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SYSTEMATIC REVIEWS AND META-ANALYSES

The effect of PCSK9 inhibitors on brain stroke prevention: A systematic review and meta-analysis

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KEYWORDS
PCSK9 inhibitors;
Brain stroke;
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Hemorrhagic brain stroke;
Cognitive function

Abstract *Background and aims:* Although proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors have been shown to improve cardiovascular outcomes, their effects on brain stroke risk are unclear. The present meta-analysis aimed to evaluate the effects of PCSK9 inhibitors on brain stroke prevention.

Methods and results: We searched PubMed, Embase, Cochrane Library, Web of Science, and ClinicalTrials.gov for research published until December 30, 2020, to find randomized controlled trials (RCTs) of PCSK9 inhibitors for brain stroke prevention. Relative risk (RR) and 95% confidence intervals (CIs) were used to represent the outcomes. Seven RCTs with 57,440 participants, including 29,850 patients treated with PCSK9 inhibitors and 27,590 control participants, were included. PCSK9 inhibitors were associated with significant reductions in total brain stroke risk (RR, 0.77; 95% CI, 0.67–0.88; $P < 0.001$) and ischemic brain stroke risk (RR, 0.76; 95% CI, 0.66, 0.89; $P < 0.001$) in comparison with the control group. There was no significant difference in cardiovascular mortality (RR, 0.95; 95% CI, 0.84–1.07; $P = 0.382$) and the risk of hemorrhagic brain stroke (RR, 1.00; 95% CI, 0.66–1.51; $P = 0.999$) between patients treated with PCSK9 inhibitors and controls. PCSK9 inhibitors did not significantly increase the incidence of neurocognitive adverse events (RR, 1.02; 95% CI, 0.81–1.29; $P = 0.85$). Moreover, subgroup analysis showed no difference in cognitive function disorder risks among different PCSK9 inhibitors and treatment times.

Conclusions: PCSK9 inhibitors significantly reduced the risk of total brain stroke and ischemic brain stroke without increasing the risk of brain hemorrhage and neurocognitive impairment.

Introduction

Brain stroke is the leading cause of disability and death worldwide. Every year, stroke affects 13.7 million people and causes 5.5 million deaths, indicating the high global burden of brain stroke [1]. Effective brain stroke prevention is essential for reducing the burden of brain stroke. Lipid-lowering therapy is the cornerstone of brain stroke prevention, and low-density lipoprotein cholesterol (LDL-C) levels are the primary intervention targets. Previous studies have shown that reducing LDL-C levels could effectively reduce the risk of atherosclerotic cardiovascular disease

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(ASCVD) and ischemic brain stroke [2]. Statin therapy is an important modality for reducing LDL-C levels. However, many patients cannot tolerate statin therapy or fail to achieve the LDL-C goal despite intensive statin therapy or even combination therapy with other lipid-lowering drugs. Therefore, effective and safe treatments for lowering lipids are necessary in such patients [3].

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are novel lipid-lowering drugs that reduce LDL-C receptor degradation by binding to PCSK9 molecules. Recent studies have shown that PCSK9 inhibitors can reduce LDL-C levels by as much as 60% and prevent cardiovascular events [4]. Several meta-analyses have also established that PCSK9 inhibitors show better efficacy and safety in reducing lipid levels, improving cardiovascular outcomes, and increasing clinical benefits in patients with ASCVD [5,6].

However, the preventive effects of PCSK9 inhibitors on brain stroke, especially ischemic brain stroke and hemorrhagic brain stroke, remain unclear. Milionis conducted a relevant meta-analysis, showing that PCSK9 inhibitors did not reduce the risk of brain stroke; however, these findings were inconsistent with the results of multiple clinical trials, possibly because of the few included studies [7]. The FOURIER and ODYSSEY OUTCOMES trials are new large clinical studies of the effects of PCSK9 inhibitors on cardiovascular outcomes in people at high risk for ASCVD. These studies reported that PCSK9 inhibitors significantly reduced the incidence of cardiovascular endpoint events in comparison with placebo, and reduced the risk of brain stroke and ischemic brain stroke [8,9]. Navkaranbir also conducted a related meta-analysis, indicating that PCSK9 inhibitors significantly reduce the risk of ischemic brain stroke without increasing cognitive impairment [10]. However, the studies by Milionis and Navkaranbir only evaluated the impact of PCSK9 inhibitors on ischemic brain stroke risk; they did not assess the effect of PCSK9 inhibitors on total brain stroke prevention or determine whether the use of PCSK9 inhibitors increases the risk of hemorrhagic stroke and/or cognitive impairment. In addition, since these meta-analyses were conducted earlier, they did not include the subsequent large-scale FOURIER and ODYSSEY OUTCOMES trials. Thus, it is necessary to re-evaluate the effects of PCSK9 inhibitors on the prevention of brain stroke events. We performed this systematic review and meta-analysis to examine the effects of PCSK9 inhibitors on brain stroke outcomes in primary and secondary prevention.

Methods

Search methods

We conducted a systematic review and meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines. The study was registered in PROSPERO (CRD42020173628). We searched the PubMed, Embase, Cochrane Library, Web of Science, and ClinicalTrials.gov databases from inception to December 2020 to identify RCTs of PCSK9 inhibitors for brain stroke prevention, with no restrictions on language or date. The keywords were "proprotein Convertase 9," "PCSK9," "antibodies," "antagonist*," "inhibit*," "alirocumab," "evolocumab," "inclisiran," "stroke," "cerebrovascular accident," and "randomized" (see Supplementary material).

Eligibility criteria

The inclusion criteria were as follows: (1) stage 2 or 3 RCTs reporting brain stroke outcomes; (2) studies with at least 500 participants; (3) a medication time of at least 6 months; and (4) a follow-up period of approximately 1 year. We excluded non-human studies, case reports, case–control studies, non-randomized studies, studies with duplicate data, and clinical trials of bococizumab.

Two researchers independently screened the studies. The irrelevant and repetitive literature was excluded by reviewing the titles and abstracts, and the researchers then reviewed the full texts that met the inclusion criteria. Disagreements were resolved through consultation with a third researcher.

Data extraction

Data extraction was independently performed by two researchers. Disagreements were resolved through discussions with a third researcher. Data extraction included study name, author, year of publication, study type, number of participants, drug and dose duration, control type, median follow-up time, baseline characteristics of the patients, brain stroke endpoint events, cardiovascular mortality, and adverse drug reactions. The main outcomes were brain stroke, ischemic brain stroke, and hemorrhagic brain stroke. Secondary outcomes included cardiovascular mortality and neurocognitive impairment.

Quality assessment

The quality of the included studies was independently assessed by two researchers using the Cochrane Collaboration risk of bias tool. The evaluation included selection bias, performance bias, detection bias, attrition bias, reporting bias, and other biases. Disagreements were resolved by a third researcher.

Statistical analysis

Meta-analysis was performed using Revman 5.3 and Stata 12.0. Relative risk (RR) and 95% confidence interval (CI) were used to represent the primary and secondary outcomes, respectively. The heterogeneity test of the included studies was conducted according to the Cochrane Q test and I^2 statistic. Fixed-effects models were used to calculate the overall relative risk with $I^2 < 50\%$ or $P > 0.1$. When $I^2 \geq 50\%$ or $P \leq 0.1$, we analyzed the sources of heterogeneity and used randomized effects models.

A subgroup analysis of neurocognitive function was performed based on the different types of PCSK9 inhibitors or treatment times. Sensitivity analysis was used to evaluate the consistency and robustness of the results. Publication bias was detected using funnel charts and Egger's tests. Statistical significance was set at $p < 0.05$.

Results

Study recruitment and characteristics

From 494 identified records, we finally obtained 211 articles after removal of duplicates; subsequently, we excluded 155 articles after reviewing their titles and abstracts, and evaluated the full text of 56 articles. Seven studies were finally included. The study selection flowchart is presented in Fig. 1. The seven RCTs enrolled 57,440 participants. Of these, 29,850 participants were treated with the PCSK9 inhibitors, and 27,590 were treated with placebo or control therapy. The study population included 41,613 men (72.4%) with an average age of 63 years. Across both groups, 41,122 (71.6%) subjects received high-intensity statin therapy and 3219 (5.6%) received ezetimibe. The median duration of follow-up was approximately 1–2.8 years. The characteristics of the individual studies are summarized in Tables 1 and 2.

Risk of bias assessment

All studies reported random sequence generation, allocation concealment, and blinding of participants and personnel, except the ORION-10 and ORION-11 studies, which were unclear for random sequence generation, and the OSLER studies, which were unblinded for patients and investigators. The GLAGOV study and ORION-10 and ORION-11 studies were unblinded for outcome assessment, and the ODYSSEY LONG TERM was unclear for outcome assessment. The risk of bias assessment in the included studies is shown in Supplemental Fig. S1.

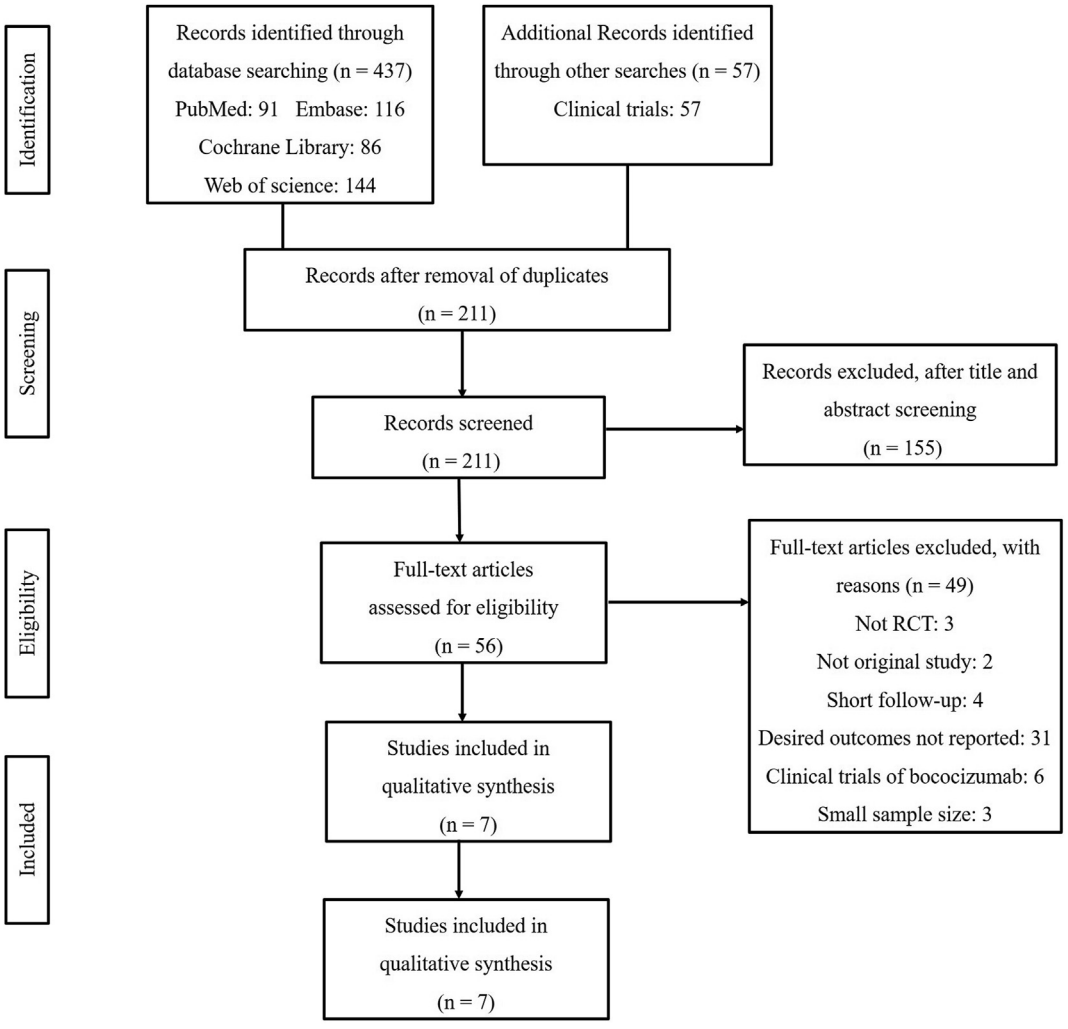

Figure 1 Flow diagram for study selection according to Preferred Reporting Items for Systematic Reviews and Meta-Analysis.

Table 1 Baseline characteristics of the included studies.

Study	Year	Phase	Sample size	Age (SD), years	Male participants, %	High-intensity statin therapy, %	Ezetimibe, %	LDL-C (IQR), mg/dL	Intention	Control	Follow-up period, years
FOURIER [8]	2017	3	27,564	63 (9)	20,795 (75.4)	19,103 (69.3)	1440 (5.2)	92 (80,109)	Evolocumab	Placebo	2.2
GLAGOV [11]	2016	3	968	59.8 (9.2)	699 (72.2)	570 (58.9)	18 (1.9)	92.5 ± 27.2	Evolocumab	Placebo	1.5
ODYSSEY LONG TERM [12]	2015	3	2341	60	1457 (62.2)	1095 (46.8)	334 (14.3)	122	Alirocumab	Placebo	1.5
ODYSSEY OUTCOMES [9]	2018	3	18,924	58.6	14,164 (74.8)	16,811 (88.8)	554 (2.9)	92 ± 31	Alirocumab	Placebo	2.8
OSLER-1 and OSLER-2 [13]	2015	2 and 3	4465	58	2255 (50.5)	1210 (27.1)	605 (13.5)	120	Evolocumab	Standard therapy	Approximately 1
ORION-10 [14]	2020	3	1561	66.1	1083 (69.4)	1062 (68.0)	154 (9.9)	104.7 ± 38.3	Inclisiran	Placebo	1.5
ORION-11 [14]	2020	3	1617	64.8	1160 (71.7)	1271 (78.6)	114 (7.1)	105.5 ± 39.1	Inclisiran	Placebo	1.5

SD, standard deviation; IQR, interquartile range.

Table 2 Outcome reports of the included studies.

Study	PCSK9 inhibitors					Control				
	Brain stroke	Ischemic brain stroke	Hemorrhagic brain stroke	Cardiovascular mortality	Neurocognitive impairment	Brain stroke	Ischemic brain stroke	Hemorrhagic brain stroke	Cardiovascular mortality	Neurocognitive impairment
FOURIER [8]	207	171	29	251	217	262	226	25	240	202
GLAGOV [11]	2	–	–	3	7	3	–	–	4	6
ODYSSEY LONG TERM [12]	–	9	–	27	65	–	2	–	26	35
ODYSSEY OUTCOMES [9]	123	111	15	240	143	170	152	18	271	167
OSLER-1 and OSLER-2 [13]	3	–	–	4	27	2	–	–	3	4
ORION-10 [14]	11	7	–	7	–	7	4	–	5	–
ORION-11 [14]	2	1	0	9	–	8	3	1	10	–

Main outcomes

The effect of PCSK9 inhibitors on brain stroke prevention

Six trials enrolling 55,095 participants were included in the analysis of total brain stroke. The total brain stroke events in the PCSK9 inhibitor group and the control group were 348 and 452, respectively. Thus, PCSK9 inhibitors significantly reduced the total brain stroke risk in comparison with controls (RR, 0.77; 95% CI 0.67–0.88; $P < 0.001$; heterogeneity: $P = 0.463$, $I^2 = 0\%$; Fig. 2).

The effect of PCSK9 inhibitors on ischemic brain stroke prevention

Five trials involving 52,003 participants were included in the analysis of ischemic brain stroke. Of these, the PCSK9 inhibitor group and the control group reported 299 and 387 ischemic brain stroke events, respectively. Thus, PCSK9 inhibitors also significantly reduced ischemic brain stroke risk in comparison with controls (RR, 0.76; 95% CI 0.66, 0.89; $P < 0.001$; heterogeneity: $P = 0.357$, $I^2 = 8.7\%$; Fig. 3).

The effect of PCSK9 inhibitors on hemorrhagic brain stroke prevention

Three trials consisting of 48,103 participants were included in the analysis of hemorrhagic brain stroke. Of these, the PCSK9 inhibitor group and the control group reported 44 and 44 hemorrhagic brain stroke events, respectively. There was no significant difference in the hemorrhagic brain stroke risk between the two groups (RR, 1.00; 95% CI 0.66–1.51; $P = 0.999$; heterogeneity: $P = 0.598$, $I^2 = 0\%$; Fig. 4).

Secondary outcomes

The effect of PCSK9 inhibitors on cardiovascular mortality outcomes

Seven RCTs were included in this analysis. Cardiovascular death outcomes were reported for 518 patients in the PCSK9 inhibitor group and 540 patients in the control group. Thus, PCSK9 inhibitors did not reduce cardiovascular mortality (RR, 0.95; 95% CI 0.84–1.07; $P = 0.382$; heterogeneity: $P = 0.406$, $I^2 = 2.5\%$; Fig. 5).

The effect of PCSK9 inhibitors on neurocognitive function

Five RCTs were included in this analysis. Neurocognitive impairment events were reported for 459 patients in the PCSK9 inhibitor group and 414 in the control group. Overall, PCSK9 inhibitors did not increase the incidence of neurocognitive impairment (RR, 1.02; 95% CI 0.81–1.29; $P = 0.85$; heterogeneity: $P = 0.1$, $I^2 = 48.6\%$, Fig. 6). The results of subgroup analysis grouped according to the different types of PCSK9 inhibitors or treatment times showed that the heterogeneity of each subgroup did not decrease. Therefore, we did not find a source of heterogeneity. In addition, there was no difference among subgroups, indicating that different PCSK9 inhibitors ($P = 0.06$) and treatment times ($P = 0.36$) had no significant effect on cognitive function (Figs. 7 and 8).

Sensitivity analyses

The heterogeneity of neurocognitive impairment outcomes before and after omitting the OSLER study were ($P = 0.1$, $I^2 = 49\%$) and ($P = 0.49$, $I^2 = 0\%$), respectively, and the combined effects were (RR, 1.023; 95% CI 0.810–1.292; $P = 0.85$) and (RR, 0.97; 95% CI 0.85–1.11; $P = 0.71$), respectively. Since the OSLER trial was a source of heterogeneous neurocognitive impairment outcomes, we found that heterogeneity was significantly reduced after omitting the OSLER study. The results of the sensitivity analysis for other outcomes remained consistent after the elimination of the included studies one-by-one (Supplemental Fig. S2).

Publication bias

There was no indication of publication bias for the main and secondary outcomes by visual assessment of

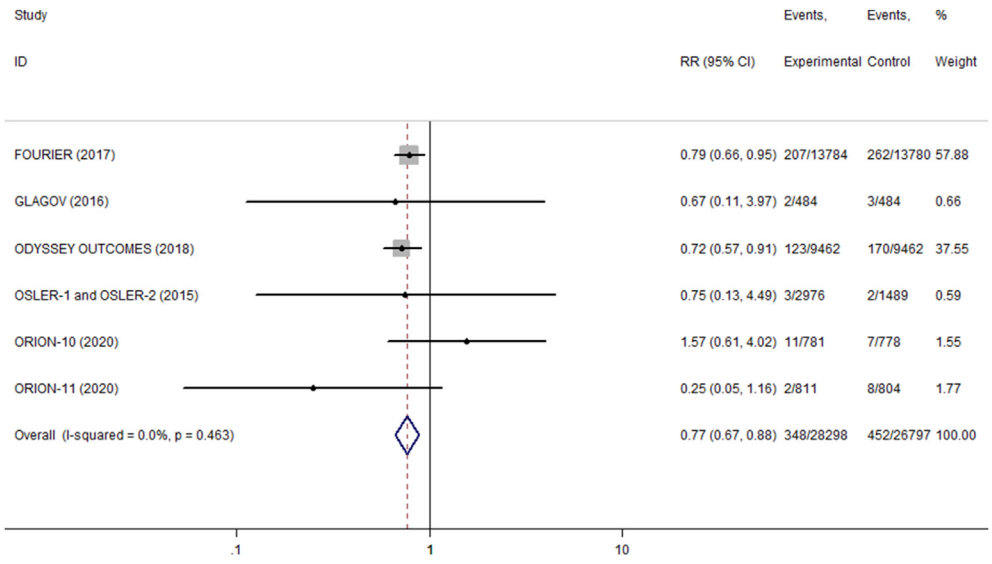

Figure 2 The effect of PCSK9 inhibitors on brain stroke.

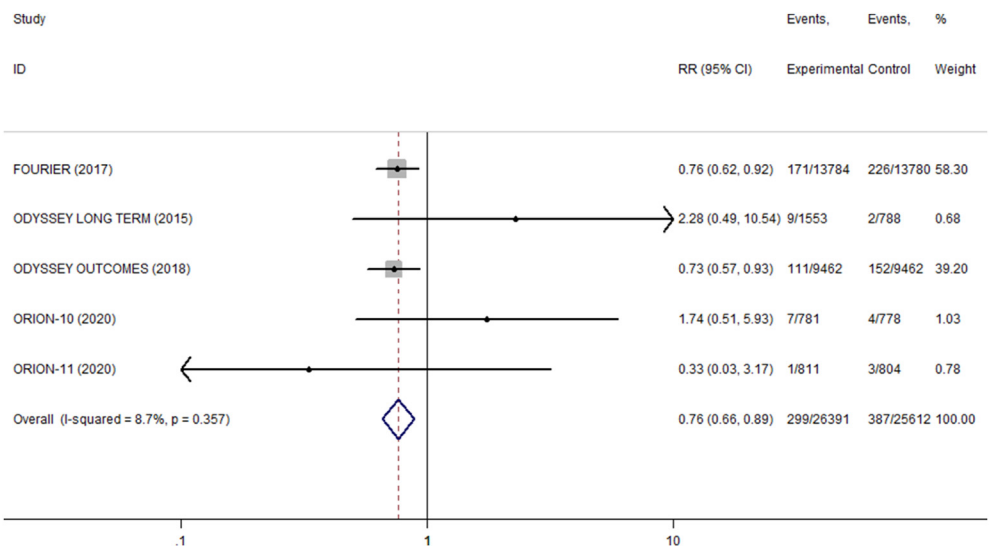

Figure 3 The effect of PCSK9 inhibitors on ischemic brain stroke.

funnel plots (Supplemental Fig. S3) and Egger's test ($P > 0.05$).

Discussion

In this meta-analysis, we investigated the efficacy and safety of PCSK9 inhibitors for brain stroke prevention. The findings of our meta-analysis suggested that PCSK9 inhibitors were associated with a lower risk of total brain stroke and ischemic brain stroke without increasing the risk of hemorrhagic brain stroke and neurocognitive impairment. PCSK9 inhibitors effectively reduced the incidence of ischemic brain stroke, with good safety. Thus, PCSK9 inhibitors may serve as an excellent treatment for brain stroke prevention.

For ASCVD, one of the major risk factors is the LDL-C level. Reducing LDL-C levels can effectively prevent the progression of atherosclerosis and improve cardiovascular outcomes [15]. PCSK9 inhibitors are novel drugs that target LDL-C levels. The US Food and Drug Administration approved two PCSK9 inhibitors, evolocumab and alirocumab, for lipid-lowering therapy in patients with familial hypercholesterolemia or high-risk ASCVD [16]. Our meta-analysis showed that PCSK9 inhibitors decreased the RR of brain stroke by 23% and ischemic brain stroke by 24%. Notably, several large meta-analyses have also demonstrated that PCSK9 inhibitors could reduce the overall brain stroke risk and increase meaningful clinical benefits, which was consistent with our research findings, but these studies did not comprehensively report the effect of PCSK9 inhibitors on ischemic brain stroke or

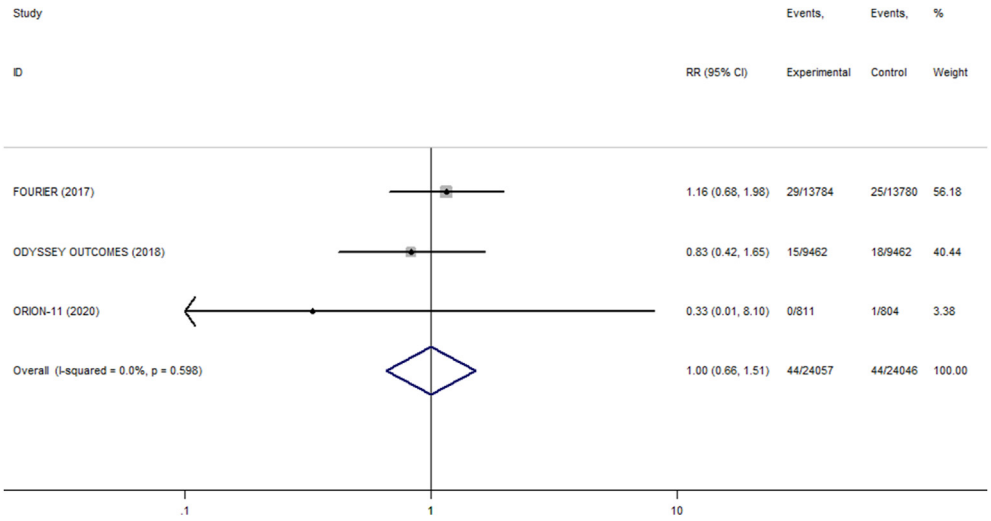

Figure 4 The effect of PCSK9 inhibitors on hemorrhagic brain stroke.

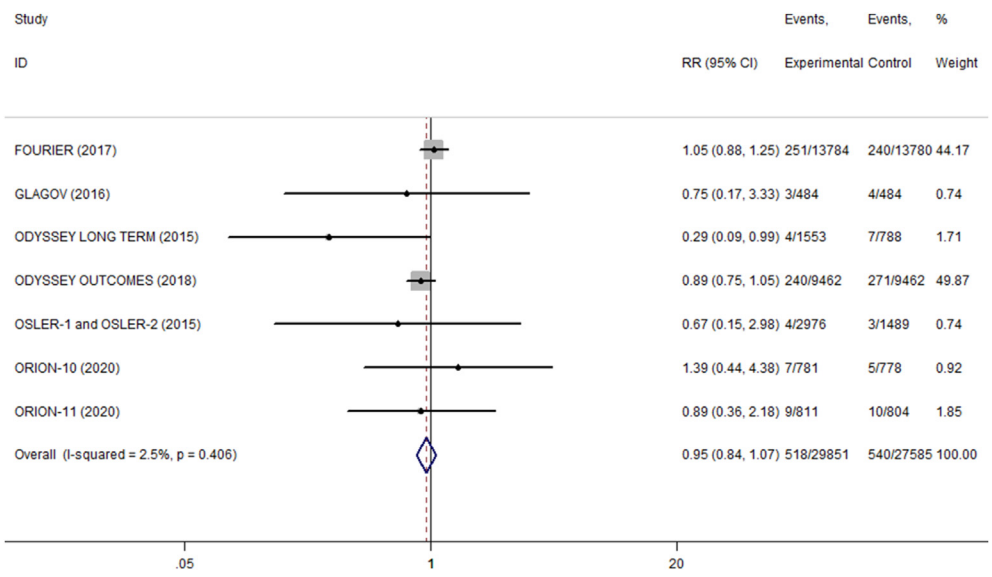

Figure 5 The effect of PCSK9 inhibitors on cardiovascular mortality.

hemorrhagic brain stroke [17–19]. In addition, these studies did not include the latest ORION-10 and ORION-11 studies, which were two phase three clinical trials of inclisiran. However, Milionis et al. conducted a rounded meta-analysis including two RCTs consisting of 4465 patients, showing that PCSK9 inhibitors did not significantly reduce the rates of brain stroke and ischemic brain stroke [7]. The reason why Milionis's findings were inconsistent with ours was because we included multiple subsequent clinical trials that were not available to Milionis at the time. In addition, in comparison with our study, the clinical outcomes could not be reliably observed in the previous meta-analysis owing to the short follow-up time.

Based on postmarketing reports, observational studies, and small RCTs of statins, the FDA issued a warning that statins may be associated with cognitive impairment by lowering LDL-C levels [18]. However, there is a lack of large clinical trials and meta-analyses to confirm whether lipid-lowering therapy has an adverse impact on cognition. Thus, the relationship between lipid-lowering therapy and impaired cognitive function remains controversial.

PCSK9 inhibitors are novel lipid-lowering drugs that target PCSK9 [20]. Some clinical trials have revealed that the use of PCSK9 inhibitors may be related to neurocognitive adverse events, which may be caused by significantly decreased LDL-C levels or the drugs themselves [13,21]. Our meta-analysis found that PCSK9 inhibitors were not significantly associated with the incidence of neurocognitive adverse events. The

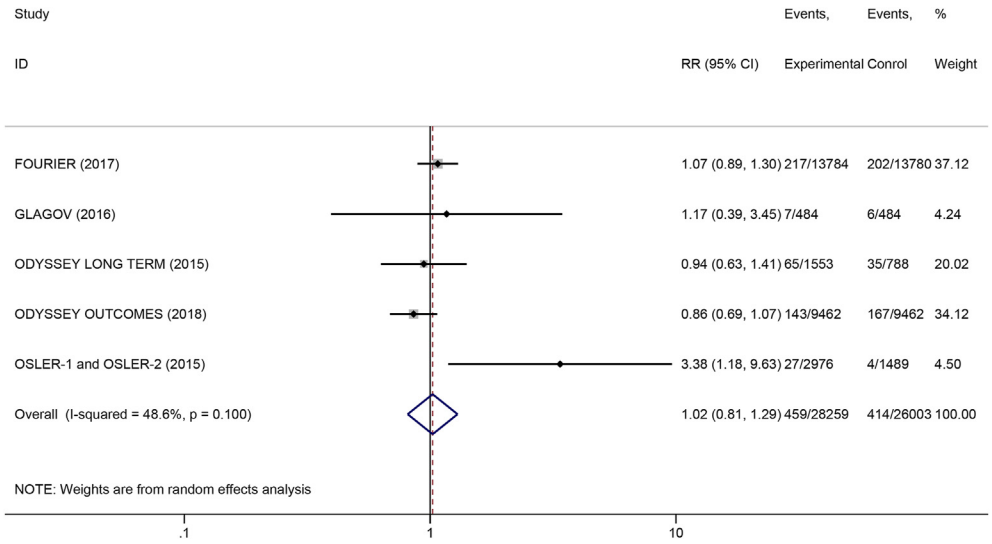

Figure 6 The effect of PCSK9 inhibitors on neurocognitive impairment.

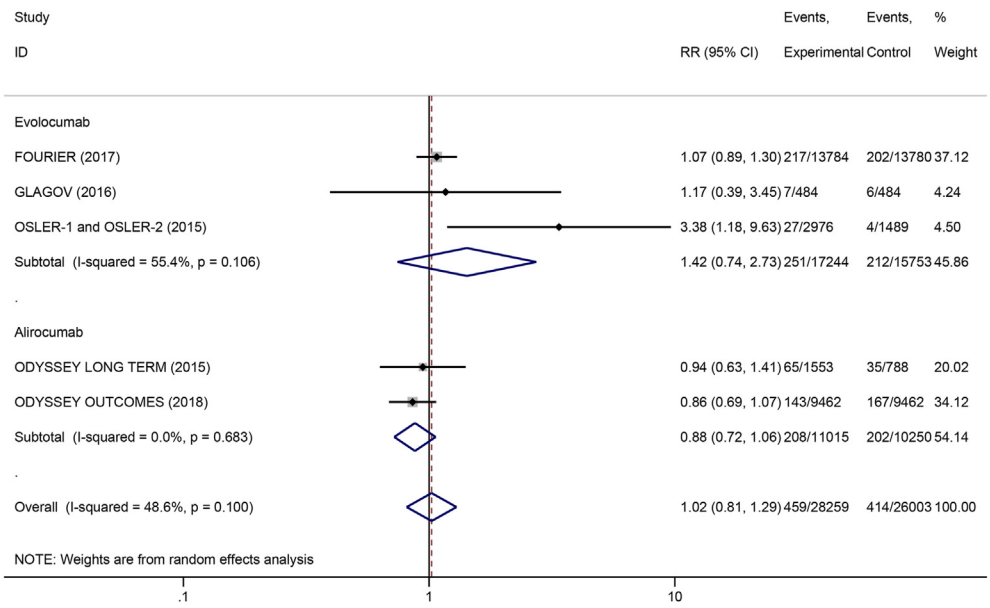

Figure 7 The effect of PCSK9 inhibitors on cognitive impairment through subgroup analysis by different PCSK9 inhibitors.

prospective EBBINGHAUS study has also confirmed that evolocumab had no adverse effects on cognitive function, suggesting no significant difference in the primary end point (executive function) and secondary end points (working memory, episodic memory, and psychomotor speed) between the evolocumab and placebo groups [22]. Harvey also conducted a relevant meta-analysis including 14 RCTs of alirocumab, indicating that the use of alirocumab did not increase the rate of neurocognitive adverse events [23]. We conducted sensitivity analysis for neurocognitive impairment outcomes and found that the heterogeneity was significantly reduced after omitting the OSLER study, considering the OSLER trial as a source of heterogeneity. The heterogeneity between the OSLER study and other studies may be due to the study design. The OSLER study used standard treatment (LDL-C treatment recommended by the local guidelines) as a control, while the remaining studies used a placebo as a control.

In our study, we found that PCSK9 inhibitors were not significantly associated with cardiovascular mortality. This finding was in accordance with the FOURIER trial, in which

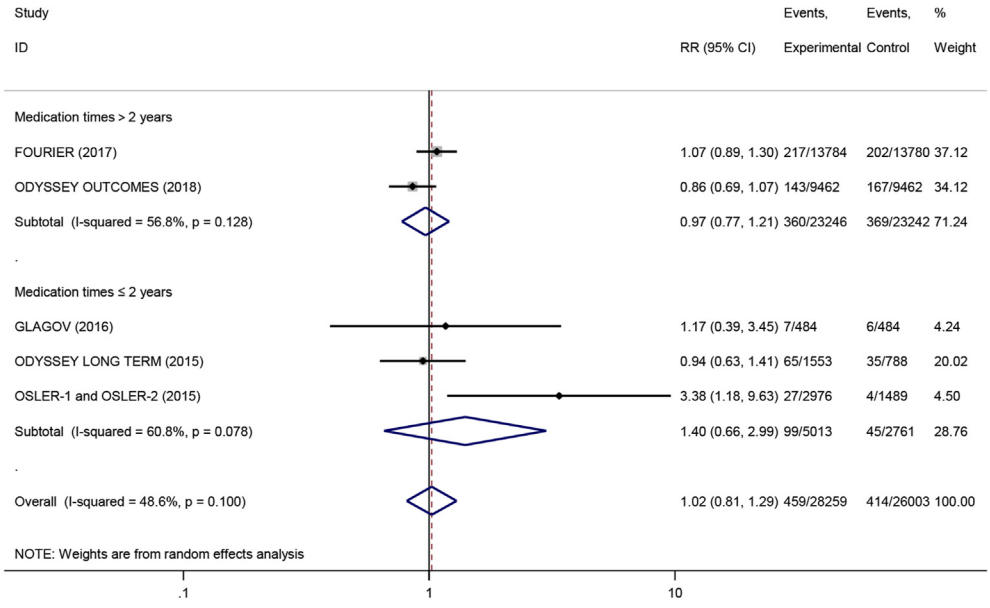

Figure 8 Subgroup analysis by different treatment times of PCSK9 inhibitors on cognitive impairment.

although evolocumab could significantly reduce the risk of cardiovascular events, it had no observed effect on cardiovascular mortality at a median follow-up time of 2.2 years [8]. These observations were consistent with a meta-analysis of clinical trials of PCSK9 inhibitors, which showed that despite the reduction in the incidence of cardiovascular adverse events benefiting from lowering LDL cholesterol, similar clinical benefits were not found in cardiovascular mortality using PCSK9 inhibitors [24,25]. However, unlike the results for cardiovascular mortality in the ODYSSEY OUTCOMES trial, all-cause mortality was reduced by 15% with the use of airocumab at a median follow-up time of 2.8 years. A longer follow-up time may be needed to observe the mortality benefit of PCSK9 inhibitors [9].

This meta-analysis had several limitations. First, the enrolled participants were not homogeneous, and included patients with heterozygous familial hypercholesterolemia, statin-intolerant patients, hyperlipidemia patients with different LDL-C levels, patients with atherosclerotic cardiovascular disease, and patients with previous acute coronary syndrome. Second, the OSLER study used standard treatment as a control, while the other included studies used a placebo as a control, which may be the main source of the heterogeneity associated with the OSLER study. Third, the follow-up duration in the studies ranged from approximately 1 year to 2.8 years, while long-term follow-up (>3 years) is more conducive to observe PCSK9 inhibitors for the prevention of cardiovascular outcomes. Finally, we were unable to perform subgroup analysis of PCSK9 inhibitors across different factors due to lack of patient-level data, and we could not assess the relationship between the magnitude of LDL-C reduction and the benefits of brain stroke endpoints with PCSK9 inhibitors.

Conclusions

In conclusion, our systematic review and meta-analysis demonstrated that PCSK9 inhibitors were associated with a lower risk of total brain stroke and ischemic brain stroke without increasing the incidence of hemorrhagic brain stroke and neurocognitive impairment events. In addition, PCSK9 inhibitors were not significantly associated with cardiovascular mortality. Therefore, PCSK9 inhibitors may be safe and effective for primary and secondary brain stroke prevention.

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Declaration of competing interest

All authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.numecd.2021.03.026.

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