

Limitations of subgroup analysis of underpowered clinical trials for making causal inference about treatment effects

Milad Nazarzadeh, MSc^{1,2,3}, Kazem Rahimi, MD, FRCP^{1,2,4*}

¹ The George Institute for Global Health, University of Oxford, 1st Floor, Hayes House, 75 George Street, Oxford OX1 2BQ, UK

² Deep Medicine, Oxford Martin School, University of Oxford, Oxford, United Kingdom

³ The Collaboration Center of Meta-Analysis Research, School of Health, Torbat Heydariyeh University of Medical Sciences, Torbat Heydariyeh, Iran

⁴ NIHR Oxford Biomedical Research Centre, Oxford University Hospitals NHS Foundation Trust, Oxford, United Kingdom

* Corresponding author: Kazem Rahimi, The George Institute for Global Health UK, University of Oxford, Oxford, United Kingdom; email address: kazem.rahimi@georgeinstitute.ox.ac.uk; Tel: +44 (0) 1865 617200; Fax: +44 (0) 1865 617202; Postal code and address: 1st Floor, Hayes House, 75 George Street, Oxford, OX1 2BQ, United Kingdom

We would like to thank Dr. Greve for his interest in our paper and for bringing their related work to our attention, which we read with interest. In their work, Greve et al.,¹ conduct a post-hoc analysis of Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) trial and identify a statistical interaction between treatment (Simvastatin-Ezetimibe versus placebo), pre-treatment low-density lipoprotein (LDL), and peak aortic jet velocity as a measure of aortic stenosis progression. Their analysis revealed that treatment is associated with 0.03 m/s [95% CI 0.01 to 0.04] lower peak aortic jet velocity per year for each 1 mmol/L higher pre-treatment LDL.¹ Assessment of this interaction in further subgroups showed a marginally significant interaction for the effect of simvastatin-ezetimibe treatment on change in peak aortic jet velocity only at the highest quartile of pre-treatment LDL in patients with mild aortic stenosis.¹

Although these findings are very interesting, their meaning and implication differ fundamentally from our work. In our Mendelian randomization study,² we sought to find the causal association between dyslipidemia and risk of incident aortic stenosis and other major valvular conditions, with the aim of filling the gap in knowledge from previous published clinical trials. However, the main hypothesis in Greve et al.,¹ work was to study the interaction of treatment effect by the level of LDL at baseline and aortic stenosis severity. Whether such findings can be interpreted as reliable and causal, in particular when the main study has failed to show an effect, is disputed.^{3,4}

The post-hoc analysis of SEAS as reported by Greve et al.,¹ tested the hypothesis that the lack of effect in the main study could have masked important effects in some particular subgroups (i.e., those with higher pre-treatment LDL or less severe valve disease). While, this question was not investigated by us, the findings of the report by Greve et al., can only be considered as hypothesis-generating, since the main analysis of the SEAS trial found no overall effect of treatment on change in measured peak aortic jet velocity.³ We also note that in meta-analyses of large-scale clinical trials of statin therapy, there has been no evidence of interaction by baseline LDL-cholesterol on atherosclerotic events.⁵ Therefore, the apparent interaction in the post-hoc study of a relatively small trial raises the question of possible type I error, requiring further research.

Conduct of new large-scale LDL-lowering clinical trials for primary prevention of valvular heart disease have numerous challenges. In the absence of clinical trials with sufficient statistical power and long-term follow-up, the findings of our Mendelian randomization study provide the most compelling evidence for the effect of lipid-lowering treatment on reducing the risk of incident aortic stenosis.

Conflict of interest: The authors declare that there is no conflict of interest.

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