Original Article

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

Huseyin Naci, MHS; Jasper Brugts, MD, PhD, MSc; Tony Ades, PhD

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;6:00-00.)**

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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From the LSE Health, London School of Economics and Political Science, London, United Kingdom (H.N.); Department of Cardiology, Erasmus Medical Center, Rotterdam, The Netherlands (J.B.); and School of Social and Community Medicine, University of Bristol, Bristol, United Kingdom (T.A.).

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Correspondence to Huseyin Naci, MHS, LSE Health, London School of Economics and Political Science, 20 Houghton St, London WC2A 2AE, United Kingdom. E-mail h.naci@lse.ac.uk

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 of 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.

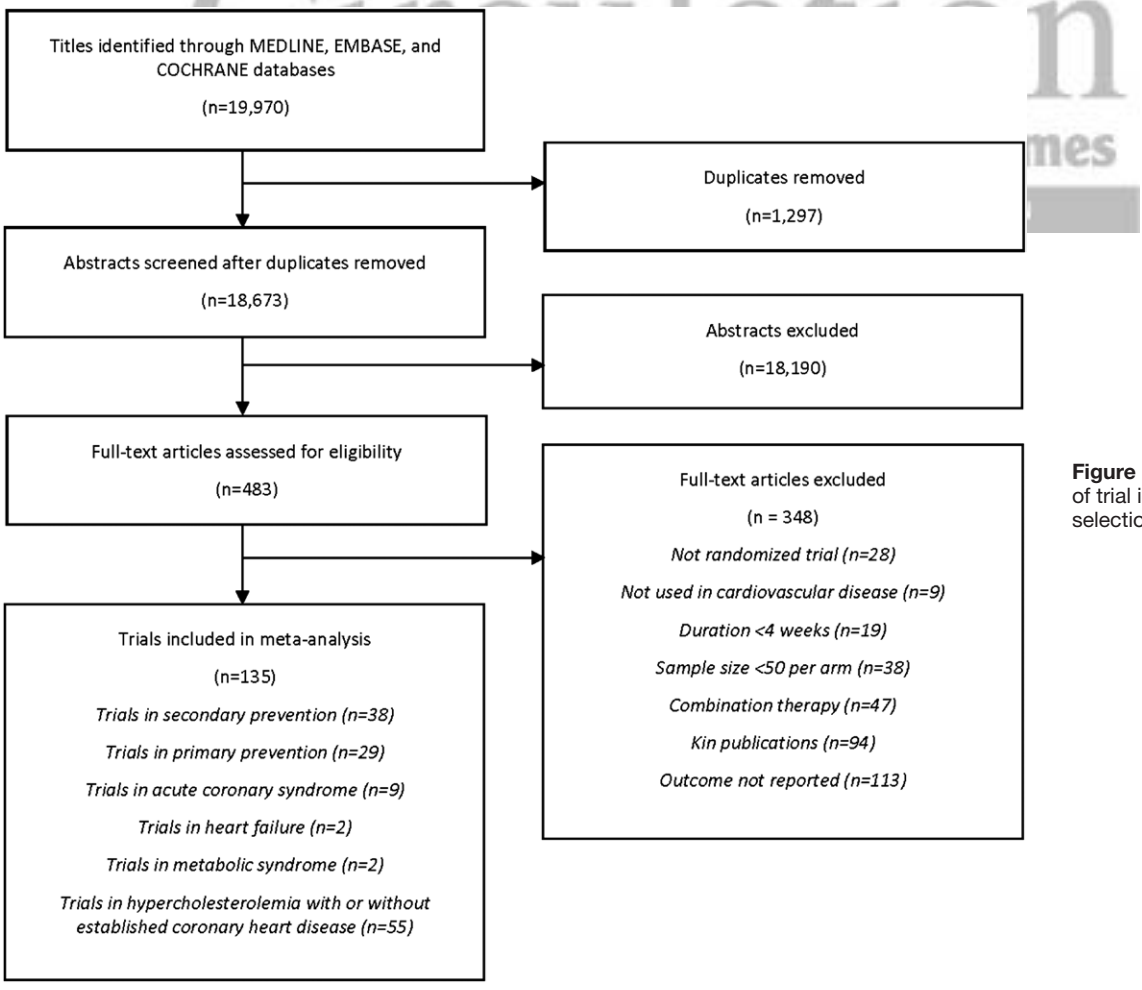

Figure 1. Flow diagram of trial identification and selection.

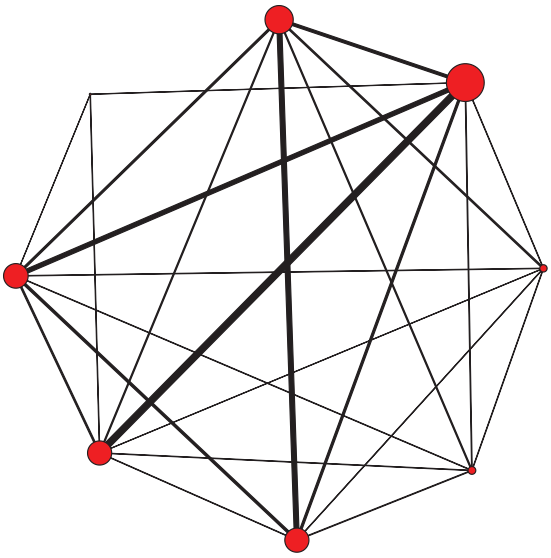

Figure 2. Network of available comparisons for the drug-level analysis. Connecting lines indicate the existing direct pairwise comparisons between 2 treatments. The width of the lines is proportional to the number of pairwise comparisons between 2 treatments, and the size of every node is proportional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

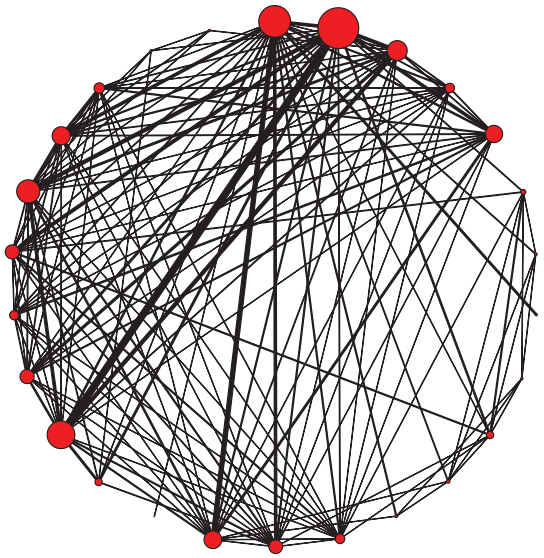

Figure 3. Network of available comparisons for dose-specific analysis. Connecting lines indicate the existing direct pairwise comparisons between 2 treatments. The width of the lines is proportional to the number of pairwise comparisons between 2 treatments, and the size of every node is proportional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

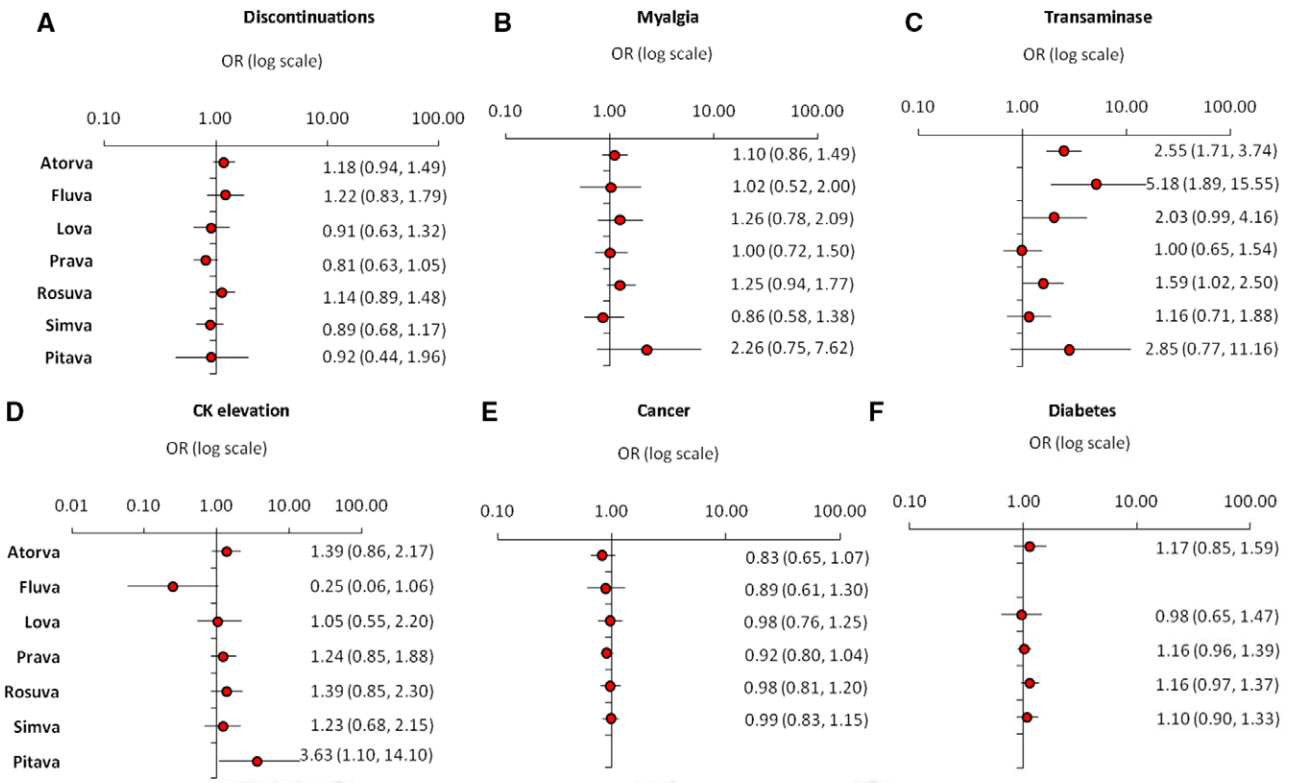

Figure 4. Findings of drug-level network meta-analyses: effect of statins compared with control on (**A**) discontinuations because of adverse events, (**B**) occurrence of myalgia, (**C**) clinically meaningful elevation in hepatic transaminases, (**D**) clinically meaningful elevation in CK levels, (**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.

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 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,

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.

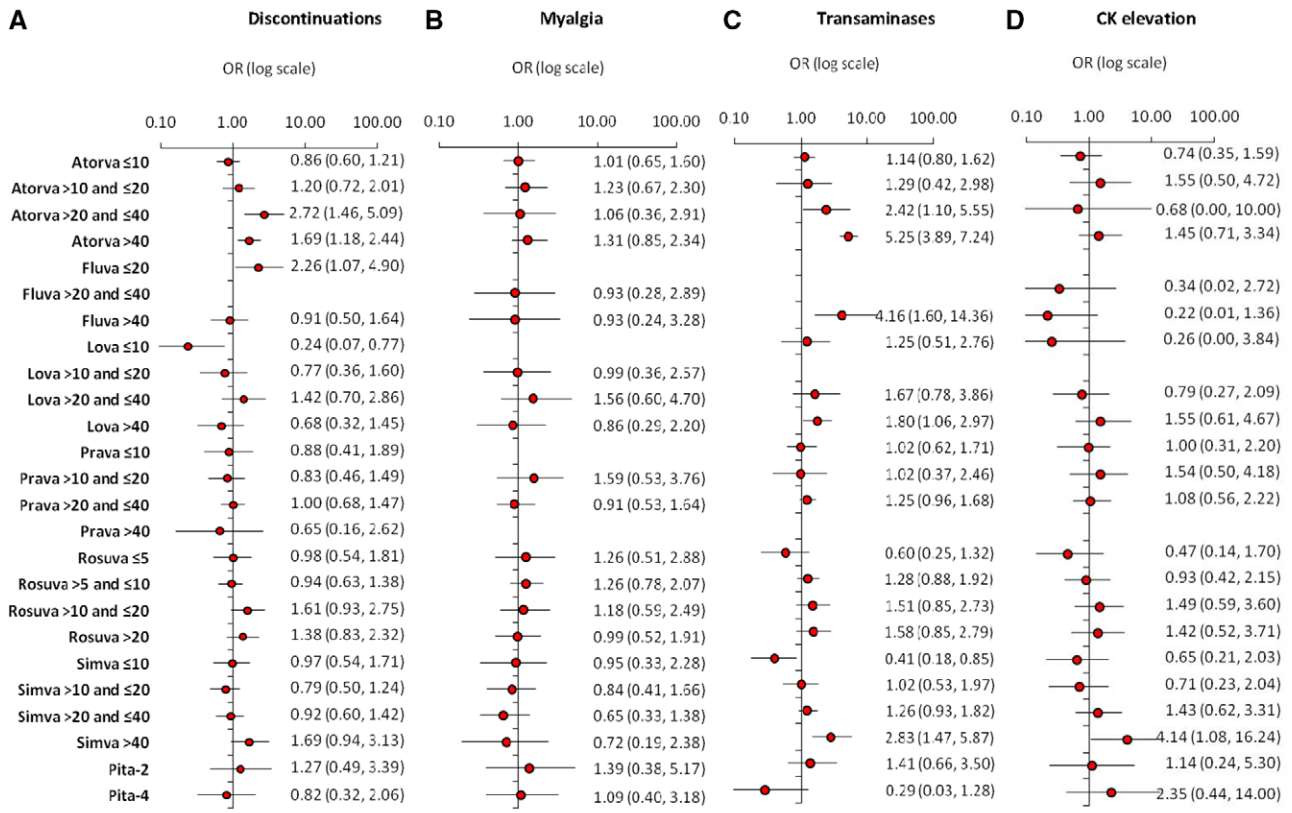

Figure 5. Findings of dose-level network meta-analyses: effects of statin–dose combinations compared with control on (**A**) discontinuations because of adverse events, (**B**) occurrence of myalgia, (**C**) clinically meaningful elevation in hepatic transaminases, and (**D**) clinically meaningful elevation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

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 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

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.

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, 1.10–14.10; Figure 4D). Individuals randomized to fluvastatin had significantly higher 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

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.

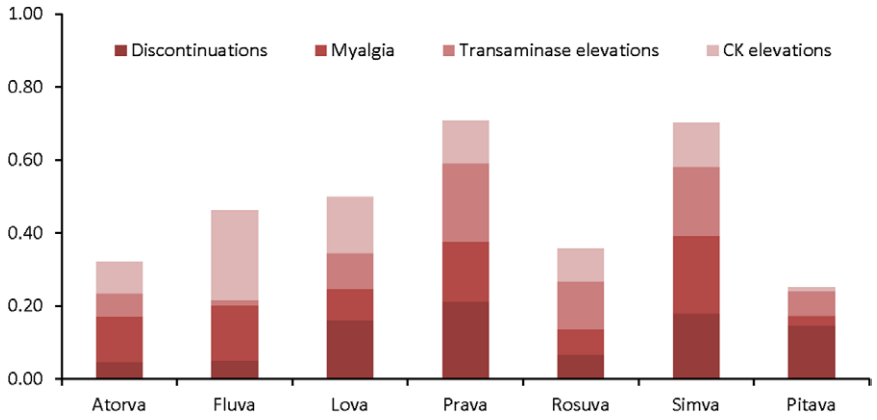

Figure 6. Overall ranking of individual statins in placebo-controlled and active-comparator trials of participants by their overall probability to be the best treatment in terms of discontinuations because of adverse events, myalgia, hepatic transaminase elevation, and CK elevation. In addition to the 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.

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 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]

Disclosures

None.

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Cardiovascular Quality and Outcomes

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

Huseyin Naci, Jasper Brugts and Tony Ades

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SUPPLEMENTAL MATERIAL

Analytic Approach Details

For all binary outcomes of interest, we assumed that the number of events per trial arm had a binomial distribution. We used the logit function to link the probability of an event in each arm of each trial, the trial-specific baseline effect (treatment effect of the control arm), and the relative treatment effect of the treatment compared with control. We set noninformative (i.e., vague or flat) priors [N(0, 1002)] for trial specific baselines and relative treatment effects. In our random-effects models, we also set noninformative priors for the between-trial variance [$\sigma \sim$ Uniform(0,2)].

All analyses employed a long burn-in period (50,000 iterations) and follow-up period (80,000-100,000 iterations) to allow for convergence. Trace plots for key parameters for each analysis were systematically reviewed (i.e., visually inspected) to assess convergence in terms of stability.

A systematic procedure was followed to ensure that the choice of initial values used in WinBugs models did not have a substantial impact on the findings. We evaluated the convergence of models in WinBugs by performing 3-chain analyses with widely dispersed starting values, and evaluating their convergence using the Brooks-Gelman-Rubin (BGR) diagnostic plots.

Sensitivity of the findings to prior distributions was not evaluated for any of the analyses presented in this paper. However, we performed such sensitivity analyses by varying the prior distributions from less informative to more informative values and examining the variability observed in the credibility intervals of point estimates for all-cause mortality and major coronary event outcomes, as reported previously (Naci H et al., 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, Eur J Prev Cardiol, 2013). We did not have any reason to expect that the models used for the analyses in this paper would behave differently in terms of their sensitivity to priors.

We formally evaluated the goodness of fit of our models using the total residual deviance (posterior mean of the deviance under a given model minus the deviance for the saturated model). In each model, we compared the residual deviance with the total number of data points in the dataset. We expected that each data point would contribute about 1 point to the posterior mean deviance. In cases where total residual deviance was considerably higher than the number of individual data points (i.e., 5-7 points), the difference was due to the large number of data points with zero cells. As expected, models could not predict a zero cell since probabilities at zero or one were ruled out, which resulted in the total residual deviance estimates to appear large when there were a large number of zero cells.

Assessment of model fit for the drug-level analysis

	Effective number of parameters, pD	Total residual deviance
Discontinuations due to adverse events	155	235
Myalgia	76	141
Transaminase elevations	105	158
CK elevations	63	117

Assessment of model fit for the dose-level analysis

	Effective number of parameters, pD	Total residual deviance
Discontinuations due to adverse events	208	319
Myalgia	110	172
Transaminase elevations	117	202
CK elevations	90	142

Our inconsistency assessment for the outcomes evaluated in this paper was based on qualitative criteria. In a stepwise manner, we first performed pairwise meta-analyses on all available direct comparisons. We then compared the findings of these pairwise meta-analyses with the results of network meta-analysis findings (what we refer to as “mixed” findings, combining direct and indirect evidence). We considered this approach to be adequate since we previously performed a more formal statistical evaluation of inconsistency in this evidence network (Naci H et al., 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, Eur J Prev Cardiol, 2013). In particular, we explored potential inconsistency in the evidence network for all-cause mortality and major coronary network outcomes using an approach developed by Salanti and colleagues (and implemented in R). For these clinical benefit outcomes, we identified all possible first-order (triangles) and second-order (quadrilaterals) closed loops formed by the network of statins. For each closed loop we then estimated the difference between the direct and indirect evidence. As a rough guide for the presence of inconsistency, we evaluated the “inconsistency factor” and its uncertainty within each closed loop formed in the network. This assessment did not find any evidence of inconsistency in our evidence network.

ONLINE ONLY Table 1 – List of Included Studies and Baseline Characteristics

Study Number	Publication Year	Trial Name		Mean Age	Baseline LDL	Blinding	Treatment	Dose of treatment	Number of patients randomized
TWO ARM TRIALS									
1	1988	LSG-III[1]	Hypercholesterolemia with or without CHD	48.7	282.3	Single-blind	Lovastatin	40mg/day	87
				49.9	271.1		Lovastatin	80mg/day	89
2	1993	PMSG[2]	Hypercholesterolemia with or without CHD	55.0	181.4	Double-blind	Pravastatin	20mg/day	530
				55.0	180.2		Placebo	NA	532
3	1993	SPSG[3]	Hypercholesterolemia with or without CHD	52.0	207.0	Double-blind	Simvastatin	Started at 10mg/day	275
				53.0	212.0		Pravastatin	Started at 10mg/day	275
4	1993	LPSG[4]	Hypercholesterolemia with or without CHD	54.0	194.0	Double-blind	Lovastatin	80mg/day	339
				54.0	196.0		Pravastatin	40mg/day	333
5	1994	4S[5]	Secondary Prevention	58.6	188.3	Double-blind	Placebo	NA	2223
				58.6	188.3		Simvastatin	Started at 20mg/day	2221
				55.6	169.4		Simvastatin	20mg/day	193
6	1997	POST-CABG[6]	Secondary Prevention	61.7	156.1	Not clear	Lovastatin	Started at 40mg/day	676
				61.7	154.4		Lovastatin	Started at 2.5mg/day	675
7	1998	LIPID[7]	Secondary Prevention	62.0	150.0	Double-blind	Placebo	NA	4502
				62.0	150.0		Pravastatin	40mg/day	4512

8	2000	GISSI-P[8]	Secondary Prevention	59.7	151.8	Open-label	Pravastatin	20mg/day	2138
				60.0	151.5		Placebo	NA	2133
9	2002	GREACE[9]	Secondary Prevention	58.0	180.0	Open-label	Atorvastatin	Started at 10mg/day	800
				59.0	179.0		Usual care (12% of this group received statins)	NA	800
10	1998	Bak et al. 1998[10]	Primary Prevention	54.6	199.2	Double-blind	Placebo + Diet	NA	54
				55.3	204.6		Pravastatin + Diet	20mg/day	53
11	2000	Barter et al. 2000[11]	Hypercholesterolemia with or without CHD	57.1	201.9	Open-label	Atorvastatin	Started at 10mg/day	691
				56.2	200.3		Simvastatin	Started at 10mg/day	337
12	1994	PMSG-Diabetes[12]	Primary Prevention in Diabetes	58.3	164.4	Double-blind	Pravastatin	Started at 10mg/day	167
				58.3	166.7		Placebo	NA	158
13	1997	Bertolini et al. 1997[13]	Hypercholesterolemia with or without CHD	56.0	194.1	Double-blind	Atorvastatin	Started at 10mg/day	227
				57.0	196.1		Pravastatin	Started at 20mg/day	78
14	1997	CIS[14]	Secondary Prevention	49.8	164.5	Double-blind	Simvastatin	Started at 20mg/day	129
				48.8	167.4		Placebo	NA	125
15	2006	DISCOVERY-Alpha[15]	Hypercholesterolemia with or without CHD	58.4	179.2	Open-label	Rosuvastatin	10mg/day	555
				58.0	176.9		Atorvastatin	10mg/day	382
16	1993	MARS[16]	Secondary Prevention	58.0	151.2	Double-blind	Lovastatin	Started at 40mg/day	123
				58.0	154.7		Placebo	NA	124
17	1994	EXCEL[17]	Hypercholesterolemia	56.0	180.0	Double-blind	Placebo	NA	1663

			with or without CHD	56.0	180.1		Lovastatin	Started at 20mg/day	6582
18	2001	Branchi et al. 2001[18]	Hypercholesterolemia with or without CHD	55.8	224.3	Open-label	Atorvastatin	10mg/day	117
				57.5	231.0		Simvastatin	20mg/day	118
19	2004	PROVE IT-TIMI 22[19]	Acute Coronary Syndrome	58.3	106.0	Double-blind	Pravastatin	Started at 40mg/day	2063
				58.1	106.0		Atorvastatin	80mg/day	2099
20	2004	CARDS[20]	Primary Prevention in Diabetes	61.8	116.8	Double-blind	Placebo	NA	1410
				61.5	117.6		Atorvastatin	10mg/day	1428
21	2007	METEOR[21]	Primary Prevention	57.0	155.0	Double-blind	Rosuvastatin	40mg/day	702
				57.0	154.0		Placebo	NA	282
22	1997	ASG-I[22]	Hypercholesterolemia with or without CHD	57.0	187.9	Double-blind	Atorvastatin	10mg/day	529
				58.0	182.9		Lovastatin	20mg/day	120
23	1997	Davidson et al. 1997[23]	Hypercholesterolemia with or without CHD	52.0	199.0	Double-blind	Simvastatin	40mg/day	147
				52.0	199.0		Simvastatin	80mg/day	147
24	2007	SAGE[24]	Secondary Prevention	72.4	147.5	Double-blind	Atorvastatin	80mg/day	446
				72.6	144.0		Pravastatin	40mg/day	445
25	1998	AFCAPS/TexCAPS[25]	Primary Prevention	58.0	150.0	Double-blind	Placebo	NA	3301
				58.0	150.0		Lovastatin	Started at 20mg/day	3304
26	2008	GISSI-HF[26]	Heart Failure	68.0	122.2	Double-blind	Rosuvastatin	10mg/day	2285
				68.0	121.0		Placebo	NA	2289
27	1997	LCAS[27]	Secondary Prevention	58.4	146.2	Double-blind	Fluvastatin	40mg/day	156

				59.1	144.6		Placebo	NA	163
28	2001	ASSET[28]	Hypercholesterolemia with or without CHD	60.9	181.2	Double-blind	Atorvastatin	10mg/day	730
				60.1	181.9		Simvastatin	10mg/day	694
29	1995	Jacobson et al. 1995[29]	Primary Prevention	57.0	210.0	Double-blind	Pravastatin	20mg/day	182
				55.9	211.0		Placebo	NA	63
30	1995	REGRESS[30]	Secondary Prevention	56.5	166.3	Double-blind	Pravastatin	40mg/day	450
				55.9	166.7		Placebo	NA	434
31	2007	Kyeong et al. 2007[31]	Acute Coronary Syndrome	63.5	139.1	Open-label	Rosuvastatin	10mg/day	60
				63.4	137.7		Atorvastatin	20mg/day	57
32	1999	TARGET TANGIBLE[32]	Secondary Prevention	60.5	188.0	Open-label	Atorvastatin	Started at 10mg/day	1897
				60.9	186.0		Simvastatin	Started at 10mg/day	959
33	1996	CAIUS[33]	Primary Prevention	54.9	180.2	Double-blind	Pravastatin	40mg/day	151
				55.1	182.1		Placebo	NA	154
34	1996	SHIGA Pravastatin Study[34]	Secondary Prevention	62.0	139.0	Open-label	Pravastatin	20mg/day	102
				62.0	135.7		Placebo	NA	105
35	2000	WWEDSS[35]	Hypercholesterolemia with or without CHD	52.7	228.2	Double-blind	Simvastatin	40mg/day	436
				52.9	224.3		Simvastatin	80mg/day	669
36	2005	BELLES[36]	Primary Prevention	64.2	175.3	Double-blind	Atorvastatin	80mg/day	305
				64.5	173.6		Pravastatin	40mg/day	309
37	1999	Riegger et al. 1999[37]	Secondary Prevention	59.4	198.0	Double-blind	Fluvastatin	Started at 40mg/day	187

				60.2	193.0		Placebo	NA	178
38	1996	CARE[38]	Secondary Prevention	59.0	139.0	Double-blind	Placebo	40mg/day	2078
				59.0	139.0		Pravastatin	NA	2081
39	1995	KAPS[39]	Primary Prevention	57.5	185.6	Double-blind	Placebo	NA	223
				57.3	185.6		Pravastatin	40mg/day	224
40	2001	MIRACL[40]	Acute Coronary Syndrome	65.0	124.0	Double-blind	Placebo	NA	1548
				65.0	124.0		Atorvastatin	80mg/day	1538
41	1999	IQLMG[41]	Hypercholesterolemia with or without CHD	50.0	210.0	Double-blind	Simvastatin	20mg/day	194
				52.0	205.0		Pravastatin	40mg/day	193
42	1999	FLARE[42]	Secondary Prevention	60.0	153.1	Double-blind	Fluvastatin	80mg/day	409
				61.0	152.8		Placebo	NA	425
43	1995	WOSCOPS[43]	Primary Prevention	55.1	192.0	Double-blind	Placebo	NA	3293
				55.3	192.0		Pravastatin	40mg/day	3302
44	1990	Stein et al. 1990[44]	Hypercholesterolemia with or without CHD	59.0	309.4	Open-label	Simvastatin	20mg/day	84
				59.0	322.1		Simvastatin	40mg/day	81
45	1998	EDS-US[45]	Primary Prevention	55.5	245.2	Double-blind	Simvastatin	40mg/day	207
				54.3	245.2		Simvastatin	80mg/day	314
46		PACT[46]	Acute Coronary Syndrome	59.0	179.0	Double-blind	Pravastatin	Started at 20mg/day	1710
				59.0	179.0		Placebo	NA	1698
47	1994	LRTSG[47]	Secondary Prevention	62.0	130.0	Double-blind	Lovastatin	80mg/day	203

				62.0	126.0		Placebo	NA	201
48	1996	QLMG[48]	Primary Prevention	49.3	195.0	Double-blind	Lovastatin	40mg/day	211
				51.0	202.0		Pravastatin	40mg/day	215
49	2002	MRC/BHF Heart Protection Study[49]	Hypercholesterolemia with or without CHD	64.0	131.5	Double-blind	Simvastatin	40mg/day	10269
				64.0	131.5		Placebo	NA	10267
50	2003	CHESS[50]	Hypercholesterolemia with or without CHD	56.5	190.3	Double-blind	Simvastatin	80mg/day	453
				56.5	187.5		Atorvastatin	80mg/day	464
51	2003	Ballantyne et al. 2003[51]	Hypercholesterolemia with or without CHD	57.8	179.8	Double-blind	Atorvastatin	Started at 10mg/day	248
				56.9	177.9		Placebo	NA	60
52	2003	ADVOCATE[52]	Hypercholesterolemia with or without CHD	51.6	196.0	Open-label	Atorvastatin	Started at 10mg/day	82
				53.7	192.0		Simvastatin	Started at 10mg/day	76
53	2003	Bruckert et al. 2003[53]	Primary Hypercholesterolemia	75.5	200.0	Double-blind	Fluvastatin	80mg/day	607
				75.5	200.0		Placebo	NA	622
54	2002	Davidson et al. 2002[54]	Hypercholesterolemia with or without CHD	58.8	177.0	Double-blind	Placebo	NA	70
				56.4	179.0		Simvastatin	Started at 10mg/day	263
55	2003	Kerzner et al. 2003[55]	Primary Prevention	56.0	178.0	Double-blind	Lovastatin	Started at 10mg/day	220
				58.0	178.0		Placebo	NA	64
56	2002	FLORIDA[56]	Acute Coronary Syndrome	61.0	135.3	Double-blind	Fluvastatin	80mg/day	265
				60.0	139.2		Placebo	NA	275
57	2003	Melani et al. 2003[57]	Primary Hypercholesterolemia	55.1	177.9	Double-blind	Pravastatin	Started at 10mg/day	205

				53.4	177.9		Placebo	NA	65
58	2003	TREAT TO TARGET[58]	Secondary Prevention	63.0	200.7	Double-blind	Atorvastatin	20mg/day	552
				62.5	200.7		Simvastatin	20mg/day	535
59	2002	LIPS[59]	Secondary Prevention	60.0	131.0	Double-blind	Fluvastatin	80mg/day	844
				60.0	132.0		Placebo	NA	833
60	2002	PROSPER[60]	Hypercholesterolemia with or without CHD	75.3	147.0	Double-blind	Placebo	NA	1913
				75.4	147.0		Pravastatin	40mg/day	2891
61	2003	HeFH[61]	Familial hypercholesterolemia with or without CHD	48.0	292.0	Double-blind	Rosuvastatin	Started at 20mg/day	436
				47.0	288.0		Atorvastatin	Started at 20mg/day	187
62	2007	ASTRONOMER[62]	Carotid stenosis	58.0	123.0	Double-blind	Rosuvastatin	40mg/day	134
				57.9	120.7		Placebo	NA	135
63	2010	Colivicchi et al. 2010[63]	Secondary Prevention	73.9	123.0	Open-label	Atorvastatin	Started at 20mg/day	146
				75.2	126.0		Atorvastatin	80 mg/day	144
64	2008	ECLIPSE[64]	Secondary Prevention	62.5	189.2	Open-label	Rosuvastatin	Started at 10mg/day	522
				62.2	188.3		Atorvastatin	Started at 10mg/day	514
65	2009	SPACE ROCKET[65]	Acute Coronary Syndrome	62.1	128.4	Open-label	Rosuvastatin	40mg/day	633
				62.5	124.5		Simvastatin	40mg/day	630
66	2010	Kadoglou et al. 2010[66]	Carotid stenosis	64.8	162.1	Open-label	low-dose atorvastatin	10-20 mg/d	70
				63.2	167.1		high-dose atorvastatin	80 mg/d	70
67	2007	CORONA[67]	Heart Failure	73.0	137.7	Double-blind	Placebo	NA	2497

				73.0	136.9		Rosuvastatin	10mg/day	2514
68	2008	SUBARU[68]	Primary Prevention	64.4	109.3	Open-label	Atorvastatin	10mg/day	213
				66.7	102.9		Rosuvastatin	5mg/day	214
69	2010	CENTAURUS[69]	Acute Coronary Syndrome	60.0	129.0	Double-blind	Rosuvastatin	20 mg/d	437
				59.0	128.0		Atorvastatin	80 mg/d	450
70	2008	DISCOVERY-Beta[70]	Primary hypercholesterolemia with or without CHD	62.9	182.9	Open-label	Rosuvastatin	10mg/day	334
				63.9	180.2		Simvastatin	20mg/day	170
71	2010	Alcala et al. 2010[71]	Primary Prevention	48.0	178.0	Not reported	Diet	NA	70
				48.0	174.0		Pravastatin	40mg/day	61
72	2006	SPARCL[72]	Secondary Prevention	63.0	132.7	Double-blind	Atorvastatin	80mg/day	2365
				62.5	133.7		Placebo	NA	2366
73	2005	HYRIM[73]	Primary Prevention	56.8	146.2	Double-blind	Fluvastatin	40mg/day	142
				57.5	149.3		Placebo	NA	143
74	2004	Bays et al. 2004[74]	Primary hypercholesterolemia	54.9	177.5	Double-blind	Simvastatin	Started at 10mg/day	622
				56.0	177.9		Placebo	NA	148
75	2007	ANDROMEDA[75]	Primary Prevention in Diabetes	61.2	131.5	Double-blind	Rosuvastatin	Started at 10mg/day	248
				61.9	131.5		Atorvastatin	Started at 10mg/day	246
76	2008	CAP[76]	Secondary Prevention	62.8	126.0	Double-blind	Atorvastatin	10mg/day	170
				62.3	126.0		Atorvastatin	80mg/day	170
77	2004	A to Z[77]	Acute Coronary	61.0	111.0	Double-blind	Simvastatin	20mg/day	2232

			Syndrome	61.0	112.0		Simvastatin	80mg/day	2265
78	2004	PREVEND IT[78]	Microalbuminuria	50.5	154.7	Double-blind	Placebo	NA	431
				52.1	158.6		Pravastatin	40mg/day	433
79	2004	Durazzo et al. 2004[79]	Vascular surgery with or without CHD	65.9	144.6	Double-blind	Atorvastatin	20mg/day	50
				68.4	139.7		Placebo	NA	50
80	2005	DISCOVERY-Penta[80]	Hypercholesterolemia with or without CHD	59.2	171.0	Open-label	Rosuvastatin	10mg/day	358
				59.0	174.0		Atorvastatin	10mg/day	383
81	2004	Goldberg et al. 2004[81]	Primary hypercholesterolemia	59.0	174.0	Double-blind	Placebo	NA	93
				59.0	175.0		Simvastatin	Started at 10mg/day	349
82	2005	RADAR[82]	Secondary Prevention	60.7	139.2	Open-label	Rosuvastatin	Started at 10mg/day	230
				60.2	143.1		Atorvastatin	Started at 20mg/day	231
83	2006	ASPEN[83]	Primary Prevention	60.5	114.0	Double-blind	Atorvastatin	10mg/day	1211
				60.4	114.0		Placebo	NA	1199
84	2004	ALLIANCE[84]	Secondary Prevention	61.1	147.0	Open-label	Atorvastatin	Started at 10mg/day	1217
				61.3	147.2		Usual care	NA	1225
85	2005	TNT[85]	Secondary Prevention	60.9	98.0	Double-blind	Atorvastatin	10mg/day	5006
				61.2	97.0		Atorvastatin	80mg/day	4995
86	2007	POLARIS[86]	Secondary Prevention	62.6	189.3	Double-blind	Rosuvastatin	Started at 20mg/day	432
				61.6	189.0		Atorvastatin	Started at 40mg/day	439
87	2006	ATOROS[87]	Primary Prevention	53.5	205.0	Open-label	Rosuvastatin	Started at 10mg/day	60

				53.3	204.0		Atorvastatin	Started at 20mg/day	60
88	2004	PCS[88]	Secondary Prevention	59.2	128.7	Not reported	Pravastatin	10mg/day	54
				59.9	128.3		Diet	NA	66
89	2006	MEGA[89]	Primary Prevention	58.4	156.6	Open-label	Diet	NA	3966
				58.2	156.6		Pravastatin	Started at 10mg/day	3866
90	2004	REVERSAL[90]	Secondary Prevention	56.6	150.2	Double-blind	Pravastatin	40mg/day	327
				55.8	150.2		Atorvastatin	80mg/day	327
91	2005	IDEAL[91]	Secondary Prevention	61.6	121.4	Open-label	Simvastatin	Started at 20mg/day	4449
				61.8	121.6		Atorvastatin	Started at 80mg/day	4439
92	2006	Schermund et al. 2006[92]	Primary Prevention	61.0	108.0	Double-blind	Atorvastatin	10mg/day	236
				62.0	106.0		Atorvastatin	80mg/day	235
93	2004	ASCOT-LLA[93]	Primary Prevention	63.1	131.2	Double-blind	Atorvastatin	10mg/day	5168
				63.2	131.5		Placebo	NA	5137
94	2004	DISCOVERY[94]	Primary hypercholesterolemia	60.7	174.0	Open-label	Rosuvastatin	10mg/day	686
				60.8	170.2		Atorvastatin	10mg/day	338
95	2005	CORALL[95]	Primary Prevention in Diabetes	61.0	163.6	Open-label	Rosuvastatin	Started at 10mg/day	131
				59.0	171.3		Atorvastatin	Started at 20mg/day	132
96	2007	Yu et al. 2007[96]	Secondary Prevention	66.0	116.0	Double-blind	Atorvastatin	10mg/day	55
				66.0	105.0		Atorvastatin	80mg/day	57
97	2008	JUPITER[97]	Primary Prevention	66.0	108.0	Double-blind	Rosuvastatin	20mg/day	8901

				66.0	108.0		Placebo	NA	8901
98	2008	Sdringola et al. 2008[98]	Secondary Prevention	64.0	130.0	Double-blind	Placebo	NA	73
				70.0	128.0		Atorvastatin	80mg/day	72
99	2007	DISCOVERY-Asia[99]	Secondary Prevention	60.3	167.1	Open-label	Rosuvastatin	10mg/day	950
				60.8	169.4		Atorvastatin	10mg/day	472
100	1995	Guillen et al. 1995[100]	Hypercholesterolemia with or without CHD	47.8	155.8	Double-blind	Placebo	NA	74
				46.8	156.8		Pravastatin	Started at 10mg/day	76
101	2006	PULSAR[101]	Secondary Prevention	60.2	165.1	Open-label	Rosuvastatin	10mg/day	504
				60.7	164.9		Atorvastatin	20mg/day	492
102	2011	SATURN[102]	Secondary Prevention	57.9	119.9	Double-blind	Atorvastatin	80mg/day	519
				57.4	120.0		Rosuvastatin	40mg/day	520
103	2002	ALLHAT[103]	Primary Prevention	66.4	145.6	Open-label	Pravastatin	Started at 20mg/day	5,170
				66.3	145.5		Usual Care	NA	5,185
104	2011	Eriksson et al.[104]	Primary Prevention	60.1	166.3	Double-blind	Pitavastatin	4mg/day	236
				60.9	167.0		Simvastatin	40mg/day	119
105	2011	Gumprecht et al.[105]	Mixed Hyperlipidemia and Diabetes with or without CHD	59.1	143.0	Double-blind	Pitavastatin	4mg/day	275
				59.8	145.9		Atorvastatin	20mg/day	137
106	2005	URANUS[106]	Primary Prevention in Diabetes	63.5	177.9	Double-blind	Rosuvastatin	Started at 10mg/day	232
				65.0	177.9		Atorvastatin	Started at 10mg/day	233
THREE-ARM TRIALS									

107	2007	Lewis et al. 2007[107]	Hypercholesterolemia with Chronic, Well Compensated Liver Disease	49.9	138.8	Double-blind	Pravastatin	80mg/day	163
				49.8	140.5		Placebo	NA	163
				58.4	184.0		Simvastatin	40mg/day	111
108	2000	Farnier et al. 2000[108]	Hypercholesterolemia with or without CHD	50.0	247.0	Open-label	Atorvastatin	10mg/day	109
				51.0	237.0		Simvastatin	20mg/day	109
				51.0	242.0		Simvastatin	10mg/day	54
109	2012	LUNAR[109]	Acute Coronary Syndrome	53.0	138.4	Open-label	Rosuvastatin	20mg/day	248
				52.8	138.8		Rosuvastatin	40mg/day	251
				52.9	133.2		Atorvastatin	80mg/day	257
110	1994	OCS[110]	Secondary Prevention	63.4	187.2	Double-blind	Simvastatin	40mg/day	206
				63.4	187.6		Simvastatin	20mg/day	208
				63.7	182.1		Placebo	NA	207
111	2000	Stein et al. 2000[111]	Mixed Hyperlipidemia and Diabetes with or without CHD	53.0	156.0	Double-blind	Placebo	NA	130
				53.0	156.0		Simvastatin	40mg/day	130
				53.0	156.0		Simvastatin	80mg/day	130
112	2003	Mohler et al. 2003[112]	Peripheral Arterial Disease	69.0	125.0	Double-blind	Atorvastatin	10mg/day	120
				68.0	125.0		Atorvastatin	80mg/day	120
				67.0	125.0		Placebo	NA	114
113	2002	Olsson et al. 2002[113]	Hypercholesterolemia with or without CHD	56.3	188.0	Double-blind	Rosuvastatin	Started at 5mg/day	138
				57.8	185.9		Rosuvastatin	Started at 10mg/day	134

				58.2	188.1		Atorvastatin	Started at 10mg/day	140
114	2007	SOLAR[114]	Hypercholesterolemia with or without CHD	63.0	170.0	Open-label	Rosuvastatin	10mg/day	542
				62.3	167.0		Atorvastatin	10mg/day	544
				61.9	167.0		Simvastatin	20mg/day	546
115	2004	Schwartz et al. 2004[115]	Secondary Prevention	62.0	188.0	Double-blind	Rosuvastatin	Started at 5mg/day	127
				62.0	186.0		Rosuvastatin	Started at 10mg/day	128
				62.0	188.0		Atorvastatin	Started at 10mg/day	128
116	2005	COMETS[116]	Metabolic Syndrome	58.1	170.2	Double-blind	Rosuvastatin	10mg/day	165
				57.3	168.2		Atorvastatin	10mg/day	157
				57.8	170.9		Placebo	NA	79
117	2009	VYMET[117]	Metabolic Syndrome	60.0	142.0	Double-blind	Atorvastatin	10mg/day	229
				58.0	139.0		Atorvastatin	20mg/day	229
				60.0	140.0		Atorvastatin	40mg/day	228
118		PATROL[118]	Primary Prevention	61.5	162.0	Not reported	Atorvastatin	10 mg/day	101
				61.7	172.0		Rosuvastatin	2.5mg/day	100
				63.4	164.0		Pitavastatin	2 mg/day	101
FOUR-ARM TRIALS									
119	2005	DISCOVERY Netherlands[119]	Hypercholesterolemia with or without CHD	61.0	172.5	Open-label	Rosuvastatin	10mg/day	621
				62.0	168.2		Atorvastatin	10mg/day	189
				62.0	171.3		Simvastatin	20mg/day	194

				60.0	170.9		Pravastatin	40mg/day	211
120	1998	Brown et al. 1998[120]	Secondary Prevention	62.0	173.0	Open-label	Atorvastatin	Started at 10mg/day	78
				62.0	170.0		Fluvastatin	Started at 20mg/day	76
				64.0	175.0		Lovastatin	Started at 20mg/day	78
				63.0	172.0		Simvastatin	Started at 10mg/day	76
121	2000	Recto et al. 2000[121]	Hypercholesterolemia with or without CHD	59.0	193.4	Open-label	Simvastatin	20mg/day	125
				59.0	193.4		Simvastatin	40mg/day	126
				59.0	193.4		Atorvastatin	10mg/day	125
				59.0	193.4		Atorvastatin	20mg/day	126
122	2002	Brown et al. 2002[122]	Hypercholesterolemia with or without CHD	57.2	187.3	Double-blind	Rosuvastatin	Started on 5mg/day	123
				58.4	187.0		Rosuvastatin	Started on10mg/day	116
				60.0	188.5		Pravastatin	Started on 20mg/day	118
				59.4	188.0		Simvastatin	Started on 20mg/day	120
123	2002	Davidson et al. 2002[123]	Hypercholesterolemia with or without CHD	56.6	187.0	Double-blind	Placebo	NA	132
				57.9	188.0		Rosuvastatin	5mg/day	129
				57.2	185.0		Rosuvastatin	10mg/day	130
				56.4	186.0		Atorvastatin	10mg/day	128
124	2002	CHALLENGE[124]	Hypercholesterolemia with or without CHD	61.7	180.0	Open-label	Atorvastatin	10mg/day	639
				61.5	182.0		Atorvastatin	80mg/day	207
				61.3	179.0		Simvastatin	20mg/day	641

				61.5	178.0		Simvastatin	80mg/day	207
125	2001	Paoletti et al. 2001[125]	Hypercholesterolemia with or without CHD	58.5	190.0	Double-blind	Rosuvastatin	5mg/day	119
				58.5	186.0		Rosuvastatin	10mg/day	111
				58.5	189.0		Pravastatin	20mg/day	136
				58.5	188.0		Simvastatin	20mg/day	129
126	2007	IRIS[126]	Hypercholesterolemia with or without CHD	56.8	157.0	Open-label	Rosuvastatin	10mg/day	189
				55.6	153.0		Rosuvastatin	20mg/day	182
				55.8	159.0		Atorvastatin	10mg/day	185
				55.2	156.0		Atorvastatin	20mg/day	184
127	2006	ARIES[127]	Familial hypercholesterolemia and combined hyperlipoproteinemia	55.0	191.8	Open-label	Rosuvastatin	10mg/day	195
				55.4	189.6		Rosuvastatin	20mg/day	196
				54.9	189.1		Atorvastatin	10mg/day	191
				54.9	191.9		Atorvastatin	20mg/day	192
128	2009	Ose et al. 2009[128]	Primary hypercholesterolemia	58.6	184.1	Double-blind	Simvastatin	20mg/day	108
				58.4	184.0		Simvastatin	40mg/day	111
				58.7	184.6		Pitavastatin	2mg/day	315
				57.7	184.1		Pitavastatin	4mg/day	323
129	2006	STARSHIP[129]	Hypercholesterolemia with or without CHD	58.0	165.0	Open-label	Rosuvastatin	10mg/day	184
				57.8	159.0		Rosuvastatin	20mg/day	173
				56.7	164.0		Atorvastatin	10mg/day	168

				59.0	165.0		Atorvastatin	20mg/day	171
TRIALS WITH FIVE OR MORE ARMS									
130	2001	Andrews et al. 2001[130]	Hypercholesterolemia with or without CHD	61.0	179.0	Open-label	Atorvastatin	Started at 10mg/day	1902
				61.0	179.0		Fluvastatin	Started at 20mg/day	477
				62.0	178.0		Lovastatin	Started at 20mg/day	476
				61.0	179.0		Pravastatin	Started at 10mg/day	462
				61.0	176.0		Simvastatin	Started at 10mg/day	468
131	2000	Gentile et al. 2000[131]	Primary Prevention in Diabetes	59.0	213.0	Open-label	Atorvastatin	10mg/day	84
				58.0	199.0		Simvastatin	10mg/day	78
				59.0	208.0		Pravastatin	20mg/day	81
				58.0	210.0		Lovastatin	20mg/day	80
				61.0	218.0		Placebo	NA	86
132	2003	Davidson et al. 2003[132]	Primary Hypercholesterolemia	58.4	181.8	Double-blind	Lovastatin	10mg/day	167
				58.2	189.5		Lovastatin	20mg/day	164
				58.5	189.5		Lovastatin	40mg/day	170
				58.4	189.5		Fluvastatin	20mg/day	170
				58.9	185.8		Fluvastatin	40mg/day	167
133	2006	MERCURY II[133]	Hypercholesterolemia with or without CHD	61.9	167.1	Open-label	Rosuvastatin	20mg/day	392
				61.9	169.0		Atorvastatin	10mg/day	403
				61.9	168.1		Atorvastatin	20mg/day	395

				61.9	169.4		Simvastatin	20mg/day	402
				61.9	168.8		Simvastatin	40mg/day	401
134	2005	MERCURY I[134]	Hypercholesterolemia with or without CHD	62.0	164.9	Open-label	Rosuvastatin	10mg/day	538
				61.8	162.7		Atorvastatin	10mg/day	529
				62.2	166.7		Atorvastatin	20mg/day	925
				61.9	165.1		Simvastatin	20mg/day	543
				62.7	164.3		Pravastatin	40mg/day	521
135	2003	STELLAR[135]	Primary Prevention	58.0	188.0	Open-label	Rosuvastatin	10mg/day	158
				58.0	187.0		Rosuvastatin	20mg/day	164
				58.0	194.0		Rosuvastatin	40mg/day	158
				58.0	189.0		Atorvastatin	10mg/day	158
				58.0	190.0		Atorvastatin	20mg/day	156
				58.0	189.0		Atorvastatin	40mg/day	160
				58.0	190.0		Atorvastatin	80mg/day	167
				58.0	189.0		Simvastatin	10mg/day	167
				58.0	189.0		Simvastatin	20mg/day	164
				58.0	187.0		Simvastatin	40mg/day	159
				58.0	190.0		Simvastatin	80mg/day	165
				58.0	189.0		Pravastatin	10mg/day	162
				58.0	187.0		Pravastatin	20mg/day	166

				58.0	190.0		Pravastatin	40mg/day	164

ONLINE ONLY Table 2 – Methodological quality of included trials

Study Number	Trial Name	Blinding	Random sequence generation	Allocation concealment	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Sponsor
1	LSG-III	Single-blind	Unclear	Unclear	Unclear	Unclear	Yes	Industry
2	PMSG	Double-blind	Unclear	Unclear	Yes	Yes	Yes	Industry
3	SPSG	Double-blind	Unclear	Unclear	Unclear	No	Yes	Industry
4	LPSG	Double-blind	Unclear	Unclear	Unclear	Yes	Yes	Industry
5	4S	Double-blind	Yes	Yes	Yes	Yes	Yes	Industry
6	POST-CABG	Not clear	Yes	No	No	Yes	Yes	Industry
7	LIPID	Double-blind	Yes	Unclear	Unclear	Yes	Yes	Industry*
8	GISSI-P	Open-label	Yes	No	No	Unclear	Yes	Academic
9	GREACE	Open-label	Unclear	No	No	Yes	Yes	Academic
10	Bak et al. 1998	Double-blind	Yes	Unclear	Yes	Yes	Yes	Industry
11	Barter et al. 2000	Open-label	No	Unclear	No	Unclear	Yes	Industry
12	PMSG-Diabetes	Double-blind	Unclear	Unclear	Unclear	Unclear	Unclear	Industry
13	Bertolini et al. 1997	Double-blind	Unclear	Unclear	No	No	Yes	Industry
14	CIS	Double-blind	Unclear	Unclear	Unclear	Unclear	Yes	Industry
15	DISCOVERY-Alpha	Open-label	Yes	Yes	No	Yes	Yes	Industry
16	MARS	Double-blind	Yes	Unclear	Yes	Yes	Yes	Industry*
17	EXCEL	Double-blind	Yes	Yes	Unclear	Unclear	Yes	Industry

18	Branchi et al. 2001	Open-label	Unclear	Unclear	No	Yes	Yes	Unclear
19	PROVE IT-TIMI 22	Double-blind	Yes	Unclear	Unclear	Yes	Yes	Industry
20	CARDS	Double-blind	Yes	Unclear	No	Yes	Yes	Industry
21	METEOR	Double-blind	Yes	Yes	Yes	Yes	Yes	Industry
22	ASG-I	Double-blind	No	No	Yes	Yes	Yes	Industry
23	Davidson et al. 1997	Double-blind	Unclear	No	Unclear	Unclear	Yes	Industry
24	SAGE	Double-blind	Unclear	Unclear	Yes	Yes	Yes	Industry
25	AFCAPS/TexCAPS	Double-blind	No	Unclear	No	Yes	Yes	Industry
26	GISSI-HF	Double-blind	Yes	Yes	Yes	Yes	Yes	Industry
27	LCAS	Double-blind	No	No	Unclear	No	Yes	Industry
28	ASSET	Double-blind	No	No	No	No	Yes	Industry
29	Jacobson et al. 1995	Double-blind	Unclear	Unclear	Yes	Unclear	Yes	Industry
30	REGRESS	Double-blind	Unclear	Unclear	Yes	Yes	Yes	Industry
31	Kyeong et al. 2007	Open-label	No	No	No	No	Unclear	Academic
32	TARGET TANGIBLE	Open-label	Unclear	No	No	Unclear	Unclear	Industry
33	CAIUS	Double-blind	Yes	Yes	Yes	Yes	Yes	Industry
34	SHIGA Pravastatin Study	Open-label	Unclear	No	Yes	No	Unclear	Industry
35	WWEDSS	Double-blind	Yes	Unclear	Unclear	Yes	Yes	Industry
36	BELLES	Double-blind	Unclear	Unclear	Yes	No	Yes	Industry
37	Riegger et al. 1999	Double-blind	Unclear	Unclear	Yes	Yes	Yes	Industry

38	CARE	Double-blind	Yes	Unclear	Yes	Yes	Yes	Industry
39	KAPS	Double-blind	Yes	Unclear	Yes	Unclear	Yes	Industry
40	MIRACL	Double-blind	Unclear	Unclear	Yes	Yes	Yes	Industry
41	IQLMG	Double-blind	Unclear	Unclear	Unclear	Unclear	Unclear	Industry
42	FLARE	Double-blind	Unclear	Unclear	Yes	Yes	Yes	Industry
43	WOSCOPS	Double-blind	No	No	Yes	Yes	Yes	Industry
44	Stein et al. 1990	Open-label	No	No	Yes	Yes	Yes	Industry
45	EDS-US	Double-blind	Yes	Unclear	Unclear	Yes	Yes	Industry
46	PACT	Double-blind	Unclear	Unclear	Unclear	Yes	Yes	Industry
47	LRTSG	Double-blind	Unclear	Unclear	Unclear	No	Yes	Industry
48	QLMG	Double-blind	No	Unclear	Unclear	No	Yes	Not reported
49	MRC/BHF Heart Protection Study	Double-blind	Yes	Yes	Yes	Yes	Yes	Government
50	CHESS	Double-blind	Unclear	Unclear	Unclear	No	Yes	Industry
51	Ballantyne et al. 2003	Double-blind	Unclear	Unclear	Yes	Yes	Yes	Industry
52	ADVOCATE	Open-label	No	No	Yes	Yes	Yes	Industry
53	Bruckert et al. 2003	Double-blind	Unclear	Unclear	Unclear	Yes	Yes	Industry
54	Davidson et al. 2002-b	Double-blind	Yes	Unclear	Yes	Yes	Yes	Industry
55	Kerzner et al. 2003	Double-blind	No	No	Unclear	Unclear	Yes	Industry
56	FLORIDA	Double-blind	Unclear	Unclear	Unclear	Yes	Yes	Industry
57	Melani et al. 2003	Double-blind	Yes	Unclear	No	Yes	Yes	Industry

58	TREAT TO TARGET	Double-blind	Yes	Yes	Unclear	Unclear	Unclear	Industry
59	LIPS	Double-blind	No	Unclear	Yes	Yes	Yes	Industry
60	PROSPER	Double-blind	Yes	Yes	Yes	Yes	Yes	Industry*
61	HeFH	Double-blind	No	Unclear	Unclear	Unclear	Yes	Industry
62	ASTRONOMER	Double-blind	Yes	No	Yes	Yes	Yes	Industry*
63	Colivicchi et al. 2010	Open-label	Unclear	No	Yes	Yes	Yes	Academic
64	ECLIPSE	Open-label	Unclear	No	Unclear	Yes	Yes	Industry
65	SPACE ROCKET	Open-label	Yes	Yes	Yes	Yes	Yes	Industry*
66	Kadoglou et al. 2010	Open-label	No	No	Unclear	Unclear	Yes	Government
67	CORONA	Double-blind	Yes	Yes	Yes	Yes	Yes	Industry
68	SUBARU	Open-label	Yes	Unclear	Unclear	Yes	Yes	Government
69	CENTAURUS	Double-blind	Yes	Unclear	Unclear	Yes	Yes	Industry
70	DISCOVERY-Beta	Open-label	Yes	Yes	Unclear	No	Yes	Industry
71	Lewis et al. 2007	Double-blind	Unclear	No	No	No	Yes	Industry
72	Alcala et al. 2010	Not reported	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
73	SPARCL	Double-blind	Unclear	Unclear	Yes	Yes	Yes	Industry
74	HYRIM	Double-blind	Unclear	Unclear	Unclear	Yes	Yes	Industry
75	Bays et al. 2004	Double-blind	No	No	Unclear	No	Yes	Industry
76	ANDROMEDA	Double-blind	Yes	No	Unclear	No	Yes	Industry
77	CAP	Double-blind	Yes	Yes	Unclear	No	Yes	Industry

78	A to Z	Double-blind	Yes	Yes	Yes	Yes	Yes	Industry
79	PREVEND IT	Double-blind	Yes	Yes	Yes	Yes	Yes	Industry
80	Durazzo et al. 2004	Double-blind	Yes	Unclear	Yes	Yes	Yes	Government
81	DISCOVERY-Penta	Open-label	Unclear	No	No	No	Unclear	Industry
82	Goldberg et al. 2004	Double-blind	Yes	Unclear	Yes	No	Yes	Industry
83	RADAR	Open-label	Unclear	No	No	No	Yes	Industry
84	ASPEN - Primary Prevention	Double-blind	Unclear	Unclear	Yes	No	Yes	Industry
85	ALLIANCE	Open-label	Unclear	No	No	Yes	Yes	Industry
86	TNT	Double-blind	Unclear	Unclear	Yes	Yes	Yes	Industry
87	POLARIS	Double-blind	Unclear	Unclear	Unclear	No	Unclear	Industry
88	ATOROS	Open-label	Unclear	Unclear	Unclear	Unclear	Yes	Academic
89	PCS	Not reported	Unclear	Unclear	Unclear	Unclear	Yes	Industry
90	MEGA	Open-label	Yes	No	Yes	Unclear	Yes	Industry
91	REVERSAL	Double-blind	Yes	Yes	Yes	Unclear	Yes	Industry
92	IDEAL	Open-label	Yes	No	Yes	Yes	Yes	Industry
93	Schermund et al. 2006	Double-blind	Yes	No	Yes	Unclear	Yes	Industry
94	ASCOT-LLA	Double-blind	Unclear	Unclear	Yes	Unclear	Yes	Industry
95	DISCOVERY	Open-label	No	No	No	No	Yes	Industry
96	CORALL	Open-label	Unclear	No	No	Yes	Yes	Industry
97	Yu et al. 2007	Double-blind	Yes	Yes	Unclear	Yes	Yes	Industry

98	JUPITER	Double-blind	Yes	Yes	Yes	Yes	Yes	Industry
99	Sdringola et al. 2008	Double-blind	Unclear	Unclear	Yes	Unclear	Yes	Industry
100	DISCOVERY-Asia	Open-label	Yes	No	No	No	Yes	Industry
101	Guillen et al. 1995	Double-blind	Unclear	Unclear	Unclear	Unclear	Yes	Industry
102	PULSAR	Open-label	Unclear	No	No	No	Yes	Industry
103	SATURN	Double-blind	Yes	Yes	Yes	Yes	Yes	Industry*
104	ALLHAT	Open-label	Yes	No	No	Yes	Yes	Government
105	Eriksson et al.	Double-blind	Yes	Yes	No	Yes	Yes	Industry
106	Gumprecht et al.	Double-blind	Yes	Yes	Yes	Yes	Yes	Industry
107	URANUS	Double-blind	Unclear	Unclear	Unclear	Yes	Yes	Industry
108	Farnier et al. 2000	Open-label	No	Unclear	Yes	Yes	Yes	Industry
109	LUNAR	Open-label	Unclear	No	Yes	Yes	Unclear	Industry
110	OCS	Double-blind	Yes	Unclear	Yes	Yes	Yes	Industry
111	Stein et al. 2000	Double-blind	Unclear	Unclear	Unclear	Unclear	Yes	Industry
112	Mohler et al. 2003	Double-blind	Unclear	Unclear	Unclear	Yes	Yes	Industry
113	Olsson et al. 2002	Double-blind	Unclear	Unclear	Unclear	Yes	Yes	Industry
114	SOLAR	Open-label	Unclear	No	No	No	Yes	Industry
115	Schwartz et al. 2004	Double-blind	Yes	Unclear	Unclear	Yes	Yes	Industry

116	COMETS	Double-blind	Unclear	Unclear	Unclear	Yes	Yes	Industry
117	VYMET	Double-blind	Yes	Yes	Yes	Unclear	Yes	Industry
118	PATROL	Not reported	Yes	Unclear	No	Unclear	Yes	Government
119	DISCOVERY Netherlands	Open-label	Unclear	No	No	Yes	Yes	Industry
120	Brown et al. 1998	Open-label	Unclear	No	No	Yes	Yes	Industry
121	Recto et al. 2000	Open-label	Unclear	No	No	Unclear	Yes	Industry
122	Brown et al. 2002	Double-blind	Yes	Unclear	Unclear	Yes	Yes	Industry
123	Davidson et al. 2002	Double-blind	Unclear	Unclear	Unclear	Yes	Yes	Industry
124	CHALLENGE	Open-label	Yes	No	Yes	Unclear	Yes	Industry
125	Paoletti et al. 2001	Double-blind	Unclear	Unclear	Unclear	Yes	Yes	Industry
126	IRIS	Open-label	Unclear	No	No	Unclear	Yes	Industry
127	ARIES	Open-label	Unclear	No	No	Unclear	Yes	Industry
128	Ose et al. 2009	Double-blind	Yes	Yes	Yes	Unclear	Yes	Industry
129	STARSHIP	Open-label	Unclear	No	No	Unclear	Yes	Industry
130	Ballantyne et al. 2001	Open-label	Unclear	No	No	No	Yes	Industry
131	Gentile et al. 2000	Open-label	Unclear	No	No	Yes	Yes	Government
132	Davidson et al. 2003	Double-blind	Yes	Unclear	Unclear	Unclear	Yes	Industry

133	MERCURY II	Open-label	No	No	No	No	Yes	Industry
134	MERCURY I	Open-label	No	No	No	No	Yes	Industry
135	STELLAR	Open-label	Unclear	No	No	Unclear	Yes	Industry

** Investigators declared that the funding body had no involvement in study design, analysis, and reporting.*

ONLINE ONLY Exhibit 1 – Sensitivity of the findings to meta-regression analyses for **(A)** discontinuations due to adverse events; **(B)** myalgia; **(C)** transaminase elevations; and **(D)** CK elevations.

(A) Discontinuations due to adverse events

	Adjusted for Publication Year	**Adjusted for Mean Age at Baseline**	**Adjusted for Mean LDL-C concentration at baseline**
Meta-regression coefficient	0.00 (-0.06, 0.05)	-0.02 (-0.06, 0.01)	0.01 (0.00, 0.02)
Atorvastatin	1.18 (0.94, 1.49)	1.24 (0.99, 1.56)	1.21 (0.97, 1.52)
Fluvastatin	1.21 (0.83, 1.79)	1.24 (0.85, 1.79)	1.23 (0.84, 1.79)
Lovastatin	0.91 (0.61, 1.34)	0.94 (0.65, 1.34)	0.91 (0.63, 1.3)
Pravastatin	0.81 (0.62, 1.05)	0.83 (0.65, 1.07)	0.82 (0.64, 1.05)
Rosuvastatin	1.14 (0.88, 1.48)	1.19 (0.92, 1.54)	1.18 (0.91, 1.52)
Simvastatin	0.88 (0.67, 1.17)	0.91 (0.69, 1.19)	0.9 (0.69, 1.18)
Pitavastatin	0.91 (0.43, 1.96)	0.95 (0.45, 1.98)	0.94 (0.45, 1.98)

(B) Myalgia

	Adjusted for Publication Year	**Adjusted for Mean Age at Baseline**	**Adjusted for Mean LDL-C concentration at baseline**
Meta-regression coefficient	-0.02 (-0.1, 0.06)	-0.03 (-0.08, 0.01)	0.01 (0.00, 0.02)
Atorvastatin	1.06 (0.82, 1.45)	1.12 (0.87, 1.49)	1.16 (0.90, 1.56)
Fluvastatin	0.99 (0.49, 1.87)	1.04 (0.54, 1.94)	1.03 (0.54, 1.96)
Lovastatin	1.10 (0.60, 2.03)	1.19 (0.75, 1.93)	1.24 (0.78, 2.00)
Pravastatin	0.95 (0.67, 1.46)	1.09 (0.76, 1.60)	1.04 (0.76, 1.52)
Rosuvastatin	1.21 (0.91, 1.69)	1.26 (0.95, 1.75)	1.29 (0.97, 1.82)
Simvastatin	0.82 (0.56, 1.31)	0.87 (0.59, 1.34)	0.90 (0.59, 1.40)
Pitavastatin	1.87 (0.70, 5.62)	1.96 (0.74, 6.24)	2.09 (0.80, 6.32)

(C) Transaminase elevation

	Adjusted for Publication Year	**Adjusted for Mean Age at Baseline**	**Adjusted for Mean LDL-C concentration at baseline**
Meta-regression coefficient	-0.02 (-0.1, 0.07)	-0.02 (-0.11, 0.07)	0 (-0.01, 0.02)
Atorvastatin	2.5 (1.66, 3.69)	2.58 (1.69, 3.87)	2.6 (1.69, 3.86)
Fluvastatin	5.6 (2.02, 16.94)	5.58 (2.04, 16.98)	5.67 (2.01, 17.4)
Lovastatin	1.88 (0.86, 4.25)	1.97 (0.95, 4.16)	2.04 (1, 4.26)
Pravastatin	0.96 (0.59, 1.56)	0.99 (0.64, 1.54)	1.01 (0.64, 1.56)
Rosuvastatin	1.58 (1.01, 2.53)	1.65 (1.01, 2.65)	1.64 (1.02, 2.59)
Simvastatin	1.12 (0.67, 1.9)	1.17 (0.7, 1.96)	1.16 (0.71, 1.92)
Pitavastatin	2.84 (0.71, 11.06)	2.96 (0.76, 11.87)	2.99 (0.77, 11.73)

(D) CK elevation

	Adjusted for Publication Year	**Adjusted for Mean Age at Baseline**	**Adjusted for Mean LDL-C concentration at baseline**
Meta-regression coefficient	-0.03 (-0.17, 0.08)	-0.11 (-0.31, 0.05)	0.02 (-0.01, 0.04)
Atorvastatin	1.37 (0.64, 2.73)	1.41 (0.75, 2.79)	1.48 (0.75, 2.91)
Fluvastatin	0.08 (0, 0.68)	0.11 (0, 0.69)	0.11 (0, 0.92)
Lovastatin	0.94 (0.27, 3.88)	0.86 (0.33, 2.82)	1.08 (0.43, 3.33)
Pravastatin	1.18 (0.55, 2.35)	1.1 (0.62, 2.09)	1.24 (0.68, 2.29)
Rosuvastatin	1.44 (0.69, 2.94)	1.49 (0.81, 3.11)	1.48 (0.8, 3.04)
Simvastatin	1.1 (0.41, 2.35)	1.15 (0.51, 2.31)	1.12 (0.46, 2.32)
Pitavastatin	5.61 (1.04, 43.63)	5.37 (1.22, 35.91)	5.69 (1.18, 36.56)

ONLINE ONLY Exhibit 2 – Sub-group analyses by primary and secondary prevention populations and sensitivity analysis excluding open-label trials for **(A)** discontinuations due to adverse events; **(B)** myalgia; **(C)** transaminase elevations; and **(D)** CK elevations.

(A) Discontinuations due to adverse events

	Base-case	**Secondary Prevention**	**Primary Prevention**	**Double-blind Trials**
Atorvastatin	1.18 (0.94, 1.49)	1.99 (1.07, 3.80)	1.13 (0.66, 2.01)	1.06 (0.89, 1.27)
Fluvastatin	1.22 (0.83, 1.79)	0.97 (0.42, 2.30)	-	0.95 (0.70, 1.29)
Lovastatin	0.91 (0.63, 1.32)	0.61 (0.13, 2.66)	0.88 (0.41, 1.84)	0.84 (0.64, 1.10)
Pravastatin	0.81 (0.63, 1.05)	1.80 (0.86, 4.25)	0.85 (0.51, 1.49)	0.76 (0.63, 0.92)
Rosuvastatin	1.14 (0.89, 1.48)	1.88 (0.77, 4.61)	1.11 (0.59, 2.20)	0.98 (0.80, 1.21)
Simvastatin	0.89 (0.68, 1.17)	1.19 (0.57, 2.55)	1.07 (0.41, 2.76)	0.85 (0.66, 1.11)
Pitavastatin	0.92 (0.44, 1.96)	-	1.03 (0.35, 3.05)	0.67 (0.29, 1.59)

(B) Myalgia

	Base-case	**Secondary Prevention**	**Primary Prevention**	**Double-blind Trials**
Atorvastatin	1.10 (0.86, 1.49)	1.21 (0.67, 3.87)	1.11 (0.44, 2.91)	1.00 (0.79, 1.34)
Fluvastatin	1.02 (0.52, 2.00)	3.18 (0.57, 21.58)	-	1.03 (0.33, 3.28)
Lovastatin	1.26 (0.78, 2.09)	-	-	1.49 (0.91, 2.74)
Pravastatin	1.00 (0.72, 1.50)	1.73 (0.62, 8.34)	1.05 (0.34, 3.39)	0.88 (0.64, 1.33)
Rosuvastatin	1.25 (0.94, 1.77)	1.30 (0.62, 4.89)	1.20 (0.45, 3.62)	1.12 (0.82, 1.61)
Simvastatin	0.86 (0.58, 1.38)	0.76 (0.37, 2.82)	-	1.34 (0.71, 2.78)
Pitavastatin	2.26 (0.75, 7.62)	-	-	2.42 (0.81, 8.75)

(C) Transaminase elevations

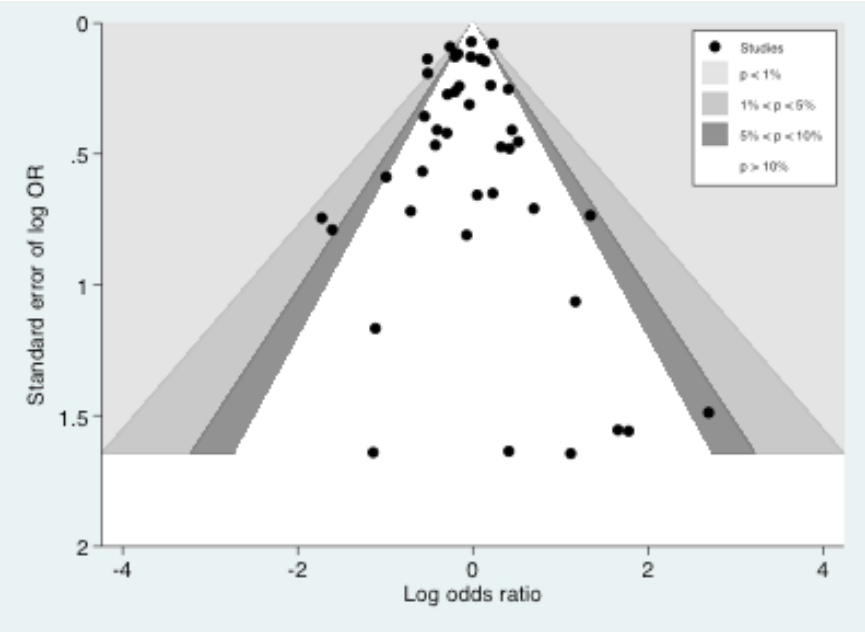
	Base-case	Secondary Prevention	Primary Prevention	Double-blind Trials
Atorvastatin	2.55 (1.71, 3.74)	3.92 (1.39, 10.34)	1.83 (1.02, 4.59)	2.83 (1.84, 4.28)
Fluvastatin	5.18 (1.89, 15.55)	6.42 (1.52, 31.96)	-	4.59 (1.58, 15.72)
Lovastatin	2.03 (0.99, 4.16)	2.01 (0.36, 11.07)	1.63 (0.46, 6.19)	2.02 (1.07, 4.18)
Pravastatin	1.00 (0.65, 1.54)	0.99 (0.34, 2.75)	0.95 (0.43, 1.60)	1.03 (0.67, 1.60)
Rosuvastatin	1.59 (1.02, 2.50)	1.79 (0.36, 8.26)	1.42 (0.71, 3.34)	1.48 (0.95, 2.40)
Simvastatin	1.16 (0.71, 1.88)	0.97 (0.31, 2.87)	-	0.97 (0.50, 1.68)
Pitavastatin	2.85 (0.77, 11.16)	-	2.04 (0.51, 9.99)	-

(D) CK Elevations

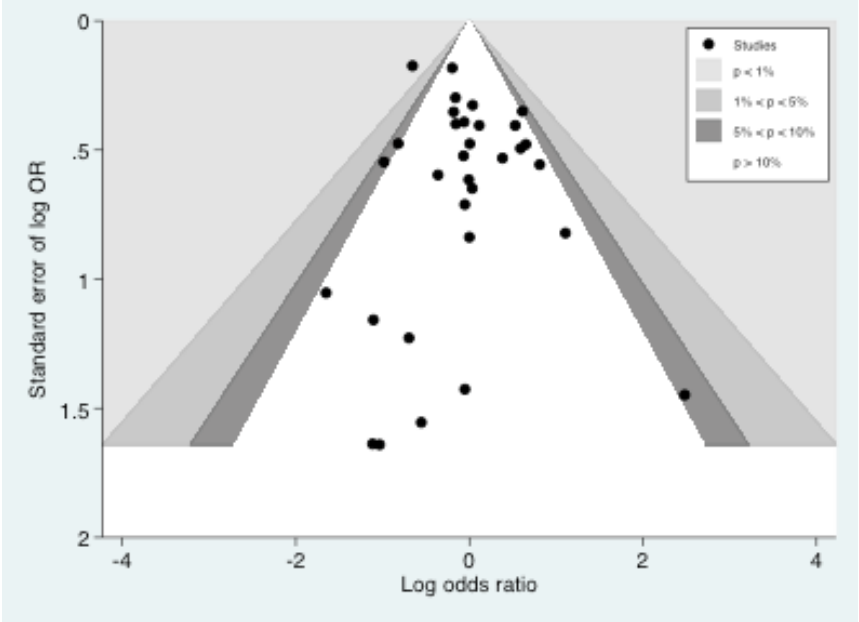
	Base-case	Secondary Prevention	Primary Prevention	Double-blind Trials
Atorvastatin	1.39 (0.86, 2.17)		0.74 (0.10, 4.95)	1.12 (0.47, 2.54)
Fluvastatin	0.25 (0.06, 1.06)	0.21 (0.01, 2.46)	0.17 (0.00, 13.36)	0.21 (0.02, 1.13)
Lovastatin	1.05 (0.55, 2.20)		0.99 (0.07, 13.79)	1.13 (0.43, 3.66)
Pravastatin	1.24 (0.85, 1.88)	2.58 (0.17, 83.9)	1.21 (0.32, 5.73)	1.23 (0.62, 2.61)
Rosuvastatin	1.39 (0.85, 2.30)		1.35 (0.25, 7.1)	1.42 (0.62, 2.98)
Simvastatin	1.23 (0.68, 2.15)		0.31 (0.00, 48.39)	1.21 (0.41, 3.27)
Pitavastatin	3.63 (1.10, 14.10)	0.08 (0.00, 6.13)	2.79 (0.14, 66.15)	4.30 (0.40, 151.80)

ONLINE EXHIBIT 3 – Assessment of publication bias by contour-enhanced funnel plots for **(A)** discontinuations due to adverse events, **(B)** myalgia, **(C)** transaminase elevations, and **(D)** CK elevations.

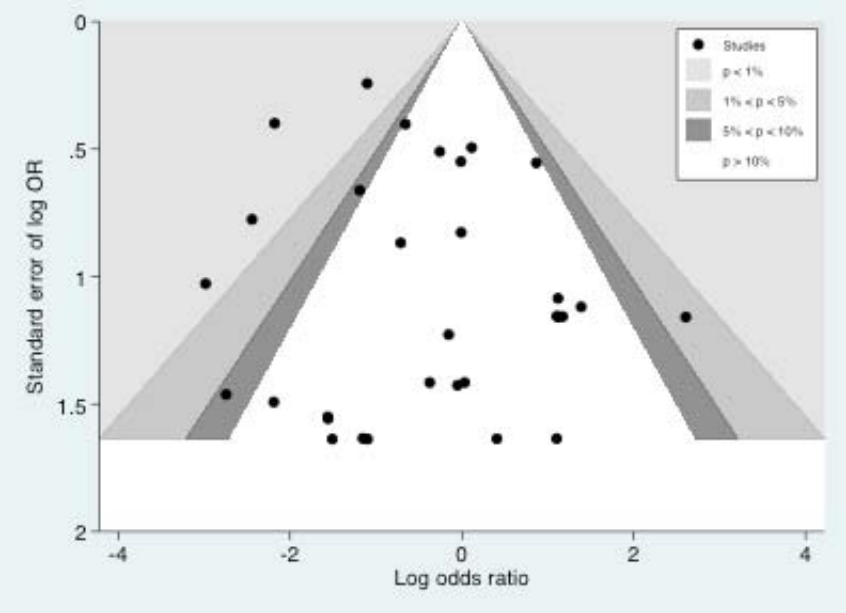
(A) Discontinuations due to adverse events



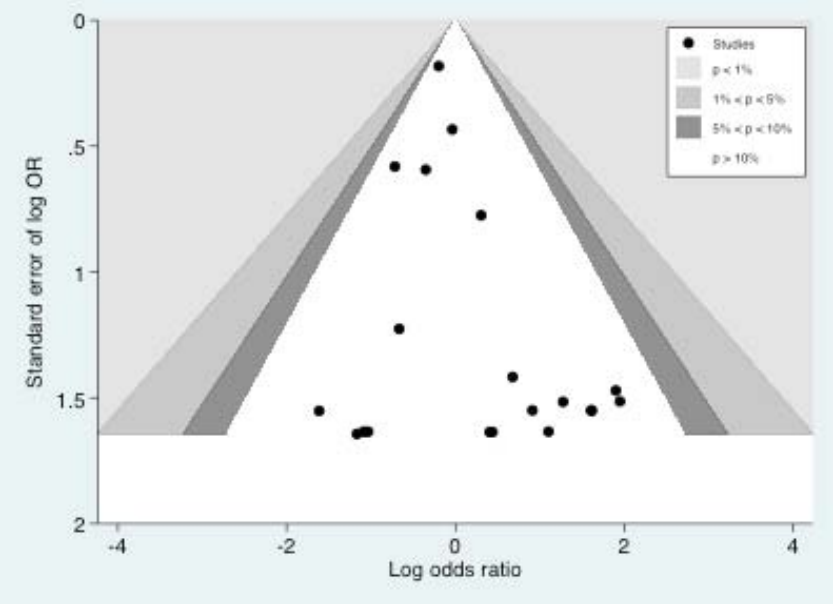
(B) Myalgia



(C) Transaminase elevations



(D) CK elevations



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