Stroke

CLINICAL AND POPULATION SCIENCES

Lipid-Lowering Therapy and Hemorrhagic Stroke Risk

Comparative Meta-Analysis of Statins and PCSK9 Inhibitors

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BACKGROUND AND PURPOSE: Statins were shown to increase hemorrhagic stroke (HS) in patients with a first cerebrovascular event in 2006 (SPARCL), likely due to off-target antithrombotic effects, but continued to sometimes be used in patients with elevated HS risk due to absence of alternative medications. Recently, the PCSK9Is (proprotein convertase subtilisin kexin 9 inhibitors) have become available as a potent lipid-lowering class with potentially less hemorrhagic propensity.

METHODS: We performed a systematic comparative meta-analysis assessing HS rates across all completed statin and PCSK9I randomized clinical trials with treatment >3 months, following PRISMA guidelines. In addition to HS rates across all trials, causal relation was probed by evaluating for dose-response relationships by medication (low versus high medication dose/potency) and by presence and type of preceding brain vascular events at inception (none versus ischemic stroke/transient ischemic attack versus HS).

RESULTS: The systematic review identified 36 statin randomized clinical trials (204 918 patients) and 5 PCSK9I randomized clinical trials (76 140 patients). Across all patient types and all medication doses/potencies, statins were associated with increased HS: relative risk 1.15, P=0.04; PCSK9Is were not (P=0.77). In the medication dose/potency analysis, higher dose/potency statins (7 trials, 62 204 patients) were associated with magnified HS risk: relative risk, 1.53; P=0.002; higher dose/potency PCSK9Is (1 trial, 27 564 patients) were not (P=0.99). In the type of index brain vascular injury analysis for statins (5 trials, 9772 patients), prior ischemic stroke/transient ischemic attack was associated with a magnified risk of HS: relative risk, 1.43; P=0.04; and index intracerebral hemorrhage was associated with an extremely high effect estimate of risk of recurrent HS: hazard ratio, 4.06. For PCSK9Is, prior ischemic stroke/transient ischemic attack (1 trial, 5337 patients) was not associated with increased HS risk (P=0.97).

CONCLUSIONS: Statins increase the risk of HS in a medication dose- and type of index brain vascular injury-dependent manner; PCSK9Is do not increase HS risk. PCSK9Is may be a preferred lipid-lowering medication class in patients with elevated HS risk, including patients with prior HS.

GRAPHIC ABSTRACT: An online graphic abstract is available for this article.

Key Words: hemorrhagic stroke ■ ischemic stroke ■ lipids ■ proprotein convertase, subtilisin-kexin type 9 ■ statins ■ transient ischemic attack

The therapeutic use of statins was an important advance in the primary and secondary prevention of atherosclerotic ischemic cardiovascular disease in the 21st century.[1,2] However, several studies have suggested that statins may increase the risk of hemorrhagic stroke, somewhat offsetting their beneficial effects in preventing ischemic stroke and myocardial infarction.[3] While the favorable effects of statins in reducing ischemic events is primarily directly related to their on-target cholesterol-lowering effects with plaque stabilization, the

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Nonstandard Abbreviations and Acronyms

HS	hemorrhagic stroke
PCSK9Is	proprotein convertase subtilisin kexin 9 inhibitors
RCT	randomized clinical trial
LDL	low-density lipoprotein
SAH	subarachnoid hemorrhage
RR	relative risk
HR	hazard ratio
A/C	active/control
ACS	acute coronary syndrome
ASCVD	atherosclerotic cardiovascular disease
BMI	body mass index
C-A	difference between control versus active
CHD	coronary heart disease
CKD	chronic kidney disease
CV	cardiovascular
CVRF	cardiovascular risk factors
DM	diabetes
FH	familial hypercholesterolemia
IS	ischemic stroke
MT	maximally tolerated
PVD	peripheral vascular disease
AIS	acute ischemic stroke
TIA	transient ischemic attack
ICH	intracerebral hemorrhage

potential hemorrhagic propensity of statins has been attributed to off-target pharmacological effects of this drug class. Well-documented (not cholesterol-lowering mediated) antithrombotic properties of statins include antiplatelet, anticoagulant, and fibrinolytic effects.[4] This disjunction raises the possibility that cholesterol-lowering medications from other medication classes that do not have off-target antithrombotic effects could provide beneficial reduction in ischemic events unmitigated by a countering increase in hemorrhagic stroke. Multiple new classes of cholesterol-lowering medications have entered into clinical practice since the introduction of statins, including PCSK9Is (proprotein convertase subtilisin kexin 9 inhibitors, eg, evolucumab and alirocumab), selective cholesterol-absorption inhibitors (eg, ezetimibe), and ATP-citrate lyase inhibitors (eg, bempedoic acid). With this advent of a poststatin era, medications other than statins may be advantageous to use in patients with cerebral hemorrhagic propensities.[5,6]

Among the more recently developed medications, the PCSK9Is are the most potent in lipid-lowering effect, exceeding statins, while having much less association with identified off-target antithrombotic effects.[7] They exert their effects by degrading LDL (low-density lipoprotein) receptors on the liver surface, increasing receptor turnover thereby enhancing clearance of circulating LDL. In addition, like statins they have been studied in multiple large randomized trials providing sufficient power to characterize hemorrhagic as well as ischemic stroke events. Accordingly, we undertook a formal meta-analytic review to compare and contrast hemorrhagic stroke rates in randomized clinical trials of statins and PCSK9Is.

METHODS

The authors declare that all supporting data are available within the article and in the Data Supplement. This study was performed in accordance with the recommendations of the Meta-Analysis of Observational Studies in Epidemiology.[8]

Data Sources and Searches

We systematically searched PubMed and the clinical trial registry maintained at clinicaltrials.gov from 1966 to June 2020. Separate search strategies were performed to identify individual trials and meta-analyses of statin medications and of PCSK9 inhibitors and covered the time period from 1966 to June 2020. For statins, the PubMed search terms were "hydroxymethylglutaryl-CoA reductase inhibitors" or "statin" or "cholesterol-lowering", and "cerebral hemorrhage" or "intraparenchymal hemorrhage" or "intracerebral hemorrhage" or "hemorrhagic stroke", and "clinical trial" or "randomized control trial" or "randomized clinical trial" or "meta-analysis." For PCSK9 inhibitors, the PubMed search terms were "PCSK9 inhibitors" or "evolocumab" or "evolucumab" or "alirocumab" or "ralpancizumab" or "bococizumab", and "cerebral hemorrhage" or "intraparenchymal hemorrhage" or "intracerebral hemorrhage" or "hemorrhagic stroke", and "clinical trial" or "randomized control trial" or "randomized clinical trial" or "meta-analysis". We also reviewed the introduction and discussion sections of retrieved trials and meta-analyses to identify additional studies.

Study Selection

For statins, inclusion criteria for this study were (1) randomized trial of statins versus control or of higher dose statins versus lower dose statins; (2) study therapy duration >3 months; and (3) intracerebral hemorrhage/hemorrhagic stroke rates reported. For PCSK9I medications inclusion criteria were (1) randomized trial of PCSK9I versus control or of higher dose PCSK9I versus lower dose PCSK9I; (2) study therapy duration >3 months; and (3) intracerebral hemorrhage/hemorrhagic stroke rates reported.

Extraction of Design Elements and Data From Trials

All data were extracted independently by 2 investigators (Drs Sanz-Cuesta and Saver), with discrepancies resolved by consensus discussion. Where specified, we used hemorrhagic strokes, including both intraparenchymal hemorrhages and subarachnoid hemorrhages, but not subdural hematoma, as the outcome events. When only intraparenchymal hemorrhage was reported, that value was used.[9]

Statistical Analysis

We projected that medications that provoked hemorrhage would show a gradient of risk based on patient type and medication dose. With regard to patients, individuals without prior ischemic or hemorrhagic stroke producing injured brain would be at lowest risk, individuals with prior ischemic stroke at intermediate risk, and individuals with prior hemorrhagic stroke at highest risk. With regard to dosing, lower medication doses/potency would have less risk than higher doses/potency. Based on this framework, we analyzed trials in 4 groupings:

1. All patients/any dose—includes trials enrolling both patients with and without prior stroke and trials comparing low dose/potency versus control, high dose/potency versus control, and high dose/potency versus low dose/potency.
2. Cerebral ischemia patients/any dose—includes only patients with a history of ischemic stroke or transient ischemic attack at entry treated long-term (>3 months) but includes trials comparing low dose/potency versus control, high dose/potency versus control, and high dose/potency versus low dose/potency.
3. All patients/high dose or high potency—includes trials enrolling both patients with and without history of stroke but only trials comparing high dose/potency versus control.
4. Patients with hemorrhagic stroke/any dose—includes only patients with a history of hemorrhagic stroke at entry but includes trials comparing low dose/potency versus control, high dose/potency versus control, and high dose/potency versus low dose/potency.

For statins, high dose/potency was defined as atorvastatin 80 mg, simvastatin 80 mg, pravastatin 40 mg, or rosuvastatin 20 mg per day.[10] For PCSK9Is, high potency was defined as LDL levels <10 mg/dL.

Data were analyzed according to the intention-to-treat principle. Relative risk (RR) with 95% CI was used to quantify the effect of each lipid-lowering class versus control or high dose versus low dose upon hemorrhagic stroke. When existing meta-analyses incorporating all identified RCTs already had performed such an analysis, the results were extracted from the existing reports. When such existing meta-analyses were not identified, we computed a random-effects estimate based on the Mantel-Haenszel method, using Review Manager software, version 5.3, to create forest plots and funnel, traffic light, and summary plots.[11]

RESULTS

Identification and Characterization of Statin Trials

For statins, the systematic search yielded 65 records, among which 8 records were excluded as not being RCTs or meta-analyses based on study titles and 17 after detailed screening of study abstracts and full text (Figure 1). Among the 37 meta-analyses and recent RCTs, after exclusion of individual RCTs and less comprehensive meta-analyses fully subsumed by more comprehensive meta-analyses, a total of 36 RCTs were identified enrolling 204 918 individuals meeting study entry criteria. Characteristics of the trials are shown in Table I in the Data Supplement. The meta-analyses and trials addressed the 4 analytic groups in the following manner:

1. All patients/any dose: Considering trials enrolling nonstroke patients, patients with stroke, or both and testing any dose/potency of statin, high or low, a total of 33 RCTs enrolling 203 305 individuals reported hemorrhagic stroke rates. These trials were analyzed in the meta-analysis of Cheng et al,[12] with the search not identifying any salient subsequent RCTs.
2. Cerebral ischemia patients/any dose: Considering trials reporting results separately in patients with a history of ischemic stroke or transient ischemic attack at entry but testing any statin dose/potency, a total of 5 RCTs enrolling 9772 individuals with cerebral ischemia reported hemorrhagic stroke rates. These trials were analyzed in the meta-analysis of Teoh et al,[13] with the search not identifying any salient subsequent RCTs.
3. All patients/high dose or high potency: Considering trials enrolling nonstroke patients, patients with stroke, or both but only testing high-dose statins versus control, a total of 7 RCTs enrolling 62 204 patients were identified. These trials were analyzed in the meta-analysis of Pandit et al,[10] with the search not identifying any salient subsequent RCTs.
4. Patients with hemorrhagic stroke/any dose: Considering trials reporting results separately in patients with a history of hemorrhagic stroke at entry but testing any statin dose/potency, the search identified 1 RCT enrolling 93 individuals with hemorrhagic stroke, with allocation to high-dose statin or control.[3]

Identification and Characterization of PCKS9I Trials

For PCSK9Is, the systematic search yielded 53 records, among which 2 were excluded as not being RCTs or meta-analyses and 1 was excluded for being a meta-analysis on a different topic after review of study records and full text (Figure 2). Among the 50 RCTs identified, 45 were excluded for not reporting data on hemorrhagic stroke events. A total 5 RCTs enrolling 76 140 individuals were identified fully meeting study entry criteria. The trials addressed the 4 analytic groups in the following manner:

1. All patients/any dose: Considering trials enrolling nonstroke patients, patients with stroke, or both and testing any dose/potency of PCSK9Is, high or low, a total of 5 RCTs enrolling 76 140 individuals reported hemorrhagic stroke rates. Tested medications included evolocumab (1 trial, 27 564 patients),[14] alirocumab (2 trials, 21 285 patients),[15,16] and bococizumb (2 trials, 27 333 patients).[17] Characteristics of the trials are shown

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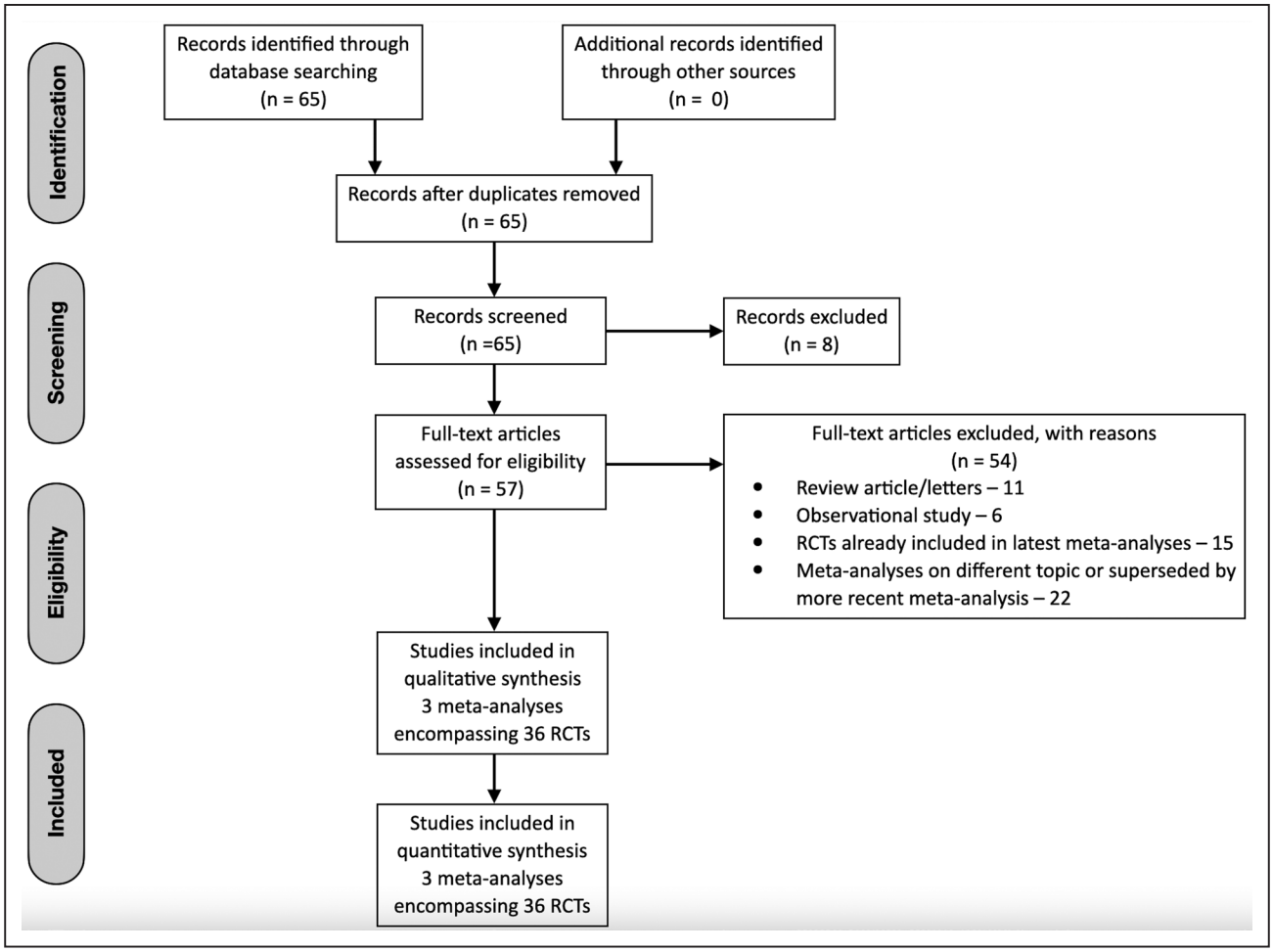

Figure 1. A total of 65 records were reviewed for statins.
Eight records were excluded after the initial screening. Fifty-four were further excluded after thorough assessment for the inclusion criteria. Finally, 3 meta-analyses with a total of 40 unique trials were assessed. RCT indicates randomized clinical trial.

in the Table. We meta-analytically combined these 5 RCTs using RevMan.

2. Cerebral ischemia patients/any dose: Considering trials reporting results separately in patients with a history of ischemic stroke or transient ischemic attack at entry but testing any PCSK9I dose, a total of 1 RCT enrolling 8011 individuals with cerebral ischemia reported hemorrhagic stroke rates.[18]
3. All patients/high dose or high potency: Considering trials enrolling nonstroke patients, patients with stroke, or both but only testing high dose or high potency PCSK9Is versus control, a total of 1 RCT was identified. Trial results permit comparison of 2669 predominantly PCSK9I treated patients with ultra-low achieved LDL levels (<20 mg/dL) versus 4395 predominantly control patients with relatively high achieved LDL levels (≥100 mg/dL).[19]
4. Patients with hemorrhagic stroke/any dose: Considering trials reporting results separately in patients with a history of hemorrhagic stroke at entry but testing any PCSK9I dose, no salient RCT was identified.

Hemorrhagic Stroke Rates in Statin Trials

All patients/any dose: Across the 33 RCTs (203 305 patients), there was a significant increased risk of hemorrhagic stroke with statins compared with control and high dose compared with low dose statins, 0.42% versus 0.36%; RR, 1.15 [95% CI, 1.00–1.32]; P=0.04.[12] Mild heterogeneity (I^2=22.1%; P=0.13) was detected across these RCTs. Publication bias was examined using funnel plots, and none was detected.[12]

Cerebral ischemia patients/any dose: Across the 5 RCTs (9772 patients), there was a significant increased risk of hemorrhagic stroke with statins compared with control among cerebral ischemia patients, 1.64% versus 1.14%; RR, 1.43 [95% CI, 1.02–2.02]; P=0.04 (Figure 3A). No heterogeneity (I^2=0%; P=0.58) was detected across these RCTs. Funnel plot analysis did not indicate presence of major publication bias (Figure IA in the Data Supplement). Risk of bias in individual RCTs was generally moderate (Figure IIA in the Data Supplement).

All patients/high dose or high potency: Across the 7 RCTs (62 204 patients), there was a significant increased

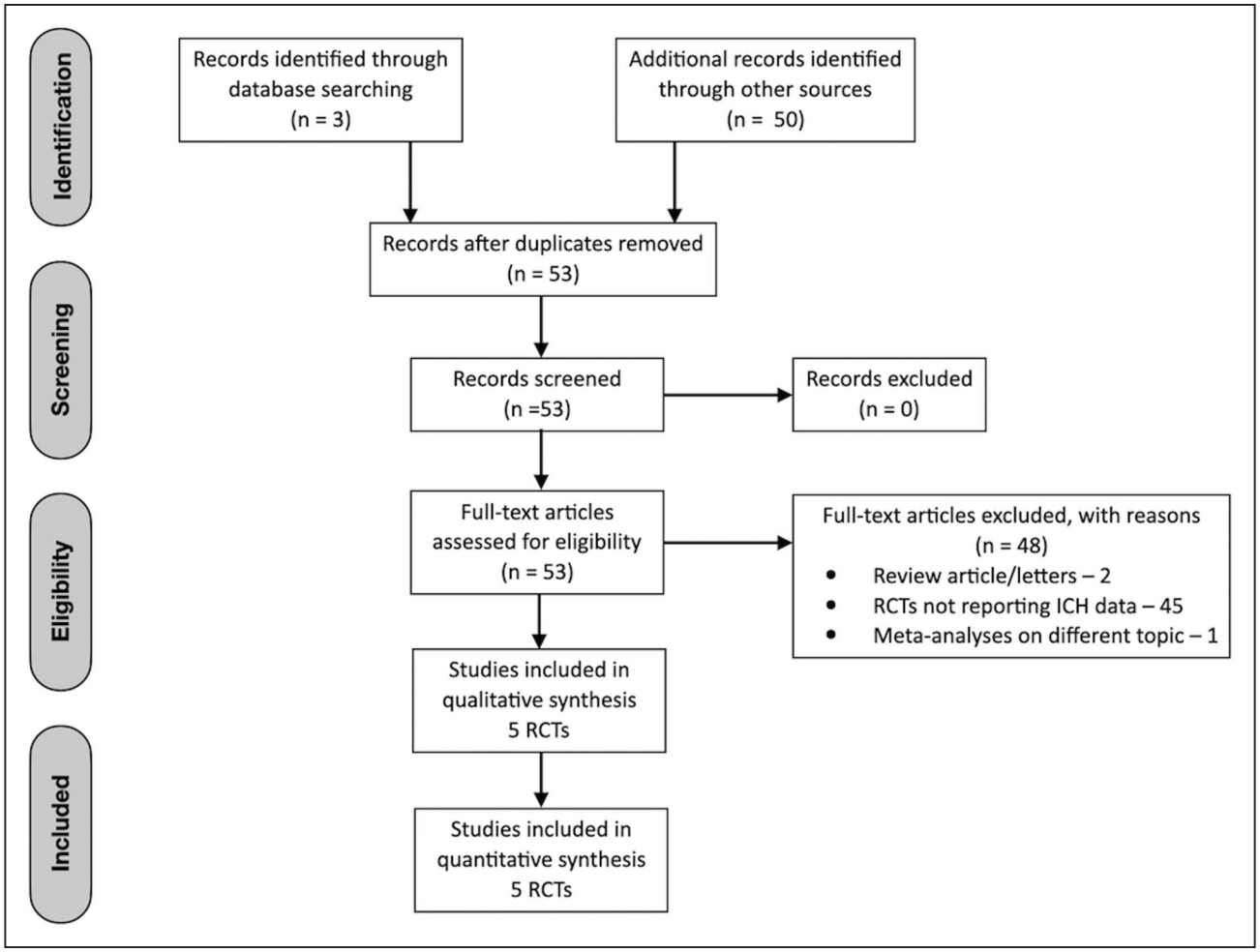

Figure 2. A total of 53 records were reviewed for PCSK9Is (proprotein convertase subtilisin kexin 9 inhibitors).
No record was excluded after the initial screening. Forty-eight were further excluded after thorough assessment for the inclusion criteria. Finally, 5 trials were included for meta-analysis. ICH indicates intracerebral hemorrhage; and RCT, randomized clinical trial.

risk of hemorrhagic stroke with high-dose statins compared with control, 0.41% versus 0.27%; RR, 1.53 (95% CI, 1.16–2.01); *P*=0.002.[10] Moderate but nonsignificant heterogeneity was detected (I^2=40%; *P*=0.12). No publication bias was observed through Begg's funnel plot.[10]

Patients with hemorrhagic stroke/any dose: In the 1 RCT reporting a subset of patients enrolled with history of intracerebral hemorrhage (93 patients), there was a nonsignificant increased risk of hemorrhagic stroke with high-dose statin compared with control, 15.55% versus 4.17%; hazard ratio (HR), 4.06 (95% CI, 0.84–19.57); *P*=0.10.[2] Risk of bias the individual RCT was low (Figure IIB in the Data Supplement).

Hemorrhagic Stroke Rates in PCSK9I Trials

All patients/any dose: Across the 5 RCTs (76 140 patients), there was not a significant increased risk of hemorrhagic stroke with PCSK9Is added to maximally tolerated statins compared with maximally tolerated statins alone, 0.09% versus 0.09%; RR, 0.93 (95% CI, 0.58–1.51); *P*=0.77 (Figure 4). No significant heterogeneity was noted across the trials (I^2=0; *P*=0.70). Funnel plot analysis did not indicate presence of publication bias (Figure IB in the Data Supplement). Risk of bias in individual RCTs was ranged from low to moderate (Figure IIC in the Data Supplement).

Patients with cerebral ischemia/any dose: In the 1 RCT reporting a subset of patients enrolled with history of ischemic stroke (5337 patients), there was not a significant increased risk of hemorrhagic stroke with PCSK9Is added to maximally tolerated statins compared with maximally tolerated statins alone, 0.52% versus 0.53%; RR, 0.99 (95% CI, 0.47–2.07); *P*=0.97.[18]

All patients/high dose or high potency: In the 1 RCT (27 564 patients) reporting analysis of the achieved lipid levels and hemorrhagic stroke, no relation between quintile of achieved LDL and hemorrhagic stroke was noted. Compared with patients with achieved LDL levels of ≥100 mg/dL—HR 1.00 (reference), 0.16%, HRs were LDL 70 to 99 mg/dL—HR 1.57, 0.23%; LDL 50 to 69 mg/dL—HR

Table. Characteristics of the PCSK9Is RCTs Reporting HS as Adverse Event Included in the Meta-Analysis

Trial	Year	Population	Qualifying LDL-C	PCSK9I type	PCSK9I dose, mg/2w	Added lipid-lowering Rx in both A+C	Follow-up duration in both A+C, mean (m)	Randomized patients (A/C)	Age, mean (y)	Male sex (%)	BMI, kg/m²	C-A LDL-C (%)
FOURIER[13]	2017	ASCVD, including IS	≥70 mg/dL (1.8 mmol/L)	Evolocumab	140	MT statins	26	13 769/ 13 756	63	75.4	85 kg	59
ODYSSEY Outcomes[14]	2018	ACS	≥70 mg/dL (1.8 mmol/L)	Alirocumab	150	MT statins ±other	34	5276/5297	59	74.8	28.5	54.7
ODYSSEY Long Term[15]	2015	FH	≥70 mg/dL (1.8 mmol/L)	Alirocumab	150	MT statins ±other	18.5	8386/8374	60	62.2	30.3	52.4
		CHD risk equivalents, including IS										
SPIRE-1[16]	2017	CV event, including IS	≥70 mg/dL (1.8 mmol/L)	Bococizumab	150	MT statins	7	1550/788	63	73.6	30.1	39.3
		DM, CKD, or PVD+CVRF										
		FH										
SPIRE-2[16]	2017	CV event, including IS	≥100 mg/dL (2.6 mmol/L)	Bococizumab	150	MT statins	12	9482/9462	62	65.4	30.4	37.5
		DM, CKD, or PVD+CVRF										
		FH										

A/C indicates active/control; ACS, acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; C-A, difference between control vs active; CHD, coronary heart disease; CKD, chronic kidney disease; CV, cardiovascular; CVRF, cardiovascular risk factors; DM, diabetes; FH, familial hypercholesterolemia; HS, hemorrhagic stroke; IS, ischemic stroke; LDL-C, low-density lipoprotein cholesterol; m, months; MT, maximally tolerated; PCSK9I, proprotein convertase subtilisin kexin 9 inhibitor; PVD, peripheral vascular disease; RCT, randomized clinical trial; and w, weeks.

1.39, 0.20%; LDL 20 to 49 mg/dL—HR 1.55, 0.24%; and LDL <20 mg/dL—HR 0.71, 0.11%, *P* value for trend 0.99.[19]

DISCUSSION

In this meta-analysis of randomized controlled trials enrolling over 200 000 patients in statin studies and over 75 000 patients in PCSK9-inhibitor studies, allocation to statins was associated with a modest but genuine increase in hemorrhagic stroke, while allocation to PCSK9 inhibitors was not. Further supporting a causal relationship of statins and hemorrhagic stroke were indications for statins, but not PCSK9 inhibitors, of a dose-response relationship (low versus high medication dose/potency) and of graded risk relationship by type of index

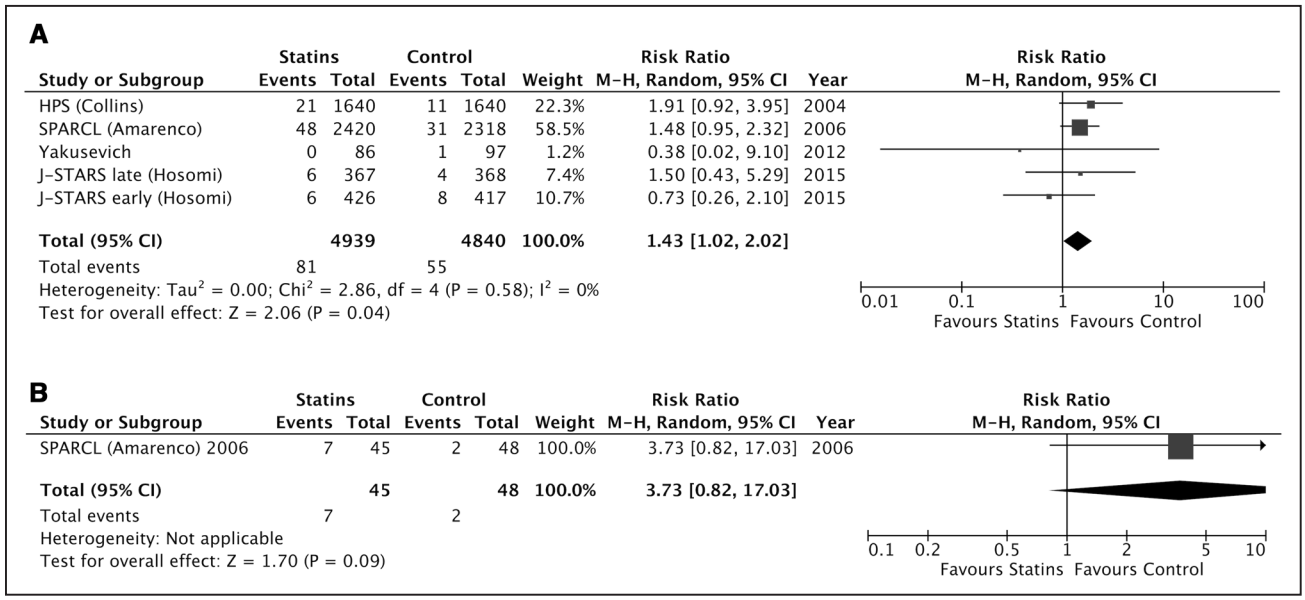

Figure 3. Forest plots showing risk of hemorrhagic stroke.
A, Risk of hemorrhagic stroke in statin randomized clinical trials (RCTs) in patients with index ischemic stroke or transient ischemic attack (TIA); (**B**) risk of hemorrhagic stroke in statin RCTs in patients with index hemorrhagic stroke. HPS indicates Heart Protection Study trial; J-STARS, Japan Statin Treatment Against Recurrent Stroke trial; and SPARCL, Stroke Prevention by Aggressive Reduction in Cholesterol Levels trial.

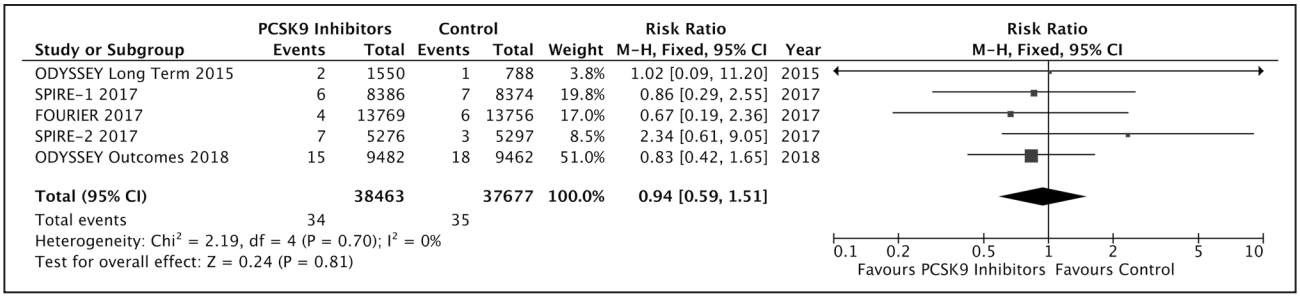

Figure 4. Forest plot showing risk of hemorrhagic stroke in PCSK9 (proprotein convertase subtilisin kexin 9 inhibitors) inhibitor randomized clinical trials (RCTs) enrolling both patients without and with history of ischemic stroke or transient ischemic attack (TIA).

FOURIER indicates Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk trial; ODYSSEY Long Term, Long-Term Safety and Tolerability of Alirocumab Versus Placebo on Top of Lipid-Modifying Therapy in High Cardiovascular Risk Patients With Hypercholesterolemia trial; ODYSSEY Outcomes, Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab trial; SPARCL, Stroke Prevention by Aggressive Reduction in Cholesterol Levels trial; and SPIRE, Evaluation of Bococizumab in Reducing the Occurrence of Major Cardiovascular Events in High-Risk Subjects trials.

brain vascular injury at inception (none versus ischemic stroke/TIA versus hemorrhagic stroke). Among every 10 000 patients treated with a statin, 6 excess hemorrhagic strokes occurred across all patients and statin doses, 14 with treatment with high-dose statins, 50 with treatment of patients with ischemic stroke, and a best estimate of 1138 with treatment of patients with hemorrhagic stroke.

For statins, these findings are perforce consistent with prior studies, as the data is abstracted from the three most comprehensive meta-analyses of all-patient/all-dose, high dose, and prior ischemic stroke RCTs and the one salient trial for prior hemorrhagic stroke.[3,10,12,13] For each of the meta-analyses, there was no-to-moderate heterogeneity and none with high heterogeneity, indicating good consistency of results across trials. The findings of these meta-analyses contrast with some meta-analyses by other groups that did not find elevated hemorrhagic stroke risk with statins, but those studies were limited by: (1) less comprehensive inclusion of relevant RCTs and (2) analysis not only of RCTs, but also observational studies, which are vulnerable to confounding by indication.[20–23] To our knowledge, the current study is the first meta-analysis reporting the risk of hemorrhagic stroke with PCSK9Is. There was no heterogeneity across the trials, indicating the aggregate findings were consistent with each of the individual prior trials.

A novel aspect of the current study was to analyze RCTs grouped into graded levels of expected hemorrhagic stroke rates if evaluated medications did have a hemorrhagic propensity. Statins showed a profile consistent with hemorrhage causation, with lowest risk estimates among all patients/all dose RCTs, intermediate risk estimates among high dose/potency RCTs

Patients	Statin / PCSK9i Dose	Expected HS Risk Magnitude if Medication is HS-Causing	Statins		PCSK9Is	
			Risk ratio/ Hazard ratio (95% CI)	P value	Risk ratio/ Hazard Ratio (95% CI)	P value
Nonstroke + Stroke	Any dose	Low	1.15 (1.00-1.32)[11]	0.04	0.93 (0.58-1.51)	0.77
AIS/TIA	Any dose	Medium	1.43 (1.02-2.02)	0.04	0.99 (0.47–2.07)[17]	0.97
Nonstroke + Stroke	High dose or high lipid-lowering	Medium	1.53 (1.16-2.01)[10]	0.002	HR trend across 5 LDL levels*[18]	0.99
ICH	Any dose	Extremely High	4.06* (0.84-19.57)[2]	0.10		

AIS – acute ischemic stroke; HS – hemorrhagic stroke; ICH – intracerebral hemorrhage; LDL – low density lipoprotein; TIA – transient ischemic attack
* The more exact hazard ratio was used when available. For the remaining analyses, risk ratios were used.

Figure 5. Summary heat-map figure-table showing relative risk of hemorrhagic stroke for statins and PCSK9Is (proprotein convertase subtilisin kexin 9 inhibitors) in different patient groups and different doses/achieved lipid-lowering.

and among RCTs enrolling patients with prior ischemic brain vascular injury, and highest risk estimate in an RCT enrolling patients with prior hemorrhagic brain vascular injury. PCSK9 inhibitors, in contrast, showed a profile consistent with no hemorrhagic tendency, with absence of hemorrhage risk in both low and intermediate risk trials (Figure 5).

With regard to pathophysiologic mediators, the disjunction between the hemorrhagic propensity of statins and that of PCSK9 inhibitors excludes a direct relationship to the cholesterol-lowering effects of the medications, as PCSK9 inhibitors are more potent in lowering lipid levels than are statins.[7] Accordingly, the likely mechanism is greater off-target antithrombotic effects for statins than for PCSK9 inhibitors. Antithrombotic properties of statins are well established, including: anticoagulant effects (in part though downregulation of tissue factor and upregulation of thrombomodulin); antiplatelet effects (in part through inhibition of platelet thromboxane A2 and platelet isoprostane formation); and profibrinolytic effects (in part through inhibit the expression of plasminogen activator inhibitor-1 and upregulate tissue-type plasminogen activator from vascular smooth muscle and endothelial cells via inhibition of Rho geranylgeranylation).[4] Some potential pathways for off-target antithrombotic effects have been identified for PCSK9 inhibitors.[24] However, in human patients, they have shown no net effect on fibrinogen and D-dimer levels, the strongest clinical markers of thrombogenicity.[25]

The differential hemorrhagic propensity of statins and PCK9 inhibitors has potential clinical implications. Though the absolute magnitude of hemorrhage increase with statins is low, the absence of hemorrhage increase with PCSK9 inhibitors are an additional potential advantage of this medication class, in addition to their greater lipid-lowering effects. Consideration might be given to clinical trials and clinical use of PCSK9 inhibitors rather than high-dose statins in populations at particular risk of hemorrhagic stroke, such as patients with prior hemorrhagic stroke and patients with multiple cerebral microbleeds.[26]

This study has limitations. First, for analysis of dose-effects, statin dosing potency was analyzed by medication classification and dose levels while PCSK9-inhibitor dosing potency was analyzed by achieved lipid-lowering levels. Second, the duration of follow-up was longer in some statin trials than any of the PCSK9 inhibitor trials, but 2 large PCSK9 inhibitor trials did have a substantial proportion of patients with follow-up beyond 3 years. Third, in the PCSK9 inhibitor meta-analysis, 32% of the patients came from trials of bococizumab, a medication associated with the development of antidrug antibodies over time, attenuating LDL-cholesterol lowering effects by 29%. However, findings were similar in the 68% of patients enrolled in trials of evolocumab and alirocumab, medications not associated with antidrug antibodies. Fourth, hemorrhagic stroke events were infrequent in individual trials so that each study estimate had wide CIs. However, with meta-analytic integration of data the CIs were narrower.

CONCLUSIONS

Statins increase the risk of hemorrhagic stroke, and the risk is magnified in a medication dose-dependent and type of vascular brain injury-dependent manner; PCSK9 inhibitors do not increase hemorrhagic stroke risk. PCSK9 inhibitors may be a preferred lipid-lowering medication class in patients with elevated risk of HS, including patients with prior hemorrhagic stroke.

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Dr Saver serves or has served on clinical trial steering committees for Johnson & Johnson and Amgen. The other author reports no conflicts.

Supplemental Materials

Online Table I
Online Figures I and II
References 10,12,13

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