A Meta-Analysis of Cardiovascular Outcomes in Patients With Hypercholesterolemia Treated With Inclisiran

Pro-protein convertase subtilisin/kexin type 9 (PCSK-9) inhibitors are currently a class 1 recommendation for the secondary prevention of atherosclerotic cardiovascular disease (ASCVD) in patients judged to be at very high risk for future ASCVD events in addition to maximally tolerated statins and ezetimibe.[1] Recently, Inclisiran, a chemically synthesized small interfering RNA therapeutic agent that reduces hepatic synthesis of PCSK9, was developed with the intent to reduce plasma low-density lipoprotein cholesterol (LDL-C) levels.[2] However, the efficacy of Inclisiran in cardiovascular event reduction remains unclear. Therefore, we performed a meta-analysis of randomized controlled trials (RCTs) comparing cardiovascular outcomes in patients treated with Inclisiran compared with control in patients with hypercholesterolemia treated with maximally tolerated dose statins with or without additional lipid-lowering therapy.

We performed an extensive search of electronic databases including PubMed/Medline, CENTRAL, Google Scholar, and ClinicalTrials.gov from inception till May 1, 2020. We included participants from RCTs that were assigned to at least 2 doses of 284 mg or more of Inclisiran throughout the trial period. The primary outcome of our meta-analysis was ischemic cardiovascular outcomes. Outcomes were analyzed as dichotomous variables, and risk ratios (RR) and their respective 95% confidence intervals (CI) were obtained using the Mantel-Haenszel method and a random-effects model was used. Review Manager version 5.3 (RevMan; Cochrane Collaboration) was used to analyze all study data.

A total of 3 published studies,[3–5] 4 RCTs; randomizing 3,783 patients (1,895 to Inclisiran and 1,888 to placebo) were included in this meta-analysis. Mean age of study participants was 62.6 ± 9.1 years, and 67.3% of participants were men. At baseline, mean LDL-C was 122.9 ± 46.0 mg/dl, 91.8% of patients were on maximum tolerated statin therapy, 35.2% had diabetes mellitus, and 84.5% had ASCVD. Safety outcome data were available for 3,738 patients (98.8%) with a mean follow-up duration of 458 days (range 210 to 540 days). All participants were receiving guideline-recommended medical therapy for hypercholesterolemia.

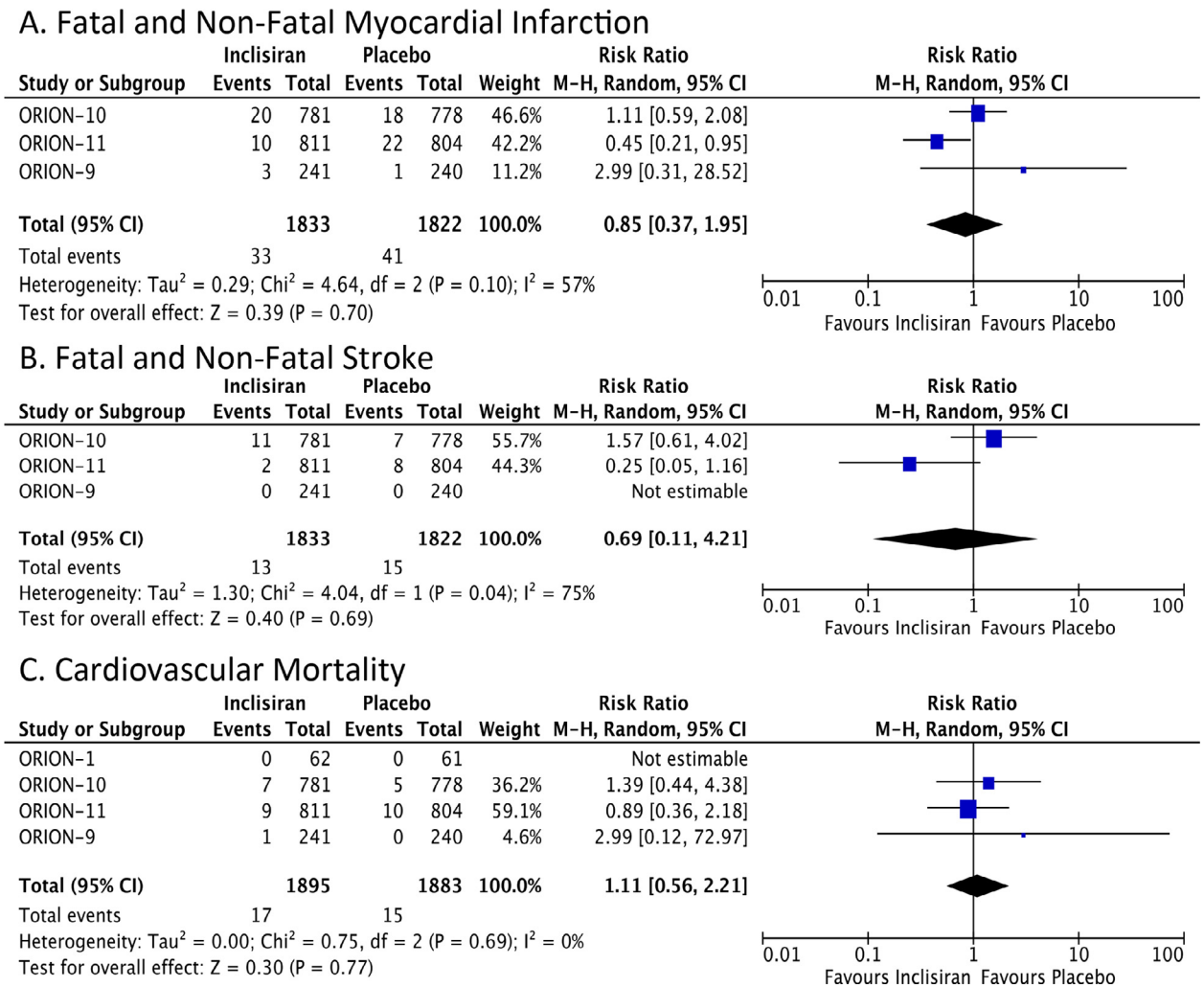

Figure 1. Forrest plots of cardiovascular ischemic outcomes in patients treated with Incliciran compared with placebo. CI = Confidence Interval; M-H = Mantel-Haenszel.

Three trials, 2 studies, reported data on fatal and nonfatal myocardial infarction and stroke.[4,5] Overall, there was no statistically significant difference in the risk of myocardial infarction in patients randomized to Inclisiran compared with placebo (1.8% vs 2.3%; RR: 0.85 [95% CI 0.37 to 1.95]; p = 0.70, I^2 = 57%; Figure 1). Additionally, there was no observed significant difference in the risk of fatal and nonfatal stroke in the Inclisiran arm compared with placebo (0.7% vs 0.8%; RR: 0.69 [95% CI 0.11 to 4.21]; p = 0.69, I^2 = 75%; Figure 1). A total of 4 RCTs, 3 studies, reported on cardiovascular related mortality throughout the respective trial periods.[3–5] In total, there was no significant reduction in cardiovascular related mortality in the Inclisiran group compared with control (0.9% vs 0.8%; RR: 1.11 [95% CI 0.56 to 2.21]; p = 0.77, I^2 = 0%; Figure 1).

In this study, there were no observed significant reductions in cardiovascular ischemic endpoints with Inclisiran compared with placebo in patients with hypercholesterolemia treated with maximally tolerated medical therapy with residual risk for future ASCVD (all p >0.05). Although Inclisiran lead to significant reductions in absolute LDL-C and PCSK-9 levels across all 4 included trials,[3–5] this effect seems to be independent of reductions in ischemic end point events. Meanwhile, PCSK9 inhibitors have been shown to significantly reduce cardiovascular events proportional to the magnitude of the absolute reduction in LDL-C in a meta-analysis of 25 trials.[6] Limitations of this meta-analysis include a relatively small sample size, lack of individual patient level data, and the limited availability of longer term follow-up data.

In conclusion, this study demonstrates that the significant decreases in LDL-C and PCSK-9 levels in patients treated with Inclisiran compared with control in patients with hypercholesterolemia on maximum tolerated statins reported in individual trials were not concordant with any significant decrease in cardiovascular ischemic end points. Hence, a deeper and more detailed investigation into the efficacy of Inclisiran is warranted.

Disclosures

The authors have no conflicts of interest to disclose.

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