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ORIGINAL REPORT

Statin use and the risk of developing diabetes: a network meta-analysis

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ABSTRACT

Purpose Randomized controlled trials have shown mixed findings regarding the association of statins and diabetes. This systematic literature review and network meta-analysis (NMA) was performed to update evidence on this association to possibly assist clinicians in making more informed treatment choices.

Methods We identified studies relevant to our NMA by performing study searches in databases like Embase, Cochrane, and PubMed, published between August 2010 and June 2014. Pre-2010 studies were identified from bibliography of previously published meta-analyses. Unpublished study data were found from clinicaltrial.gov. Data synthesis was performed by pairwise meta-analysis and NMA within a Frequentist framework.

Results Twenty nine trials in which 1 63 039 participants had been randomized were included in this review; among these 1 41 863 were non-diabetic patients. The direct meta-analysis showed that statins, as a class, significantly increased the likelihood of developing diabetes by 12% (pooled OR 1.12; 95%CI 1.05–1.21; I^2 36%; $p = 0.002$; 18 RCTs). In the NMA, atorvastatin 80 mg was associated with a highest risk of diabetes, with OR of 1.34 (95%CI 1.14–1.57) followed by rosuvastatin (OR: 1.17; 95%CI: 1.02–1.35). The ORs (95%CIs) for simvastatin 80 mg, simvastatin, atorvastatin, pravastatin, lovastatin and pitavastatin were 1.21 (0.99–1.49), 1.13 (0.99–1.29), 1.13 (0.94–1.34), 1.04 (0.93–1.16), 0.98 (0.69–1.38) and 0.74 (0.31–1.77), respectively. High-dose atorvastatin increased the odds of developing diabetes even when compared with pravastatin, simvastatin and low-dose atorvastatin in the NMA.

Conclusions Based on the results, statins, as a class, increased the risk of diabetes significantly in the pairwise meta-analysis. Overall, there appears to be a small increased risk of incident diabetes, particularly with more intensive statin therapy, although more data would be valuable to increase the robustness of this interpretation, given that the lower confidence intervals of our study analyses are close to, or just crossing one. Copyright © 2016 John Wiley & Sons, Ltd.

KEY WORDS—safety; statins; cardiovascular disease; type 2 diabetes; systematic review; meta-analysis; network meta-analysis; pharmacoepidemiology

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INTRODUCTION

Cardiovascular diseases (CVDs) are a major cause of illness and death worldwide. Elevated blood cholesterol levels, specifically the low-density lipoprotein (LDL) cholesterol, are associated with a higher risk of heart attack, stroke and heart failure.[1] Several studies have shown that correction of dyslipidaemia significantly decreases the risk of CVD events.[2,3] Statins (3-hydroxy 3-methylglutaryl coenzyme A reductase inhibitors) are one of the mainstays of treatment and widely used for lowering cholesterol for the prevention of CVD.[4] Beyond their LDL-lowering effects, statins due to their pleiotropic effect also reduce vascular inflammation, improve endothelial function and decrease thrombus formation.[5–7]

It has been known that statins can modulate insulin secretion and sensitivity.[8,9] However, recent findings from some randomized controlled trials (RCTs) showed that statins can raise blood sugar, and more patients on statin therapy were diagnosed with diabetes mellitus. The Justification for Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin [10] and Prospective Study of Pravastatin in the Elderly at Risk [11] trials found that patients randomized to rosuvastatin and pravastatin, respectively developed, a significantly higher incidence of type 2 diabetes compared with placebo. Conversely, results from the West of Scotland Coronary Prevention Study [12] showed that pravastatin therapy might reduce the frequency of diabetes. This led researchers to conduct several systematic literature reviews and

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meta-analyses to assess the contradicting findings of these trials. Sattar *et al.*[13] conducted a meta-analysis of 13 RCTs and concluded that statin therapy was associated with a 9% increased risk for incidence of diabetes. Two years later, the same finding was reported by Mills *et al.*[14] within a pooled estimate of 17 RCTs. Researchers have also conducted network meta-analyses (NMA) of RCTs to investigate the impact of different types and doses of statins on new-onset diabetes.[15–17]

Although Sattar *et al.*[13] and Mills *et al.*[14] were concurrent in their findings that statin use significantly increases the risk of diabetes mellitus; these studies derived the pooled estimate with the statin class as a whole, rather than individual statins. Moreover, these studies analysed only the direct evidence. Such analyses often undermine even the beneficial effects of some statins that have been shown to reduce the incidence of diabetes.[12,18,19] Alberton *et al.* conducted a meta-analysis and also evaluated indirect comparisons to identify differing risk effects across statins; however, they did not provide sufficient evidence for diabetes in the indirect comparisons.[15] Navarese *et al.*[16] and Naci *et al.*[17] both employed NMA methodology for evaluating the association of statin use and diabetes, but these reviews did not include published or unpublished evidence for pitavastatin.

With the current controversy on the utility of statins and the associated risks, well-researched evidence becomes imperative to accurate clinical decision making. Randomized controlled trials are more frequently conducted to evaluate efficacy endpoints rather than adverse reactions. Therefore, RCTs are not sufficiently powered to detect differences in safety outcomes, unlike real-world observational studies. However, as NMA combine the direct and indirect estimates, it may yield a more refined and precise estimate for the interventions directly compared and broaden inference with the population sampled. We aimed to use NMA to assess the direct and indirect evidence from published and unpublished studies to bring forth valuable evidence about statins and their association with diabetes mellitus.[10–12]

METHODS

Type of studies, participants, and intervention

Randomized controlled trials, published in English, that used any of the statins for CVDs and specified incidence of diabetes were evaluated for inclusion. Trials unclear for allocation concealment and method of randomization, and open label studies were also included but quality of these studies was taken into consideration. Quasi-randomized trials and nonrandomized studies were excluded.

Identification of studies

We identified the studies, relevant to our NMA by performing study searches in databases like Embase, Cochrane and PubMed published between August 2010 and June 2014. We identified the studies prior to August 2010 from the bibliography of previously published systematic literature reviews and meta-analyses.[13,14] We also looked for unpublished trials from clinicaltrial.gov.

Two researchers evaluated the results of the search strategy to identify potentially relevant trials and retrieved the full-text articles. Both researchers independently assessed each of these trials for inclusion in the review using an eligibility form based on the review inclusion criteria. We resolved any disagreements by discussion, with referral to a third researcher, if required.

Two reviewers independently entered data into a data extraction form. We collected data on study characteristics, including methods, participants, interventions and outcomes. Any disagreement was resolved by referring to the trial report and through discussion and consultation with the third reviewer.

Risk of bias assessment

The risk of bias (RoB) was assessed for each included study using the Cochrane Collaboration criteria.[20] These included random sequence generation, allocatin concealment, blinding of participants and outcome assessment, incomplete outcome data and selective outcome reporting. As selective reporting was not relevant to our review, we removed it from the RoB summary figure. The RoB of each study was explicitly judged on each criterion and classified as 'low', 'high' or 'unclear'. To summarize the overall RoB for a study, we considered randomization, allocation concealment, blinding and monitoring and detection of diabetes in order to classify each study as 'low risk of bias' when all four criteria were met; 'high risk of bias' when none of the criteria were met; and 'moderate risk of bias' in the remaining cases. For detection of diabetes, we judged study at 'low' RoB if reviewers used any international standard criteria or used two fasting glucose values $\geq$7.0 mmol/L. If it was detected using only one value or diabetes was identified as spontaneous reporting only, we judged the study as 'high' RoB. The RoB of each study was assessed

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independently by the two reviewers and any disagreement was resolved by discussion to reach consensus.

Data synthesis

For each pairwise comparison and each outcome at each time point, we used odds ratio (OR) with 95% confidence interval (95%CI) as a measure of the association between the treatment used and efficacy. If the outcomes were negative, ORs < 1 corresponded to beneficial treatment effects of the first treatment compared with the second treatment.

Heterogeneity or inconsistency can be the result of an uneven distribution of important clinical and methodological effect modifiers across studies (heterogeneity) or across comparisons (inconsistency). The presence of statistical heterogeneity was assessed by visual inspection of the forest plots and by calculating the I^2 statistic and its confidence limits. Wherever significant heterogeneity was detected, we perform the meta-regression analysis to explore the source of heterogeneity. Potential sources of heterogeneity or inconsistency include different participant baseline characteristics, different treatment dose and influence of funders.

First, conventional pairwise meta-analyses was conducted for all outcomes and comparisons, provided that at least two studies were available, using a random-effects model.[21] We performed the pairwise meta-analysis using RevMan 5.1®. We then performed a NMA for incidence of diabetes mellitus within a Frequentist framework, assuming an equal heterogeneity parameter tau ( ) across all comparisons.

It is essential to check the assumptions of the analysis before drawing conclusions while using NMA methodology. The most important assumption is that the network of comparisons is consistent, such that direct and indirect evidence on the same comparisons agree. Joint analysis can be misleading if the network is substantially inconsistent. Inconsistency can be present if the trials in the network have very different protocols and their inclusion and exclusion criteria are not comparable, or may result from an uneven distribution of effect modifiers across groups of trials that compare different treatments. In order to estimate network inconsistency, we calculated the difference between indirect and direct estimates in each closed-loop formed by the network of trials (using the Bucher method) and their relative 95%CI. We then examined whether there were any material discrepancies; if the 95%CI did overlap with 1 the hypothesis of consistency was not rejected, as described in Salanti *et al.*[22]

In order to assess the presence of small-study effects, we used the funnel plot. The application of the funnel plots in NMA need to account for the fact that studies estimate effects for different comparison. Therefore, to judge the symmetry, a single reference line cannot be used. To account for the different summary effect with each set of studies, Chaimani *et al.* suggested the use of 'comparison-adjusted' funnel plot'.[23] In the 'comparison-adjusted' funnel plot, the horizontal axis presents the difference between the study-specific effect sizes from the corresponding comparison-specific summary effect.

We used the STATA 12.0® routines to perform all the analyses based on Chaimani *et al.*[23]

RESULTS

Preferred Reporting Items for Systematic Reviews and Meta-analyses flow diagram is represented in Figure 1. Twenty nine trials in which 1 63 039 participants had been randomized were included in this review; among these 1 41 863 were non-diabetic patients. The duration of the trials ranged from 3 months to 6.1 years, with the median duration being 4.8 years. Mean age of the patients ranged from 53 to 75 years in the studies. The body mass index (BMI) and LDL-cholesterol levels ranged from 23 to 31 kg/m^2 and 97 to 192 mg/dL, respectively among the studies. Majority of the studies reported the use of other cardiovascular medications. Tables 1 and 2 provide details on the characteristics of the included studies.

Risk of bias in the included studies

The RoB of the included studies is summarized in Figures S1 and S2. Considering our predefined criteria (randomisation, allocation concealment, blinding and based on detection of diabetes) to assess the RoB, four of the 29 studies were judged at low,[10,24–26] and the remaining 25 at moderate RoB. None of the studies were judged at high RoB.

Risk of developing diabetes

Pairwise meta-analysis (direct comparisons). Of the 29 trials[10–12,18,19,24–47] directly comparing statin versus placebo or any other active agent, 16 trials[10–12,18,19,25–29,32–35,37,39] compared one of the statins (atorvastatin, lovastatin, pravastatin, rosuvastatin and simvastatin) versus placebo or usual care, two[31,38] compared any statin versus no

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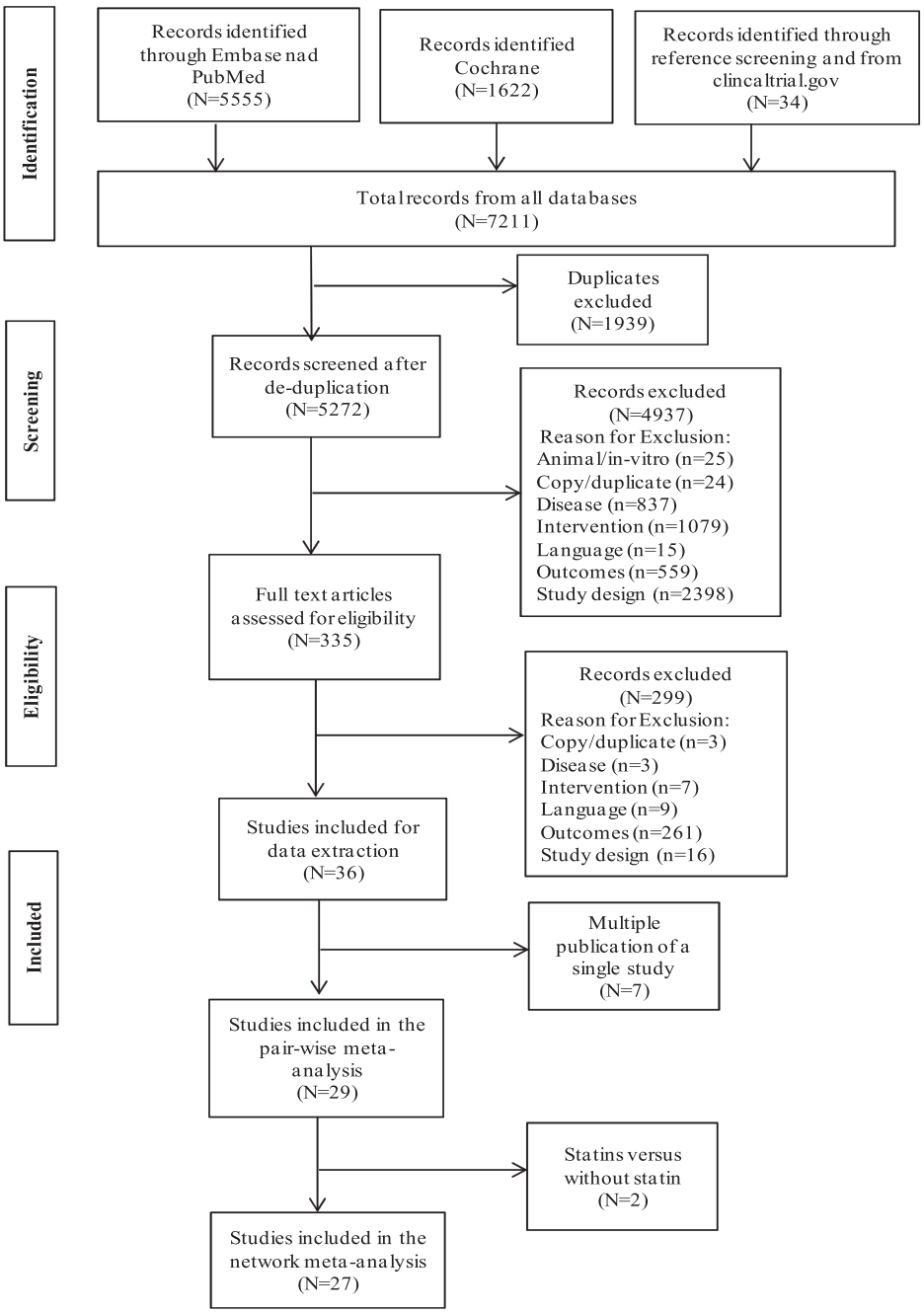

Figure 1. Preferred reporting items for systematic reviews and meta-analyses flow diagram

statin treatment and seven trials[24,30,36,40,41,44,45] compared intensive statin treatment versus moderate statin treatment. Four of the seven pitavastatin trials compared pitavastatin to other statins.[42,43,46,47] Of the 18 trials comparing statin with control, only four[10,11,38,39] showed that statin significantly increased the risk of developing diabetes.

The meta-analysis derived that, statins significantly increased the likelihood of developing diabetes to 12% (pooled OR 1.12; 95%CI 1.05–1.21; I^2 36%; $p=0.002$; 18 RCTs) in the random-effects model (Figure 2). Only rosuvastatin was shown to increase the risk of developing diabetes significantly ([pooled OR 1.18; 95%CI 1.04–1.33; I^2 0%; $p=0.009$; 4 RCTs] Figure 2).

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Table 1. Characteristics of included studies

Study name	Country (ies)	Study design	Study duration
PMSGCRP 1993[27]	Australia, Belguim, Finland, Germany, Israel, Sweden, UK	RCT, double-blind	3.1 years
4S 1994[28]	Norway	RCT, double-blind	5.4 years
Downs 1998 (AFCAPS/TEXCAPS)[33]	US	RCT, double-blind	5.2 years
GISSI PREV 2000[19]	Italy	RCT, open-label	3.2 years
Freeman 2001 (WOSCOPS)[12]	UK	RCT, double-blind	4.8 years
ALLHAT 2002[29]	US, Puerto Rico, US Virgin Islands, and Canada	RCT, open-label	4.8 years
Saito 2002[45]	Japan	RCT, double-blind	12 weeks
Shepherd 2002 (PROSPER)[11]	Scotland, Ireland, and Netherlands	RCT, double-blind	3.2 years
Collins 2003 (HPS)[25]	UK, Ireland, Norway, Sweden	RCT, double-blind	5 years
Keech 2003 (LIPID)[18]	Australia (67 centres) and New Zealand (20 Centres)	RCT, double-blind	6.1 years
Pedersen 2005 (IDEAL)[40]	Norway, Sweden, Iceland, Denmark, Finland, Netherland	RCT, Open label, blinded end-point	4.8 years
Amarenco 2006 (SPARCL)[39]	International	RCT, double-blind	4.9 years
Nakamura 2006 (MEGA)[35]	Japan	RCT, open-label	5.3 years
Kjekshus 2007 (NCT00206310; CORONA)[34]	19 European countries, Russia, and South Africa	RCT, double-blind	Median 32.8 months (2.7 years)
Ridker 2008 (Jupiter; NCT00239681)[10]	Multicountry	RCT, double-blind	60 months (5 years)
Tavazzi 2008 (GISSI HF)[26]	Italy	RCT, double-blind	3.9 years
Budinski 2009[42]	International	RCT, double-blind	12 weeks
Ose 2009[46]	International	RCT, double-blind	12 weeks
Athyros 2010 (GREACE)[31]	Greece	RCT, open label, survival study	3 years
Chan 2010 (ASTRONOMER, ISRCTN 32424163)[32]	Canada	RCT, double-blind	3.5 years
Armitage 2010 (ISRCTN74348595, SEARCH trial)[30]	UK	RCT, double-blind	Mean: 6.7 (SD1.5) person-years
Collier 2011 (ASCOT-LLA)[37]	UK	RCT, double-blind	Median 3.3 years
Nozue 2012 (TRUTH)[44]	Japan	RCT, open label	32 weeks
Chen 2013[24]	14 countries	RCT, double-blind	3.5 months
Kurogi 2013 (COMPACT-CAD)[43]	Japan	RCT, open label	2.3 years
Shen 2013 (NCT00097786; NAVIGATOR)[38]	38 countries	Re-analysis-NAVIGATOR trial	Median 5.0 years
NK-104-4.01CH[47]	China	RCT, open label	12 weeks
Ong 2014 (TNT)[36]	Australia	RCT, double-blind	Median 4.9 years
INTREPID[41]	USA	RCT, double-blind	12/52 weeks

NR = not reported; RCT = randomised controlled trial; IQR = interquartile range; SE = standard error; SD = standard deviation; ERN/LRPT = Extended-release niacin/laropiprant; IFG = impaired fasting glucose.

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Table 1. Characteristics of included studies

Study name	Study groups	No. of patients	Age, Mean (SD) years
PMSGCRP 1993[27]	Pravastatin 20 mg vs placebo	530 vs 532	55 (range: 20–86) vs 55 (range: 22–77)
4S 1994[28]	Simvastatin vs placebo	2221 vs 2223	Men:58.2 (7.3) vs 58.1 (7.2) Women:60.5 (6.4) vs 60.5 (5.7)
Downs 1998 (AFCAPS/TEXCAPS)[33]	Lovastatin vs placebo	3304 vs 3301	58.0 (7.0) vs 58.0 (7.0)
GISSI PREV 2000[19]	Pravastatin vs usual care	2138 vs 2133	59.3
Freeman 2001 (WOSCOPS)[12]	Pravastatin 40 mg vs placebo	3302 vs 3293	55.3 (5.5) vs 55.1 (5.5)
ALLHAT 2002[29]	Pravastatin vs usual care	5170 vs 5185	66.4 (7.6) vs 66.3 (7.5)
Saito 2002[45]	Pitavastatin 2 mg vs pravastatin 10 mg	240	20–75
Shepherd 2002 (PROSPER)[11]	Pravastatin vs placebo	2891 vs 2913	75.4 (3.3) vs 75.3 (3.4)
Collins 2003 (HPS)[25]	Simvastatin40 mg vs placebo	10 269 vs 10 267	<65: 85% vs 20%65–70: 87% vs 18%70: 84% vs 12%
Keech 2003 (LIPID)[18]	Pravastatin vs placebo	4512 vs 4502	Median (IQR): 62 (55–67) vs 62 (55–68)
Pedersen 2005 (IDEAL)[40]	Atorvastatin 80 mg vssimvastatin 20–40 mg	4439 vs 4449	61.8 (9.5) vs 61.6 (9.5)
Amarenco 2006 (SPARCL)[39]	Atorvastatin 80 mg vs placebo	2365 vs 2366	63.0 (0.2) vs 62.5 (0.2)
Nakamura 2006 (MEGA)[35]	Diet + pravastatin vs Diet	3866 vs 3966	58.2 (7.3) vs 58.4 (7.2)
Kjekshus 2007 (NCT00206310; CORONA)[34]	Rosuvastatin vs placebo	2514 vs 2497	73 (7.1) vs 73 (7.0)
Ridker 2008 (Jupiter; NCT00239681)[10]	Rosuvastatin vs placebo	8901 vs 8901	Median 66 vs 66
Tavazzi 2008 (GISSI HF)[26]	Rosuvastatin vs placebo	2285 vs 2289	68 (11) vs 68 (11)
Budinski 2009[42]	Pitavastatin 2–4 mg vs atorvastatin 10–20 mg	616 vs 205	58.3 (9.6)
Ose 2009[46]	Pitavastatin 2–4 mg vs simvastatin 20–40 mg	631 vs 217	58.7 (8.8)
Athyros 2010 (GREACE)[31]	Statin vs no statin	880 vs 720	58.5 (11.9) vs 59.6 (11.3)
Chan 2010 (ASTRONOMER, ISRCTN 32424163)[32]	Rosuvastatin vs placebo	134 vs 135	58.0 (12.9) vs 57.9 (14.3)
Armitage 2010 (ISRCTN74348595, SEARCH trial)[30]	Simvastatin 80 mg vs 20 mg	6031 vs 6033	<60: 406/1880 vs 424/1885≥60 to <70: 574/2414 vs 601/2414≥70: 497/1737 vs 528/1734
Collier 2011 (ASCOT-LLA)[37]	Atorvastatin vs placebo (≥65 years)	2189 vs 2256	71.1 (4.1) vs 71.1 (4.0)
	Atorvastatin vs placebo (<65 years)	2979 vs 2881	57.2 (5.6) vs 57.0 (5.7)
Nozue 2012 (TRUTH)[44]	Pitavastatin 4 mg vs pravastatin 20 mg	58 vs 61	67
Chen 2013[24]	ERN/LRPT + Simvastatin 20 vs ERN/LRPT + Simvastatin 40	297 vs 436	54.1 (10.8) vs 55.0 (10.3)
	Atorvastatin 10 vs 20 vs 40 vs 80	298 vs 439 vs 437 vs 433	53.7 (10.6) vs 54.8 (10.8) vs 55.1 (10.1) vs 54.7 (10.5)
Kurogi 2013 (COMPACT-CAD)[43]	Pitavastatin 2–4 mg vs atorvastatin 10–20 mg	65 vs 64	68.4(9.1) vs 68.9 (10.2)
Shen 2013 (NCT00097786; NAVIGATOR)[38]	Statins vs no Statins	1353 vs 4793	Median (range): 63 (58–68) vs 63 (58–68)
NK-104-4.01CH[47]	Pitavastatin 4 mg vs atorvastatin 20 mg	476	18–75
Ong 2014 (TNT)[36]	Atorvastatin 10 mg vs 80 mg	5006 vs 4995	60.9 (8.8) vs 61.2 (8.8)
INTREPID[41]	Pitavastatin 4 mg vs pravastatin 40 mg	123 vs 124	18–65

NR = not reported; RCT = randomised controlled trial; IQR = interquartile range; SE = standard error; SD = standard deviation; ERN/LRPT = Extended-release niacin/laropiprant; IFG = impaired fasting glucose.

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Table 1. Characteristics of included studies

Study name	Gender, Female; *n* (%)	Ethnicity; n (%)
PMSGCRP 1993[27]	119 (23) vs 128 (24)	NR
4S 1994[28]	407 (18) vs 420 (19)	NR
Downs 1998 (AFCAPS/TEXCAPS)[33]	499 (15) vs 498 (15)	White:2925 (89) vs 2935 (89) Black:105 (3) vs 101 (3) Hispanic:247 (7) vs 240 (7)
GISSI PREV 2000[19]	13.7%	NR
Freeman 2001 (WOSCOPS)[12]	NR	NR
ALLHAT 2002[29]	2511 (48.6) vs 2540 (49.0)	White, non-Hispanic: 2107 vs 2129 Black, non-Hispanic: 1769 vs 1722 White, Hispanic: 759 vs 803 Black, Hispanic: 210 vs 181 Other: 325 vs 350
Saito 2002[45]	NR	NR
Shepherd 2002 (PROSPER)[11]	1495 (51.71) vs 1505 (51.66)	NR
Collins 2003 (HPS)[25]	0.82 vs 0.16	NR
Keech 2003 (LIPID)[18]	756 (17) vs 760 (17)	NR
Pedersen 2005 (IDEAL)[40]	849 (19.1) vs 852 (19.2)	NR
Amarenco 2006 (SPARCL)[39]	938 (39.7) vs 970 (41)	NR
Nakamura 2006 (MEGA)[35]	2638 (68) vs 2718 (69)	NR
Kjekshus 2007 (NCT00206310; CORONA)[34]	593 (24) vs 587 (24)	NR
Ridker 2008 (Jupiter; NCT00239681)[10]	3426 (38.5) vs 3375 (37.9)	White: 6358 vs 6325 Black: 1100 vs 1124 Hispanic: 1121 vs 1140 Other: 322 vs 312
Tavazzi 2008 (GISSI HF)[26]	543 (23.8) vs 489 (21.4)	NR
Budinski 2009[42]	338 (54.9) vs 105 (51)	NR
Ose 2009[46]	391 (62) vs 111 (51.2)	NR
Athyros 2010 (GREACE)[31]	182 (20.7) vs 162 (18.4)	NR
Chan 2010 (ASTRONOMER, ISRCTN 32424163)[32]	53 (39.5) vs 50 (37.0)	White: 131 (97.8) vs 133 (98.5)
Armitage 2010 (ISRCTN74348595, SEARCH trial)[30]	200/1026 (19.5%)	NR
Collier 2011 (ASCOT-LLA)[37]	409 (18.7) vs 464 (20.6) 570 (19.13) vs 499 (17.32)	White 2105 (96.2) vs 2167 (96.1) White 2784 (93.5) vs 2696 (93.6)
Nozue 2012 (TRUTH)[44]	20 (16.8)	NR
Chen 2013[24]	165 (55.6) vs 237 (54.4) 169 (56.7) vs 248 (56.5) vs 232 (53.1) vs 258 (59.6)	White: 245 (82.5) vs 321 (73.6) Hispanic: 37 (12.5) vs 90 (20.6) Black: 10 (3.4) vs 7 (1.6) Other: 5 (1.7) vs 18 (4.1) White: 242 (81.2) vs 314 (71.5) vs 323 (73.9) vs 316 (73) Hispanic: 37 (12.4) vs 91 (20.7) vs 86 (19.7) vs 83 (19.2) Black: 11 (3.7) vs 8 (1.8) vs 7 (1.6) vs 8 (1.8) Others: 8 (2.7) vs 26 (5.9) vs 21 (4.8) vs 26 (6.0)
Kurogi 2013 (COMPACT-CAD)[43]	12 (18.5) vs 12 (18.7)	NR
Shen 2013 (NCT00097786; NAVIGATOR)[38]	690 (51) vs 2684 (56)	Black: 28 (2.1) vs 134 (2.8)
NK-104-4.01CH[47]	NR	NR
Ong 2014 (TNT)[36]	961 (19) vs 941 (19)	NR
INTREPID[41]	20 (16.3) vs 15 (12.1)	NR

NR = not reported; RCT = randomised controlled trial; IQR = interquartile range; SE = standard error; SD = standard deviation; ERN/LRPT = Extended-release niacin/laropiprant; IFG = impaired fasting glucose.

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Table 2. Characteristics of included studies

Study name	Study design	Study duration	Study groups
PMSGCRP 1993[37]	RCT, double-blind	3.1 years	Pravastatin 20 mg vs placebo
4S 1994[28]	RCT, double-blind	5.4 years	Simvastatin vs Placebo
Downs 1998 (AFCAPS/TEXCAPS)[33]	RCT, double-blind	5.2 years	Lovastatin vs Placebo
GISSI PREV 2000[19]	RCT, open-label	3.2 years	Pravastatin vs Usual care
Freeman 2001 (WOSCOPS)[12]	RCT, double-blind	4.8 years	Pravastatin 40 mg vs Placebo
ALLHAT 2002[29]	RCT, open-label	4.8 years	Pravastatin vs Usual care
Saito 2002[45]	RCT, double-blind	12 weeks	Pitavastatin 2 mg vs Pravastatin 10 mg
Shepherd 2002 (PROSPER)[11]	RCT, double-blind	3.2 years	Pravastatin vs Placebo
Collins 2003 (HPS)[25]	RCT, double-blind	5 years	Simvastatin 40 mg vs Placebo
Keech 2003 (LIPID)[18]	RCT, double-blind	6.1 years	Pravastatin vs placebo
Pedersen 2005 (IDEAL)[40]	RCT, Open label, blinded end-point	4.8 years	Atorvastatin 80 mg vsSimvastatin 20e40 mg
Amarenco 2006 (SPARCL)[39]	RCT, double-blind	4.9 years	Atorvastatin 80 mg vs Placebo
Nakamura 2006 (MEGA)[35]	RCT, open-label	5.3 years	Diet + pravastatin vs Diet
Kjekshus 2007 (NCT00206310; CORONA)[34]	RCT, double-blind	Median 32.8 months (2.7 years)	Rosuvastatin vs placebo
Ridker 2008 (Jupiter; NCT00239681)[10]	RCT, double-blind	60 months (5 years)	Rosuvastatin vs Placebo
Tavazzi 2008 (GISSI HF)[26]	RCT, double-blind	3.9 years	Rosuvastatin vs Placebo
Budinski 2009[42]	RCT, double-blind	12 weeks	Pitavastatin 2–4 mg vs Atorvastatin 10–20 mg
Ose 2009[46]	RCT, double-blind	12 weeks	Pitavastatin 2–4 mg vs Simvastatin 20–40 mg
Athyros 2010 (GREACE)[31]	RCT, open label, survival study	3 years	Statin vs no statin
Chan 2010 (ASTRONOMER, ISRCTN 32424163)[32]	RCT, double-blind	3.5 years	Rosuvastatin vs placebo
Armitage 2010 (ISRCTN74348595, SEARCH trial)[30]	RCT, double-blind	Mean: 6.7 (SD1.5) person-years	Simvastatin 80 mg vs 20 mg
Collier 2011 (ASCOT-LLA)[37]	RCT, double-blind	Median 3.3 years	Atorvastatin vs placebo (≥65 years) Atorvastatin vs placebo (<65 years)
Nozue 2012 (TRUTH)[44]	RCT, open label	32 weeks	Pitavastatin 4 mg vs Pravastatin 20 mg
Chen 2013[24]	RCT, double-blind	3.5 months	ERN/LRPT + Simvastatin 20 vs ERN/LRPT + Simvastatin 40 Atorvastatin 10 vs 20 vs 40 vs 80
Kurogi 2013 (COMPACT-CAD)[43]	RCT, open label	2.3 years	Pitavastatin 2–4 mg vs Atorvastatin 10–20 mg
Shen 2013 (NCT00097786; NAVIGATOR)[38]	Re-analysis- NAVIGATOR trial	Median 5.0 years	Statins vs No Statins
NK-104-4.01CH[47]	RCT, open label	12 weeks	Pitavastatin 4 mg vs Atorvastatin 20 mg
Ong 2014 (TNT)[36]	RCT, double-blind	Median 4.9 years	Atorvastatin 10 mg vs 80 mg
INTREPID[41]	RCT, double-blind	12/52 weeks	Pitavastatin 4 mg vs Pravastatin 40 mg

NR = not reported; RCT = randomised controlled trial; MI = myocardial infarction. CABG = coronary artery bypass grafting; PCI = percutaneous coronary intervention; HTN = hypertension. AF = atrial fibrillation; ACEi = angiotensinogen converting enzyme inhibitor; ARB = angiotensin receptor blocker; PTCA = percutaneous transluminal coronary angioplasty; OHA = oral hypoglycaemic agents; IQR = interquartile range; SE = standard error; SD = standard deviation; CHF = congestive heart failure. HR = hazard ratio; LVH = left ventricular hypertrophy; TIA = transient ischaemic attack; ECG = electrocardiogram; PVD = peripheral vascular disease; ERN/LRPT = extended-release niacin/laropiprant; IFG = impaired fasting glucose; PAD = peripheral artery disease; FBG = fasting blood glucose; CCB = calcium channel blocker; COPD = chronic obstructive pulmonary disease; ICD = implantable cardioverter-defibrillator; HIV = human immunodeficiency virus; CAD = coronary artery disease.

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Table 2. Characteristics of included studies

Study name	No of patients	History of previous events; n (%)
PMSGCRP 1993[37]	530 vs 532	MI: 172 (32) vs 194 (36)
4S 1994[28]	2221 vs 2223	Previous CABG or angioplasty: 189 (9) vs 151 (7)
Downs 1998 (AFCAPS/TEXCAPS)[33]	3304 vs 3301	Family history of premature CHD: 497 (15) vs 538 (16)
GISSI PREV 2000[19]	2138 vs 2133	NR
Freeman 2001 (WOSCOPS)[12]	3302 vs 3293	NR
ALLHAT 2002[29]	5170 vs 5185	CHD: 695 (13.4) vs 780 (15.0)
Saito 2002[45]	240	NR
Shepherd 2002 (PROSPER)[11]	2891 vs 2913	Angina: 806 (27.9) vs 753 (25.8) Claudication: 198 (6.8) vs 192 (6.6) MI: 377 (13) vs 399 (13.7) Stroke or TIA: 328 (11.3) vs 321 (11) PAD surgery: 67 (2.3) vs 56 (1.9)
Collins 2003 (HPS)[25]	10 269 vs 10 267	Prior MI: 87% vs 22% Other CHD: 85% vs 18% No CHD: 83% vs 11%
Keech 2003 (LIPID)[18]	4512 vs 4502	MI: 2879 (64) vs 2875 (64) Unstable angina: 1633 (36) vs 1627 (36) Stroke: 171 (4) vs 198 (4) PTCA only: 502 (11) vs 486 (11) CABG only: 1217 (27) vs 1219 (27) Both PTCA and CABG: 135 (3) vs 133 (3)
Pedersen 2005 (IDEAL)[40]	4439 vs 4449	MI: 1231 (28.1) vs 1262 (28) CABG: 732 (16.5) vs 747 (16.8)
Amarenco 2006 (SPARCL)[39]	2365 vs 2366	Stroke: 1655 (70) vs 1613 (68.2) TIA: 708 (29.9) vs 752 (31.8)
Nakamura 2006 (MEGA)[35]	3866 vs 3966	NR
Kjekshus 2007 (NCT00206310; CORONA)[34]	2514 vs 2497	MI: 1510 (60) vs 1494 (60)Past or current angina pectoris: 1831 (73) vs 1807 (72) CABG or PCI: 660 (26) vs 638 (26) Stroke: 315 (13) vs 309 (12)
Ridker 2008 (Jupiter; NCT00239681)[10]	8901 vs 8901	NR
Tavazzi 2008 (GISSI HF)[26]	2285 vs 2289	MI: 727 (31.8) vs 774 (33.8) Stroke: 99 (4.3) vs 109 (4.8) CABG: 296 (13) vs 319 (13.9) PCI: 185 (8.1) vs 192 (8.4) ICD: 146 (6.4) vs 155 (6.8) AF: 440 (19.3) vs 477 (20.8)
Budinski 2009[42]	616 vs 205	NR
Ose 2009[46]	631 vs 217	NR
Athyros 2010 (GREACE)[31]	880 vs 720	NR
Chan 2010 (ASTRONOMER, ISRCTN 32424163)[32]	134 vs 135	NR
Armitage 2010 (ISRCTN74348595, SEARCH trial)[30]	6031 vs 6033	MI alone: 656/2955 vs 669/2890 +Other CHD: 631/2484 vs 658/2557+Other vascular: 164/524 vs 205/538 +DM: 225/633 vs 245/634
Collier 2011 (ASCOT-LLA)[37]	2189 vs 2256	Previous stroke or TIA: 285 (13) vs 319 (14.1)
	2979 vs 2881	Previous stroke or TIA: 200 (6.7) vs 197 (6.8)
Nozue 2012 (TRUTH)[44]	58 vs 61	CAD: 119 (100)Multivessel PCI: 8 (6.7)
Chen 2013[24]	297 vs 436	NR
	298 vs 439 vs 437 vs 433	NR
Kurogi 2013 (COMPACT-CAD)[43]	65 vs 64	PCI: 55 (84.6) vs 55 (86.0)MI: 33 (50.8) vs 32 (50.0)CAD: 12 (18.5) vs 13 (20.3)
Shen 2013 (NCT00097786; NAVIGATOR)[38]	1353 vs 4793	CABG: 41 (3) vs 67 (1.4)Angina: 175 (13) vs 508 (10.6)
NK-104-4.01CH[47]	476	NR
Ong 2014 (TNT)[36]	5006 vs 4995	MI: 2888 (57.7) vs 2945 (59) Angina: 4067 (81.2) vs 4084 (81.8) Cerebrovascular accident: 263 (5.3) vs 255 (5.1)PAD: 570 (11.4) vs 603 (12.1) CHD: 404 (8.1) vs 377 (7.6) Arrhythmia: 927 (18.5) vs 907 (18.2) Angioplasty: 2719 (54.3) vs 2688 (53.8)CABG: 2338 (46.7) vs 2317 (46.4)
INTREPID[41]	123 vs 124	NR

NR = not reported; RCT = randomised controlled trial; MI = myocardial infarction. CABG = coronary artery bypass grafting; PCI = percutaneous coronary intervention; HTN = hypertension. AF = atrial fibrillation; ACEi = angiotensinogen converting enzyme inhibitor; ARB = angiotensin receptor blocker; PTCA = percutaneous transluminal coronary angioplasty; OHA = oral hypoglycaemic agents; IQR = interquartile range; SE = standard error; SD = standard deviation; CHF = congestive heart failure. HR = hazard ratio; LVH = left ventricular hypertrophy; TIA = transient ischaemic attack; ECG = electrocardiogram; PVD = peripheral vascular disease; ERN/LRPT = extended-release niacin/laropiprant; IFG = impaired fasting glucose; PAD = peripheral artery disease; FBG = fasting blood glucose; CCB = calcium channel blocker; COPD = chronic obstructive pulmonary disease; ICD = implantable cardioverter-defibrillator; HIV = human immunodeficiency virus; CAD = coronary artery disease.

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Table 2. Characteristics of included studies

Study name	Co-morbidities; n (%)
PMSGCRP 1993[37]	HTN: 251 (47) vs 253 (48) Angina: 198 (37) vs 231 (43)
4S 1994[28]	HTN: 570 (26) vs 584 (26) Claudication: 130 (6) vs 123 (6) DM: 105 (5) vs 96 (4)
Downs 1998 (AFCAPS/TEXCAPS)[33]	HTN: 719 (22) vs 729 (22) Non-insulin treated DM: 84 (3.0) vs 71 (2.0) Non-insulin-treated DM or FBG ≥ 126 mg/dl: 126 (3.8) vs 113 (3.4)
GISSI PREV 2000[19]	DM: 13.6%HTN: 36.5%
Freeman 2001 (WOSCOPS)[12]	Angina: 164 (5) vs 174 (5) Intermittent claudication: 97 (3) vs 96 (3) DM: 41 (1) vs 35 (1) HTN: 531 (16) vs 506 (15)Minor ECG abnormality: 275 (8) vs 259 (8)
ALLHAT 2002[29]	DM: 1855 (35.9) vs 1783 (34.4)
Saito 2002[45]	NR
Shepherd 2002 (PROSPER)[11]	DM: 303 (10.5) vs 320 (11) HTN: 1799 (62.2) vs 1793 (61.6) Vascular disease: 1306 (45.2) vs 1259 (43.2)
Collins 2003 (HPS)[25]	NR
Keech 2003 (LIPID)[18]	Systemic HTN: 1867 (41) vs 1891 (42) DM: 396 (9) vs 386 (9) Obesity: 823 (18) vs 788 (18)
Pedersen 2005 (IDEAL)[40]	DM: 532 (12.0) vs 537 (12.1) HTN: 1461 (32.9) vs 1469 (33.0) CVD: 353 (8.0) vs 376 (8.5) PVD: 182 (4.1) vs 195 (4.4) CHF: 293 (6.6) vs 244 (5.5) AF: 347 (7.8) vs 336 (7.6)
Amarenco 2006 (SPARCL)[39]	HTN: 1476 (62.4) vs 1452 (61.4) DM: 395 (16.7) vs 399 (16.9)
Nakamura 2006 (MEGA)[35]	HTN: 1613 (42) vs 1664 (42) DM: 804 (21) vs 828 (21)
Kjekshus 2007 (NCT00206310; CORONA)[34]	HTN: 1594 (63) vs 1581 (63) DM: 743 (30) vs 734 (29) Current AF or flutter: 609 (24) vs 585 (23)
Ridker 2008 (Jupiter; NCT00239681)[10]	Metabolic syndrome: 3652 (41) vs 3723 (41.8)
Tavazzi 2008 (GISSI HF)[26]	HTN: 1260 (55.1) vs 1224 (53.5) DM: 625 (27.4) vs 571 (25) PVD: 184 (8.1) vs 160 (7) COPD: 538 (23.5) vs 522 (22.8) Neoplasia: 76 (3.3) vs 91 (4.0)
Budinski 2009[42]	NR
Ose 2009[46]	NR
Athyros 2010 (GREACE)[31]	DM: 173 (19.7%) vs 140 (19.4%) Metabolic syndrome: 365 (41.4%) vs 347 (48.2%)
Chan 2010 (ASTRONOMER, ISRCTN 32424163)[32]	NR
Armitage 2010 (ISRCTN74348595, SEARCH trial)[30]	NR
Collier 2011 (ASCOT-LLA)[37]	DM: 570 (26) vs 620 (27.5) LVH: 570 (26) vs 620 (27.5) ECG abnormalities : 383 (17.5) vs 378 (16.8) PVD: 155 (7.1) vs 142 (6.3) DM: 688 (23.1) vs 654 (22.7) LVH: 404 (13.6) vs 415 (14.4) ECG abnormalities : 358 (12.0) vs 351 (12.2) PVD: 106 (3.6) vs 111 (3.9)
Nozue 2012 (TRUTH)[44]	DM: 50 (42)HTN: 75 (63.1)
Chen 2013[24]	DM: 9 (3.0) vs 20 (4.6)Metabolic syndrome: 185 (62.3) vs 296 (67.9) DM: 11 (3.7) vs 20 (4.6) vs 26 (5.9) vs 27 (6.2) Metabolic syndrome: 194 (65.1) vs 301 (68.6) vs 295 (67.5) vs 315 (72.7)
Kurogi 2013 (COMPACT-CAD)[43]	DM: 27 (41.5) vs 25 (39.1)HTN: 54 (83.1) vs 53 (82.8)
Shen 2013 (NCT00097786; NAVIGATOR)[38]	HTN: 1036 (76.6) vs 4002 (83.5) CHF: 38 (2.8) vs 172 (3.6)
NK-104-4.01CH[47]	NR
Ong 2014 (TNT)[36]	HTN: 2721 (54.4) vs 2692 (53.9) DM: 753 (15) vs 748 (15)
INTREPID[41]	HIV infection

NR = not reported; RCT = randomised controlled trial; MI = myocardial infarction. CABG = coronary artery bypass grafting; PCI = percutaneous coronary intervention; HTN = hypertension. AF = atrial fibrillation; ACEi = angiotensinogen converting enzyme inhibitor; ARB = angiotensin receptor blocker; PTCA = percutaneous transluminal coronary angioplasty; OHA = oral hypoglycaemic agents; IQR = interquartile range; SE = standard error; SD = standard deviation; CHF = congestive heart failure. HR = hazard ratio; LVH = left ventricular hypertrophy; TIA = transient ischaemic attack; ECG = electrocardiogram; PVD = peripheral vascular disease; ERN/LRPT = extended-release niacin/laropiprant; IFG = impaired fasting glucose; PAD = peripheral artery disease; FBG = fasting blood glucose; CCB = calcium channel blocker; COPD = chronic obstructive pulmonary disease; ICD = implantable cardioverter-defibrillator; HIV = human immunodeficiency virus; CAD = coronary artery disease.

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Table 2. Characteristics of included studies

Study name	Co-medications; n (%)
PMSGCRP 1993[37]	NR
4S 1994[28]	Aspirin: 822 (37) vs 815 (37) β-blockers: 1258 (57) vs 1266 (57) CCBs: 712 (32) vs 668 (30) Isosorbide mono/dinitrate: 684 (31) vs 727 (33) Thiazides: 151 (7) vs 138 (6) Warfarin: 29 (1) vs 51 (2) Fish oil: 283 (13) vs 293 (13)
Downs 1998 (AFCAPS/TEXCAPS)[33]	Antihypertensives: 661 (20) vs 695 (21.1) ACEi: 244 (7.4) vs 257 (7.8) α-blockers: 68 (2.1) vs 67 (2.0) β-blockers: 141 (4.3) vs 156 (4.7) CCBs: 171 (5.2) vs 170 (5.1) Diuretics: 203 (6.1) vs 203 (6.1) Oestrogen ± progestins: 155 (31.1) vs 137 (27.5) NSAIDs: 494 (15) vs 445 (13.5) OHDs: 41 (1.2) vs 43 (1.3) Thyroid replacement hormone: 132 (4) vs 107 (3.2)Aspirin: 571 (17.3) vs 561 (17)
GISSI PREV 2000[19]	Antiplatelet agents > 90%β-blockers 42.7%ACEi 40.2%
Freeman 2001 (WOSCOPS)[12]	NR
ALLHAT 2002[29]	Women taking oestrogen: 390 (15.5) vs 399 (15.7)Aspirin: 1566 (30.3) vs 1637 (31.6)Antihypertensives: 4641 (89.8) vs 4663 (89.9)
Saito 2002[45]	NR
Shepherd 2002 (PROSPER)[11]	NR
Collins 2003 (HPS)[25]	NR
Keech 2003 (LIPID)[18]	Aspirin: 3726 (83) vs 3689 (82) β-blocker: 2090 (46) vs 2152 (48) Calcium antagonist: 1563 (35) vs 1610 (36) ACEi: 720 (16) vs 719 (16) Nitrate: 1599 (35) vs 1610 (36) Diuretic: 727 (16) vs 761 (17) Insulin: 60 (1) vs 49 (1) OHD: 236 (5) vs 262 (6)
Pedersen 2005 (IDEAL)[40]	Aspirin: 3494 (78.7) vs 3536 (79.5) Warfarin or dicoumarol: 558 (12.6) vs 559 (12.6) β-blockers: 3377 (76.1) vs 3281 (73.7) CCBs: 882 (19.9) vs 840 (18.9) ACEi: 1296 (29.2) vs 1367 (30.7) ARBs: 263 (5.9) vs 270 (6.1)
Amarenco 2006 (SPARCL)[39]	Antiplatelet therapy: 2067 (87.4) vs 2063 (87.2) ACEi: 683 (28.9) vs 667 (28.2) CCBs: 350 (14.8) vs 359 (15.2) β-blocker: 414 (17.5) vs 422 (17.8) ARBs: 110 (4.7) vs 102 (4.3) Vitamin K antagonist: 139 (5.9) vs 154 (6.5)
Nakamura 2006 (MEGA)[35]	Antihypertensives: 1491 (39) vs 1549 (39) CCBs: 1017 (26) vs 1048 (26) ACEi/ARB: 473 (12) vs 512 (13) β-blockers: 318 (8) vs 329 (8) Diuretics: 111 (3) vs 128 (3) Aspirin: 36 (1) vs 42 (1)
Kjekshus 2007 (NCT00206310; CORONA)[34]	Loop or thiazide diuretic: 2231 (89) vs 2185 (88) Aldosterone antagonist: 986 (39) vs 979 (39) ACEi or ARB: 2292 (91) vs 2307 (92) β-blocker: 1887 (75) vs 1879 (75) Digitalis glycoside: 845 (34) vs 803 (32) Antiarrhythmic therapy: 306 (12) vs 289 (12) Antiplatelet or anticoagulant therapy: 2273 (90) vs 2251 (90)
Ridker 2008 (Jupiter; NCT00239681)[10]	Aspirin: 1481 (16.6) vs 1477 (16.6)
Tavazzi 2008 (GISSI HF)[26]	Previous medical treatment was given
Budinski 2009[42]	NR
Ose 2009[46]	NR
Athyros 2010 (GREACE)[31]	Aspirin and otherantiplatelet agents, β-blockers, ACE inhibitors or ARB, Nitrates, CCBs, Diuretics
Chan 2010 (ASTRONOMER, ISRCTN 32424163)[32]	NR
Armitage 2010 (ISRCTN74348595, SEARCH trial)[30]	NR
Collier 2011 (ASCOT-LLA)[37]	NR
	NR
Nozue 2012 (TRUTH)[44]	Aspirin: 117 (98.3)Thienopyridines: 118 (99.2)ACEi:61 (51.3)β-blocker: 13 (10.9)CCBs: 60 (50.4)
Chen 2013[24]	NR
	NR
Kurogi 2013 (COMPACT-CAD)[43]	Statin:25 (38.5) vs 24 (37.5) CCBs: 31 (47.7) vs 33 (51.6) β-blocker: 22 (33.8) vs 20 (31.3) ACEi: 22 (33.8) vs 22 (34.4) ARBs: 23 (35.4) vs 23 (35.9) Insulin: 20 (30.8) vs 5 (7.8) Sulfonylurea: 9 (13.8%) vs 7 (10.9) α-glucosidase inhibitor: 6 (9.2) vs 5 (7.8) Antiplatelet agents: 65 (100) vs 63 (98.4)Nitrate: 15 (23.1) vs 14 (21.9)
Shen 2013 (NCT00097786; NAVIGATOR)[38]	NR
NK-104-4.01CH[47]	NR
Ong 2014 (TNT)[36]	NR
INTREPID[41]	NR

NR = not reported; RCT = randomised controlled trial; MI = myocardial infarction. CABG = coronary artery bypass grafting; PCI = percutaneous coronary intervention; HTN = hypertension. AF = atrial fibrillation; ACEi = angiotensinogen converting enzyme inhibitor; ARB = angiotensin receptor blocker; PTCA = percutaneous transluminal coronary angioplasty; OHA = oral hypoglycaemic agents; IQR = interquartile range; SE = standard error; SD = standard deviation; CHF = congestive heart failure. HR = hazard ratio; LVH = left ventricular hypertrophy; TIA = transient ischaemic attack; ECG = electrocardiogram; PVD = peripheral vascular disease; ERN/LRPT = extended-release niacin/laropiprant; IFG = impaired fasting glucose; PAD = peripheral artery disease; FBG = fasting blood glucose; CCB = calcium channel blocker; COPD = chronic obstructive pulmonary disease; ICD = implantable cardioverter-defibrillator; HIV = human immunodeficiency virus; CAD = coronary artery disease.

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Table 2. Characteristics of included studies

Study name	N developing diabetes/N non-diabetic patients
PMSGCRP 1993[37]	1/530 vs 0/532
4S 1994[28]	198/2116 vs 193/2126
Downs 1998 (AFCAPS/TEXCAPS)[33]	72/3094 vs 74/3117
GISSI PREV 2000[19]	96/1743 vs 105/1717
Freeman 2001 (WOSCOPS)[12]	75/2999 vs 93/2975
ALLHAT 2002[29]	238/3017 vs 212/3070
Saito 2002[45]	1/84 vs 1/81
Shepherd 2002 (PROSPER)[11]	165/2510 vs 127/2513
Collins 2003 (HPS)[25]	335/7291 vs 293/7282
Keech 2003 (LIPID)[18]	126/3150 vs 138/3067
Pedersen 2005 (IDEAL)[40]	240/3907 vs 209/3912
Amarenco 2006 (SPARCL)[39]	166/1908 vs 115/1916
Nakamura 2006 (MEGA)[35]	172/3013 vs 164/3073
Kjekshus 2007 (NCT00206310; CORONA)[34]	100/1771 vs 88/1763
Ridker 2008 (Jupiter; NCT00239681)[10]	270/8901 vs 216/8901
Tavazzi 2008 (GISSI HF)[26]	225/1660 vs 215/1718
Budinski 2009[42]	1/576 vs 2/179
Ose 2009[46]	1/592 vs 0/202
Athyros 2010 (GREACE)[31]	29/707 vs 25/580
Chan 2010 (ASTRONOMER, ISRCTN 32424163)[32]	1/134 vs 0/135
Armitage 2010 (ISRCTN74348595, SEARCH trial)[30]	625/6031 vs 587/6033
Collier 2011 (ASCOT-LLA)[37]	61/2189 vs 70/2256 140/2979 vs 109/2881
Nozue 2012 (TRUTH)[44]	2/38 vs 2/31
Chen 2013[24]	New diagnosis of IFG: 1/605 (0.2)New onset diabetes: 6/703 (0.9) New diagnosis of IFG: 1/1343 (0.1)New onset diabetes: 3/1523 (0.2)
Kurogi 2013 (COMPACT-CAD)[43]	1/36 vs 3/35
Shen 2013 (NCT00097786; NAVIGATOR)[38]	Progression to diabetes; unadjusted HR 1.30 (95%CI 1.14 to 1.48), baseline adjusted HR 1.30 (95%CI 1.13 to 1.49)
NK-104-4.01CH[47]	9/280 vs 2/142
Ong 2014 (TNT)[36]	308/4253 vs 351/4274
INTREPID[41]	0/123 vs 4/124

NR = not reported; RCT = randomised controlled trial; MI = myocardial infarction. CABG = coronary artery bypass grafting; PCI = percutaneous coronary intervention; HTN = hypertension. AF = atrial fibrillation; ACEi = angiotensinogen converting enzyme inhibitor; ARB = angiotensin receptor blocker; PTCA = percutaneous transluminal coronary angioplasty; OHA = oral hypoglycaemic agents; IQR = interquartile range; SE = standard error; SD = standard deviation; CHF = congestive heart failure. HR = hazard ratio; LVH = left ventricular hypertrophy; TIA = transient ischaemic attack; ECG = electrocardiogram; PVD = peripheral vascular disease; ERN/LRPT = extended-release niacin/laropiprant; IFG = impaired fasting glucose; PAD = peripheral artery disease; FBG = fasting blood glucose; CCB = calcium channel blocker; COPD = chronic obstructive pulmonary disease; ICD = implantable cardioverter-defibrillator; HIV = human immunodeficiency virus; CAD = coronary artery disease.

In the comparison of intensive versus moderate statin therapy, we found that intensive treatment significantly increased the risk of diabetes in the pooled estimate (pooled OR 1.12; 95%CI 1.01–1.24; I^2 13%; $p = 0.04$; 7 RCTs) under the random-effects model. (Figure 3a)

Four of the seven pitavastatin trials,[42,43,46,47] which compared pitavastatin with other equivalent potency statins showed reduction in odds of diabetes in the pitavastatin arm; however, this difference was not statistically significant (pooled OR 0.69; 95%CI 0.18–2.65; I^2 31%; $p = 0.59$; 4 RCTs) in the random-effects model. (Figure 3b)

Meta-regression. We performed the meta-regression analysis for the main pairwise meta-analysis to explore the reasons for low-moderate heterogeneity (I^2: 36%, Figure 2). We entered the covariates such as age, follow-up duration, BMI and LDL levels in the meta-regression model, which are reported to be strongly related to the likelihood of developing diabetes in the literature. All the variables were entered, at a time, in the analysis to perform a joint test for all covariates. None of the covariates was significantly associated with the difference between the studies for development of diabetes (p-value

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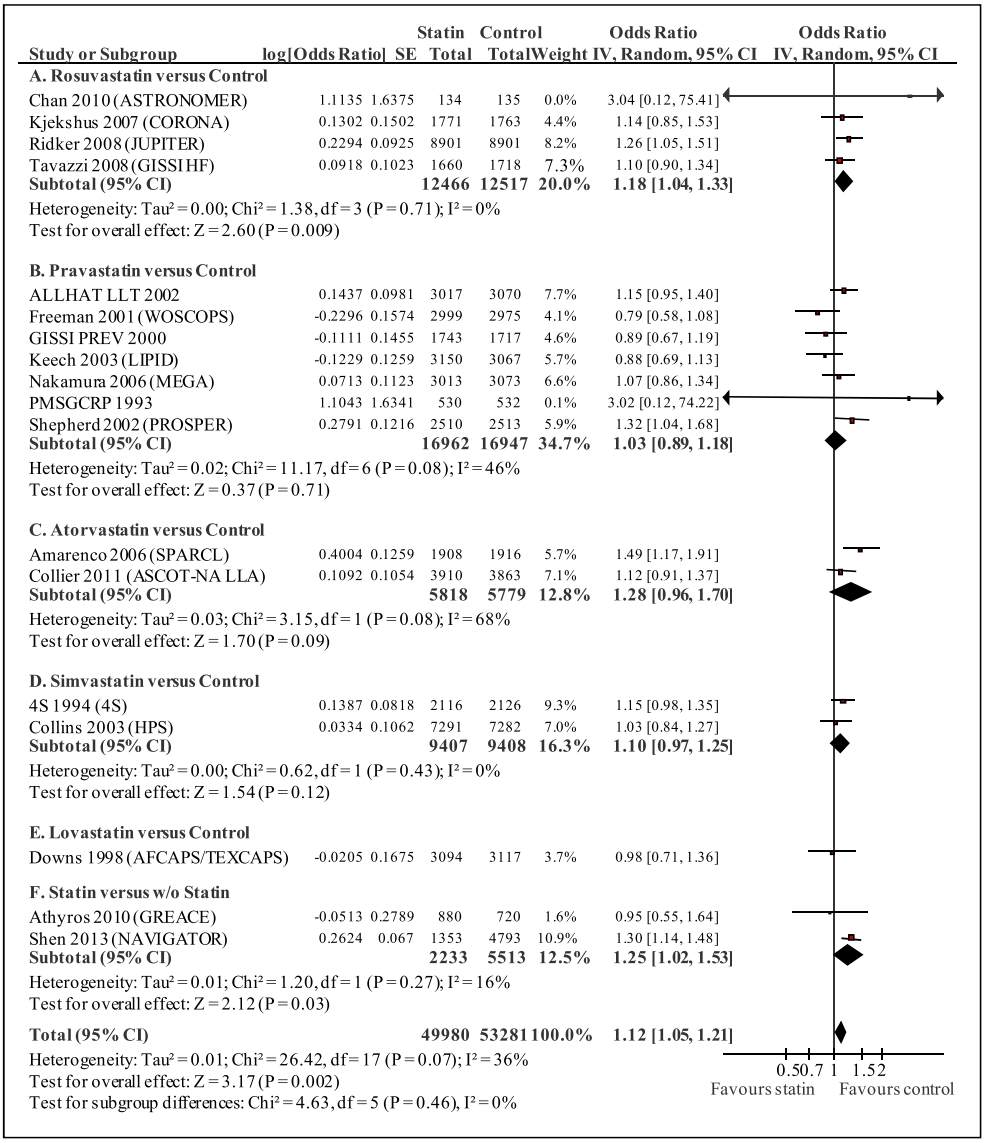

Figure 2. Forest plot for pairwise meta-analysis

for the joint test 0.25) [Appendix Table S1]. However, around 6% of the heterogeneity was explained by these covariates, resulting in around 29% residual heterogeneity in the adjusted model.

Network meta-analysis (combination of direct and indirect comparisons). We included 27 studies in the NMA; two studies[31,38] compared any statin versus without statin and were excluded from the analysis (Figure 1). Pravastatin versus placebo (seven studies) was the most prevalent comparison followed by rosuvastatin versus placebo (four studies) and atorvastatin versus pitavastatin (three studies). Figure 4 shows network of the treatments for the development of diabetes. Each line links the treatments directly compared in the trial. The thickness of the edge is proportional to the mean control group risk for the comparisons included in the network; the width of the circle is proportional to the number of studies involving the specific treatment. No visible difference in the thickness of the edges supports the fulfilment of transitivity assumption of the network. The colour of the edge depicts RoB for that comparison; red for 'high', green for 'low' and yellow for 'unclear' RoB. From the figure, it can be seen that placebo was the most commonly used comparator.

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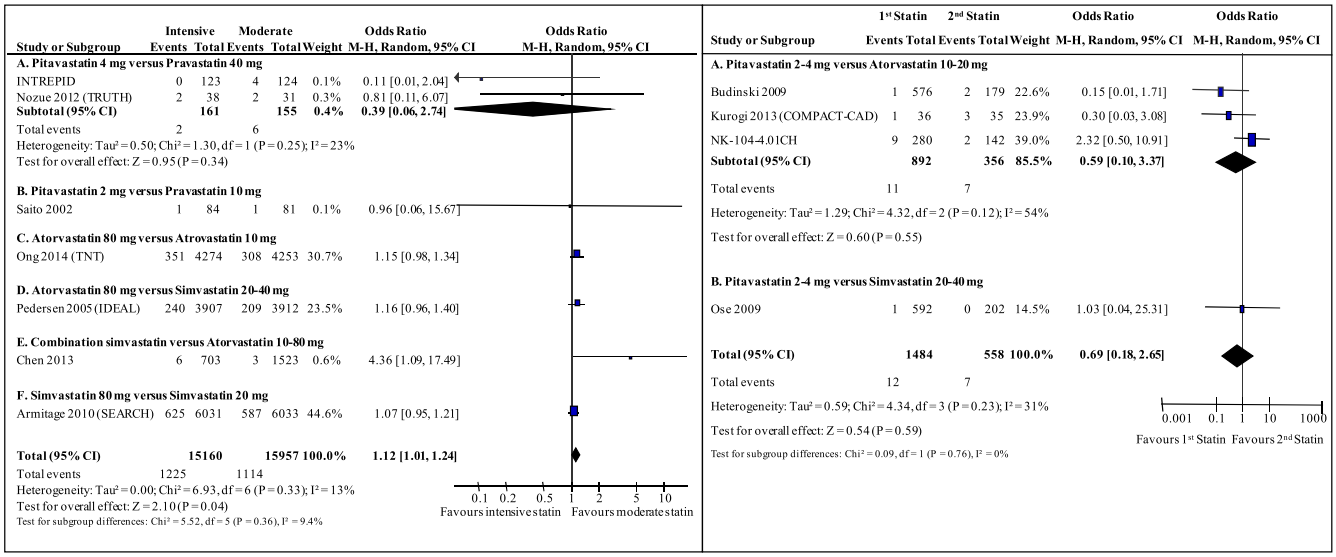

Figure 3. (a) Forest plot: Intensive versus moderate statin treatment; (b) Forest plot: equal potency statin treatment

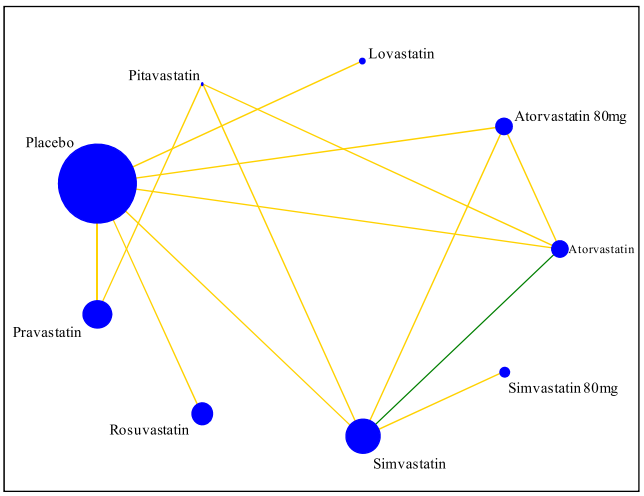

Figure 4. Network plot of available direct comparisons. Thickness of the edge is proportional to the mean control group risk for the comparisons included in the network; the width of the circle (node) is proportional to the number of studies involving the specific treatment; colour of the edge indicate risk of bias in a comparison (red = high, yellow = moderate and green = low)

There was evidence of statistical and clinical inconsistency in the two triangular loops atorvastatin–placebo–simvastatin and atorvastatin–atorvastatin 80 mg-simvastatin with the ratio of odds ratio ROR 4.4; 95%CI 1.08–18.04 and ROR 4.41; 95%CI 1.08–18.09, respectively. Other triangular loops; atorvastatin–pitavastatin–simvastatin, atorvastatin–atorvastatin 80 mg-placebo and atorvastatin 80 mg-placebo–simvastatin and quadrilateral loops; pitavastin–placebo–pravastatin–simvastatin and atorvastatin–pitavastin–placebo–pravastatin in the network did not show significant inconsistency (Figure 5).

Summary odds ratios with their 95%CIs and predictive intervals (PrIs) is shown as forest plot or interval plot for each statin versus placebo and statin versus active comparator in Figure 6. Rosuvastatin and atorvastatin 80 mg increased the risk of developing diabetes significantly compared with placebo. Atorvastatin 80 mg was ranked highest for increasing the risk of diabetes with OR 1.34 (95%CI 1.14–1.57) followed by OR: 1.17 (95%CI 1.02–1.35) for rosuvastatin, 1.21 (95%CI 0.99–1.49) for simvastatin 80 mg, 1.13 (95%CI 0.99–1.29) for simvastatin, 1.13 (95%CI 0.94–1.34) for atorvastatin, 1.04 (95%CI 0.93–1.16) for pravastatin, 0.98 (95%CI 0.69–1.38) for lovastatin, and 0.74 (95%CI 0.31–1.77) for pitavastatin.

In the NMA, atorvastatin 80 mg increased the odds of developing diabetes even compared with pravastatin (OR: 1.29; 95%CI: 1.06–1.56), simvastatin (OR: 1.18; 95%CI 1.01–1.39), and atorvastatin 10 mg ([OR: 1.19; 95%CI: 1.01–1.40] Figure 6).

Contribution plot for all the possible direct and indirect comparisons is presented in Figure S3. From the figure, it can be seen that simvastatin versus placebo is the most influential comparison with the contribution of 16.2% followed by pravastatin versus placebo with 13% for the entire network. Atorvastatin 80 mg versus simvastatin is the least influential comparison in the entire network with weight of just 0.1% and benefits most from the network as little direct evidence

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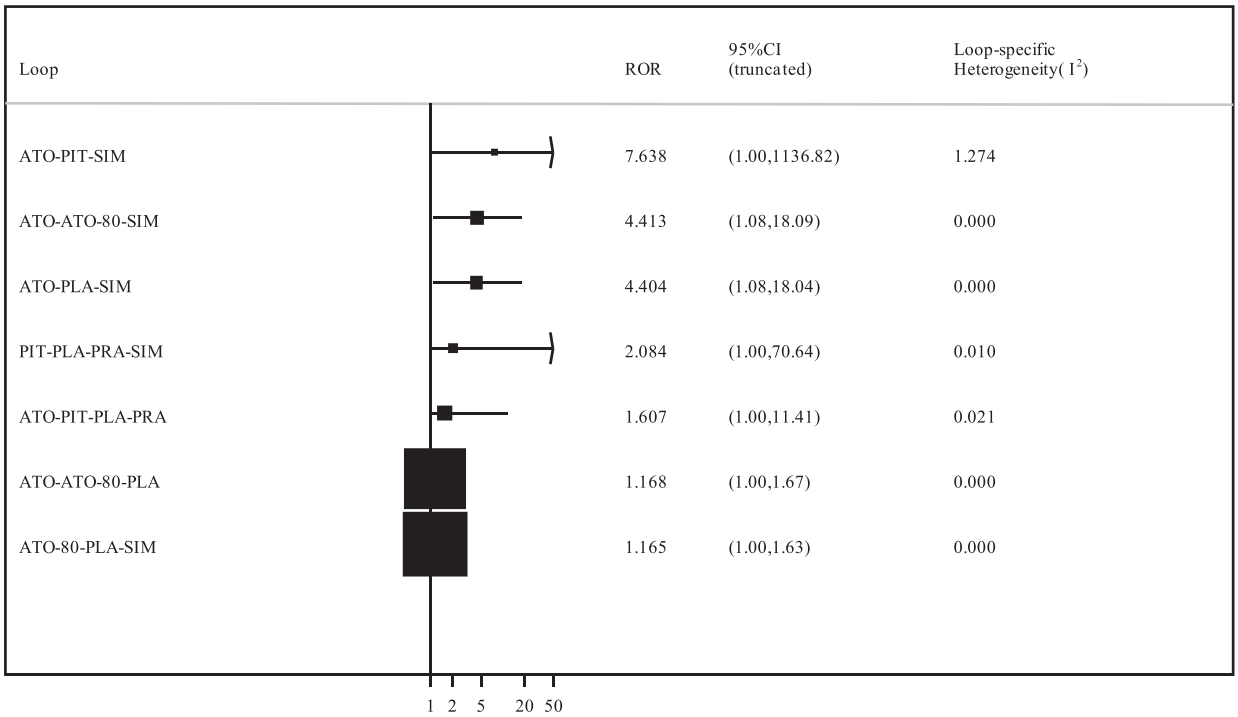

Figure 5. Inconsistency plot for evaluating consistency within first order closed loops. Risk of odds ratio between direct and indirect evidence is reported on X-axis. ATO = atorvastatin; PLA = placebo; SIM = simvastatin; PRA = pravastatin; PIT = pitavastatin; ATO-80 = atorvastatin 80 mg; ROR = ratio of odds ratio; CI = confidence interval

exists for it. It is interesting to note that, in the pairwise estimate, simvastatin significantly increased the odds of developing diabetes compared with atorvastatin ([OR 4.36; 95%CI 1.09–17.49] Figure 2) and seemed to have limited power, but after obtaining the benefit from network, this comparison reduced to non-significant ([OR 1.00; 95%CI 0.83–1.22] Figure 6).

Publication bias. Figure S4 shows the 'comparison-adjusted' funnel plot for our network. In this plot, the horizontal axis presents the difference between the study-specific effect sizes from the corresponding comparison-specific summary effect. In the absence of small studyeffects, the comparison-adjusted funnel plot should be symmetric around the zero line. In our analysis, although small study effects were seen for some of the studies, these comparison-specific studies were symmetrically distributed around the line of no difference.

Hydrophilic versus lipophilic statins. Subgroup analysis including 19 studies[3,10,12,18,19,25–29,32–35,37,39,41,44,45] that compared hydrophilic or lipophilic statins with placebo or to each other was performed. In the subgroup analysis, lipophilic statins increased the risk of developing diabetes significantly compared with placebo (OR: 1.14; 95%CI: 1.02–1.28) in the mixed estimate. However, for the head-to-head comparison in the mixed estimate, lipophilic statins did not increase the risk significantly when compared with hydrophilic statins (OR: 1.05; 95%CI: 0.9–1.23). [Figure S5]

DISCUSSION

Our study was aimed to use NMA to generate evidence on whether statin use predisposed patients to a risk of developing diabetes. Our analysis was limited to the onset of diabetes and did not take into account the exacerbation of diabetes-related complications in pre-existing diabetes patients. We included 29 studies for the pairwise meta-analysis and 27 articles for the NMA. Our pairwise meta-analysis demonstrated an increasing risk to diabetes at 12%, with low-moderate heterogeneity. The low-moderate heterogeneity suggests that most variation was attributable to chance alone. Rosuvastatin was the only statin associated with statistically significant higher odds of increasing diabetes to 18%.

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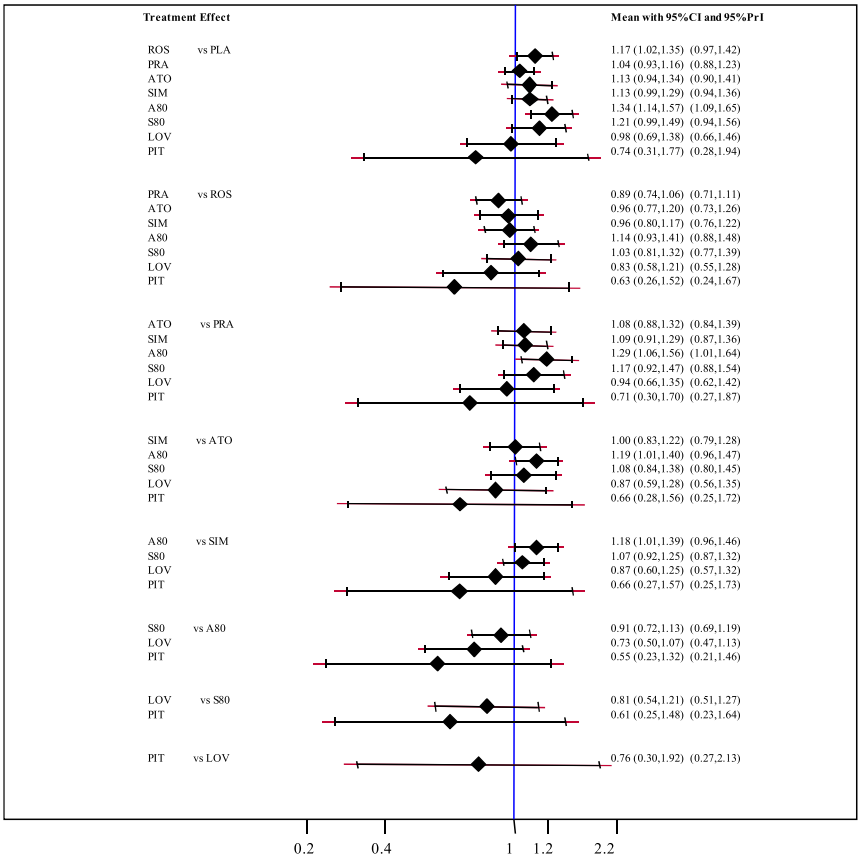

Figure 6. Forest plot (Interval plot): each statin versus placebo and statin versus active comparator. Black lines around the diamond for each comparison indicate the confidence interval while the red line indicates the predictive interval. This plot depicts estimated summary effects along with their confidence intervals and their corresponding PrI for all comparisons and summarizes in one plot the relative mean effects, predictions and the impact of heterogeneity on each comparison. The plot indicates that for one of these comparisons (ROS vs PLA), the PrI is wide enough compared with the CI to suggest that in a future study, the rosuvastatin can have lesser risk of developing diabetes than placebo, although the lower CI limit does not cross the line of no effect. CI = confidence interval; PrI = predictive interval; ROS = rosuvastatin; PLA = placebo; PRA = pravastatin; ATO = atorvastatin; SIM = simvastatin; A80 = atorvastatin 80 mg; S80 = simvastatin 80 mg; LOV = lovastatin; PIT = pitavastatin

Two of the earlier systematic reviews and meta-analyses[13,14] had already concluded that statin significantly increased the risk of diabetes by about 9%. Our pairwise meta-analysis also found a similar risk at 13% without significant heterogeneity. Sattar *et al.*[13] included 13 RCTs with 91 140 participants, of whom 4278 developed diabetes during a mean of 4 years (2226 assigned statins and 2052 assigned control treatment). Mills *et al.*[14] evaluated the incidence of diabetes available from 17 RCTs enrolling 1 11 003 individuals, 2215 assigned to statin and 2048 to control developed diabetes. Sattar *et al.*[13] reported that among statins, rosuvastatin was the only statin that was associated with statistically significantly higher odds of diabetes in three trials. We also found the similar results for rosuvastatin in the pooled analysis of the four trials that we included. Additionally, Sattar *et al.*[13] reported that hydrophilic and lipophilic statins were associated with similar risk for developing diabetes compared with placebo. We found lipophilic statins to be significantly associated with 14% higher risk of diabetes compared with placebo. This can be explained by the fact that lipophilic statins have higher half-life and are excreted slowly and therefore, remain in the body longer. Sattar *et al.*[13] could not probably detect this difference because of the limited number of studies included, thereby providing less power to the comparison. However, in the head-to-head comparison in the network meta-analysis, there was no significant difference between hydrophilic and lipophilic statins for the likelihood of developing diabetes.

Naci *et al.*[16]conducted a comprehensive NMA involving 246 955 participants from 135 RCTs to evaluate the comparative tolerability and harms of individual statins. This review found similar results as our study for the pairwise meta-analysis; however, in the NMA, there were no statistically detectable differences between individual statins for the

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incidence of diabetes mellitus. Navarese *et al.*[17] investigated the impact of different types and doses of statins on new-onset diabetes employing the NMA methodology. This study included similar subset of studies as Naci *et al.*[16] for the diabetes outcomes and also found that none of the individual statins increased the odds of developing diabetes. Their study did not find any significant association between higher-dose statins like atorvastatin 80 mg and diabetes. Conversely, from the NMA, we found that atorvastatin 80 mg and rosuvastatin significantly increased the risk of developing diabetes by 34% and 17%, respectively. We also found that higher-dose atorvastatin even increased the risk of diabetes compared with other statins like pravastatin, simvastatin and low-dose atorvastatin. Furthermore, simvastatin 80 mg versus placebo has an effect size marginally higher than rosuvastatin vs placebo (1.21 vs 1.17) and the lower CIs of statistically insignificant simvastatin 80 mg and of significant rosuvastatin are close to 1 (0.99 vs 1.02). The difference in the results between the previous NMAs and our NMA could be attributed to two reasons. Firstly, to explore the association between statins and diabetes, Naci *et al.*[16] and Navarese *et al.*[17] included around 17 studies in the network, whereas our NMA included 27 studies (total 29 studies) in the network with published and unpublished evidence. Secondly, these two NMAs did not include pitavastatin trials unlike our study. Pitavastatin trials contributed around 10% in the overall network and therefore increased the power of our network benefitting the other comparisons which had limited direct evidence. This shows the utility of NMA in increasing the power of the comparisons through addition of the indirect estimates to the direct estimates. Another difference between the previous NMAs and ours is in the methodology employed for fitting the model. We adopted a Frequentist analytic approach, which would be expected to yield identical results as compared with the analyses conducted within a Bayesian framework with non-informative priors as used by Naci *et al.*[16] and Navarese *et al.*[17]

Minimizing the risk of bias is of major importance for a good quality systematic literature review. In this review, we therefore restricted the meta-analysis to RCTs, ideally with proper randomisation, allocation concealment and blinding. However, not all the studies fulfilled all of these criteria. Around 50% of the studies were at 'high' or 'unclear' RoB for attrition bias and for method employed for detection of diabetes. We included the published as well as unpublished trials, which provide good statistical power to our review. The method of detection of diabetes varied among the trials, and we included method of detection as one of the parameters in assessment of RoB and also coloured the edges of the network according to overall bias of the study. This is to provide readers' guidance for judging the results of any comparison.

Preiss *et al.*[48] in a meta-analysis of intensive dose versus moderate dose statin found that intense dose statins were significantly associated with higher odds of diabetes to 12%. We found similar result in our pairwise meta-analysis and NMA too, atorvastatin 80 mg increased the risk of diabetes significantly compared with placebo and some of the active statin treatment. Vallejo-Vaz *et al.*[49] conducted a meta-analysis of RCTs to evaluate the effects of pitavastatin on glycaemia and new onset diabetes in non-diabetic individuals using data from 15 trials. This study found that pitavastatin decreased the risk of diabetes compared with other statin treatment; however, the association was non-significant. We also found similar results for pitavastatin compared with other equipotent statin treatments.

Recently, Swerdlow *et al.*[50] used a Mendelian randomisation approach, which is considered to be a powerful proof of causality and found single nucleotide polymorphisms (SNP) in the HMGCR gene, rs17238484 was associated with higher risk of type 2 diabetes. But limitation of this approach should also be kept in mind. The power of Mendelian randomisation lies in its ability to avoid the often substantial confounding seen in conventional observational epidemiology. This confounding can be reintroduced in Mendelian randomisation in case of linkage disequilibrium and if the selected gene has pleiotropic effect. In Swerdlow *et al.*,[50] two selected SNPs, rs17238484 and rs12916, were in strong linkage disequilibrium and have pleiotropic effect. Additionally, they, in their principal analysis with the rs17238484 SNP, found pooled OR 1.02 (95%CI: 1.00 to 1.05; $p = 0.09$) for association with diabetes. Contrary to reported in the paper, this is not a significant association. They however, in their subsidiary analysis, used the rs12916 SNP and found significant association with this SNP to diabetes.

As with any evidence review, our study has some limitations. In view of the lack of head-to-head studies of statins, we performed indirect comparisons cognizant of the limitations of this approach. Use of this methodology requires assumptions about the comparability of the included RCTs with respect to similarity of patient characteristics and methodological quality. However, clinicians and patients are faced with the dilemma of choosing from among these

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statins in the absence of robust comparative data about their relative safety. We found evidence of inconsistency in the atorvastatin–placebo–simvastatin atorvastatin–atorvastatin 80 mg-simvastatin triangular loops; therefore, mixed estimates related to this loop should be interpreted with caution.

We assessed the risk of diabetes across all trials and all statins for the CVDs. However, we recognize that this may be inappropriate in this case for several reasons. Different statins and existing co-morbidities may be associated with different risk profiles for developing diabetes.

For this review, we limited inclusion to RCTs and their open-label extensions. However long-term observational studies, including population-based registries, can provide realistic longer-term estimates of the risks of biologics in the 'real world', although they too have their limitations. These may include indication bias and differences in healthcare setting, country of origin of study, which may impact the choice of statins and make generalizability challenging.

In the context of the aforementioned limitations, our study used the best available evidence to show no potential risk of diabetes with the different classes of statins that were compared. However, large, long-term studies are required to assess this risk and the potential causes, with long-term statin use.

CONCLUSION

Based on the results, statins, as a class, increased the risk of diabetes significantly in the pairwise meta-analysis. Overall, there appears to be a small increased risk of incident diabetes, particularly with more intensive statin therapy, although more data would be valuable to increase the robustness of this interpretation, given that the lower confidence intervals of our study analyses are close to, or just crossing one.

CONTRIBUTORS

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Data extraction: D.T., A.P., V.J., A.M.
Data analysis: D.T.
Data interpretation: D.T., S.N.
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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

KEY POINTS

- Statins, as a class, significantly increased the likelihood of developing diabetes by 12% in the direct meta-analysis
- High-dose atorvastatin ranked highest followed by rosuvastatin in increasing the odds of diabetes in the network meta-analysis
- Rosuvastatin increased the risk of diabetes in both, pairwise as well as network meta-analysis
- Intensive statin treatment and lipophilic statins have more likelihood of developing diabetes

PRIOR POSTINGS AND PRESENTATIONS

This topic was presented as a poster in the 20th Annual Meeting, International Society of Pharmacoeconomics and Outcomes Research (ISPOR), Philadelphia, USA and received ISPOR Poster Finalists Award.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article at the publisher's web site.

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