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Comparative benefits of statins in the primary and secondary prevention of major coronary events and all-cause mortality: a network meta-analysis of placebo-controlled and active-comparator trials

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Abstract

Background: The extent to which individual statins vary in terms of clinical outcomes across all populations, in addition to secondary and primary prevention has not been studied extensively in meta-analyses.

Methods: We systematically studied 199,721 participants in 92 placebo-controlled and active-comparator trials comparing atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, and simvastatin in participants with, or at risk of developing, cardiovascular disease. We performed pairwise and network meta-analyses for major coronary events and all-cause mortality outcomes, taking into account the dose differences across trials. Systematic review registration: PROSPERO 2011:CRD42011001470.

Results: There were only a few trials that evaluated fluvastatin. Most frequent comparisons occurred between pravastatin and placebo, atorvastatin and placebo, and rosuvastatin and atorvastatin. No trial directly compared all six statins to each other. Across all populations, statins were significantly more effective than control in reducing all-cause mortality (OR 0.87, 95% credible interval 0.82–0.92) and major coronary events (OR 0.69, 95% CI 0.64–0.75). In terms of reducing major coronary events, atorvastatin (OR 0.66, 95% CI 0.48–0.94) and fluvastatin (OR 0.59, 95% CI 0.36–0.95) were significantly more effective than rosuvastatin at comparable doses. In participants with cardiovascular disease, statins significantly reduced deaths (OR 0.82, 95% CI 0.75–0.90) and major coronary events (OR 0.69, 95% CI 0.62–0.77). Atorvastatin was significantly more effective than pravastatin (OR 0.65, 95% CI 0.43–0.99) and simvastatin (OR 0.68, 95% CI 0.38–0.98) for secondary prevention of major coronary events. In primary prevention, statins significantly reduced deaths (OR 0.91, 95% CI 0.83–0.99) and major coronary events (OR 0.69, 95% CI 0.61–0.79) with no differences among individual statins. Across all populations, atorvastatin (80%), fluvastatin (79%), and simvastatin (62%) had the highest overall probability of being the best treatment in terms of both outcomes. Higher doses of atorvastatin and fluvastatin had the highest number of significant differences in preventing major coronary events compared with other statins. No significant heterogeneity or inconsistency was detected.

Conclusions: Statins significantly reduce the incidence of all-cause mortality and major coronary events as compared to control in both secondary and primary prevention. This analysis provides evidence for potential differences between individual statins, which are not fully explained by their low-density lipoprotein cholesterol-reducing effects. The observed differences between statins should be investigated in future prospective studies.

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Introduction

Statins are widely used to prolong survival and reduce the occurrence of coronary and cerebrovascular events in patients with cardiovascular disease. Prior meta-analyses have demonstrated the effectiveness of statins in secondary prevention,[1–10] among the elderly,[11,12] and in individuals with diabetes.[13,14] Initially focused on secondary prevention, statin therapy has become more common as the limits of treatment have expanded over time to include persons at progressively lower risk of developing cardiovascular disease.[15] As the number of individuals eligible for statin therapy continues to increase both in primary and secondary prevention, two questions warrant further investigation. First, there is no consensus around the benefit of statins in primary prevention.[16] Although previous meta-analyses have provided evidence in support of the use of statins in individuals with no evidence of cardiovascular disease,[17] recent studies challenged these findings.[18,19] Second, whether individual statins vary in terms of their effect on clinical outcomes when compared head-to-head is unclear and has not been studied in a comprehensive manner in previous meta-analyses.[20] Information regarding the relative clinical value of different statins in primary and secondary prevention of cardiovascular disease is needed to better inform patients, clinicians, and other healthcare decision makers.

Previous network meta-analyses that indirectly compared individual statins were limited to placebo-controlled trials and did not take into account evidence from a large number of active-comparator trials.[21–23] Equally importantly, these analyses did not differentiate between primary- and secondary-prevention populations.[24] Finally, previous network meta-analyses did not assess differences in dosages of individual statins across populations and did not compare statins at similar doses.

We report a comprehensive network meta-analysis that combines evidence from both placebo-controlled and active-comparator trials. We evaluate the effect of statins on major coronary events and all-cause mortality across all populations, in addition to secondary and primary prevention of cardiovascular disease separately. We also compare the effectiveness of different statins head-to-head in these patient populations, taking into account dose differences across the included set of trials.

Methods

Study protocol

We developed a protocol and subsequently made it publicly available on the first author's institutional website before starting this study (PROSPERO registration: 2011:CRD42011001470).[25]

Search strategy and selection criteria

We searched MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials to identify studies published between 1 January 1985 and 1 January 2011. To identify the active-comparator trials that were not included in previous meta-analyses, we developed a search strategy using the search terms atorvastatin, fluvastatin, simvastatin, lovastatin, pravastatin, rosuvastatin, cholesterol, cardiovascular disease, and hydroxymethylglutaryl-CoA reductase inhibitors/therapeutic use. We also performed manual searches using the authors' files and reference lists from original communications and review articles to cross check references. Two researchers (BT, HT) independently performed abstract, title, and full-text screening. A third researcher approved study selection (HN).

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, pravastatin, rosuvastatin, and simvastatin if they had more than 50 participants per trial arm, lasted longer than 4 weeks, and reported major coronary events or all-cause mortality. Both fixed-dose and titration designs were included. Per pre-defined criteria, we excluded trials conducted in patients with renal insufficiency.

Trial categorization

Whenever possible, we categorized included trials as primary prevention, secondary prevention, or mixed

patient population. Trials that included at least 80% of participants without established cardiovascular disease or reported data separately on a sole primary prevention group were categorized as primary prevention. Trials that included at least 80% of participants with established cardiovascular disease or reported data separately on a sole secondary prevention group were categorized as secondary prevention. All remaining trials were categorized as having a mixed patient population.

Whenever possible, we used data extracted in previous meta-analyses to benefit from earlier attempts at contacting authors of trials and obtaining unpublished information. For instance, for the analysis of the primary prevention trials, data inputs used in the recent meta-analysis by Ray et al.[18] were used to ensure that only patients without coronary artery disease at baseline were included.

Outcomes

Primary outcomes were major coronary events and all-cause mortality. We defined the composite of major coronary events as deaths from coronary heart disease and non-fatal myocardial infarctions.

Data extraction

We used a structured form to extract data on trial and patient population characteristics, and outcomes. Full list of data extraction elements can be found on our publicly available protocol. We also extracted information on study quality using the Cochrane risk-of-bias tool. One researcher extracted data (HN) and another independently checked for accuracy (BT).

Statistical analysis

We first qualitatively summarized included trials, describing the types of direct and indirect comparisons and important clinical and methodological variables (such as trial population, year of publication, age, and risk of cardiovascular disease).

For each pairwise comparison between two treatments, we calculated the relative effect with a 95% confidence interval. First, we performed classical pairwise meta-analyses to synthesize studies that compared the same two treatments using the Mantel–Haenszel (fixed-effect) and Der Simonian Laird (random-effects) method.[26] 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 effects of statins, we conducted network meta-analyses.[27] This type of analysis allowed for combining the direct within-trial comparisons between two treatments (atorvastatin vs. control) with indirect comparisons constructed from trials that had one treatment in common (atorvastatin vs. control and simvastatin vs. control).[28] This analysis preserved the within-trial randomized treatment comparison of each trial while combining all available comparisons between treatments. Study-level relative treatment effects were combined using random-effects models using Bayesian Markov chain Monte Carlo methods.[29] We considered the findings significant when the 95% credible intervals (CI) for odds ratios (OR) did not include the null value 1.00. We assessed the probability that each statin is best by calculating its treatment effect compared with control and counting the proportion of iterations of the Markov chain in which each statin has the highest treatment effect, the second highest, and so on. This approach took into account the magnitude of the estimated odds ratio as well as the uncertainty around it. We developed rankograms and cumulative probability plots to graphically present the distribution of ranking probabilities and estimated the surface under the cumulative ranking (SUCRA) line for each statin.[30] To estimate inconsistency between direct and indirect evidence, we calculated the ratio of relative effects for indirect vs. direct evidence. We defined inconsistency as the disagreement between direct and indirect evidence with a 95% CI excluding 1.[31]

To obtain a comprehensive estimate of the effect of statins in major coronary events and all-cause mortality, 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. We also performed separate analyses for the primary and secondary prevention populations, as categorized by the criteria mentioned above.

For the base-case analysis, we excluded trials with high doses (80 mg/day for atorvastatin, fluvastatin, lovastatin, simvastatin, and $\geq$40 mg/day for rosuvastatin) and evaluated the benefits of statins at comparable doses. In a sensitivity analysis, we also included trials that evaluated statins at high doses. A dose-specific analysis explored the effects of individual statins at low, medium, and high doses separately. We categorized doses as low ($\leq$20 mg/day), medium (21–40 mg/day), and high (>40 mg/day) for atorvastatin, fluvastatin, lovastatin, pravastatin, and simvastatin. For rosuvastatin, doses $\leq$10 mg/day was categorized as low, 11–20 mg/day as medium, and >20 mg/day as high.

We also investigated whether potential heterogeneity and inconsistency across the evidence base in the

network meta-analysis could be explained by differences in study-level covariates. We performed meta-regression analyses to evaluate whether differences in trial publication year, patients' baseline LDL concentration, and age could explain potential heterogeneity. We performed all meta-regression analyses by allowing for a common treatment–covariate interaction for each statin compared to control.[32]

All analyses were based on the total number of randomly assigned participants. We conducted pairwise meta-analyses in STATA 11.0, multiple-treatments meta-analyses in WinBugs 1.4.3, and evaluated inconsistency in the trial network using R 2.11.1. Graphical presentation of the trial network, inconsistency plots, rankograms, and SUCRA plots were developed in R 2.11.1.

Results

We included 92 trials (Figure 1), totalling 199,721 participants (Supplemental Table S1). Overall, the average trial duration was 116 weeks (2.2 years). There were 59 two-armed placebo-controlled trials and the remaining 33 were two- or multi-armed active-comparator trials. Of the 15 possible pairwise comparisons between the six statins, nine were available for the all-cause mortality outcome and only six were available for the major coronary events outcome. There were only a few trials that evaluated fluvastatin. Most frequent comparisons occurred between pravastatin and placebo, atorvastatin and placebo, and rosuvastatin and atorvastatin. There were 4709 participants in the placebo-controlled trials of fluvastatin as compared to 54,617 and 28,762 in the placebo-controlled trials of pravastatin and rosuvastatin, respectively. No trial directly compared all six statins with each other (Figure 2).

The overall quality of included trials was rated as moderate. Older trials were more prone to bias with inadequate sequence generation and treatment allocation concealment. A large number of trials did not report details about randomization procedures and allocation concealment. Only a small number of trials were at low risk of bias.

Pairwise meta-analysis findings: benefit of statin therapy vs. control

In the pairwise meta-analysis of statin therapy vs. control, 157,217 participants contributed information on 12,398 deaths, and 153,578 participants contributed information on 9715 major coronary events. Overall, statin therapy was associated with a reduction in all-cause mortality (OR 0.87, 95% CI 0.82–0.92) (Figure 3) and major coronary events (OR 0.69, 95% CI 0.64–0.75) when compared to control (Figure 4). Among statins, only fluvastatin and pravastatin were associated with a significant reduction in all-cause mortality compared with the control, while atorvastatin, lovastatin, rosuvastatin, and simvastatin were not. Atorvastatin, fluvastatin, pravastatin, and simvastatin were associated with significantly fewer major coronary events than control treatment.

In the secondary prevention population, statin therapy was associated with a significant reduction in all-cause mortality (OR 0.82, 95% CI 0.75–0.90) and major coronary events (OR 0.69, 95% CI 0.62–0.77) when compared to control. Fluvastatin and pravastatin resulted in significantly fewer deaths as compared to control (Figure 3), while atorvastatin, fluvastatin, and pravastatin led to significantly fewer major coronary events than control treatment (Figure 4).

In the primary prevention population, statin therapy was associated with a significant reduction in all-cause mortality (OR 0.91, 95% CI 0.83–0.99) (Figure 3) and major coronary events (OR 0.69, 95% CI 0.61–0.79) (Figure 4). In this population, only rosuvastatin had sufficient evidence for a significant benefit on all-cause mortality, while atorvastatin, fluvastatin, lovastatin, and pravastatin did not. Atorvastatin, lovastatin, pravastatin, and rosuvastatin were associated with significantly fewer major coronary events as compared to control.

Overall, statistical heterogeneity in pairwise comparisons of statin therapy vs. control in all-cause mortality was low to moderate in analyses of primary prevention (I^2 8.9%), secondary prevention (I^2 14.8%), and all populations together (I^2 22.6%). We observed moderate heterogeneity in pairwise comparisons of statin therapy vs. control in major coronary events (I^2 29.4% in secondary prevention, I^2 40.2% in primary prevention, and I^2 40.9% in all populations together).

Network meta-analysis findings: comparative benefits of statins

In addition to the trials included in the pairwise comparisons of statin therapy vs. control, there were 39 direct head-to-head statin comparisons, providing information on 43,174 participants. In the base-case network meta-analysis, 64 and 48 trials provided information for the all-cause mortality and major coronary events analyses, respectively. In total, 161,379 participants were included in the base-case analysis on all-cause mortality, which provided information on 11,914 deaths. For the major coronary events outcome, there were 9363 events among 151,520 participants.

In the sensitivity analysis inclusive of high-dose trials, 80 and 62 trials provided information for the all-cause mortality and major coronary events analyses,

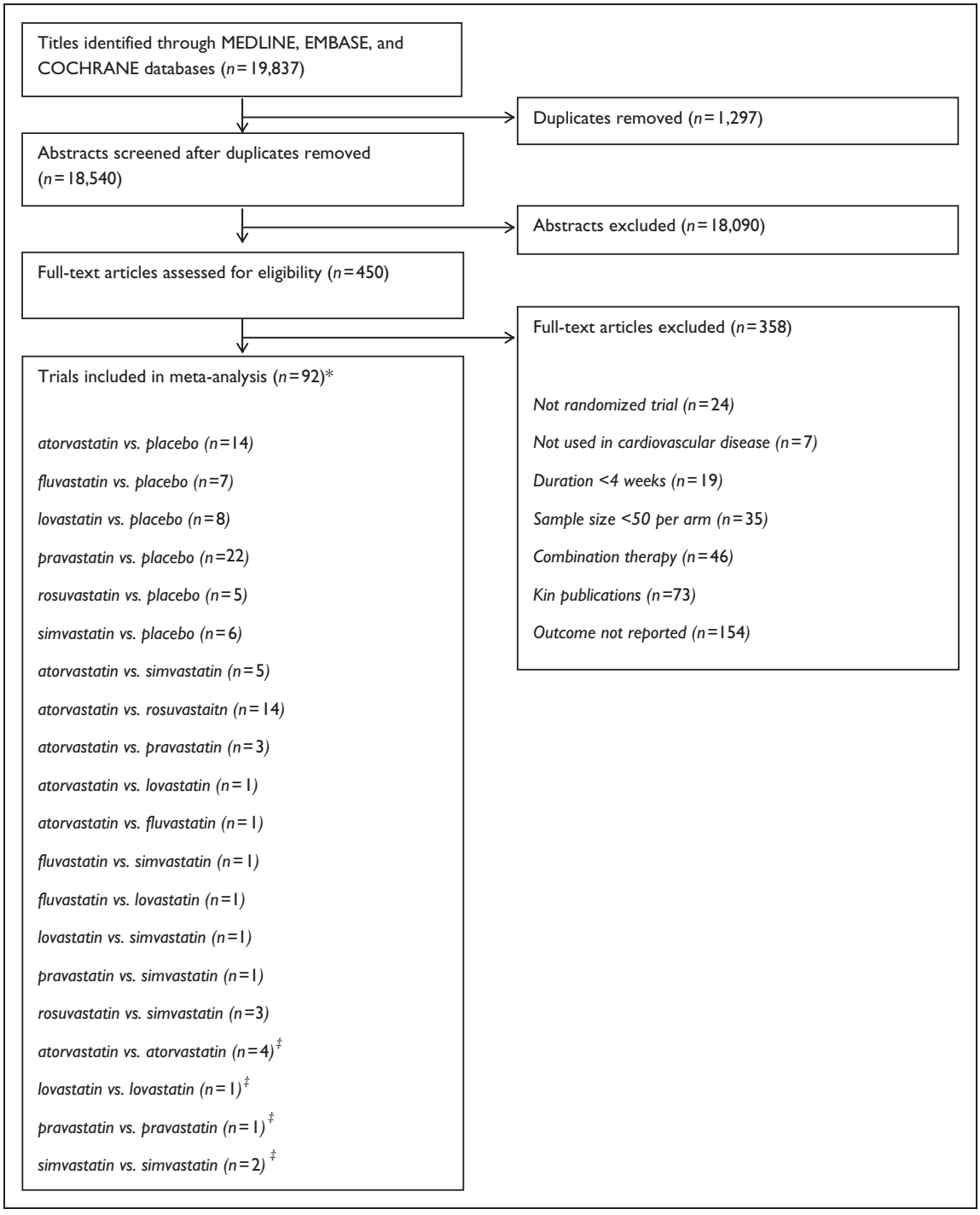

Figure 1. Flow diagram of trial identification and selection.
*Ninety-two randomized trials correspond to 101 comparisons because some trials had more than two arms.
‡Eight randomized trials compared the same statin at a high dose vs. low dose.

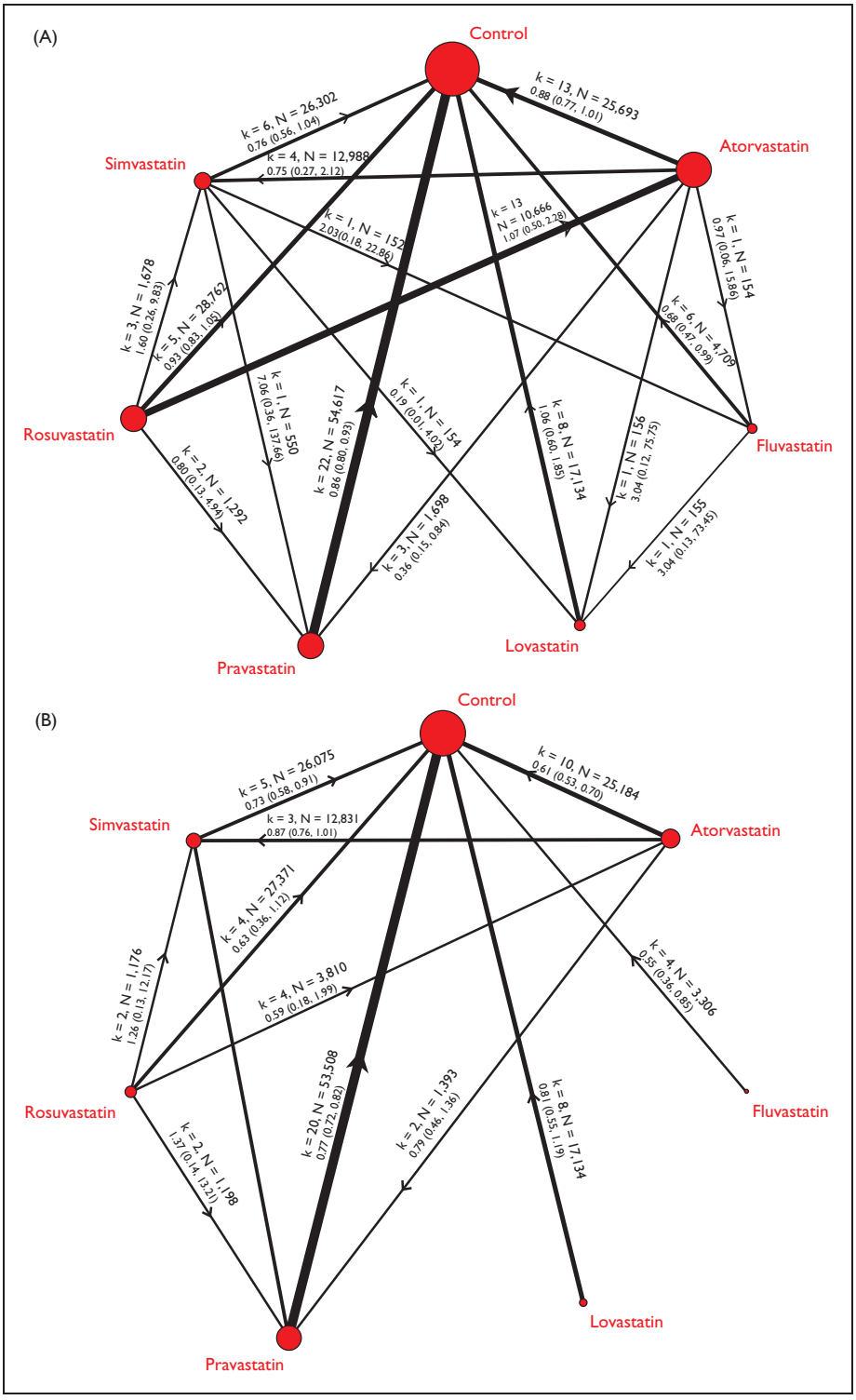

Figure 2. Network of eligible pairwise comparisons for (A) all-cause mortality and (B) major coronary events in placebo-controlled and active-comparator trials of participants with and without prior coronary heart disease at baseline (overall population). Connecting lines indicate the direct pairwise comparison between two treatments (k = number of pairwise comparisons; N = overall number of participants; odds ratios and 95% confidence intervals are given). Arrows depict the direction of comparison (e.g. atorvastatin vs. control). Supplementary Figures S1 (all-cause mortality) and S2 (major coronary events) provide separate network diagrams for secondary and primary prevention populations. A total of 93 out of 101 comparisons are shown in these network diagrams as eight trials compared the same statin (high vs. low dose comparisons), which are not depicted in this figure.

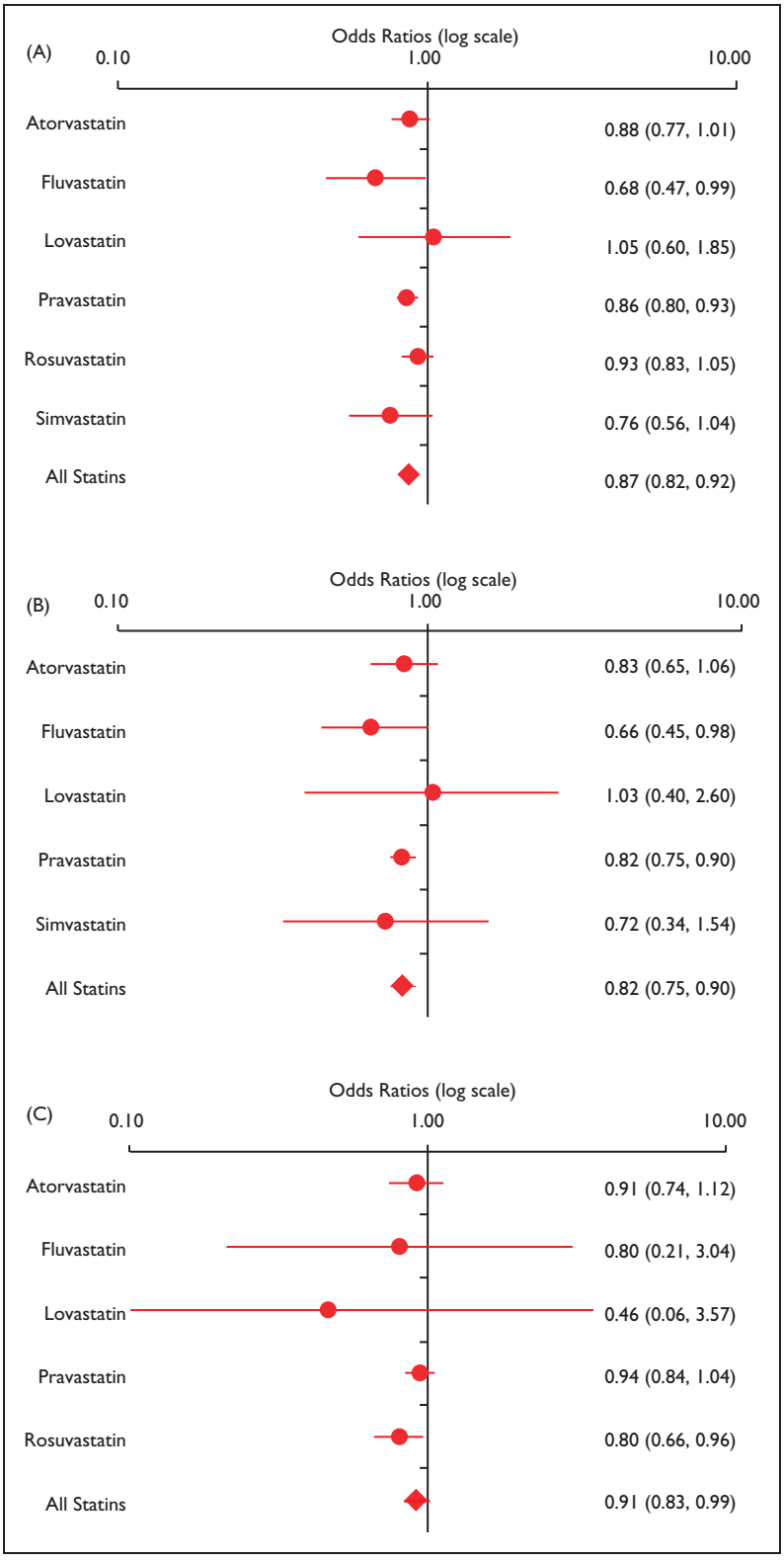

Figure 3. Findings of pairwise meta-analyses: effect of statins compared to control on all-cause mortality in placebo-controlled trials of participants (A) with and without prior coronary heart disease at baseline (overall population), (B) with coronary heart disease at baseline (secondary prevention), (C) without coronary heart disease at baseline (primary prevention). Results shown are based on an analysis of 157,217 participants in placebo-controlled trials. Supplementary Figures S3 (overall population), S4 (secondary prevention), and S5 (primary prevention) provide the list of studies and their findings included in separate meta-analyses.

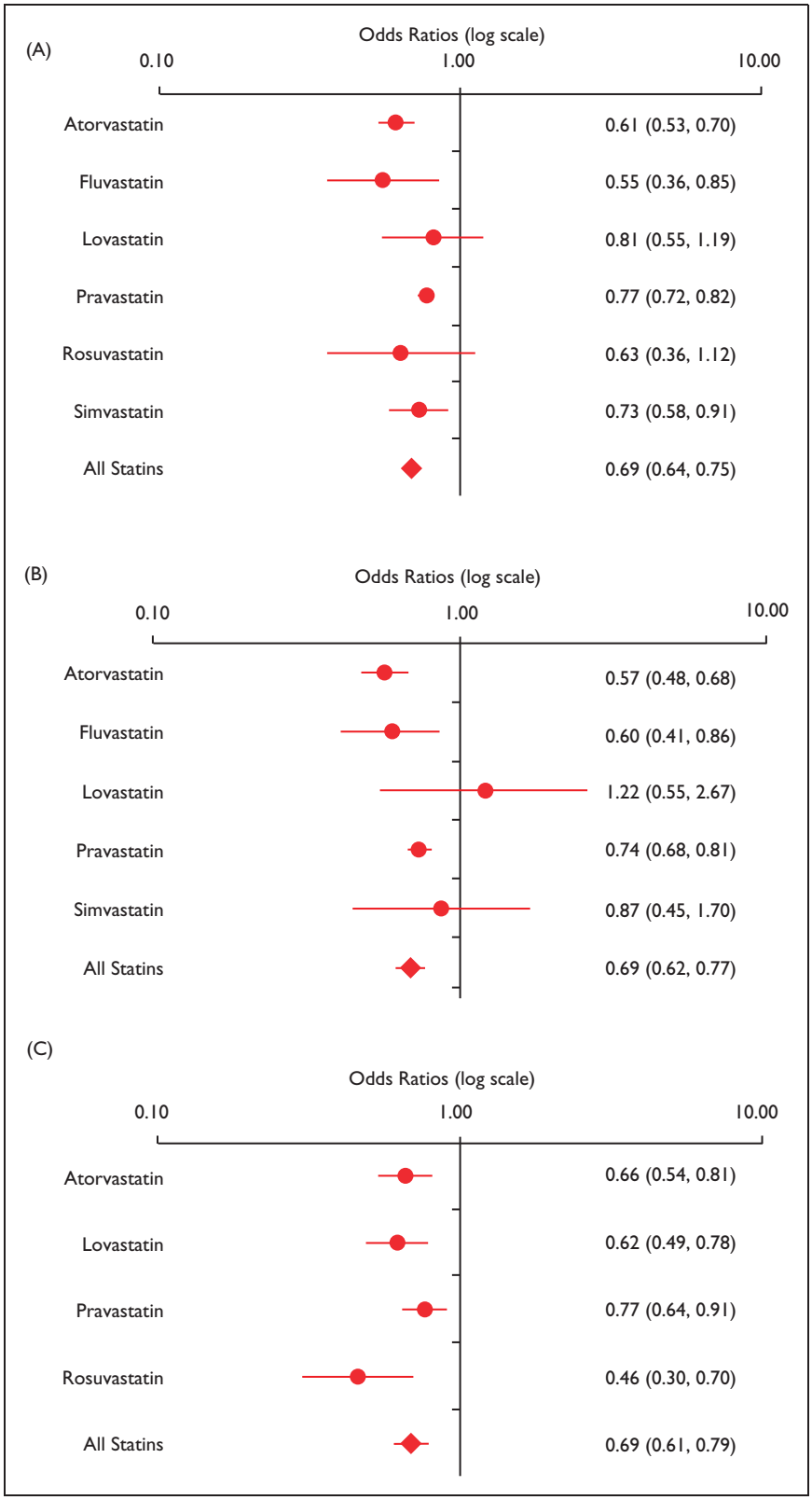

Figure 4. Findings of pairwise meta-analyses: effect of statins compared to control on major coronary events in placebo-controlled trials of participants (A) with and without prior coronary heart disease at baseline (overall population), (B) with coronary heart disease at baseline (secondary prevention), (C) without coronary heart disease at baseline (primary prevention). Results shown are based on an analysis of 153,578 participants. Supplementary Figures S6 (overall population), S7 (secondary prevention), and S8 (primary prevention) provide the list of studies and their findings included in separate meta-analyses.

respectively. In total, 183,844 participants were included in the sensitivity analysis on all-cause mortality, which provided information on a total of 13,210 deaths. For the major coronary events outcome, there were 10,664 events among 173,062 participants.

In the dose-specific analysis that included all placebo-controlled, active-comparator, and dose-comparison trials, a total of 13,892 deaths among 196,765 participants in 86 trials, and 11,515 major coronary events among 186,375 participants in 69 trials, were included.

In the base-case analysis, the average dose was 16.7 mg/day for atorvastatin as compared to 40.0 mg/day for fluvastatin, 39.3 mg/day for lovastatin, 30.9 mg/day for pravastatin, 14.8 mg/day for rosuvastatin, and 33.3 mg/day for simvastatin. In this analysis, there were no significant differences among statins in terms of all-cause mortality when all trials of primary prevention, secondary prevention, and mixed patient populations were pooled (Figure 5). For the overall population, rosuvastatin resulted in significantly fewer major coronary events compared to atorvastatin and fluvastatin. Among participants with established cardiovascular disease, atorvastatin was associated with significantly fewer major coronary events compared to pravastatin and simvastatin. There were no statistical differences among individual statins without established cardiovascular disease.

In the sensitivity analysis, the average dose of atorvastatin was 39.6 mg/day as compared to 72.3 mg/day for fluvastatin, 40.7 mg/day for lovastatin, 31.2 mg/day for pravastatin, 17.2 mg/day for rosuvastatin, and 33.3 mg/day for simvastatin. There were no significant differences in the treatment benefit among statins when we pooled trials of primary prevention, secondary prevention, and mixed patient populations for both all-cause mortality and major coronary events (Figure 6). However, among participants with established cardiovascular disease, atorvastatin was associated with significantly fewer major coronary events compared to pravastatin. Participants randomized to lovastatin were estimated to experience significantly more major coronary events than those randomized to atorvastatin, fluvastatin, and simvastatin in trials of secondary prevention. There were no detectable statistical differences among statins for participants without established cardiovascular disease.

When we ranked statins according to cumulative probability of reducing all-cause mortality and major coronary events across all populations, atorvastatin (80%), fluvastatin (79%), and simvastatin (62%) were among the most effective treatments at comparable doses (Figure 7). In a sensitivity analysis, fluvastatin (89%), atorvastatin (76%), and simvastatin (60%) consistently ranked as the most effective treatments when high-dose trials were included in the analysis.

In the dose-specific analysis, low-dose atorvastatin and low-dose pravastatin resulted in significantly fewer deaths than control treatment while other statins did not have adequate evidence to show superiority over placebo (Figure 8). Statins in higher doses did not have a greater impact on all-cause mortality than lower doses. In terms of major coronary events, all statins except for low-dose lovastatin, high-dose lovastatin, low-dose rosuvastatin, high-dose rosuvastatin, and low-dose simvastatin were associated with significantly fewer major coronary events as compared to control treatment. Higher doses of atorvastatin and fluvastatin had the highest number of significant differences compared with other statins (Supplementary Figure S13).

There was no evidence of inconsistency in the trial network as the direct estimate of the summary effect did not differentiate from the indirect estimate in each loop of the network for both outcomes (Supplementary Figures S14 and 15). Comparative benefit estimates of statins did not change in meta-regression analyses when we adjusted for publication year and baseline mean age of patients. Although we detected a modest association between mean LDL concentrations of patients at baseline and effects of statins, comparative effect estimates did not change after adjustment (Supplementary Exhibit S1).

Discussion

This network meta-analysis of 199,721 participants provides evidence on the statistically and clinically meaningful benefits of statins in both primary and secondary prevention of all-cause mortality and major coronary events. Overall, statins were associated with an 18% reduction in relative odds of all-cause mortality among patients with cardiovascular disease. In primary prevention, statin therapy resulted in a modest but significant 9% reduction in relative odds of all-cause mortality. Benefits of statins in reducing the relative odds of major coronary events by 31% were consistent across primary and secondary prevention populations. This meta-analysis is the most comprehensive study to investigate the comparative effect of different statins using both placebo-controlled and active-comparator trials and separately for primary- and secondary-prevention populations. Existing statin trial evidence appeared asymmetric given the extremely small numbers of individuals included in fluvastatin trials relative to other statins. Across all populations, our base-case analysis provided evidence to suggest that there may be differences among individual statins for preventing coronary events. Among statins, atorvastatin, fluvastatin, and simvastatin were likely to be ranked superior to their alternatives at comparable doses across all populations.

(A)

Atorvastatin	1.11 (0.42, 2.79)	0.78 (0.52, 1.14)	0.91 (0.72, 1.11)	0.85 (0.64, 1.07)	0.99 (0.73, 1.28)
1.13 (0.70, 1.85)	Fluvastatin	0.71 (0.26, 1.87)	0.82 (0.33, 2.13)	0.76 (0.30, 2.00)	0.89 (0.34, 2.32)
0.83 (0.57, 1.16)	0.74 (0.42, 1.20)	Lovastatin	1.16 (0.80, 1.68)	1.08 (0.73, 1.61)	1.26 (0.84, 1.89)
0.82 (0.65, 1.11)	0.73 (0.48, 1.16)	0.99 (0.74, 1.47)	Pravastatin	0.93 (0.75, 1.17)	1.08 (0.85, 1.39)
0.66 (0.48, 0.94)	**0.59 (0.36, 0.95)**	0.79 (0.56, 1.22)	0.81 (0.58, 1.04)	Rosuvastatin	1.16 (0.88, 1.53)
0.83 (0.58, 1.10)	0.74 (0.43, 1.15)	1.00 (0.69, 1.38)	1.02 (0.68, 1.24)	1.27 (0.82, 1.67)	Simvastatin

(B)

Atorvastatin	1.02 (0.20, 5.00)	0.93 (0.20, 4.13)	0.65 (0.24, 1.22)	0.70 (0.08, 4.18)	0.68 (0.24, 1.43)
–	Fluvastatin	0.92 (0.13, 6.56)	0.62 (0.12, 2.62)	0.67 (0.05, 7.52)	0.66 (0.13, 2.74)
0.65 (0.26, 1.77)	–	Lovastatin	0.68 (0.16, 2.56)	0.72 (0.06, 7.99)	0.72 (0.16, 2.90)
0.65 (0.43, 0.99)	–		Pravastatin	1.09 (0.12, 8.42)	1.06 (0.52, 2.15)
–	–	–	–	Rosuvastatin	0.97 (0.12, 9.24)
0.68 (0.38, 0.98)	–	1.02 (0.36, 2.60)	1.05 (0.61, 1.39)	–	Simvastatin

(C)

Atorvastatin	0.99 (0.18, 5.43)	0.96 (0.45, 3.47)	0.97 (0.49, 2.17)	0.98 (0.32, 2.47)	–
–	Fluvastatin	1.01 (0.19, 6.68)	1.00 (0.19, 5.21)	0.98 (0.15, 5.53)	–
1.05 (0.51, 2.27)	–	Lovastatin	1.01 (0.34, 2.00)	1.02 (0.22, 2.32)	–
0.90 (0.54, 1.84)	–	0.86 (0.48, 1.81)	Pravastatin	1.02 (0.34, 2.17)	–
1.41 (0.59, 3.45)	–	1.35 (0.52, 3.33)	1.55 (0.63, 3.24)	Rosuvastatin	–
–	–	–	–	–	Simvastatin

Figure 5. Base-case analysis findings: comparative effect of individual statins on all-cause mortality (in white) and major coronary events (in grey) according to network meta-analysis of participants (A) with and without coronary heart disease at baseline (overall population), (B) with coronary heart disease at baseline (secondary prevention), and (C) without coronary heart disease at baseline (primary prevention). Values are odds ratios (95% CI). 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, odds ratios less than 1 favour the column-defining treatment. To obtain odds ratios for comparisons in the opposite direction, reciprocals should be taken.

(A)

Atorvastatin	1.22 (0.80, 1.86)	0.82 (0.57, 1.16)	0.95 (0.78, 1.13)	0.91 (0.73, 1.10)	1.01 (0.73, 1.10)
1.11 (0.72, 1.80)	Fluvastatin	0.66 (0.40, 1.13)	0.77 (0.51, 1.18)	0.74 (0.48, 1.15)	0.82 (0.53, 1.27)
0.83 (0.58, 1.11)	0.74 (0.42, 1.20)	Lovastatin	1.16 (0.81, 1.65)	1.11 (0.77, 1.60)	1.23 (0.85, 1.80)
0.84 (0.70, 1.05)	0.76 (0.48, 1.18)	1.02 (0.77, 1.48)	Pravastatin	0.96 (0.78, 1.17)	1.06 (0.86, 1.32)
0.75 (0.57, 1.02)	0.67 (0.41, 1.09)	0.90 (0.65, 1.40)	0.89 (0.68, 1.17)	Rosuvastatin	1.11 (0.88, 1.40)
0.84 (0.64, 1.01)	0.75 (0.44, 1.17)	1.01 (0.73, 1.41)	1.00 (0.73, 1.22)	1.12 (0.76, 1.47)	Simvastatin

(B)

Atorvastatin	1.20 (0.72, 1.99)	0.97 (0.42, 2.25)	0.90 (0.66, 1.15)	0.49 (0.12, 1.56)	0.98 (0.68, 1.26)
0.97 (0.67, 1.52)	Fluvastatin	0.82 (0.33, 2.07)	0.75 (0.44, 1.23)	0.41 (0.09, 1.39)	0.82 (0.47, 1.37)
0.47 (0.27, 0.83)	**0.48 (0.24, 0.94)**	Lovastatin	0.92 (0.39, 2.12)	0.51 (0.09, 1.97)	1.00 (0.42, 2.33)
0.77 (0.64, 0.95)	0.79 (0.52, 1.17)	1.65 (0.96, 2.90)	Pravastatin	0.55 (0.13, 1.77)	1.09 (0.77, 1.50)
–	–	–	–	Rosuvastatin	1.98 (0.60, 8.40)
0.86 (0.67, 1.01)	0.88 (0.54, 1.29)	**1.82 (1.01, 3.22)**	1.12 (0.83, 1.34)	–	Simvastatin

(C)

Atorvastatin	1.13 (0.25, 5.41)	1.02 (0.59, 2.33)	1.00 (0.67, 1.60)	1.07 (0.51, 1.87)	–
–	Fluvastatin	0.93 (0.19, 4.72)	0.90 (0.19, 4.01)	0.93 (0.18, 4.34)	–
1.10 (0.65, 1.95)	–	Lovastatin	0.98 (0.46, 1.65)	1.06 (0.35, 1.91)	–
0.88 (0.63, 1.43)	–	0.81 (0.51, 1.38)	Pravastatin	1.08 (0.51, 1.75)	–
1.44 (0.73, 2.83)	–	1.30 (0.61, 2.70)	1.61 (0.80, 2.98)	Rosuvastatin	–
–	–	–	–	–	Simvastatin

Figure 6. Sensitivity analysis findings: comparative effect of individual statins on all-cause mortality (in white) and major coronary events (in grey) according to network meta-analysis of participants (A) with and without coronary heart disease at baseline (overall population), (B) with coronary heart disease at baseline (secondary prevention), and (C) without coronary heart disease at baseline (primary prevention). Values are odds ratios (95% CI). 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, odds ratios less than 1 favour the column-defining treatment. To obtain odds ratios for comparisons in the opposite direction, reciprocals should be taken.

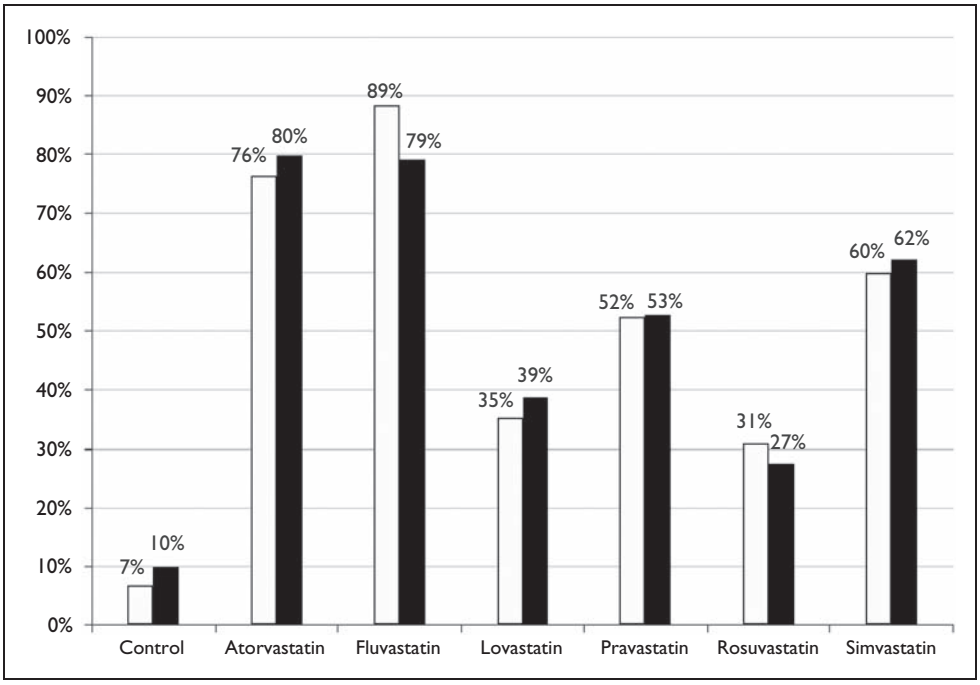

Figure 7. Overall ranking of statins in placebo-controlled and active-comparator trials of participants with and without prior coronary heart disease at baseline (overall population) by their overall probability to be the best treatment in terms of both reducing the risk of all-cause mortality and major coronary events (black). Sensitivity of the overall ranking to inclusion of high-dose trials is also presented (white). Each statin was scored with points up to a maximum of 50 for all-cause mortality and 50 for major coronary events (overall maximum score 100), with data from rankograms and SUCRAs. Supplementary Figures S9–S12 present rankograms and SUCRAs.

Although the benefits of statins in the secondary prevention setting are well documented,[9] their impact in individuals free of cardiovascular disease has been disputed.[16] The present analysis suggests that all-cause mortality benefits of statins are clinically and statistically significant. With reductions estimated at 9%, our analysis confirms the all-cause mortality benefit of statin therapy observed in previous meta-analyses.[17] In contrast to most recent reviews,[18] our analysis achieved a higher precision around this estimate (with statistical significance) as a result of including trials with very few events that were not considered previously.

Our analysis emphasizes that clinical objectives of primary prevention of cardiovascular disease should not be limited to reductions in all-cause mortality and that decisions about whether to use statins for patients without established cardiovascular disease should include consideration of other outcomes. Our finding that the benefits of statins in preventing major coronary events are consistent across primary and secondary populations provides supporting evidence for prescribing statins to high-risk individuals who stand to benefit from this therapy. This is particularly important as the prevention of coronary events also prevents individuals from graduating into a considerably higher risk category.

In addition to pairwise meta-analyses that compared statins to control treatment, we also performed network meta-analysis, which is a relatively new method that differs from pairwise meta-analysis by incorporating data from both direct (from head-to-head comparisons within trials) and indirect (from comparisons between trials) sources of evidence. Using this approach, we combined the results of placebo-controlled and active-comparator trials, allowing for more informed estimates of the relative effect of individual statins that have not been compared head-to-head in clinical trials. As with traditional 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. We also assumed consistency in the trial network when we combined both active-comparator and placebo-controlled trials.

Our analysis differed from previous network meta-analyses in three important aspects. First, our review incorporated data from a comprehensive list of trials irrespective of placebo or active controls. Second, we provided comparative estimates separately for primary

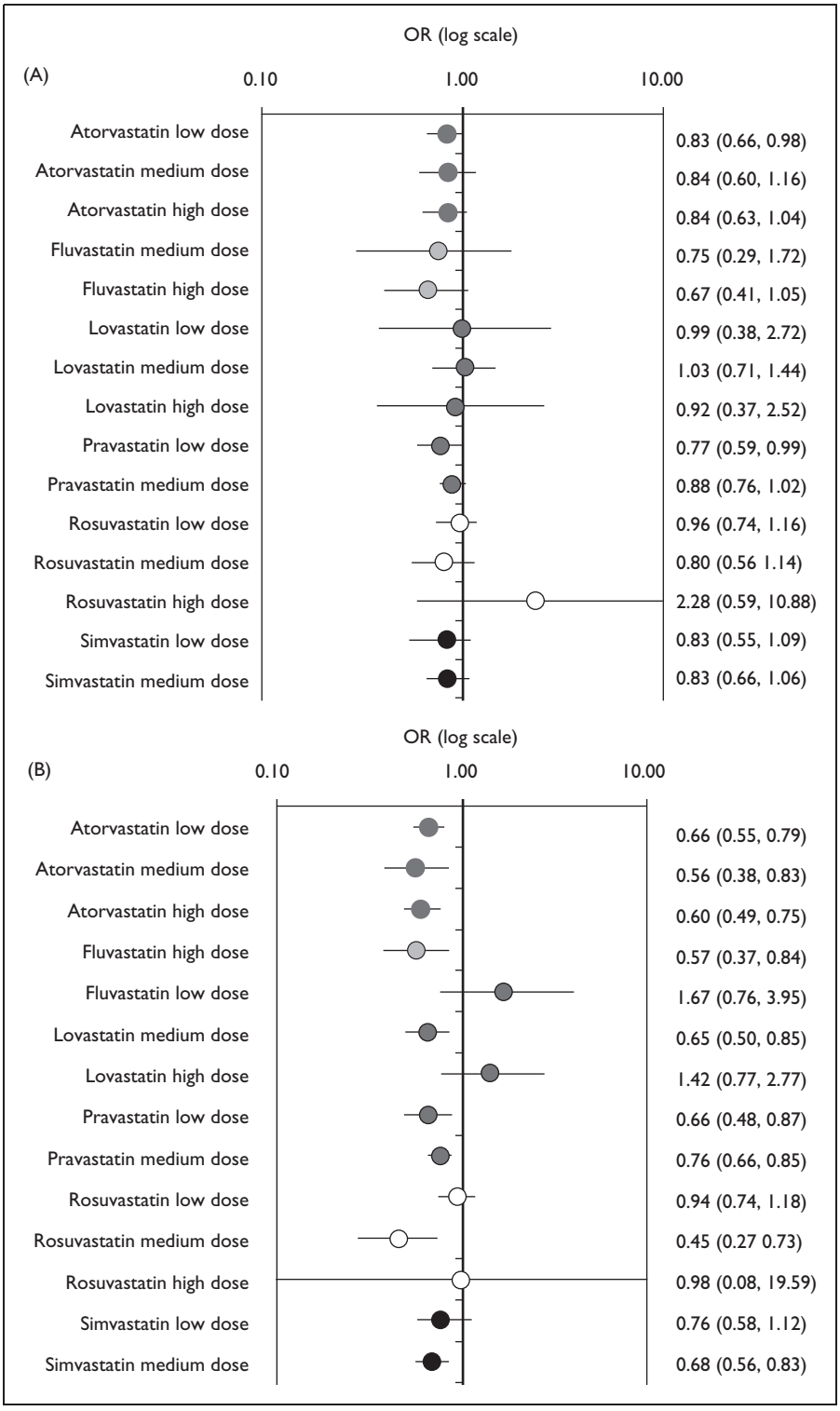

Figure 8. Dose-specific analysis findings: comparative effect of individual statins compared to control for (A) all-cause mortality and (B) major coronary events in placebo-controlled and active-comparator trials of participants with and without prior coronary heart disease at baseline (overall population).

and secondary prevention populations. Third, we made an attempt to evaluate the comparative efficacy of individual statins at similar doses.

Our base-case analysis detected significant differences among individual statins with potential implications for prescribing decisions in clinical practice. Doses considered in our base-case analysis were comparable and, as expected, resulted in approximately 30–40% reductions from baseline serum low-density lipoprotein cholesterol (LDL-C) levels.[7] Atorvastatin and fluvastatin performed significantly better than rosuvastatin in terms of reducing major coronary events across all populations. Atorvastatin and fluvastatin had a strong effect in reducing mortality and morbidity among individuals with established cardiovascular disease. Among individuals with established disease, atorvastatin resulted in marginally fewer major coronary events as compared with pravastatin and simvastatin. Relative treatment effects for statins were not sensitive to the findings of the meta-regression analysis and the sensitivity analysis that included intensive dose trials. In the sensitivity analysis, atorvastatin was significantly more effective than lovastatin and pravastatin in reducing major coronary events in the secondary prevention setting. Also, fluvastatin was more effective than lovastatin in reducing major coronary events. Unfortunately, fluvastatin and simvastatin had insufficient evidence in the primary prevention setting as there was no trial for either statin that provided information for their effectiveness in high-risk individuals without established disease.

Our dose-specific analysis paralleled the findings of previous meta-analyses in that statins at higher doses do not reduce all-cause mortality more so than statins at lower doses.[33] Similar to previous meta-analyses, there was a general dose-response relationship across placebo-controlled and active-comparator trials in terms of reducing major coronary events. However, this relationship was not apparent for all statins. For instance, low-dose and high-dose formulations of lovastatin fared worse than the medium-dose formulation.[34–37] Similarly, currently available randomized evidence is not adequate to suggest that high-dose rosuvastatin is beneficial in reducing major coronary events.[38–40] Although high-dose formulations of atorvastatin and fluvastatin have not been compared directly in trials, the findings of our network meta-analysis provided compelling evidence that these agents are equally effective in reducing the occurrence of major coronary events. Placebo-controlled trials of atorvastatin and fluvastatin were comparable in terms of known relative treatment effect modifiers and individuals in the placebo arms experienced major coronary events at similar rates.[41–45] Given the greatly differing incremental LDL-C-lowering effects of high-dose atorvastatin and fluvastatin,[7] this analysis suggests that incremental LDL-C-reducing effects alone may not be responsible for the comparative benefits of statins. In the case of fluvastatin, prospective studies should further evaluate whether pleiotropic effects are responsible for its favourable benefits relative to other statins.[46]

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. This was particularly the case for the trials of lovastatin and fluvastatin. However, the implications of this in our analysis were not clear. The quality of reporting remains well below an acceptable level, particularly for older trials, which complicates assessments of their conduct and validity.[47] Second, there were only a few head-to-head trials of statins that were prospectively designed to capture differences in clinical outcomes as primary endpoints. Third, there was an apparent asymmetry in the evidence network where specific interventions appear to be avoided (e.g. fluvastatin), which may be indicative of a biased clinical research agenda. The reasons behind this should be investigated further. Fourth, heterogeneity ranged from low to moderate across various pairwise meta-analyses of statins vs. control. Although the estimate of between-study heterogeneity was low in network meta-analyses, it remains a possibility that our analysis did not fully account for heterogeneity due to 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 association between publication year and baseline age of patients. According to meta-regressions, findings of our analysis were consistent with previous reviews that showed that the impact of statins might vary modestly across differing levels of baseline LDL-C.

Heterogeneity that is unexplained or unaccounted for may introduce bias only if it influences different statins to a different extent.[48] For instance, it is possible that there is an imbalance across the included set of trials in terms of baseline characteristics: trials of atorvastatin may have included patients who were on average older than those of pravastatin. Although baseline age is not a relative effect modifier, as shown in previous individual patient-level meta-analyses, there may be imbalances across studies in terms of unmeasured or unknown relative effect modifiers. Hence, we caution, as we would in any meta-analysis, that any comparison of statins should be tempered by the differences that may result from additional (unobserved or

unmeasured) differences in patient populations across different trials. An individual patient-level data meta-analysis such as that produced by the Cholesterol Treatment Trialists' Collaboration[9,49] may provide a more nuanced examination of the comparative benefits of statins in specific subgroups – such as those with or without cardiovascular disease, by age, and diabetes status.

In spite of these limitations, this study has important methodological strengths. Our review is the largest meta-analysis on statin therapy to-date. We included 39 direct head-to-head statin comparisons, providing information on 43,174 participants that were not considered in prior meta-analyses on clinical outcomes. Due to the comprehensive nature of our review, our findings are generalizable to patients in clinical practice. We included a broad range of patients and observed that the benefits of statins are consistent in studies with populations that varied in age, geographic region, and severity of underlying illness, which adds to the strength of our overall inferences – providing conclusive evidence that statins work in both primary and secondary prevention, and that there may be differences between individual statins, which should be investigated in future prospective studies.

What are the clinical implications of this network meta-analysis when initiating statin therapy? First, there is strong evidence that statins as a class are effective in the primary and secondary prevention of major coronary events and all-cause mortality. According to the findings of this comprehensive analysis, there is consistently strong evidence on the benefits of atorvastatin and simvastatin, which should be favoured in clinical practice. Although fluvastatin ranked superior to its alternatives in our analyses, we caution against over-interpreting this finding, particularly given the small number of trials that evaluated this agent. Future studies on fluvastatin are needed to confirm its favourable effect on mortality and coronary disease outcomes. Finally, we acknowledge the multifaceted nature of making prescribing decisions and urge prescribers to also consider other important outcomes such as harmful side effects when choosing among individual statins.

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Statement

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