Comparative tolerability and harms of individual statins: a study-level network meta-analysis of 246 955 participants from 135 randomized, controlled trials

Comparative Tolerability and Harms of Individual Statins
A Study-Level Network Meta-Analysis of 246 955 Participants From 135 Randomized, Controlled Trials

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Background—Our objective was to estimate the comparative harms of individual statins using both placebo-controlled and active-comparator trials.

Methods and Results—We systematically reviewed randomized trials evaluating different statins in participants with and without cardiovascular disease. We performed random-effects pairwise and network meta-analyses to quantify the relative harms of individual statins. We included 55 two-armed placebo-controlled and 80 two- or multiarmed active-comparator trials including 246 955 individuals. According to pairwise meta-analyses, individual statins were not different than control in terms of myalgia, creatine kinase elevation, cancer, and discontinuations because of adverse events. Statins as a class resulted in significantly higher odds of diabetes mellitus (odds ratio, 1.09; 95% confidence interval, 1.02–1.16) and transaminase elevations (odds ratio, 1.51; 95% confidence interval, 1.24–1.84) compared with control. When individual statins were compared in network meta-analyses, there were numerous statistically detectable differences, favoring simvastatin and pravastatin. According to dose-level comparisons, individual statins resulted in higher odds of discontinuations with higher doses of atorvastatin and rosuvastatin. Similarly, higher doses of atorvasatin, fluvastatin, lovastatin, and simvastatin were associated with higher odds of transaminase elevations. Simvastatin at its highest doses was associated with creatine kinase elevations (odds ratio, 4.14; 95% credible interval, 1.08–16.24). Meta-regression analyses adjusting for study-level age at baseline, low-density lipoprotein cholesterol level, and publication year did not explain heterogeneity. There was no detectable inconsistency in the network.

Conclusions—As a class, adverse events associated with statin therapy are not common. Statins are not associated with cancer risk but do result in a higher odds of diabetes mellitus. Among individual statins, simvastatin and pravastatin seem safer and more tolerable than other statins. **(*Circ Cardiovasc Qual Outcomes*. 2013;06:390-399.)**

Key Words: cardiovascular disease ■ coronary disease ■ cardiovascular agents ■ Hydroxymethylglutaryl-CoA Reductase Inhibitors ■ adverse effects ■ meta-analysis ■ statins

Statins are widely used to prolong survival and reduce the occurrence of coronary and cerebrovascular events in patients with and without cardiovascular disease. Prior meta-analyses have demonstrated the effectiveness of statins for the primary and secondary prevention of cardiovascular disease,[1–5] with consistent benefits across subgroups, including the elderly,[6] women,[7] and individuals with diabetes mellitus.[2] Initially focused on secondary prevention, statin therapy has become more common because the limits of treatment have expanded over time to include people at progressively lower risk of developing cardiovascular disease.[8] As the number of individuals eligible for statin therapy continues to increase,[9] the comparative tolerability and harms of different statins warrant further investigation.

There is no comprehensive analysis on the comparative adverse event profiles of different statins, which builds on the totality of the existing randomized, controlled trial evidence base. Although large-scale meta-analyses confirmed that the frequency of clinically significant side effects associated with statin therapy is low,[10] more research is needed to synthesize the evidence on a more diverse range of outcomes that are important for individuals receiving statins. These range from previously studied outcomes, such as cancer[11–13] and diabetes mellitus,[14,15] to muscle aches and clinically meaningful elevations in liver enzymes, which may be among factors contributing to nonadherence to long-term statin therapy.[16,17] Information regarding the relative tolerability and harms of different statins in the prevention of cardiovascular disease is needed to better inform patients, clinicians, and other healthcare decision makers.

Several reviews established the favorable safety profile of statins.[18–22] An important limitation of previous reviews is their focus on placebo-controlled trials, which did not take into account evidence from a large number of trials with direct head-to-head comparisons of statins. Equally important,

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WHAT IS KNOWN

- The frequency of clinically significant side effects associated with statin therapy is low.
- There is no comprehensive analysis on the comparative adverse event profiles of different statins that builds on both placebo-controlled and active-comparator trials.

WHAT THE STUDY ADDS

- Higher doses of some statins are associated with larger numbers of transaminase and creatine kinase elevations, and discontinuations because of adverse events.
- There are clinically meaningful differences among individual statins, with simvastatin and pravastatin likely to be ranked superior to their alternatives in terms of their safety profile.

previous reviews did not assess differences in dosages of individual statins across populations and did not compare statins at similar doses.

Our objective in this study was to systematically review and synthesize the totality of the randomized, controlled trial evidence on different statins and determine their comparative tolerability and harms across a range of populations eligible for statin therapy.

Methods

Systematic Review

Our search strategy was based on a publicly available protocol previously developed by the study authors to evaluate the comparative clinical benefits of statins.[23] We searched MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials to identify studies published between January 1, 1985, and March 10, 2013. To identify the relevant literature, we developed a search strategy using the search terms atorvastatin, fluvastatin, simvastatin, lovastatin, pravastatin, rosuvastatin, cholesterol, cardiovascular disease, and hydroxymethylglutaryl-coenzyme A reductase inhibitors/therapeutic use. Our updated search in MEDLINE adopted Cochrane Collaboration's sensitivity and precision-maximizing strategy.[24] We searched for pitavastatin trials post hoc separately because our protocol did not include pitavastatin (protocol finalization coincided with the Food and Drug Administration approval of this agent). We also performed manual searches using the authors' files and reference lists from original communications and review articles to cross-check references. Two researchers (B.T., H.T.) independently performed abstract, title, and full-text screening. A third researcher approved study selection (H.N.).

We included open-label and double-blind randomized, controlled trials comparing one statin with another at any dose or with control (placebo, diet, or usual care) for adults with, or at risk of developing, cardiovascular disease. We included trials of atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin if they had >50 participants per trial arm and lasted >4 weeks based on prespecified inclusion and exclusion criteria.

Outcomes of interest were determined after protocol finalization. We included trials that reported tolerability (number of participants who discontinued the study medication because of adverse events), elevations in hepatic transaminases (number of participants with clinically meaningful elevations in either alanine aminotransferase or aspartate aminotransferase, 3× baseline values as commonly defined by trial investigators), elevations in creatine kinase (CK; number of participants with clinically meaningful increases in baseline CK levels as defined by trial investigators, ranging from 3× to 10× higher than baseline concentrations), myalgia (number of individuals with muscle pain, as defined by trial investigators), myopathy (number of participants with 10× baseline CK levels associated with muscle symptoms), and rhabdomyolysis (number of participants with severe muscle damage, as diagnosed by trial investigators). In addition, we were interested in the incidence of cancer and diabetes mellitus (as defined by trial investigators), so trials reporting these outcomes were also eligible for inclusion. Both fixed dose and titration designs were included. As per our protocol, we excluded trials conducted in patients with renal insufficiency.

We used a structured form developed in MS Excel to extract data on trial and patient population characteristics and outcomes. We also extracted information on the methodological quality of included studies. In particular, information was collected on blinding, random sequence generation, allocation concealment, indications of incomplete outcome data, indications of selective reporting (possible for trials with published protocols), and industry sponsorship. One researcher extracted data (H.N.) and another independently checked for accuracy (B.T.).

Statistical Analysis

We qualitatively summarized included trials, describing the types of direct and indirect comparisons and important clinical and trial design characteristics. For each pairwise comparison between 2 treatments, we calculated the relative effect with a 95% confidence interval (CI). We performed classical pairwise meta-analyses to synthesize studies that compared the same 2 treatments using the DerSimonian–Laird (random-effects) method. Forest plots of the relative treatment effects from the individual trials and pairwise meta-analyses were visually inspected to search for heterogeneity. We also statistically inspected heterogeneity using the I^2 measure.

To determine the comparative tolerability and harms of individual statins, we conducted network meta-analyses, which are generalizations of indirect comparisons with >2 (or multiple pairs of) treatments being compared indirectly and ≥1 pair of treatments compared both directly and indirectly.[25,26] This type of analysis allowed for simultaneously combining the direct within-trial comparisons between 2 treatments (eg, atorvastatin versus control) with indirect comparisons constructed from trials that had 1 treatment in common (eg, atorvastatin versus control and simvastatin versus control).[27] This analysis preserved the within-trial randomized treatment comparison of each trial while combining all available comparisons between treatments. We combined study-level relative treatment effects using Bayesian Markov chain Monte Carlo methods in WinBUGS version 1.4.3. We used the model developed by Dias et al[28] for the UK National Institute of Health Clinical Excellence Decision Support Unit. This was based on modeling the outcomes in every treatment group of every study and specifying the relationships among the relative effects across studies making different comparisons, while taking into account the correlations between treatment effects within multiarm trials. Our models adopted random effects. The random-effects model took into account potential heterogeneity by assuming that each treatment was drawn from the same distribution, whose mean and variance were estimated from the data.[29] Additional details of our analytic approach are provided in the online-only Data Supplement Appendix.

Findings were reported in terms of odds ratios (OR). The difference between treatments was assessed on the basis of 95% CI in pairwise meta-analyses and 95% credible intervals (CrI) in network meta-analyses. CrIs may be interpreted as Bayesian equivalents of 95% CIs. The 95% CrI can be interpreted as indicating a 95% probability that the true OR falls within the reported range. If a 95% CrI does not include the null value 1.00, this can be interpreted as indicating <5% probability that there is no difference between the 2 comparators (referred to as significant difference between treatments hereafter). Given the Bayesian nature of the statistical analyses, *P* values are not estimated and reported for network meta-analyses.

We assessed the probability that each statin has the most favorable harm profile by calculating its treatment effect compared with control treatment and counting the proportion of iterations for which each statin has the highest treatment effect (ie, least harmful), the second highest, and so on. This approach took into account the magnitude of the estimated treatment effect, as well as the uncertainty around it. We graphically presented the distribution of ranking probabilities and estimated the surface under the cumulative ranking line for each statin.[30] The surface under the cumulative ranking line for each statin would be 1.00 when a treatment is certain to be the best (most favorable tolerability and harm profile) and 0.00 when a treatment is certain to be the worst (least favorable tolerability and harm profile). Ranking probabilities were estimated for the 4 outcomes with the most data (discontinuations because of adverse events, myalgia, elevations in hepatic transaminases, and elevations in CK levels) and combined in a composite measure with each of the 4 outcomes contributing 0.25 to the total ranking score of 1.00.

To obtain a comprehensive estimate of the comparative tolerability and harms of individual statins, our network meta-analysis pooled all primary and secondary prevention trials in addition to trials with mixed patient populations, including all placebo-controlled and active-comparator trials eligible for inclusion in this review. In subgroup analyses, we also investigated the comparative effects of individual statins in primary and secondary prevention separately.

Primary analyses were at the drug level (referred to as drug-level network meta-analyses hereafter), comparing individual statins to each other (eg, atorvastatin versus simvastatin). Sensitivity analyses were dose specific and explored the comparative harms of individual statins at different doses separately (referred to as dose level hereafter). Each statin–dose combination was treated as a different treatment, and no trends were fitted or assumed. The following daily doses were considered for atorvastatin, lovastatin, pravastatin, and simvastatin: ≤10 mg, >10 and ≤20 mg, >20 and ≤40 mg, and >40 mg. For fluvastatin, daily doses were ≤20 mg, >20 and ≤40 mg, and >40 mg. For rosuvastatin, the daily doses were ≤5 mg, >5 and ≤10 mg, >10 and ≤20 mg, and >20 mg. For pitavastatin, 2 and 4 mg/d formulations were considered. All analyses were based on the total number of randomly assigned participants.

We investigated whether potential heterogeneity and inconsistency across the evidence base in the network meta-analysis of discontinuations, myalgia, transaminase elevations, and CK elevations could be explained by mean age at baseline, mean low-density lipoprotein cholesterol concentration at baseline, or the publication year of the trial using meta-regression analyses. All meta-regression analyses allowed for a common treatment–covariate interaction for each statin compared with control.[31] An additional sensitivity analysis excluded open-label trials and explored the comparative harms and tolerability of individual statins in double-blind trials.

For all outcomes, we also qualitatively evaluated the consistency of relative treatment effects obtained from an analysis of head-to-head trials with those obtained from an analysis combining both placebo-controlled and active-comparator trials. In particular, we first performed pairwise meta-analyses on all available direct comparisons (ie, direct evidence) and then compared the findings of these pairwise meta-analyses with the results of network meta-analysis (ie, mixed evidence). The consistency of the relative treatment effects was visually inspected for potential differences between estimates obtained from 2 sets of analyses (ie, direct and mixed estimates). We checked for discrepancy in terms of the direction of effect, as well as its magnitude, and confirmed that all 95% intervals greatly overlapped, which suggested adequate consistency. We also evaluated small-study effects using contour-enhanced funnel plots, which tested a composite hypothesis of publication and reporting bias, and chance.

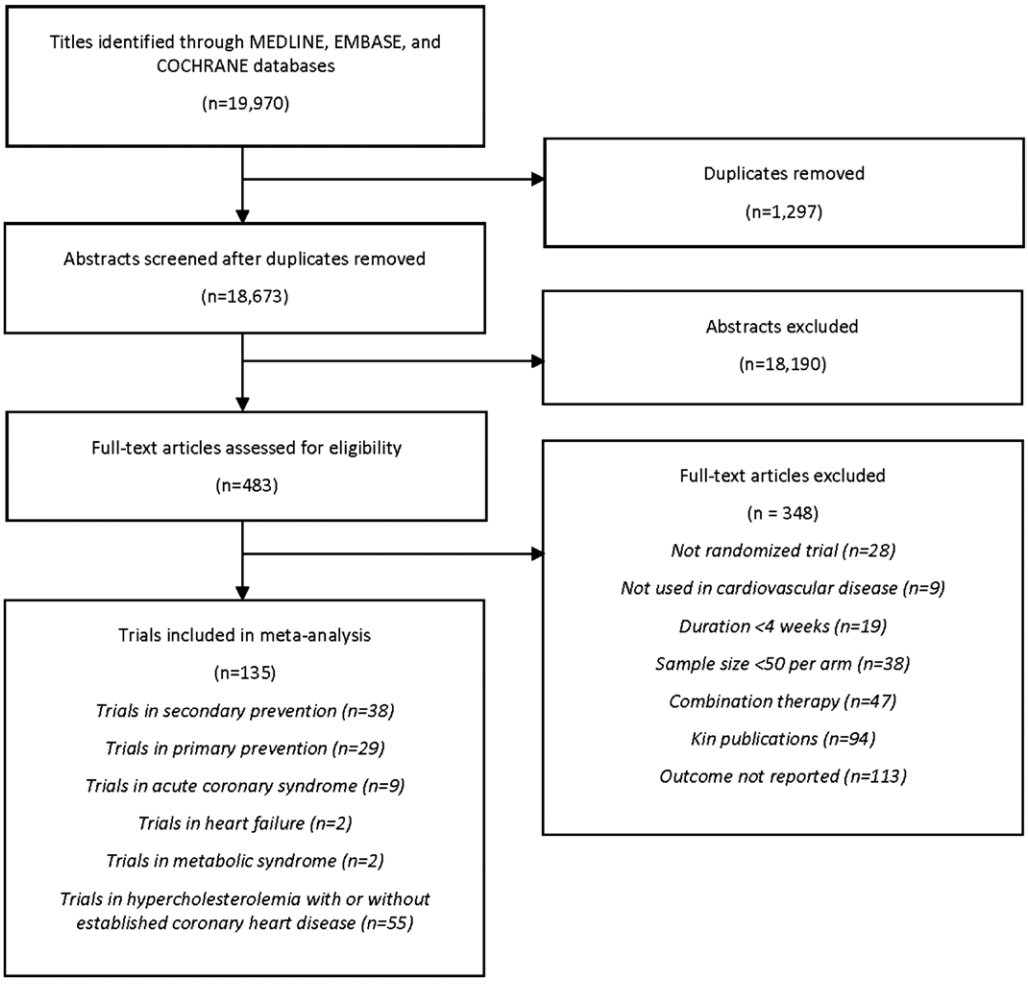

Figure 1. Flow diagram of trial identification and selection.

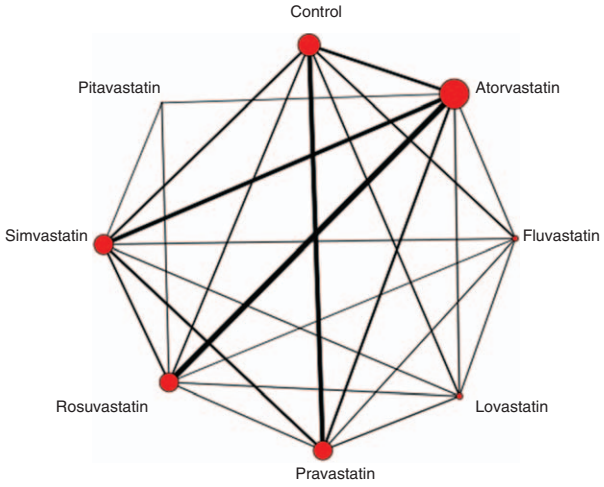

Figure 2. Network of available comparisons for the drug-level analysis. Connecting lines indicate the existing direct pairwise comparisons between 2 treatments. The width of the lines is proportional to the number of pairwise comparisons between 2 treatments, and the size of every node is proportional to the number of participants.

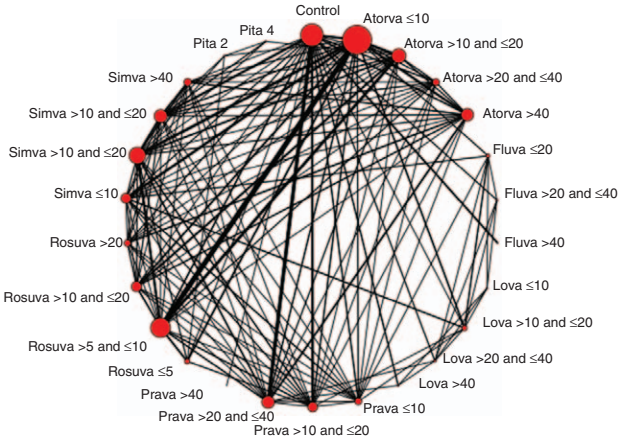

Figure 3. Network of available comparisons for dose-specific analysis. Connecting lines indicate the existing direct pairwise comparisons between 2 treatments. The width of the lines is proportional to the number of pairwise comparisons between 2 treatments, and the size of every node is proportional to the number of participants.

Results

Our review included 135 trials (Figure 1), totaling 246 955 participants. Overall, the average trial follow-up was 68 weeks (1.3 years). There were 55 two-armed placebo-controlled trials, and the remaining 80 were 2-armed or multiarmed active-comparator trials. Of the 28 possible pairwise comparisons between the 8 treatments (7 statins and control), 22 were available. Most frequent comparisons occurred between pravastatin and placebo, atorvastatin and placebo, and rosuvastatin and atorvastatin. A total of 53 325 participants received atorvastatin, whereas 35 404 participants received simvastatin and 29 557 received pravastatin. No trial directly compared all 7 statins with each other for the drug-level comparison (Figure 2). Similarly, a small number of fluvastatin, lovastatin, and pitavastatin trials contributed to the dose-level network meta-analysis. No trial directly compared all statin–dose combinations with each other (Figure 3). Based on analyses on discontinuations because of adverse events, myalgia, transaminase elevations, and CK elevations, there was no evidence of differential effects between more precise and less precise trials according to contour-enhanced funnel plots (ie, no evidence of small-study effects).

The overall methodological quality of included trials was moderate. Older trials had lower methodological quality with inadequate sequence generation and treatment allocation concealment. A large number of trials did not report details about randomization procedures and allocation concealment. Only 11 trials had high methodological quality on all 6 items.

Discontinuations Because of Adverse Events

According to the pairwise meta-analysis of placebo-controlled trials including 76 462 participants, statins as a class were not significantly different than control (OR, 0.95; 95% CI, 0.83–1.08; I^2, 21.9%). In the trials that directly compared individual statins head-to-head, simvastatin was significantly more tolerable than atorvastatin (OR, 0.61; 95% CI, 0.42–0.89; I^2, 71.9%) and rosuvastatin (OR, 0.49; 95% CI, 0.27–0.88; I^2, 0.0%).

In the drug-level network meta-analysis of individual statins, 131 503 participants contributed information on 7811 events (6% of all participants). Individual statins were similar to control in terms of discontinuations because of adverse events (Figure 4A). When compared head-to-head, participants randomized to pravastatin (OR, 1.46; 95% CrI, 1.10–1.92) and simvastatin (OR, 1.34; 95% CrI, 1.06–1.69) were significantly less likely to stop treatment because of adverse events compared with those randomized to atorvastatin (Table 1).

The dose-level network meta-analysis of discontinuations because of adverse events included 151 823 participants, providing information on 8719 discontinuations. Atorvastatin at >20 and ≤40 mg/d (OR, 2.72; 95% CrI, 1.46–5,09) and atorvastatin at >40 mg/d (OR, 1.69; 95% CrI, 1.18–2.44) led to significantly more discontinuations compared with control. There was no strong dose–response relationship for most statin–dose combinations (higher doses did not necessarily result in higher discontinuation rates; Figure 5A).

Myalgia

When the placebo-controlled trials of statins were pooled as a class in a pairwise meta-analysis including 43 531 participants, statins were not significantly different than control treatment (OR, 1.07; 95% CI, 0.89–1.29; I^2, 22.1%) in terms of myalgia incidence. The pairwise meta-analysis of head-to-head simvastatin versus atorvastatin trials showed that participants randomized to simvastatin had lower odds of experiencing myalgia compared with those receiving atorvastatin (OR, 0.56; 95% CI, 0.42–0.75; I^2, 0.0%).

Although the direction and magnitude of the difference between simvastatin and atorvastatin were similar in the drug-level network meta-analysis, there was greater variability around this estimate when all eligible direct and indirect trials were combined (OR, 0.78; 95% CrI, 0.55–1.13; reciprocals

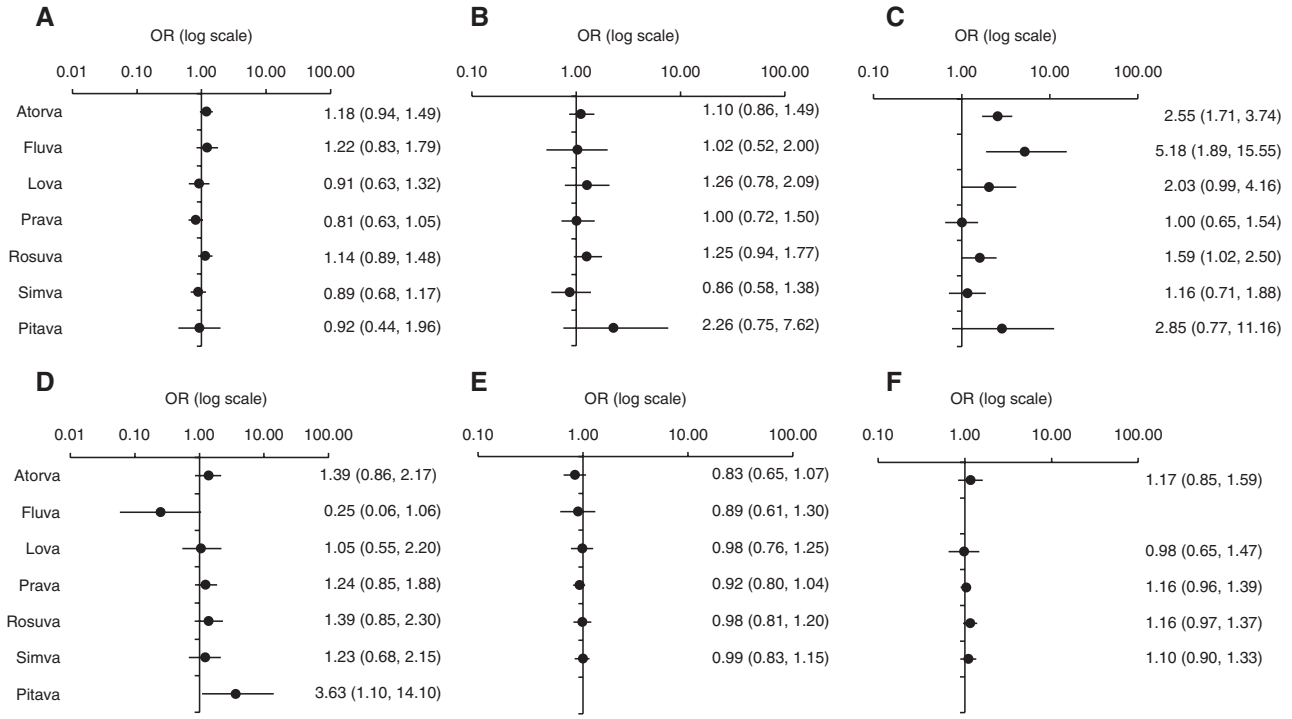

Figure 4. Findings of drug-level network meta-analyses: effect of statins compared with control on (**A**) discontinuations because of adverse events, (**B**) occurrence of myalgia, (**C**) clinically meaningful elevation in hepatic transaminases, (**D**) clinically meaningful elevation in CK levels, (**E**) incidence of cancer, and (**F**) incidence of diabetes mellitus. There were no data to estimate cancer incidence with pitavastatin and diabetes mellitus incidence with fluvastatin and pitavastatin. CK indicates creatine kinase; OR, odds ratio.

reported in Table 1). According to the findings of the network meta-analysis including 84 391 participants with 1986 myalgia events (2% of all participants), there were no significant differences between individual statins.

In the dose-level network meta-analysis including 99 433 participants with 2533 events, there was a lack of an apparent dose–response relationship for myalgia (Figure 5B) with no statistically detectable differences between individual statin–dose combinations and control treatment.

Transaminase Elevations

The pairwise meta-analysis of placebo-controlled trials including 122 665 participants showed that participants randomized to statins had significantly higher odds of experiencing alanine aminotransferase and aspartate aminotransferase elevations compared with those randomized to control (OR, 1.51; 95% CI, 1.24–1.84; I^2, 52.3%). Among the trials that directly compared pravastatin and atorvastatin, participants randomized to pravastatin had significantly lower odds of transaminase elevations (OR, 0.27; 95% CI, 0.10–0.74; I^2, 61.3%).

In the drug-level network meta-analysis of individual statins, 165 534 participants contributed information on 2075 clinically meaningful elevations in hepatic transaminases (1% of all participants). Individuals randomized to atorvastatin (OR, 2.55; 95% CrI, 1.71–3.74) and fluvastatin (OR, 5.18; 95% CrI, 1.89–15.55) had higher odds of transaminase elevations (Figure 4C). When compared head-to-head, pravastatin (OR, 0.39; 95% CrI, 0.24–0.65), rosuvastatin (OR, 0.63; 95% CrI, 0.42–0.94), and simvastatin (OR, 0.45; 95% CrI, 0.28–0.73) had lower odds of transaminase elevations compared

Table 1. Findings of Drug-Level Network Meta-Analyses, Showing the OR Comparing Statins (95% Credible Interval): Comparative Head-to-Head Effects of Individual Statins on Myalgia (top half of the table) and Discontinuations Because of Adverse Events (bottom half of the table)

Atorvastatin	1.08 (0.56, 2.17)	0.87 (0.54, 1.46)	1.1 (0.77, 1.53)	0.88 (0.71, 1.08)	1.28 (0.88, 1.80)	0.49 (0.15, 1.42)
0.97 (0.64, 1.47)	Fluvastatin	0.81 (0.37, 1.71)	1.02 (0.48, 2.02)	0.82 (0.40, 1.58)	1.19 (0.56, 2.37)	0.46 (0.12, 1.52)
1.30 (0.87, 1.94)	1.33 (0.83, 2.14)	Lovastatin	1.26 (0.7, 2.15)	1.00 (0.58, 1.68)	1.46 (0.80, 2.54)	0.57 (0.15, 1.79)
1.46 (1.10, 1.92)	1.50 (0.97, 2.33)	1.13 (0.75, 1.7)	Pravastatin	0.80 (0.55, 1.19)	1.17 (0.74, 1.82)	0.45 (0.13, 1.35)
1.04 (0.85, 1.27)	1.07 (0.69, 1.65)	0.80 (0.52, 1.22)	0.71 (0.52, 0.97)	Rosuvastatin	1.46 (0.98, 2.14)	0.56 (0.17, 1.64)
1.34 (1.06, 1.69)	1.37 (0.89, 2.14)	1.03 (0.67, 1.57)	0.91 (0.67, 1.26)	1.28 (0.98, 1.69)	Simvastatin	0.39 (0.12, 1.12)
1.29 (0.62, 2.66)	1.32 (0.57, 3.06)	0.99 (0.43, 2.26)	0.88 (0.41, 1.89)	1.24 (0.59, 2.58)	0.96 (0.46, 2.02)	Pitavastatin

Comparisons between drugs should be read from left to right, and the estimate is in the cell in common between the column-defining treatment and the row-defining treatment. For both outcomes, ORs <1 favor the column-defining treatment. To obtain ORs for comparisons in the opposite direction, reciprocals should be taken. OR indicates odds ratio.

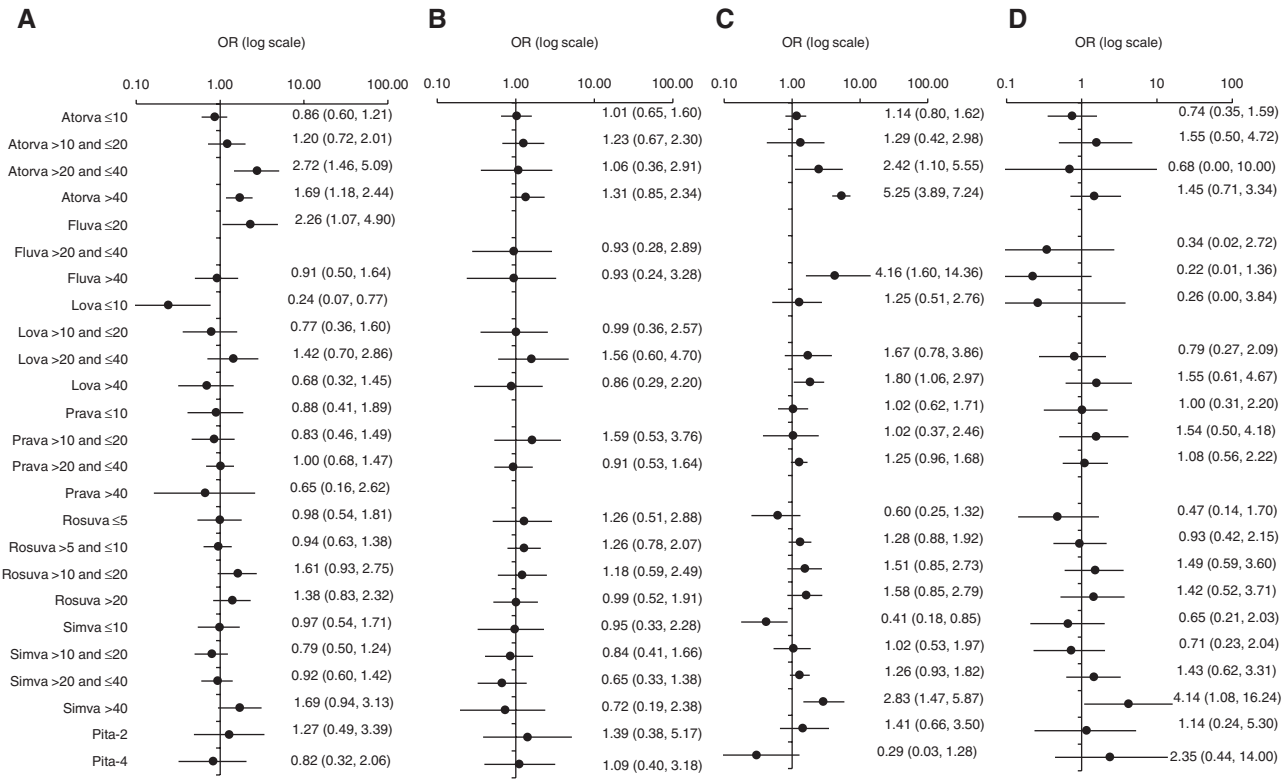

Figure 5. Findings of dose-level network meta-analyses: effects of statin–dose combinations compared with control on (**A**) discontinuations because of adverse events, (**B**) occurrence of myalgia, (**C**) clinically meaningful elevation in hepatic transaminases, and (**D**) clinically meaningful elevation in CK levels. CK indicates creatine kinase; OR, odds ratio.

with atorvastatin (reciprocals reported in Table 2). Fluvastatin resulted in significantly higher odds of elevations than pravastatin (OR, 5.19; 95% CrI, 1.75–16.73), rosuvastatin (OR, 3.25; 95% CrI, 1.08–10.50), and simvastatin (OR, 4.50; 95% CrI, 1.49–14.19).

The dose-level network meta-analysis for clinically meaningful elevations in hepatic transaminases included 188 503 participants, providing information on 2298 events. There was a clear dose–response relationship for atorvastatin, lovastatin, and simvastatin, with higher doses resulting in higher odds of transaminase elevations (Figure 5C). Individuals receiving simvastatin at ≤10 mg/d had lower odds of experiencing transaminase elevations compared with those receiving control (OR, 0.41; 95% CrI, 0.18–0.85). Atorvastatin at >20 and ≤40 mg/d (OR, 2.42; 95% CrI, 1.10–5.55), atorvastatin at >40 mg/d (OR, 5.25; 95% CrI, 3.89–7.24), fluvastatin at >40 mg/d (OR, 4.16; 95% CrI, 1.60–14.36), and simvastatin at >40 mg/d (OR, 2.83; 95% CrI, 1.47–5.87) resulted in significantly higher odds of elevations than control.

CK Elevations

When the placebo-controlled trials of statins were pooled in a pairwise meta-analysis including 101 324 participants, statins as a class were not significantly different than control treatment (OR, 1.13; 95% CI, 0.85–1.51; I^2, 20.4%). In the drug-level network meta-analysis of individual statins, 127 571 participants provided information on 721 individuals with clinically meaningful CK elevations (0.6% of all participants). According to this analysis, pitavastatin resulted in significantly more CK elevations than control treatment (OR, 3.63; 95% CrI,

Table 2. Findings of Drug-Level Network Meta-Analyses: Comparative Head- to-Head Effects of Individual Statins on CK (top half of the table) and Transaminase Elevations (bottom half of the table).

Atorvastatin	5.59 (1.22, 25.52)	1.32 (0.54, 2.88)	1.13 (0.65, 1.78)	0.99 (0.64, 1.53)	1.13 (0.65, 1.97)	0.38 (0.10, 1.23)
0.49 (0.15, 1.42)	Fluvastatin	0.24 (0.05, 1.17)	0.20 (0.04, 0.88)	0.18 (0.04, 0.81)	0.20 (0.04, 0.94)	0.07 (0.01, 0.46)
1.26 (0.57, 2.73)	2.58 (0.76, 9.03)	Lovastatin	0.84 (0.39, 1.94)	0.76 (0.34, 1.85)	0.86 (0.37, 2.23)	0.29 (0.06, 1.18)
2.55 (1.54, 4.14)	5.19 (1.75, 16.73)	2.03 (0.90, 4.56)	Pravastatin	0.89 (0.51, 1.63)	1.01 (0.55, 2.00)	0.34 (0.09, 1.18)
1.60 (1.06, 2.38)	3.25 (1.08, 10.5)	1.27 (0.55, 2.93)	0.63 (0.36, 1.10)	Rosuvastatin	1.14 (0.62, 2.19)	0.38 (0.10, 1.23)
2.20 (1.36, 3.52)	4.50 (1.49, 14.19)	1.76 (0.75, 4.12)	0.87 (0.47, 1.57)	1.38 (0.79, 2.38)	Simvastatin	0.34 (0.08, 1.13)
0.89 (0.24, 3.23)	1.82 (0.34, 10.00)	0.71 (0.16, 3.13)	0.34 (0.08, 1.35)	0.55 (0.15, 2.04)	0.40 (0.10, 1.56)	Pitavastatin

CK, creatine kinase. Comparisons between drugs should be read from left to right, and the estimate is in the cell in common between the column-defining treatment and the row-defining treatment. For both outcomes, ORs <1 favor the column-defining treatment. To obtain ORs for comparisons in the opposite direction, reciprocals should be taken. OR indicates odds ratio.

1.10–14.10; Figure 4D). Individuals randomized to fluvastatin had significantly lower odds of experiencing CK elevations compared with all other statins, except for lovastatin (Table 2).

The dose-level network meta-analysis for clinically meaningful elevations in baseline CK levels included 137 980 participants, providing information on 778 individuals who experienced elevations. There was a small dose–response relationship with lovatatin and simvastatin, with higher doses resulting in higher odds of elevations (Figure 4D). Simvastatin at >40 mg/d resulted in significantly higher odds of experiencing elevations compared with control treatment (OR, 4.14; 95% CrI, 1.08–16.24).

Cancer

The pairwise meta-analysis of placebo-controlled trials including 100 523 participants showed that statins as a class were not significantly different than control treatment (OR, 0.96; 95% CrI, 0.91–1.02; I^2, 0.0%). Similarly, there was no evidence from the drug-level network meta-analyses that individual statins were different than control treatment on the basis of 5511 cancer occurrences among 105 450 participants (5.2% of all participants). There was also no evidence of potential head-to-head differences between individual statins (Table 3).

Diabetes Mellitus

On the basis of placebo-controlled trials including 113 698 participants, the pairwise meta-analysis showed that statins as a class were statistically significantly different than control (OR, 1.09; 95% CrI, 1.02–1.16; I^2, 2.8%). According to placebo-controlled trials, rosuvastatin resulted in significantly higher odds of diabetes mellitus compared with control (OR, 1.16; 95% CI, 1.02–1.31; I^2, 0.0%). However, the drug-level network meta-analysis did not achieve statistical significance for any of the individual statins as a result of wider 95% CrIs (rosuvastatin had a similar effect size estimate in both pairwise and network meta-analyses; Figure 4D). Also, there were no statistically detectable differences between individual statins in terms of diabetes mellitus incidence (Table 3).

Additional Outcomes

There was limited information on both myopathy and rhabdomyolysis outcomes. In the drug-level network meta-analysis, individual statins were not significantly different than control: atorvastatin (OR, 1.21; 95% CrI, 0.25–4.95), pravastatin (OR, 1.06; 95% CrI, 0.18–4.81), rosuvastatin (OR, 0.91; 95% CrI, 0.12–4.43), and simvastatin (OR, 1.23; 95% CrI, 0.29–4.21). There was no evidence of potential differences between individual statins in terms of myopathy outcomes (results not shown). Similarly, drug-level network meta-analysis showed that individual statins were not different than control treatment in terms of rhabdomyolysis: atorvastatin (OR, 1.33; 95% CrI, 0.31–6.92), pravastatin (OR, 0.20; 95% CrI, 0.00–11.15), rosuvastatin (OR, 0.19; 95% CrI, 0.00–9.22), and simvastatin (OR, 2.03; 95% CrI, 0.40–14.81). There were no statistically detectable differences between individual statins in terms of rhabdomyolysis.

When the individual statins were ranked in terms of the magnitude of the estimated treatment effect, as well as the uncertainty around it, pravastatin (0.71) and simvastatin (0.70) had the highest combined score out of a total of 1.00, suggesting that these statins had the most favorable tolerability and harm profile on the basis of discontinuations because of adverse events, myalgia, transaminase elevations, and CK elevations (Figure 6). Baseline low-density lipoprotein cholesterol concentration, baseline mean age of the study population, and publication year did not explain the observed heterogeneity in the evidence base. Estimate of between-study heterogeneity in the drug-level network meta-analyses did not decrease in meta-regression analyses. According to the sensitivity analyses, findings from the base-case network meta-analyses did not change when adjusting for baseline low-density lipoprotein cholesterol concentration, mean age, and publication year in meta-regression analyses, with statistically nonsignificant coefficients (results provided in the online-only Data Supplement Appendix). Limiting the analysis to double-blind trials also did not change the observed ORs. Although small sample size was a limitation of subgroup analyses, we did not obtain materially different comparative harm and tolerability estimates for individual statins in primary versus secondary prevention populations (results provided in the online-only Data Supplement Appendix).

Discussion

This network meta-analysis of 246 955 participants provides evidence on the comparative tolerability and harms of individual statins using both placebo-controlled and active-comparator trials. Overall, statins as a class are associated with an increased risk of diabetes mellitus and hepatic transaminase elevations, with no statistically detectable effect on myalgia, myopathy, rhabdomyolysis, and cancer. Across the totality of the evidence base, higher doses of some statins result in higher

Table 3. Findings of Drug-Level Network Meta-Analyses: Comparative Head- to-Head Effects of Individual Statins on Diabetes (top half of the table) and Cancer (bottom half of the table)

Atorvastatin	-	1.18 (0.71, 1.99)	1.12 (0.79, 1.62)	1.01 (0.69, 1.47)	1.06 (0.72, 1.57)
0.94 (0.59, 1.47)	Fluvastatin	-	-	-	-
0.86 (0.60, 1.20)	0.91 (0.58, 1.43)	Lovastatin	0.95 (0.62, 1.46)	0.85 (0.54, 1.33)	0.90 (0.56, 1.41)
0.90 (0.69, 1.20)	0.97 (0.65, 1.45)	1.06 (0.81, 1.42)	Pravastatin	0.90 (0.70, 1.12)	0.94 (0.72, 1.21)
0.84 (0.62, 1.16)	0.90 (0.58, 1.39)	0.99 (0.73, 1.36)	0.94 (0.73, 1.19)	Rosuvastatin	1.05 (0.80, 1.40)
0.84 (0.66, 1.08)	0.90 (0.60, 1.37)	0.98 (0.75, 1.34)	0.93 (0.77, 1.15)	0.99 (0.78, 1.30)	Simvastatin

Comparisons between drugs should be read from left to right, and the estimate is in the cell in common between the column-defining treatment and the row-defining treatment. For both outcomes, ORs <1 favor the column-defining treatment. To obtain ORs for comparisons in the opposite direction, reciprocals should be taken. OR indicates odds ratio.

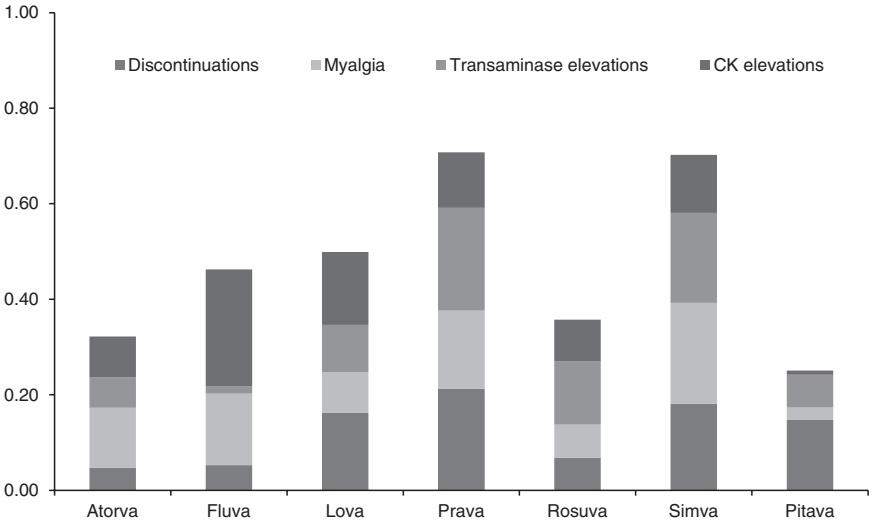

Figure 6. Overall ranking of individual statins in placebo-controlled and active-comparator trials of participants by their overall probability to be the best treatment in terms of discontinuations because of adverse events, myalgia, hepatic transaminase elevation, and CK elevation. In addition to the overall score for each statin, the relative contribution of each of the 4 outcomes to the overall score is also shown. Each statin was scored with points up to a maximum of 0.25 for each outcome (overall maximum score: 1.00). Higher scores indicate a better tolerability and safety profile. CK indicates creatine kinase.

odds of experiencing transaminase elevations, CK elevations, and discontinuations because of adverse events. When compared head-to-head in network meta-analyses, there are differences among individual statins, with simvastatin and pravastatin likely to be ranked superior to their alternatives in terms of their safety profile.

Although the benefits of statins for individuals with established cardiovascular disease are well documented,[9] their effect in individuals free of cardiovascular disease has been disputed.[8,32–34] Recent meta-analyses based on both individual patient-level data[4] and study-level reports[5] confirm that all-cause mortality benefits of statins in the primary prevention setting are clinically and statistically significant. These recent findings provide supporting evidence for initiating statin therapy in individuals who are at an increased risk of developing cardiovascular disease. Nevertheless, expanding the limits of statin therapy to a wider population of individuals may have important safety implications. Although rare, adverse events associated with statin therapy range from mild to moderate and seem to increase with treatment intensity. With notable exceptions,[35] randomized trial evidence on the long-term safety of individual statin treatments remains limited.

Our review confirms the findings of previous pairwise meta-analyses in that statins as a class are associated with higher odds of developing diabetes mellitus[15] and experiencing hepatic transaminase elevations.[36] There is a lack of evidence that statins are associated with an increased risk of developing cancers. Although our review did not find statistical evidence of myopathy, this may be because of an underdetection of muscle toxicity in clinical trials.[37–39]

At the population level, mortality and cardiovascular benefits of statin therapy greatly overweigh its potential harms, even taking into account the recent finding that statin use is associated with a modest increase in diabetes mellitus incidence.[40] At the individual level, however, there may be a risk of exposing a large group of individuals to the (primarily minor) harms of statin therapy for the benefit of a smaller number of individuals. This brings into sharp focus the importance of correctly identifying the set of individuals who stand to benefit from statin therapy. There are emerging tools that can be used to predict personalized long-term harms and benefits associated with statin therapy.[41]

Available statins differ to a various extent in pharmacological properties, and it would be expected that they differ in terms of their clinical efficacy.[42,43] Nonetheless, their comparative harms had not been evaluated in a comprehensive manner in previous reviews. In addition to pairwise meta-analysis that compared statins with control treatment, we performed network meta-analysis, which is a relatively new method that differs from pairwise meta-analysis by incorporating data from both direct (from trials that include a specific pairwise comparison) and indirect (from a network of trials that do not include that comparison) sources of evidence. We previously used this method to compare individual statins in terms of their cholesterol-lowering effects, as well as their effects on deaths, coronary events, and cerebrovascular events.[44–46]

Our findings show that there are statistically detectable differences between individual statins in terms of their tolerability, hepatic transaminase elevations, and CK elevations. At the drug level, individuals receiving simvastatin and pravastatin seem to have the lowest odds of experiencing myalgia, transaminase and CK elevations, and discontinuations because of adverse events.

Our dose-specific analysis parallels the findings of previous meta-analyses in that more intensive statin therapy is associated with greater risk of harm and less favorable tolerability compared with lower doses.[19,47–49] Similar to previous studies, we observed a general dose–response relationship across placebo-controlled and active-comparator trials in terms of discontinuations because of adverse events, transaminase elevations, and CK elevations.

As with any meta-analysis, our network meta-analysis required an assumption of similarity across the pooled set of trials in terms of patient population and trial characteristics. More specifically, we assumed that the distribution of relative treatment effect modifiers (eg, baseline cholesterol levels) was balanced across different treatment comparisons in the evidence network. An imbalance in the distribution of these variables in a single randomized, controlled trial would result in within-trial heterogeneity; an imbalance across

trials would result in between-study heterogeneity in pairwise meta-analyses; and an imbalance across different treatment comparisons would result in inconsistency in network meta-analyses, potentially biasing the results. To account for such imbalances, we evaluated several study-level characteristics in the meta-regression analyses. Specifically, our analyses suggested that baseline mean age, low-density lipoprotein cholesterol concentration, and trial publication year did not have an impact on the observed findings.

Findings of this study should be interpreted in light of its limitations. First, as a literature-based meta-analysis, our analysis shares the limitations of the published evidence base. The quality of included trials was moderate, with older trials being more prone to bias than newer trials. Second, given the large volume of available studies in the literature, our meta-analysis did not use individual patient-level data, which would have advantages when exploring potential differences across relative treatment effect modifiers. Third, although there was no evidence of small-study effects, there was an apparent asymmetry in the evidence network where specific interventions seem to be avoided (eg, fluvastatin). For instance, the relative effect of fluvastatin on CK elevations was estimated on the basis of 8 events observed in 4 trials including 2646 participants. Similarly, there were only 4 trials of fluvastatin, which reported hepatic transaminase elevations. As expected, the evidence base for pitavastatin was also sparse. Although pitavastatin was recently approved by the Food and Drug Administration, it has been in use in other settings since 2003 (most notably in Japan and South Korea) without a corresponding evidence base in the English language literature. Fourth, there was considerable heterogeneity across various pairwise meta-analyses of statins versus control, particularly for hepatic transaminase elevations. It remains a possibility that our analysis did not fully account for heterogeneity as a result of unobserved or unmeasured factors. However, we used a random-effects model, and our analyses took into account potential unexplained heterogeneity across the studies. We also performed meta-regressions to further evaluate heterogeneity and inconsistency and did not detect a significant effect of study-level characteristics.

Despite these limitations, our study has important methodological strengths. First, this review is the largest meta-analysis on the harms of statin therapy to date, including almost a quarter million trial participants. Second, we incorporated data from a comprehensive list of trials, irrespective of placebo or active controls, including all clinically used statins. In total, we included 80 active-comparator trials with or without a placebo or usual care arm. Third, we evaluated the dose-comparative harms of individual statins.

Our findings have important clinical implications. First, there is strong evidence that statins as a class are generally safe with uncommon side effects. According to the findings of this comprehensive analysis, there is consistently strong evidence on the comparatively favorable side effect profile of simvastatin and pravastatin, particularly at low-to-moderate doses, which should be favored in clinical practice. This meta-analysis sheds new light on the discussion of the relationship between statins and diabetes mellitus incidence and confirms that statin use is not associated with cancer incidence. Finally, we acknowledge the complex nature of making prescribing decisions and urge prescribers to consider the findings of this analysis in light of the comparative benefit profiles of individual statins in preventing all-cause mortality in addition to cardiovascular and cerebrovascular events.[44–46]

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Disclosures

None.

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