# "Latest Update on Statins for Diabetes".

## Module 3

# Clinical Guidelines for Statin Therapy in Newly Diagnosed Diabetes

# CONTENT

# Introduction

Atherosclerotic cardiovascular disease is a leading cause of death worldwide, and LDL cholesterol is a major causal risk factor.1 Diabetes substantially increases the risk of atherosclerotic cardiovascular disease.2 Randomised controlled trials have shown that prolonged reduction of LDL cholesterol concentrations with a 3-hydroxy-3-methylglutaryl-coenzyme A (HMG Co-A) reductase inhibitor (ie, a statin) reduces the incidence of myocardial infarction and ischaemic stroke by about a quarter for every 1 mmol/L reduction in LDL cholesterol,3 with consistent effects in individuals with and without diabetes.4 Statins have few confirmed adverse effects,5 but metaanalyses of summary data in published reports from large randomised controlled trials of statin therapy indicated that standard statin regimens increased the risk of newonset diabetes by about 10% compared with placebo or usual care6 and that more intensive statin regimens produced a further 10% relative increase in risk.7 However, due to the limited information available for these metaanalyses of summary data, assessment of the effects of statin therapy on the risk of developing new diabetes is incomplete. In particular, little is known about which types of people are at particularly high risk of developing diabetes due to a statin, the timing of any excess risk after commencing therapy, or the effects of statin therapy on glycaemic control in people with known diabetes. To provide insights into these and related questions, we sought individual participant data on all recorded diabetes-related adverse events, treatments for diabetes, and measures of glycaemia recorded within the large, long-term, double-blind, randomised controlled trials of statin therapy that participate in the Cholesterol Treatment Trialists' (CTT) Collaboration.

# Methods

Search strategy and selection criteria Methods were described prospectively in the published CTT Collaboration protocol.8 Briefly, we conducted a meta-analysis of individual participant data from randomised controlled trials of statin therapy participating in the CTT Collaboration. Double-blind, randomised controlled trials of statin therapy were eligible for inclusion if there were no protocol-mandated differences between treatment groups other than those created by allocation to receive statin versus placebo or allocation to receive more intensive statin therapy versus less intensive statin therapy; they involved at least 1000 participants; and there was a mean scheduled follow-up of at least 2 years. We requested individual participant data related to all adverse events recorded during the scheduled period of treatment and follow-up. These data included the timing of such events, use of other medications (including glucose-lowering medications), physical measurements, any comorbidities, and laboratory results (including glucose and HbA1c values; appendix p 2). Data analysis We converted data into a common domain-based format on the basis of the Clinical Data Interchange Standards Consortium Study Data Tabulation Model,9,10 and all adverse event terms were mapped to the Medical Dictionary for Regulatory Activities, version 20.0 (appendix pp 3–6).10 Diabetes-related adverse events were diabetes diagnosis, diabetes-specific complications related to ketosis and glucose control, and any other diabetes-specific complications (appendix pp 3–6). Glucose-lowering drugs were identified by use of a drug dictionary based on Martindale (appendix p 7).11 Glucose concentrations were categorised according to fasting status and assumed to be non-fasting when fasting status was unknown. HbA1c values were recorded as percentages rather than mmol/mol because most of the trials were conducted before the introduction of the International Federation of Clinical Chemistry and Laboratory Medicine standard units for HbA1c. 12 Baseline diabetes was defined as a recorded history of diabetes, adverse event of diabetes (appendix pp 3–6) on or before the date of participant assignment to a treatment group, use of glucose-lowering medication (appendix p 7), fasting plasma glucose concentration of 7·0 mmol/L or higher or random plasma glucose of 11·1 mmol/L or higher, or HbA1c value of 6·5% or higher. For participants without baseline diabetes, the outcome of new-onset diabetes was defined as the first record after participant assignment to a treatment group of an adverse event of diabetes, use of glucoselowering medication, at least two measurements (not necessarily consecutive) of fasting plasma glucose concentration 7·0 mmol/L or higher or random plasma glucose concentration of 11·1 mmol/L or higher, or at least one HbA1c value of 6·5% or higher (based on widely used biochemical thresholds).13,14 For participants with baseline diabetes, the outcome of worsening glycaemia was defined as a recording after participant assignment to a treatment group of an adverse event relating to ketosis or complications of glucose control, an HbA1c increase (from baseline) of 0·5% or higher, or escalation of glucose-lowering medication (ie, starting such medication for participants not on medication at baseline, starting insulin for those not on insulin therapy at baseline, or an increase in the number of non-insulin glucose-lowering medications, with or without insulin). Variables for which data were extracted were specified previously.8 We calculated the log-rank observed-minus-expected statistic (o – e) and its variance (v) for the first occurrence of each outcome among participants assigned to a treatment group in each trial.15

The inverse-varianceweighted average of log of the rate ratio (log RR) across all trials was then calculated as S/V (with variance 1/V, and hence with 95% CI of S/V± 1·96/√V), where S is the sum of (o − e) over all trials and V is the sum of v over all trials. This approach gives nearly identical estimates to the hazard ratio from a trial-stratified Cox regression model. Prespecified subgroup analyses included analyses according to particular baseline participant characteristics, by year of treatment, and for different statin regimens or intensities. Standard $\chi^2$ tests for heterogeneity (or trend) in the log RR were conducted to assess whether the effect in any given subgroup differed materially from the overall effect seen in all participants.15 Exploratory analyses examined the effects of weighting each trial by the trial-specific absolute LDL cholesterol concentration difference at 1 year (as previously described).3 Overall RRs are reported with 95% CIs, but all other RRs (eg, in subgroup analyses) are reported with 99% CIs to provide some allowance for multiple comparisons. The effects of allocation to statin therapy on mean glucose concentrations and HbA1c values after assignment to a treatment group were calculated using inverse-variance-weighted metaanalyses. In addition to the prespecified subgroup analyses, additional post-hoc analyses were done to further explore variation according to baseline levels of glycaemia by dividing participants into quartiles defined hierarchically on the basis of HbA1c, fasting glucose concentration (if HbA1c value was not available), or random glucose concentration (if neither HbA1c value or fasting glucose concentration were available). A further post-hoc analysis explored the effect of statin therapy on mean difference in weight subdivided by statin intensity and presence of baseline diabetes. Results are reported separately for low-intensity or moderate-intensity and high-intensity statin regimens (according to the American Heart Association– American College of Cardiology guideline definition;16 appendix p 8). Only two trials17,18 allowed for direct assessments of high-intensity statin versus placebo, but indirect assessments of the effects of high-intensity statin therapy were calculated as described previously.19 To estimate the average absolute effect of statin therapy on the underlying rate of particular outcomes, we applied the RR (or its lower and upper 95% CIs) to the absolute rate in the appropriate comparator group. We used the summary RRs for all statin regimens in 16 trials17,18,20–33 of statin versus placebo to estimate the absolute excess annual rate of new-onset diabetes according to quartiles of baseline glycaemia and a risk score of new-onset diabetes, developed using a Poisson regression model (with the logarithm of follow-up time set as an offset variable) that incorporated univariate predictors of new-onset diabetes (namely baseline age, sex, BMI, triglycerides, estimated glomerular filtration rate [eGFR], HDL cholesterol concentration, and glycaemia; appendix p 28). All analyses were based on the intention-to-treat principle. Analyses were done using SAS (version 9.4) and R (version 4.1.3). In all trials, participants gave informed consent. Ethics approval for this meta-analysis was subsequently granted by the UK National Health Service Health Research Authority (21/SC/0071). Role of the funding source The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

# Results

Of the trials in the CTT Collaboration, individual participant data were available from 19 eligible doubleblind trials17,18,20–36 of any statin regimen versus placebo (123 940 participants; median follow-up of 4·3 years), of which 16 trials17,18,20–33 (117 437 participants) included participants with and without a history of diabetes, and three trials34–36 (6503 participants) recruited only participants with a history of diabetes (table). One trial20 (6605 participants) compared a low-intensity statin regimen with placebo, 16 trials21–36 (95 890 participants) compared a moderate-intensity statin with placebo, and two trials17,18 (21 445 participants) compared a highintensity statin regimen with placebo. Among all 19 trials, 22 925 (18%) of 123940 participants had a known history of diabetes at randomisation, and an additional 2776 (2%) participants met our definition of baseline diabetes (appendix p 9). Individual participant data were also available from four double-blind trials37–40 of more versus less intensive statin regimens (30 724 participants; median follow-up of 4·9 years; table). In these four trials, two trials39,40 (14 163 participants; median follow-up of 4·1 years) compared high-intensity versus moderate-intensity statin regimens, and two trials37,38 (16 561 participants; median follow-up of 5·6 years) compared two moderate-intensity statin regimens. Among all four trials of more versus less intensive statin, 4589 (15%) of 30 724 participants had a known history of diabetes at baseline, and an additional 751 (2%) met our definition of baseline diabetes (appendix p 9). In the 14 trials20–33 of low-intensity or moderate-intensity statin versus placebo that included participants without diabetes at baseline, allocation to statin therapy resulted in a 10% relative increase in new-onset diabetes (2420 of 39 179 participants assigned to statin therapy [1·3% per year] vs 2214 of 39266 participants assigned to placebo [1·2% per year]; RR 1·10, 95% CI 1·04–1·16), which corresponded to a mean absolute excess of 0·12% (95% CI 0·04–0·20) during each year of treatment (figure 1). The RRs were similar irrespective of the mode of diagnosis (figure 1; appendix pp 12–15). The placebo event rate for new-onset diabetes was substantially higher in the two trials of high-intensity statin (905 of 9859 participants assigned to placebo [3·5% per year]) than in the 14 trials of low-intensity or moderate-intensity statins (1·2% per year), and this difference was driven by biochemical diagnosis of diabetes (788 of 9859 participants assigned to placebo [3·0% per year] for high-intensity statins vs 1369 of 39266 participants assigned to placebo [0·8% per year] for low-intensity or moderate-intensity statins; figure 1). Notably, in the high-intensity statin trials, HbA1c was measured at least once after assignment to a treatment group in 14345 (72%) of 19 794 participants without diabetes at baseline (all of which were in the JUPITER trial17) and glucose concentration was measured at least twice after assignment to a treatment group in 9785 (49%) of 19 794 participants without diabetes at baseline, making a biochemical diagnosis possible. By comparison, HbA1c values after assignment to a treatment group were available for just 2434 (3%) of 78 445 participants and glucose concentrations after assignment to a treatment group were available for 29008 (37%) of 78 445 participants in the low-intensity or moderate-intensity trials. In the two trials17,18 of highintensity statin versus placebo that included participants without baseline diabetes, allocation to statin therapy resulted in a 36% relative increase in new-onset diabetes (1221 of 9935 participants assigned to statin therapy [4·8% per year] vs 905 of 9859 participants assigned to placebo [3·5% per year]; RR 1·36, 95% CI 1·25–1·48; figure 1), representing an absolute annual excess of 1·27% (95% CI 0·88–1·69).

Although the absolute excess risk of new-onset diabetes varied depending on the method of diagnosis, the RRs were broadly similar (appendix p 16). Further information on the risks of new-onset diabetes for statin regimens of differing intensity was available from four trials of more versus less intensive statin therapy.37–40 Compared with less intensive statin therapy, more intensive statin therapy resulted in a 10% proportional increase in new-onset diabetes (RR 1·10, 95% CI 1·02–1·18), corresponding to an absolute annual excess of 0·22% (95% CI 0·05–0·41; appendix pp 17–18). The RR for high-intensity statin derived indirectly by combining selected trials of more versus less intensive statin and lowintensity or moderate-intensity statin versus placebo was 1·27 (95% CI 1·11–1·44; data not shown), which was similar to the estimate obtained in the direct comparison of high-intensity statin versus placebo (1·36, 1·25–1·48; figure 1). Overall, at a given level of statin intensity, the relative effects on new-onset diabetes did not vary much in different types of participants (eg, by age, sex, race or ethnicity, history of vascular disease, BMI, eGFR, quartiles of glycaemia, diabetes risk score, and lipid characteristics; appendix pp 19–24), between statins (appendix p 15), or over time (appendix pp 25–26). In particular, the RRs for new-onset diabetes were similar among quartiles of baseline glycaemia and quartiles of baseline-defined risk of new-onset diabetes (appendix pp 19, 21). They were also similar when RRs were weighted for absolute differences in LDL cholesterol at 1 year between trials (low-intensity or moderate-intensity statin versus placebo, RR 1·09, 95% CI 1·03–1·15; highintensity statin versus placebo, 1·31, 1·21–1·41). In the trials of statin versus placebo, glucose concentrations were recorded systematically at baseline and follow-up among all people without diabetes in seven trials and HbA1c values were recorded in this way in two trials (appendix p 2). The mean increase in glucose concentration during the treatment period compared with participants assigned to receive placebo was 0·04 mmol/L for both low-intensity or moderateintensity (95% CI 0·03–0·05) and high-intensity statin therapy (0·02–0·06), and the corresponding increases in HbA1c values were 0·06% (0·00–0·12) for lowintensity or moderate-intensity and 0·08% (0·07–0·09) for high-intensity statin therapy (appendix p 10). The annual rate of development of new-onset diabetes in the placebo group was substantially greater in higher versus lower quartiles of baseline glycaemia. Consequently, the majority (ie, approximately 62%) of excess cases of new-onset diabetes occurred among participants in the highest quarter of the baseline glycaemia distribution for both low-intensity or moderateintensity and high-intensity statin therapy (figure 2). The proportion of excess cases in the top quarter increased only slightly to approximately 67% when baseline age, sex, BMI, triglycerides, eGFR, and HDL cholesterol were added to glycaemia in a diabetes risk score (figure 2). Among people with diabetes at baseline, allocation to low-intensity or moderate-intensity statin resulted in a 10% relative increase in worsening glycaemia compared with placebo (6224 of 12109 participants assigned to statin therapy [16·3% per year] vs 5902 of 11941 participants assigned to placebo [15·4% per year]; RR 1·10 [95% CI 1·06 to 1·14]; absolute annual excess 1·49% [0·87 to 2·13]), and in the high-intensity trials, allocation to this group resulted in a 24% relative increase in worsening glycaemia (338 of 805 participants assigned to statin therapy [16·0% per year] vs 295 of 846 participants assigned to placebo [12·8% per year]; 1·24 [1·06 to 1·44]; absolute annual excess 3·02% [0·73 to 5·69]; figure 3). In the trials of low-intensity or moderate-intensity statin versus placebo and the trials of more versus less intensive statin versus placebo, the relative effects on worsening glycaemia were larger in the earlier than later years of follow-up (appendix pp 26–27).

The mean increase in glucose concentration during the treatment period compared with participants assigned to receive placebo was 0·12 mmol/L (95% CI 0·04 to 0·21) for low-intensity or moderate-intensity statin therapy and 0·22 mmol/L (–0·02 to 0·45) for high-intensity statin therapy, and the corresponding increases in HbA1c were 0·09% (0·05 to 0·14) for low-intensity or moderate intensity statin therapy and 0·24% (0·09 to 0·38) for high intensity statin therapy (appendix p 10). 12 placebo-controlled trials recorded at least one measure of bodyweight in participants without diabetes after assignment to a treatment group. In these participants, the mean baseline weight was 78·14 kg (SD 14·67), and allocation to statin therapy resulted in an increase of 0·16 kg (95% CI 0·08 to 0·24) at 1 year and 0·30 kg (0·22 to 0·37) at the final measurement (appendix p 11) compared with placebo. 11 placebocontrolled trials recorded at least one measure of bodyweight in participants with diabetes after assignment to a treatment group. In these participants, the mean baseline weight was 81·27 kg (SD 14·61), and allocation to statin therapy resulted in an increase of 0·02 kg (–0·10 to 0·14) at 1 year and 0·04 kg (–0·15 to 0·23) at the final measurement compared with placebo.

# Discussion

This meta-analysis advances our understanding of the adverse effects of statin therapy on diabetes. The results show that statin therapy causes a moderate dosedependent increase in new diagnoses of diabetes, that most of the excess of new-onset diabetes occurs among individuals who are already at high risk of diabetes (ie, their plasma markers of glycaemia are close to the diagnostic threshold for diabetes), and that new-onset diabetes in these individuals is likely to be explained by small statin-induced increases in markers of glycaemia (ie, plasma glucose and HbA1c). The relative effects on worsening glycaemic control in people with known diabetes largely mirrored those for new-onset diabetes. The JUPITER trial was the first large randomised trial of statin therapy to report a significant increase in the risk of incident diabetes (270 participants assigned to receive 20 mg rosuvastatin vs 216 participants assigned to receive placebo; p=0·01; corresponding to a 25% proportional increase in physician-diagnosed diabetes for participants in the rosuvastatin group).17 More recently, the REPRIEVE trial reported a higher rate of incident diabetes in participants assigned to receive 4 mg pitavastatin daily compared with placebo (RR 1·35, 95% CI 1·09–1·66).41 Atorvastatin has also been reported to induce a small increase in blood glycaemia within a few months of starting treatment, both in people without diabetes42 and in those with diabetes.43 Small population-wide shifts in blood glycaemia (of the magnitude seen in our analyses) can have a large relative effect on the proportion of a population exceeding a diagnostic threshold level near the tail of the distribution (figure 4), as evidenced by other drugs that produce small changes in glycaemia but result in moderately large relative changes in the risk of diabetes. For example, in the Diabetes Prevention Program trial, allocation to metformin reduced HbA1c by approximately 0·1% and also reduced the risk of diabetes by 31% compared with placebo,45 and in the dal-OUTCOMES trial, which studied dalcetrapib, a reduction in HbA1c of a similar size resulted in approximately 23% reduction in risk compared with placebo.46 Overall, there was little availability of data from postrandomisation glycaemic measures among people without known diabetes (appendix p 2). This scarcity was particularly true for HbA1c, which was recorded systematically at baseline and at least once during followup among all people without diabetes in only two trials of statin versus placebo (GISSI-HF trial of low-intensity or moderate-intensity statin therapy31 [mean baseline HbA1c 5·5%]; JUPITER trial of high-intensity statin therapy17 [mean baseline HbA1c 5·7%]; appendix p 9). The paucity of HbA1c data is not surprising because HbA1c did not become a widely recognised diabetes diagnostic marker until 2011,14 which was after the inception of all trials included in our analyses. Additionally, it was not always possible to reliably ascertain whether glucose concentration was measured in a fasting or non-fasting state. Given these caveats, to allow for systematic differences in data capture between trials and ensure that the absolute excess rates of new-onset diabetes between trials were comparable, we analysed the excess rates excluding diagnoses made with biochemical measures of glycaemia alone. When this exclusion was made, the RRs overall for low-intensity or moderate-intensity and high-intensity statin therapy were similar to when such biochemical measures were included (figure 1). In the high-intensity statin trials, the event rate for the development of new-onset diabetes was substantially higher in both the intervention and placebo groups than that seen in the low-intensity or moderate-intensity statin trials.

This higher rate was driven by a greater proportion of trial participants in the high-intensity statin trials, particularly in the JUPITER trial, having at least one follow-up HbA1c measurement. Biochemically determined diabetes rates were 3·0% per annum for high-intensity trials and 0·8% for low-intensity or moderate-intensity therapy trials in the placebo groups, whereas rates of diabetes determined by reports of diabetes-related adverse events and use of glucoselowering medication in the placebo groups for the same groups of trials were similar (figure 1). This finding indicates that, although the relative excesses of new-onset diabetes observed for low-intensity or moderate-intensity statin versus placebo and high-intensity statin versus placebo are likely to be robust and generalisable, the differences in absolute excesses of diagnoses of diabetes between these two groups of trials were determined predominantly by the proportion of trial participants for whom a biochemical diagnosis was made solely through an HbA1c measurement after randomisation. In practice, such measurements might not be obtained routinely in people without diabetes, but it is likely that the rate of diagnosis of diabetes would be higher than it currently is if such a practice was widely adopted. The RRs for new-onset diabetes did not vary significantly over time. We hypothesise that the reason for this finding is that, in each successive year of follow-up, a new group of people becomes at risk of exceeding the diagnostic threshold for diabetes because of an agerelated increase in glycaemia, and those taking a statin will be slightly more likely to do so. For high-intensity statin therapy, the absolute rates were observed to be greater for JUPITER compared with SPARCL, particularly when biochemical measurements of glycaemia were included as a diagnostic criterion (appendix p 16). By contrast, among people with a known diagnosis of diabetes at baseline, the early excess of worsening glycaemia with a statin did not persist in the long term (appendix pp 26–27), perhaps because glycaemic control is typically monitored in such individuals and likely to be managed. Previous scientific literature has suggested that the increased risk of diabetes caused by statin therapy might be partly due to an increase in bodyweight, which in turn increases diabetes risk.47 Data from several trials and meta-analyses have provided an indication of the probable association between bodyweight and diabetes. In the DPP trial, among 3234 individuals without diabetes, lifestyle intervention reduced bodyweight by 5·6 kg and was associated with a 58% (95% CI 48 to 66) reduction in the incidence of type 2 diabetes.45 Evidence also exists from meta-analyses of randomised controlled trials of lifestyle interventions for diabetes prevention: in one analysis, compared with usual treatment, a mean bodyweight reduction of 2·45 kg (95% CI −3·56 to −1·33) was associated with a 37% (0·51 to 0·79) reduction in progression to type 2 diabetes at 3 years.48 The observed increase in bodyweight due to statin therapy in participants without diabetes in our analyses (ie, 0·30 kg at final measurement; appendix p 11) was much smaller than in these studies. It therefore seems implausible that such a small change in bodyweight would explain more than a small proportion of the observed increase in diagnoses of diabetes due to statin therapy. A comparison of the cardiovascular benefits and risks of diabetes from statin therapy based on the results of the JUPITER trial49 previously concluded that the cardiovascular benefits of rosuvastatin greatly outweighed the risks of new-onset diabetes, despite this trial being conducted in a primary prevention setting among apparently healthy people (without hyperlipidaemia but with increased concentration of CRP on a high-sensitivity CRP test). Notably, vascular benefits of statin therapy represent the net effect of the aggregate effects of statins on blood lipids and glycaemia, such that any theoretical adverse effects of statins on cardiovascular risk that might arise from small increases in glycaemia (or, indeed, from any other mechanism) are already accounted for in the overall reduction in cardiovascular risk that is seen with statin therapy in these trials. Furthermore, the risk of future new major vascular events is significantly greater following major vascular events than following a diagnosis of diabetes.50,51

It was not possible to assess clinically significant microvascular complications of diabetes in our analyses both because of the absence of longer-term adverse event data (since development of such complications typically requires many years of exposure to poor glycaemic control) and the absence of any consistent detailed diagnostic information (eg, retinal photographs and measures of microalbuminuria or proteinuria). However, in a meta-analysis of randomised controlled trials comparing less intensive with more intensive glucose control, there was a 20% relative increase in risk high-intensity trials and 0·8% for low-intensity or moderate-intensity therapy trials in the placebo groups, whereas rates of diabetes determined by reports of diabetes-related adverse events and use of glucoselowering medication in the placebo groups for the same groups of trials were similar (figure 1). This finding indicates that, although the relative excesses of new-onset diabetes observed for low-intensity or moderate-intensity statin versus placebo and high-intensity statin versus placebo are likely to be robust and generalisable, the differences in absolute excesses of diagnoses of diabetes between these two groups of trials were determined predominantly by the proportion of trial participants for whom a biochemical diagnosis was made solely through an HbA1c measurement after randomisation. In practice, such measurements might not be obtained routinely in people without diabetes, but it is likely that the rate of diagnosis of diabetes would be higher than it currently is if such a practice was widely adopted. The RRs for new-onset diabetes did not vary significantly over time. We hypothesise that the reason for this finding is that, in each successive year of follow-up, a new group of people becomes at risk of exceeding the diagnostic threshold for diabetes because of an agerelated increase in glycaemia, and those taking a statin will be slightly more likely to do so. For high-intensity statin therapy, the absolute rates were observed to be greater for JUPITER compared with SPARCL, particularly when biochemical measurements of glycaemia were included as a diagnostic criterion (appendix p 16). By contrast, among people with a known diagnosis of diabetes at baseline, the early excess of worsening glycaemia with a statin did not persist in the long term (appendix pp 26–27), perhaps because glycaemic control is typically monitored in such individuals and likely to be managed. Previous scientific literature has suggested that the increased risk of diabetes caused by statin therapy might be partly due to an increase in bodyweight, which in turn increases diabetes risk.47 Data from several trials and meta-analyses have provided an indication of the probable association between bodyweight and diabetes. In the DPP trial, among 3234 individuals without diabetes, lifestyle intervention reduced bodyweight by 5·6 kg and was associated with a 58% (95% CI 48 to 66) reduction in the incidence of type 2 diabetes.45 Evidence also exists from meta-analyses of randomised controlled trials of lifestyle interventions for diabetes prevention: in one analysis, compared with usual treatment, a mean bodyweight reduction of 2·45 kg (95% CI −3·56 to −1·33) was associated with a 37% (0·51 to 0·79) reduction in progression to type 2 diabetes at 3 years.48 The observed increase in bodyweight due to statin therapy in participants without diabetes in our analyses (ie, 0·30 kg at final measurement; appendix p 11) was much smaller than in these studies. It therefore seems implausible that such a small change in bodyweight would explain more than a small proportion of the observed increase in diagnoses of diabetes due to statin therapy. A comparison of the cardiovascular benefits and risks of diabetes from statin therapy based on the results of the JUPITER trial49 previously concluded that the cardiovascular benefits of rosuvastatin greatly outweighed the risks of new-onset diabetes, despite this trial being conducted in a primary prevention setting among apparently healthy people (without hyperlipidaemia but with increased concentration of CRP on a high-sensitivity CRP test). Notably, vascular benefits of statin therapy represent the net effect of the aggregate effects of statins on blood lipids and glycaemia, such that any theoretical adverse effects of statins on cardiovascular risk that might arise from small increases in glycaemia (or, indeed, from any other mechanism) are already accounted for in the overall reduction in cardiovascular risk that is seen with statin therapy in these trials.

Furthermore, the risk of future new major vascular events is significantly greater following major vascular events than following a diagnosis of diabetes.50,51 It was not possible to assess clinically significant microvascular complications of diabetes in our analyses both because of the absence of longer-term adverse event data (since development of such complications typically requires many years of exposure to poor glycaemic control) and the absence of any consistent detailed diagnostic information (eg, retinal photographs and measures of microalbuminuria or proteinuria). However, in a meta-analysis of randomised controlled trials comparing less intensive with more intensive glucose control, there was a 20% relative increase in risk of clinically significant renal complications (absolute excess risk 0·4% per year) and a 13% relative increase in risk of clinically significant retinal complications (absolute excess risk 0·2% per year) due to exposure to 0·9% higher HbA1c over 5 years in major diabetes trials,52 so the changes induced by a statin are likely to be too small to result in a material change in the risk of microvascular disease in people with diabetes. Our findings have several implications for clinical practice. First, our findings make clear that the majority of new diagnoses of diabetes resulting from statin therapy will occur among people who are already close to the biochemical diagnostic threshold for diabetes. In our study, approximately 62% of cases of new-onset diabetes attributable to statin therapy occurred among individuals in the top quarter of the glycaemia distribution, and adding other risk factors to glycaemia resulted in only a modest increase (to approximately 67%) in the proportion of cases attributable to statin therapy than for glycaemia alone. Our findings also imply that, since the effect of statin therapy on measures of glycaemia within an individual is small (ie, considerably smaller than the combined variation of within-individual53 and laboratory analytical variation54), there is likely to be little clinical benefit in measuring glucose concentrations and HbA1c values routinely after starting statin therapy with the aim of making comparisons to values taken before the initiation of a statin. However, people should continue to be screened for diabetes and associated risk factors and have their glycaemic control monitored in accordance with current clinical guidelines. Although our study emphasises the effects of various statin regimens on the risk of a new diagnosis of diabetes, it does have some limitations. The most important of these limitations is that most of the included trials were not principally designed to test a hypothesis of the effects of statin therapy on diabetes. As aforementioned, one consequence of this was a paucity of data for measures of glycaemia among those without diabetes. Event rates for cases resulting from measurement of fasting plasma glucose might have been overestimated if participants did not fast, although the absolute differences between active and placebo groups would not be materially biased, and exclusion of cases of biochemically determined diabetes did not substantially affect findings. Moreover, cases of diabetes in our analysis were constructed by use of trial data, and we were unable to assess type of diabetes, but we expect that the vast majority of cases in participants of the age included in the trials would have been type 2 diabetes. Very occasionally, glucose-lowering medication might have been used for an indication other than diabetes, and although we were able to count initiation and escalation of diabetes treatment, we were not able to analyse any changes in doses of these medications. The intention-to-treat analyses of the effects of allocation to statin therapy in this meta-analysis preserve the randomised comparisons within each trial, but might of course result in some underestimation of the full effects of taking statin therapy in the long term.Additionally, some data were unavailable for our analyses: data from 218 (8·5%) of 2555 participants in the AURORA trial,32 27 (0·5%) of 4982 participants in the CORONA trial,30 and 1088 (6·5%) of 16 714 participants in the JUPITER17 trial were not provided because of data privacy concerns. However, it is unlikely that missing data would have affected our main conclusions.

Among people without diabetes, statin therapy produces a dose-dependent increase in the rate of diagnosis of diabetes by inducing a very small increase in glycaemia. People are most at risk of exceeding the diagnostic threshold for diabetes due to statin therapy if their glycaemic control is close to the threshold before treatment. The diabetes-related risks arising from the small changes in glycaemia resulting from statin therapy are greatly outweighed by the benefits of statins on major vascular events when the direct clinical consequences of these outcomes are taken into consideration.

# Figures

| | Year of publication of primary results | Number of participants | Treatment comparison | Median follow up, years | Mean LDL cholesterol concentration, mmol/L (SD) | Mean age, years (SD) | Mean BMI, kg/m² (SD) | Mean estimated GFR, mL/min per 1·73 m² (SD) | Women, n (%) | White participants, n (%) | Participants with a history of vascular disease, n (%) | Participants with diabetes at baseline, n (%)* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Statin *vs* placebo (19 trials) | .. | 123 940 | .. | 4·3 | 3·5 (0·7) | 63 (8) | 27·2 (4·1) | 69·5 (15·0) | 34 533 (28%) | 60 152 (81%)† | 59 610 (48%) | 25 701 (21%) |
| Low-intensity statin (one trial) | .. | 6605 | .. | 5·0 | 3·9 (0·4) | 58 (7) | 26·9 (3·1) | 65·4 (11·6) | 997 (15%) | 5860 (89%) | 0 | 232 (4%) |
| AFCAPS/TexCAPS[28] | 1998 | 6605 | Lovastatin 20–40 mg/day *vs* placebo | 5·0 | 3·9 (0·4) | 58 (7) | 26·9 (3·1) | 65·4 (11·6) | 997 (15%) | 5860 (89%) | 0 | 232 (4%) |
| Moderate-intensity statin (16 trials) | .. | 95 890 | .. | 4·6 | 3·6 (0·8) | 63 (8) | 27·2 (4·2) | 69·5 (15·3) | 25 254 (26%) | 49 877 (80%)† | 54 879 (57%) | 23 818 (25%) |
| 4S[29] | 1994 | 4444 | Simvastatin 20–40 mg/day *vs* placebo | 5·4 | 4·9 (0·7) | 59 (7) | 26·0 (3·3) | NA | 827 (19%) | NA | 4444 (100%) | 202 (5%) |
| WOSCOPS[25] | 1995 | 6595 | Pravastatin 40 mg/day *vs* placebo | 4·8 | 5·0 (0·5) | 55 (6) | 26·0 (3·2) | 77·8 (12·4) | 0 | NA | 1066 (16%) | 143 (2%) |
| CARE[26] | 1996 | 4159 | Pravastatin 40 mg/day *vs* placebo | 4·9 | 3·6 (0·4) | 59 (9) | 27·6 (4·4) | 67·2 (15·7) | 576 (14%) | 3851 (93%) | 4159 (100%) | 667 (16%) |
| LIPID[27] | 1998 | 9014 | Pravastatin 40 mg/day *vs* placebo | 5·9 | 3·9 (0·8) | 61 (8) | 26·8 (3·8) | 70·6 (16·3) | 1516 (17%) | NA | 9014 (100%) | 1077 (12%) |
| LIPS[22] | 2002 | 1677 | Fluvastatin 80 mg/day *vs* placebo | 4·0 | 3·4 (0·8) | 60 (10) | 26·5 (3·3) | 67·6 (15·5) | 271 (16%) | 1650 (98%) | 1677 (100%) | 204 (12%) |
| HPS[24] | 2002 | 20 536 | Simvastatin 40 mg/day *vs* placebo | 5·2 | 3·4 (0·8) | 64 (8) | 27·6 (4·4) | 72·2 (16·5) | 5082 (25%) | 19 901 (97%) | 17 386 (85%) | 5973 (29%) |
| PROSPER[18] | 2002 | 5804 | Pravastatin 40 mg/day *vs* placebo | 3·3 | 3·8 (0·8) | 75 (3) | 26·8 (4·2) | 56·7 (13·6) | 3000 (52%) | NA | 2565 (44%) | 760 (13%) |
| ASCOT-LLA[19] | 2003 | 10 240 | Atorvastatin 10 mg/day *vs* placebo | 3·3 | 3·4 (0·7) | 63 (9) | 28·6 (4·6) | 68·4 (12·9) | 1919 (19%) | 9687 (95%) | 1684 (16%) | 2699 (26%) |
| ALERT[23] | 2003 | 2102 | Fluvastatin 40–80 mg/day *vs* placebo | 5·5 | 4·1 (1·0) | 50 (11) | 25·8 (4·5) | 49·6 (17·0) | 715 (34%) | 2039 (97%) | 409 (19%) | 430 (20%) |
| CARDS[30] | 2004 | 2838 | Atorvastatin 10 mg/day *vs* placebo | 4·2 | 2·9 (0·8) | 61 (8) | 28·8 (3·6) | 64·2 (11·3) | 909 (32%) | 2676 (94%) | 106 (4%) | 2838 (100%) |
| 4D[31] | 2005 | 1255 | Atorvastatin 20 mg/day *vs* placebo | 2·7 | 3·3 (0·8) | 66 (8) | 27·6 (4·8) | NA | 578 (46%) | 924 (74%) | 1041 (83%) | 1255 (100%) |
| ASPEN[34] | 2006 | 2410 | Atorvastatin 10 mg/day *vs* placebo | 4·0 | 2·9 (0·7) | 60 (8) | 28·9 (3·8) | 65·9 (12·8) | 811 (34%) | 2029 (84%) | 747 (31%) | 2410 (100%) |
| CORONA[36] | 2007 | 4982 | Rosuvastatin 10 mg/day *vs* placebo | 2·7 | 3·6 (0·9) | 72 (7) | 26·4 (3·6) | 55·4 (15·1) | 1175 (24%) | NA | 4982 (100%) | 1481 (30%) |
| GISSI-HF[35] | 2008 | 4574 | Rosuvastatin 10 mg/day *vs* placebo | 3·9 | 3·1 (0·9) | 68 (11) | 27·1 (4·5) | 66·3 (20·4) | 1032 (23%) | 4574 (100%) | 4574 (100%) | 1771 (39%) |
| AURORA[37] | 2009 | 2555 | Rosuvastatin 10 mg/day *vs* placebo | 3·9 | 2·6 (0·9) | 64 (9) | 24·8 (3·9) | NA | 969 (38%) | NA | 1025 (40%) | 747 (29%) |
| HOPE-3[33] | 2016 | 12 705 | Rosuvastatin 10 mg/day *vs* placebo | 5·5 | 3·3 (0·9) | 66 (6) | 27·1 (4·7) | 79·6 (16·1) | 5874 (46%) | 2546 (20%) | 0 | 1161 (9%) |
| High-intensity statin (two trials) | .. | 21 445 | .. | 2·6 | 2·9 (0·5) | 65 (9) | 27·6 (4·0) | 70·7 (14·6) | 8282 (39%) | 4415 (93%)† | 4731 (22%) | 1651 (8%) |
| SPARCL[38] | 2006 | 4731 | Atorvastatin 80 mg/day *vs* placebo | 4·9 | 3·5 (0·6) | 63 (11) | 27·9 (5·2) | 65·2 (13·8) | 1908 (40%) | 4415 (93%) | 4731 (100%) | 909 (19%) |
| JUPITER[67] | 2008 | 16 714 | Rosuvastatin 20 mg/day *vs* placebo | 1·9 | 2·7 (0·5) | 65 (8) | 27·5 (3·6) | 72·3 (14·8) | 6374 (38%) | NA | 0 | 742 (4%) |
| More intensive *vs* less intensive statin (double blind; four trials) | .. | 30 724 | .. | 4·9 | 2·5 (0·6) | 62 (9) | 28·4 (5·1) | 72·2 (15·6) | 5965 (19%) | 28 865 (94%) | 30 724 (100%) | 5340 (17%) |

(Table continues on next page)

| | Year of publication of primary results | Number of participants | Treatment comparison | Median follow up, years | Mean LDL cholesterol concentration, mmol/L (SD) | Mean age, years (SD) | Mean BMI, kg/m² (SD) | Mean estimated GFR, mL/min per 1·73 m² (SD) | Women, n (%) | White participants, n (%) | Participants with a history of vascular disease, n (%) | Participants with diabetes at baseline, n (%)* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| (Continued from previous page) | | | | | | | | | | | | |
| Comparison of moderate-intensity regimens (two trials) | .. | 16 561 | .. | 5·6 | 2·4 (0·6) | 63 (9) | 28·0 (4·3) | 74·8 (16·8) | 3152 (19%) | 15 679 (95%) | 16 561 (100%) | 2339 (14%) |
| A to Z[37] | 2004 | 4497 | Simvastatin 40 mg/day then 80 mg/day *vs* placebo then simvastatin 20 mg/day | 2·0 | 2·1 (0·5) | 60 (11) | 27·6 (4·8) | 68·4 (16·0) | 1100 (24%) | 3825 (85%) | 4497 (100%) | 1059 (24%) |
| SEARCH[38] | 2010 | 12 064 | Simvastatin 80 mg/day *vs* 20 mg/day | 7·0 | 2·5 (0·6) | 64 (9) | 28·1 (4·1) | 77·2 (17·1) | 2052 (17%) | 11 854 (98%) | 12 064 (100%) | 1280 (11%) |
| Comparison of high-intensity *vs* moderate-intensity regimens (two trials) | .. | 14 163 | .. | 4·1 | 2·5 (0·6) | 60 (10) | 29·0 (6·0) | 69·1 (14·3) | 2813 (20%) | 13 186 (93%) | 14 163 (100%) | 3001 (21%) |
| PROVE-IT[39] | 2004 | 4162 | Atorvastatin 80 mg/day *vs* pravastatin 40 mg/day | 2·1 | 2·6 (0·7) | 58 (11) | 29·5 (5·7) | 78·8 (18·7) | 911 (22%) | 3776 (91%) | 4162 (100%) | 1034 (25%) |
| TNT[40] | 2005 | 10 001 | Atorvastatin 80 mg/day *vs* 10 mg/day | 5·0 | 2·5 (0·5) | 61 (9) | 28·8 (6·1) | 65·0 (12·4) | 1902 (19%) | 9410 (94%) | 10 001 (100%) | 1967 (20%) |
| All trials | .. | 154 664 | .. | 4·4 | 3·3 (0·7) | 63 (8) | 27·5 (4·3) | 70·1 (15·1) | 40 498 (26%) | 89 017 (85%)† | 90 334 (58%) | 31 041 (20%) |

All trials randomised in a 1:1 allocation. Some participants in the AURORA (*n*=218), CORONA (*n*=27), and JUPITER (*n*=1088) trials withdrew consent for use of their data after the trial, and hence data from these participants is excluded. The ASCOT-LLA trial excludes 65 participants for whom data were not available due to protocol violations, and so are not included in the number of participants or percentages shown. 4D=Die Deutsche Diabetes Dialyse Studie. 4S=Scandinavian Simvastatin Survival Study. AFCAPS/TexCAPS=Air Force/Texas Coronary Atherosclerosis Prevention Study. ALERT=Assessment of Lescol in Renal Transplantation. ASCOT-LLA=Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm. ASPEN=Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-Insulin-Dependent Diabetes Mellitus. A to Z=Aggrastat to Zocor. AURORA=A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events. CARDS=Collaborative Atorvastatin Diabetes Study. CARE=Cholesterol And Recurrent Events. CORONA=Controlled Rosuvastatin Multinational Trial in Heart Failure. GISSI-HF=Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza cardiaca. HOPE-3=Heart Outcomes Prevention Evaluation-3 trial. HPS=Heart Protection Study. JUPITER=Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin. LIPID=Long-term Intervention with Pravastatin in Ischaemic Disease. LIPS=Lescol Intervention Prevention Study. NA=not available. PROSPER=PROspective Study of Pravastatin in the Elderly at Risk. PROVE-IT=Pravastatin or Atorvastatin Evaluation and Infection Therapy. SEARCH=Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine. SPARCL=Stroke Prevention by Aggressive Reduction in Cholesterol Levels. TNT=Treating to New Targets. WOSCOPS=West of Scotland Coronary Prevention Study. *Baseline diabetes is defined as participants with a history of diabetes plus those retrospectively defined as having diabetes at baseline on the basis of adverse events, glucose-lowering medication, or glucose or $HbA_{1c}$ measurements at the time of assignment to a treatment group. †Percentages were calculated after excluding the seven trials where information on race and ethnicity was not provided (the relevant denominators are therefore 73 832 for all trials of statin *vs* placebo, 62 496 for trials of moderate-intensity statin therapy *vs* placebo, 4731 for trials of high-intensity statin therapy *vs* placebo, and 104 556 for all trials).

***Table:*** **Characteristics of the participating trials**

| | Events (% per annum) | | Observed−expected | | Rate ratio (CI) |
|---|---|---|---|---|---|
| | Statin | Placebo | o−e | var(o−e) | |
| **Low-intensity or moderate-intensity statin** | **(n=39 179)** | **(n=39 266)** | | | |
| Diabetes-related adverse events | 1224 (0·7) | 1153 (0·6) | 32·3 | 594·1 | 1·06 (99% CI 0·95–1·17) |
| Diabetes determined from co-medication | 764 (0·4) | 680 (0·4) | 40·2 | 357·0 | 1·12 (99% CI 0·98–1·28) |
| Subtotal: diabetes-related adverse events and co-medication | 1523 (0·8) | 1396 (0·8) | 60·3 | 728·6 | 1·09 (95% CI 1·01–1·17) |
| Biochemically determined diabetes | 1497 (0·8) | 1369 (0·8) | 67·7 | 715·8 | 1·10 (99% CI 1·00–1·21) |
| Any new-onset diabetes | 2420 (1·3) | 2214 (1·2) | 106·8 | 1156·8 | 1·10 (95% CI 1·04–1·16) |
| **High-intensity statin** | **(n=9935)** | **(n=9859)** | | | |
| Diabetes-related adverse events | 246 (0·9) | 174 (0·7) | 37·0 | 105·0 | 1·42 (99% CI 1·11–1·83) |
| Diabetes determined from co-medication | 198 (0·8) | 159 (0·6) | 20·1 | 89·2 | 1·25 (99% CI 0·95–1·64) |
| Subtotal: diabetes-related adverse events and co-medication | 297 (1·1) | 229 (0·9) | 35·1 | 131·5 | 1·31 (95% CI 1·10–1·55) |
| Biochemically determined diabetes | 1078 (4·1) | 788 (3·0) | 149·3 | 465·7 | 1·38 (99% CI 1·22–1·55) |
| Any new-onset diabetes | 1221 (4·8) | 905 (3·5) | 163·9 | 530·8 | 1·36 (95% CI 1·25–1·48) |

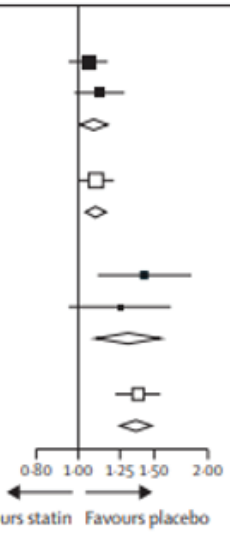


***Figure 1:*** **Effect of statin *vs* placebo on new-onset diabetes by statin intensity**
Test for heterogeneity between low-intensity or moderate-intensity and high-intensity regimens for the outcome of any new-onset diabetes (p<0·0001). Var(o−e) represents the variance of the log-rank observed-minus-expected statistic.

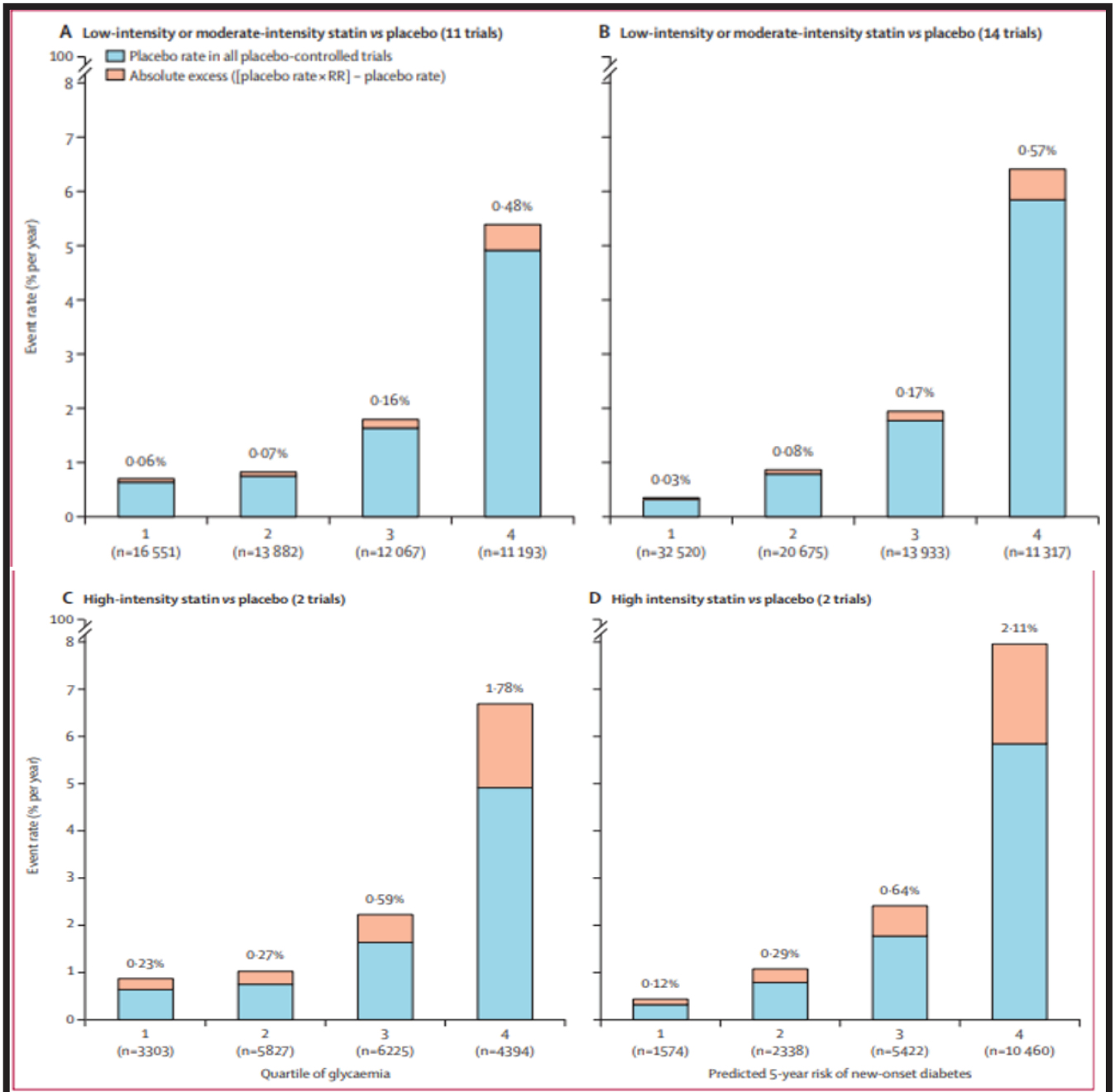


***Figure 2:*** **Absolute excess rates of new-onset diabetes in trials of statin versus placebo**
Rates are shown by quartile of glycaemia (A) and quartile of predicted 5-year risk of new-onset diabetes (B) for low-intensity or moderate-intensity statins and by quartile of glycaemia (C) and quartile of predicted 5-year risk of new-onset diabetes (D) for high-intensity statins. The rate ratio for each group at a specific level of intensity is assumed to be constant. Mean $HbA_{1c}$ for group 1 of glycaemia is 4·72%, for group 2 of glycaemia is 5·51%, for group 3 of glycaemia is 5·80%, and for group 4 of glycaemia is 6·17% for low-intensity or moderate-intensity therapy. Mean $HbA_{1c}$ for group 1 of glycaemia is 5·13%, for group 2 is 5·51%, for group 3 is 5·79%, and for group 4 is 6·14% for high-intensity therapy. Details of the risk score for new-onset diabetes are described in the methods and in the appendix (p 28). Individuals were categorised into four equally sized groups of predicted 5-year risk of new-onset diabetes: <2·9% (group 1), 2·9% to <5·7% (group 2), 5·7% to <11·5% (group 3), and ≥11·5% (group 4).

| | Events (% per annum) | | Observed–expected | | Rate ratio (CI) |
|---|---|---|---|---|---|
| | Statin | Placebo | o–e | var(o–e) | |
| **Low-intensity or moderate-intensity statin** | **(n=12109)** | **(n=11941)** | | | |
| Ketosis or glucose control complications | 308 (0·6) | 299 (0·6) | 2·2 | 151·7 | 1·01 (99% CI 0·82–1·25) |
| Worsening $HbA_{1c}$ | 2732 (6·4) | 2484 (5·9) | 181·8 | 1284·2 | 1·15 (99% CI 1·07–1·24) |
| Escalation of diabetes co-medication | 4081 (9·3) | 3924 (9·0) | 100·9 | 1680·4 | 1·06 (99% CI 1·00–1·13) |
| Any worsening glycaemia | 6224 (16·3) | 5902 (15·4) | 252·5 | 2737·5 | 1·10 (95% CI 1·06–1·14) |
| **High-intensity statin** | **(n=805)** | **(n=846)** | | | |
| Ketosis or glucose control complications | 7 (0·3) | 5 (0·2) | 1·1 | 3·0 | 1·42 (99% CI 0·32–6·30) |
| Worsening $HbA_{1c}$ | 108 (3·9) | 78 (2·7) | 20·2 | 45·8 | 1·55 (99% CI 1·06–2·27) |
| Escalation of diabetes co-medication | 254 (11·9) | 231 (10·0) | 20·5 | 120·8 | 1·18 (99% CI 0·94–1·50) |
| Any worsening glycaemia | 338 (16·0) | 295 (12·8) | 33·3 | 157·2 | 1·24 (95% CI 1·06–1·44) |

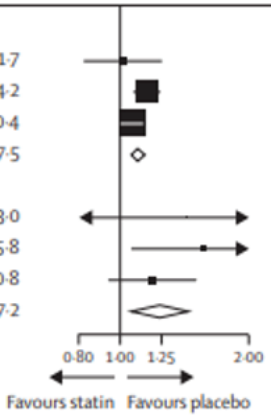


***Figure 3*: Effect of statin vs placebo on worsening glycaemia by statin intensity**
Test for heterogeneity between low-intensity or moderate-intensity and high-intensity regimens for the outcome of any worsening glycaemia (p=0·15). Var(o–e) represents the variance of the log-rank observed-minus-expected statistic.

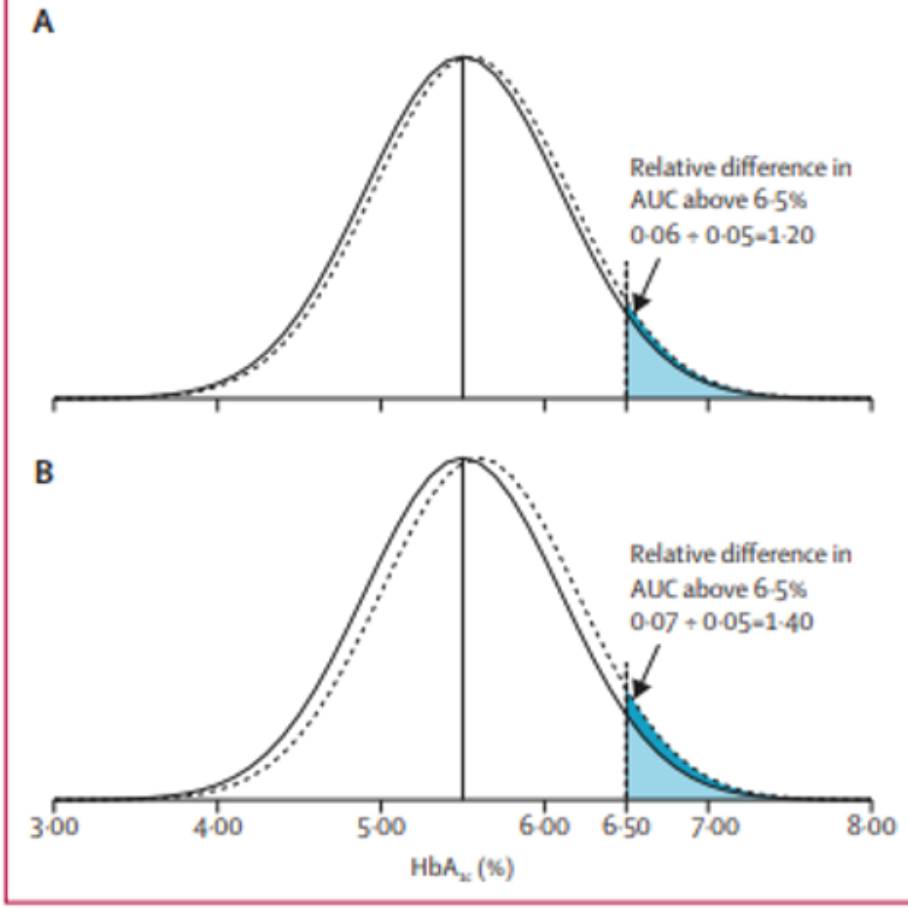


***Figure 4*: Examples of the effects of population-wide upwards shifts in mean $HbA_{1c}$**
Effects of population-wide upwards shifts of 0·05% (A) or 0·10% (B) in mean $HbA_{1c}$ on the proportion above the threshold level of 6·50%. We assumed a normal distribution of $HbA_{1c}$ with a mean of 5·50% (SD 0·60). The SD is taken from the UK Biobank population.[44] AUC=area under the curve.

## Evidence before this study

We searched Medline and the Cochrane Central Register of Controlled Trials for randomised trials and meta-analyses published between Jan 1, 1990, and April 1, 2022, that specifically assessed the effects of statin regimens on new-onset diabetes and worsening glycaemia. For example, to identify meta-analyses in Medline, we used the BMJ systematic review search strategy in combination with ("statin.mp." or "exp HydroxymethylglutarylCoA Reductase Inhibitors/") and ("exp Diabetes Mellitus, Type 1/" or "diabet*.mp" or "exp Diabetes Mellitus/"). Meta-analyses published up until April, 2022, have used summary data from randomised controlled trials to assess the effects of statin therapy on new-onset diabetes. These analyses suggested that statin therapy increases the likelihood of new-onset diabetes being diagnosed, with more intensive statin therapy leading to larger increases. However, they had insufficient detail to investigate these findings in depth, including which individuals were at particular risk, when the effect emerged and its persistence, the effects of different statin regimens, and the effects on glycaemic control in individuals with diabetes.

## Added value of this study

Obtaining individual participant data on all recorded diabetes-related adverse events and treatments, along with serial glycaemia measures, from large, long-term, blinded, randomised controlled trials has allowed the effect of statin therapy on the development of new-onset diabetes and worsening glycaemia to be assessed more comprehensively than has previously been possible with summary level data. Low-intensity or moderate-intensity regimens resulted in a 10% relative increase in new-onset diabetes compared with placebo, and high-intensity statin regimens resulted in a 36% relative increase. These increases persisted when biochemically determined diagnoses of diabetes were excluded. The rate ratios were consistent with a small increase in glycaemia due to statin therapy. These effects were widely generalisable to the different types of participants studied and persisted while treatment continued. The absolute excesses for new-onset diabetes were highest among those individuals in whom measures of glycaemia were already close to the diagnostic threshold for diabetes. Within each trial, the main determinant of the magnitude of the absolute excess was the proportion of trial participants having at least one follow-up HbA1c measurement rather than the proportional increase in risk associated with statin therapy. Any theoretical adverse effects of statins on cardiovascular risk that might arise from these small increases in glycaemia (or, indeed, from any other mechanism) are already accounted for in the overall reduction in cardiovascular risk that is seen with statin therapy in these trials. Our analyses strongly suggest that the absolute benefits of statin therapy greatly outweigh any excess risks of diabetes associated with the small increase in glycaemia they induce.

## Implications of all the available evidence

Statin therapy produces a small increase in glycaemia, which translates into a moderate increase in the rate at which individuals are diagnosed with new-onset diabetes (or worsening glycaemic control among those with diabetes). The mean changes in glycaemia are small, and the evidence of the beneficial effects on major vascular events provides reassurance about the net benefits of using statin therapy in individuals who are at increased risk of developing diabetes or have already developed it.

For the use or a Registered Medical Practitioner or a Hospital or a Laboratory only


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