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Response to letters from Torp-Pedersen and colleagues and de Courson and colleagues

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This commentary refers to 'Blood pressure and the uncertainty of prediction using hazard ratio', by C. Torp-Pedersen *et al.*, on page 4219; 'Blood pressure variability and risk of cardiovascular event: is it appropriate to use the future for predicting the present?', by H. de Courson *et al.*, on page 4220.

We are glad for the opportunity to discuss the methodological questions to our analysis[1] raised by Torp-Pedersen and colleagues and de Courson and colleagues.[2,3] We fully agree that conditioning on the future poses difficulties for interpretation. We therefore acknowledged this challenge in the Methods and Discussion sections, and to address this challenge, we performed two sets of supplementary analyses in which this challenge is avoided. In the first analysis, blood pressure variability up to 24 months is used as a covariate in the analysis of cardiovascular events after 24 months (Supplementary Table 5). The second analysis is a matched case–control analysis where the variability estimates are based on recordings before the events for each of the cases, and on the same number of early recordings for the matched controls (Supplementary Table 6). These two sets of supplementary analyses utilize a smaller fraction of the observations, but together the three ways of analysing the data provide support for our conclusion that visit-to-visit blood pressure variability is important for risk of future cardiovascular events. We additionally considered using time-dependent methods, but as noted by de Courson and colleagues there are methodological issues, for example, that we would have to base our variability estimate either on an increasing number of measurements with increasing length of follow-up, or on a constant, low number of measurements. Jointly modelling blood pressure variability and time to event is an interesting option, although it may be challenging, given a complex data structure with many missing observations and that visit-to-visit variability has to be estimated based on several partly time-lagged observations.

Torp-Pedersen and colleagues also write that the number of blood pressure measurements and the time between them was ignored in our analysis of visit-to-visit blood pressure variability. We agree that number and timing of measurements is important for calculation of blood pressure variability. However, the time between measurements was the same for all measurements in our analysis (6 months, as we restricted our analysis to visits performed from 6 months onwards), and for the clear majority of participants the number of visits was close to the maximum number (mean 9 visits, maximum 10 visits), both for those with and without events. Additionally, the two sets of supplementary analyses mentioned in the previous paragraph either have much less variation in number of measurements (Supplementary Table 5) or virtually no difference (Supplementary Table 6). For these reasons, we think that our measure of visit-to-visit blood pressure variability is valid, and that readers can interpret the results without a fear of being misled, as suggested by Torp-Pedersen and colleagues.

Finally, we are unsure what Torp-Pedersen and colleagues refer to when they write that 'the study seems to indicate that blood pressure variability provides predictive power beyond blood pressure'. We certainly agree that hazard ratios cannot be used to quantify predictive power, and we made no attempt to do so. One reason is that visit-to-visit variability as measured in the VALUE trial is not suited as a predictor on the individual participant level, since repeated and standardized measurements over long time periods is unrealistic in clinical practice. Predictions for individuals based on blood pressure measurements must be based on recordings over shorter time periods, such as ambulatory blood pressure measurements, and then the methods suggested by Torp-Pedersen and colleagues are clearly relevant.

Conflict of interest: S.E.K. reports personal fees from ABDiiBRAHiM, Bayer, MSD and Takeda. The other authors have nothing to disclose.

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