Preventive Cardiology – Risk Factors and Prevention, Diabetes and the Heart

Efficacy of inclisiran versus placebo in atherosclerotic cardiovascular disease: A systematic review and meta-analysis

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Introduction: LDL-C reduction is central to secondary prevention in ASCVD. Inclisiran, a siRNA targeting hepatic PCSK9, is administered on day 1, day 90 and every six months, providing sustained LDL-C lowering in randomised, placebo-controlled trials. Long-term efficacy, including prior-MI subgroups, is unreported, motivating this systematic review and meta-analysis.
Methods: We included six unique randomised, double-blind, placebo-controlled trials: ORION-1, 10, 11, 15, 18 and a Chinese RCT. A post-hoc pooled analysis of ORION-10 and ORION-11 was excluded to prevent double counting. Random-effects inverse-variance models were applied by stratum, and pooled estimates were reported with 95% CI, I^2 statistics, and prediction intervals when $k \geq 3$. Strata with fewer than three trials were summarized descriptively. Outcomes evaluated included placebo-corrected percentage change in LDL-C at the longest shared follow-up period of approximately 330 to 510 days, effects at approximately 90 and 180 days, absolute LDL-C change at day 180 and time-adjusted change after day 90. Prior MI subgroup analyses were presented at the trial level where available.
Results: At approximately 330 to 510 days, the pooled placebo-corrected percentage change in LDL-C was -52.46% with a 95% CI of -60.89 to -44.03, derived from three trials, with $I^2 = 56.58\%$ and a prediction interval of -65.78 to -39.14, demonstrating durable long-term LDL-C lowering across regions. At approximately 180 days, the pooled estimate was directionally consistent but heterogeneous with $k = 2$ and $I^2 = 81.47\%$, reflecting regimen and landmark differences between phase 2 and regional trials. At approximately 90 days, a single-trial estimate indicated a placebo-corrected percentage change of -38.60% with a 95% CI of -54.70 to -22.50. Absolute LDL-C reduction at day 180 in ORION-15 at a 300 mg dose was -70.9 mg/dL with a 95% CI of -78.9 to -62.9 versus placebo. Time-adjusted percentage change after day 90 was -53.8% in ORION-10 and -49.2% in ORION-11. Prior MI subgroup estimates, where reported, aligned directionally with overall effects.
Conclusion: This systematic review and meta-analysis shows inclisiran provides substantial and durable LDL-C reductions across randomised trials, with a pooled long-term effect of -52.46% at 330-510 days and trial-level time-adjusted reductions near 50%. These findings support inclisiran as an infrequently dosed adjunct for secondary prevention in ASCVD. Clinical outcomes were not pooled and heterogeneity at 180 days warrants cautious interpretation and sensitivity analyses by trial phase, regimen and region. This meta-analysis provides a harmonized assessment of long-term LDL-C lowering across all major trials and highlights its consistent efficacy across patient subgroups, including those with prior myocardial infarction.