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LETTER

ADVANCE and glycaemia thresholds: a need to clarify the statistical approach. Reply to Currie CJ [letter]

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To the Editor: We thank Professor Currie for his interesting interpretation [1] of the complex analyses undertaken to examine the relationship between HbA_{1c} and outcomes in the ADVANCE trial cohort [2].

With respect to the use of time-weighted average HbA_{1c} levels, we used several different approaches for assessing HbA_{1c} levels including baseline values and time-dependent covariates. Each gave similar findings to those presented. The averaging method published was required by reviewers and deemed most understandable by clinicians.

With respect to potential treatment effects, we regard the randomised comparisons between the intensive and the standard glucose control groups, reported in our main results paper of 2008, to be the paramount result [3]. This takes account of the achieved difference in HbA_{1c} of 0.67% on average, and 0.7% at the end of the study, as well as differences in treatments. Since all models in our more recent paper adjusted for assignment to the intensive or standard glucose control treatment strategies [2], it was deemed unnecessary and excessive also to adjust for use of therapeutic classes, including sulfonylureas and insulins, which were more commonly used in the intensive glucose control group. This approach was also followed by the ACCORD trial investigators in similar post hoc epidemiological analyses [4]. Furthermore, we avoided further post-randomisation adjustment since we believed this would introduce bias by indication.

Although unexpected, our finding of a difference in the magnitude of the association between HbA_{1c} and major outcomes by randomised treatment group was also reported by the ACCORD investigators [4]. Using updated average HbA_{1c} levels, ACCORD reported higher adjusted all-cause mortality risks for each 1% higher HbA_{1c} in the intensive compared with standard glucose treatment arms (intensive HR 1.66 [95% CI 1.46, 1.49] vs standard HR 1.14 [95% CI 0.95, 1.38]) [4].

Duality of interest J. Chalmers holds a research grant from Servier as a principal investigator for ADVANCE. S. Zoungas, J. Chalmers and M. Woodward have received lecturing fees from Servier. There are no other dualities of interest relevant to this manuscript.

Contribution statement All authors were responsible for drafting the letter and reviewing it critically for important intellectual content. All authors approved the version to be published.

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