Meta-Analysis of Impact of Different Types and Doses of Statins on New-Onset Diabetes Mellitus

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Recent reports indicate that statins are associated with an increased risk for new-onset diabetes mellitus (DM) compared with placebo and that this relation is dose dependent. The aim of this study was to perform a comprehensive network meta-analysis of randomized controlled trials (RCTs) investigating the impact of different types and doses of statins on new-onset DM. RCTs comparing different types and doses of statins with placebo were searched for using the MEDLINE, Embase, and Cochrane databases. A search of RCTs pertinent to this meta-analysis covering the period from November 1994 to October 2012 was conducted by 2 independent investigators using the MEDLINE, Cochrane, Google Scholar, and Embase databases as well as abstracts and presentations from major cardiovascular meetings. Seventeen RCTs reporting the incidence of new-onset DM during statin treatment and including a total of 113,394 patients were identified. The RCTs compared either a statin versus placebo or high-dose versus moderate-dose statin therapy. Among different statins, pravastatin 40 mg/day was associated with the lowest risk for new-onset DM compared with placebo (odds ratio 1.07, 95% credible interval 0.86 to 1.30). Conversely, rosuvastatin 20 mg/day was numerically associated with 25% increased risk for DM compared with placebo (odds ratio 1.25, 95% credible interval 0.82 to 1.90). The impact on DM appeared to be intermediate with atorvastatin 80 mg/day compared with placebo (odds ratio 1.15, 95% credible interval 0.90 to 1.50). These findings were replicated at moderate doses. In conclusion, different types and doses of statins show different potential to increase the incidence of DM. **(Am J Cardiol 2013;111:1123−1130)**

Although generally well tolerated, statins, compared with placebo, have been associated with a higher incidence of new-onset diabetes mellitus (DM) in several experimental studies and a meta-analysis of 13 randomized controlled trials (RCTs).[1,2] Another meta-analysis of 5 studies showed a dose-dependent effect of statins on the incidence of DM.[3] On the basis of these findings, the US Food and Drug Administration has recently added information to statin labels regarding the impact of these agents on DM.[4] The constellation of statins is wide, with differences concerning active compounds, associated effects, and therapeutic doses. The recent concerns about the safety of statins pose therapeutic dilemmas regarding which type and dose of statin may minimize the risk for developing DM. To date, appropriately powered head-to-head comparisons among statins with regard to the DM end point are lacking. Given the perceived need to understand the specific risk for developing DM associated with one statin compared with another and to relate that to the administered dose of the drug, a network meta-analysis is timely and warranted. Accordingly, we performed a comprehensive network meta-analysis of RCTs investigating the impact of different types and doses of statins on new-onset DM.

Methods

Established methods were used in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement for reporting systematic reviews and meta-analyses in health care interventions.[5] A search of pertinent RCTs conducted from November 1994 to October 2012 was performed by 2 independent investigators covering the MEDLINE, Cochrane, Google Scholar, and Embase databases as well as abstracts and presentations from major cardiovascular meetings, using the search string "statins AND/OR diabetes." The internal validity of the RCTs was assessed by 2 independent reviewers.

Citations were screened at the title and abstract level and retrieved as full reports. Inclusion criteria were (1) studies in

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See page 1129 for disclosure information.

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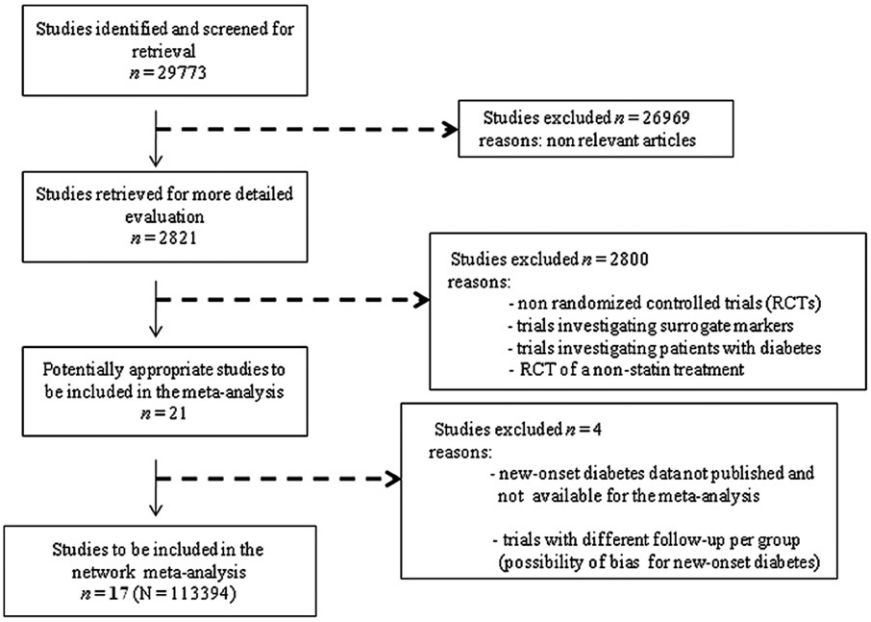

Figure 1. Flow diagram of the network meta-analysis.

humans, (2) RCTs, and (3) studies comparing patients treated with high-dose statins versus placebo or with high- versus moderate-dose statins connected in a network with a third comparison (placebo or statin) and reporting the incidence rates of new-onset DM in both arms. To be consistent with other large meta-analyses and to provide robust estimates, we excluded trials with follow-up $\leq$1 year and including $<$1,000 patients.

A network meta-analysis was planned with respect to new-onset DM as an end point to compare (1) high-dose statins versus placebo and different high doses of statins, 2) moderate-dose statins versus placebo and different moderate doses of statins, and (3) high-dose versus moderate-dose statins. This research tool remains a well-established method capable of comparing different treatments using a common reference treatment while maintaining the randomization design and integrating data from direct and indirect comparisons.[6,7]

New-onset DM was defined as any adverse event report of DM, or starting glucose-lowering medication, or a fasting plasma glucose level $\geq$7 mmol/L (either 1 or 2 values, depending on the frequency of measurement in the trial). Dichotomous outcome variables were compared using odds ratios (ORs) and 95% credible intervals (CIs) by means of network meta-analysis using a Bayesian hierarchical random-effects model. Analysis was based on non-informative prior findings for effect sizes and precision. Convergence and lack of autocorrelation were checked and confirmed after 10,000 iterations. The final summary statistics were based on a further 100,000 iterations, after discarding the initial 10,000-iteration burn-in. Sensitivity analysis was conducted by repeating the main computations using a fixed-effect method. Pairwise contrasts were examined, and heterogeneity was assessed using the I^2 statistic, with values $<$25%, $\geq$25% and $\leq$50%, and $>$50%, respectively, representing mild, moderate, and severe heterogeneity. Inconsistency between direct and indirect evidence sources was assessed by inspection of the model fit and by comparing the results of the pairwise meta-analyses with the estimates from the network meta-analysis. We computed the probability that each statin agent was the best treatment in terms of inducing less DM. The ranking of the competing drugs was assessed with the median of the posterior distribution for the rank of each drug; cumulative ranking probabilities curves for competing statin treatments were built. The surface under the cumulative ranking curve (SUCRA) was derived by using the posterior probabilities for each treatment to be among the n best options; SUCRA would take a value of 1 when the treatment is certain to be the best and of 0 when the treatment is certain to be the worst. A Bayesian random-effects meta-regression was performed to formally explore whether the effect on DM is related to the power of statins to reduce cholesterol or rather to a molecule-dependent mechanism. Additionally, the potential effect on the results of different body mass indexes (BMIs) across the studies as a proxy for different cardiovascular risk profiles was investigated; specifically, in the meta-regression analysis, the Bayesian OR for DM of each statin versus placebo was regressed against the percentage of low-density lipoprotein (LDL) cholesterol reduction using BMI as a covariate. The goodness of fit of the model to the data was assessed using the residual deviance.

Results

The flow diagram of the study is shown in Figure 1. Seventeen RCTs[8–24] fulfilling the eligibility criteria and comprising a total of 113,394 patients were eventually included for data abstraction. Table 1 lists the main characteristics of the included studies. Fourteen RCTs compared a statin with placebo, and 3 studies compared high- with moderate-dose statin therapy. The high daily doses of statins

Table 1
Main clinical characteristics of the included randomized controlled trials

Study	Year	Trial Population	Trial Design	Compared Regimens	DM at Baseline		Mean Duration of Follow-Up (yrs)	New DM Cases in Compared Regimens	Mean BMI (kg/m^2)	Mean Age (yrs)	Relative LDL Reduction
					Yes	No					
ASCOT-LLA[8]	2003	Hypertension, CV risk factors, no history of CAD	Double-blind	Atorvastatin 10 mg vs placebo	2,532 (24.6%)	7,773 (75.4%)	3.3*†	154 (3.9%) vs 134 (3.5%)	28.6†	63.0†	34.8% at 12 mos‡
HPS[9]	2003	History of CVD	Double-blind	Simvastatin 40 mg vs placebo	5,963 (29.0%)	14,573 (71.0%)	5.0	335 (4.6%) vs 293 (4.0%)	27.2	65.0	29.4% average in trial
JUPITER[10]	2008	No CVD	Double-blind	Rosuvastatin 20 mg vs placebo	0 (0%)	17,802 (100.0%)	1.9*	270 (3.0%) vs 216 (2.4%)	28.4*	66.0*	50.0% at 12 mos
WOSCOPS[11]	2001	No previous MI, elevated cholesterol	Double-blind	Pravastatin 40 mg vs placebo	621 (9.4%)	5,974 (90.6%)	4.8	75 (2.5%) vs 93 (3.1%)	25.9	55.0	23.7% at 12 mos
LIPID[12§]	2003	MI or UA in previous 3 yrs	Double-blind	Pravastatin 40 mg vs placebo	2,017 (22.4%)	6,997 (77.6%)	6.0	126 (3.6%) vs 138 (3.9%)	Not reported	62.0*	25% (during 5 yrs)
CORONA[13]	2007	Systolic CHF	Double-blind	Rosuvastatin 20 mg vs placebo	1,477 (29.5%)	3,534 (70.5%)	2.7*†	100 (5.6%) vs 88 (5.0%)	27.0‡	73.0†	45.1% at 3 mos)‡
PROSPER[14]	2002	Elderly patients with CVD or at high risk	Double-blind	Pravastatin 40 mg vs placebo	781 (13.5%)	5,023 (86.5%)	3.2	165 (6.6%) vs 127 (5.1%)	26.5	76.0	30.7% at 12 mos
MEGA[15]	2006	No CVD, elevated cholesterol	Open trial	Pravastatin 10−20 mg vs no treatment	1,746 (22.3%)	6,086 (77.7%)	5.3	172 (5.7%) vs 164 (5.3%)	23.8	58.3	17.1% at 12 mos
AFCAPS/TexCAPS[16]	1998	No CVD	Double-blind	Lovastatin 20−40 mg vs placebo	394 (6.0%)	6,605 (94.0%)	5.2†	72 (2.3%) vs 74 (2.4%)	27.0†	58.0†	26.7% at 12 mos
4S[17]	1994	Previous MI or angina	Double-blind	Simvastatin 20−40 mg vs placebo	202 (4.5%)	4,242 (95.5%)	5.4*	198 (9.4%) vs 193 (9.1%)	25.9	58.6	36.7% at 12 mos
ALLHAT-LLT[18]	2002	CAD or CAD risk factors	Open trial	Pravastatin 40 mg vs no treatment	4,268 (41.2%)	6,087 (58.8%)	4.8†	238 (7.9%) vs 212 (6.9%)	29.0	66.4	18.1% at 24 mos
GISSI-HF[19]	2008	CHF	Double-blind	Rosuvastatin 10 mg vs placebo	1,196 (26.1%)	3,378 (73.9%)	3.9*	225 (13.6%) vs 215 (12.5%)	26.7	67.0	34.9% at 12 mos
GISSI Prevenzione[20]	2000	MI within past 6 mos	Open trial	Pravastatin 20 mg vs no treatment	811 (19.0%)	3,460 (81.0%)	2.0*	96 (5.5%) vs 105 (6.1%)	26.3	59.3	11.5% at 12 mos
PROVE-IT−TIMI 22[21]	2004	Recent ACS	Double-blind	Atorvastatin 80 mg vs pravastatin 40 mg	767 (18.4%)	3,395 (81.6%)	2.0	101 (5.9%) vs 99 (5.9%)	29	58	22%
TNT[22]	2005	Stable CAD	Double-blind	Atorvastatin 80 mg vs atorvastatin 10 mg	2,406 (24.1%)	7,595 (75.9%)	5.0	418 (11.0%) vs 358 (9.4%)	28	61	22%
IDEAL[23]	2005	Previous MI	Double-blind	Atorvastatin 80 mg vs simvastatin 20−40 mg‡	1,427 (16.0%)	7,461 (84.0%)	4.8*	240 (6.4%) vs 209 (5.6%)	27	62	16%
SPARCL[24]	2006	Previous stroke or TIA	Double-blind	Atorvastatin 80 mg vs placebo	794 (16.8%)	3,937 (83.2%)	4.9	166 (8.7%) vs 115 (6.0%)	27.15	62.5	NA

ACS = acute coronary syndrome; AFCAPS/TexCAPS = Air Force/Texas Coronary Atherosclerosis Prevention Study; ALLHAT-LLT = Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial−Lipid-Lowering Trial; ASCOT-LLA = Anglo-Scandinavian Cardiac Outcomes Trial−Lipid Lowering Arm; CAD = coronary artery disease; CHF = chronic heart failure; CORONA = Controlled Rosuvastatin Multinational Trial in Heart Failure; CV = cardiovascular; CVD = cardiovascular disease; 4S = Scandinavian Simvastatin Survival Study; GISSI = Gruppo Italiano per lo Studio Della Sopravvivenza Nell'Infarto Miocardico; GISSI-HF = Gruppo Italiano per lo Studio Della Sopravvivenza Nell'Infarto Miocardico−Heart Failure; HPS = Heart Protection Study; IDEAL = Incremental Decrease in End Points Through Aggressive Lipid Lowering; JUPITER = Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin; LIPID = Long-Term Intervention With Pravastatin in Ischemic Disease; MEGA = Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese; MI = myocardial infarction; NA = not available; PROSPER = Prospective Study of Pravastatin in the Elderly at Risk; PROVE-IT−TIMI 22 = Pravastatin or Atorvastatin Evaluation and Infection Therapy−Thrombolysis In Myocardial Infarction 22; SPARCL = Stroke Prevention by Aggressive Reduction in Cholesterol Levels; TIA = transient ischemic attack; TNT = Treating to New Targets; UA = unstable angina; WOSCOPS = West of Scotland Coronary Prevention Study.

* Median.

† Data from total cohort including patients with DM at baseline.

‡ If, at 24 weeks, plasma total cholesterol level was >190 mg/dl (5.0 mmol/L), the dose of simvastatin could be increased to 40 mg/day. The dose of atorvastatin could be decreased to 40 mg/day for adverse events.

§ Includes only patients with normal fasting glycemia at baseline.

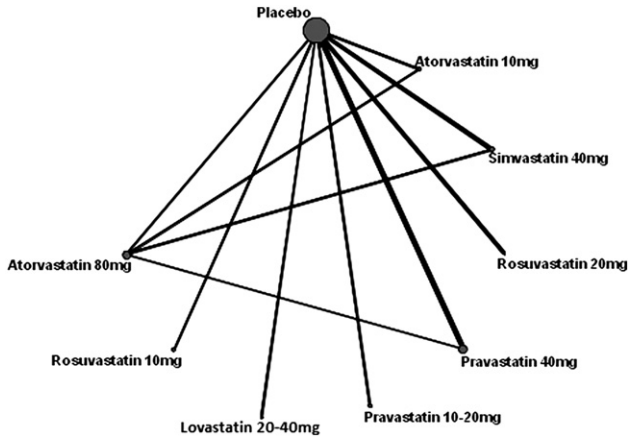

Figure 2. Evidence network of statins included in the meta-analysis. The nodes are the different treatments, and the edges represent trials comparing 2 treatments (statin or placebo). The widths of the lines are proportional to the number of trials comparing each pair of treatments. There is no line when there is no direct randomized comparison.

used in the RCTs were atorvastatin 80 mg, lovastatin 20 to 40 mg, pravastatin 40 mg, rosuvastatin 20 mg, and simvastatin 40 mg. The moderate doses were atorvastatin 10 mg, pravastatin 10 to 20 mg, and rosuvastatin 10 mg, all administered once daily. The included statins were connected in a network, as shown in Figure 2. The final model reached a posterior mean residual deviance of 34.46 (the number of data points was 34), indicating a very good fit of the model. The estimated effects from the pairwise meta-analyses were comparable with the results of the network meta-analysis, suggesting no evidence of inconsistency.

A total of 9 studies including 64,137 patients contributed to the analysis of new-onset DM in patients treated with high-dose statins, compared with a placebo control group. In the overall cohort, there was a total of 4,610 cases of new-onset DM: 7.28% (2,335 of 32,070) in the high-dose statin group and 7.09% (2,275 of 32,067) in the control group. As shown in Figure 3, treatment with rosuvastatin 20 mg/day, compared with placebo, was associated with a numeric 25% relative increase in the risk for developing new-onset DM. The impact on the risk for DM with atorvastatin 80 mg/day was less evident. Conversely, therapy with pravastatin 40 mg/day was associated with the lowest risk for DM, almost comparable with placebo treatment. The results for simvastatin 40 mg/day were substantially comparable with those for rosuvastatin 20 mg/day. Pravastatin 40 mg/day was associated with a consistent relative risk reduction of new-onset DM (16%) compared with rosuvastatin 20 mg/day, and atorvastatin 80 mg/day resulted in an approximately 8% relative risk reduction for new-onset DM compared with high-dose rosuvastatin.

Eleven studies including 63,558 patients reported rates of DM in patients treated with either moderate doses of statins or placebo. In patients treated with moderate-dose statins, there were 2,601 cases of DM among 31,764 patients (8.18%) compared with 2,527 cases among 31,794 patients (7.95%) in the control group. Figure 3 shows that even moderate-dose rosuvastatin therapy still created the highest risk for DM. Treatment with atorvastatin 10 mg/day was almost comparable with placebo, whereas pravastatin 10 mg/day was associated with a numerically lower risk for DM compared with placebo. The results also show a numerically lower risk associated with pravastatin treatment compared with rosuvastatin. At moderate doses, the risks for DM with atorvastatin and rosuvastatin were comparable.

Figure 3 presents the effect on new-onset DM of high versus moderate doses of statins. The risk for DM was generally increased with higher dose statin regimens. With rosuvastatin 20 mg/day, a 12% increase in the relative risk for DM was observed, compared with rosuvastatin 10 mg/day. High-dose pravastatin was associated with a slightly increased relative risk (7%) compared with low-dose pravastatin. The risk for DM did not appear to increase comparing lower with higher dose atorvastatin.

Figure 4 summarizes the likelihood of being the best high-dose statin treatment in terms of inducing less DM compared with placebo. Pravastatin at high doses was found to have the highest probability to be in the top ranks for the best treatment, presenting a relative SUCRA of 0.53. Atorvastatin at high doses ranked second, with a SUCRA of 0.37. The lowest 2 positions belonged to high-dose rosuvastatin and simvastatin, associated with SUCRAs of 0.30 and 0.29, respectively.

Figure 5 summarizes the probabilities of noninferiority to placebo for various threshold values, expressed as ORs, for statin therapy compared with placebo.

As shown, it is possible to be $\geq$60% certain that compared with placebo, pravastatin 40 mg/day is $<$1.1-fold worse. Conversely, with rosuvastatin 20 mg/day, this probability is reduced to approximately 20%.

By meta-regression, the ORs and 95% CIs for different types and doses of statins compared with placebo adjusted for the covariate LDL reduction were comparable with those in the overall analyses without the covariate (Table 2); the β coefficient in the meta-regression analysis with LDL reduction as a covariate were very low, therefore excluding a relation between the OR for DM with different statins compared with placebo and the percentage of LDL reduction with the different statins (Table 2). The meta-regression model fitted the data very well, with a posterior mean residual deviance of 36.3 (compared with 34 data points).

The β coefficient in the meta-regression with BMI variations treated as a covariate was -0.008795, with a 95% CI of -0.0248 to 0.00675, which is narrow and includes 0, suggesting that mean BMI does not explain variations in treatment effects among studies and across treatment comparisons. Sensitivity analysis on the basis of fixed-effect methods confirmed the results found with the random-effects meta-analysis, as listed in Table 3.

Discussion

The present study is the largest and most comprehensive study thus far comparing rates of new-onset DM among different types and doses of statins. The main findings derived from a population of 113,394 patients were as follows: (1) there was a gradient for the risk for new-onset DM across different types and doses of statins, (2) pravastatin therapy was numerically associated with the lowest rate

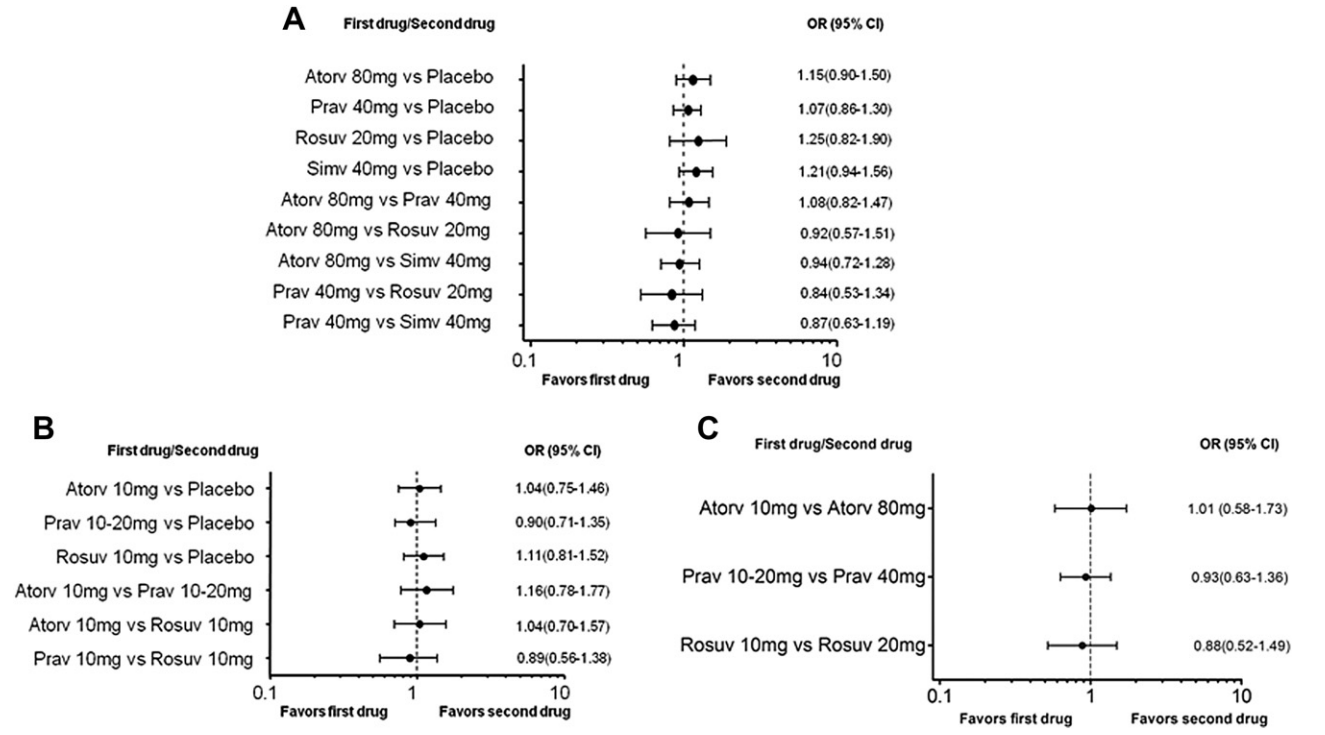

Figure 3. Pooled ORs and 95% CIs determined by the network meta-analysis for *(A)* high doses of a statin compared with placebo or with another statin, *(B)* moderate doses of a statin compared with placebo or with another statin, and *(C)* moderate doses compared with high doses of a statin. Atorv = atorvastatin; Prav = pravastatin; Rosuv = rosuvastatin; Simv = simvastatin.

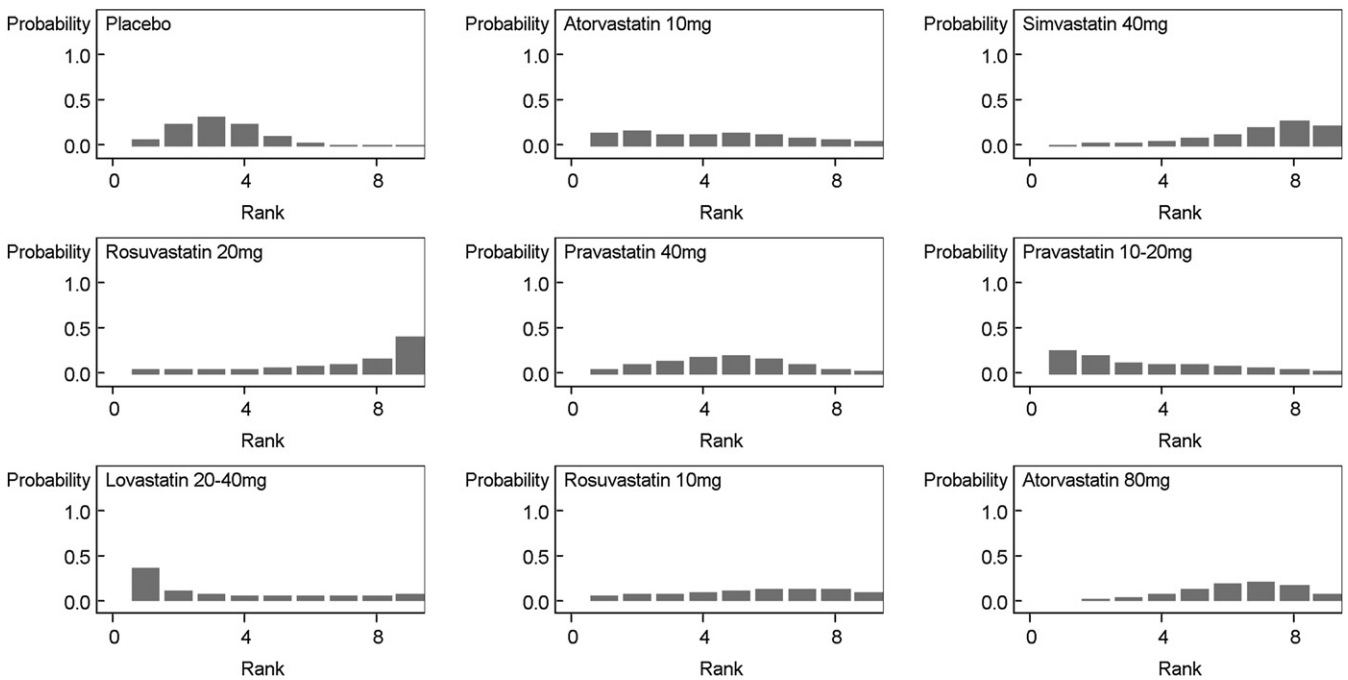

Figure 4. Ranking probability plots for competing statins drawn by extrapolating at the middle of each interval of the step function. On the horizontal axis is the possible rank of each treatment (from the first best rank to the worse according to outcome). On the vertical axis is the probability for each treatment to have that rank with respect to the odds of new-onset DM.

of new-onset DM compared with other statins, whereas treatment with rosuvastatin was associated with the highest numeric incidence of DM, (3) the cumulative probabilities indicated that high-dose pravastatin had the highest probability to be the safest treatment in terms of new-onset DM, with rosuvastatin and simvastatin performing least well in

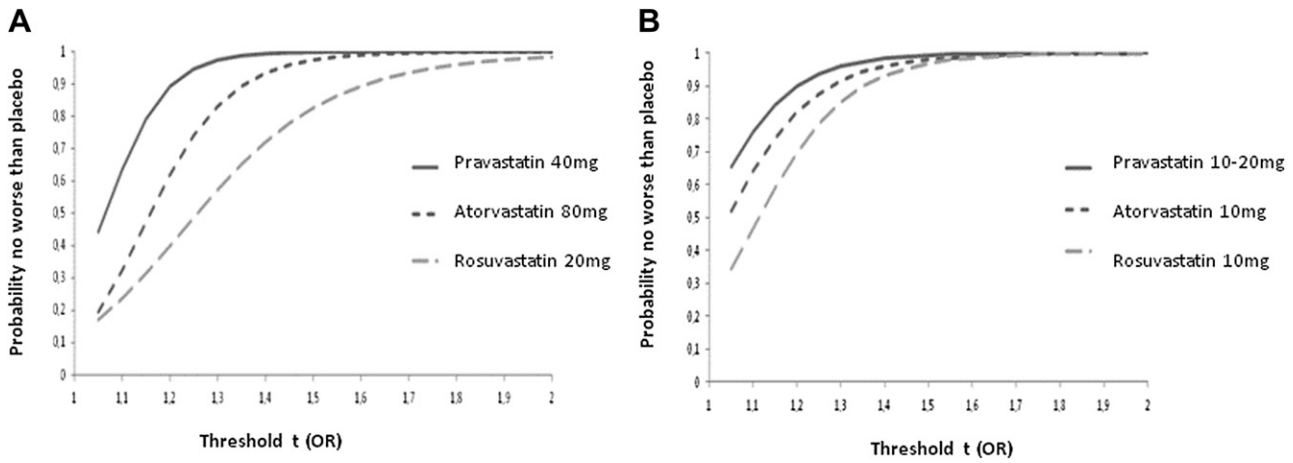

Figure 5. Probabilities to be no worse than placebo for *(A)* high doses of statins and *(B)* moderate doses of statins regarding the incidence of new-onset DM by a certain threshold *t* value (on the horizontal axis) measured on an OR scale.

Table 2
Odds ratios and 95% credible intervals of diabetes among different statins adjusted for percentage of low-density lipoprotein cholesterol reduction as covariate

Comparison	OR	95% CI
Atorvastatin 10 mg vs Placebo	1.04	0.74−1.48
Pravastatin 20 mg vs placebo	0.99	0.68−1.41
Rosuvastatin 10 mg vs placebo	1.10	0.78−1.58
Simvastatin 40 mg vs placebo	1.21	0.93−1.57
Atorvastatin 80 mg vs placebo	1.15	0.90−1.51
Lovastatin 40 mg vs placebo	0.97	0.58−1.61
Pravastatin 40 mg vs placebo	1.06	0.85−1.30
Rosuvastatin 20 mg vs placebo	1.25	0.75−2.01

Beta coefficient = 0.0003 (95% CI −0.01 to 0.01); residual deviance = 36.3.

this ranking, (4) compared with placebo, high-dose pravastatin provided the most robust safety profile compared with the other high-dose statins, with a ≥60% margin of certainty not to be 1.1-fold worse than placebo, (5) these findings were confirmed with moderate doses of statins, and (6) for each statin, increased doses carried a numerically higher risk for new-onset DM compared with moderate doses.

Numerous RCTs[8−24] have shown consistent benefits with statins in reduction of mortality and cardiovascular events, especially in the diabetic population, in which cardiovascular disease is the leading cause of mortality. In contrast, a recent meta-analysis revealed that statin therapy is associated with an increased risk for developing DM.[4] Moreover, a newly published meta-analysis showed a dose-dependent effect, with a 12% higher relative risk for developing DM on intensive-dose statin therapy compared with moderate-dose therapy.[5] Potential molecular explanations for the increased risk for DM observed with statin therapy include modifications in insulin signaling in peripheral tissues, exacerbating insulin resistance, and/or interaction with pancreatic β-cell function, impairing insulin secretion.[25] Further suggested mechanisms influencing the risk for DM with statins are the power of particular statins to reduce cholesterol concentration and the fact that patients are sometimes aware of their treatment allocation in trials[26]; this bias may lead those with substantially reduced LDL cholesterol to become complacent and assume poorer lifestyles, gain weight, and ultimately develop DM. However, the present study clearly showed by meta-regression that the risk for developing DM was not influenced by the different abilities of statins to reduce cholesterol; on the basis of this additional datum, this meta-analysis prompts the experimental investigation of molecule-dependent mechanisms responsible for DM onset. Notably, our findings are consistent with an experimental study recently performed by Koh et al,[27] who found that rosuvastatin is more potent and less hydrophilic than pravastatin and is associated with adverse metabolic effects, including increases in insulin resistance and glycosylated hemoglobin; conversely, pravastatin proved to be safe by decreasing these 2 parameters. In agreement with our findings, the Irish Health Services Executive Primary Care Reimbursement Services national pharmacy claims database[28] demonstrated that rosuvastatin was associated with the highest increase in new-onset DM compared with other statins.

A recent meta-analysis showed a significant benefit with statins in patients with a 5-year risk for major vascular events <10%, demonstrating that this benefit exceeds any hazard of statin therapy, including DM.[29] Understanding the risk for DM across the spectrum of different statins is important to balance the risks and benefits when administering specific statins. In the present report, a numeric 25% increase in the relative risk for DM was found with high doses of rosuvastatin compared with placebo, whereas high-dose pravastatin only moderately enhanced this risk by 7%; this datum derived from the present large scale network meta-analysis is comparable with the reported 27% increase in the relative risk for DM in rosuvastatin-treated patients compared with placebo-treated patients detected in the Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) trial.[10] The estimated risk for new-onset DM associated with rosuvastatin found in our meta-analysis is almost twice as high as the overall risk with statin treatment reported in the meta-analysis by Sattar et al.[2]

Table 3
Odds ratios and 95% credible intervals of diabetes among different statin types and doses

Comparison	High-Dose Statin		Moderate-Dose Statin	
	Random Effects	Fixed Effect	Random Effects	Fixed Effect
Atorvastatin vs placebo	1.15 (0.90−1.50)	1.13 (1.00−1.27)	1.04 (0.75−1.46)	1.00 (0.85−1.17)
Lovastatin vs placebo	0.98 (0.59−1.61)	0.98 (0.71−1.36)	NA	NA
Pravastatin vs placebo	1.07 (0.86−1.30)	1.07 (0.95−1.20)	0.90 (0.71−1.35)	1.00 (0.78−1.27)
Rosuvastatin vs placebo	1.25 (0.82−1.90)	1.25 (1.0−1.54)	1.11 (0.81−1.52)	1.10 (0.88−1.4)
Simvastatin vs placebo	1.21 (0.94−1.56)	1.27 (1.13−1.41)	NA	NA
Atorvastatin vs pravastatin	1.08 (0.82−1.47)	1.04 (0.90−1.21)	1.16 (0.78−1.77)	1.18 (0.90−1.55)
Atorvastatin vs rosuvastatin	0.92 (0.57−1.51)	0.90 (0.71−1.12)	0.93 (0.59−1.48)	0.90 (0.72−1.13)
Atorvastatin vs simvastatin	0.94 (0.72−1.28)	0.88 (0.80−0.97)	NA	NA
Pravastatin vs rosuvastatin	0.84 (0.53−1.34)	0.85 (0.67−1.06)	0.87 (0.58−1.30)	0.90 (0.71−1.15)
Pravastatin vs simvastatin	0.87 (0.63−1.19)	0.84 (0.73−0.99)	NA	NA
Rosuvastatin vs simvastatin	1.03 (0.63−1.68)	1.0 (0.81−1.23)	NA	NA

Estimates derived from fixed-effect and random-effects models are reported.

The findings of this large network meta-analysis are the first to provide information on the specific risk for DM associated with different types and doses of statins. Because of the limited available direct evidence, large 95% CIs were found around the overall estimates; in contrast, the stability of the results in several probability and ranking analyses make the overall conclusions justified. If the findings of this network meta-analysis were confirmed in powered head-to-head comparisons, they would have important implications for the future management of millions of individuals receiving statins worldwide; indeed, a new scenario of statin therapy could be envisaged in which personalized statin therapy might emerge as the most effective and safest strategy.

As with any meta-analysis, our study shares the limitations of the original studies. Methods for the diagnosis of incident DM varied among trials, which is common in such studies. In the original West of Scotland Coronary Prevention Study (WOSCOPS) trial, the diagnostic criteria for DM were nonstandard, with a requirement for an increase in fasting glucose of $\geq$2.0 mmol/L during the trial. However, for the present analysis, standard criteria for the diagnosis of DM from a reanalysis of WOSCOPS were used.[11] These data were made available in the previously published meta-analysis by Sattar et al.[2]

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Disclosures

The authors have no conflicts of interest to disclose.

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