the effect of statins on strokes and the need for revascularisation.

Notably, of the 13 trials in CTT with non-diabetic individuals, we provide data for incident diabetes for nine trials; therefore, this estimate of the risk benefit, although informative, could be slightly inaccurate. Risk benefit considerations can differ between specific groups of patients—eg, statin therapy has not shown cardiovascular benefit in two large trials of patients with heart failure, but risk of development of diabetes while on statins was increased in both trials. In view of the evidence for the benefits of statins on macrovascular events in patients with and without diabetes, the small excess risk of incident diabetes is favourably balanced by cardiovascular benefit, implying that clinical decision-making should not be changed for patients in whom statin therapy is recommended—ie, people with existing cardiovascular disease or at medium-to-high risk of such disorders.

Our meta-analysis incorporated almost all completed large trials, providing good statistical power. The meta-analysis was undertaken with summary data and ORs because HRs were not available in all trials. Thus, analyses of individual participants’ data could yield further insights. Methods for diagnosis of incident diabetes varied between trials, which is common in such studies. This variation, when combined with the differing trial population groups, resulted in varying rates between trials for development of diabetes. In CORONA and HPS, diagnoses were based on physician reporting only, rather than on physician reporting and documented biochemical analyses. Exclusion of these two trials by analysis of the eleven trials with biochemical analyses produced a null result (p=0.10). Although the summary ORs were similar to those for the primary analysis, the absence of significance was perhaps in part attributable to reduced power.

We used either one or two glucose concentrations of 7.0 mmol/L as a diagnostic criterion, dependent on the frequency of measurement. Results obtained lend support

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**Figure 4:** Meta-regression of (A) baseline age, (B) baseline BMI, and (C) on-treatment percentage reduction in LDL-cholesterol concentration for incident diabetes

Meta-regression p value=0.019 (A), p=0.177 (B), p=0.102 (C).
to this pragmatic approach. The two trials with the lowest calculated occurrence of diabetes (ACAPS TexCAPS and WOSCOPS) were primary-prevention trials with low diabetes risk (low BMIs compared with ASCOT-LLA and JUPITER). The four trials with the highest frequency included participants known to be at high risk of diabetes—PROSPER (participants aged 70–82 years with or at high risk of cardiovascular disease), GISSI Prevenzione (myocardial infarction within the last 6 months), and GISSI HF plus CORONA (heart failure, a well-known diabetogenic state).

For the WOSCOPS study, we reported individual risk of diabetes with pravastatin treatment as null, whereas reduced risk was reported elsewhere. However, non-standard criteria were previously used for diagnosis of diabetes, with a requirement for a rise in fasting glucose of 2.0 mmol/L or more during the trial. Therefore, we used standard criteria for diagnosis in a reanalysis of WOSCOPS, producing data that were easily compared with other trials. However, use of 2001 WOSCOPS data would not have changed the overall meta-analysis result (data available on request). Finally, only results for patients with normal fasting glucose concentrations are available for LIPID.

Data for incident diabetes and changes in blood glucose concentrations in trials comparing statin to statin are available, some of which show a worsening in glucose homeostasis on high doses or powerful statins. However, these data were not included because the assumption that any possible increase in incident diabetes on statin therapy is related to dose is untested. As far as we are aware, our analysis was only missing data from three other trials (8985 non-diabetic participants)—CARE, SPARCL, and LIPS. Studies of more than 1000 patients are unlikely to be unpublished. Finally, to estimate the total number of person-years of follow-up, we assumed that the median approximated to the arithmetic mean in some trials, and in a few trials we quoted baseline BMI, baseline age, change in LDL-cholesterol concentrations, and follow-up from the entire cohort when data specific to non-diabetic patients were unavailable.

Our data suggest that surveillance for dysglycaemia might be useful for older people receiving statin therapy. We recommend that development of diabetes is specified as a secondary endpoint in future large endpoint statin trials, and suggest that, when possible, reports of long-term follow-up in existing trials should also include incident diabetes. In view of the overwhelming benefit of statins for reduction of cardiovascular events, the small absolute risk for development of diabetes is outweighed by cardiovascular benefit in the short and medium term in individuals for whom statin therapy is recommended. We therefore suggest that clinical practice for statin therapy does not need to change for patients with moderate or high cardiovascular risk or existing cardiovascular disease. However, the potentially raised diabetes risk should be taken into account if statin therapy is considered for patients at low cardiovascular risk or patient groups in which cardiovascular benefit has not been proven.

**Contributors**

NS and DP contributed equally and were joint first authors, and KKR and IF contributed equally and were joint senior authors. NS, DP, PW, and DJF developed the original idea for the report. NS and DP wrote the first draft. DP and PW undertook the literature search. SRKS, KKR, and DP coordinated and did the statistical analyses. HM, BMB, A/JMdeC, JIM, JW, PWF, CJP, DJS, RGW, JS, BRD, SLP, RM, RMM, APM, AT, GT, JK, TRP, TJC, AMG, MBC, JRD, HH, YO, KM, and IF analysed and provided original trial data. All authors contributed to interpretation of results, drafting of the first submission, and revision of the report.

**Conflicts of interest**

Trials in this report were supported by research grants from the pharmaceutical industry. All authors apart from NS, DP, HMM, PW, SRKS, DJF, A/JMdeC, and KKR were members of steering committees for some of these trials. NS has received consulting and lecture fees from Merck & Co, Pfizer, and AstraZeneca, and has received research grant support from Pfizer. JMM has received payment from AstraZeneca for advisory boards and lectures, JW has received research grants and minor speaker fees from Bristol-Myers Squibb, Astra-Zeneca, Pfizer, and Merck & Co. PWM has been involved in clinical trials of statins that were sponsored by BMS and AstraZeneca, and also received lecture fees from Bristol-Myers Squibb. CJP has received honoraria, research support, and has served on advisory boards for AstraZeneca, Merck & Co, Pfizer, Sanofi-Aventis, Servier, Roche, Bristol-Myers Squibb, and Diadexus Inc. DJS has received research funding from Bristol-Myers Squibb and funding for consultancy work from Pfizer and AstraZeneca. RGCW has received support from Bristol-Myers Squibb as an investigator during the PROSPER trial. JS has worked as a consultant to AstraZeneca and a speaker for AstraZeneca and Pfizer. RM and RMM have received honoraria for lectures and institutional research grants from Bristol-Myers Squibb and AstraZeneca. APM has received research support and honoraria for lectures from AstraZeneca. ET has received honoraria for lectures and contributions for research from AstraZeneca, Pfizer, and Sanofi-Aventis. JK has served as chairman for the steering committees of the 4S and CoroNa trial, receiving honoraria for lectures and consultation from Merck & Co and AstraZeneca. TRP has received research grants from Pfizer and Merck & Co, and consulting and speaker honoraria from Pfizer, AstraZeneca, and Merck & Co-Schering Plough. TJC is a former employee and present contract employee of Merck & Co, and a shareholder in Merck & Co and Pfizer. AMG is a consultant for AstraZeneca, KOWZ Pharmaceuticals, Merck & Co, and Roche, is on advisory boards for DuPont and Novartis, and serves on corporate boards for Aegerion Pharmaceuticals, Ariad Pharmaceuticals, and Vatera Capital. MBC has been a consultant and speaker for AstraZeneca, and a consultant for Merck & Co and GlaxoSmith Kline. YO has received consulting and lecture fees from Daiichi-Sankyo Company. KM has received honoraria from Daiichi Sankyo, Banyu Pharmaceuticals, Pfizer, Novartis, Astellas Pharma, Shionogi & Co, Kyowa Hakko Kirin Co, Bayer Healthcare, and Mitsubishi Tanabe Pharma. KKR has received honoraria for attending advisory boards and for giving lectures, and has received unrestricted education and research grants from Pfizer, AstraZeneca, Merck & Co, Bristol-Myers Squibb, and Schering Plough. IF has previously received research funding and honoraria for presentations from Bristol-Myers Squibb in relation to the WOSCOPS trial, and research funding and honoraria for presentations from Bristol-Myers Squibb and the Sankyo Company for the Prosper trial. JRD is a USA government employee and the views expressed here are not those of the Veteran Affairs or Federal Government. RGW receives support from the Netherlands Genomics Initiative/Netherlands Organisation for Scientific Research (NGI/NWO 911-03-016). GT was co-chairman (with LT) on the GISSI-HF trial, which was in part funded by an institutional grant from AstraZeneca. RN has received honoraria from Dai-ichi Sankyo, Merk Bangu, and Pfizer, Japan. SRKS is supported by the Gates Cambridge Trust and the ORS Awards scheme at the University of Cambridge. DP, HMM, PW, BMB, A/JMdeC, DJF, BRD, SLP, and JRD declare that they have no conflicts of interest.
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