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Aprotinin revisited: rebuttal of comments by DeSantis and Lazaridis

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Dear Editor,
We appreciate the interest that DeSantis and Lazaridis [1] have expressed in our study [2]. We are indeed in agreement that the residual confounding which is introduced by covariate imbalance could have introduced bias into our estimates of the effects of aprotinin withdrawal on clinical outcomes. Although we provide readers with *t*-tests, we are also in agreement that they are an inappropriate metric of the covariate balance achieved through propensity matching. For this reason, we also present the accepted measure of covariate imbalance as defined by Rosenbaum and Rubin [3], namely standardised differences (standardised percentage bias). In the published manuscript, Fig. 1 and eTable 1 demonstrate that standardised differences were found to be <5 % in the all-patient analysis and <10 % in the

high-risk analysis. This is within the accepted threshold for significant imbalance of 10 %. We are therefore confident that our results were not biased by residual confounding within the 24 key patient characteristics for which we matched patients. Of course, this parameter does not apply to the residual confounding which may have been introduced by imbalance in any *unmeasured* characteristics. However, in eTable 6 we model the effects of a number of potentially confounding unmeasured variables upon our results and demonstrate that they do not alter our conclusions.

To clarify our methodology, to account for the intra-group correlation introduced by the propensity matching process, we computed errors which allow for this clustering effect ('cluster confidence intervals') for both our logistic regression and Cox regression (time-to-event analyses). We elected not to convert to generalised linear models since they are used to estimate risk differences, not odds ratios, which made it difficult to compare with our previously generated odds ratios and hazard ratios.

In summary, our methodology anticipated that bias and confounding may have contributed to our results. Despite appropriate adjustments we demonstrated an increase in bleeding, morbidity and mortality that coincided with the withdrawal of aprotinin. Our results do not demonstrate cause and effect; however this real-world analysis highlights

important limitations of the existing evidence relating to the indications for aprotinin in cardiac surgery.

Conflicts of interest The authors declare no conflicts of interest in relation to this work.

References

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