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Review Article

Proprotein convertase subtilisin kexin 9 (PCSK9) inhibitors to treat hypercholesterolemia: Effect on stroke risk

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ABSTRACT

Background/purpose: A reduction of cardiovascular events has been reported in phase 2 and 3 trials of the proprotein convertase subtilisin kexin 9 (PCSK9) inhibitors alirocumab and evolocumab. We aimed to investigate the effect PCSK9 inhibition on stroke risk in a meta-analysis involving data from randomized studies with alirocumab and evolocumab.

Methods: Data from pre-specified combined analysis of 4465 patients who completed phase 2 or 3 studies of evolocumab over a period of 1 year and a randomized trial on alirocumab including 2341 patients with hyperlipidemia on maximally tolerated statin who were at high risk for coronary heart disease over a period of 1.5 years were used.

Results: The number of patients having an ischemic stroke was small in both trials. PCSK9 inhibition showed no significant effect on stroke rate (risk ratio 1.43; 95% CI, 0.45–4.57, $p = 0.55$). No significant differences in stroke risk were evident when transient ischemic attacks were included in the analysis (risk ratio 0.65; 95% CI, 0.25–1.68, $p = 0.37$). No hemorrhagic strokes were reported in either study.

Conclusion: Although a benefit towards reduction of cardiovascular events in the overall has been documented, longer exposure is warranted to be able to evaluate the effect on stroke risk.

1. Introduction

Hypercholesterolemia and risk of stroke have been a controversial issue because of a relatively weak association, diverging associations for ischemic and hemorrhagic strokes, and a possible neuroprotective effect of high lipid levels in acute stroke. Aggressive treatment with statins with or without ezetimibe (an inhibitor of cholesterol absorption) has been associated with modest but significant decrease in stroke risk [1–3]. Nevertheless, there is a need to further lower of low-density lipoprotein (LDL)-cholesterol, especially in subjects at high cardiovascular risk or with severe forms of hypercholesterolemia despite maximum doses of conventional drugs and/or in those intolerant to existing therapies. Statins remain the mainstay of LDL-cholesterol lowering treatment. Emerging therapeutic approaches to further lower LDL-cholesterol involve blocking LDL-receptor degradation by serum proprotein convertase subtilisin kexin 9 (*PCSK9*) [4,5] Human monoclonal antibodies that target *PCSK9* and its interaction with the LDL-receptor (AMG145, REGN727, and RN316) have been tested in phase I–III clinical trials for the treatment of hyperlipidemia in patients at high cardiovascular risk [4,6].

The cardiovascular benefits of PCSK9 inhibitors are yet unproven and long-term efficacy and safety are under further investigation [7]. Regarding alirocumab only limited post-hoc data suggest that it may decrease the incidence of cardiovascular events, while evolocumab has been reported to reduce the incidence of cardiovascular events in pre-specified but exploratory analysis based on a relatively small number of events [7]. Indeed, rates of composite adjudicated cardiovascular events in the ODYSSEY LONG TERM (Long-term Safety and Tolerability of Alirocumab in High Cardiovascular Risk Patients with Hypercholesterolemia Not Adequately Controlled with Their Lipid Modifying Therapy) [8] and OSLER (Open-label Study of Long-term Evaluation Against LDL-cholesterol) 1 and 2 trials have been recently reported [9].

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We included available data of these two studies in a meta-analysis to assess the impact of PCSK9 inhibitors on stroke risk.

2. Methods and statistical analysis

A pre-specified combined analysis of 4465 patients who completed 1 of 12 phase 2 or 3 studies of evolocumab and who were then randomized to either evolocumab plus standard of care vs. standard of care alone in an open-label extension study over an average of 11 months, was conducted across the OSLER 1 and 2 studies [9]. In the ODYSSEY LONG TERM trial, 2341 patients with hyperlipidemia on maximally tolerated statin who were at high risk for coronary heart disease were randomized to either alirocumab or placebo [8].

Fixed-effects and random effects meta-analysis of the selected studies were applied on the basis of within-study comparisons, thereby avoiding any biases being caused by methodological differences between studies. Heterogeneity was assessed with Cochran's Q test and I-squared (I^2, which ranges between 0% and 100%, with lower values representing less heterogeneity). These indices were used to assess the percentage of variability across studies, which is due to heterogeneity rather than chance. Heterogeneity was considered significant when $p < 0.10$ for the Q test or $I^2 > 50\%$. All statistical analyses were conducted using the Comprehensive Meta-analysis software version 2.2.064 (Biostat, Englewood, NJ).

3. Results

The effects on lipid-parameters of both agents are shown in Table 1. PCSK-9 inhibition resulted in a global improvement of the lipid profile and profound reductions of LDL-cholesterol, apolipoprotein B and lipoprotein (a) levels.

In the OSLER 1 and 2 studies, the pre-specified composite of death, myocardial infarction, hospitalization for unstable angina, coronary revascularization, stroke, transient ischemic attack, and hospitalization for heart failure was reduced by 53% (95% confidence interval, CI: 22% to 72%; $p = 0.003$) [9].

In a post-hoc analysis of selected cardiovascular events in the ODYSSEY LONG TERM study, the rate of first adjudicated major cardiovascular event (a composite of death due to coronary disease, myocardial infarction, ischemic stroke, or unstable angina requiring hospitalization) was lower with alirocumab than with placebo (1.7% vs. 3.3%; hazard ratio: 0.52; 95% CI: 0.31 to 0.90, $p = 0.02$) [8].

Adverse events occurred in 69% of patients treated with evolocumab vs. 65% in the standard-of-care group, with no difference in the rate of serious adverse events (7.5% in each group). Only 2.4% of patients in the evolocumab group stopped treatment due to an adverse event. Neurocognitive events were reported more frequently with evolocumab (0.9% vs. 0.3%), with no apparent relationship to the achieved LDL-C [9].

Patients in the alirocumab group had higher rates of injection-site reactions (5.9% vs. 4.2%), myalgia (5.4% vs. 2.9%), neurocognitive events (1.2% vs. 0.5%), and ophthalmologic events (2.9% vs. 1.9%) over a period of 78 weeks [8].

The number of patients having an ischemic stroke was small in both studies: in the OSLER studies, a total number of 3 strokes in the active treatment (vs. 2) and 1 TIA (vs. 5), while 9 vs. 2 fatal or nonfatal ischemic strokes were reported in the ODYSSEY. PCSK-9 inhibition did not affect stroke rates in the overall (risk ratio 1.43; 95% CI, 0.45–4.57, $p = 0.55$) (Fig. 1A). No differences in the pooled data from random-effects models were noted, and no significant trial heterogeneity was detected (Q-value = 0.864, $p = 0.35$, $I^2 = 0.0\%$). No significant differences in stroke risk were evident when transient ischemic attacks were included in the analysis (Fig. 1B). No hemorrhagic strokes were reported in either study.

4. Discussion

The link between serum cholesterol levels and incident stroke has not been clearly established in epidemiological studies and remains controversial [10]. However, there is ample evidence that statins reduce stroke risk in selected patient groups, including patients with diabetes [11] and patients with coronary artery disease [12]. This apparent paradox has been attributed to the heterogeneity of strokes as a group and to the specific characteristics of statins [13]. Besides their ability to reduce LDL-cholesterol levels, statins have a number of pleiotropic effects (i.e. improve endothelial function, modulate thrombogenesis, attenuate inflammatory and oxidative stress damage), which may influence the process of atherosclerosis at various stages [14].

Aggressive lipid-lowering treatment with statins either alone [1,2,12] or in combination with ezetimibe favorably affected the risk of ischemic stroke [3]. However, two long term trials with PCSK9 inhibitors did not show any additional benefit with regard to stroke risk [8,9], and our combined analysis of these trials did not find significant effects on stroke rates.

One possible explanation for this is the very low stroke rate in patients receiving either conventional or novel treatment in both trials. In a meta-analysis of primary prevention trials with statins, the number of patients needed to treat (NNT) for five years to prevent a stroke was double than the NNT to prevent a coronary heart disease event (155 vs. 88) [15]. This finding in addition to the documented efficacy of antihypertensive, antithrombotic and aggressive lipid-lowering preventive measures currently implemented indicate the need for much larger long-term randomized trials to show a potential impact on stroke risk.

Patients in the ODYSSEY LONG TERM trial were at high risk for cardiovascular events (including stroke) since they were diagnosed with heterozygous familial hypercholesterolemia (17.1%), or with established coronary heart disease (41%) or a coronary heart disease risk equivalent (68%) [8]. Moreover, the mean age was 60 years, 35% of patients had type 2 diabetes, 21% were smokers, 99.9% were treated with a statin and their mean LDL-cholesterol was 122 mg/dl (3.1 mmol/L) [8]. On the other hand, in the OSLER studies the mean

Table 1
Percentage changes in serum lipid parameters in ODYSSEY LONG TERM trial (at 24 weeks) and OSLER trial (at 12 weeks).

Variable	ODYSSEY LONG TERM trial			OSLER trial		
	Alirocumab plus standard-of-care N = 1523	Placebo plus standard-of-care N = 777	p value	Evolocumab N = 2976	Standard-of-care N = 1489	p value
Total cholesterol	−38.8	−0.4	<0.001	−32.2	+3.8	<0.001
LDL-cholesterol	−62.8	+0.7	<0.001	−60.9	N/A	<0.001
HDL-cholesterol	+4.2	−0.7	<0.001	+8.7	+1.7	<0.001
Non-HDL-cholesterol	−53.1	+0.6	<0.001	−46.1	+5.9	<0.001
Triglycerides	−15.8	+1.4	<0.001	−9.1	+3.5	<0.001
Apolipoprotein B	−54.3	+1.2	<0.001	−41.7	+5.5	<0.001
Apolipoprotein A-I	+4.2	+1.2	<0.001	+6.8	+2.6	<0.001
Lipoprotein (a)	−30.2	−3.9	<0.001	−25.5	0.0	<0.001

Abbreviations: ODYSSEY LONG TERM; Long-term Safety and Tolerability of Alirocumab in High Cardiovascular Risk Patients with Hypercholesterolemia Not Adequately Controlled with Their Lipid Modifying Therapy), OSLER; Open-label Study of Long-term Evaluation Against LDL-cholesterol, LDL; low-density lipoprotein, non-HDL; non-high-density lipoprotein.

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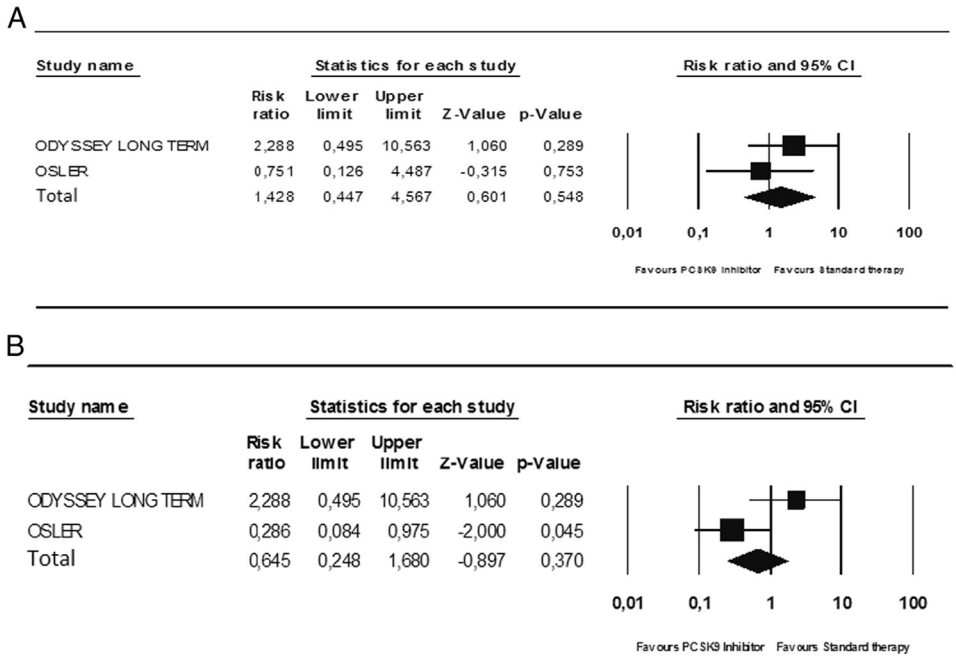

Fig. 1. Effects of PCSK9 inhibitors on the risk of (A) ischemic stroke events alone and (B) plus transient ischemic attacks in the OSLER trials. Abbreviations: ODYSSEY LONG TERM; Long-term Safety and Tolerability of Alirocumab in High Cardiovascular Risk Patients with Hypercholesterolemia Not Adequately Controlled with Their Lipid Modifying Therapy), OSLER; Open-label Study of Long-term Evaluation Against LDL-cholesterol.

age of the patients was 58 years, and 80.4% had at least one cardiovascular risk factor, including hypertension, type 2 diabetes, metabolic syndrome, smoking, family history of premature coronary artery disease [9]. About 46% were classified as having moderately high or high risk for cardiovascular events, including stroke. As many as 20% of patients had established coronary artery disease, and 10% had a history of cerebrovascular or peripheral artery disease. About 70% of patients were receiving a statin and the mean LDL-cholesterol levels on enrolment were 120 mg/dL (3.1 mmol/L) [9].

Anti-PCSK9 monoclonal antibodies represent a newly introduced therapeutic modality and consequently safety concerns have been raised. No clear drug-related toxicities have been reported although the duration of therapy in phase 2 studies was generally short (up to 12 weeks) [4,5]. No neutralizing antibodies have been reported in the trials to date. Other theoretical safety concerns on the basis of other roles and targets of PCSK9 beyond LDL-receptor degradation include an increased risk for viral infections (because some LDL-receptors function as viral entry receptors), insulin resistance and glucose intolerance (reported in humans carrying the R46L PCSK9 loss-of-function-mutation), and increased visceral adiposity, which is due to decreased free fatty acid clearance related to changes in other lipoproteins targeted by PCSK9 [16–18]. Taking into account the short duration of published studies low frequency but clinical relevant signals regarding adverse events cannot be excluded.

Reassuringly, the currently available limited data do not show any hint of an increased rate of hemorrhagic stroke. Regarding effects of PCSK9 inhibitors on other neurological outcomes, the Food and Drug Administration has requested for assessments of neurocognitive adverse events especially in the longer-term studies. Indeed, there was a numerical (statistically non-significant) increase in the rate of neurocognitive events in OSLER and ODYSSEY LONG TERM trials in the active treatment group compared with the control group [8,9]. Although there could be a class effect if real, there can be differential specificity that leads one monoclonal to have an off-target effect. It should be noted that these events were self-reported and not evaluated using a specific neurocognitive tool [4]. The ongoing EBBINGHAUS (Evaluating PCSK9 Binding antiBody Influence oN coGnitive HeAlth in High cardiovascular Risk Subjects) study (NCT02207634) is prospectively evaluating this issue in a subgroup of patients with apparently normal cognitive function enrolled in a phase 3 cardiovascular outcomes study with evolocumab.

5. Conclusion

PCSK9 inhibitors are considered a major breakthrough in cardiovascular risk modification. The safety and tolerability of alirocumab and evolocumab, which have been most extensively studied for periods of up to two years appears promising. Although, a reduction of cardiovascular events in this period has been documented, longer exposure is necessary to evaluate their effects on stroke as well as potentially delayed adverse effects, such as neurocognitive impairment and cancer.

Conflict of interest

None.

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