Comparative effectiveness and safety of statins as a class and of specific statins for primary prevention of cardiovascular disease: A systematic review, meta-analysis, and network meta-analysis of randomized trials with 94,283 participants

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Background The current guidelines of statins for primary cardiovascular disease (CVD) prevention were based on results from systematic reviews and meta-analyses that suffer from limitations.

Methods We searched in PubMed for existing systematic reviews and individual open-label or double-blinded randomized controlled trials that compared a statin with a placebo or another, which were published in English until January 01, 2018. We performed a random-effect pairwise meta-analysis of all statins as a class and network meta-analysis for the specific statins on different benefit and harm outcomes.

Results In the pairwise meta-analyses, statins as a class showed statistically significant risk reductions on non-fatal MI (risk ratio [RR] 0.62, 95% CI 0.53-0.72), CVD mortality (RR 0.80, 0.71-0.91), all-cause mortality (RR 0.89, 0.85-0.93), non-fatal stroke (RR 0.83, 0.75-0.92), unstable angina (RR 0.75, 0.63-0.91), and composite major cardiovascular events (RR 0.74, 0.67-0.81). Statins increased statistically significantly relative and absolute risks of myopathy (RR 1.08, 1.01-1.15; Risk difference [RD] 13, 2-24 per 10,000 person-years); renal dysfunction (RR 1.12, 1.00-1.26; RD 16, 0-36 per 10,000 person-years); and hepatic dysfunction (RR 1.16, 1.02-1.31; RD 8, 1-16 per 10,000 person-years). The drug-level network meta-analyses showed that atorvastatin and rosuvastatin were most effective in reducing CVD events while atorvastatin appeared to have the best safety profile.

Conclusions All statins showed statistically significant risk reduction of CVD and all-cause mortality in primary prevention populations while increasing the risk for some harm risks. However, the benefit-harm profile differed by statin type. A quantitative assessment of the benefit-harm balance is thus needed since meta-analyses alone are insufficient to inform whether statins provide net benefit. (Am Heart J 2019;210:18-28.)

The use of statins by patients with known cardiovascular disease (CVD) for preventing recurrent coronary or vascular events is little disputed.[1] However, heated discussions about the role of statins for primary prevention continue.[1-4] While some, including major clinical guideline developers, see great potential for statins to lower the burden of CVD and recommend life-long use of statins for millions of healthy individuals,[5-8] others argue that the evidence-base and decision support for individuals and health care professionals is not yet developed enough. Effects from randomized controlled trials (RCTs) often leave uncertainty due to short trial durations that cannot reveal all long-term adverse events,[9] incomplete transparency on harm outcomes,[9-11] and due to concerns about the applicability of results to the entire spectrum of primary prevention populations (e.g., older adults, women, or non-white).[2,10-13]

Undoubtedly, further investigation on long-term effects of statins as well as access to and independent analysis of

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existing individual patient data on harm outcomes are needed. But a number of steps can already be taken now on the existing published data to better elucidate the role of statins for primary prevention. The current guidelines used results from systematic reviews and meta-analyses that suffer from limitations. Firstly, some of the previous meta-analyses reported the effect of statins on composite outcomes only. This approach is problematic when statins have opposite directions of effect for some outcomes or if the effect sizes on different outcomes vary substantially.[14-16] Secondly, some systematic reviews assessed statins as a class, which may obscure the efficacy and safety differences between statins.[17] Thirdly, some of the systematic reviews mixed primary and secondary prevention populations while the effects could differ and often low dose statins are used for primary prevention.[3,11,14] In order to make optimal use of existing RCTs to inform the debate on statins, we carried out a comprehensive systematic review, meta-analysis and network meta-analysis of RCTs to estimate the effectiveness and safety of statins as a class and of individual statins for primary prevention of CVD.

Methods

We undertook the systematic review and network meta-analysis according to a review protocol and adhered to PRISMA with the extension for network meta-analysis for reporting.[18]

Information source and search

There are a number of existing systematic reviews on statins, which were conducted at different time points. It is thus unlikely that individual studies would be missed from the search of all the systematic reviews. Instead of duplicating the entire search, we searched for systematic reviews on statins on PubMed published in English between January 1, 2013, to November 30, 2016, with search strings: statins and tolerability, safety, harms efficacy, effects, cardiovascular disease, systematic review, or meta-analysis (see Supplement Appendix 1). We then retrieved all the individual trials included in each systematic review and also checked for the list of excluded studies in those systematic reviews. We updated the search until Jan 01, 2018 to identify trials that were published after the last systematic review.

Study selection

Our review and analysis was restricted to the use of statins for primary CVD prevention; i.e., effectiveness and safety of statins for people without history of any CVD events at baseline. We included open-label or double-blinded RCTs that compared a statin vs. a placebo or another statin.

We considered six statins simvastatin, lovastatin, fluvastatin, atorvastatin, pravastatin, and rosuvastatin for which trials on primary prevention were available.

Figure 1 shows summary of the study selection. We included RCTs if they reported results on at least one benefit or harm outcome. Benefit outcomes (i.e. to be prevented by statins) included fatal and non-fatal stroke, fatal and non-fatal myocardial infarction (MI), unstable angina, heart failure, CVD- and all-cause mortality. Harm events included all cancers, type 2 diabetes, myopathy, renal dysfunction, hepatic dysfunction, nausea and headache, and treatment discontinuation due to adverse effects attributed to statins. We considered the outcomes as defined by the trial investigators. While definitions for most of the outcomes were clear, few trials used both clinical features and serum biomarkers to define specifically myopathy and hepatic dysfunction. The trials that used biomarkers defined myopathy as an increase of creatine kinase to 10 times the level at baseline or higher, and hepatic dysfunction as increase of alanine aminotransferase or aspartate aminotransferase to more than 3 times the baseline concentration.

We excluded trials on primary prevention that did not report at least one outcome of interest; if they included participants with clinically different risk profile from that of a primary prevention population (e.g., participants with renal insufficiency), and if they compared a statin with another active drug or a statin combined with an active drug. To minimize information loss, we also included trials that recruited participants with history of CVD but only if the proportion was less than 10% of total sample size and if the cases were balanced between statin and placebo arms. Since one can argue for or against the inclusion of these trials, we performed sensitivity analyses by excluding them.

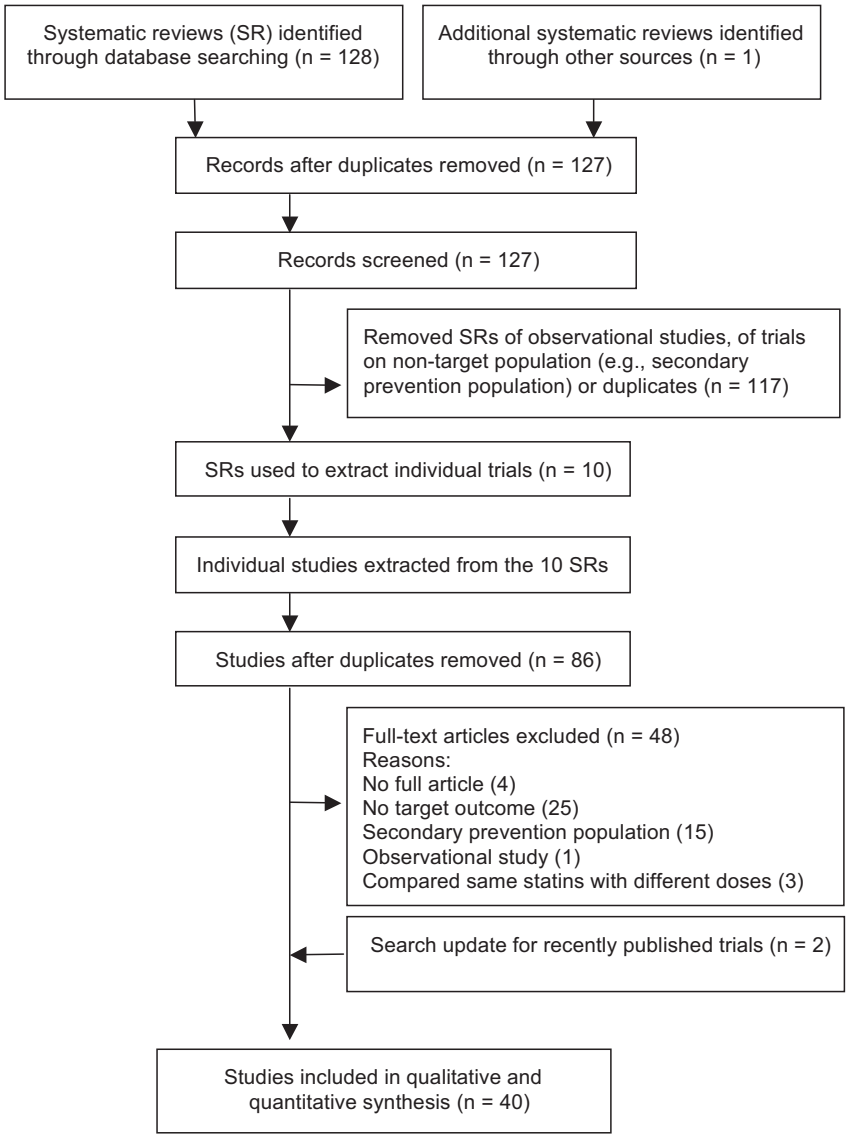
Data extraction and quality assessment

Two reviewers (HGY & MK) independently performed the screening, full text assessment, quality assessment and data extraction and a third reviewer (MAP) was consulted in case of disagreements. We extracted events from each trial and baseline study-level factors that may be associated with heterogeneity of efficacy or tolerability of statins between studies, including year of publication, trial duration, average age, BMI, and baseline LDL cholesterol, proportion of male sex, doses of statins, proportion of participants with type 2 diabetes and hypertension (see Supplement Table 1). We assessed the study-level risk-of-bias using Cochrane criteria (see for detailed criteria and values on Supplement Appendix 2 and Supplement Table 2).[19]

Data synthesis and analysis

First, we performed a random-effect pairwise meta-analysis for the placebo-controlled trials by pooling all statins as a class for each benefit and harm outcome and estimated the risk ratio (RR) with a 95% confidence interval (CI) using the DerSimonian–Laird method. We inspected heterogeneity using the I-statistic.[20] The absolute risk differences (RD) for the placebo-controlled

Figure 1



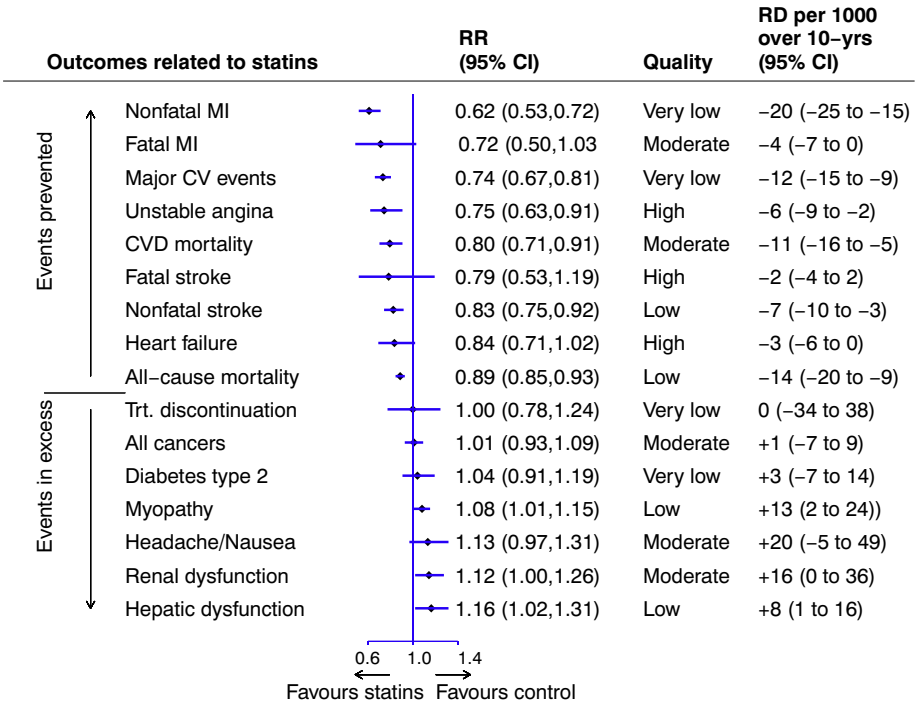
Flowchart for selection of studies.

effects were calculated using the baseline risks from the control arms of individual trials and a common RR from the summary estimates of the meta-analysis using the MOVER-R algorithm.[21] The 95% CI for the baseline risk was estimated using the Wilson score.[22] We took the median follow-up time (in person-years) of the trials to estimate the baseline risk. Second, we carried out a statin drug-level network meta-analysis that (i) took into account the correlation within multi-arm and between studies, (ii) yielded indirect estimates for treatments that had not been compared head-to-head directly and mixed with the direct estimates, (iii) and ranked treatments.[23-25] We used frequentist multivariate random-effects meta-analysis to estimate the RR and 95% CI for each of the outcome using the restricted maximum likelihood estimation method and a proportional between-study covariance structure.[24] We ranked the different statins according the surface under the cumulative ranking curve (SUCRA) to show which statins were more likely to be effective and more likely to be tolerable. We performed the analyses on Stata 13.1 (Stat 2013, StataCorp LP).

Assessment of intransitivity and inconsistency assumptions

We looked into the epidemiological and clinical plausibility for assessing the transitivity of effects–an assumption that accounts for whether distributions of

Figure 2



Overall effects of statins on the different benefit and harm outcomes.The figure presents the overall effects (in risk ratio) of statins compared with placebo from each random effect pairwise meta-analysis model of the different outcomes (see Supplement Figure 4.1–4.15.). The risk differences were the number of events that would be prevented or increased per 1000 people treated with statins over 10 years (see methods and Supplement Table 5). The outcomes are ordered based on the magnitude and direction of the point estimates. The quality indicates the confidence of the evidence assessed based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) (see Supplement Table 3.1). CVD, Cardiovascular disease; Major CV events, major cardiovascular events; RD, risk difference; RR, risk ratio.

possible effect modifiers are similar between trials.[26,27] We also checked inconsistency to assess whether combining direct and indirect evidence is justifiable.[28] We calculated the inconsistency factors together with their 95% CI's for the closed-loops available using the node-splitting method,[29] which tests the direct estimate of a comparison with the indirect estimates coming from the entire network unlike the loop-specific approach that compares with the indirect estimate pooled from a specific loop.[30] For multi-arm trials, for which the node-splitting or loop-specific methods are not appropriate, we used the design-by-treatment-interaction method.[24] We assumed common within-loop heterogeneity for the node-splitting approach and a common heterogeneity variance for all comparisons in the network for the design-by-treatment-interaction method.[30] Moreover, we checked the global inconsistency test using inconsistency model that relaxes consistency assumptions completely.[31]

Quality of evidence

We assessed the quality or confidence of the direct estimates using the standard Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach based on the five domains (risk-of-bias,[32] inconsistency,[33] indirectness,[34] imprecision,[35] and publication bias.[36] For the network estimates, we adopted the GRADE approach with the extension for network meta-analysis (see Supplement Appendix 3 and Supplement Tables 3.1 and 3.2).[37]

Sensitivity analysis

We assessed the sensitivity of estimates to the baseline characteristics (low/moderate vs. high doses of statins, risk-of-bias, proportion of male sex, mean age, year of publication, duration of study, BMI, proportion of people with type 2 diabetes, proportion of people with hypertension, and mean LDL cholesterol) using a multivariate random-effects meta-regression.[38] Such explorations of heterogeneity are prone to misleading false-positive results ($P < .05$) due to aggregation (of baseline factors) bias, heterogeneity of variance, weights assigned to studies or more study characteristics modeled with fewer number of studies.[31] Therefore, we ran the regression analysis on one factor at a time and estimated the p-values using permutation test.[38] We furthermore

explored the impact on effect estimates excluding trials that included participants with history of CVD (9/40), higher proportion (>90%) of DM cases (9/40), high-dose statins (5/40), and trials with high risk-of-bias (16/40).

Role of the funding source

A Swiss Government Excellence Scholarship and the North–South Cooperation at the University of Zurich funded the study but they had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Forty trials fulfilled the predefined eligibility criteria (Figure 1) that included 94,283 participants. Thirty-three trials were placebo-controlled and seven were head-to-head comparison of statins. Based on dose labeling of the American College of Cardiology/American Heart Association,[6] the majority of the trials tested low-dose (10/40) or moderate-dose (25/40) of statins, but the remaining (5/40) used high-dose statins. The primary outcomes of all the trials were the CVD events or all-cause mortality; and none of the trials considered harm outcomes as a primary outcome.

Not all trials reported all outcomes. The forest plots with the list of studies included for each outcome are presented in Supplement Figure 4.1–4.15 and the network plots are shown in Figures 3 and 4, which also show the estimate matrices for each contrast. The median follow-up time was 1 year (Interquartile range [IQR], 3.6 months to 3.8 years).

The median age of the enrolled participants was 58.3 years (IQR, 46-76); BMI 28 kg/m^2 (IQR, 27-28); total cholesterol 232 mg/dl (213-265); LDL cholesterol 155 mg/dl (128-185) and HDL cholesterol 49.0 mg/dl (46.0-54.0). The median of the proportion of participants with type 2 diabetes was 14% (3-95); hypertension, 42% (27-84); male sex, 61% (48-77); smoker, 28% (17-45) and white Caucasian, 92% (83-95). Fifteen trials were of good, 9 of fair and 16 of poor qualities, but most trials of poor quality were small, which contributed little to the overall effect (see Supplement Table 2).

Effects of statins on benefit outcomes

Figure 2 presents the pair-wise meta-analytic estimates for all outcomes, including the rating on the quality of evidence (see Supplement Table 5 for more details of the RD). Figures 3 and 4 illustrate the network plots, results of network meta-analyses, and quality of the evidence for all benefit outcomes. The sources of evidence (direct and indirect) with their quality are presented in Supplement Table 3.2 for all outcomes.

Non-fatal MI. Statins as a class reduced the risk of non-fatal MI statistically significantly compared with placebo (RR 0.62, 0.53 to 0.72; I^2 = 28.6%; quality, moderate; number of trials included in this analysis, 16). In absolute terms, 20 non-fatal MI events would be prevented per 1000 people treated with statins over 10 years (RD −20, −25 to −15 per 10,000 person-years). The drug-level network meta-analysis showed that atorvastatin, rosuvastatin and pravastatin, but not lovastatin, reduced non-fatal MI events statistically significantly, with atorvastatin ranked as the most effective treatment (SUCRA 85%).

Fatal MI. While atorvastatin showed statistically significant relative risk reduction of fatal MI, the other specific statins as well as statins as a class showed no statistically significant effect (RR 0.72, 0.50 to 1.03; I^2 = 0; quality, low; RD −4, −7 to 0 per 10,000 person-years; 6 trials).

Non-fatal stroke. Statins as a class reduced the risk of non-fatal stroke by 17% (RR 0.83, 0.75 to 0.92; I^2 = 0; quality, moderate; 16 trials) or prevented seven events per 1000 people treated with statins over 10 years (RD −7; −10 to −3 per 10,000 person-years). The drug-level network meta-analysis showed that only the effect of rosuvastatin and atorvastatin reached statistical significance.

Fatal stroke. Neither statins as a class (RR 0.79, 0.53 to 1.19; I^2 = 0; quality, moderate; RD −2, −4 to 2 per 10,000 person-years; 6 trials) nor individual statins had a statistically significant effect on fatal stroke. Pravastatin showed an increased risk compared with placebo, but the effect was not statistically significant.

All-cause mortality. Statins as a class reduced incidences of mortality as compared with the placebo (RR 0.89, 0.85 to 0.93; I^2 = 0%; quality, moderate; RD −14, −20 to −9 per 10,000 person-years; 24 trials). Individually, pravastatin, atorvastatin, and rosuvastatin demonstrated statistically significant risk reduction of all-cause mortality.

CVD mortality. Statins as a class were attributed to 21% RR reduction of CVD mortality, which corresponded to preventing 11 events per 1000 people treated with statins for 10 years (RR 0.80, 0.71 to 0.91; I^2 = 35.2%; quality, high; RD −11, −16 to −5 per 10,000 person-years; 15 trials). However, the drug-level analysis showed that only the effect of rosuvastatin and pravastatin reached statistical significance.

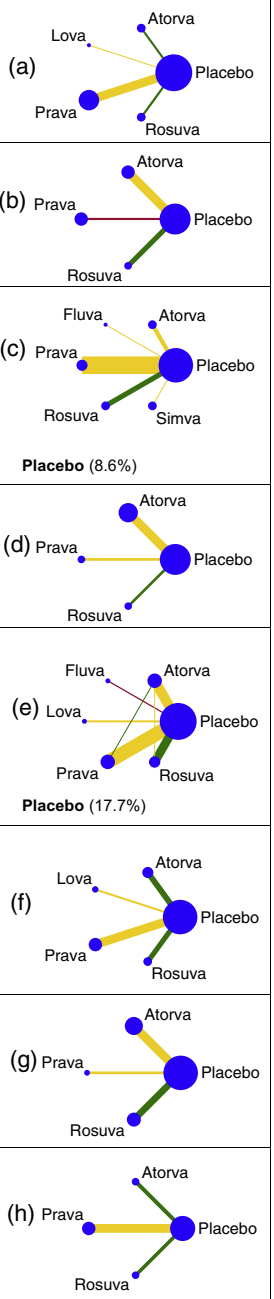
Unstable angina. Fewer events of unstable angina occurred in the statin groups than in the placebo groups (RR 0.75, 0.63 to 0.91; I^2 = 0; quality, high; RD −6, −9 to −2 per 10,000 person-years; 8 trials). While the estimate of risk reduction favored each of the specific statins compared with the placebo, only the effect of atorvastatin was statistically significant.

Heart failure. Neither the RR nor RD showed statistically significant effectiveness of statins as class (RR 0.84; 95% CI 0.71 to 1.02; I^2 = 0; quality, moderate; RD −3, −6 to 0 per 10,000 person-years; 5 trials). Participants randomized to atorvastatin even had more heart failure events compared with placebo, but this was not statistically significant.

Major cardiovascular events. We assessed the results on a composite outcome of all major cardiovascular events excluding fatal stroke and heart failure for which

Figure 3

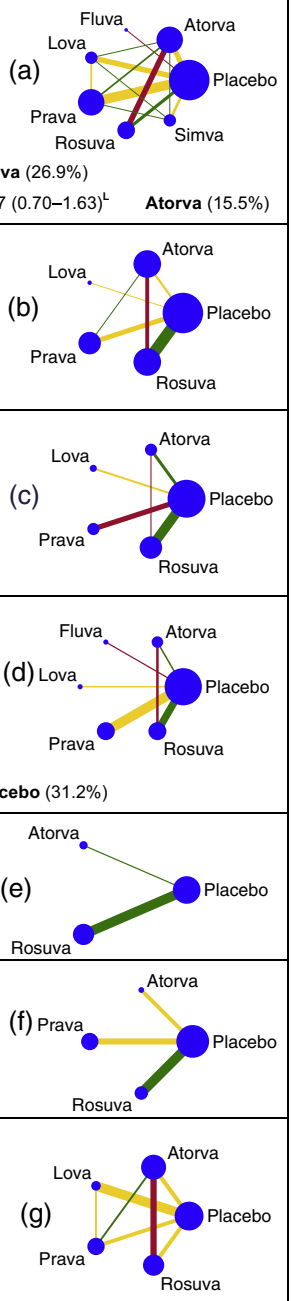
					Network plots
Nonfatal MI					
Atorva (84.7%)					
0.95 (0.55–1.63)^{M}	**Rosuva** (79.8%)				
0.66 (0.42–1.17)^{L}	0.72 (0.49–1.11)^{L}	**Prava** (48.0%)			
0.47 (0.13–1.78)^{L}	0.50 (0.13–1.87)^{L}	0.71 (0.18–2.47)^{L}	**Lova** (24.6%)		
0.47 (0.32–0.69)^{H}	0.50 (0.35–0.72)^{H}	0.71 (0.50–0.90)^{M}	1.00 (0.28–3.55)^{L}	**Placebo** (12.8%)	
Fatal MI					
Atorva (87.6%)					
0.60 (0.16–2.19)^{L}	**Rosuva** (65.0%)				
0.45 (0.11–3.65)^{VL}	0.76 (0.14–6.35)^{VL}	**Prava** (35.5%)			
0.40 (0.18–0.88)^{M}	0.67 (0.13–3.11)^{M}	0.88 (0.24–1.87)^{H}	**Placebo** (11.9%)		
Nonfatal stroke					
Simva (75.8%)					
0.86 (0.16–4.75)^{VL}	**Fluva** (70.3%)				
0.82 (0.32–2.12)^{L}	0.95 (0.22–4.09)^{VL}	**Rosuva** (60.9%)			
0.73 (0.28–1.90)^{L}	0.84 (0.19–3.65)^{L}	0.89 (0.61–1.29)^{L}	**Atorva** (57.6%)		
0.56 (0.22–1.43)^{L}	0.65 (0.15–2.78)^{L}	0.69 (0.52–0.92)^{M}	0.77 (0.57–1.06)^{L}	**Prava** (26.8%)	
0.52 (0.21–1.30)^{L}	0.60 (0.14–2.53)^{L}	0.63 (0.49–0.82)^{M}	0.71 (0.54–0.94)^{M}	0.92 (0.80–1.05)^{L}	**Placebo** (8.6%)
Fatal stroke					
Rosuva (79.0%)					
0.72 (0.16–3.16)^{M}	**Atorva** (70.2%)				
0.50 (0.12–2.00)^{M}	0.69 (0.41–1.16)^{M}	**Placebo** (31.9%)			
0.33 (0.05–2.18)^{L}	0.46 (0.12–1.82)^{L}	0.67 (0.19–2.37)^{L}	**Prava** (18.9%)		
All-cause mortality					
Fluva (70.1%)					
0.99 (0.30–3.32)^{M}	**Atorva** (68.7%)				
0.97 (0.29–3.24)^{M}	0.98 (0.85–1.13)^{L}	**Prava** (59.1%)			
0.96 (0.29–3.23)^{VL}	0.97 (0.83–1.14)^{L}	0.99 (0.86–1.15)^{L}	**Rosuva** (54.8%)		
0.85 (0.24–2.94)^{L}	0.85 (0.61–1.19)^{L}	0.87 (0.63–1.21)^{VL}	0.88 (0.63–1.23)^{VL}	**Lova** (29.1%)	
0.84 (0.25–2.79)^{M}	0.85 (0.76–0.95)^{M}	0.86 (0.79–0.94)^{H}	0.87 (0.77–0.98)^{VL}	0.99 (0.72–1.35)^{L}	**Placebo** (17.7%)
CVD mortality					
Lova (78.4%)					
0.88 (0.42–1.85)^{L}	**Rosuva** (74.4%)				
0.80 (0.38–1.67)^{L}	0.91 (0.61–1.35)^{L}	**Prava** (59.9%)			
0.67 (0.32–1.39)^{L}	0.76 (0.51–1.13)^{M}	0.89 (0.63–1.26)^{L}	**Atorva** (29.0%)		
0.60 (0.30–1.20)^{L}	0.69 (0.51–0.92)^{H}	0.80 (0.64–0.99)^{M}	0.90 (0.70–1.17)^{M}	**Placebo** (8.0%)	
Unstable angina					
Atorva (83.7%)					
0.87 (0.57–1.33)^{L}	**Rosuva** (59.8%)				
0.83 (0.51–1.35)^{L}	0.95 (0.58–1.56)^{L}	**Prava** (49.2%)			
0.68 (0.51–0.92)^{M}	0.78 (0.57–1.07)^{M}	0.83 (0.56–1.22)^{L}	**Placebo** (7.3%)		
Heart failure					
Prava (80.6%)					
1.02 (0.54–1.90)^{L}	**Rosuva** (76.1%)				
0.73 (0.56–0.96)^{M}	0.72 (0.41–1.27)^{M}	**Placebo** (28.6%)			
0.65 (0.38–1.09)^{L}	0.64 (0.31–1.31)^{M}	0.88 (0.56–1.38)^{M}	**Atorva** (15.2%)		



Statin drug-level network meta-analyses for benefit outcomes.The Figure presents relative effects (in risk ratio) and 95% CI of statins compared with placebo for each benefit outcome and with their corresponding network plots (*a-h*) of the available direct comparisons. The edges of the network plots are colored according to the average study-level risk-of-bias of trials involved in the direct comparison and weighted according to the number of participants included in the trials. The red, yellow and green respectively represent poor, fair or good quality. The nodes are weighted based on the number of trials included in each comparison. The probabilities beside the statin names are the treatment ranking based on SUCRA and thus the treatments are ordered according the magnitude from left to right. The risk ratio in each cell should be read as the treatment in the column name of a specific cell compared to the treatment in same row to the right. To obtain the risk ratio of the comparisons in the opposite direction, reciprocals should be taken. Quality of the evidence of the drug-level estimates are designated by VL, L, M, and H representing for very low, low, moderate and high, respectively (see Supplement Table 3.2). The statins are identified with their prefix names. CVD, Cardiovascular disease; MI, myocardial infarction; SUCRA, surface under the cumulative ranking curve.

Figure 4

Treatment discontinuation					Network plots
Fluva (81.9%)					
1.18 (0.36–3.90)^{VL}	**Simva** (70.2%)				
1.47 (0.55–3.92)^{VL}	1.24 (0.55–2.83)^{L}	**Lova** (60.9%)			
1.56 (0.58–4.19)^{VL}	1.32 (0.58–3.03)^{VL}	1.06 (0.67–1.67)^{VL}	**Rosuva** (54.6%)		
1.68 (0.66–4.25)^{VL}	1.42 (0.67–3.03)^{L}	1.14 (0.83–1.58)^{L}	1.08 (0.77–1.51)^{M}	**Placebo** (39.7%)	
1.83 (0.69–4.86)^{VL}	1.55 (0.68–3.51)^{L}	1.24 (0.83–1.88)^{L}	1.17 (0.76–1.80)^{L}	1.09 (0.80–1.48)^{L}	**Prava** (26.9%)
1.95 (0.74–5.17)^{VL}	1.66 (0.74–3.70)^{L}	1.33 (0.86–2.05)^{L}	1.25 (0.89–1.76)^{L}	1.16 (0.87–1.55)^{L}	1.07 (0.70–1.63)^{L} **Atorva** (15.5%)
Myopathy					
Rosuva (75.3%)					
1.02 (0.75–1.40)^{L}	**Prava** (75.1%)				
1.16 (0.58–2.31)^{L}	1.13 (0.59–2.17)^{L}	**Lova** (45.0%)			
1.16 (0.88–1.53)^{M}	1.13 (0.98–1.31)^{L}	1.00 (0.53–1.88)^{L}	**Placebo** (38.1%)		
1.32 (0.89–1.94)^{VL}	1.28 (0.97–1.70)^{M}	1.14 (0.57–2.26)^{L}	1.14 (0.86–1.50)^{L}	**Atorva** (16.5%)	
Type 2 diabetes					
Rosuva (80.2%)					
1.06 (0.69–1.61)^{M}	**Atorva** (62.2%)				
1.16 (0.90–1.49)^{M}	1.10 (0.76–1.58)^{M}	**Placebo** (44.1%)			
1.19 (0.71–1.99)^{VL}	1.12 (0.63–2.01)^{L}	1.02 (0.65–1.61)^{L}	**Lova** (43.5%)		
1.32 (0.89–1.97)^{VL}	1.25 (0.79–1.99)^{VL}	1.14 (0.84–1.54)^{VL}	1.12 (0.65–1.93)^{VL}	**Prava** (20.0%)	
Hepatic dysfunction					
Fluva (93.2%)*					
3.17 (0.55–18.11)^{VL}	**Lova** (62.7%)				
4.01 (0.77–20.81)^{VL}	1.26 (0.47–3.37)^{L}	**Rosuva** (54.4%)			
4.78 (0.99–23.15)^{VL}	1.51 (0.64–3.56)^{L}	1.19 (0.68–2.09)^{L}	**Prava** (50.3%)		
5.01 (0.96–26.18)^{VL}	1.58 (0.59–4.26)^{L}	1.25 (0.59–2.67)^{M}	1.05 (0.54–2.02)^{L}	**Atorva** (35.0%)	
5.19 (1.10–24.41)^{VL}	1.64 (0.74–3.65)^{L}	1.30 (0.74–2.28)^{VL}	1.09 (0.80–1.48)^{L}	1.04 (0.58–1.85)^{M}	**Placebo** (31.2%)
Renal dysfunction					
Atorva (76.7%)					
1.13 (0.65–1.95)^{M}	**Rosuva** (65.0%)				
1.29 (0.75–2.19)^{M}	1.14 (1.01–1.29)^{M}	**Placebo** (8.3%)			
All cancers					
Prava (61.7%)					
1.06 (0.87–1.29)^{L}	**Rosuva** (53.4%)				
1.06 (0.91–1.24)^{L}	1.00 (0.89–1.13)^{M}	**Placebo** (48.8%)			
1.10 (0.86–1.39)^{L}	1.03 (0.83–1.28)^{L}	1.03 (0.86–1.24)^{L}	**Atorva** (36.1%)		
Headache and nausea					
Prava (72.8%)					
1.27 (0.49–3.32)^{L}	**Lova** (58.8%)				
1.29 (0.44–3.77)^{VL}	1.02 (0.54–1.92)^{L}	**Rosuva** (51.2%)			
1.39 (0.50–3.82)^{M}	1.09 (0.61–1.96)^{L}	1.07 (0.64–1.79)^{VL}	**Atorva** (40.2%)		
1.46 (0.57–3.76)^{L}	1.14 (0.96–1.36)^{L}	1.13 (0.61–2.08)^{L}	1.05 (0.60–1.84)^{L}	**Placebo** (27.1%)	



Statin drug-level network meta-analyses for harm outcomes.The figure presents relative effects (in risk ratio) and 95% CI of statins compared with placebo for each harm risk and with their corresponding network plots (*a-g*) of the outcomes showing the available direct comparisons. The edges of the network plots are colored according to the average study-level risk-of-bias of trials involved in the direct comparison and weighted according to the number of participants included in the trials. The red, yellow and green respectively represent for poor, fair or good quality. The nodes are weighted based on the number of trials included in each comparison. The probabilities beside the statin names are the treatment ranking based on SUCRA and thus the treatments are ordered according the magnitude from left to right. The risk ratio in each cell should be read as the treatment in the column name of a specific cell compared to the treatment in same row to the right. To obtain risk ratio for comparisons in the opposite direction, reciprocals should be taken. Quality evidences of the drug-level estimates re designated by VL, L, M, and H representing for very low, low, moderate and high, respectively (see Supplement Table 3.2). The statins are identified with their prefix names. * indicates unreliable estimate for the SUCRA that may be obtained from a wider confidence interval of the effect estimates on which the SUCRA computation relies. The statins are identified with their prefix names. SUCRA, surface under the cumulative ranking curve.

some of the specific statins showed reverse effect as well as excluding the all-cause mortality to avoid double counting with CVD mortality. Statins as a class reduced risk of major cardiovascular events by 26% or prevented 14 events per 1000 people over 10 years (RR 0.74, 0.67 to 0.81; I^2 = 49.5; quality, moderate; RD −14, −20 to −9 per 10,000 person-years; 23 trials).

Harm outcomes associated with the use of statins

Treatment discontinuation due to adverse events. None of the class-level or drug-level effects showed a significant effect on treatment discontinuation (Figures 2 & 4). Although not statistically significant, more discontinuation events were observed in the statin groups compared with placebo, except for pravastatin and atorvastatin.

Myopathy. Statins as a class showed statistically significant relative and absolute risk increase of myopathy (RR 1.08, 1.01 to 1.15; I^2 = 0; quality, moderate; RD 13, 2 to 24 per 10,000 person-years; 16 trials). However, none of the specific statins demonstrated a statistically significant effect.

Type 2 diabetes. Neither statins as a class (RR 1.04, 0.91 to 1.19; I^2 = 43.7%; quality, very low; RD 3, −7 to 14 per 10,000 person-years; 6 trials) nor specific statins showed statistically significant differences in effects. However, the observed events and the SUCRA showed that participants randomized to atorvastatin and rosuvastatin had more diabetes events compared with the placebo.

Hepatic dysfunction. Statins as a class increased risk of hepatic dysfunction by 16% (RR 1.16, 1.02 to 1.31; I^2 = 0; quality, low; 12 trials). This was associated with 8 excess hepatic dysfunctions in 1000 people over 10 years (RD 8, 1 to 16 per 10,000 person-years). The specific statins were associated with higher risks, but only the effect of fluvastatin reached at a statistical significance with a five times higher risk compared with placebo.

Renal dysfunction. The relative risk of renal dysfunction was higher with statins as a class compared with placebo, which corresponded to 16 excess events in 1000 people treated with statins over 10 years (RR 1.12, CI 1.00 to 1.26; I^2 = 4.6; quality, moderate; RD 16, 0 to 36 per 10,000 person-years; 4 trials). The drug-level effect of rosuvastatin, but not atorvastatin, was statistically significant.

All cancers. Statins as a class (RR 1.01, 0.93 to 1.09; I^2 = 0; quality, low; RD 1, −7 to 9 per 10,000 person-years; 9 trials) and the individual statins showed no statistically significant risk increase of cancers.

Headache and nausea. Neither the class-level (RR 1.13, 0.97 to 1.31; I^2 = 1.9%; quality, low; RD 20, −5 to 49 per 10,000 person-years; 5 trials) nor the individual statins showed statistically significant increase of headache or nausea risks. Although not statistically significant, the excess risk favors the specific statins compared with placebo.

Inconsistency assessment

The 95% CI of the inconsistency factors of the existing closed-loops (showed in Figures 3 & 4) did not exclude zero implying that there was no observed inconsistency between direct and indirect evidence (see Supplement Table 6).

Sensitivity analyses

Supplement Table 7 presents the detailed results of the random-effect meta-regression for study-level characteristics on each outcome. Most of the factors, including the dose, were not associated with effect differences. Statins may reduce non-fatal MI if LDL cholesterol is elevated (p-value = 0.043), but the effect size was close to the null effect (RR = 0.99). The effect also diminished when we fitted the model on dichotomized levels of LDL (normal vs. high) (p-value = 0.088). Furthermore, exclusion of trials with higher proportion of DM cases, high-risk people, and risk-of-bias as well as trials that tested high-dose statins did not lead to significant differences in the estimates. Only the exclusion of trials that tested high-dose trials diminished the significant effect on renal dysfunction (Table I).

Publication bias

Using funnel plots, we observed possible publication bias for the outcomes non-fatal MI, major CV events, and all-cause mortality. However, these were not supported by Peters test. See Supplement Figure 1 and Supplement Table 8 for detailed results.

Discussion

Our study found that statins as a class had significant relative and absolute effects for primary prevention on most CVD outcomes and all-cause mortality while increasing the risk of some harms. The individual statins did not have same benefit-risk profile. Atorvastatin and rosuvastatin were the most effective, whereas atorvastatin appeared to be the safest statin.

One of the weaknesses of many of the previous meta-analyses on primary prevention is that they analyzed the effect of statins on composite outcomes,[17,39,40] which could potentially mislead clinical decisions and would make it difficult for clinicians and patients to make trade-offs between the specific benefit and harm outcomes.[14-16] Our study estimated effects for the different outcomes individually and found statistically significant effects of statins as a class in reducing risks of non-fatal strokes, non-fatal MI, CVD deaths, and all-cause mortality. However, statins did not show statistically significant risk reduction of fatal MI, fatal stroke, and heart failure, which could be due to sparse events, differences in trial populations,

Table I. Sensitivity analyses testing the impact of excluding trials with specific characteristics

Benefit and harm outcomes	All data	Data with history of CVD excluded	Data with high-dose trials excluded	Data with high proportion of diabetes excluded	Data with high risk-of-bias trials excluded
	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)
Non-fatal MI	0.62 (0.53-0.72)	0.55 (0.45-0.67)	0.68 (0.61-0.76)	0.61 (0.52-0.73)	0.61 (0.51-0.73)
Fatal MI	0.72 (0.50-1.03	NA	0.73 (0.49-1.07)	0.83 (0.55-1.25)	0.68 (0.41-1.13)
Major CV events	0.74 (0.67-0.81)	0.71 0.61-0.82()	0.78 (0.73-0.85)	0.74 (0.66-0.82)	0.74 (0.66-0.82)
Unstable angina	0.75 (0.63-0.91)	0.79 (0.63-0.93)	0.76 (0.63-0.91)	0.76 (0.63-0.91)	0.74 (0.60-0.91)
CVD mortality	0.80 (0.71-0.91)	0.78 (0.65-0.93)	0.82 (0.71-0.94)	0.80 (0.70-0.91)	0.81 (0.71-0.92)
Fatal stroke	0.79 (0.53-1.19)	0.74 (0.49-1.13)	0.79 (0.53-1.19)	0.83 (0.56-1.25)	0.80 (0.53-1.19)
Non-fatal stroke	0.83 (0.75-0.92)	0.72 (0.61-0.83)	0.82 (0.72-0.93)	0.82 (0.73-0.92)	0.80 (0.70-0.91)
Heart failure	0.84 (0.71-1.02)	0.95 (0.74-1.23)	NA	NA	NA
All-cause mortality	0.89 (0.85-0.93)	0.87 (0.81-0.93)	0.90 (0.85-0.94)	0.89 (0.85-0.93)	0.90 (0.86-0.94)
Trt. Discontinuation	1.00 (0.78-1.24)	1.07 (0.84-1.35)	0.98 (0.78-1.22)	1.04 (0.82-1.33)	1.04 (0.82-1.32)
All cancers	1.01 (0.93-1.09)	1.00 (0.92-1.08)	1.04 (0.95-1.14)	NA	1.02 (0.94-1.11)
Type 2 diabetes	1.04 (0.91-1.19)	NA	1.00 (0.87-1.14)	NA	1.03 (0.87-1.22)
Myopathy	1.08 (1.01-1.15)	1.07 (1.01-1.13)	0.10 (1.03-1.20)	1.06 (1.01-1.13)	1.06 (1.00-1.13)
Headache/nausea	1.13 (0.97-1.31)	1.13 (0.97-1.31)	1.13 (0.97-1.32)	0.12 (0.97-1.31)	1.12 (0.97-1.31)
Renal dysfunction	1.12 (1.00-1.26)	NA	1.28 (0.76-2.18)	NA	NA
Hepatic dysfunction	1.16 (1.02-1.31)	1.16 (0.98-1.90)	1.13 (0.95-1.34)	1.15 (1.01-1.32)	1.22 (1.04-1.44)

CVD, Cardiovascular disease; CV events, cardiovascular events; NA, not available (ie, trials with the column characteristics not available); RR, risk ratio; Trt., treatment.

adjudication processes or short trial duration. In addition to these possible reasons, the effect on heart failure could be associated with poor or inconsistent ascertainments or it could be due to causes other than high levels of cholesterol where statins do not have any effect. The effect on fatal stroke may also have resulted from opposite effect direction of statins on different stroke types; i.e., statins could reduce the risk of ischemic but increase the risk of hemorrhagic stroke.[1] Analyzed individually, pravastatin showed rather increased risk on fatal stroke to which hemorrhagic stroke is the major contributor. While this could be due to the play of chance, it needs further investigation because other secondary prevention trials and observational data also suggest that statins increase risk of hemorrhagic stroke due to extensively lowered cholesterol-levels.[1,3,41,42]

Contrary to the most recent systematic review conducted to inform the US Preventive Service Task Force, [17] our data showed statistically significant excess risks of statins as a class on myopathy and renal and hepatic dysfunctions. Nevertheless, the specific statins had greatly varying benefit-harm profiles although the effects did not all reach statistical significance. The individual statins showed risk reduction consistently on most of the CVD outcomes, with atorvastatin and rosuvastatin being the two most effective statins. The harm profile of the statins was diverse, with atorvastatin appearing the safest across all the harm outcomes except diabetes for which atorvastatin as well as rosuvastatin rather showed the highest excess risk. The effect of atorvastatin and rosuvastatin on diabetes could be explained by the fact that these two statins are more potent in reducing absolute reduction in LDL cholesterol compared with the other statins.[43,44] This may lead to an increase of LDL-receptors that damage pancreatic cells causing diabetes.[41] While diabetic patients are more commonly assumed to have a high CVD risk and thus are recommended to take statins,[5-8] our sensitivity analysis did not demonstrate any modifying effect of diabetes. However, it was difficult to examine this using our data because the proportion of diabetes was low in many of the trials.

Relying exclusively on trials for the assessment of harm outcomes may lead to judging statins too favorably. Although the magnitude of the difference is not well known, trials sometimes underestimate harms compared to real world estimates,[9] sometimes due to low power, risk mitigation strategies (e.g. not including patients at increased risks for specific harms),[9,14] insufficient ascertainment or reporting biases of harms.[9,45] In the case of statins, the low quality of evidence on harms in our study also suggests that trials may underestimate the harms. The estimates of increased risk of harms from the trials are substantially lower than estimates from observational studies.[46] Evidence from observational data could complement some gaps of trial data, such as detecting long-term effects, but are at higher risk of bias. Therefore, clinical guideline developers should take none of the evidence sources alone to assess harm outcomes, but consider estimates from trials and observational data.

While our findings show that the relative effect estimates were similar compared to secondary populations,[4,17,39,47] the closeness of the estimates does not necessarily mean similarity in importance of statins for primary and secondary prevention of CVD because the absolute risk differences could be different. Overall, the findings imply that statin recommendation should consider simultaneously absolute CVD risk as well as absolute harm risks of individuals. However the data as well as the methods of the systematic reviews are not sufficient for assessing benefit-harm balance of statins

for individuals. For example, we may easily calculate the benefit-harm balance from the results displayed in Figure 2, which yielded 13 net harm events per 10,000 person-years implying that the harms outweigh the benefits. However, such a naïve calculation is misleading because the different outcomes in the trial population neither could have equal baseline risks to real world populations nor do they have similar importance to patients.[48] Thereby, a comprehensive and quantitative benefit-harm balance assessment taking into account treatment effects, baseline risks, and the importance of different outcomes relative to each other is needed to examine the overall net benefit and to identify people who benefit from statins.[49]

It is worth noting that our findings should be interpreted in view of the following limitations. We considered some trials in our analysis that included participants with a certain level of history of CVD. While risk stratification is important in the context of considering which patients should be treated, all of the trials (except HOPE-3,[50] and JUPITER,[51] which used risk scores and biomarkers, respectively) included participants based on cholesterol levels.[2] While the CVD risk was not identical across all studies, we did not find different relative effects in sensitivity analyses with more restrictive criteria for inclusion in the analysis. Because not all outcomes were reported in each study, the quality of evidence for most statin-specific comparisons was low, which makes it difficult to draw a robust conclusion. We were unable to test inconsistency for some outcomes, especially for most benefit outcomes due to lack of closed loops. On the other hand, while we did not find a statistical indication for inconsistency and intransitivity in the closed-loops available, it is worth noting that the statistical test does not prove the absence of inconsistency. Finally, we depended on reported aggregate data due to the challenge in accessing patient individual data.

Conclusion

Our study found that statins as a class as well as specific statins were effective in preventing cardiovascular events and all-cause mortality in primary prevention populations, but on the other hand increased risk of unwanted side effects. Although most treatment effects for the individual statins had low quality evidence, the available data showed that the individual statins did not have same benefit-harm profiles. Atorvastatin and rosuvastatin appeared to be the most effects and atorvastatin the safest statin across most of the outcomes.

Contributors

MAP and HGY conceived and conceptualized the research idea. HGY and MK performed the screening, full text assessment, quality assessment and data extraction and MAP approved the data. HGY did data analyses, HEA contributed and MAP supervised the analysis. MAP, HGY and HEA framed the results and HGY drafted the manuscript. MAP, HEA and MK made revisions on the draft and approved the final version. MAP supervised the whole study process and is guarantor.

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Appendix. Supplementary data

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