RESEARCH ARTICLE

Prevention of myocardial infarction and stroke with PCSK9 inhibitors treatment: a metanalysis of recent randomized clinical trials

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Abstract

Purpose Proprotein convertase subtilisin/kexin 9 (PCSK9) inhibitors treatment induce large reductions in low-density lipoprotein cholesterol (LDLc) and major cardiovascular events. Clinical trials might have been underpowered to test the effect of PSCK9 inhibitors treatment on myocardial infarction and stroke, two of the most relevant cardiovascular events, since all analyzed a combined endpoint.

Methods we performed a meta-analysis, with currently available studies involving PCSK9 inhibitors and event rate adjudication, with the aim of assessing treatment effects on myocardial infarction and stroke.

Results We included 81,700 patients, 41,979 treated with a PSCK9 inhibitors: 17,244 with evolocumab; 13,720 with bococizumab and 11,015 with alirocumab. A total of 1,319 cases of myocardial infarctions were registered in the treatment group vs. 1,608 in controls, resulting in 19.0% reduction associated with PCSK9 treatment (RR: 0.81, 95% CI 0.76–0.87). Similarly, PCSK9 inhibitors treatment resulted in a 25% reduction of stroke (RR: 0.75, 95% CI 0.65–0.85) when all studies were analyzed together and the statistically significant heterogeneity was not observed in the analysis restricted to end-point based clinical trials. PCSK9 inhibitors treatment had no effect on mortality (RR: 0.95, 95% CI 0.86–1.04).

Conclusions PCSK9 inhibitors reduce the incidence of myocardial infarction by 19% and stroke by 25%.

Keywords PCSK9 · LDLc · Acute coronary syndrome · Stroke · Meta-analysis

Introduction

Low density lipoprotein cholesterol (LDLc) is the leading effector of atherosclerosis, the underlying cause of coronary heart disease and myocardial infarction [1]. LDLc reduction has been clearly associated to lower incidence of CHD and, therefore, is considered a primary target in cardiovascular prevention [2, 3]. The proprotein convertase subtilisin/kexin 9 (PCSK9) is a circulating protease that binds to the low-density lipoprotein (LDL) receptor leading to its intracellular degradation what reduces the activity of the receptor and promotes higher levels of serum LDLc [4, 3]. Thereafter, monoclonal antibodies that inhibit PCSK9 were developed and clinical trials have demonstrated that PCSK9 inhibitors treatment

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reduce LDLc [5, 6] and, also, major cardiovascular events (MACE) [7–10]. A recent metanalysis verified the effect of alirocumab or evolocumab on MACE and mortality[10].

Primary and secondary end-point of clinical trials testing the effect of PCSK9 inhibitors were based on composite events (including cardiovascular death, myocardial infarction, stroke and revascularization) [7–9]. Non-fatal MACE have a high incidence in stable patients with chronic coronary heart disease [11, 12] but also after a myocardial infarction [13–15]; interestingly, non-fatal MACE preclude incidence of death in the post-myocardial infarction setting [15]. Since the specific effect of PCSK9 inhibitors on myocardial infarction or stroke was not analyzed in clinical trials [7–9] or metanalyses [10],we performed a meta-analysis to assess in detail the effect of PCSK9 inhibitors treatment on these events.

Methods

We performed a systematic search (using PUBMED, EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL), and Google Scholar), without language restriction, for randomized trials using the Medical Subject Headings terms "PCSK9", "PCSK9 inhibitor", "Evolocumab", "Alirocumab" or "Bococizumab". Since the objective of our study was assessing the incidence of myocardial infarction and stroke, we excluded trials with < 3 months of follow-up because event rate was very low, or none, and major cardiovascular events were not defined by protocol or were not adjudicated and validate by a specific board. This confirmed that 6 randomized clinical trials were the evidence supporting the mid-term effect of PCSK9 inhibitors on cardiovascular events and, thereafter, we performed a metanalysis including the following 6 clinical trials: the OSLER I-II trials [5], the ODYSSEY Long Term [6], the FOURIER trial [7], the GLAGOV trial [16], the SPIRE I-II [8] and the ODYSSEY Outcomes trial [9]. The primary outcomes for the metanalysis were myocardial infarction and stroke incidence. We performed the same analysis with all 6 studies and also with only the 3 pivotal endpoint-based randomized clinical trials (EBCT) [7–9]. Information on sample size, treatment type and outcomes were collected from the published papers. For the eligible studies, two authors independently abstracted data into a standardized form; discrepancies in data extraction and quality assessment were resolved by discussion or consensus with a third author.

Statistical analyses

We performed an intention-to-treat meta-analysis in line with recommendations from the Cochrane Collaboration and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement [17]. Relative risk reductions and percent incidences were used. Myocardial

infarction and stroke incidence were reported in the 6 trials. The percentage of variability across studies attributable to heterogeneity beyond chance was estimated using the I^2 statistic and potential sources of heterogeneity between trials were tested by meta-regression analyses. A random effects model was selected when the significant heterogeneity was observed; otherwise, a fixed-effect model was applied. The identification of potential sources of heterogeneity between trials was tested by meta-regression analyses. The Egger test was used to assess the small-study effects [18]. All analyses were performed using STATA 14.3 (StataCorp. 2009. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP).

Results

We included 81,7000 patients, 41,979 treated with a PSCK9 inhibitors: 17,244 with evolocumab; 13,720 with bococizumab and 11,015 with alirocumab (Table 1). A total of 1,319 cases of myocardial infarction were registered in the treatment group vs. 1,608 in controls, resulting in 19.0% reduction associated with PCSK9 treatment (Fig. 1). Results were similar in both types of studies although a non-significant heterogeneity was detected (p = 0.052). Metaregression analyses did not demonstrate the implication of the study (p = 0.45), study drugs (p = 0.26), age (p = 0.89), hypertension (p = 0.81) or diabetes (p = 0.81) on such result. The funnel plot (Fig. 2A) and the Egger test (p = 0.38) excluded relevant bias or small-study effects.

A total of 872 strokes were registered. PCSK9 inhibitors treatment resulted in a 25% reduction of stroke when all studies were analyzed together (Fig. 3). The effect was were mainly driven by the results of EBCT and no significant heterogeneity was observed. Once again, the funnel plot (Fig. 2B) and the Egger test (p = 0.74) excluded relevant bias or small-study effects.

We finally tested the effect of PCSK9 inhibitors on mortality. As shown in Fig. 4, treatment effect was neutral for mortality and significant heterogeneicity was observed in EBCT; the funnel plot (Fig. 2C) and the Egger test (p = 0.22) excluded relevant bias or small-study effects. The study drug (p < 0.001) and the type of study (p < 0.001) were the main sources of heterogenicity.

Discussion

This meta-analysis supports the benefit of PCSK9 inhibitors in cardiovascular prevention by a significant and large reductions on myocardial infarction and stroke incidence. PCSK9

Fig. 1 Forest plots showing the pooled relative risk (RR) with 95% confidence intervals for myocardial infarction incidence
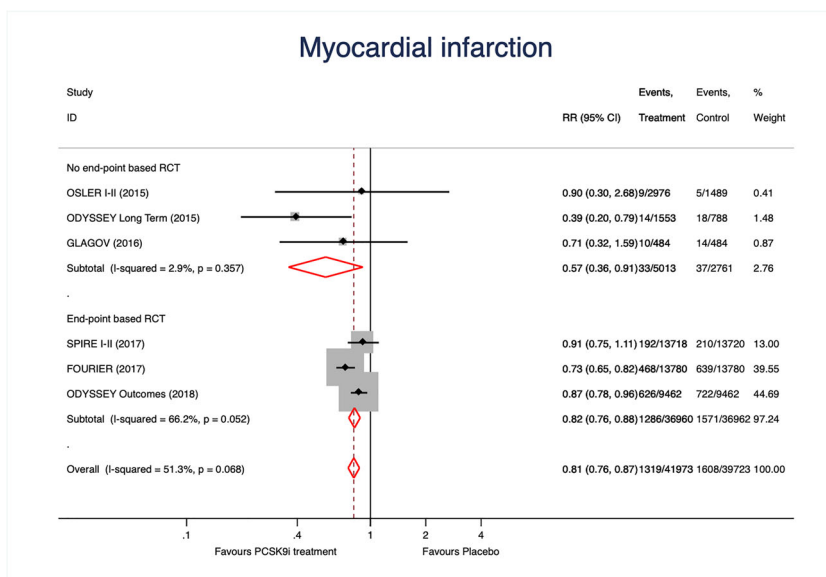
inhibitors decrease LDLc by > 50% with a very specific mechanism that make them very safe and effective on LDLc and MACE incidence prevention [7–9]. Moreover, the results of our meta-analysis add compelling evidence of the significant reductions on myocardial infarction and stroke.

PCSK9 inhibitors are one of the last advances in lipid-lowering drugs and have emerged very fast from phase-I trials to EBCT. The OSLER [5] and the ODYSSEY Long Term [6] were not designed to assess the effect of the study drugs on MACE but the positive results on MACE were very well received. The EBCT involving PCSK9 inhibitors were stopped when the incidence of primary and secondary

endpoints were accomplished [7, 9] or when the evidence of neutralizing antibodies against bococizumab were clearly outlined [8]. These issues have two clear consequences: follow-up was shorter than most EBCT involving lipid-lowering treatments and none of the studies were statistically powered to demonstrate reductions in specific endpoints. Therefore, a meta-analysis might be pertinent and clinically relevant since a clear tendency to better outcomes was noted in most studies. A previous metanalysis [10] summarized the results of clinical trials only with evolocumab or alirocumab and our study highlights a clear and consistent protective effect of PCSK9 inhibitors on myocardial infarction and stroke.
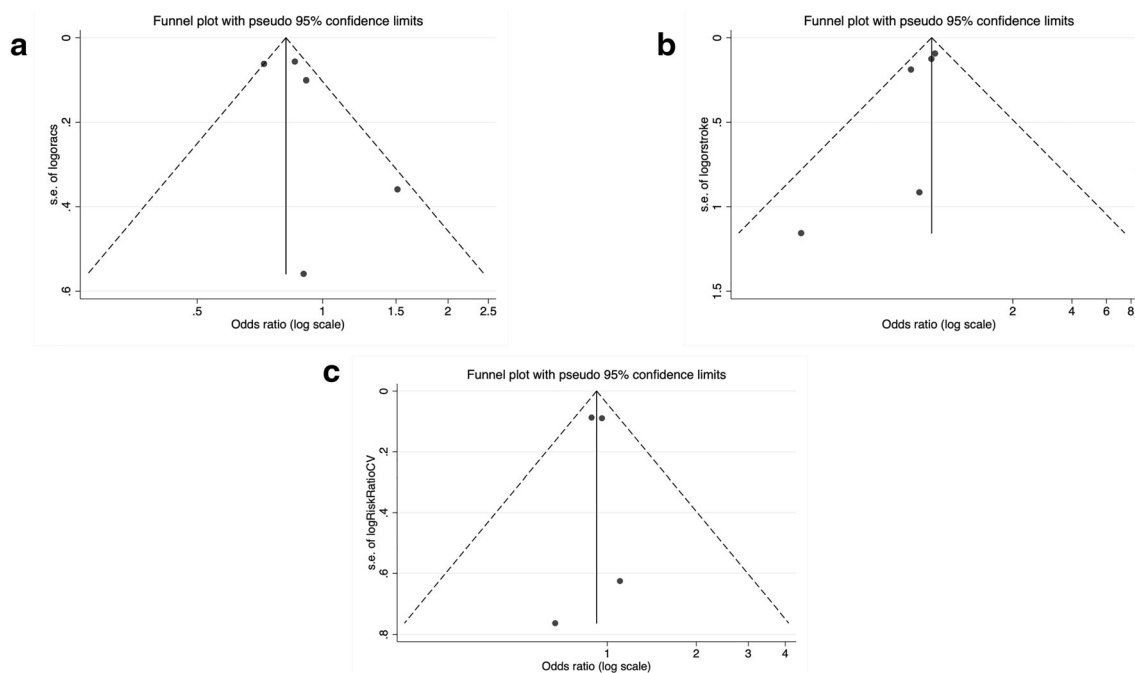

Fig. 2 Funnel plots for myocardial infarction (A), stroke (B) and all-cause mortality (C)

Table 1 Clinical features and number of myocardial infarction (MI) and strokes reported in each clinical trial

Trial	Study Drug	Number of PCSK treated	Number of controls	Age	DM (%)	HT (%)	Smoking (%)	Number of MI		Number of strokes	
								Treated	**Controls**	**Treated**	**Controls**
OSLER I-II	Evolocumab	2976	1489	58.1	13.0	52	15.5	9	5	1	3
ODYSSEY Long Term	Alirocumab	1553	788	60.4	34.5	-	20.5	14	18	9	2
Glagov	Evolocumab	484	484	59.8	20.5	83	23.3	1	14	2	3
FOURIER	Evolocumab	13784	13780	62.5	36.5	80.0	28.3	468	639	207	262
SPIRE I-II	Bococizumab	13720	13718	63.3	47.5	80.8	24.5	192	210	45	75
ODYSSEY	Alirocumab	9462	9462	58.5	29.0	65.0	24.0	626	722	111	152
Total:		**41,979**	**39,721**	**60.5**	**32.1**	**69.5**	**22.6**	**1,319**	**1,608**	**375**	**497**

DM; diabetes mellitus; HT: hypertension

Casula, et a l[10] also included studies with very short-term follow-up, such as 8 or 12 weeks, were no events were recorded or MACE were codified as side effects with no clear methodology. We decided to include all patients treated with any PCSK9 inhibitor for > 3 months in order to provide the most reliable evidence related to PCSK9 inhibitors.

Evolocumab and alirocumab are currently being used worldwide [19–22]; bococizumab will not be available in clinical practice since its efficacy was clearly impaired by neutralizing antibodies [8] but we decide to include the results of the SPIRE program in order to assess the effect of the whole PCSK9 inhibitors; moreover, more molecules could be developed in the future. Treatment of hypercholesterolemia has been focused on targeting LDL production and intestinal reabsorption, with statins and ezetimibe respectively [2, 3]. After wide and well-supported evidence, statins are the cornerstone of LDLc reduction in primary and secondary

prevention [2, 3, 23]. Nonetheless, monotherapy with statins is usually not enough for treatment target achievement [24, 25, 23] and the addition of ezetimibe has demonstrated to be effective for reduction of LDLc and cardiovascular events prevention [26]. Nonetheless, ezetimibe combined with statins is not widely used in high-risk patients. For example, the EUROASPIRE V highlighted, a part from the low rates LDLc control, that less than 10% of patients with coronary heart disease were receiving combined treatment with statin and ezetimibe [27]. In fact, despite > 75% of the patients in the FOURIER [7] and ODISSEY Outcomes [9] trials were receiving high-doses of statins less than 7% sere also on ezetimibe. PCSK9 inhibitors are a completely new, and complementary, strategy for LDLc reduction that can be used as monotherapy or combined with any other lipid-lowering drugs[28]. Combination of statin plus ezetimibe received a recommendation class I (level of evidence B) for the first time in the 2019

Fig. 3 Forest plots showing the pooled relative risk (RR) with 95% confidence intervals for stroke incidence
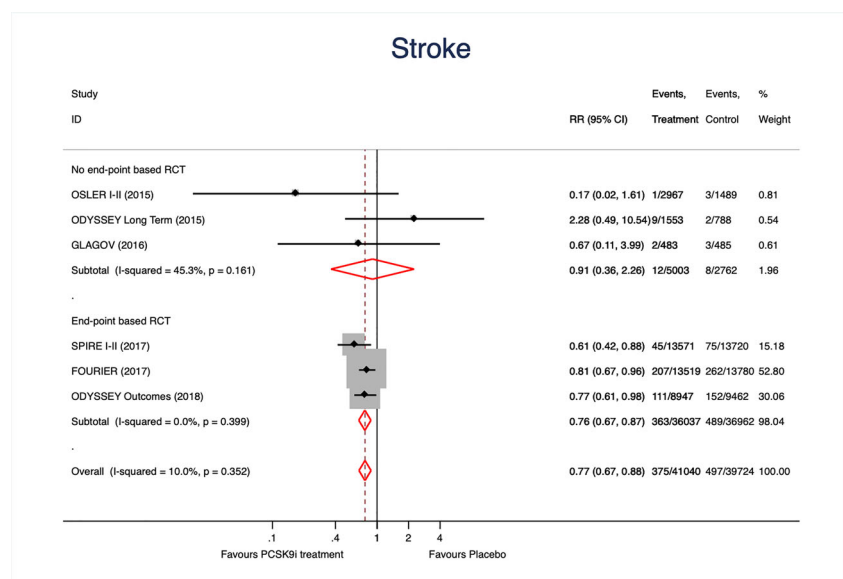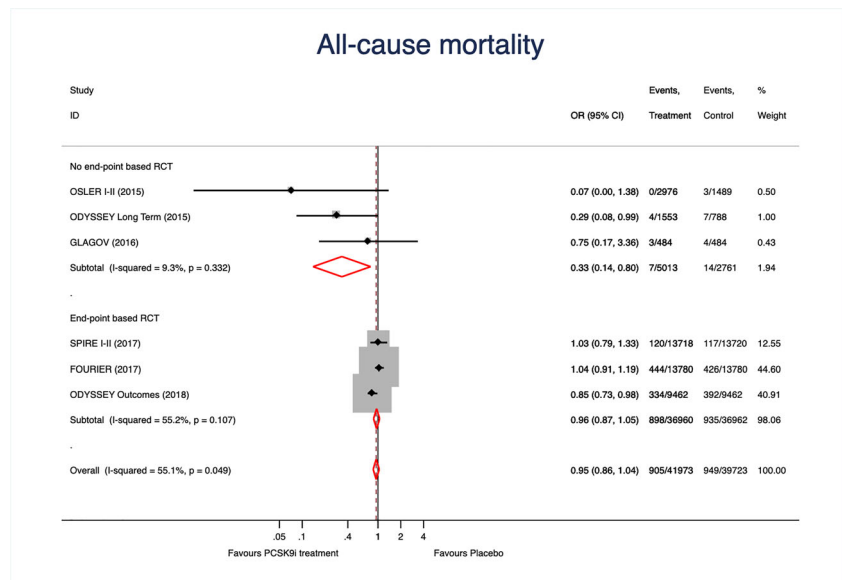
Fig. 4 Forest plots showing the pooled relative risk (RR) with 95% confidence intervals for mortality

ESC/EAS guidelines[3], but for patients not achieving their treatment goal in secondary prevention, the addition of a PCSK9 inhibitor has recommendation class I (level of evidence A). Since treatment targets were also lowered to LDLc < 45 m/dl in patients with high-cardiovascular risk, or established cardiovascular disease, PCSK9 inhibitors seem to be most accurate combination strategy in this setting.

We performed a meta-analysis with currently available studies that constitute the cornerstone in the knowledge related to PCSK9 inhibitors effects. There is scarce evidence in the actual effect and safety of this therapy in real-world patients [19–21] as well as long-term safety or cost-efficiency according to current fees [2]. A recent study in a wide population area of Spain estimated that the overall prevalence of people suitable for PCSK9 treatment, under current indications, was < 5%; nonetheless, when in the subset of patients with coronary heart disease or familial hypercholesterolemia were analyzed it increased up to 20% and 75% respectively [29]. These estimations have also been verified in a large registry of patients with chronic stable coronary heart disease in Spain [30] and a greater population with atherosclerotic cardiovascular disease [31]. Despite these estimations, we believe that efforts should be focused on defining which patients would benefit mostly from PCSK9 inhibitors treatment, the so-call priority patients. Based on currently available evidence, patients that would obtain the most benefit from PCSK9 inhibitors treatment are those at higher cardiovascular risk, such as patients with recent myocardial infarction (< 2 years) [9], diabetes [32], multivessel disease [33] or peripheral arterial disease [34].

Our metanalysis also showed that PCSK9 inhibitors treatment did not reduce mortality. A recent metanalysis highlighted that mortality benefit can be expected only in patients with baseline LDLc > 100 mg/dl [35]. PCSK9 inhibitors are currently reimbursed in Spain, and most European countries, only for patients with LDLc > 100 mg/dl despite optimal lipid-lowering treatment and it has been recently demonstrated the effect on LDLc reduction, under such indications, is the same as clinical trials [36]. It should also be noted that inclusion criteria of the EBCT involving PCSK9 inhibitors was baseline LDLc > 70 mg/dl [7–9]. Moreover, EBCT tested the effect of PCSK9 inhibitors on top of statin-treated patients and, therefore, patients in the control group were all receiving statins and most of them on high dose s[7–9]. A recent subanalysis of the ODYSSEY Outcomes trial demonstrated that occurrence of non-fatal cardiovascular events have a great impact on prognosis and they increase 2-fold the incidence of mortality afterwards [37]; alirocumab reduced significantly major cardiovascular event rates and, thus, a relevant effect on mortality could have been observed in a longer follow-up reflecting that the analysis of long-term mortality should be analyzed with much complex methodology, taking into account intermediate events. Moreover, subsequent subanalyses of the ODYSSEY Outcomes trial [15] and the FOURIER trial[38] highlighted that PCSK9 inhibitors reduced total MACES incidence. Therefore, the long-term effect of PCSK9 inhibitors treatment, that has not been evaluated yet, will probably provide reductions on mortality as well. Meanwhile, we believe that our metanalysis provides clinically relevant information on myocardial infarction and stroke prevention by PCSK9 inhibitors.

Our study might be limited by the fact that it only included randomized clinical trials and, therefore, patients' characteristics, medication adherence and other clinical features might not be fully representative of daily clinical practice. Nonetheless, there is scarce evidence related to PCSK9 inhibitors treatment on real-world patients [19, 20, 36] and we believe that our results can help the generalization of these therapies in very-high risk patients in whom LDLc control remains a treatment challenge [39, 27, 2, 3].

In conclusion, this meta-analysis demonstrates that PCSK9 inhibitors treatment reduces myocardial infarction by 19% and stroke by 25%. We believe that these results provide solid evidence for treating patients at high-risk, with non-controlled LDLc, with PCSK9 inhibitors.

Compliance with ethical standards

Conflict of interest   Authors declare no conflict of interest related to the results of this study.

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