

Genetic proxies for PCSK9 inhibition associated with lower lipoprotein(a): effects on coronary artery disease and ischemic stroke

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ABSTRACT

Introduction: Lipoprotein (Lp(a)) is considered to be a causal independent risk factor for atherosclerotic cardiovascular disease. While there are no specific Lp(a)-lowering treatments, *post hoc* analyses from two landmark trials suggest that PCSK9 inhibitors can reduce Lp(a) levels. However, it remains unknown whether any effects of currently available LDL-lowering approaches on Lp(a) could influence cardiovascular event rates on top of their LDL-lowering effects.

Methods: We identified 16 variants as proxies for PCSK9 inhibitors, 11 for statins, and 3 for ezetimibe using data from a GWAS meta-analysis of the GLGC Consortium and the UK Biobank for LDL-cholesterol (188,577 and 357,366 individuals, respectively). For the drug classes that we identified significant effects on Lp(a) ($p < 0.05$) for, we explored associations with coronary artery disease (CAD) (CardioGramPLUS4D Consortium: 60,801 cases and 184,305 control), ischemic stroke (IS), and IS subtypes (i.e., large artery, cardioembolic, small vessel; MEGASTROKE Consortium: 60,341 cases, 454,450 controls). To examine whether any effect of those drug classes on Lp(a) could explain part of their overall effect on CAD and IS, we performed two-step mediation MR analyses. We estimated the effect of genetically predicted Lp(a) on risk of CAD, IS, and IS subtypes by using 62 variants in the vicinity (± 300 kb) of the *LPA* gene that were associated with Lp(a) levels at $p < 5 \times 10^{-8}$ (clumped at $r^2 < 0.10$).

Results: We found a significant association between genetic proxies for PCSK9 inhibitors and lower Lp(a) levels (beta per 1-SD-decrement in LDL-cholesterol: -0.11, 95%CI: -0.15 to -0.06) without evidence for heterogeneity ($p = 0.87$), and robust results in sensitivity analyses. There were no significant associations of genetic proxies for statins and ezetimibe with Lp(a) levels. Genetic proxies for PCSK9 inhibitors were associated with lower risks for CAD (OR: 0.75, 95%CI: 0.64-0.88) and large artery stroke (OR: 0.74, 95%CI: 0.56-0.99), but there were no significant associations with any IS (OR: 0.98, 95%CI: 0.85-1.13), cardioembolic stroke (OR: 1.00, 95%CI: 0.75-1.35), or small vessel stroke (OR: 1.15, 95%CI: 0.86-1.54). The proportions of the total effects of genetic proxies for PCSK9 inhibitors on CAD and large artery stroke explained by Lp(a)-lowering were 6% (95%CI: 1-10) and 3% (95%CI: -1-7%), respectively.

Conclusions: Genetic proxies for PCSK9 inhibition are significantly associated with lower Lp(a) levels. Yet, our data suggest that this effect explains only a small proportion of the overall association between proxies for PCSK9 inhibitors and risk of CAD and IS.