**PCSK9 inhibitors and small interfering RNA therapy for cardiovascular risk reduction: a systematic review and meta-analysis**

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**Background:** Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of morbidity and mortality globally. Despite Class IA indications for high intensity statin therapies in those with ASCVD or at risk, they are underutilized and/or insufficient, and large proportions remain above LDL-C thresholds with residual risk. As monotherapy or on a background of statin therapy, Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors (Evolocumab, Alirocumab) or small interfering RNA (siRNA) therapy (Inclisiran) have been demonstrated to lower LDL-C and ASCVD events, but meta-analyses of these therapies and their individual outcomes are lacking.

**Purpose:** The purpose of this study was to perform a systematic review and meta-analysis of the effects of PCSK9 inhibitors and small interfering RNA (siRNA) therapy on LDL-C reduction and major adverse cardiac events (MACE).

**Methods:** Using Pubmed, Embase, Cochrane Library and clinicaltrials.gov until Jan 2023, we extracted randomized controlled trials (RCTs) of PCSK9 inhibitors (Evolocumab, Alirocumab) and siRNA therapy (Inclisiran) for primary or secondary prevention of MACE. Using random-effects models, we pooled the relative risks (RR) and 95% confidence intervals (CI) and weighted least-squares mean difference in LDL-C levels. We estimated odds ratios with 95% CIs among MACE subtypes and all-cause mortality. Fixed-effect model was used, and heterogeneity was assessed using the I² statistic.

**Results:** LDL-C percentage change was reported in 47 (RCTs) (n = 267,900) evaluating two PCSK9 inhibitors and one siRNA therapy. Of those, 21 studies (n = 211,058) included treatment with Evolocumab (140mg), 22 (n = 47,320) included Alirocumab (75mg), and 4 studies (n = 9,522) included Inclisiran (284mg and 300mg). Compared with placebo, after a median of 24 weeks, Evolocumab reduced LDL-C by -61.09% (95% CI: -64.81, -57.38, p < 0.01) and Alirocumab reduced LDL-C by -46.35% (95% CI: -51.75, -41.13, p < 0.01). Inclisiran 284mg reduced LDL-C by -54.83% (95% CI: -59.04, -50.62, p = 0.05) and Inclisiran 300mg reduced LDL-C by -43.11% (95% CI: -52.42, -33.80, p = 0.01).

After a median of 26 months, Evolocumab reduced the risk of myocardial infarction (MI), OR 0.72 (95% CI: 0.64, 0.81, p < 0.01), coronary revascularization, OR 0.77 (95% CI: 0.70, 0.84, p < 0.01), stroke, OR 0.79 (95% CI: 0.66, 0.94, p = 0.01) and overall MACE, OR 0.85 (95% CI: 0.80, 0.89, p < 0.01). Alirocumab reduced MI, OR 0.57 (0.38, 0.86, p = 0.01), cardiovascular mortality OR 0.35 (95% CI: 0.16, 0.77, p = 0.01), all-cause mortality OR 0.60 (95% CI: 0.43, 0.84, p < 0.01), and overall MACE OR 0.35 (0.16, 0.77, p = 0.01). Insufficient MACE data has been reported for Inclisiran.

**Conclusion:** PCSK9 inhibitors (Evolocumab, Alirocumab) and siRNA therapy (Inclisiran) significantly reduce LDL-C by >40% in high-risk individuals. Additionally, Alirocumab and Evolocumab reduce the risk of MACE, and Alirocumab reduced cardiovascular and all-cause mortality.
Evolocumab MACE Forest Plots

Alirocumab MACE Forest Plots