SAFETY OF APROTININ IN ADULT CARDIAC SURGERY: REVISITING THE VALIDITY OF A MIXED-TREATMENT COMPARISON META-ANALYSIS

To the Editor:

I read with great interest the article by Howell and colleagues[1] on a mixed-treatment meta-analysis of trials of aprotinin in adult cardiac surgery drawn from the publications identified in a previous Cochrane review.[2] In their publication, Howell and colleagues[1] concluded that this reanalysis demonstrated no increase in the risk of mortality for patients treated with aprotinin relative to either placebo or other antifibrinolytic agents.

Recently, a variety of sophisticated statistical methods have been proposed to provide direct and indirect estimates of comparative treatment effects. Such evidence synthesis approach can be informative when relative treatment effects are consistent across all trials and there is high agreement between direct and indirect estimates. To achieve relevant clinical impact, however, the validity of methods must convince both the epidemiologic and clinical audiences. I believe that the limitations described here question the validity of the published results[1] and thus their utility in guiding medical decision making.

First, Howell and colleagues[1] did not adequately discuss the statistical models (and their limitations) for estimating indirect and mixed-treatment comparisons, implying that they could provide more accurate and precise results than direct pairwise comparisons. Indirect and mixed-treatment comparisons are based on assumptions of transitivity (if A is much better than B, and B is better than C, then A is assumed to be better than C) and consistency (agreement between various sources of evidence), assumptions that can be verified conceptually and epidemiologically but are, however, subject to substantial uncertainty. Consideration of these aspects will naturally lead clinicians and systematic reviewers in evaluating the underlying assumptions, will encourage exploration of potential disagreements between trials thus giving better insight into the research question, and will add transparency to the choices being made regarding comparative data synthesis.[3]

Second, bias in small trials of antifibrinolytics is notorious, and often selective reporting is intractable. Various approaches to deal with publication bias and to account for effect modifiers or to evaluate the risk of bias have been developed.[3] Indeed, the reporting bias effect in mixed-treatment comparisons may differ from that in conventional meta-analyses.[4] Howell and colleagues[1] failed to mention, however, that the Cochrane review[2] they used for their mixed-treatment comparisons noted evidence of publication bias in trials testing aprotinin. This led to a probable overestimation of the blood-sparing effect of the drug, thus bringing into question the results provided in Figure 5 in the article of Howell and colleagues.[1] Conversely, no publication bias was reported in relation to clinical outcomes of death,[2] but a trend was seen toward increased mortality among those patients receiving aprotinin relative to those who received tranexamic acid or ε-aminocaproic acid.

Third, I believe that the main limitation of the meta-analysis by Howell and colleagues is the relatively small number of deaths (highly dependent on the Blood Conservation Using Antifibrinolytics in a Randomized Trial [BART] study), which clearly limits the power of the analyses. Along the same line, antifibrinolytic trials have been conducted for different durations, explaining the variation in amounts of evidence as a result of variations across trials in characteristics of cardiac patients, surgical procedures, or outcome assessment[5] (eg, mortality during surgery, in-hospital mortality, 30-day mortality).

In summary, I believe that Howell and colleagues have unintentionally overinterpreted the evidence and ignored assumptions inherent in mixed-treatment meta-analysis. This has led to overly categoric conclusions from an interesting approach fraught with uncertainty.

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References

1. Howell N, Senanayake E, Freemantle N, Pagano D. Putting the record straight on aprotinin as safe and effective: results from a mixed treatment meta-analysis of trials of aprotinin. *J Thorac Cardiovasc Surg*. Epub 2012 Aug 10.
2. Henry DA, Carless PA, Moxey AJ, O'Connell D, Stokes BJ, Fergusson DA, et al. Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion. *Cochrane Database Syst Rev.* 2011;(3):CD001886.
3. Salanti G. Indirect and mixed-treatment comparison, network, or multiple treatments meta-analysis: many names, many benefits, many concerns for the next generation evidence synthesis tool. *Res Syn Meth*. Epub 2012 Jun 11. doi: 10.1002/jrsm.1037.
4. Trinquart L, Abbé A, Ravaud P. Impact of reporting bias in network meta-analysis of antidepressant placebo-controlled trials. *PLoS One*. 2012;7:e35219.
5. Rosén M. The aprotinin saga and the risks of conducting meta-analyses on small randomised controlled trials—a critique of a Cochrane review. *BMC Health Serv Res*. 2009;9:34.

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Reply to the Editor:

We thank Dr Catalá-López for his interest in our study.[1] In reply to

some of the methodologic issues raised, we point out that randomized trials minimize bias because, as Fisher noted, the simple act of randomization assures the internal validity of the test for significance.[2] In other words, randomization allocates subjects on the basis of the play of chance and thus enables us to consider just 2 orthogonal alternative explanations for any treatment effect observed; that is, that the difference in treatment effect is due to chance or is due to the experimental therapies. Dr Catalá-López is presumably aware of the design advantages of the randomized trials through his regulatory work.

Mixed treatment analyses are commonly used by technology assessment groups, such as the National Institute for Clinical Excellence in the United Kingdom, to summarize data on several treatments for a common condition.[3] Our work builds on the thoughtful conventional meta-analysis from which our data were drawn and confirms that no adverse treatment effect associated with aprotinin is found even when we take this approach.

Small-study bias is less likely to be an issue when it comes to comparative studies; in any case, however, it is likely to be of smaller magnitude than the bias in nonrandomized studies. Thus Catalá-López seems to be missing the point; however we analyze the data from randomized trials, we cannot find a problem associated with aprotinin use, and the regulatory concern and action surrounding this potentially useful agent thus has not been to the benefit of patients.

Finally, we wonder whether employment by a regulatory body that made an incorrect decision to withdraw the use of aprotinin does constitutes a declarable conflict of interest.

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References

1. Howell N, Senanayake E, Freemantle N, Pagano D. Putting the record straight on aprotinin as safe and effective: results from a mixed treatment meta-analysis of trials of aprotinin. *J Thorac Cardiovasc Surg*. Epub 2012 Aug 10.
2. Armitage P. Fisher, Bradford Hill, and randomization. *Int J Epidemiol*. 2003;32:925-8; discussion 945-8.
3. NICE Decision Support Unit (DSU). TSDs completed or currently in progress. Available at: http://www.nicedsu.org.uk/Technical-Support-Documents(1985314).htm. Accessed April 25, 2012.

http://dx.doi.org/10.1016/j.jtcvs.2012.11.003

IMPORTANCE OF STANDARDIZATION OF SURGICAL TECHNIQUES IN ANALYZING NEUROLOGIC OUTCOMES

To the Editor:

We read with great interest the article by Chaudhuri and colleagues[1] about carbon dioxide insufflation in open-chamber cardiac surgery. Insufflation of carbon dioxide in the pericardial cavity to prevent the development of cardiac or neurologic damage from air embolism has been mentioned in the literature since 1967.[2] Manual deairing proved to be highly inefficient in the elimination of air emboli even when it was done with very meticulous technique. Improvement was seen when echocardiography was introduced as a standard clinical method for recording air bubbles in the process of deairing heart cavities, with the deairing procedure performed under visual control.[3]

With the help of transcranial Doppler ultrasonography, it was found that despite the detailed deairing, one of the biggest sources of air embolism occurs during distribution of blood from the heart–lung machine to the empty, beating heart, when the heart begins to eject actively.[4] In that respect the article provides the necessary safety guidance on the duration of the deairing procedure with and without carbon dioxide insufflation in pericardial cavity without fear for the development of neurocognitive damage. In addition to age, hypercholesterolemia, aortic burden, and coronary artery disease, however, neurologic outcome after cardiac surgery is also influenced by other factors as a consequence of applied surgical technique.

We do not want to split hairs, but remarks that we discuss here are regularly the subject of fierce debate at our clinic. In addition to aortic burden, surgical manipulation on the aorta has significant impact on development of neurologic sequelae or recovery from the same. Patients who underwent surgical myocardial revascularization as additional procedure with open heart cavities make up a quarter of patients in the study of Chaudhuri and colleagues.[1] The increased number of surgical manipulations on the aorta as a result of the revascularization strategy, single or multiple clamping applied during the formation of the proximal anastomosis, could lead to a higher degree of neurocognitive impairments.[5] This concern is especially pronounced in light of the multicenter character of study, which did not allow the possibility of selecting the surgical techniques that would be used in the study, because some surgeons probably had rigid personal views about issues of technique. Occurrence of gross neurologic outcomes, such as stroke, transient ischemic attack, or delirium, was not described in the postoperative period, although such could be expected in a study of this size on the basis of previous studies.[6]