Lipid Lowering Therapy, Low-Density Lipoprotein Level and Risk of Intracerebral Hemorrhage − A Meta-Analysis

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Background: The association of lipid lowering therapy and intracerebral hemorrhage risk is controversial. *Methods:* We performed a cumulative meta-analysis of lipid lowering trials that reported intracerebral hemorrhage. Statin, fibrate, ezetimibe, PCSK9, and CETP trials were included. We explored whether the association of lipid lowering therapy and risk of intracerebral hemorrhage may vary by baseline low-density lipoprotein (LDL) level, mean change in LDL or baseline cardiovascular risk of population. *Results:* Among 39 trials (287,651 participants), lipid lowering therapy was not associated with a statistically significant increased risk of intracerebral hemorrhage (ICH) in primary and secondary prevention trials combined (odds ratio [OR], 1.12; 95% confidence interval [CI], .98-1.28). Lipid lowering was associated with an increased risk of ICH in secondary prevention trials (OR, 1.18; 95% CI, 1.00-1.38), but not in primary prevention trials (OR, 1.01; 95% CI, .78-1.30), but the test for interaction was not significant (*P* for interaction = .31). Meta-regression of baseline LDL or difference in LDL reduction between active and control did not explain significant heterogeneity between studies for ICH risk. Of 1000 individuals treated for 1 year for secondary prevention, we estimated 9.17 (95% CI, 5.78-12.66) fewer ischemic strokes and .48 (95% CI, .06-1.02) more ICH, and a net reduction of 8.69 in all stroke per 1000 person-years. *Conclusions:* The benefits of lipid lowering therapy in prevention of ischemic stroke greatly exceed the risk of ICH. Concern about ICH should not discourage stroke clinicians from prescribing lipid lowering therapy for secondary prevention of ischemic stroke.

Key Words: Stroke—intracerebral hemorrhage—lipid lowering therapy—meta-analysis

Introduction

Randomized controlled trials have shown that low-density lipoprotein cholesterol (LDL-C) lowering with statins (3-hydroxy-3-methylglutaryl−coenzyme A reductase inhibitors) reduce the risk of ischemic stroke,[1] but there is controversy about whether lipid lowering agents increase the risk of intracerebral hemorrhage (ICH).[2,3] While epidemiological studies report a positive association between

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high serum LDL-C and ischemic stroke,[4-6] the association with LDL-C and ICH appears inverse.[6-8]

Prior meta-analyses, evaluating the association of statin therapy and ICH, have reported no overall increase in risk of ICH,[10] although one large trial reported an increased risk of ICH among those randomized to high-dose statin therapy.[11] Proposed mechanisms, through which an increased risk of ICH may be mediated, include low levels of LDL-C weakening the endothelium of intracerebral arteries, causing hemorrhagic stroke in the setting of hypertension.[6] Another potential mechanism is the pleiotropic antiplatelet/antithrombotic effect of lipid lowering therapies, especially statins.[12] To date, meta-analyses of randomized controlled trials evaluating statin therapy, have reported on the risk of ICH, but have not explored all lipid lowering therapies and whether baseline LDL, or cardiovascular risk changes the association of all lipid lowering therapies with ICH.

In this meta-analysis of lipid lowering phase III trials, we sought to determine whether lipid lowering therapy increased the risk of ICH overall, and within prespecified subgroups of participants (ie, those with lower baseline LDL-C level, larger magnitude of LDL reduction and prior cardiovascular disease).

Methods

Cumulative Meta-Analysis

We extracted data from 2 previous meta-analyses: one of randomized controlled trials of statin therapy for cardiovascular prevention, reporting ICH outcomes[10] and the other of randomized controlled trials of fibrates for prevention of cardiovascular outcomes, reporting ICH.[13] We limited our search to dates not included in these reviews (2012-2018) and repeated primary data extraction for all papers to confirm accuracy.

Selection Criteria

We performed a systematic review, adhering to the PRISMA guidelines,[14] to select randomized controlled trials of lipid lowering therapy that reported hemorrhagic stroke on follow-up. We included all trials with: subjects greater than 18 years, lipid lowering therapy and hemorrhagic stroke outcome data. We limited our search to published, peer-reviewed studies in English.

Search Strategy

We developed a search strategy for the PUBMED database. The database was searched from January 2012 to May 2018. Four reviewers (C.J., S.R., M.C., and R.M.) independently screened titles and abstracts. Full texts were sourced for relevant articles. Inclusion criteria were assessed independently, and the final list was agreed by consensus. We also screened the reference list of similar review articles and earlier published meta-analyses obtained in our search.

Data Extraction

For each study, we extracted the title, year of publication, active and control numbers, major bleeding and stroke outcome data. Stroke outcome was classified as either ischemic or hemorrhagic, if available. We also collected baseline mean LDL-C, mean low-density lipoprotein cholesterol, and change in LDL-C from baseline to follow-up (if available). We labeled the studies as either primary or secondary prevention. We used a definition of greater than 50% baseline cardiovascular disease (stroke, myocardial infarction) as our secondary prevention cut-off. Reviewers independently extracted data, compared for inconsistencies, and merged into a final data set.

Data Synthesis and Analysis

We present a descriptive analysis of each individual trial and summarize this analysis in both table (Supplementary Table I) and figures (Figs 1-3). We calculated odds ratio (OR) and 95% confidence intervals (CI) from individual studies. Weighted pooled treatment effects were calculated using a random effects model. The variability across studies due to heterogeneity was estimated with the I^2 statistic. We tested for an interaction between subgroup relative risks by dividing the difference in log relative risk by its standard error.[15] Statistical analysis was performed using the Metafor package[16] on R Statistical Software (V3.4.3).

Results

In total, 39 randomized controlled trials were eligible that recruited 287,651 participants and reported 27,376 deaths, 7092 ischemic strokes, and 1035 ICHs. Our updated search results found 1026 studies, 974 were excluded after title and abstract screening, 29 were excluded after full text review including 18 studies that did not report ICH, leaving 5 studies for inclusion (Supplementary Figure 1). Thirty-one were trials of statins,[17-27,11,28-47] 4 were studies of fibrates,[48-51] 2 were studies of statins in combination with ezetimibe,[49,52] one was a study of a proprotein convertase subtilisin/kexin type 9 inhibitor[53] and one was a study of a cholesteryl ester transfer protein inhibitor.[54] The mean follow-up across all studies was 3.97 years. The mean age was 62.4 years in the active group and 62.4 years in the control group. 38,750 (26.9%) patients were female in the active group and 37,949 (26.4%) were female in the control group.

Meta-Analysis of ICH

In all trials, ICH occurred in 549 (.38%) patients in the active group and 486 (.34%) patients in the control group

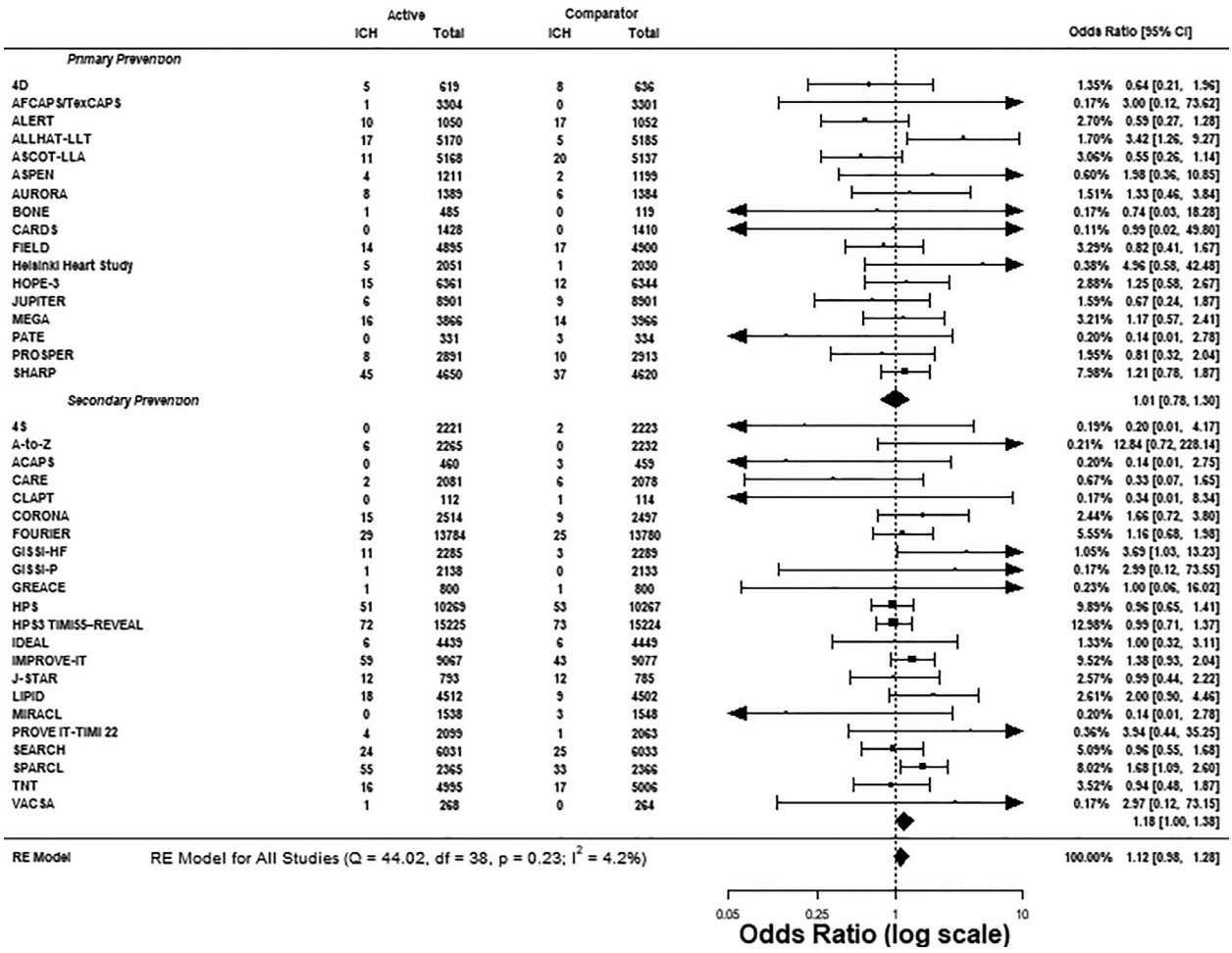

Figure 1. *Lipid lowering and intracerebral hemorrhage. Forest plot for intracerebral hemorrhage. Forest plot showing the effect of lipid lowering therapy on intracerebral hemorrhage. The forest plot is divided in 2 sections according to type of prevention trial (1) primary and (2) secondary. The squares and bars represent the mean values and 95% confidence intervals of the effect sizes, while the size of the squares reflects the weight of the studies. The combined effects (subsummary and summary) appear as diamonds and the vertical dashed line represents the line of no effect.*

(OR, 1.12; 95% CI, .98-1.28; Fig 1). The *P* for heterogeneity was .23, $I^2 = 4.2\%$, Q = 44.02, and degrees of freedom = 38.

Meta-Analysis of ICH (Primary and Secondary Prevention)

We repeated the analysis, separately, for primary and secondary prevention trials. Active therapy was associated with an increased risk for ICH in secondary prevention trials (OR, 1.18; 95% CI, 1.00-1.38; Fig 1). The *P* for heterogeneity was .2646, $I^2 = 5.36\%$, Q = 24.6078, and degrees of freedom = 21. Active therapy was not associated with an increased risk for ICH in primary prevention trials (OR, 1.01; 95% CI, .78-1.30; Fig 1). The *P* for heterogeneity was .31, $I^2 = 12.44\%$, Q = 18.3126, and degrees of freedom = 16. The *P* for interaction was not significant (.31).

Meta-Analysis of Ischemic Stroke and All-Cause Mortality

Ischemic stroke occurred in 3213 (2.23%) patients in the active group and 3879 (2.7%) patients in the control group. Lipid lowering therapy was associated with a significant decrease in ischemic stroke (OR, .82; 95% CI, .76-.88) and all-cause mortality (OR, .94; 95% CI, .90-.98; Figs 2 and 3).

Meta-Regression — Baseline LDL, LDL Reduction (Active) and Difference in LDL Reduction Between Active and Control

Three meta-regressions were performed to examine whether any between-study heterogeneity could be explained by baseline LDL-C value, mean LDL-C difference pre- and post-treatment and by the difference in mean LDL-C reduction between active and control treatments. The regression coefficient for baseline LDL-C was not statistically significant at .0005 (95% CI, −.0044 to .0054, *P* = .8323, $I^2 = 7.45\%$; Fig 3). The regression coefficient for mean LDL-C difference was small and not statistically significant at .0039 (95% CI, −.0050 to .01280, *P* = .3914, $I^2 = .00\%$) (Supplementary Figure 3). The regression coefficient for difference in LDL-C reduction was

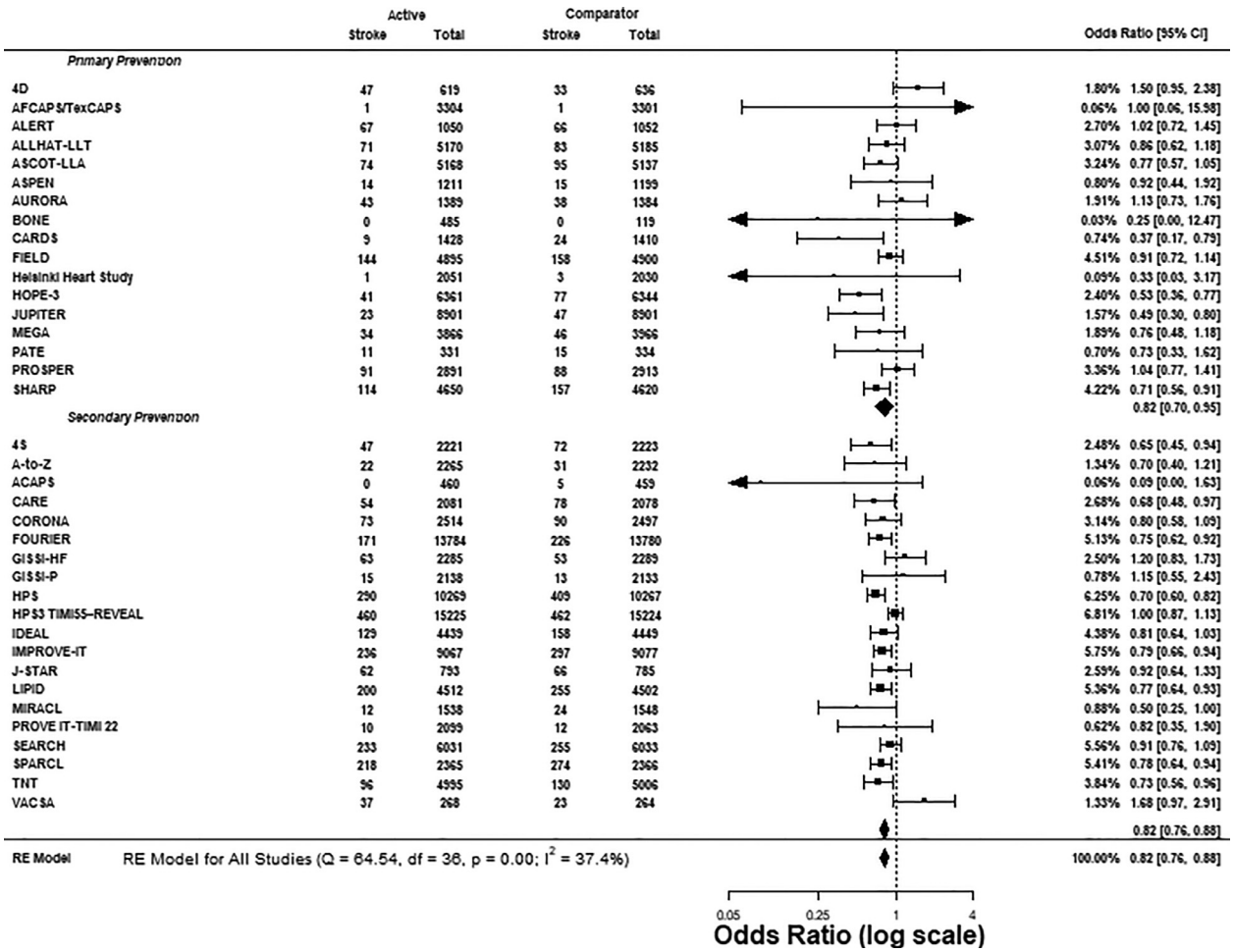

Figure 2. *Lipid lowering and ischemic stroke. Forest plot for ischemic stroke. Forest plot showing the effect of lipid lowering therapy on ischemic stroke. The forest plot is divided in 2 sections according to type of prevention trial (1) primary (2) secondary. The squares and bars represent the mean values and 95% confidence intervals of the effect sizes, while the size of the squares reflects the weight of the studies. The combined effects (subsummary and summary) appear as diamonds and the vertical dashed line represents the line of no effect.*

small and not statistically significant at .0011 (95% CI, −.0080 to .0103, $P = .8068$, $I^2 = 7.88\%$; Supplementary Figure 4).

Discussion

Main Findings

We performed a systematic review and meta-analysis of all randomized controlled trials of lipid lowering therapy to investigate the relationship between lipid lowering and ICH. We did not find a statistically significant increased risk of ICH with lipid lowering overall (OR, 1.12; 95% CI, .98-1.28), but on subgroup analysis of trials, secondary prevention was significant for lipid lowering and ICH risk in secondary prevention trials (OR, 1.18; 95% CI, 1.00-1.38), however, the P for interaction was not significant (.31). Lipid lowering therapy was associated with a statistically significant reduced risk of ischemic stroke (OR, .82; 95% CI, .76-.88). An additional meta-regression analysis was performed: baseline LDL (active), difference in LDL reduction (active) or difference in LDL reduction between active and control did not explain significant heterogeneity between studies for ICH risk.

Prior meta-analyses have not reported an increased risk of ICH with lipid lowering,[1,10,55] but these only included statin trials. In contrast, we included trials of all lipid lowering therapies on the premise that lower LDL levels may increase the risk of ICH, as suggested by epidemiologic studies,[6-8] and may not be related to a class effect. Therefore, our work builds on these studies by adding data from additional statin trials since 2012 (2), lipid lowering fibrate trials (4), proprotein convertase subtilisin/kexin type 9 inhibitors (1), cholesteryl ester transfer protein inhibitors (1) and a meta-regression of baseline LDL, LDL reduction (active), and LDL reduction between active and control.

The ICH risk becomes more apparent with an increased event rate, this occurs in 2 scenarios, one, when there is a higher risk of bleeding, that is, secondary prevention higher risk population and two, large studies.

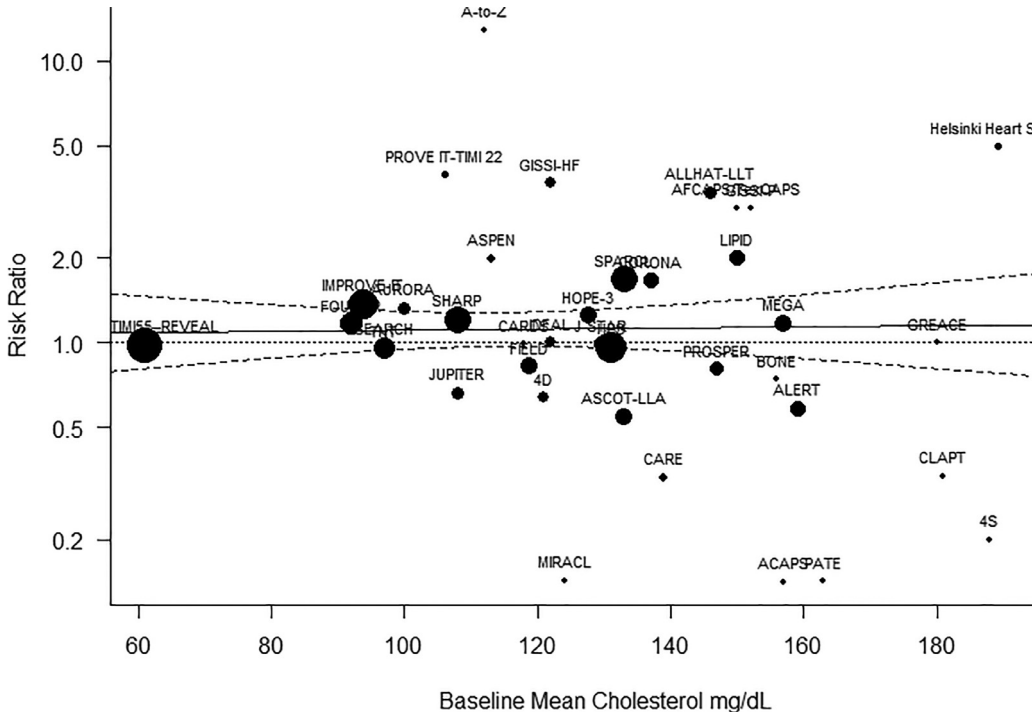

Figure 3. *Meta-regression scatterplot – baseline mean LDL (active) and intracerebral hemorrhage. A scatterplot of the risk ratio for each study by baseline LDL cholesterol (predictor). Each study is represented by a circle. The circle sizes are proportional to the inverse of the standard errors (ie, larger/more precise studies are shown as larger points). The solid line represents the predicted average risk ratio as a function of baseline LDL cholesterol (predictor). The dashed lines represent the 95% confidence interval.*

Supplementary Figure 5 demonstrates these 2 scenarios by showing a linear association between ICH event rates and ischemic stroke rates, which is expected and consistent with other epidemiological observations and relates to common risk factors for ischemic stroke and ICH.

There is uncertainty and reluctance to continue lipid lowering medications immediately postacute stroke.[9] The 2013 ACC/AHA guidelines only give statin prescribing a moderate IIa rating.[56] To illustrate how our findings apply to everyday clinical practice, we applied the relative risk of lipid lowering on ICH (1.12) to the absolute baseline risk of ICH from the control group of our meta-analysis (.34%). The corresponding Number Needed to Harm for ICH with lipid lowering was 2451 (95% CI, 1158-20875). We then applied the relative risk of lipid lowering on ischemic stroke (.82) to the baseline risk of ischemic stroke from the control group of our meta-analysis (2.7%). The corresponding Number Needed to Treat for preventing ischemic stroke with lipid lowering was 206 (95% CI, 150-328). This means, of 1000 individuals treated for 1 year with lipid lowering therapy, we estimated 9.17 (95% CI, 5.78-12.66) fewer ischemic strokes and .41 (95% CI, .05-.86) more ICH, and a net reduction of 8.77 in all stroke per 1000 person-years. We were unable to identify a clinical scenario that would discourage stroke clinicians from prescribing lipid lowering therapy.

Strengths and Limitations

The definition of ICH varies between clinical studies and failure to classify correctly could lead to a nondifferential misclassification bias. Eighteen studies did not report ICH outcome data and had to be excluded from the analysis, introducing a possible reporting bias. There was clinical heterogeneity between the participants in the selected trials, as this was not an individual participant level meta-analysis, we were unable to consider prior history of ICH. Strengths of this systematic review include the inclusion of 5 classes of lipid lowering drugs and subgroup analysis by prevention type and combining the relative risk reduction of lipid lowering and ICH with the absolute risk of ICH which should provide some level of reassurance to physicians with regards to the risk-benefit profile of lipid lowering in stroke patients.

Implications

In conclusion, lipid lowering therapy is not associated with a statistically significant increased risk of ICH overall. Baseline LDL level, change in LDL post-treatment or difference in LDL reduction between active and control are not associated with a statistically significant increased risk of ICH.

In the general population, the benefits of lipid lowering therapy in prevention of ischemic stroke greatly exceed the risk of ICH.

Contributors

C.J., S.R., M.C., and R.M. were responsible for data collection. C.J. performed the analysis. All authors contributed to data interpretation and critical revision of the report.

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The corresponding author certifies that no other persons have made substantial contributions to the research and/or manuscript.

Disclosures

All authors declare no competing interests.

Supplementary Materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jstrokecerebrovasdis.2019.02.018.

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