

## University of Dundee

### Reply

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## Reply: Authors response to Biondi-Zoccai et al

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We thank Biondi-Zoccai and colleagues for their correspondence(1). They query a secondary finding in our study regarding the lack of difference between the two electronic cigarette (EC) arms(2). However, they also admit in their letter that the risks of nicotine without tobacco combustion are low. Whilst nicotine may exert pharmacologic effects, we tested the acute impact of switching away from tobacco cigarettes (TC) in the design of VESUVIUS. We state clearly that avoidance of tobacco toxicants may have produced the majority of the benefit seen as both EC arms demonstrated significant benefit over TC. Clearly, further investigation is required to understand the impact of nicotine on longer term vascular function. It should also be noted that larger randomized clinical trials on nicotine replacement therapy have not shown these to be associated with an increased CV risk (3).

In relation to the lack of difference seen in other biomarkers, they quote their own work in a smaller study which is not significantly different from our primary finding i.e. switching to EC has less unfavorable impact than TC in the acute phase. Furthermore, the biomarkers we examined were qualitatively different from those analysed by their study. Changes in pulse wave velocity indicate change in *structure*. Changes in Flow Mediated Dilatation that was observed in our trial indicate change in *function* which temporally precedes structural change. Therefore, longer term follow-up studies could yield further positive benefits from switching.

They question the replacement of dropouts in order to achieve adequate power in each group. Firstly, this was a mechanistic exploratory study and the pre-specified primary analysis was per protocol. Secondly, there is no question of bias as all patients were randomized into either EC arm until a minimum of 36 participants were achieved in each group for adequate power. Furthermore, an intention to treat analysis would not answer

their question about nicotine as by definition, those who dropped out did not attend for their post-switch vascular assessment. Therefore no data would be available on the efficacy of EC with versus without nicotine in drop-outs.

Finally, they note that the choice of EC may not be comparable to other devices. This is discussed in the Limitations section. We used a common EC device closest to the most popular EC strength in surveys(4) which would be broadly representative of public use in the UK but we agree that further comparisons are worthwhile.

## References

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