Reviewer's report

Title: The impact of administration of tranexamic acid in reducing the use of red blood cells and other blood products in cardiac surgery.

Version: 2 Date: 8 June 2006

Reviewer: Ryan Lennon

Reviewer's report:

General

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Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

1. The fundamental flaw in the analysis is the choice of endpoints. The primary endpoint ought to be harder than "further treatment" given that the purpose of the analysis is to estimate the effect of non-randomized treatment with tranexamic acid (TA). It is quite possible, perhaps very likely, that in a hospital where TA is clearly believed to be beneficial, physicians were more aggressive (maybe subconsciously so) in responding to blood loss in patients who had not received TA. Tables 8 and 9 could be consistent with such a hypothesis. If the amount of blood loss were higher in the NTA group, but physicians were more likely to transfuse NTA patients with little blood loss, this would pull the distribution of units transfused downward in the NTA group. Table 9 consists of patients who did not return to theatre. One may consider these patients to be less aggressively treated and these patients had similar rates of transfusion. This does not mean that the entire estimated benefit of TA is necessarily due to this bias, but much of it may be. The estimated effect is really a combination of clinical efficacy and physician response. Given the authors concern that large-scale clinical trials with TA are unlikely to occur, it is important to estimate TA's clinical effect with as little bias as possible. The authors ought to employ blood loss as their primary endpoint. If the authors choose to retain the current endpoints (in addition to blood loss) they should comment on the selection bias for these soft endpoints in the limitations section.

The authors' argument in response to reviewers that including blood loss may "distract a reader from ... what matters" is nonsense. If I were a patient, blood loss would certainly matter. Return to theatre and transfusion are merely responses to that blood loss. It is unfortunate that other hard endpoints such as mortality are not available.

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Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

1. In Table 2, report actual p-values instead of "ns" or "< 0.05". There is no need to blunt that information.
2. In Table 2, the test for comparing "Priority" should be accomplished by either a single chi-square test or a single rank sum test with the categories scored as 1=elective, 2=urgent, 3=emergency. The current three separate tests are highly correlated and possibly misleading.

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Discretionary Revisions (which the author can choose to ignore)

1. The choice between multivariable regression models and propensity score approach for covariate adjustment is often determined by analyst preference. Both have the same limitations in that neither can account for unmeasured covariates (outside of those covariates' associations with the measured covariates). If one has the variables to produce a regression model, they can also use a propensity score approach. Advantages of the propensity score approach are: 1) allows the analyst to consider more parameters (especially interactions) than the multivariable model may be able to numerically support; 2) when grouping the patients into propensity score-based strata and estimating the effect within those strata, it may become clear that the treatment has stronger effects in different groups of patients, e.g. a larger effect in higher risk patients; 3) the analyst does not have to build/describe separate models for each
endpoint; 4) the model for the propensity score often indicates the amount of selection bias to be overcome via the c-statistic. With regards to this last point, while a higher c-statistic means that the propensity score discriminates well between the two groups, it also means that the two groups were very different to begin with and that unmeasured covariates may be similarly unbalanced. The advantages of the multiple regression model is that 1) it is easier to conduct; 2) it produces estimates of the associations between the covariates and the endpoint. The paper would be stronger with a propensity score approach, but this is not necessary. However, since the main focus of the paper is estimating the effect of TA, and not building models for the endpoints, the authors should allow all relevant covariates in the model, regardless of statistical significance. They should also allow for non-linear associations between the continuous covariates and the endpoints.

2. Table 2 - The summary of EuroScore does not indicate which group has the higher scores in general. Consider reporting additional statistics to make this clearer, e.g. mean, 95th percentile, etc.

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No

Declaration of competing interests:

I declare that I have no competing interests.