Review

Comparative effects of statins on major cerebrovascular events: a multiple-treatments meta-analysis of placebo-controlled and active-comparator trials

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Summary

Statins are important in the prevention of major cerebrovascular events. Whether, and the extent to which, individual statins differ in terms of their effect on these outcomes has not been studied. The aim of this review was to evaluate the comparative effects of individual statins on major cerebrovascular events. We systematically reviewed 61 trials including 187,038 individuals with, or at risk of developing, cardiovascular disease. We performed pair-wise and multiple-treatments meta-analyses for major cerebrovascular events, in addition to fatal and non-fatal strokes separately. Across all populations, statins were significantly more effective than control in reducing major cerebrovascular events [odds ratio (OR): 0.82, 95% CI: 0.77, 0.87] with no differences among individual statins. Statins were also effective in patients with established cardiovascular disease (OR: 0.83, 95% CI: 0.75, 0.91) and in those without (OR: 0.80, 95% CI: 0.71, 0.91). Considering individual statins, significant risk reductions were achieved with atorvastatin (OR: 0.74, 95% CI: 0.63, 0.85), pravastatin (OR: 0.86, 95% CI: 0.76, 0.97) and simvastatin (OR: 0.75, 95% CI: 0.62, 0.88) as compared with control on major cerebrovascular events across all populations. Statins led to significant reductions in the risk of non-fatal strokes (OR: 0.77, 95% CI: 0.71, 0.85) but not of fatal strokes (OR: 0.96, 95% CI: 0.80, 1.15). Findings were not sensitive to dose differentials of individual statins across the trials. No significant heterogeneity or inconsistency was detected. Statins significantly reduce the incidence of major cerebrovascular events as compared with control. Our analysis provided evidence to confirm the class effect of statins in preventing major cerebrovascular events.

Introduction

Stroke is among the leading causes of death and disability worldwide. Annually, ~16 million incident strokes occur globally, causing an estimated total of 5.7 million deaths.1 About half of stroke survivors experience physical or cognitive impairment, impacting their physical function, social function and activities of daily living.2 In addition to its health impact, stroke is costly to individuals, their families and the wider society—with an economic burden amounting to an estimated $65.5 billion in the USA alone.3,4
Although the evidence from epidemiological studies remains inconclusive,5,6 lipid management is an important milestone in the prevention of stroke.7 Hydroxymethylglutaryl-CoA (HMG-CoA) reductase inhibitors, also known as statins, effectively reduce the risk of strokes.8,9 Recent reviews and meta-analyses of randomized controlled trials have confirmed the considerable benefits of statins in the prevention of strokes among individuals with a history of established cardiovascular disease.10–15 Previous meta-analyses showed that statins effectively reduce the risk of stroke in the elderly,16,17 among diabetics18,19 and in individuals with no established cardiovascular disease.20–22 According to analyses of individual patient-level data from different trials, there appear to be a significant trend towards greater proportional reductions in stroke being associated with greater mean absolute low-density lipoprotein (LDL) cholesterol reductions.23 Indeed, in direct comparisons of different dosing regimens, high-dose statin therapy reduces the risk of stroke to a greater extent compared with standard doses.24

An important question that remains unanswered in previous meta-analyses is whether individual statins are different in terms of their effect on the risk of stroke in individuals with or without a history of established cardiovascular disease. Earlier meta-analyses did not address this question in part because their focus was to establish the class effect of statins over control treatment on the basis of placebo-controlled trials. Incidence of cerebrovascular events was not an endpoint of interest in previous reviews that compared statins head-to-head in network meta-analyses.21,25–27 Only one review indirectly compared statins (atorvastatin, pravastatin and simvastatin) in terms of major cerebrovascular events but this study was based on a small number of placebo-controlled trials, without making use of the valuable information from active-comparator trials of statins.28

The objective of our study was to systematically review the placebo-controlled and active-comparator trials of statins, and perform a multiple-treatments meta-analysis of individual statins in terms of their effect on major cerebrovascular events across all populations, in addition to secondary and primary prevention of cardiovascular disease separately.

Methods

Systematic review methods

We searched MEDLINE, EMBASE, Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Trials to identify studies published between 1 January 1985 and 1 January 2011. To comprehensively identify the active-comparator trials that were not included in previous meta-analyses of placebo-controlled trials, we used the search terms ‘atorvastatin’, ‘fluvastatin’, ‘simvastatin’, ‘lovastatin’, ‘pravastatin’, ‘rosuvastatin’, ‘cholesterol’, ‘cardiovascular disease’ and ‘HMG-CoA reductase inhibitors/therapeutic use’. Two researchers (BT and HT) independently performed abstract, title and full-text screening. A third researcher approved study selection (HN).

We included open-label and double-blind randomized controlled trials comparing one statin with another statin at therapeutic dose or with control (placebo, diet or usual care) for adults with, or at risk of developing, cardiovascular disease. We included trials of atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin and simvastatin if they had more than 50 participants per trial arm, lasted longer than 4 weeks and reported major cerebrovascular events. Both fixed dose and titration designs were included. Per pre-defined criteria, we excluded trials conducted in patients with renal insufficiency.

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

The primary outcome was major cerebrovascular events. In line with previous meta-analyses, we defined the composite of major cerebrovascular events as fatal- and non-fatal strokes and transient ischaemic attacks. As secondary endpoints, we evaluated fatal- and non-fatal strokes separately. For the analysis on non-fatal strokes, transient ischaemic attacks were not included.

We used a structured form to extract data on trial (reference, publication year, design features such as blinding and dosing regimen) and patient population characteristics (age, baseline LDL cholesterol, cardiovascular risk factors), and outcome measures. One researcher extracted data (HN) and another independently checked for accuracy (BT). To ensure quality, we checked the consistency of extracted data with previously published meta-analyses.

Statistical analysis methods

We first qualitatively summarized included trials, describing the types of direct and indirect comparisons. For each pair-wise comparison between two
statins, we calculated the odds ratio (OR) with a 95% confidence interval. First, we performed classical pair-wise meta-analyses to synthesize studies that compared the same two statins using the DerSimonian Laird (random-effects) method.\textsuperscript{29} The random-effects meta-analysis model assumed the observed estimates of treatment effect could vary across studies because of real differences in the treatment effect in each study and sampling variability (chance).\textsuperscript{30} Forest plots of the relative treatment effects from the individual trials and pair-wise meta-analyses were visually inspected to search for heterogeneity. We also statistically inspected heterogeneity using the $I^2$ statistic, which was used to estimate the percentage of total variation among studies that can be considered to be due to heterogeneity. We used rough thresholds of 25, 50 and 75% to define low, moderate and high heterogeneity, and investigated moderate and high heterogeneity by inspecting trial-level variables that may explain observed differences.

To determine the comparative effects of statins, we conducted multiple-treatments meta-analyses.\textsuperscript{31} In these analyses, study-level relative treatment effects were combined using random-effects models within a Bayesian framework using Markov chain Monte Carlo methods.\textsuperscript{32,33} We used the model developed by Dias et al.\textsuperscript{34} for the National Institute of Health Clinical Excellence Decision Support Unit in the UK. This was based on modelling the outcomes in every treatment group of every study, and specifying the relations among the relative effects across studies making different comparisons.

To obtain a comprehensive estimate of the effect of statins in major cerebrovascular events, the multiple-treatments meta-analysis pooled all primary and secondary prevention trials in addition to trials with mixed patient populations. This analysis included all placebo-controlled and active-comparator trials eligible for inclusion in this review. We also performed separate analyses for the primary and secondary prevention populations, as categorized by the criteria mentioned earlier. For the base case analysis, we included trials at all doses. We separately evaluated the impact of dose differentials across the trials by excluding high-dose trials (80 mg/day for atorvastatin, fluvastatin, lovastatin, simvastatin and $\geq$40 mg/day for rosuvastatin) in a sensitivity analysis and evaluating the benefits of statins at comparable doses.

Results

We included 61 trials (Figure 1), totalling 187 038 individuals. Overall, the average trial duration was 140 weeks (2.7 years). There were 51 two-armed placebo-controlled trials and the remaining 10 were two- or multi-armed active-comparator trials. There were 28 secondary prevention and 12 primary prevention trials. The remaining were in individuals who experienced acute coronary syndromes ($n$=8) and those with mixed populations ($n$=13). Of the 15 possible pair-wise comparisons between the six statins, only five were available for the major cerebrovascular events outcome. No trial directly compared all six statins to each other (Figure 2). Characteristics of included trials are summarized in Supplementary Table S1.

Benefit of statin therapy vs. control: findings of the pair-wise meta-analyses

In the pair-wise meta-analysis of statin therapy vs. control across all populations, 171 731 individuals contributed information on 4533 events. Overall, statin therapy was associated with a reduction in the risk of major cerebrovascular events (OR: 0.82, 95% CI: 0.77, 0.87) when compared with control (Figure 3). Among statins, atorvastatin, pravastatin and simvastatin were associated with a significant reduction in major cerebrovascular events compared with the control, while atorvastatin, fluvastatin, lovastatin and rosvuastatin were not.

In the secondary prevention population, statin therapy was associated with a significant reduction in major cerebrovascular events (OR: 0.83, 95% CI: 0.75, 0.91) when compared with control (Figure 3). Only atorvastatin resulted in significantly fewer events as compared with control in this population.

In the primary prevention population, statin therapy was associated with a significant reduction in major cerebrovascular events (OR: 0.80, 95% CI: 0.71, 0.91) (Figure 3). In this population, only atorvastatin and rosvuastatin had sufficient evidence for a significant benefit on major cerebrovascular events, while atorvastatin, fluvastatin, pravastatin did not. Simvastatin did not have any trials in primary prevention.

Overall, statistical heterogeneity in pair-wise comparisons of statin therapy vs. control in all-cause mortality was low in analyses of primary prevention ($I^2$: 9.2%), secondary prevention ($I^2$: 0.0%) and all populations together ($I^2$: 0.0%). We observed high heterogeneity in pair-wise comparisons of rosvuastatin vs. control ($I^2$: 8.1.3%), mainly as a result of the differences in patient populations between JUPITER (primary prevention), GISSI-HF and CORONA (heart failure).
61 trials when primary and secondary prevention populations within trials are considered separately.

Figure 1. Flow diagram of study identification and selection.

Figure 2. Network diagram of available comparisons.
Comparative benefits of statins on major cerebrovascular events: findings of the multiple-treatments meta-analyses

In addition to the trials included in the pair-wise comparisons of statin therapy vs. control, there were 11 direct head-to-head statin comparisons, providing information on 20,072 participants. In the multiple-treatments meta-analysis, 61 placebo-controlled and active-comparator trials provided information for major cerebrovascular events analysis. In total, 187,038 individuals were included in this analysis, which provided information on 4,913 events.

In this analysis, there were no significant differences among statins in terms of major cerebrovascular events when all trials of primary prevention, secondary prevention and mixed patient populations were pooled (Figure 5). There were also no statistical differences among individual statins in terms of reducing the risk of major cerebrovascular events in primary and secondary prevention of cardiovascular disease.

The findings of the multiple-treatments meta-analysis were not sensitive to dose differentials across trials (Figure 4). When high-dose trials were excluded from the analysis, estimated comparative benefits of individuals were not materially different and there were no statistically meaningful differences between statins (Figure 5).

Comparative benefits of statins on non-fatal and fatal strokes

Across all populations, statins were effective in reducing the incidence of non-fatal strokes (OR: 0.77, 95% CI: 0.71, 0.85) as compared with control treatment (Figure 6). Only rosuvastatin (OR: 0.69, 95% CI: 0.44, 0.99) and simvastatin (OR: 0.69, 95% CI: 0.45, 0.96) had sufficient statistical power to show superiority over control treatment across all populations. Statins were not effective in reducing the risk of fatal strokes (OR: 0.96, 95% CI: 0.80, 1.15) although atorvastatin was independently superior to control treatment in preventing fatal strokes (OR: 0.49, 95% CI: 0.30, 0.80). There were no statistical differences between the individual statins.

Discussion

This multiple-treatments meta-analysis of 187,038 individuals provides evidence on the statistically and clinically meaningful benefits of statins in reducing the risk of major cerebrovascular events in both primary and secondary prevention.

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**Figure 3.** Multiple-treatments meta-analysis findings: comparative effects of statins compared with control on major cerebrovascular events.

**Figure 4.** Sensitivity analysis findings: comparative effects of statins compared with control on major cerebrovascular events.
individuals with or without established cardiovascular disease. Overall, statins were associated with an 18% reduction in relative odds of major cerebrovascular events across all populations. Benefits of statins in reducing the relative odds of major cerebrovascular events by ~18% were consistent across primary and secondary prevention populations. Across all populations, given the lack of statistical difference between different statins, our analysis provided evidence to confirm the class effect of statins in preventing major cerebrovascular events.

Our overall findings reinforce and extend the results of previous meta-analyses on statin therapy. Previous reviews elucidated the importance of lipid management with statins in the prevention of strokes and found consistent evidence that would warrant advocating statin use for the prevention of incident strokes. Clinical practice guidelines also recommend statin therapy in secondary prevention of stroke for patients with non-cardioembolic stroke. As SPARCL was the only trial that investigated the benefits of statins for the secondary prevention of strokes in individuals with a history of transient ischaemic attack or stroke, we did not explore the comparative benefits of statins in this population separately. Our base-case analysis in individuals with or without a history of established cardiovascular disease did not detect significant differences among individual statins. However, it remains a possibility that there are actual differences between individual statins which could not be detected in our analysis.

Indeed, although there were no statistical differences, our review suggested that the randomized trial evidence base for some statins was more robust and consistent than it was for others. This was particularly the case for atorvastatin and simvastatin. There was essentially no detectable heterogeneity across the trials of atorvastatin and simvastatin with consistent evidence for their benefits in the prevention of major cerebrovascular events. Unlike simvastatin that did not have evidence in individuals with no history of cardiovascular disease, atorvastatin was able to reach statistical significance in both primary and secondary prevention populations (as well as across all populations) as compared with control treatment. Although atorvastatin led to a significant reduction in the risk of fatal strokes, unexpectedly, it was not associated with significantly fewer non-fatal strokes as compared with control. Trial evidence for fluvastatin and lovastatin was inconsistent across individuals with and without cardiovascular disease and there was large uncertainty around the benefits of these agents in the prevention of strokes. Finally, there was substantial heterogeneity in the evidence base for rosuvastatin. Given the small number of trials, JUPITER appeared to drive the pooled estimates for rosuvastatin, specifically for individuals without a history of cardiovascular disease.

In addition to pair-wise meta-analyses that compared statins with control treatment, we also performed multiple-treatments meta-analysis, which is a relatively new method that differs from pair-wise meta-analysis by incorporating data from both direct (from head-to-head comparisons within trials) and indirect (from comparisons between trials) sources of evidence. Using this approach, we combined the results of placebo-controlled and active-comparator trials, allowing for more informed estimates of the relative effect of individual statins that have not been compared head-to-head in clinical trials. Our analysis differed from previous multiple-treatments meta-analyses in two important aspects. First, our review incorporated data from a comprehensive list of trials irrespective of placebo or active controls. Second, we provided comparative estimates separately for populations in primary and secondary prevention of cardiovascular disease.
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. There were only a few head-to-head trials of statins that were prospectively designed to capture differences in clinical outcomes as primary endpoints. Second, as a multiple-treatments meta-analysis combining direct and indirect sources of evidence, it remains a possibility that potential imbalances in the occurrence of effect modifiers across the contrasts impacted the results, potentially confounding the comparative estimates between statins.

In spite of these limitations, this study has important methodological strengths. Our review is the largest meta-analysis on the benefits of statin therapy on cerebrovascular events to date. We included 11 direct head-to-head statin comparisons, providing information on additional 20,072 individuals that were not considered in prior meta-analyses on strokes. Our statistical models were appropriate for the evidence base as we did not detect any significant heterogeneity in the trial network. Although there was no considerable heterogeneity, we still used a random-effects model to take into account potential unexplained heterogeneity across the studies.

**Supplementary data**

Supplementary material is available at *QJM* online.

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**Conflict of interest:** Dr Fleurence is an employee of the Patient-Centered Outcomes Research Institute (PCORI). The views expressed in this article do not necessarily represent those of PCORI.

**References**