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Aprotinin revisited

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Dear Editor,

We read with great interest the article entitled “Increased perioperative mortality following aprotinin withdrawal: a real-world analysis of blood management strategies in adult cardiac surgery” by Walkden et al. [1]. In a propensity matched study of 6,608 patients, the authors report evidence that the withdrawal of aprotinin in 2008 has resulted in increased cardiac surgery complication rates, including kidney injury, blood transfusion, and mortality. In two similar studies, we assessed the affect of the November 2007 withdrawal of aprotinin and subsequent use of lysine analogues, in patients undergoing coronary artery bypass grafting (CABG) on transfusion, post-operative events, and mortality, within a single institution ($n = 781$), also using propensity matching to adjust for baseline confounding [2, 3]. Similar to Walkden et al., these two studies reported a decreased risk of blood product transfusion and a trend toward a reduced risk of renal dysfunction in the aprotinin versus the lysine analogue group. The current larger study by Walkden et al. confirms and further elaborates on

these findings. Applying more rigorous statistical modeling procedures in the light of propensity matching, DeSantis et al. [3] found an additional increased risk in the number of blood products required in the subset of patients for whom transfusion was required, in the lysine analogue versus aprotinin groups.

However, we have some comments about the analyses used in the current study. First, when assessing the relative benefit of aprotinin versus other agents, one must be fastidious in determining whether covariate balance has been achieved by propensity matching, since, as Walkden et al. recognize, residual confounding can cause biased estimates [4]. The t tests used to assess post-propensity matching balance in this paper are not appropriate for assessing match balance since p values are sample size-dependent measures of association, and therefore may distort assessments of covariate balance [5]. A comparison of covariate distributions across matched groups (e.g., Q–Q plots by treatment group for continuous variables) would have better illustrated covariate balance. Finally, it is also unclear whether Cox proportional hazard or logistic regression models accounted for propensity matching, since the exact procedures used in STATA are not identified. It is stated in the Methods that “cluster confidence intervals” were used. The meaning of this is not clear unless analytics for clustered data were used, such as conditional logistic regression, generalized linear mixed models, and stratified proportional hazards or frailty models for time to event outcomes.

This study, in conjunction with our findings and others, adds to the evidence that aprotinin effectively reduces blood loss and decreases the need for transfusion, and that its

overall benefits outweigh the risks in isolated CABG surgery. Nevertheless, statistically rigorous studies with transparent, unambiguous reporting are going to be required to clarify the benefits versus risks of aprotinin.

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

References

1. Walkden GJ, Verheyden V, Goudie R, Murphy GJ (2013) Increased perioperative mortality following aprotinin withdrawal: a real-world analysis of blood management strategies in adult cardiac surgery. *Intensive Care Med* 39(10):1808–1817. doi: [10.1007/s00134-013-3020-y](https://doi.org/10.1007/s00134-013-3020-y)
2. DeSantis SM, Toole JM, Kratz JM, Uber WE, Wheat MJ, Stroud MR, Ikonomidis JS, Spinale FG (2011) Early postoperative outcomes and blood product utilization in adult cardiac surgery: the post-aprotinin era. *Circulation* 124(11 Suppl):S62–S69
3. DeSantis SM, Lazaridis C, Ji S, Spinale FG (2013) Analyzing propensity matched zero-inflated count outcomes in observational studies. *J Appl Stat*. doi: [10.1080/02664763.2013.834296](https://doi.org/10.1080/02664763.2013.834296)
4. Rubin DB (2006) *Matched Sampling for Causal Effects*. Cambridge University Press, Cambridge
5. Imai K, King G, Stuart EA (2008) Misunderstandings between experimentalists and observationalists about causal inference. *J R Stat Soc Ser A* 171:481–502

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