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META-ANALYSIS

Statins and glycaemic control in individuals with diabetes: a systematic review and meta-analysis

Sebhat Erqou · C. Christine Lee · Amanda I. Adler

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Abstract
Aims/hypotheses Current evidence indicates that statins increase the risk of incident diabetes; however, the relationship between statins and glycaemic control in people with established diabetes has not been well characterised. To address this question, we conducted a meta-analysis of randomised controlled trials (RCTs) of statins in patients with diabetes for whom there was available data on glycaemic control.
Methods We identified studies published between January 1970 and November 2013 by searching electronic databases and reference lists. We included RCTs in which the intervention group received statins and the control group received placebo or standard treatment, with >200 participants enrolled, with the intervention lasting >12 weeks and with pre- and post-intervention HbA_{1c} reported. We combined study-specific estimates using random-effects model meta-analysis.
Results In a pooled analysis of nine trials involving 9,696 participants (4,980 statin, 4,716 control) and an average follow-up of 3.6 years, the mean HbA_{1c} of participants randomised to statins was higher than those randomised to the control group: mean difference (95% CI) was 0.12% (0.04, 0.20) or 1.3 mmol/mol (0.4, 2.2); p=0.003. There was moderate heterogeneity across the studies (I^2=54%, p=0.014) not explained by available study-level characteristics. This review was limited by the small number of studies, available data on only three statins and sparse reporting on changes in use of glucose-lowering medications.
Conclusions/interpretation Statin treatment is associated with a modest increase in HbA_{1c} in patients with diabetes.

Keywords Diabetes mellitus · Glycaemic control · HbA_{1c} · Meta-analysis · Statins · Systematic review

Abbreviations

CARDS	Collaborative Atorvastatin Diabetes Study
DALI	Diabetes Atorvastatin Lipid Intervention
RCT	Randomised controlled trial

Introduction

Statin therapy is the cornerstone of primary and secondary prevention of cardiovascular disease [1]. As diabetes is an important risk factor for cardiovascular disease and is considered a cardiovascular disease risk equivalent, treatment guidelines indicate that most patients with diabetes would benefit from statin therapy [2–4]. Recent clinical guidelines from the American College of Cardiology and the American Heart Association recommended that all patients with diabetes who are 40–75 years of age should be placed on moderate- or high-intensity statin therapy to prevent or delay cardiovascular disease [5].

Despite their important role in the prevention and delay of cardiovascular disease, there is evidence suggesting that

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statins worsen glycaemia and increase the risk of developing type 2 diabetes by approximately 10–12% [6, 7]. The effect of statins on incident diabetes appears to differ by dose and type, with higher doses conferring higher risk than lower doses [8] and with atorvastatin and rosuvastatin being associated with a higher risk than pravastatin [9]. However, the effect of statins on glycaemic control in patients with pre-existing diabetes is less clear. Some studies have reported that statins may adversely affect the glycaemic profile, with a mean increase in HbA_{1c} concentration of 0.3% or less in patients with diabetes [7, 10–13], while other studies have reported no worsening or even a potential benefit of statins on the glycaemic control in patients with diabetes [14–16]. However, most studies were either observational studies or uncontrolled trials, were small in size and had short follow-up periods limiting the available evidence to delineate the effect of statins on glycaemic control in diabetes [10, 17]. This is further complicated by the potentially important differences between different statin types and doses; for instance, a number of studies have suggested that treatment with atorvastatin, but not pitavastatin, may lead to significant deterioration in glycaemic control in patients with diabetes [11, 17, 18]. In this study, we conducted a meta-analysis of randomised controlled trials (RCTs) to assess the effects of statin therapy on glycaemia, as measured by $HbA_{1c,}$ in patients with diabetes.

Methods

Literature search We sought RCTs of statins comprised either entirely, or containing a subgroup, of patients with type 1 or type 2 diabetes with available data on HbA_{1c} concentrations before and after statin therapy. Two authors (S. Erqou, C. C. Lee) systematically and independently searched the electronic databases of MEDLINE and EMBASE for studies published between January 1970 and November 2013, using key terms related to diabetes, statins and glycaemia. We searched MEDLINE using medical subject heading (MeSH) terms and free text keywords related to 'haemoglobin A_{1c}', 'diabetes mellitus' and 'statins'. We also searched EMBASE using 'map term to subject heading' in Advanced Ovid Search, using similar search terms. We supplemented the literature search by scanning the reference lists of relevant articles.

Study selection The database search identified 718 citations from MEDLINE and 434 citations from EMBASE. Two authors (S. Erqou, C. C. Lee) accessed the titles, abstracts and/or full texts, and selected potentially relevant studies based on pre-defined inclusion criteria. We included RCTs in which the intervention group received statins and the control group received placebo or standard treatment, with >200 participants enrolled, with intervention lasting >12 weeks and with pre- and post-intervention HbA_{1c} reported. Glycaemic control need not have been the primary endpoint of the trials. Where a study had duplicate publications [19, 20], we selected the report with the largest number of participants [20]. Nine studies [16, 20–27] met the inclusion criteria and were included in the current report (Fig. 1).

Data extraction Two authors (S. Erqou, C. C. Lee) used standardised forms to extract information from the publications. We extracted data on the type of diabetes, time since diagnosis, type and dose of statins in interventions, duration of follow-up, baseline and follow-up HbA_{1c} concentrations (with their SDs) and, where available, the proportion of participants receiving glucose-lowering medications or insulin at baseline and at follow-up. To help better understand the included studies, we also extracted information on baseline characteristics of the participants, including demographics (e.g. age, sex, ethnicity), medical history (e.g. history of hypertension and cardiovascular disease), clinical variables (e.g. blood pressure, BMI) and laboratory data (e.g. serum LDL-cholesterol, triacylglycerols). We also sought data on differences in use of oral hypoglycaemic agents between patients randomised to statin and control, but the data were too limited for analyses.

Data analysis Of the nine clinical trials included in the present analysis, three [20, 21, 27] reported their results in two subgroups (Table 1); we analysed these separately, giving a total of 12 data points in the meta-analysis. To limit potential

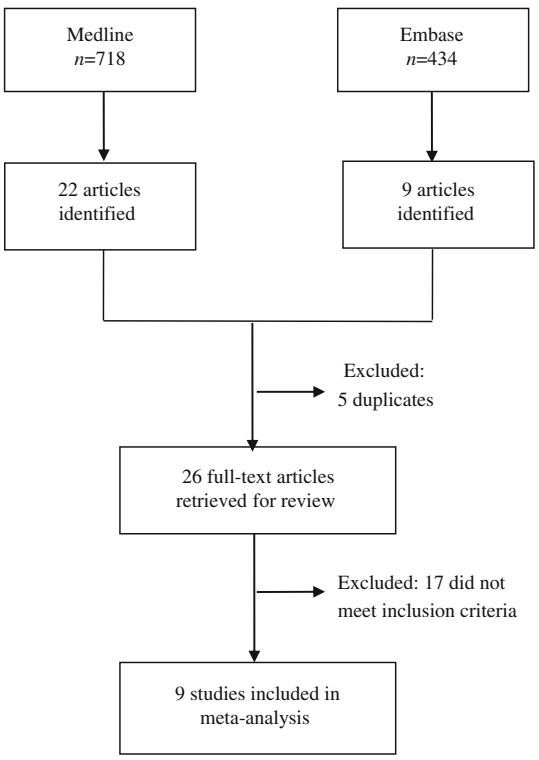

Fig. 1 Study flow diagram

Table 1 Characteristics of the nine clinical trials included in the present analysis

Study author, year	Study location	Study name	Statin:dose (mg)	Statin/Control (*n*)	Sex (% male)	Ethnicity (% white)	Diabetes type	Follow-up (years)	Baseline characteristics						
									Mean age (years)	Mean time since diagnosis (years)	HbA_{1c}, statin/control (%)	Smokers (%)	Mean BMI (kg/m^2)	Mean SBP (mmHg)	Mean LDL-cholesterol (mmol/l)
Neil et al, 2010 [20][a]	UK	AFFORD	Atorva:20	169/166	62	92	2	0.3	63	5	7.0/6.9	28	30.8	148	3.21
Neil et al, 2010 [20][a]	UK	AFFORD	Atorva:20	163/160	55	92	2	0.3	65	4	6.9/7.0	28	30.8	145	3.28
Tajima et al, 2008 [26]	Japan	MEGA	Prava:10–20	853/893	42	0	NR	5	59	NR	6.9/6.9	20	24.2	NR	4.09
Konduracka et al, 2008 [22]	Poland	NA	Atorva:40	154/50	45	100	1	0.5	36	26	7.29/7.51	NR	25.5	125	3.15
Knopp et al, 2006 [24]	Multi	ASPEN	Atorva:10	1,211/1,199	66	84	2	4	61	8	7.6/7.5	12	28.9	133	2.92
Collins et al, 2003 [23]	UK	HPS	Simva:40	544/543	70	NR	1 and 2	4.6	62	11.2	6.99/7.06	13	NR	NR	NR
Colhoun et al, 2004 [25]	UK	CARDS	Atorva:10	1,428/1,410	68	95	2	4	62	7.90	7.87/7.81	22	28.7	144	3.03
Freed et al, 2002 [21][a]	Multi	NA	Atorva:10	77/67	62	72	2	0.3	60	5.8	7.9/7.8	NR	32	NR	3.00
Freed et al, 2002 [21][a]	Multi	NA	Atorva:20	71/67	63	80	2	0.3	60	4.9	7.6/7.8	NR	33	NR	3.18
DALI, 2001 [27][a]	Neth	DALI	Atorva:10	73/72	60	86	2	0.6	60	11.1	8.3/8.3	21	30	146	3.70
DALI, 2001 [27][a]	Neth	DALI	Atorva:80	72/72	53	82	2	0.6	60	12.2	8.4/8.3	17	30	145	3.70
Behounek et al, 1994 [16]	Multi	NA	Prava:10–20	165/156	50	NR	2	0.3	58	NR	7.56/7.6	NR	NR	139.8	4.24

The primary outcomes were cardiovascular disease outcomes for references [21–25], endothelial function for reference [19] and lipid outcomes for references [15, 20, 26]

[a] Freed et al, Neil et al and the DALI study group reported comparisons in two subsets (presented separately herein)

AFFORD, Atorvastatin in Factorial with Omega-3 EE90 Risk Reduction in Diabetes; ASPEN, Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-Insulin-Dependent Diabetes Mellitus; CARDS, Collaborative Atorvastatin Diabetes Study; Atorva, atorvastatin; HPS, Heart Protection Study; MEGA, Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese; Multi, study performed in more than two countries; Neth, the Netherlands; NA, not applicable; NR, not reported; Prava, pravastatin; SBP, systolic blood pressure; Simva, simvastatin

bias arising from between-study differences with regards to statin therapy, mean HbA_{1c} concentrations and measurement methods, we performed all analyses using only within-study comparisons. The quality of the studies was assessed using US Preventive Task Force quality rating criteria for RCTs, the Jadad score [28]. We calculated the mean HbA_{1c} concentration difference at follow-up between patients randomised to statin and those randomised to control. We estimated the variance of the mean HbA_{1c} difference between the statin and control groups by summing the individual variances of mean HbA_{1c} concentration for the statin and treatment groups. The variance of the mean HbA_{1c} concentration was estimated by dividing the variance of the HbA_{1c} concentration by the number of participants in the group; the square root of the variance gave the standard error of the mean HbA_{1c}. We pooled the mean HbA_{1c} difference across the studies (and subgroups) using random-effects model meta-analysis, which makes allowance for between-study heterogeneity [29]. We also pooled the mean HbA_{1c} concentration at follow-up in the statin and control groups separately using similar methods. We reported the main effect of statins (i.e. mean difference in HbA_{1c} concentration) in both traditional units (as percentages) and International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) units (as mmol/mol) [30]. We provided pooled estimates along with their 95% CIs. For comparison, we combined the estimates using fixed-effect model meta-analysis.

We assessed heterogeneity between studies using Q and I^2 statistics. The Q statistic is the χ^2 test for heterogeneity with a degree of freedom equal to one minus the number of studies included in meta-analysis; this assesses whether observed differences in results between studies are due to chance alone [31]. The I^2 statistic estimates the percentage of total variation across studies due to a true difference rather than chance [32]. In general, I^2 values greater than 60–70% indicate the presence of substantial heterogeneity. We explored sources of heterogeneity by comparing the mean differences in HbA_{1c} between subgroups defined by the following study-level characteristics: mean baseline HbA_{1c}, type of statin used, diabetes type, diabetes duration and follow-up duration. We assessed the presence of publication bias by using funnel plot and the Egger test of bias [33]. Statistical tests were two-sided and used a significance level of $p<0.05$. We performed all analyses using Stata 13 (Stata Corp LP, College Station, TX, USA).

Results

Nine clinical trials [16, 20–27] involving 9,696 participants (4,980 statin, 4,716 control) were included in the current analysis. While all the included studies reported glycaemic control as an outcome, their primary endpoints were incident cardiovascular diseases or other outcomes such as LDL-cholesterol concentration or endothelial function. The participants randomised to statin and control groups within each study were generally similar with regards to several baseline characteristics, indicating successful randomisation. Details of the studies analysed are shown in Table 1. The proportion of men in the studies ranged between 42% and 70% (weighted average, 61%). The average age of the participants by study ranged between 36 and 65 years (weighted average, 60 years). Six studies included only patients with type 2 diabetes, one study included patients with type 1 diabetes and another study included both patients with type 1 diabetes and with type 2 diabetes. The average time since diagnosis of diabetes ranged between 4 and 26 years. The participants had been followed for an average of 4 months to 5 years (weighted average, 3.6 years). In studies that reported their assay methods, HPLC was used to measure HbA_{1c}. The Jadad quality assessment of the trials showed that most scored 4 and 5 points (out of 5), while two studies [22, 26] scored 3 points (electronic supplementary materials [ESM] Tables 1, 2). The mean baseline HbA_{1c} across the studies (weighted average) was 7.46% (58 mmol/mol) in the statin group and 7.43% (57.7 mmol/mol) in the control group.

Three of the studies reported their results in two subsets. Freed et al [21] compared the effect of atorvastatin at doses of 10 mg and of 20 mg. Neil et al [20] compared the effect of atorvastatin at a dose of 20 mg in four arms, where one statin and one control group received an additional omega-3 supplement. The Diabetes Atorvastatin Lipid Intervention (DALI) study group [27] compared the effect of atorvastatin at doses of 10 mg and 80 mg. We analysed these subsets separately, giving a total of 12 comparisons. Subsidiary analyses by combining the subsets using fixed-effect model meta-analysis before pooling with the rest of the studies yielded very similar results.

In random-effects model analysis, the pooled HbA_{1c} concentration at follow-up was 7.53% (95% CI 7.20, 7.86) in the statin group and 7.41% (95% CI 7.11, 7.72) in the control group (Fig. 2). The pooled mean HbA_{1c} difference across the studies involving participants with type 2 diabetes only was 0.17% (95% CI 0.07, 0.27), while the pooled estimate for the three studies involving participants with type 1 diabetes, a mixed population or unknown diabetes type was 0.03% (95% CI −0.08, 0.14) (Fig. 3). The overall pooled mean difference in HbA_{1c} was 0.12% (95% CI 0.04, 0.20, $p=0.003$) (Fig. 3 and ESM Fig. 1) and the corresponding value in fixed-effect model analysis was 0.13% (95% CI 0.08, 0.17, $p<0.001$). (ESM Fig. 2) The corresponding value of the overall pooled estimate in SI units was 1.3 mmol/mol (95% CI 0.4, 2.2). There was moderate heterogeneity across the studies ($I^2=54\%$, $p=0.014$), not explained by available study-level characteristics; however, we observed a trend towards a stronger effect for trials on atorvastatin compared with trials on

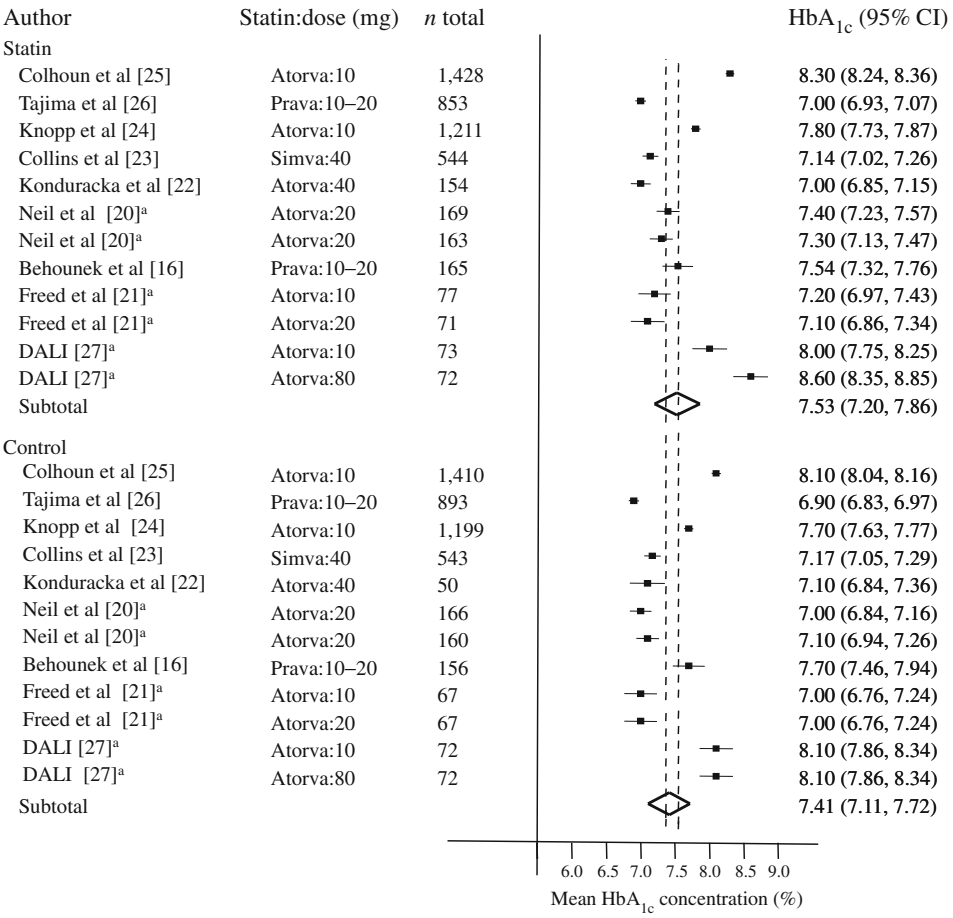

Fig. 2 Average follow-up HbA_{1c} levels in nine clinical trials of statins in diabetes. [a]Studies by Neil et al, Freed et al and the DALI study group reported comparisons in two subgroups and are presented here separately. Black boxes represent the HbA_{1c} concentration in % and the horizontal bars show the 95% CIs. The size of the boxes is proportional to the inverse variance. The diamond represents the pooled effect estimate and 95% CI and the dotted vertical line centred on the diamond has been added to assist visual interpretation. Atorva, atorvastatin; Prava, pravastatin; Simva, simvastatin. To convert values for HbA_{1c} in % into mmol/mol, subtract 2.15 and multiply by 10.929

pravastatin or simvastatin, for trials that comprised participants with type 2 diabetes compared with those comprised of participants with type 1 diabetes or mixed populations and also for trials in which there was larger reduction in LDL-cholesterol (>1.1 mmol/l) compared with those with smaller reduction in LDL-cholesterol (<1.1 mmol/l) (Fig. 4). There was no strong evidence suggesting the presence of publication bias (i.e. there was no funnel-plot asymmetry and Egger's test for bias was not statistically significant [p=0.80]).

Discussion

Currently available trial data, involving predominantly participants with type 2 diabetes, indicate a modest effect of statin use on HbA_{1c} concentration. In a pooled analysis of nine trials involving 9,696 participants and an average follow-up of 3.6 years, we found that the mean HbA_{1c} of participants randomised to statins was 0.12% (95% CI 0.04, 0.20) higher than those randomised to control. There may have been heterogeneity of effect among the three statins studied in these trials (atorvastatin, pravastatin and simvastatin), but more studies are needed to determine whether atorvastatin has a stronger effect given the limited data available on pravastatin and simvastatin in this meta-analysis. Similarly, further data are needed to determine the possible heterogeneity of effect by type of diabetes or by degree of LDL-cholesterol reduction noted in this meta-analysis.

The small effect of statins on HbA_{1c} concentration observed in this meta-analysis, although statistically significant, may have little clinical impact. For example, while a 1 mmol/l lowering of LDL-cholesterol (all other things being equal) might be expected to reduce the risk of cardiovascular disease by approximately 20% [34], a 0.12% increase in HbA_{1c} would not be expected to have material effect on cardiovascular disease risk [35]. However, various statin types and doses may have differing adverse effects on glycaemic control, as indicated in previous reports [11, 17, 18], as well as being implied in our study where we found a trend towards this, which may have attenuated the pooled effect in the current meta-analysis. Furthermore, in clinical trials that spanned a longer period of follow-up, there may have been a differential change in glucose-lowering medications of participants randomised to statin and control arms that could potentially offset the effect of statin therapy. The current analysis,

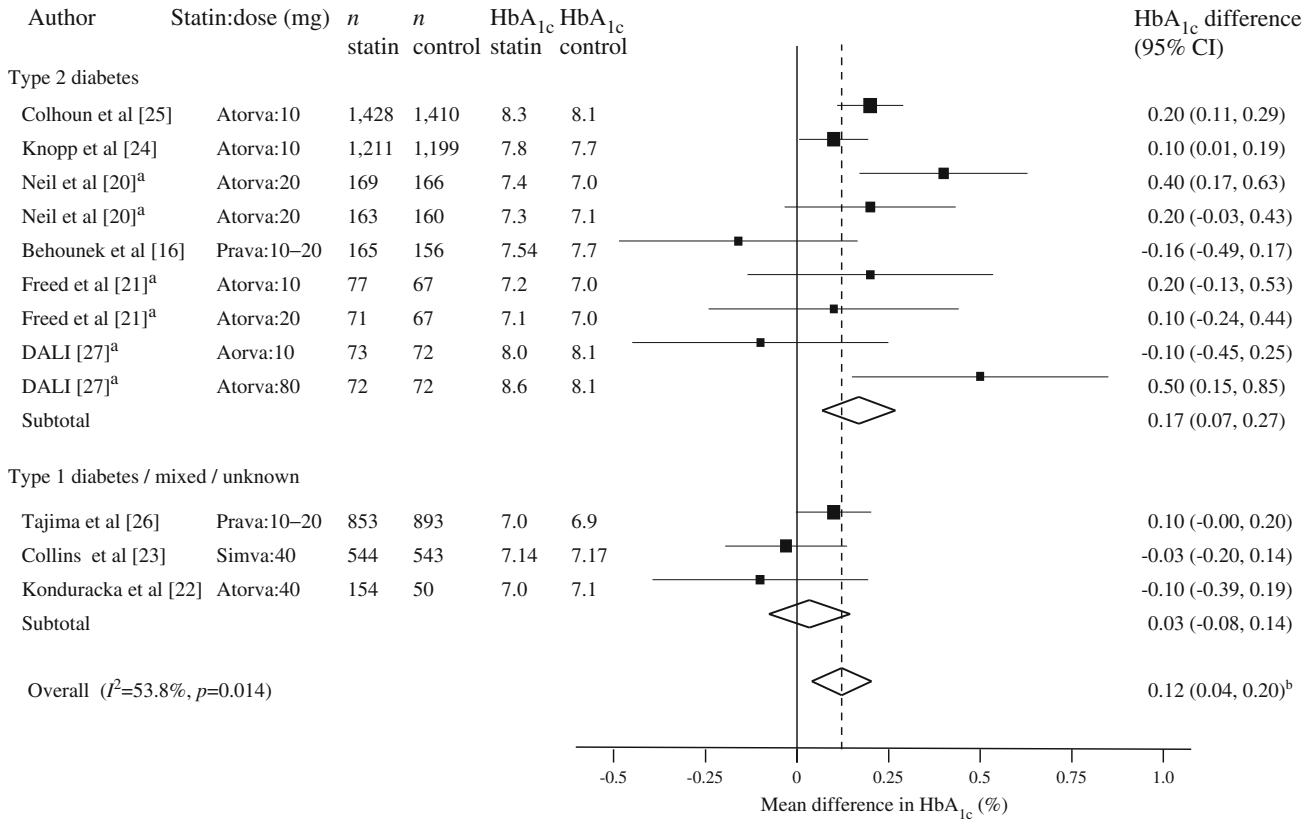

Fig. 3 Mean difference in HbA_{1c} at follow-up in nine clinical trials of statins in diabetes, by diabetes type. [a]Studies by Neil et al, Freed et al and the DALI study group reported comparisons in two subgroups and are presented separately herein. [b]The overall *p* value for main effect of statin was 0.003. For explanation of abbreviations and symbols, see the legend to Fig. 2. To convert values for HbA_{1c} in % into mmol/mol, subtract 2.15 and multiply by 10.929

therefore, raises awareness of clinicians to the potential dysglycaemic effect of statins in diabetic patients.

The magnitude of effect of statin use on glycaemic control among patients with diabetes that we observed in our study (i.e. a 0.12% [1.3 mmol/mol] absolute increase in mean HbA_{1c} concentration [equivalent to 0.02% higher HbA_{1c} level]), is smaller than the effect of statin use on the risk of new-onset diabetes reported in a previous meta-analysis of randomised clinical trials (approximately 10% increase in risk) [6]. This difference may be at least partly artefactual given that the quality and amount of data available for the two meta-analyses are not comparable. However, such differences have been observed within large RCTs as well; for example, the Justification for the Use of Statins in Primary Prevention (JUPITER) study showed a materially greater increase in the risk of new-onset diabetes (26% higher risk) compared with a mean increase in HbA_{1c} of 0.3% for individuals randomised to rosuvastatin vs control [7, 36]. Possible explanations for the observed weaker effect of statin use on HbA_{1c} concentration in diabetes include bias due to differential attrition or adjustment of hypoglycaemic medication between the statin and control groups [7]. For instance, in the Collaborative Atorvastatin Diabetes Study (CARDS), 20% of the participants randomised to the statin arm vs 17% of those randomised to the control arm were switched to insulin or had insulin added to their treatment regimen by the end of the follow-up period [25].

A number of mechanisms have been proposed to explain the potential adverse effect of statins on glycaemic control. Statins may downregulate GLUT4, a membrane transport protein that plays a role in the uptake of glucose by adipocytes. Statins may also decrease insulin secretion. In addition, statins may be associated with increased insulin resistance [4, 17, 37–41]. The trend towards stronger association among patients with type 2 diabetes than among those with type 1 diabetes observed in the current analysis may corroborate the proposed mechanism of statin effect on insulin resistance. In addition, observation of differences in effect on glycaemic control among the various statins suggests that differences in potency and/or lipid solubility may be important [4]. However, limited evidence is available on these proposed mechanisms and more data are needed to clarify these hypotheses.

Our study has a number of strengths worth mentioning. First, we conducted a comprehensive review by searching complementary databases and the reference list of relevant articles. Second, pooling data from RCTs allows us to make

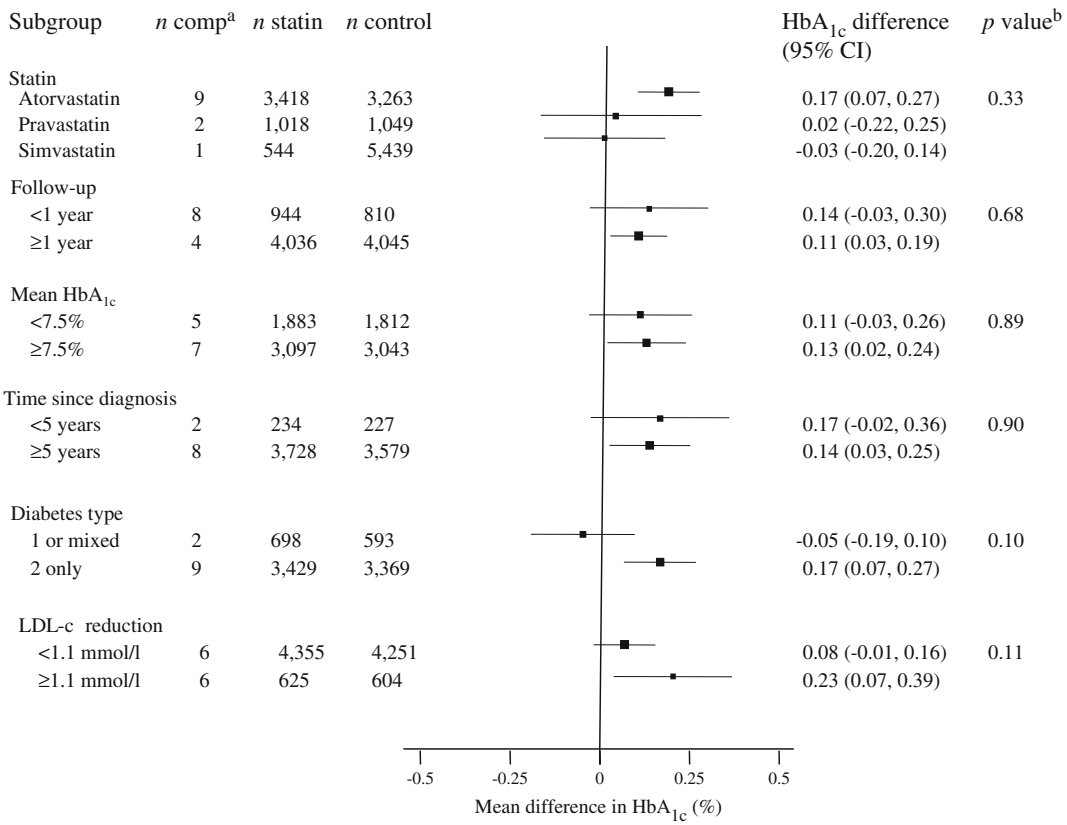

Fig. 4 Subgroup analysis of mean difference in HbA_{1c} in nine clinical trials of statins in diabetes. [a]*n* comparisons may add up to >9, as Freed et al, Neil et al and the DALI study group reported two subsets (counted separately herein). [b]The *p* values are tests of significance for difference between the subgroup effects. For explanation of abbreviations and symbols, see the legend to Fig. 2. To convert values for HbA_{1c} in % into mmol/mol, subtract 2.15 and multiply by 10.929

inferences about causality (i.e. that statins per se worsen glycaemia). Third, we used strict pre-defined criteria to ensure the quality of the trials included and to ensure their relevance to answering the clinical question. For instance, we excluded studies with <3 month follow-up period, as HbA_{1c} measures the average blood glucose concentration over a 3 month period. Finally, despite considerable differences between the studies, we did not observe either substantial heterogeneity in the meta-analysis or statistical evidence for publication bias.

There are also a few caveats that limit the inferences that can be made from the present analysis. First, there were a small number of studies with about 10,000 total participants available for this review. Second, while we conducted a comprehensive review of the published literature, we were not able to capture data from unpublished studies or informally published material, which might affect the pooled estimate. However, the effect of any bias due to such omission is likely to be minimal since the outcome of interest for this analysis (the effect of statins on glycaemic control) was different from the primary outcome of most of the individual studies (the effects of statins on lipid concentrations or cardiovascular disease risk). Third, we only had data on atorvastatin, pravastatin and one study on simvastatin, hence inferences regarding the effect of different statins is limited. Fourth, the selected studies did not generally report changes in the use of glucose-lowering medications, which might influence the effect of statins on HbA_{1c} concentration. Last, as the present work is a literature-based meta-analysis, we did not have access to individual participant data, and could not explore heterogeneity in detail. Although a number of RCTs of statins included people with diabetes, only the few studies we included reported HbA_{1c} concentration. In the future, a collaborative meta-analysis that pools together these data (both published and unpublished), allowing more detailed, consistent and powerful analyses, should help to provide a more definite answer than has been possible thus far.

The results of this study are not expected to change current clinical practice, insofar as the benefits of statins in patients with diabetes far outweigh the disadvantages, since statins reduce cardiovascular disease risk materially in this population [35] while their impact on glycaemic control is not certain. However, assuming a normal distribution of effect of statins on HbA_{1c} values, a significant proportion of patients might be expected to have statin-associated changes in HbA_{1c} of greater than 0.12 percentage points, possibly dependent on the type and dose of the statin. Hence, healthcare providers

and patients may need to watch for worsening glycaemia in anticipation of intensifying statin treatment.

In conclusion, limited evidence indicates that statin treatment is associated with a modest increase in HbA_{1c} in patients with diabetes. Future collaborative meta-analysis of available randomised clinical trials would help to further characterise the effect of statins on glycaemic control in diabetes.

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Duality of interest The authors declare that there is no duality of interest associated with this manuscript.

Contribution statement SE designed the study, wrote the manuscript, analysed and interpreted the data, revised the manuscript critically for important intellectual content and approved the final version for publication. CCL designed the study, interpreted the data, revised the manuscript critically for important intellectual content and approved the final version for publication. AIA interpreted the data, revised the manuscript critically for important intellectual content and approved the final version for publication. SE and CCL are responsible for the integrity of the work as a whole.

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