**Efficacy and Safety of Alirocumab and Evolocumab: A Systematic Review and Meta-Analysis of Randomized Controlled Trials**

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**Abstract**

**Aims:** The effect of low-density lipoprotein cholesterol lowering therapy with alirocumab or evolocumab on individual clinical efficacy and safety endpoints remains unclear. We aimed to evaluate the efficacy and safety of alirocumab and evolocumab.

**Methods and results:** We performed a review of randomized controlled trials (RCT) comparing treatment with alirocumab or evolocumab versus placebo or other lipid-lowering therapies up to March 2018. Primary efficacy endpoints were all-cause death, cardiovascular death, myocardial infarction (MI) and stroke. We estimated risk ratios (RR) and 95% confidence intervals (CI) using random effect Mantel-Haenszel models. We included 39 RCTs comprising 66,478 patients of which 35,896 were treated with PCSK9 inhibitors (14,639 with alirocumab and 21,257 with evolocumab) and 30,582 with controls. Mean weighted follow-up time across trials was 2.3 years with an exposure time of 150,617 patient-years. Overall, the effects of PCSK9 inhibition on all-cause death and cardiovascular death were not statistically significant (p=0.14 and p=0.34, respectively). PCSK9 inhibitors were associated with lower risk of MI (1.49 vs. 1.93 per 100 patient-year; RR: 0.80; 95% CI: 0.74-0.86; I2=0%; p<0.0001), ischemic stroke (0.44 vs. 0.58 per 100 patient-year; RR: 0.78; 95% CI: 0.67-0.90; I2=0%; p=0.0005) and coronary revascularization (2.16 vs. 2.64 per 100 patient-year; RR: 0.83; 95% CI: 0.78-0.89; I2=0%; p<0.0001) compared with the control group. Use of a PCSK9 inhibitor was not associated with increased risk of neurocognitive adverse events (p=0.84), liver enzymes elevations (p=0.38), rhabdomyolysis (p=0.53) or new-onset diabetes mellitus (p=0.99).

**Conclusion** PCSK9 inhibition with alirocumab or evolocumab was associated with lower risk of myocardial infarction, stroke and coronary revascularization, with favorable safety profile.

**Key Words:** PCSK9; Cholesterol-lowering therapies; Cardiovascular Outcomes.

**Abbreviations**

ACVD: Atherosclerotic cardiovascular disease

LDL: low density lipoprotein cholesterol

MI = Myocardial Infarction

PCSK-9: Proprotein convertase subtilisin–kexin type 9

RCTs: Randomized controlled trials

**INTRODUCTION**

Atherosclerotic cardiovascular disease (ACVD) remains the leading cause of death worldwide.1–4 Lipid-lowering therapy with statins, targeting low-density lipoprotein cholesterol (LDL-C) levels, was demonstrated to reduce the risk of ACVD events in both primary and secondary prevention populations.5 However, a substantial proportion of patients cannot tolerate statins, do not achieve a significant reduction in LDL-C levels despite use of high-intensity statin therapy or may remain at significant residual risk for ACVD events despite being on maximally-tolerated statin therapy.5–7 Over a decade ago, proprotein convertase subtilisin–kexin type 9 (PCSK9) emerged as a therapeutic target to treat hypercholesterolemia in humans.8 PCSK9 plays a major role in cholesterol homeostasis by reducing the amount of functional LDL receptors on the plasma membranes thereby increasing the serum levels of LDL-C.8 In fact, carriage of loss-of-function PCSK9 alleles is associated with lower cholesterol levels and reduced risk of myocardial infarction.9–11

Recently, results from phase 2 and phase 3 randomized controlled trials (RCTs) investigating the efficacy and safety of injectable monoclonal antibodies that inhibit PCSK9 have been reported.12–16 Across these studies, PCSK9 inhibition appeared to be associated with reductions in LDL-C levels by at least 60% alongside with lower rates of composite ACVD events. 12–15 These encouraging results led to the expedited approval from the Food and Drug Administration of these agents, as an adjunct to diet and maximally tolerated statin therapy for patients with familial hypercholesterolemia and/or clinical ASCVD. However, the overall effect of PCSK9 inhibitors as a class and of the individual approved agents (evolocumab and alirocumab) on hard efficacy and safety endpoints remain uncertain. We therefore performed a systematic review and meta‐analysis of RCTs to examine the efficacy and safety of PCSK9 inhibitors currently available in clinical practice.

**METHODS**

**Research strategy and selection criteria.** We conducted a systematic review of the literature according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guidelines **(Supplementary Table 1)**.17 We searched PubMed/Medline, CENTRAL (Cochrane Central Register of Controlled trials), clinicaltrials.gov and slides presentations from the latest international conferences for relevant abstracts and manuscripts published up to March 13, 2018. The following keywords were used: PCSK9 inhibitor, alirocumab, evolocumab, SAR236553, REGN727 or AMG145. Citations were screened at the title and abstract level and retrieved if considered relevant. The main inclusion criterion was a phase 2 or 3 randomized trial comparing alirocumab or evolocumab to a control strategy (placebo and/or other lipid-lowering drugs) in adult patient with dyslipidemia and/or established ACVD. There was no restriction on follow-up and study size. Observational studies (including single-arm pilot studies), case reports, case series, meta-analyses, and studies with duplicate data were excluded from this analysis. PCSK9 inhibitors not approved by the FDA, such as bococizumab, were not included in this study16. The primary efficacy endpoints of interest were: all-cause and cardiovascular death, myocardial infarction (MI) and stroke, as per individual study definitions. Primary safety endpoints of interest were: study drug discontinuation, neurocognitive adverse events, liver enzymes elevations and rhabdomyolysis. Neurocognitive adverse events were defined as per single study criteria. Liver dysfunction was defined as an increase of alanine aminotransferase or aspartate aminotransferase as reported in each study. Rhabdomyolysis was defined as an elevation of serum creatine kinase above >10 time the upper reference limit. The study is registered in PROSPERO (CRD42018090768).

**Data extraction.** Two investigators not involved in any of the selected studies (P.G. and S.S.) independently screened each title and abstract, excluding duplicates and studies not meeting the inclusion criteria. Data were extracted using prespecified data collection forms. The following relevant data were extracted: trial name, design, sample size, follow-up duration, type of control and PCSK9 dosage. Baseline characteristics of the study population and the mean LDL-C at baseline and at the maximum time of follow-up available were extracted and entered in a pre-specified structured dataset. Efficacy and safety endpoints were collected at the longest available time of follow-up according to the intention-to-treat principle. The accuracy of the abstracted data was independently confirmed by two other investigators (B.V. and D.K.) and discrepancies were resolved by consensus. Risk of bias of the included studies was assessed according to the Cochrane Collaboration guidelines.

**Statistical analysis.** Study-level data was entered in a pre-specified structured dataset and analyzed according to the intention-to-treat principle. Baseline characteristics across studies are reported with summary rate estimates. Exposure times with weighted incidence rates of adverse events per 100 patient-years of follow-up and corresponding incidence risk differences were analyzed taking into account the variable follow-up times within each study. Risk ratios (RRs) and 95% confidence intervals (CI) were estimated using Mantel-Haenszel random-effect models according to DerSimonian and Laird. Fixed effect models for all efficacy and safety outcomes were also reported, regardless of the degree of heterogeneity. Heterogeneity among trials for each outcome was estimated with chi-square tests and quantified with I2 statistics (with I2 <50%, 50 to 75% and >75% indicating low, moderate and high heterogeneity, respectively). Publication bias and small study effect for the primary efficacy and safety endpoints was estimated via visual inspection of the funnel plot and with the Harbord test. Sensitivity analyses including only placebo-controlled trials and excluding trials with low statin use (≤20% overall statin use in the trial) were also performed. A *P*<.05 was set as the threshold for statistical significance. Analyses were conducted using STATA version 14.0 (Stata Corp., College Station, Texas) and Cochrane’s Review Manager (RevMan) version 5.3 (The Cochrane Collaboration, Copenhagen, Denmark).

**RESULTS**

**Baseline Characteristics.**

The study selection flow diagram is illustrated in **Supplementary Figure 1.** A total of 39 RCTs comprising 66,478 patients were included. Of these 35,896 were treated with a PCSK9 inhibitor (14,639 with alirocumab and 21,257 with evolocumab), on top of maximally tolerated statin therapy or other adjunct lipid-lowering therapies and 30,582 were treated with placebo or control therapy. Out of 39 studies, 31 (79.4%) were placebo-controlled. Mean weighted follow-up time was 2.3 years across trials and 3.1 years and 1.7 years for alirocumab and evolocumab respectively. The exposure time was 150,617 patient-years overall and 83,289 patients-years and 67,329 patients-years for alirocumab and evolocumab, respectively. Characteristics of the included RCTs are resumed in **Supplementary Tables 2-3.** Out of 39 studies, in 7 (17.9%) statins were used in ≤20% of the study population either because of documented statin intolerance or assessment of PCSK9 inhibition as monotherapy **(Supplementary Table 2)**. Pooled estimates of baseline characteristics across trials overall and by study drug are displayed in **Table 1.** Mean pooled LDL-C levels at baseline were 128.9 mg/dL in the PCSK9 inhibitors arm and 126.6 mg/dL in the control arm. At the longest available follow-up time mean pooled LDL-C levels were 52.6 mg/dL in the PCSK9 inhibitor arm and 121.6 mg/dL in the control arm.

**Efficacy Endpoints.**

The effect of PCSK9 inhibition on clinical efficacy endpoints is reported in **Figures 1-2**, and **Supplementary Figures 2-8.** Overall, there were no significant differences between PCSK9 inhibitors and control in all-cause death (1.03 vs. 1.15 per 100 patient-years; RR: 0.93; 95% CI: 0.85-1.02; I2=13%; *P*=0.14) and cardiovascular death (0.66 vs. 0.73 per 100 patient-years; RR: 0.94; 95% CI: 0.84-1.06; I2=0%; *P*=0.34). However, use of alirocumab, but not of evolocumab, was associated with lower risk of all-cause death compared with control using fixed effect models (0.81 vs. 1.01 per 100 patient-years; RR: 0.83; 95% CI: 0.73-0.96; I2=0%; *P*=0.01). Of note, alirocumab was associated with a trend toward lower all-cause mortality after exclusion of the ODYSSEY-OUTCOMES trial (0.37 vs. 0.68 per 100 patient-years; RR: 0.59; 95% CI: 0.34-1.03; I2=0%; *P*=0.06). Compared with controls, use of PCSK9 inhibitors was associated with significant reductions in myocardial infarction (1.49 vs. 1.93 per 100 patient-years; RR: 0.80; 95% CI: 0.74-0.86; I2=0%; *P*<0.0001), ischemic stroke (0.44 vs. 0.58 per 100 patient-years; RR: 0.78; 95% CI: 0.67-0.90; I2=0%; *P*=0.0005) and coronary revascularization (2.16 vs. 2.64 per 100 patient-years; RR: 0.83; 95% CI: 0.78-0.89; I2=0%; *P*<0.0001). Individually, both evolocumab and alirocumab were associated with significant benefits on myocardial infarction, ischemic stroke and coronary revascularization **(Figures 1-2** and **Supplementary Figures 2-8)**. There were no significant differences between PCSK9 inhibitors and controls for the endpoints of unstable angina requiring hospitalization and heart failure-related hospitalizations **(Figure 2).**

**Safety Endpoints.**

Clinical safety endpoints for PCSK9 inhibitors versus control are reported in **Figures 3-4 and Supplementary Figures 9-16**. There were no significant differences in the risk of drug discontinuation between groups (1.26 vs. 1.07 per 100 patient-years; RR: 1.05; 95% CI: 0.95-1.15; I2=0%; *P*=0.32). No significant differences in the risk of neurocognitive adverse events (0.57 vs. 0.55 per 100 patient-years; RR: 1.01; 95% CI: 0.89-1.16; I2=6%; *P*=0.84), liver enzymes elevation (0.73 vs. 0.73 per 100 patient-years; RR: 0.95; 95% CI: 0.84-1.07; I2=0%; *P*=0.38), allergic reactions (2.05 vs. 1.83 per 100 patient-years; RR: 1.04; 95% CI: 0.97-1.12; I2=0%; *P*=0.29), hemorrhagic stroke (0.06 vs. 0.06 per 100 patient-years; RR: 0.93; 95% CI: 0.60-1.44; I2=53%; *P*=0.73), rhabdomyolysis (0.14 vs. 0.14 per 100 patient-years; RR: 0.89; 95% CI: 0.62-1.28; I2=0%; *P*=0.53) or new-onset diabetes mellitus (1.92 vs. 1.93 per 100 patient-years; RR: 1.00; 95% CI: 0.93-1.07; I2=0%; *P*=0.99) were observed between PCSK9 inhibitors and controls. However, PCSK9 inhibitors were associated with higher injection site reactions (1.51 vs. 0.83 per 100 patient-years; RR: 1.50; 95% CI: 1.36-1.66; I2=19%; *P*<0.0001) **(Supplementary Figure 16)**.

**Bias Assessment and Sensitivity Analyses.**

No evidence of publication bias or small study effect was found for both efficacy and safety outcomes **(Supplementary Figures 17-18)**. Internal bias assessment for each study is reported in **Supplementary Table 4.** The effect of PCSK9 inhibitors on safety and efficacy outcomes remained consistent with the application of random effect models **(Supplementary Figures 2-16).** Results for the primary efficacy remained consistent after inclusion of only placebo-controlled trials **(Supplementary Table 5)**. Effect estimates for the primary efficacy endpoints remained consistent also after exclusion of trials with low statins use (defined as ≤20% overall statin use in the trial) **(Supplementary Table 6)**. The effect of PCSK9 inhibitors on the primary efficacy endpoints was consistent when evaluated across secondary-prevention trials only versus other trials (**Supplementary Table 7),** or across trials enrolling statins-intolerant patients versus patients without statins intolerance (**Supplementary Table 8**). Of note, a significant interaction was observed in terms of the reduction in all-cause death in trials with an average baseline LDL-C level >100mg/dL versus ≤100mg/dL (**Supplementary Table 9**). Consistently, a significant interaction was present in terms of the reduction in MI when a LDL-C level at follow-up ≤50mg/dL was achieved, compared to LDL-C level >50mg/dL (**Supplementary Table 10**). Finally, no significant interaction was observed in terms of study-drug discontinuation and neurocognitive adverse events with the use of PCSK9 inhibitors and the achievement of low level of LDL-C at follow-up (i.e. ≤50mg/dL, **Supplementary Table 11**).

**DISCUSSION**

In this large, comprehensive meta-analysis of RCTs we investigated the efficacy and safety of the FDA-approved PCSK9 inhibitors, evolocumab and alirocumab, across a broad range of patients with hyperlipidemia or established ACVD. At a mean weighted follow-up time of 2.3 years, use of PCSK9 inhibitors was associated with lower risk of myocardial infarction, ischemic stroke and coronary revascularization compared with controls. While overall, we did not observe a mortality benefit with use of PCSK9 inhibitors, alirocumab, but not evolocumab, was associated with lower risk of all-cause mortality compared with controls. There were no significant differences between PCSK9 inhibitors and the control group in terms of major safety endpoints including neurocognitive adverse events, rhabdomyolysis, liver enzymes elevations, new-onset diabetes mellitus or allergic reactions. Results were consistent with restriction of the analysis to only placebo-controlled trials.

Inhibition of PCSK9 emerged as a key therapeutic target to lower LDL-C in humans. Inhibition of PCSK9 increases the extracellular membrane density of LDL receptors, thereby reducing the levels of circulating LDL-C18. Recently the FDA approved two fully human, injectable, monoclonal antibodies that inhibit PCSK9 (evolocumab and alirocumab), for the treatment of adults with familial hypercholesterolemia and/or clinical ASCVD who require additional lowering of LDL-C as an adjunct to diet and maximally tolerated statin therapy.19

In our large meta-analysis encompassing the totality of the evidence from RCTs investigating the efficacy and safety of the FDA-approved PCSK9 inhibitors, PCSK9 inhibition on top of maximally tolerated statin therapy or other adjunct lipid-lowering therapies was associated with an average absolute reduction in LDL-C levels of roughly 75.0 mg/dL from baseline compared with controls. Overall, use of PCSK9 inhibitors was associated with statistically significant relative risk reductions of myocardial infarction by 20%, ischemic stroke by 22% and coronary revascularization by 18%. Of note, significant and meaningful benefits on clinical ischemic endpoints were noted with both FDA-approved PCSK9 inhibitors, evolocumab and alirocumab. The observed effects of PCSK9 inhibitors on ASCVD events are in alignment with the mechanistic observations from the Global Assessment of Plaque Regression with a PCSK9 Antibody as Measured by Intravascular Ultrasound (GLAGOV) trial in which patients with angiographic coronary disease treated with statins, the addition of evolocumab, compared with placebo, resulted in greater reductions in total atheroma volume and plaque regression.20 Given that ACVD is in continuum across the coronary, cerebral and peripheral circulation, the benefits of aggressive cholesterol-lowering therapy extend systemically with correspondent reductions in myocardial infarction, ischemic stroke and possibly major adverse limb events as suggested by recent post-hoc analyses from the FOURIER trial. 21,22

Although post-marketing studies, observational registries and small RCTs have suggested that LDL-C lowering therapies may be associated with adverse outcomes such as neurocognitive impairment, rhabdomyolysis or significant enzymes elevation23, in this large meta-analysis PCSK9 inhibitors had an excellent safety profile with no significant differences between controls and either evolocumab or alirocumab in terms of major safety endpoints. Particularly for neurocognitive adverse events, our findings are in line with the Evaluating PCSK9 Binding Antibody Influence on Cognitive Health in High Cardiovascular Risk Subjects (EBBINGHAUS) study in which, compared with placebo, evolocumab neither improved nor worsened neurocognition among 1,974 patients enrolled in the FOURIER trial.24 With enhanced statistical power we corroborated these initial observations and further shed light on the safety profile of PCSK9 inhibitors. The only safety endpoint that occurred more frequently with use of PCSK9 inhibitors was injection site reactions; however, this was not paralleled by a greater risk of study-drug discontinuation.

The use of PCSK9 inhibitors overall was not associated with a significant benefit in terms of all-cause and cardiovascular death. However, alirocumab was associated with a statistically significant reduction in all-cause mortality by 17% using fixed-effect models compared with controls. This finding is mainly driven by the recently reported ODYSSEY-OUTCOMES trial in which the use of alirocumab was associated with a 15% relative reduction in all-cause mortality compared with placebo (p=0.026) at a median follow-up time of 2.8 years.15 However, this finding should be considered hypothesis-generating given that, in the ODYSSEY-OUTCOMES trial, all-cause mortality was a secondary endpoint planned to be tested in a hierarchical fashion. Given that in this trial coronary heart disease death (which preceded all-cause death in the hierarchical endpoint) was found to be not statistically significant reduced (p=0.38), the effect of alirocumab on all-cause mortality remains inconclusive. Although the results of our study do not firmly support a mortality benefit of PCSK9 inhibitors as a class, given the significant reductions in clinical ischemic endpoints coupled with an excellent safety profile, it remains biologically plausible that a potential survival benefit with this class of therapies could be observed with longer follow-up times and within subset of patients at greater risk of ACVD events.25 The underlying differences of the study populations and duration of follow-up of the largest trials, FOURIER and ODYSSEY OUTCOMES, may explain the variance between the two agents on long term mortality observed in our analysis. In addition, longer follow-up may be needed to observe a mortality benefit with use of PCSK9. In fact, in previous statin trials, a time of exposure of 5 to 6 years was needed to observe a mortality benefit with cholesterol-lowering therapy.26,27

**Limitations**

Our study has multiple limitations that need to be disclosed. First, the present findings are subject to the inherent limitations of the included RCTs due to study design, follow-up, definitions and events ascertainment. Second, as we lack patient-level data we remained unable to perform time-to-event analyses and to evaluate the efficacy and safety of PCSK9 inhibition across different levels of baseline patient risk. Consistently, we were unable to further characterize the interplay between the effectiveness of PCSK9 inhibitions and clinical presentation. In addition, we could not directly evaluate the effect between the magnitude of LDL-C lowering and the proportional benefits on hard ischemic endpoints observed with PCSK9 inhibitors. Third, although the majority of patient enrolled in the included studies were treated with high-intensity statin therapy some received other lipid-lowering therapies due to statin intolerance or other factors. Fourth, inclusion and exclusion criteria and study definitions across RCTs were not homogeneous despite an observed minimal heterogeneity for most of the analyzed endpoints. Fifth, although all-cause and cardiovascular mortality are now commonly treated as competing risks, this may not have been the cases in all included trials, which further limit our results regarding these endpoints. Finally, the control group included a mixture of placebo-controlled and open-label studies; however, effect estimates for the primary efficacy and safety endpoints remained consistent with restriction of the analysis to only placebo-controlled trials.

**CONCLUSIONS**

Across a broad range of patients with hyperlipidemia or established ACVD, use of PCSK9 inhibitors significantly reduced the risk of myocardial infarction, ischemic stroke and coronary revascularization. However, the effect of PCSK9 inhibitors on all-cause and cardiovascular mortality as a class remains inconclusive. No major safety issues associated with PCSK9 inhibition were observed. On the basis of this favorable benefit-risk ratio, the results of the present study support the use of PCSK9 inhibitors in clinical practice to mitigate residual ACVD risk or to reduce LDL-C for patients who cannot tolerate statin therapy.

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**Conflict of interest**

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**Figure Legends**

**Figure 1. Primary Efficacy Endpoints for PCSK9 Inhibitors versus Control.**

Results are reported as risk ratios and 95% confidence intervals estimated using Mantel-Haenszel fixed effect model. PCSK9: Proprotein convertase subtilisin–kexin type 9 inhibitors.

**Figure 2. Secondary Efficacy Endpoints for PCSK9 Inhibitors versus Control.**

Results are reported as risk ratios and 95% confidence intervals estimated using Mantel-Haenszel fixed effect model. PCSK9: Proprotein convertase subtilisin–kexin type 9 inhibitors.

**Figure 3. Primary Safety Endpoints for PCSK9 Inhibitors versus Control.**

Results are reported as risk ratios and 95% confidence interval estimated using Mantel-Haenszel fixed effect models. PCSK9: Proprotein convertase subtilisin–kexin type 9 inhibitors.

**Figure 4. Secondary Safety Endpoints for PCSK9 Inhibitors versus Control.**

Results are reported as risk ratios and 95% confidence interval estimated using Mantel-Haenszel fixed effect models. PCSK9: Proprotein convertase subtilisin–kexin type 9 inhibitors.

Take-home figure. Safety and Efficacy of PCSK9 Inhibitors.

PCSK9: Proprotein convertase subtilisin–kexin type 9 inhibitors.

**One-sentence summary:** In this large meta-analysis, PCSK9 inhibition was associated with lower risk of myocardial infarction, stroke and coronary revascularization, with favorable safety profile.