









ORIGINAL RESEARCH

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

Sylvain Bétrisey*, Moa Lina Haller , Orestis Efthimiou , PhD; Alexandre Speierer , MD; Cinzia Del Giovane, PhD; Elisavet Moutzouri , MD, PhD; Manuel R. Blum , MD, MSc; Drahomir Aujesky , MD, MSc; Nicolas Rodondi , MD, MAS; Baris Gencer , MD, MPH

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 fibrates) 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 (284301 participants) and 11 for triglyceride lowering (120984 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, 216258 participants), $RR=1.17$ (95% CI, 1.01–1.36); for PCSK-9 inhibitors (2 trials, 46488 participants), $RR=0.86$ (95% CI, 0.43–1.74); and for ezetimibe (2 trials, 21555 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, 120984 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.

REGISTRATION: URL: <https://www.crd.york.ac.uk/prospero>; Unique identifier: CRD42021275363.

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

See Editorial by Selim.

Correspondence to: Baris Gencer, MD, MPH, Institute of Primary Health Care (BIHAM), University of Bern, Mittelstrasse 43, 3012 Bern, Switzerland. Email: baris.gencer@biham.unibe.ch

*S. Bétrisey and M. L. Haller are co-first authors.

This article was sent to Neel S. Singhal, MD, PhD, Associate Editor, for review by expert referees, editorial decision, and final disposition.

Supplemental Material is available at <https://www.ahajournals.org/doi/suppl/10.1161/JAHA.123.030714>

For Sources of Funding and Disclosures, see page 11.

© 2024 The Authors. Published on behalf of the American Heart Association, Inc., by Wiley. This is an open access article under the terms of the [Creative Commons Attribution-NonCommercial-NoDerivs](https://creativecommons.org/licenses/by-nc-nd/4.0/) License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

JAHA is available at: www.ahajournals.org/journal/jaha

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 $\geq 75\%$ versus less), by geographical location of the study (trials conducted in Asia versus mainly conducted in Western countries), by aspirin/antiplatelet medication use ($\geq 90\%$ of participants versus less), by preexisting diabetes ($\geq 30\%$ versus less), and by preexisting hypertension ($\geq 50\%$ 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 ICeH, 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 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.

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

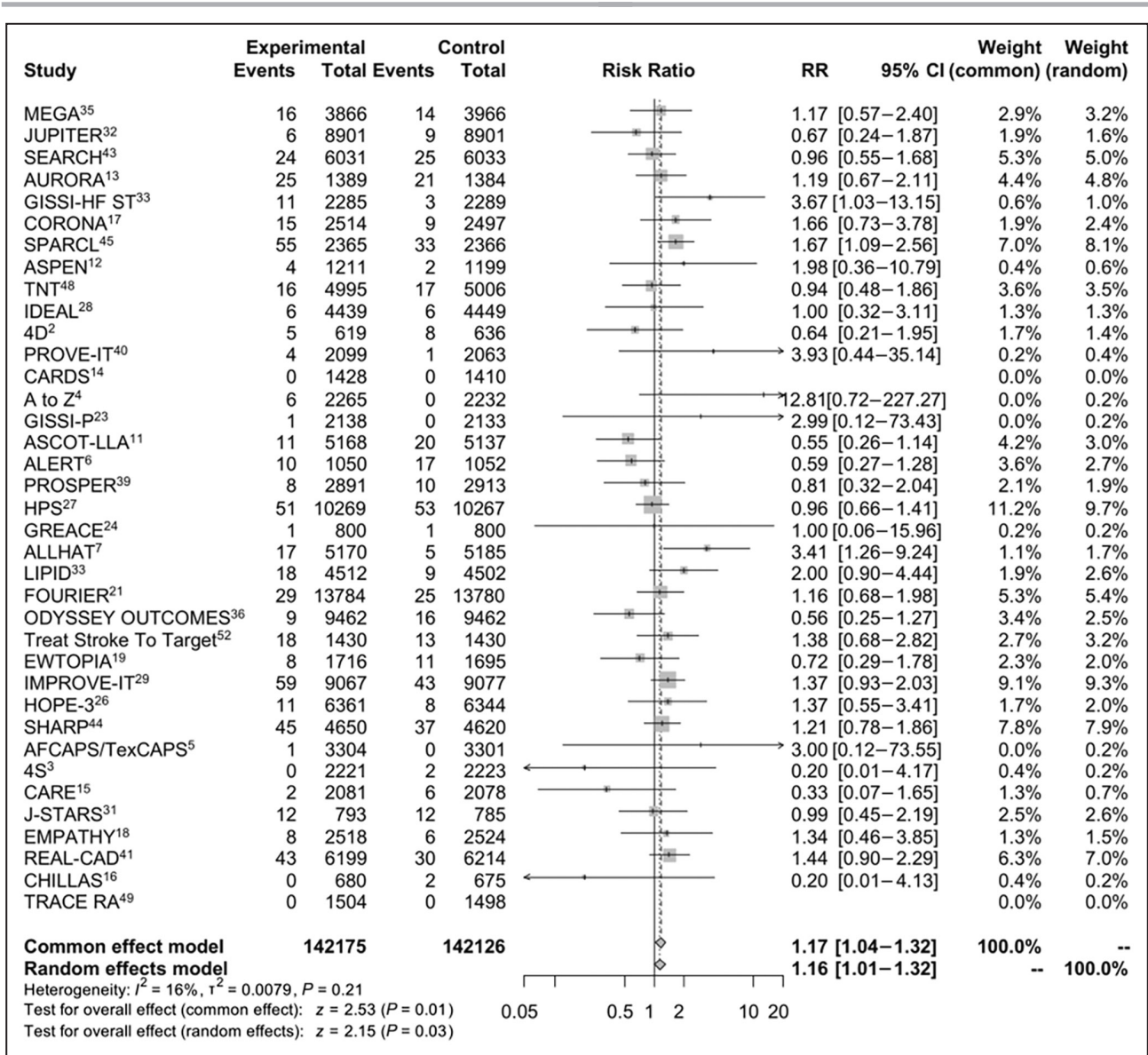


Figure 1. Forest plot of LDL-C–lowering therapy trials for the relative risk of HS events. HS indicates hemorrhagic stroke; LDL-C, low-density lipoprotein cholesterol; and RR, risk ratio.

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).^A Using the treatment-arm continuity correction, the results

^AReferences 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	284301	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	216258	450	379	1.17 (1.01–1.36)	
Statin with fixed effects					1.19 (1.04–1.36)	
Ezetimibe with random effects	2	21555	67	54	1.14 (0.64–2.03)	
Ezetimibe with fixed effects					1.24 (0.87–1.77)	
PCSK9-inhibitor with random effects	2	46488	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	55826	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	155680	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	72795	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	186754	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	97547	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	275132	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 \geq 3 mmol/L with random effects	23	137880	277	240	1.13 (0.90–1.43)	
Baseline mean LDL-C \geq 3 mmol/L with fixed effects					1.16 (0.97–1.37)	
Baseline mean LDL-C $<$ 3 mmol/L with random effects	14	146421	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	284301	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	297849	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

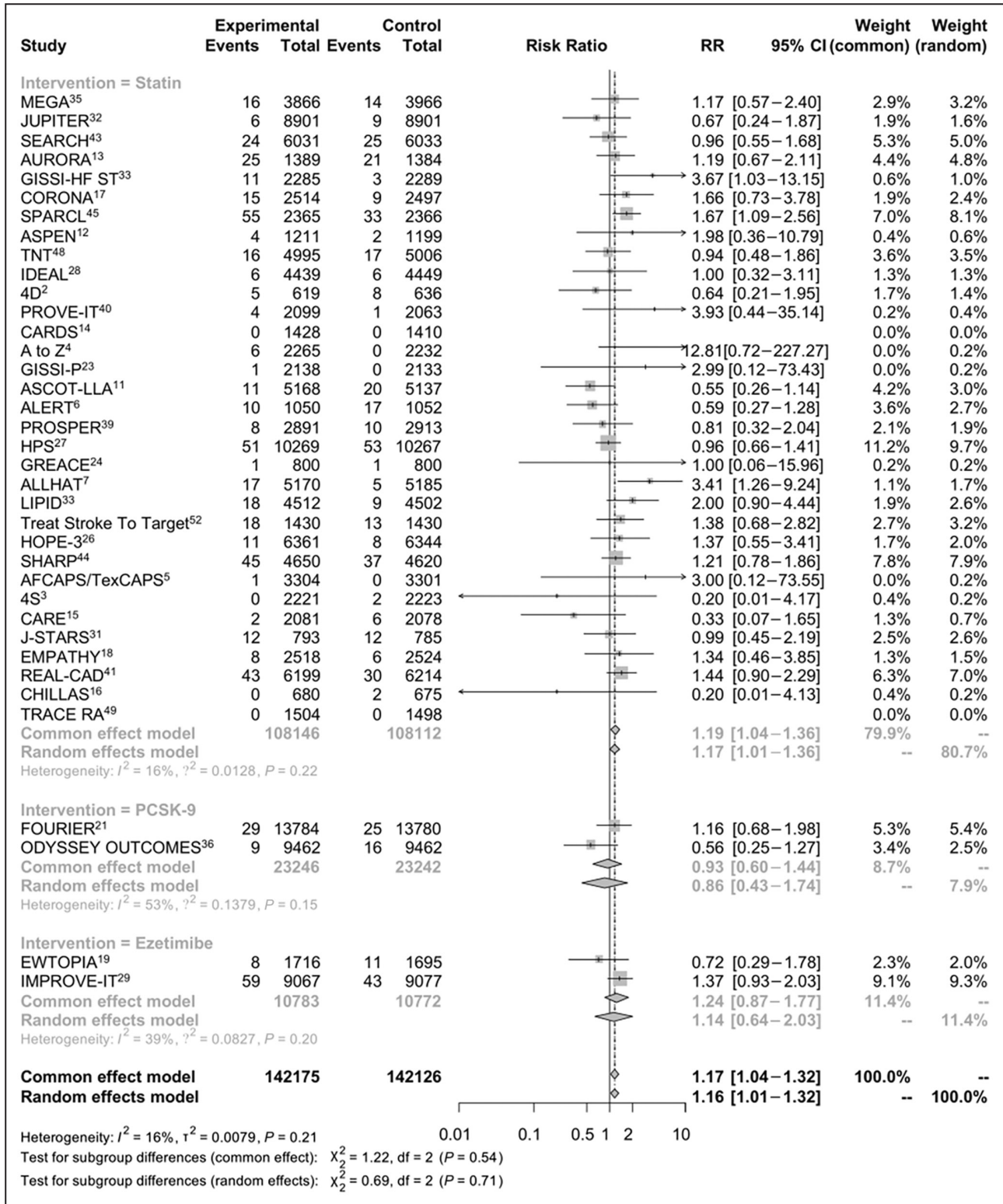


Figure 2. Effect of LDL-C-lowering therapy on the risk of HS by drug class. HS indicates hemorrhagic stroke; LDL-C, low-density lipoprotein cholesterol; and RR, risk ratio.

Downloaded from <http://ahajournals.org> by on January 7, 2025

and Figure S5).[◊] There was no evidence of effect modification by prevention type ($p_{\text{int}}=0.44$), 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 ($P_{\text{int}}=0.99$; 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 ($P_{\text{inter}}=0.14$; 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], $P_{\text{int}}=0.18$), fewer men (RR, 1.22 [95% CI, 1.01–1.48], $P_{\text{int}}=0.64$), and those including older people (RR, 1.34 [95% CI, 1.04–1.73], $P_{\text{int}}=0.23$) (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 ($P_{\text{int}}=0.50$). 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 ($p_{\text{int}}=0.50$; 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 ($p_{\text{int}}=0.48$).

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 ($p_{\text{int}}=0.69$) (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.

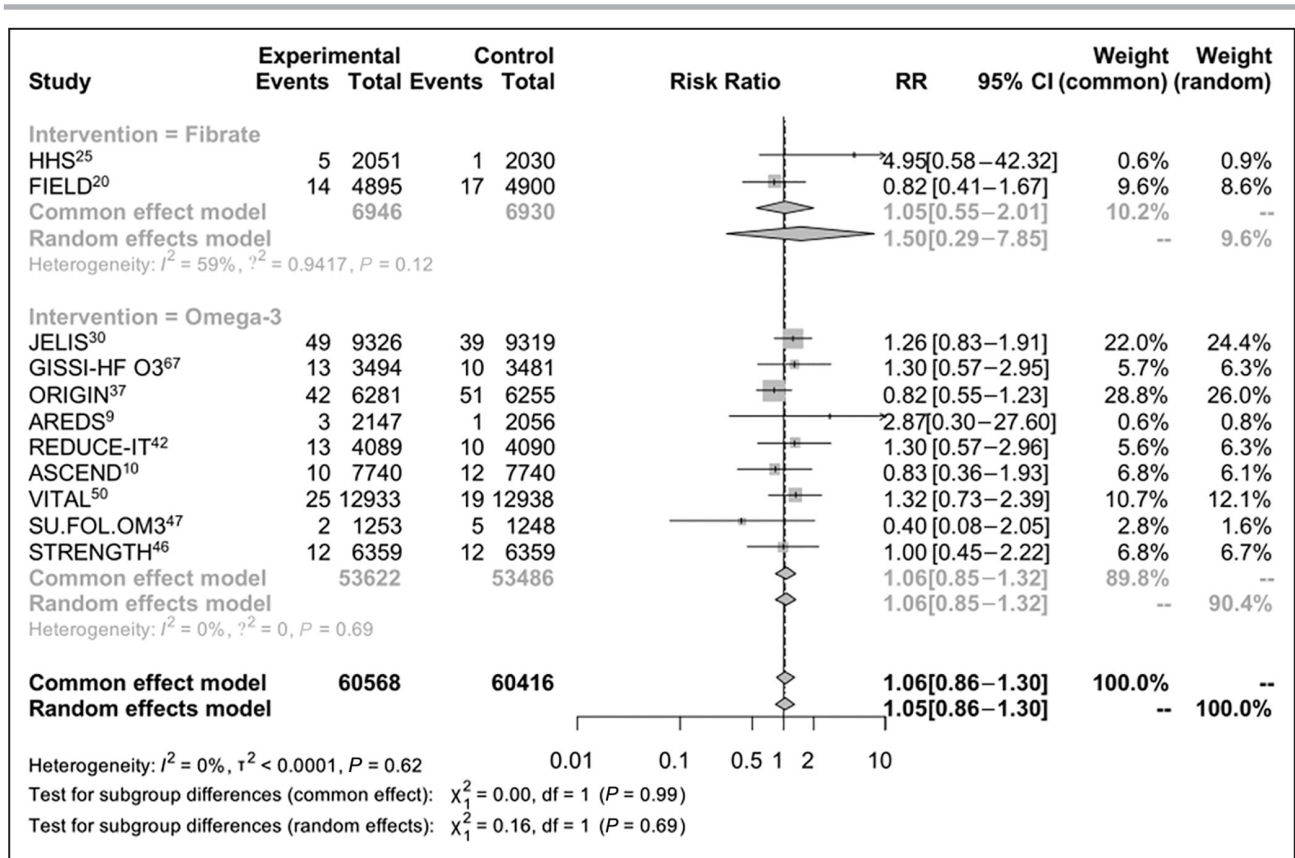


Figure 3. Forest plot of triglyceride-lowering therapy trials for the relative risk of HS events. HS indicates hemorrhagic stroke; and RR, risk ratio.

trials^{53,54,59}; we included 10 more statin trials than CTTC,^{III} 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

^{III}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 ($p_{\text{non-linearity}}=0.25$) 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 from 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

Received April 23, 2023; accepted December 12, 2023.

Affiliations

Department of General Internal Medicine, Inselspital, Bern University Hospital, University of Bern, Switzerland (S.B., M.L.H., A.S., E.M., M.R.B., D.A., N.R.); Institute of Primary Health Care (BIHAM) (S.B., M.L.H., O.E., A.S., C.D.G., E.M., M.R.B., N.R., B.G.) and Institute of Social and Preventive Medicine (ISPM) (O.E.), University of Bern, Switzerland; Department of Medical and Surgical Sciences for Children and Adults, University Hospital of Modena and Reggio Emilia, Modena, MO, Italy (C.D.G.); Department of General Internal Medicine, Spital Emmental, Burgdorf, Switzerland (E.M.); and Department of Cardiology, Geneva University Hospital (HUG), University of Geneva, Geneva, Switzerland (B.G.).

Acknowledgments

We thank Dr Kali Tal for her suggestions to improve our syntax and grammar, which made the article more readable. We would like to thank Beatrice Minder from the University Library of Bern for her help in developing the literature search strategy.

Sources of Funding

This study was partly supported by a grant from the Swiss National Science Foundation to study the role of statins among older adults in primary prevention (IICT 331C30-193.052 to Nicolas Rodondi). The sponsor played no role in designing, analyzing, or reporting of the trial. Dr Gencer's research on cardiovascular prevention is supported by the Swiss National Science Foundation (SNSF 325130_204361, SNSF 32003B_207881), Swiss Atherosclerosis Society, and Swiss Heart Foundation.

Disclosures

None.

Supplemental Material

Data S1
Tables S1–S5
Figures S1–S12

REFERENCES

- Mach F, Ray KK, Wiklund O, Corsini A, Catapano AL, Bruckert E, De Backer G, Hegele RA, Hovingh GK, Jacobson TA, et al. Adverse effects of statin therapy: perception vs. the evidence—focus on glucose homeostasis, cognitive, renal and hepatic function, haemorrhagic stroke and cataract. *Eur Heart J*. 2018;39:2526–2539. doi: [10.1093/eurheartj/ehy182](https://doi.org/10.1093/eurheartj/ehy182)
- Wanner C, Krane V, März W, Olschewski M, Mann JF, Ruf G, Ritz E. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. *N Engl J Med*. 2005;353:238–248. doi: [10.1056/NEJMoa043545](https://doi.org/10.1056/NEJMoa043545)
- Shepherd JC, Ford I, Isles CG, Lorimer AR, MacFarlane PW, McKillop JH, Packard CJ. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet*. 1994;344:1383–1389.
- de Lemos JA, Blazing MA, Wiviott SD, Lewis EF, Fox KA, White HD, Rouleau JL, Pedersen TR, Gardner LH, Mukherjee R, et al. Early intensive vs a delayed conservative simvastatin strategy in patients with acute coronary syndromes: phase Z of the A to Z trial. *JAMA*. 2004;292:1307–1316. doi: [10.1001/jama.292.11.1307](https://doi.org/10.1001/jama.292.11.1307)
- Downs JR, Clearfield M, Weis S, Whitney E, Shapiro DR, Beere PA, Langendorfer A, Stein EA, Kruyer W, Gotto AM Jr. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. *JAMA*. 1998;279:1615–1622. doi: [10.1001/jama.279.20.1615](https://doi.org/10.1001/jama.279.20.1615)
- Holdaas H, Fellström B, Jardine AG, Holme I, Nyberg G, Fauchald P, Grönhagen-Riska C, Madsen S, Neumayer HH, Cole E, et al. Effect of fluvastatin on cardiac outcomes in renal transplant recipients: a multi-centre, randomised, placebo-controlled trial. *Lancet*. 2003;361:2024–2031. doi: [10.1016/s0140-6736\(03\)13638-0](https://doi.org/10.1016/s0140-6736(03)13638-0)
- ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs usual care: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT). *JAMA*. 2002;288:2998–3007. doi: [10.1001/jama.288.23.2998](https://doi.org/10.1001/jama.288.23.2998)
- Koren MJ, Hunninghake DB; ALLIANCE Investigators. Clinical outcomes in managed-care patients with coronary heart disease treated aggressively in lipid-lowering disease management clinics: the ALLIANCE study. *J Am Coll Cardiol*. 2004;44:1772–1779. doi: [10.1016/j.jacc.2004.07.053](https://doi.org/10.1016/j.jacc.2004.07.053)
- Bonds DE, Harrington M, Worrall BB, Bertoni AG, Eaton CB, Hsia J, Robinson J, Clemons TE, Fine LJ, Chew EY. Effect of long-chain ω-3 fatty acids and lutein + zeaxanthin supplements on cardiovascular outcomes: results of the Age-Related Eye Disease Study 2 (AREDS2) randomized clinical trial. *JAMA Intern Med*. 2014;174:763–771. doi: [10.1001/jamainternmed.2014.328](https://doi.org/10.1001/jamainternmed.2014.328)
- Bowman L, Mafham M, Wallendszus K, Stevens W, Buck G, Barton J, Murphy K, Aung T, Haynes R, Cox J, et al. Effects of n-3 fatty acid supplements in diabetes mellitus. *N Engl J Med*. 2018;379:1540–1550. doi: [10.1056/NEJMoa1804989](https://doi.org/10.1056/NEJMoa1804989)
- Sever PS, Dahlöf B, Poulter NR, Wedel H, Beevers G, Caulfield M, Collins R, Kjeldsen SE, Kristinsson A, McInnes GT, et al. Prevention of

- coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. *Lancet*. 2003;361:1149–1158. doi: [10.1016/s0140-6736\(03\)12948-0](https://doi.org/10.1016/s0140-6736(03)12948-0)
12. Knopp RH, d'Emden M, Smit JG, Pocock SJ. Efficacy and safety of atorvastatin in the prevention of cardiovascular end points in subjects with type 2 diabetes: the Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in non-insulin-dependent diabetes mellitus (ASPEN). *Diabetes Care*. 2006;29:1478–1485. doi: [10.2337/dc05-2415](https://doi.org/10.2337/dc05-2415)
 13. Fellström BC, Jardine AG, Schmieder RE, Holdaas H, Bannister K, Beutler J, Chae DW, Chevaile A, Cobbe SM, Grönhagen-Riska C, et al. Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. *N Engl J Med*. 2009;360:1395–1407. doi: [10.1056/NEJMoa0810177](https://doi.org/10.1056/NEJMoa0810177)
 14. Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA, Neil HA, Livingstone SJ, Thomason MJ, Mackness MI, Charlton-Menys V, Fuller JH. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *Lancet*. 2004;364:685–696. doi: [10.1016/s0140-6736\(04\)16895-5](https://doi.org/10.1016/s0140-6736(04)16895-5)
 15. Sacks FM, Pfeffer MA, Moye LA, Rouleau JL, Rutherford JD, Cole TG, Brown L, Warnica JW, Arnold JM, Wun CC, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. *N Engl J Med*. 1996;335:1001–1009. doi: [10.1056/nejm199610033351401](https://doi.org/10.1056/nejm199610033351401)
 16. Zhao SP, Yu BL, Peng DQ, Huo Y. The effect of moderate-dose versus double-dose statins on patients with acute coronary syndrome in China: results of the CHILLAS trial. *Atherosclerosis*. 2014;233:707–712. doi: [10.1016/j.atherosclerosis.2013.12.003](https://doi.org/10.1016/j.atherosclerosis.2013.12.003)
 17. Kjekshus J, Apetrei E, Barrios V, Böhm M, Cleland JG, Cornel JH, Dunselman P, Fonseca C, Goudev A, Grande P, et al. Rosuvastatin in older patients with systolic heart failure. *N Engl J Med*. 2007;357:2248–2261. doi: [10.1056/NEJMoa0706201](https://doi.org/10.1056/NEJMoa0706201)
 18. Itoh H, Komuro I, Takeuchi M, Akasaka T, Daida H, Egashira Y, Fujita H, Higaki J, Hirata KI, Ishibashi S, et al. Intensive treat-to-target statin therapy in high-risk Japanese patients with hypercholesterolemia and diabetic retinopathy: report of a randomized study. *Diabetes Care*. 2018;41:1275–1284. doi: [10.2337/dc17-2224](https://doi.org/10.2337/dc17-2224)
 19. Ouchi Y, Sasaki J, Arai H, Yokote K, Harada K, Katayama Y, Urabe T, Uchida Y, Hayashi M, Yokota N, et al. Ezetimibe Lipid-Lowering Trial on Prevention of Atherosclerotic Cardiovascular Disease in 75 or Older (EWTOPIA 75): a randomized. *Controlled Trial*. *Circulation*. 2019;140:992–1003. doi: [10.1161/circulationaha.118.039415](https://doi.org/10.1161/circulationaha.118.039415)
 20. Keech A, Simes RJ, Barter P, Best J, Scott R, Taskinen MR, Forder P, Pillai A, Davis T, Glasziou P, et al. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. *Lancet*. 2005;366:1849–1861. doi: [10.1016/s0140-6736\(05\)67667-2](https://doi.org/10.1016/s0140-6736(05)67667-2)
 21. Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, Kuder JF, Wang H, Liu T, Wasserman SM, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med*. 2017;376:1713–1722. doi: [10.1056/NEJMoa1615664](https://doi.org/10.1056/NEJMoa1615664)
 22. Tavazzi L, Maggioni AP, Marchioni R, Barlera S, Franzosi MG, Latini R, Lucci D, Nicolosi GL, Porcu M, Tognoni G. Effect of rosuvastatin in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. *Lancet*. 2008;372:1231–1239. doi: [10.1016/s0140-6736\(08\)61240-4](https://doi.org/10.1016/s0140-6736(08)61240-4)
 23. GISSI Prevenzione Investigators. Results of the low-dose (20 mg) pravastatin GISSI Prevenzione trial in 4271 patients with recent myocardial infarction: do stopped trials contribute to overall knowledge? GISSI Prevenzione Investigators (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico). *Ital Heart J*. 2000;1:810–820.
 24. Athyros VG, Papageorgiou AA, Mergouris BR, Athyrou VV, Symeonidis AN, Basayannis EO, Demetriadis DS, Kontopoulos AG. Treatment with atorvastatin to the National Cholesterol Educational Program goal versus 'usual' care in secondary coronary heart disease prevention. The GREek Atorvastatin and Coronary-heart-disease Evaluation (GREACE) study. *Curr Med Res Opin*. 2002;18:220–228. doi: [10.1185/030079902125000787](https://doi.org/10.1185/030079902125000787)
 25. Frick MH, Elo O, Haapa K, Heinonen OP, Heinsalmi P, Helo P, Huttunen JK, Kaitaniemi P, Koskinen P, Manninen V, et al. Helsinki Heart Study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia. Safety of treatment, changes in risk factors, and incidence of coronary heart disease. *N Engl J Med*. 1987;317:1237–1245. doi: [10.1056/nejm198711123172001](https://doi.org/10.1056/nejm198711123172001)
 26. Yusuf S, Bosch J, Dagenais G, Zhu J, Xavier D, Liu L, Pais P, López-Jaramillo P, Leiter LA, Dans A, et al. Cholesterol lowering in intermediate-risk persons without cardiovascular disease. *N Engl J Med*. 2016;374:2021–2031. doi: [10.1056/NEJMoa1600176](https://doi.org/10.1056/NEJMoa1600176)
 27. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet*. 2002;360:7–22. doi: [10.1016/s0140-6736\(02\)09327-3](https://doi.org/10.1016/s0140-6736(02)09327-3)
 28. Pedersen TR, Faergeman O, Kastelein JJ, Olsson AG, Tikkanen MJ, Holme I, Larsen ML, Bendixen FS, Lindahl C, Szarek M, et al. High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction: the IDEAL study: a randomized controlled trial. *JAMA*. 2005;294:2437–2445. doi: [10.1001/jama.294.19.2437](https://doi.org/10.1001/jama.294.19.2437)
 29. Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, Darius H, Lewis BS, Ophuis TO, Jukema JW, et al. Ezetimibe added to statin therapy after acute coronary syndromes. *N Engl J Med*. 2015;372:2387–2397. doi: [10.1056/NEJMoa1410489](https://doi.org/10.1056/NEJMoa1410489)
 30. Yokoyama M, Origasa H, Matsuzaki M, Matsuzawa Y, Saito Y, Ishikawa Y, Oikawa S, Sasaki J, Hishida H, Itakura H, et al. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis. *Lancet*. 2007;369:1090–1098. doi: [10.1016/s0140-6736\(07\)60527-3](https://doi.org/10.1016/s0140-6736(07)60527-3)
 31. Hosomi N, Nagai Y, Kohriyama T, Ohtsuki T, Aoki S, Nezu T, Maruyama H, Sunami N, Yokota C, Kitagawa K, et al. The Japan Statin Treatment Against Recurrent Stroke (J-STARs): a multicenter, randomized, open-label, parallel-group study. *EBioMedicine*. 2015;2:1071–1078. doi: [10.1016/j.ebiom.2015.08.006](https://doi.org/10.1016/j.ebiom.2015.08.006)
 32. Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM Jr, Kastelein JJ, Koenig W, Libby P, Lorenzatti AJ, MacFadyen JG, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med*. 2008;359:2195–2207. doi: [10.1056/NEJMoa0807646](https://doi.org/10.1056/NEJMoa0807646)
 33. Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med*. 1998;339:1349–1357. doi: [10.1056/nejm199811053391902](https://doi.org/10.1056/nejm199811053391902)
 34. Serruys PW, de Feyter P, Macaya C, Kokott N, Puel J, Vrolix M, Branzi A, Bertolami MC, Jackson G, Strauss B, et al. Fluvastatin for prevention of cardiac events following successful first percutaneous coronary intervention: a randomized controlled trial. *JAMA*. 2002;287:3215–3222. doi: [10.1001/jama.287.24.3215](https://doi.org/10.1001/jama.287.24.3215)
 35. Nakamura H, Arakawa K, Itakura H, Kitabatake A, Goto Y, Toyota T, Nakaya N, Nishimoto S, Muranaka M, Yamamoto A, et al. Primary prevention of cardiovascular disease with pravastatin in Japan (MEGA study): a prospective randomised controlled trial. *Lancet*. 2006;368:1155–1163. doi: [10.1016/s0140-6736\(06\)69472-5](https://doi.org/10.1016/s0140-6736(06)69472-5)
 36. Schwartz GG, Steg PG, Szarek M, Bhatt DL, Bittner VA, Diaz R, Edelberg JM, Goodman SG, Hanotin C, Harrington RA, et al. Alirocumab and cardiovascular outcomes after acute coronary syndrome. *N Engl J Med*. 2018;379:2097–2107. doi: [10.1056/NEJMoa1801174](https://doi.org/10.1056/NEJMoa1801174)
 37. Bosch J, Gerstein HC, Dagenais GR, Díaz R, Dyal L, Jung H, Maggiono AP, Probstfield J, Ramachandran A, Riddle MC, et al. n-3 fatty acids and cardiovascular outcomes in patients with dysglycemia. *N Engl J Med*. 2012;367:309–318. doi: [10.1056/NEJMoa1203859](https://doi.org/10.1056/NEJMoa1203859)
 38. Campeau LK, Domanski M, Hunninghake DB, White CW, Geller NL, Rosenberg Y. The effect of aggressive lowering of low-density lipoprotein cholesterol levels and low-dose anticoagulation on obstructive changes in saphenous-vein coronary-artery bypass grafts. *N Engl J Med*. 1997;336:153–162. doi: [10.1056/nejm199701163360301](https://doi.org/10.1056/nejm199701163360301)
 39. Shepherd J, Blauw GJ, Murphy MB, Bollen EL, Buckley BM, Cobbe SM, Ford I, Gaw A, Hyland M, Jukema JW, et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. *Lancet*. 2002;360:1623–1630. doi: [10.1016/s0140-6736\(02\)11600-x](https://doi.org/10.1016/s0140-6736(02)11600-x)
 40. Cannon CP, Braunwald E, McCabe CH, Rader DJ, Rouleau JL, Belder R, Joyal SV, Hill KA, Pfeffer MA, Skene AM. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med*. 2004;350:1495–1504. doi: [10.1056/NEJMoa040583](https://doi.org/10.1056/NEJMoa040583)
 41. Taguchi I, Iimuro S, Iwata H, Takashima H, Abe M, Amiya E, Ogawa T, Ozaki Y, Sakuma I, Nakagawa Y, et al. High-dose versus low-dose pitavastatin in Japanese patients with stable coronary artery disease

- (REAL-CAD): a randomized superiority trial. *Circulation*. 2018;137:1997–2009. doi: [10.1161/circulationaha.117.032615](https://doi.org/10.1161/circulationaha.117.032615)
42. Bhatt DL, Steg PG, Miller M, Brinton EA, Jacobson TA, Ketchum SB, Doyle RT Jr, Juliano RA, Jiao L, Granowitz C, et al. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. *N Engl J Med*. 2019;380:11–22. doi: [10.1056/NEJMoa1812792](https://doi.org/10.1056/NEJMoa1812792)
 43. Armitage J, Bowman L, Wallendszus K, Bulbulia R, Rahimi K, Haynes R, Parish S, Peto R, Collins R. Intensive lowering of LDL cholesterol with 80 mg versus 20 mg simvastatin daily in 12,064 survivors of myocardial infarction: a double-blind randomised trial. *Lancet*. 2010;376:1658–1669. doi: [10.1016/s0140-6736\(10\)60310-8](https://doi.org/10.1016/s0140-6736(10)60310-8)
 44. Baigent C, Landray MJ, Reith C, Emberson J, Wheeler DC, Tomson C, Wanner C, Crane V, Cass A, Craig J, et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. *Lancet*. 2011;377:2181–2192. doi: [10.1016/s0140-6736\(11\)60739-3](https://doi.org/10.1016/s0140-6736(11)60739-3)
 45. Amarenco P, Bogousslavsky J, Callahan A III, Goldstein LB, Hennerici M, Rudolph AE, Sillesen H, Simunovic L, Szarek M, Welch KM, et al. High-dose atorvastatin after stroke or transient ischemic attack. *N Engl J Med*. 2006;355:549–559. doi: [10.1056/NEJMoa061894](https://doi.org/10.1056/NEJMoa061894)
 46. Nicholls SJ, Lincoff AM, Garcia M, Bash D, Ballantyne CM, Barter PJ, Davidson MH, Kastelein JJP, Koenig W, McGuire DK, et al. Effect of high-dose omega-3 fatty acids vs corn oil on major adverse cardiovascular events in patients at high cardiovascular risk: the STRENGTH randomized clinical trial. *JAMA*. 2020;324:2268–2280. doi: [10.1001/jama.2020.22258](https://doi.org/10.1001/jama.2020.22258)
 47. Galan P, Kesse-Guyot E, Czernichow S, Briancon S, Blacher J, Hercberg S. Effects of B vitamins and omega 3 fatty acids on cardiovascular diseases: a randomised placebo controlled trial. *BMJ*. 2010;341:c6273. doi: [10.1136/bmj.c6273](https://doi.org/10.1136/bmj.c6273)
 48. LaRosa JC, Grundy SM, Waters DD, Shear C, Barter P, Fruchart JC, Gotto AM, Greten H, Kastelein JJ, Shepherd J, et al. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *N Engl J Med*. 2005;352:1425–1435. doi: [10.1056/NEJMoa050461](https://doi.org/10.1056/NEJMoa050461)
 49. Kitas GD, Nightingale P, Armitage J, Sattar N, Belch JJJ, Symmons DPM. A multicenter, randomized, placebo-controlled trial of atorvastatin for the primary prevention of cardiovascular events in patients with rheumatoid arthritis. *Arthritis Rheumatol*. 2019;71:1437–1449. doi: [10.1002/art.40892](https://doi.org/10.1002/art.40892)
 50. Manson JE, Cook NR, Lee IM, Christen W, Bassuk SS, Mora S, Gibson H, Albert CM, Gordon D, Copeland T, et al. Marine n-3 fatty acids and prevention of cardiovascular disease and cancer. *N Engl J Med*. 2019;380:23–32. doi: [10.1056/NEJMoa1811403](https://doi.org/10.1056/NEJMoa1811403)
 51. Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, MacFarlane PW, McKillop JH, Packard CJ. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. *N Engl J Med*. 1995;333:1301–1307. doi: [10.1056/nejm199511163332001](https://doi.org/10.1056/nejm199511163332001)
 52. Amarenco P, Kim JS, Labreuche J, Charles H, Abtan J, Béjot Y, Cabrejo L, Cha JK, Ducrocq G, Giroud M, et al. A comparison of two LDL cholesterol targets after ischemic stroke. *N Engl J Med*. 2020;382:9–19. doi: [10.1056/NEJMoa1910355](https://doi.org/10.1056/NEJMoa1910355)
 53. Mihaylova B, Emberson J, Blackwell L, Keech A, Simes J, Barnes EH, Voysey M, Gray A, Collins R, Baigent C. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. *Lancet*. 2012;380:581–590. doi: [10.1016/s0140-6736\(12\)60367-5](https://doi.org/10.1016/s0140-6736(12)60367-5)
 54. McKinney JS, Kostis WJ. Statin therapy and the risk of intracerebral hemorrhage: a meta-analysis of 31 randomized controlled trials. *Stroke*. 2012;43:2149–2156. doi: [10.1161/strokeaha.112.655894](https://doi.org/10.1161/strokeaha.112.655894)
 55. Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, Bhalra N, Peto R, Barnes EH, Keech A, Simes J, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet*. 2010;376:1670–1681. doi: [10.1016/s0140-6736\(10\)61350-5](https://doi.org/10.1016/s0140-6736(10)61350-5)
 56. Rao SJ, Martin SS, Sharma G. *Fact or fiction: statins increase the risk of hemorrhagic stroke*. American College of Cardiology. 2021. Accessed March 29, 2022. <https://www.acc.org/Latest-in-Cardiology/Articles/2021/08/25/13/00/Fact-or-Fiction-Statins-Increase-the-Risk-of-Hemorrhagic-Stroke>
 57. Sett AK, Robinson TG, Mistri AK. Current status of statin therapy for stroke prevention. *Expert Rev Cardiovasc Ther*. 2011;9:1305–1314. doi: [10.1586/erc.11.106](https://doi.org/10.1586/erc.11.106)
 58. Judge C, Rutledge S, Costello M, Murphy R, Loughlin E, Alvarez-Iglesias A, Ferguson J, Gorey S, Nolan A, Canavan M, et al. Lipid lowering therapy, low-density lipoprotein level and risk of intracerebral hemorrhage—a meta-analysis. *J Stroke Cerebrovasc Dis*. 2019;28:1703–1709. doi: [10.1016/j.jstrokecerebrovasdis.2019.02.018](https://doi.org/10.1016/j.jstrokecerebrovasdis.2019.02.018)
 59. Sanz-Cuesta BE, Saver JL. Lipid-lowering therapy and hemorrhagic stroke risk: comparative meta-analysis of statins and PCSK9 inhibitors. *Stroke*. 2021;52:3142–3150. doi: [10.1161/strokeaha.121.034576](https://doi.org/10.1161/strokeaha.121.034576)
 60. Authors/Task Force Members; ESC Committee for Practice Guidelines (CPG); ESC National Cardiac Societies. 2019 ESC/EAS guidelines for the management of dyslipidaemias. Lipid modification to reduce cardiovascular risk. *Atherosclerosis*. 2019;290:140–205. doi: [10.1016/j.atherosclerosis.2019.08.014](https://doi.org/10.1016/j.atherosclerosis.2019.08.014)
 61. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71. doi: [10.1136/bmj.n71](https://doi.org/10.1136/bmj.n71)
 62. Fulcher J, O'Connell R, Voysey M, Emberson J, Blackwell L, Mihaylova B, Simes J, Collins R, Kirby A, Colhoun H, et al. Efficacy and safety of LDL-lowering therapy among men and women: meta-analysis of individual data from 174,000 participants in 27 randomised trials. *Lancet*. 2015;385:1397–1405. doi: [10.1016/s0140-6736\(14\)61368-4](https://doi.org/10.1016/s0140-6736(14)61368-4)
 63. Gencer B, Marston NA, Im K, Cannon CP, Sever P, Keech A, Braunwald E, Giugliano RP, Sabatine MS. Efficacy and safety of lowering LDL cholesterol in older patients: a systematic review and meta-analysis of randomised controlled trials. *Lancet*. 2020;396:1637–1643. doi: [10.1016/s0140-6736\(20\)32332-1](https://doi.org/10.1016/s0140-6736(20)32332-1)
 64. Sabatine MS, Wiviott SD, Im K, Murphy SA, Giugliano RP. Efficacy and safety of further lowering of low-density lipoprotein cholesterol in patients starting with very low levels: a meta-analysis. *JAMA Cardiol*. 2018;3:823–828. doi: [10.1001/jamacardio.2018.2258](https://doi.org/10.1001/jamacardio.2018.2258)
 65. Gencer A, Schutz C, Thieleman W. Influence of the particle concentration and Marangoni flow on the formation of cellulose nanocrystal films. *Langmuir*. 2017;33:228–234. doi: [10.1021/acs.langmuir.6b03724](https://doi.org/10.1021/acs.langmuir.6b03724)
 66. Marston NA, Giugliano RP, Im K, Silverman MG, O'Donoghue ML, Wiviott SD, Ference BA, Sabatine MS. Association between triglyceride lowering and reduction of cardiovascular risk across multiple lipid-lowering therapeutic classes: a systematic review and meta-regression analysis of randomized controlled trials. *Circulation*. 2019;140:1308–1317. doi: [10.1161/circulationaha.119.041998](https://doi.org/10.1161/circulationaha.119.041998)
 67. Tavazzi L, Maggioni AP, Marchioli R, Barlera S, Franzosi MG, Latini R, Lucci D, Nicolosi GL, Porcu M, Tognoni G. Effect of n-3 polyunsaturated fatty acids in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. *Lancet*. 2008;372:1223–1230. doi: [10.1016/s0140-6736\(08\)61239-8](https://doi.org/10.1016/s0140-6736(08)61239-8)
 68. Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, Goldberg AC, Gordon D, Levy D, Lloyd-Jones DM, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;129:S1–S45. doi: [10.1161/01.cir.0000437738.63853.7a](https://doi.org/10.1161/01.cir.0000437738.63853.7a)
 69. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, Cates CJ, Cheng HY, Corbett MS, Eldridge SM, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*. 2019;366:14898. doi: [10.1136/bmj.14898](https://doi.org/10.1136/bmj.14898)
 70. Efthimiou O. Practical guide to the meta-analysis of rare events. *Evid Based Ment Health*. 2018;21:72–76. doi: [10.1136/eb-2018-102911](https://doi.org/10.1136/eb-2018-102911)
 71. Deeks JJ, Higgins JPT, Altman DG (editors). Chapter 10: Analysing data and undertaking meta-analyses. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, eds. *Cochrane Handbook for Systematic Reviews of Interventions*. 2nd Edition. Chichester (UK): John Wiley & Sons; 2019:241–284.
 72. Turner RM, Jackson D, Wei Y, Thompson SG, Higgins JP. Predictive distributions for between-study heterogeneity and simple methods for their application in Bayesian meta-analysis. *Stat Med*. 2015;34:984–998. doi: [10.1002/sim.6381](https://doi.org/10.1002/sim.6381)
 73. Hansen S, Rice K. Exact inference for fixed effects meta-analysis of 2 × 2 tables. *Stat Med*. 2023;42:3333–3352. doi: [10.1002/sim.9808](https://doi.org/10.1002/sim.9808)
 74. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315:629–634. doi: [10.1136/bmj.315.7109.629](https://doi.org/10.1136/bmj.315.7109.629)
 75. Falcone GJ, Kirsch E, Acosta JN, Noche RB, Leasure A, Marini S, Chung J, Selim M, Meschia JF, Brown DL, et al. Genetically elevated LDL associates with lower risk of intracerebral hemorrhage. *Ann Neurol*. 2020;88:56–66. doi: [10.1002/ana.25740](https://doi.org/10.1002/ana.25740)
 76. Allara E, Morani G, Carter P, Gkatzionis A, Zuber V, Foley CN, Rees JMB, Mason AM, Bell S, Gill D, et al. Genetic determinants of lipids and

- cardiovascular disease outcomes: a wide-angled Mendelian randomization investigation. *Circ Genom Precis Med*. 2019;12:e002711. doi: [10.1161/circgen.119.002711](https://doi.org/10.1161/circgen.119.002711)
77. Sun L, Clarke R, Bennett D, Guo Y, Walters RG, Hill M, Parish S, Millwood IY, Bian Z, Chen Y, et al. Causal associations of blood lipids with risk of ischemic stroke and intracerebral hemorrhage in Chinese adults. *Nat Med*. 2019;25:569–574. doi: [10.1038/s41591-019-0366-x](https://doi.org/10.1038/s41591-019-0366-x)
 78. Yu Z, Zhang L, Zhang G, Xia K, Yang Q, Huang T, Fan D. Lipids, apolipoproteins, statins, and intracerebral hemorrhage: a Mendelian randomization study. *Ann Neurol*. 2022;92:390–399. doi: [10.1002/ana.26426](https://doi.org/10.1002/ana.26426)
 79. Westover MB, Bianchi MT, Eckman MH, Greenberg SM. Statin use following intracerebral hemorrhage: a decision analysis. *Arch Neurol*. 2011;68:573–579. doi: [10.1001/archneurol.2010.356](https://doi.org/10.1001/archneurol.2010.356)
 80. Björkhem I, Meaney S. Brain cholesterol: long secret life behind a barrier. *Arterioscler Thromb Vasc Biol*. 2004;24:806–815. doi: [10.1161/01.ATV.0000120374.59826.1b](https://doi.org/10.1161/01.ATV.0000120374.59826.1b)
 81. Gurevitz C, Auriel E, Elis A, Kornowski R. The association between low levels of low density lipoprotein cholesterol and intracerebral hemorrhage: cause for concern? *J Clin Med*. 2022;11:536. doi: [10.3390/jcm11030536](https://doi.org/10.3390/jcm11030536)
 82. Jin X, Chen H, Shi H, Fu K, Li J, Tian L, Teng W. Lipid levels and the risk of hemorrhagic stroke: a dose-response meta-analysis. *Nutr Metab Cardiovasc Dis*. 2021;31:23–35. doi: [10.1016/j.numecd.2020.10.014](https://doi.org/10.1016/j.numecd.2020.10.014)
 83. Aeschbacher-Germann M, Kaiser N, Speierer A, Blum MR, Bauer DC, Del Giovane C, Aujesky D, Gencer B, Rodondi N, Moutzouri E. Lipid-lowering trials are not representative of patients managed in clinical practice: a systematic review and meta-analysis of exclusion criteria. *J Am Heart Assoc*. 2023;12:e026551. doi: [10.1161/jaha.122.026551](https://doi.org/10.1161/jaha.122.026551)
 84. Moutzouri E, Adam L, Feller M, Syrogiannouli L, Da Costa BR, Del Giovane C, Bauer DC, Aujesky D, Chioloro A, Rodondi N. Low reporting of cointerventions in recent cardiovascular clinical trials: a systematic review. *J Am Heart Assoc*. 2020;9:e014890. doi: [10.1161/jaha.119.014890](https://doi.org/10.1161/jaha.119.014890)
 85. Moutzouri E, Glutz M, Abolhassani N, Feller M, Adam L, Gencer B, Del Giovane C, Bétrisey S, Paladini RE, Hennings E, et al. Association of statin use and lipid levels with cerebral microbleeds and intracranial hemorrhage in patients with atrial fibrillation: a prospective cohort study. *Int J Stroke*. 2023;18:1227. doi: [10.1177/17474930231181010](https://doi.org/10.1177/17474930231181010)
 86. Sedgwick P. Understanding the ecological fallacy. *BMJ*. 2015;351:h4773. doi: [10.1136/bmj.h4773](https://doi.org/10.1136/bmj.h4773)
 87. Taylor F, Huffman MD, Macedo AF, Moore TH, Burke M, Davey Smith G, Ward K, Ebrahim S. Statins for the primary prevention of cardiovascular disease. *Cochrane Database Syst Rev*. 2013;2013:CD004816. doi: [10.1002/14651858.CD004816.pub5](https://doi.org/10.1002/14651858.CD004816.pub5)
 88. Greenberg SM, Ziai WC, Cordonnier C, Dowlatsahi D, Francis B, Goldstein JN, Hemphill JC III, Johnson R, Keigher KM, Mack WJ, et al. 2022 Guideline for the management of patients with spontaneous intracerebral hemorrhage: a guideline from the American Heart Association/American Stroke Association. *Stroke*. 2022;53:e282–e361. doi: [10.1161/str.0000000000000407](https://doi.org/10.1161/str.0000000000000407)
 89. Abramson J, Kaplan RM, Redberg RF. Questioning the benefit of statins for low-risk populations-medical misinformation or scientific evidence? *JAMA Cardiol*. 2020;5:233. doi: [10.1001/jamacardio.2019.5117](https://doi.org/10.1001/jamacardio.2019.5117)