

Reply: How low should you go?

Prof Kazem Rahimi, FRCP¹⁻³, Zeinab Bidel, MSc,¹⁻³ Milad Nazarzadeh, MSc,^{1,2} Emma Copland, MSc,¹⁻³, Dexter Canoy, MD,¹⁻³

¹ Deep Medicine, Oxford Martin School, University of Oxford, Oxford, UK

² Nuffield Department of Women's and Reproductive Health, University of Oxford, Oxford, UK

³ NIHR Oxford Biomedical Research Centre, Oxford University Hospitals NHS Foundation Trust, Oxford, UK

Corresponding author:

Kazem Rahimi, FRCP DM MSc FESC

University of Oxford

Hayes House 1F, 75 George Street

Oxford OX1 2BQ

UK

Tel: +44 1865 617 201

E-mail: kazem.rahimi@wrh.ox.ac.uk

We thank Drs Garrison and McCormack for their interest in our study and for raising important questions concerning the study methodology.¹

We have indeed considered individual participant-level blood pressure (BP) changes in our analyses. In a separate investigation, we used repeated BP measurements for each individual to model changing differences in BP longitudinally.² This modelling ensures that we apply the same method to all studies, and consider differences in follow-up duration and frequency of remeasurements over time. We then used these modelled temporal BP values for individuals to calculate group-level differences between treatment arms for each trial. Finally, this estimated “difference in difference” BP for each trial was used to standardise the randomised effects on outcomes (expressed per 5 mmHg difference in systolic BP). By weighting the effects based on the average change in BP between randomised groups in a trial, we adhere to the intention-to-treat principle of comparisons whilst leveraging the individual-level information that helps increase the precision of the estimates.

It could be argued that using trial-level average BP difference between treatment groups assumes that BP changes are similar among subgroups with very different clinical characteristics where in reality they might have responded differently to treatment. In our earlier investigation, we explored this question and assessed the effects of treatment on BP changes by age, sex, past medical history, and previous use of antihypertensive drugs, as well as by baseline BP.² Whilst there were some variations in the achieved BP reduction amongst subgroups, BP-lowering treatment was effective in reducing BP across all strata of characteristics that we have considered. Indeed, the main driver for the differences in achieved BP reduction, as expected, was related to the trial design. For example, the overall systolic BP reduction among all trials that aimed at achieving a difference in BP was 6.3 mmHg, whereas the achieved reduction was more substantive for trials comparing more versus less intense treatment strategies (11.2 mmHg). Based on this evidence, we used the simpler model based on a single weighting factor across all subgroups in each trial. However, to provide additional empirical evidence for the limited utility of more complex modelling, we have conducted a new sensitivity analysis that rescales the effect sizes based on achieved BP reduction separately for each baseline BP category (**Figure**). The results are

almost identical to our main findings (as presented in the supplementary Figure S6 on page 19).¹

References

- 1 Rahimi K, Bidel Z, Nazarzadeh M, *et al.* Pharmacological blood pressure lowering for primary and secondary prevention of cardiovascular disease across different levels of blood pressure: an individual participant-level data meta-analysis. *The Lancet* 2021; **397**: 1625–36.
- 2 Canoy D, Copland E, Nazarzadeh M, *et al.* Effect of antihypertensive drug treatment on long-term blood pressure reduction: An individual patient-level data meta-analysis of 352,744 Participants from 51 large-scale randomised clinical trials. *medRxiv* 2021; : 2021.02.19.21252066.

Figure. Effects of blood pressure-lowering treatment on major cardiovascular events by systolic blood pressure (mmHg) at baseline.

The effect sizes rescaled based on achieved blood pressure reduction separately for each baseline systolic blood pressure categories. SBP: systolic blood pressure; HR: hazard ratio; CI: 95% confidence intervals; Adjusted p interaction: adjusted for multiple testing using Hommel's method; unadjusted p interaction: not adjusted for multiple testing.

