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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Reply to the Editor:

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