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ORIGINAL RESEARCH

Lipid-Lowering Therapy and Risk of Hemorrhagic Stroke: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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BACKGROUND: There is debate over whether statins increase risk of hemorrhagic stroke, so we assessed current evidence, including data from new statin trials and trials of nonstatin low-density lipoprotein-cholesterol (LDL-C)– and triglyceride-lowering therapies.

METHODS AND RESULTS: We performed a systematic review of large randomized clinical trials (≥1000 patients with ≥2 years follow-up) of LDL-C–lowering therapy (statin, ezetimibe, and PCSK-9 [proprotein convertase subtilisin/kexin type 9] inhibitor) and triglyceride-lowering therapy (omega-3 supplements and fibrate) that reported hemorrhagic stroke as an outcome. We searched MEDLINE, Embase, and Cochrane Library up to July 2, 2021 and updated a meta-analysis of cardiovascular statin trials published in 2012. Among our several subgroup analyses, we looked at difference depending on stroke status and also depending on age. We identified 37 trials for LDL-C lowering (284 301 participants) and 11 for triglyceride lowering (120 984 participants). Overall, we found a higher risk of hemorrhagic stroke for LDL-C lowering, risk ratio (RR) 1.16 (95% CI, 1.01–1.32, P=0.03). For statins (33 trials, 216 258 participants), RR=1.17 (95% CI, 1.01–1.36); for PCSK-9 inhibitors (2 trials, 46 488 participants), RR=0.86 (95% CI, 0.43–1.74); and for ezetimibe (2 trials, 21 555 participants), RR=1.14 (95% CI, 0.64–2.03). In statin trials of patients with previous stroke/transient ischemic attack, RR was 1.46 (95% CI, 1.05–2.04), and in trials with mean age ≥65 years old, RR=1.34 (95% CI, 1.04–1.73) (P_{int}=0.14 and P_{int}=0.23 respectively); for triglyceride lowering (11 trials, 120 984 participants), RR=1.05 (95% CI, 0.86–1.30).

CONCLUSIONS: We found evidence for a small increased risk of hemorrhagic stroke events with LDL-C–lowering therapies but no clear evidence for triglyceride-lowering therapies.

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Key Words: hemorrhagic stroke ■ intracerebral hemorrhage ■ lipid-lowering therapy ■ nonstatin ■ statin

See Editorial by Selim.

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CLINICAL PERSPECTIVE

What Is New?

- Risk of hemorrhagic stroke is slightly increased with low-density lipoprotein cholesterol–lowering therapies, regardless of preexisting cerebrovascular disease.
- Currently available data for statins provide relatively strong evidence for a harmful effect. For nonstatin therapies, such as ezetimibe or PCSK-9 (proprotein convertase subtilisin/kexin type 9) inhibitors, the evidence is too weak to draw conclusions regarding a potential increase in risk.
- There is no evidence of increased risk of hemorrhagic stroke with triglyceride-lowering therapies.

What Are the Clinical Implications?

- Clinicians and patients should seek to balance the absolute benefit of lipid-lowering therapies for reducing ischemic events against their potential small increased risk of hemorrhagic stroke.

Nonstandard Abbreviations and Acronyms

CTTC	Cholesterol Treatment Trialists' Collaboration
HS	hemorrhagic stroke
ICerH	intracerebral hemorrhage
LLT	lipid-lowering therapy
PCSK9-inhibitor	proprotein convertase subtilisin/kexin type 9 inhibitor
SPARCL	Stroke Prevention by Aggressive Reduction in Cholesterol Levels

Though the benefits of lipid-lowering therapies (LLTs) are widely demonstrated, it is unclear whether statins increase the risk of hemorrhagic stroke (HS).[1] SPARCL (Stroke Prevention by Aggressive Reduction in Cholesterol Levels; all trials' abbreviations are listed in Table S1)[2–51] was the first large trial to report a possible association between statin use and HS risk in a population with previous stroke or transient ischemic attack (TIA).[45] SPARCL showed atorvastatin was superior to placebo in reducing the primary end point of nonfatal or fatal stroke (11.2% versus 13.1%, hazard ratio [HR], 0.84 [95% CI, 0.71–0.99], P=0.03).[45] As expected, risk of ischemic stroke was lower (HR, 0.78 [95% CI, 0.66–0.94]), but risk of HS unexpectedly increased (HR, 1.66 [95% CI, 1.08–2.55]).[45] Similarly, in The Treat Stroke to Target Trial, patients with stroke/TIA exhibited a pattern of increased risk of intracranial hemorrhage (1.3% versus 0.9%, HR, 1.38 [95% CI, 0.68–2.82]) in the strategy that targeted lower low-density lipoprotein cholesterol (LDL-C) levels with statins and ezetimibe.[52]

Some evidence of higher HS risk with statins was also found in the 2012 meta-analysis conducted by the Cholesterol Treatment Trialists' Collaboration (CTTC).[53,54] In this publication, the CTTC had not yet included the SPARCL trial or other trials that exclusively enrolled patients after a stroke/TIA[31,45,52]; when they added the SPARCL and CORONA (Controlled Rosuvastatin Multinational Trial in Heart Failure) trial, the evidence of increased in HS risk strengthened even more.[17,45,55] Although several large statin trials were published after the CTTC 2012,* there is still debate over the potential risk of HS.[56,57] The findings of later meta-analyses were discrepant, likely because of variations in the study population, types of LLTs, definition of outcomes, and lipid-lowering effect.[58,59] Furthermore, those meta-analyses were limited because they did not include triglyceride-lowering drugs. They concluded there might be evidence for increased HS risk with statins and that the risk might be higher in those with preexisting brain vascular injury. However, given the lack of a clear causal association with LDL-C levels and beneficial effect statins may have on ischemic end points, there is a need to gather evidence from updated meta-analyses that include newer studies.

Though new nonstatin therapies have been added to the guidelines (PCSK9 [proprotein convertase subtilisin/kexin type 9] inhibitors, omega 3 supplements), there is still need to extensively study the question of whether a reduction in LDL-C and triglycerides increases HS risk.[60] Because HS remains a rare and debatable side effect, we conducted a systematic review and meta-analysis to evaluate the most recent body of evidence to determine risk of HS events in trials that tested statin and other LLTs.

METHODS

We submitted the protocol of this systematic review to the International Prospective Register of Systematic Reviews before we submitted our article to this journal. During the submission and review process we had to deviate from our initial intention to compare our results with the pooled RR per 1 mmol/L LDL-C reduction from CTTC as the main analysis. We changed this because of the problematic association of 2 outcomes (RR of HS, and LDL-C reduction), and because of our inability to take into account the uncertainty of LDL-C reduction in individual trials (no SD provided for LDL-C

*References 16,18,26,31,41,44,49,52.

reduction). We kept the analysis where we pooled the results with the CTTC, however, as a sensitivity analysis. All authors declare that all supporting data are available in the article or its online supplementary files; the papers we included, and their supplementary files were found on online data bank (mainly PubMed). For our study we did not require the approval of an institutional review board or informed consent. However, original studies of the meta-analysis obtained consent from participants.

Data Sources and Searches

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines and checklist for conducting a systematic review (see Supplemental Material) to identify randomized clinical trials (RCTs) of LDL-C– and triglyceride-lowering therapies that reported HS risk or other outcomes related to HS, for example, intracranial hemorrhage, intracerebral hemorrhage (ICerH), and cerebral hemorrhage.[61] To be eligible for inclusion, studies had to be RCTs on human subjects older than 18 years, with more than 1000 participants, and to have reported HS events with at least 2 years of follow-up in the original paper or in one of the meta-analyses we cited. Two years is the minimum period required to see relevant effects of lipid-lowering on clinical outcomes and to detect rare complications.[62] Our inclusion criteria align with those of the CTTC, so we could compare our results. This is important because CTTC is the most comprehensive evidence synthesis for statin trials.[53] Such a comparison was done by previous meta-analyses of studies of LLTs.[63,64]

We limited our search to peer-reviewed articles published in English and excluded duplicate data, secondary subgroup trial data analysis, posttrial follow-up studies, and trials not powered for cardiovascular outcomes. We defined statins, ezetimibe, and PCSK-9 inhibitor as LDL-C–lowering therapies, and fibrate and marine omega-3 supplementation as triglyceride-lowering therapies, as defined in the guidelines.[60] We did not consider statins to be triglyceride-lowering therapies, because statins are primarily prescribed to reduce LDL-C and not to lower triglyceride.[60]

Study Selection

We drew on the 2012 meta-analyses of the CTTC and McKinney et al,[53,54] retrieving all eligible trials from those meta-analyses and all trials mentioned on the CTTC home page (July 2021).[65] We updated our search on MEDLINE, Embase, and Cochrane Library from 2012 to July 2, 2021. To retrieve trials on PCSK-9 inhibitors and ezetimibe, we searched MEDLINE, Embase, and Cochrane Library from 2015 to July 2, 2021; we started in 2015 because the paper from IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) was published that year; IMPROVE-IT was the first large cardiovascular trial with nonstatins.[29] To retrieve trials on triglyceride lowering (fibrates and marine omega-3 supplementation), we started with the 2019 meta-analysis by Marston et al and updated it with a search in MEDLINE, Embase, and Cochrane Library from 2019 to July 2, 2021.[66] We share our search algorithm in Figure S1. Two independent authors (S.B. and A.S.) screened the trials for eligibility using Rayyan software. In case of discrepancies, the reviewers discussed and came to agreement on whether to include the study.

Data Extraction and Quality Assessment

Two independent reviewers (S.B. and A.S.) agreed on the extracted data, including baseline characteristics, type of intervention (statin, ezetimibe, PCSK-inhibitors, fibrate, or omega-3 supplements), number of HS events, and LDL-C or triglyceride levels at baseline and follow-up in both arms of included trials. If an article mentioned HS or other related outcomes in the methods section of the main paper or in the protocol, but failed to report these outcomes in their results and we could not retrieve the numbers from another meta-analysis, we contacted the corresponding authors by email (see Table S2; 3 answers).[†] For statin therapy, we also extracted the intensity (high/not high) as defined by the 2013 Blood Cholesterol Clinical Practice Guidelines.[68] High intensity corresponded to atorvastatin 40 or 80 mg and rosuvastatin 20 or 40 mg. We extracted data on absolute change in LDL-C or triglyceride levels in each arm of the trial throughout its duration, using median (or mean if not reported) follow-up duration as a reference point. If the absolute change in LDL-C or triglyceride level was not reported, we calculated it as follows: (1) difference between the reported level each group reached after randomization; and (2) difference between absolute change reported in each group. To assess quality and risk of bias, S.B. and A.S. used the RoB 2.0 as specified by the Cochrane Collaboration 2019 (Figure S2).[‡]

Statistical Analysis

For the primary analysis, we did a meta-analysis of all LDL-C–lowering trials individually, using Mantel–Haenszel fixed-effects model, and the usual inverse variance random effects model. Studies with zero events in both arms were excluded from this analysis. For the studies with zero event in 1 of the 2 arms, we included them in the Mantel–Haenszel model. For the inverse variance model, we used a continuity

[†]References 2–7,9–19,21–29,31–33,35–37,39–50,52,53,67.

[‡]References 2–7,9–33,35–37,39–50,52,67,69.

correction.[70,71] As sensitivity analysis, we used a inverse variance model with treatment-arm continuity correction, a random effects Bayesian model with informative priors for heterogeneity (based on the publication of Turner et al for pharmacological intervention versus placebo, for safety outcome),[72] and an exact method (exact inference for fixed effects meta-analysis).[73]

We conducted several subgroup analyses to explore possible explanations of heterogeneity. On the LDL-C lowering therapy (37 trials), we subgrouped by prevention (primary versus secondary versus mixed), by type of intervention (statins versus ezetimibe versus PCSK-9 inhibitors), by reported outcome (HS versus HS-related outcome), by stroke status (trials including only participants with stroke/TIA versus not), and by overall baseline LDL-C (≥3 mmol/L versus <3 mmol/L). We also ran several post hoc subgroup analyses only including statin trials. We subgrouped by statin intensity (atorvastatin 40–80 mg or rosuvastatin 20–40 mg versus lower statin doses), by mean age (mean age >65 years old versus <65 years), by sex (prevalence of men ≥75% versus less), by geographical location of the study (trials conducted in Asia versus mainly conducted in Western countries), by aspirin/antiplatelet medication use (≥90% of participants versus less), by preexisting diabetes (≥30% versus less), and by preexisting hypertension (≥50% versus less). We defined cutoffs a posteriori based on the distribution of studies. We used a chi-square test to test differences between the subgroups. We used Q and I^2 statistics to evaluate the effect of heterogeneity across included trials.

We performed another sensitivity analysis where we pooled our results with the results from the CTTC 2012, as done by a previous meta-analysis of studies of LLT.[63,64] As the CTTC reported an RR per 1 mmoL/L LDL-C reduction, we had to calculate it for each individual trial not included in the CTTC (Data S1, Table S3).[§] After this intermediate step, we ran the final meta-analysis for every 1 mmol/L reduction in LDL-C; in this analysis we included the reported overall RR per 1 mmol/L decrease from CTTC 2012 and used a random effects model.

We ran several meta-regression models to further explore possible explanations for heterogeneity. First, we explored the association between the log-RR of HS and the LDL-C level at baseline for all LDL-C–lowering trials. We also did exploratory meta-regressions to the log-RR over the delta LDL-C and the achieved LDL-C levels in the intervention group. As delta LDL-C and achieved LDL-C are not baseline characteristics, this analysis was done to explore patterns in the data. We did a meta-regression including only statin trials and treating age as a continuous variable. We did the same for the percentage of men in the trials, percentage of diabetic participants, percentage of hypertensive participants, and also percentage of participants with antiplatelet therapies.

We also performed a meta-analysis on the risk difference scale, and used the estimated effect to calculate the number needed to harm for statins. We calculated the average weighted median duration of follow-up from the duration of follow-up reported for individual participants (mean, if the median was not mentioned), where we weighted studies according to their weights in the meta-analysis.

We performed a meta-analysis to summarize the risk of HS events for the triglyceride-lowering therapies and subgrouped by type of intervention (fibrate versus marine omega-3 supplementation). As the number of trials reporting triglyceride levels was low and this is not a baseline variable, we did not do a meta-regression investigating the association between RR and delta triglyceride.

We assessed potential small study effects (related to publication bias) by generating a funnel plot and performing a regression-based Egger test.[74] For analyses we used StataMP 16 and R.

RESULTS

After screening 5501 records (5443 from MEDLINE, Embase, and Cochrane Central; 58 from 3 previous meta-analyses; Figure S3), we identified 37 trials for lowering LDL-C (284 301 participants) and 11 for lowering triglyceride (120 984 participants): 33 statin trials,[‖] 2 ezetimibe trials,[19,29] 2 PCSK-9 inhibitor trials,[21,36] 2 fibrate trials,[20,25] and 9 marine omega-3 supplementation trials.[¶] Of these, 9 trials were deemed to be at high risk of bias (Figure S2). The Egger test did not show evidence of small study effects (P=0.85 for the main analysis; Figure S4). Baseline characteristics and reported outcomes are listed in Table S4.[#]

In the LDL-C–lowering trials, 29.7% of randomized participants were women; in the triglyceride-lowering trials, 42.1% were women. Of the 48 trials, 20 reported HS, 5 intracranial hemorrhage, 3 cerebral hemorrhage, 1 lCerH, and 2 reported other HS-related outcomes. The remaining 17 trials did not report HS events, but we retrieved data of 14 trials from 2 other meta-analyses,[54,58] and data of 3 other trials were provided by the authors (Table S1). Three trials specifically reported the percentage of HS at baseline (0.5% for EWTOPIA [Ezetimibe Lipid-Lowering Trial on Prevention of

[§]References 16,18,19,21,24,26,29,31,36,41,44,45,49,52.

[‖]References 2–8,11–18,22–24,26–28,31–35,38–41,43–45,48,49,51,52.

[¶]References 9,10,30,37,42,46,50,67.

[#]References 2–7,9–19,21–29,31–33,35–37,39–50,52,53,67.

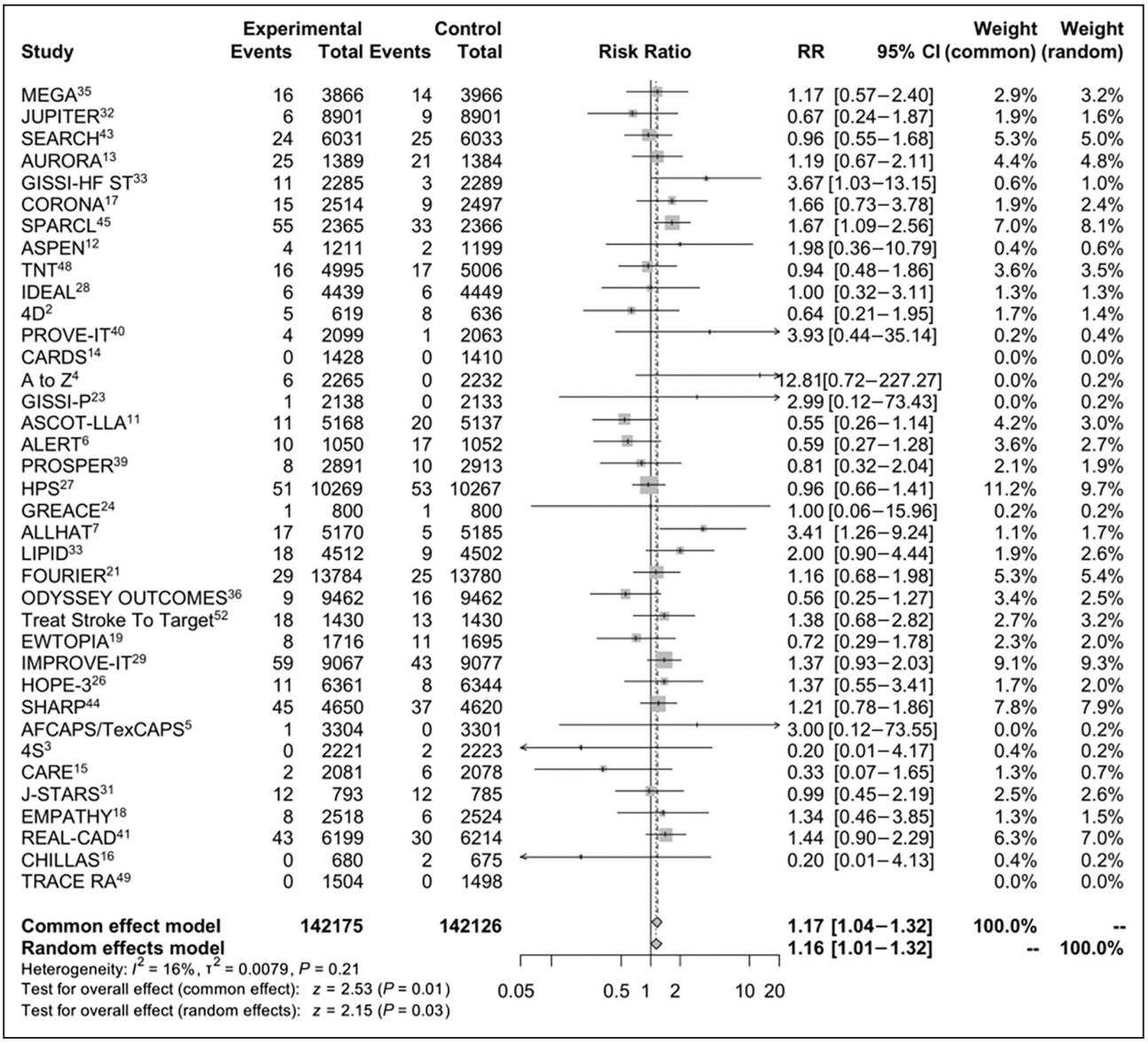

Figure 1. Forest plot of LDL-C–lowering therapy trials for the relative risk of HS events.
HS indicates hemorrhagic stroke; LDL-C, low-density lipoprotein cholesterol; and RR, risk ratio.

Atherosclerotic Cardiovascular Disease in 75 or Older], 2% for SPARCL, and 1.1% for REAL-CAD [Randomized Evaluation of Aggressive or Moderate Lipid Lowering Therapy With Pitavastatin in Coronary Artery Disease]).[19,41,45] Seven trials excluded participants with HS (CARDS [Collaborative Atorvastatin Diabetes Study], FOURIER [Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk], ODYSSEY [Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab], MEGA [Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese], JUPITER [Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin], TRACE RA [Trial of Atorvastatin for the Primary Prevention of Cardiovascular Events in Patients with Rheumatoid Arthritis], Treat Stroke to Target), and the other 38 trials did not report the percentage of HS at baseline.[14,21,32,35,36,49,52]

Main Analyses With Individual Trials

For our primary analysis, we used the individual trials for which data were available (23 from the CTTC, 14 from our search). The overall RR for HS events for LDL-C–lowering therapy using a random-effect model was 1.16 (95% CI, 1.01–1.32, P=0.03, 37 trials, 284 301 participants, 555 versus 474 events); the results were similar using the fixed effects model (Figure 1).[Δ] Using the treatment-arm continuity correction, the results

[Δ]References 2,4,11–14,17,22,23,28,32,35,40,43,45,48,53.

Table 1. Summary of Main, Subgroup, and Sensitivity Analyses on the Effect of LDL-C–lowering Therapy on the Risk of Hemorrhagic Stroke

	No. of trials	No. of patients	No. of HS in intervention	No. of HS in control	RR (95% CI)	*P* value
Main analyses with subgroups						
Overall with random effects	37	284 301	555	474	1.16 (1.06–1.32)	0.031
Overall with fixed effects					1.17 (1.04–1.32)	0.011
Overall with random effects and treatment arm continuity correction					1.16 (1.01–1.32)	0.031
Overall with fixed effects and treatment arm continuity correction					1.17 (1.04–1.32)	0.012
Statin with random effects	33	216 258	450	379	1.17 (1.01–1.36)	
Statin with fixed effects					1.19 (1.04–1.36)	
Ezetimibe with random effects	2	21 555	67	54	1.14 (0.64–2.03)	
Ezetimibe with fixed effects					1.24 (0.87–1.77)	
PCSK9-inhibitor with random effects	2	46 488	38	41	0.86 (0.43–1.74)	
PCSK9-inhibitor with fixed effects					0.93 (0.60–1.44)	
1° Prevention with random effects	7	55 826	42	37	1.14 (0.73–1.78)	
1° Prevention with fixed effects					1.15 (0.74–1.78)	
2° Prevention with random effects	19	155 680	318	250	1.26 (1.07–1.49)	
2° Prevention with fixed effects					1.27 (1.08–1.50)	
Mixed population with random effects	11	72′795	195	187	1.03 (0.78–1.35)	
Mixed population with fixed effects					1.04 (0.85–1.27)	
HS as outcome with random effects	16	186 754	374	321	1.17 (1.01–1.36)	
HS as outcome with fixed effects					1.17 (1.00–1.35)	
HS related as outcome with random effects	21	97 547	181	153	1.17 (0.88–1.56)	
HS related as outcome with fixed effects					1.18 (0.95–1.47)	
Without poststroke trials with random effects	34	275 132	470	416	1.12 (0.98–1.28)	
Without poststroke trials with fixed effects					1.13 (0.99–1.29)	
Only poststroke trials with random effects	3	9169	85	58	1.46 (1.05–2.04)	
Only poststroke trials with fixed effects					1.46 (1.05–2.04)	
Baseline mean LDL-C ≥3 mmol/L with random effects	23	137 880	277	240	1.13 (0.90–1.43)	
Baseline mean LDL-C ≥3 mmol/L with fixed effects					1.16 (0.97–1.37)	
Baseline mean LDL-C <3 mmol/L with random effects	14	146 421	278	234	1.17 (0.98–1.40)	
Baseline mean LDL-C <3 mmol/L with fixed effects					1.19 (1.00–1.41)	
	No. of trials	**No. of patients**	**No. of HS in intervention**	**No. of HS in control**	**OR (95% credible interval)**	
Overall with random effects Bayesian model	37	284 301	555	474	1.16 (0.99–1.36)	
Overall with exact non-Bayesian model					1.12 (0.96–1.29)	
	No. of trials	No. of patients	No. of ICH in intervention	No. of ICH in control	RR per 1 mmol/L LDL-C (95% CI)	*P* value
Sensitivity analysis with Cholesterol Treatment Trialists' Collaboration 2012[53]						
Overall with random effects	41	297 849	573	467	1.20 (1.06–1.36)	0.045
Overall with fixed effects					1.20 (1.06–1.36)	0.005

1° indicates primary; 2°, secondary; HS, hemorrhagic stroke; LDL-C, low-density lipoprotein cholesterol; OR, odds ratio; PCSK9, proprotein convertase subtilisin/kexin type 9; and RR, risk ratio. If not specified, the Mantel–Haenszel model was used for the fixed effects meta-analyses and the usual inverse variance model for the random effects meta-analyses. For the sensitivity analysis, the DerSimonian-Laird random effects was used.

were similar (random effects model RR, 1.16 [95% CI, 1.01–1.32], *P*=0.03; Table 1).[53] Using a random effects Bayesian model based of the odds ratio (OR) scale, the OR was 1.16 (95% credible interval, 0.99–1.36). With the exact method (exact inference for fixed effects meta-analysis), the OR was 1.12 (95% credible interval, 0.96–1.29; Table 1).[53]

The subgroup analysis by type of intervention showed an RR of 1.17 for statins (95% CI, 1.01–1.36, 33 trials), 0.86 for PCSK-9 inhibitors (95% CI, 0.43–1.74, 2

trials), and 1.14 for ezetimibe (95% CI, 0.64–2.03, 2 trials) (Figure 2 and Table 1); we found no evidence of modification according to drug class (*P* for interaction [P_{int}]=0.71; Figure 2). The subgroup analysis by prevention type indicated an RR of 1.26 in secondary prevention (95% CI, 1.07–1.49, 19 trials), 1.14 in primary prevention (95% CI, 0.73–1.78, 7 trials), and 1.03 in the mixed population (95% CI, 0.78–1.35, 11 trials) (Table 1

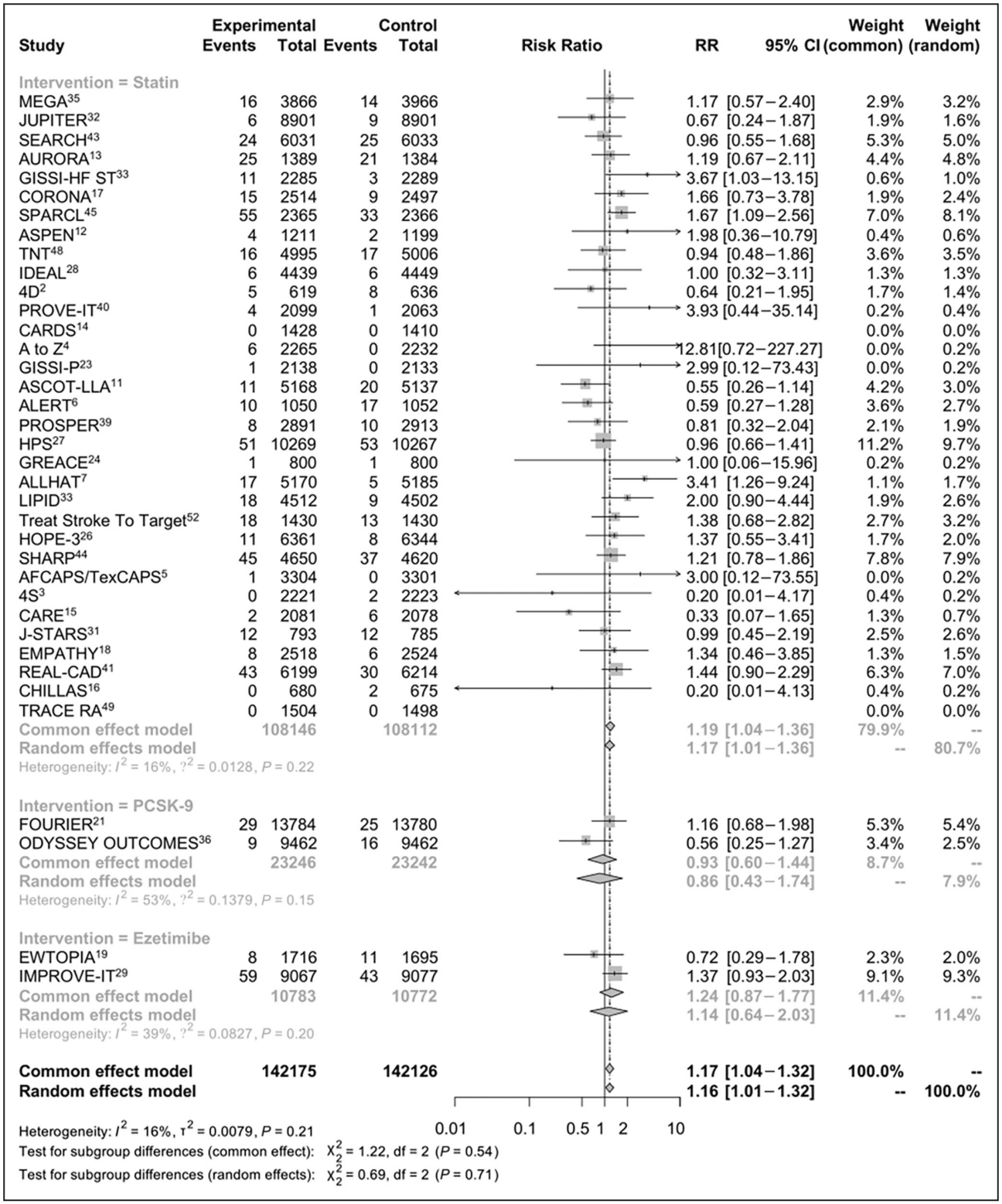

Figure 2. Effect of LDL-C–lowering therapy on the risk of HS by drug class.
HS indicates hemorrhagic stroke; LDL-C, low-density lipoprotein cholesterol; and RR, risk ratio.

and Figure S5).[◊] There was no evidence of effect modification by prevention type (p_{int}=0.44), although results were based on a mix of different drugs and were limited for primary prevention by the small number of trials and HS events (primary prevention: 42 versus 37; secondary prevention: 318 versus 250, mixed prevention: 195 versus 187 events; Figure S5). Trials specifically reporting HS had a pattern of higher risk of HS (RR, 1.17 [95% CI, 1.01–1.36]); there was no major difference with trials that reported other outcomes related to HS (P_{int}=0.99; Table 1).[53] Assessing only poststroke trials, the RR was also estimated to be higher (RR, 1.46 [95% CI, 1.05–2.04]; Table 1 and Figure S6).[↓] However, there was also almost no evidence of a difference between trials on patients with and without stroke (P_{inter}=0.14; Figure S6). There was no effect when differentiating overall mean baseline LDL-C concentration < or ≥3 mmol/L (Table 1).

In meta-regressions, we found no evidence that achieved LDL-C levels in the intervention group and risk of HS events (β coefficient −0.06, *P*=0.62; Figure S7) were related; no evidence of relationship between baseline cholesterol and the risk of HS events (β coefficient −0.05, *P*=0.67; Figure S8), and no evidence of relationship between Delta LDL-C and risk of HS events (β coefficient −0.11, *P*=0.56; Figure S9). Estimated absolute risk difference was 0.03% (95% CI, 0.01%–0.07%), corresponding to a number needed to harm 3333 for an average treatment duration of 6.7 years (Figure S10).[**]

In post hoc subgroup analyses considering only statins, we found no evidence of an effect of age, sex, geographical location of trials, aspirin/antiplatelet use, preexisting diabetes, and hypertension (Table S5). There was a pattern of higher risk in trials that included more diabetic patients (RR, 1.49 [95% CI, 1.02–2.18], P_{int}=0.18), fewer men (RR, 1.22 [95% CI, 1.01–1.48], P_{int}=0.64), and those including older people (RR, 1.34 [95% CI, 1.04–1.73], P_{int}=0.23) (Table S5). However, looking at only statin trials and considering the mean age as a continuous variable, the slope (log-OR per 1-year increase in mean age) was estimated to 0.03 (95% CI, −0.01 to 0.06), corresponding to OR 1.03 (95% CI, 0.99–1.06, *P*=0.15) per 1-year increase. The slope for the meta-regression per 1% antiplatelet use was 0.004 (95% CI, −0.002 to 0.010, *P*=0.24). The meta-regression between HS reported in statin trials and the percentage of hypertensive participants did not find any correlation. The same can be said for the percentage of diabetic participants and percentage of male participants. In stratified analyses by prevention, there was no evidence of an effect modification (P_{int}=0.50). In secondary prevention the RR was 1.32 (95% CI, 1.07–1.61), in primary prevention 1.14 (95% CI, 0.73–1.78) and in the mixed prevention population 1.06 (95% CI, 0.78–1.44) (Table S5). There was no evidence of an effect when differentiating high-intensity and low-intensity statins (p_{int}=0.50; Figure S11).[††]

Sensitivity Analysis With CTTC

For this sensitivity analysis, we pooled results from the CTTC 2012 meta-analysis with the 14 trials published later. In the 41 pooled trials (297 849 participants), we found that HS risk was higher in the intervention than the control group when participants received LDL-C–lowering therapy (RR per 1 mmoL/L LDL-C reduction, 1.20 [95% CI, 1.06–1.36], *P*=0.0045) (Table 1 and Figure S12).[‡‡] The RR per 1 mmoL/L LDL-C reduction for statins was 1.24 (95% CI, 1.08–1.42, *P*<0.01, 37 trials), 0.90 for PCSK-9 inhibitors (95% CI, 0.53–1.51, *P*=0.68, 2 trials), and 1.54 for ezetimibe (95% CI, 0.39–6.11, *P*=0.54, 2 trials) (Figure S12); there was no evidence of an effect modification (p_{int}=0.48).

Analyses With Triglyceride-Lowering Trials

The RR in trials testing triglyceride-lowering therapy was 1.05 (95% CI, 0.86–1.30, *P*=0.63, 11 trials, 120 984 participants), with no evidence of an interaction across the class of therapies (p_{int}=0.69) (Figure 3).[§§] The RR for fibrate was 1.50 (95% CI, 0.29–7.85, 2 trials) and for marine omega-3 supplementation was 1.06 (95% CI, 0.85–1.32, 8 trials) (Figure 3).

DISCUSSION

This updated meta-analysis suggests that risk of HS events increased in large cardiovascular trials that tested therapies that lowered LDL-C. We found evidence of an effect for statin trials but not for nonstatin therapies, though we found no evidence of an effect modification across different classes of therapies. In our exploratory meta-regression, there was no evidence of an association of HS risk with the amount LDL-C was reduced, the final LDL-C levels the intervention group achieved or with the baseline LDL-C levels. Triglyceride-lowering therapies did not create risk of HS events.

Our findings confirm and strengthen the existing evidence that LDL-C–lowering therapies increase the risk of HS. Previous meta-analyses included fewer

[◊]References 2,4,11–14,17,22,23,28,32,35,40,43,45,48,53.

[↓]References 2,4,11–14,17,22,23,28,32,35,40,43,45,48.

[**]References 2,4,11–14,17,22,23,28,32,35,40,43,45,48.

[††]References 2–7,11–18,22–24,26–28,31–33,35,39–41,43–45,48,49,52.

[‡‡]References 16,18,19,21,24,26,29,31,36,41,44,45,49,52.

[§§]References 10,20,25,30,37,42,46,47,50,67.

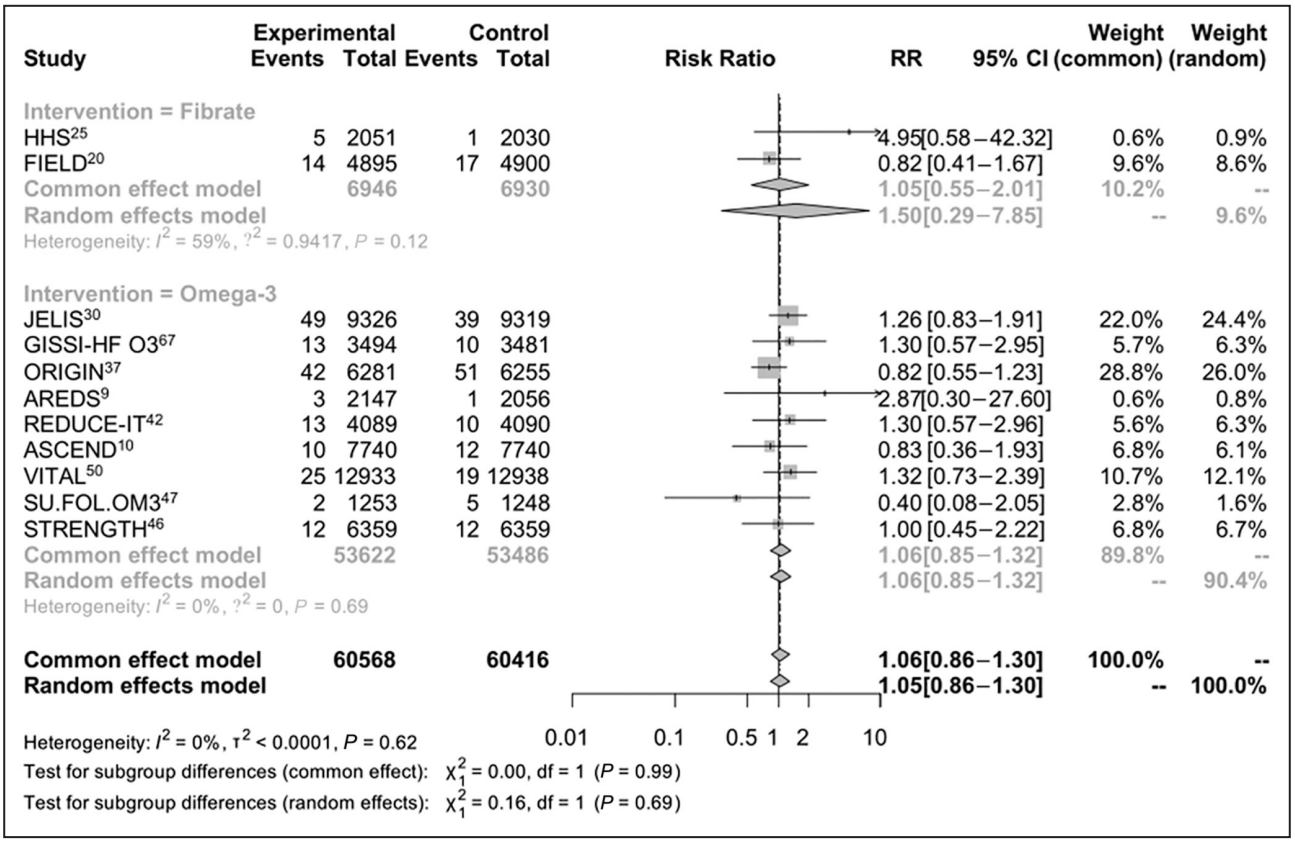

Figure 3. Forest plot of triglyceride-lowering therapy trials for the relative risk of HS events.
HS indicates hemorrhagic stroke; and RR, risk ratio.

trials[53,54,59]; we included 10 more statin trials than CTTC,[IIII] 5 more than Sanz-Cuesta et al,[16,26,41,49,52] and 7 more than McKinney et al[53,54,59,62] We also included 7 more than Judge et al (5 statins, 1 ezetimibe, and 1 PCSK9-inhibitor).[58] Adding more trials increased our overall statistical power and the power of our subgroup analyses. After adding these new data, we found no strong evidence of a subgroup difference between trials including exclusively patients who were poststroke/TIA, such as SPARCL[31,45,52] (which the CTTC analysis of 2012 had also omitted) and other trials. Finally, earlier meta-analyses did not report analyses on the absolute risk difference scale, which limited their usefulness for clinical practice and risk/benefit assessment.

In our subgroup analysis by drug class, we found some evidence of higher risk in the statin trials. Our power to detect an effect in trials that investigated ezetimibe or PCSK-9 inhibitor was limited because of the small number of trials, participants, and HS events. In further subgroup analyses of study-level characteristics considering only statins, we found no evidence of effect modification by age, sex, geographical location of trials, aspirin/antiplatelet use, preexisting diabetes, and hypertension, though in trials that included more older people, fewer men, or more patients with diabetes, there was a pattern of higher risk.

The CTTC 2012 and 2015 meta-analyses reported higher risk of HS in statin trials, but the evidence was not very strong (RR per 1 mmol/L, 1.15 [95% CI, 0.97–1.38], P=0.11; resp. 1.14 [95% CI, 0.96–1.36], P value not reported),[53,62] mainly because some key studies, such as SPARCL were not included. The recent meta-analysis of 33 RCTs by Sanz-Cuesta et al, which evaluated statins versus control and high versus low dose reported an increase in risk estimates for HS events with stronger statistical evidence (RR, 1.15 [95% CI, 1.00–1.32], P=0.04).[59] However, study eligibility criteria did not align with either the CTTC or our meta-analysis: they set different minimums for number of patients, included more small underpowered trials, and set different minimum follow-up periods. They also included medications such as bococizumab, which has not been approved. In a dose-effect analysis that included 7 RCTs, they found risk of HS with high-dose statins was higher than in controls (0.41% versus 0.27%; RR, 1.53 [95% CI, 1.16–2.01], P=0.002).[59] When we added more trials, we did not find evidence of a risk increase of HS in high-intensity trials. The meta-analyses by McKinney et al and Judge et al found very weak

[IIII]References 16,26,29,31,41,44,45,49,52,64.

evidence of increased risk of ICerH with lipid-lowering (OR, 1.08 [95% CI, 0.88–1.32], *P*=0.47, and OR, 1.12 [95% CI, 0.98–1.28], respectively).[54,58] However, they both included 7 fewer trials than we did. McKinney et al considered only statin trials; Judge et al included fibrate, ezetimibe, PCSK9, and cholesteryl ester transfer protein trials but did not separate these classes of medication in their analysis.[54,58]

Our meta-regression did not find any association with the baseline LDL-C level; our exploratory meta-regressions neither could show an association with the magnitude of LDL-C reduction or with the LDL-C levels achieved in the intervention group. Like our study, McKinney et al and Judge et al found no evidence of an association between ICerH risk and the LDL-C level achieved in the intervention group.[54,58] Our findings contrast with recent Mendelian randomization studies, which support the hypothesis that reducing LDL-C can have an effect on HS.[75–78] The mechanism that could explain the association between statins and HS has yet to be elucidated.[79] Initially, the association was thought to be explained by weakening of the endothelium caused by low cholesterol,[54,80,81] and the Mendelian randomization studies appear to support this.[76–78] A later hypothesis attributed the association to the statin's pleiotropic effects, and yet another suggested a link to antithrombotic and fibrinolytic effects.[79] This last hypothesis might explain why risk is higher in secondary prevention, and after stroke/TIA, as patients are usually treated with antithrombotics in addition to statin.

We found no evidence of an association between triglyceride-lowering drugs and HS risk. However, as the number of trials included is low, there is a need of additional studies in order to have a final answer. The meta-analysis by Xiaolin et al found no evidence that triglyceride and HS ($p_{non\text{-}linearity}$=0.25) were associated but reported a protective effect: risk of HS decreased by 7% for every 1-mmol/L increase in triglyceride in a linear trend (RR, 0.93 [95% CI, 0.89–0.97], *P*<0.001).[82] However, the analysis of Xiaolin et al included observational cohorts rather than RCTs.[82] Our data should reassure those who use omega-3 supplements, because this is common in practice.

This meta-analysis has some limitations. We were limited by the fact that definitions and HS reporting (including intracranial hemorrhage or ICerH) were not standardized but we conducted a subgroup analysis, which did not find any difference between both groups. Most trials we included had been randomized and blinded, including blinded adjudication, so if misclassification of outcomes occurred, it should have been nondifferential and bias results toward the null hypothesis. Only 3 trials specified HS as a baseline characteristic, but 25 specified stroke/TIA (Table S4). None of the trials with PCSK-9 inhibitors included patients with previous HS, so a postmarketing study might be necessary to evaluate their safety.

To our knowledge no other meta-analysis considered the different possible outcomes reported in the trials they included. This highlights the importance of standard definitions for reporting of HS events and the need to include it as a baseline characteristic in future research. Some trials did not report risk of HS events in original articles and we had to extract data form previously published meta-analyses that included those trials, most of which did not clearly describe how they gathered data. Some trials did not specifically report the change in LDL-C during the trial and we could not include these in our meta-regression analysis, but this was only exploratory and done as a secondary analysis. Our power to detect effect modification for specific subgroups of drugs might have been limited because few trials for those subgroups were included. In particular, our power to detect potential risk was far lower for nonstatin therapy.

Participants in the trials were overwhelmingly White men, so their results might not be representative of patients managed in clinical practice, although we found no effect modification by sex or geographical location.[83] Most patients had comorbidities and were taking more therapies than LLT, most frequently antiplatelets, which can affect risk of bleeding and HS, but these comedications are likely to have been evenly distributed between both arms at baseline and follow up, especially when trials were blinded. Unfortunately, most lipid-lowering trials did not adequately report cointerventions and comedications.[84] Our subgroup analysis considering the use of antiplatelets at study level found no evidence for effect modification, a finding confirmed by other published observational data that showed HS risk did not increase with statin use in patients anticoagulated for atrial fibrillation.[85] However, individual patient data are needed to answer this question definitively, because subgroup analyses at the study level are limited due to the risk of ecological fallacy.[86]

Our study was strengthened by our focus on a wide range of LDL-C lowering therapy, including statins, ezetimibe, and PCSK-9 inhibitors trials, and by our use of up-to-date evidence-based data. We used a RR per 1-mmol/L LDL-C reduction as sensitivity analysis so we could compare and combine our results with those reported in the CTTC, which was not done so far with other meta-analyses. We also included fibrate and omega-3 trials to make up for the lack of published analyses of the association between lowering triglyceride and the HS risk. Finally, we reported data with an absolute risk difference to appraise risk/benefit assessment.

What are the clinical implications of our findings? Although the RR of HS increased by 17% with statin,

absolute risk of HS remained rare throughout the trials, and the absolute risk difference attributable to statin was low, with an estimated number needed to harm of 3333 for an average treatment length of 6.7 years. The number needed to treat with statin to prevent 1 ischemic event over a period of 5 years is 49,[87] so HS risk should not preclude statin use if clinically indicated. However, direct comparison between these 2 numbers should be approached cautiously because they do not account for disease severity or potential clustering in subgroups. We need more evidence to determine whether HS cluster within a particular patient subpopulation and whether the degree of disability is comparable to ischemic strokes. Many patients or doctors still have safety concerns about using statins, but we should encourage them to balance potential low risk of HS against expected benefits. In patients with acute HS, current guidelines state that the effects of statins on short-term outcome (ischemic and hemorrhagic) are uncertain,[88] but we could reduce this uncertainty by making individual patient data from LLT trials publicly available (https://www.bmj.com/campaign/statins-open-data) so researchers can estimate and stratify risk/benefit by age, sex, and comorbidities.[89]

CONCLUSIONS

This updated meta-analysis of large cardiovascular trials suggests that LDL-C–lowering therapies is associated with a small increased risk of HS events. The evidence for an increased risk was stronger for statins, whereas there was no clear safety signal for nonstatin therapies; however, our power to detect such a risk was far lower than for statin therapy. The absolute risk difference of HS attributable to statin should not preclude its prescription if clinically indicated and given the greater effect on reducing ischemic events. There was no clear evidence for triglyceride-lowering therapies.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Data S1
Tables S1–S5
Figures S1–S12

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