Exploring the relationship of genetically proxied LDL-C lowering with incidence of atrial fibrillation and heart failure

Jiayue-Clara Jiang, Xiaodong Mo, Sonia Shah

Background

LDL-C-lowering medications, such as statins, are widely used to treat and prevent coronary artery disease (CAD). However, despite CAD being an established risk factor for atrial fibrillation (AF) and heart failure (HF), there is conflicting evidence on whether statins or LDL-C lowering have any direct beneficial effects on reducing the incidence of AF and HF.

Methods

In this study, we aimed to investigate the relationship between genetically predicted LDL-C lowering and the risk of AF and HF, accounting for CAD comorbidity, by analysing individual-level genetic and clinical data from individuals of the European ancestry from the UK Biobank (N ~ 337,000) and conducting summary-level Mendelian randomisation (MR).

Results

Amongst UK Biobank participants without pre-existing CAD, every genetically proxied 1.8 mmol/L lowering of LDL-C (average effect of statins, proxied using polygenic scores) was associated with an 18% increase in incident AF risk ($p < 0.0001$) and a 27% increase in incident HF risk ($p = 0.00013$). Amongst individuals with pre-existing CAD, there was no evidence for an association of genetically predicted LDL-C lowering with incident AF or HF risk after multiple testing correction. Summary-level MR analyses corroborated that there was no significant association of LDL-C with AF when conditioned on CAD, or with non-ischaemic HF (defined as HF cases that did not have antecedent ischaemic, valvular, and congenital heart diseases, such as CAD).

Conclusions

In conclusion, using statistical genomic methods, our analysis did not find a beneficial effect of LDL-C lowering on AF or HF risks, both in the absence of CAD and amongst individuals with pre-existing CAD. It is important to note that our findings are not intended to be interpreted as evidence against the use of cholesterol-lowering medications, as it is unclear whether the risk difference would outweigh the benefits of statins in the prevention of CAD, an established risk factor for AF and HF. Our findings highlight the need for further clinical investigation on whether LDL-C-lowering therapies, such as statins, have any direct benefits in the prevention of AF and HF risks, which is particularly pertinent for understanding the safety of the use of cholesterol-lowering medications amongst individuals with a genetic predisposition to low LDL-C levels.