

Con: Aprotinin Has a Good Efficacy and Safety Profile Relative to Other Alternatives for Prevention of Bleeding in Cardiac Surgery

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It is our position that, to reduce perioperative blood loss in patients undergoing cardiac surgery with cardiopulmonary bypass (CPB), all patients should receive a drug with antifibrinolytic properties (heretofore referred to as “antifibrinolytic drugs”), and that the drug of choice for this indication in most (if not all) patients should be a lysine analog (tranexamic acid or ϵ -aminocaproic acid), rather than aprotinin.

This position is based on several facts which have been gleaned from all the available evidence:

FACT 1.

Aprotinin, compared with lysine analogues, is at least four times more expensive.

FACT 2.

The blood-conserving superiority of aprotinin when compared with the lysine analogues has yet to be demonstrated.

FACT 3.

Aprotinin with documented allergic reactions and potential for renal failure may have an inferior safety profile.

The controversy generated by recent publications (1,2), has shifted the focus of antifibrinolytic drug choice away from efficacy to safety. We think this is a mistake; after all, we continue to use drugs with significant side effects, when they offer a clinically important benefit compared with available alternatives. Examples of this behavior in anesthesia include the use of halothane in the early 1960s and, of course, transfusion of blood products, which is germane to our argument. The primary issue here, therefore, is not the relative safety of aprotinin and lysine analogues; rather, it is whether aprotinin is more effective than lysine analogues in reducing perioperative blood loss.

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WHY SHOULD AN ANTIFIBRINOLYTIC DRUG BE USED ROUTINELY IN CARDIAC SURGERY WITH CPB?

There is a plethora of evidence that blood loss that leads to transfusion of blood products is harmful, and that the degree of harm is directly related to the amount of blood loss (3). (Although it has not been elucidated if it is the blood loss or the resultant blood transfusion that is harmful and this distinction has little practical relevance). In one study (4), transfusion of five or more units of blood was independently associated with an eight-fold increase in the risk of death, and this risk was exceeded only by postoperative renal failure and stroke. Therefore, without question, we strive to limit the transfusion of blood products. To this end it has also been clearly shown (by numerous randomized, placebo-controlled trials) that both classes of antifibrinolytic drugs reduce perioperative blood loss and red blood cell (RBC) transfusions by about 30% (5,6). Thus, the evidence is

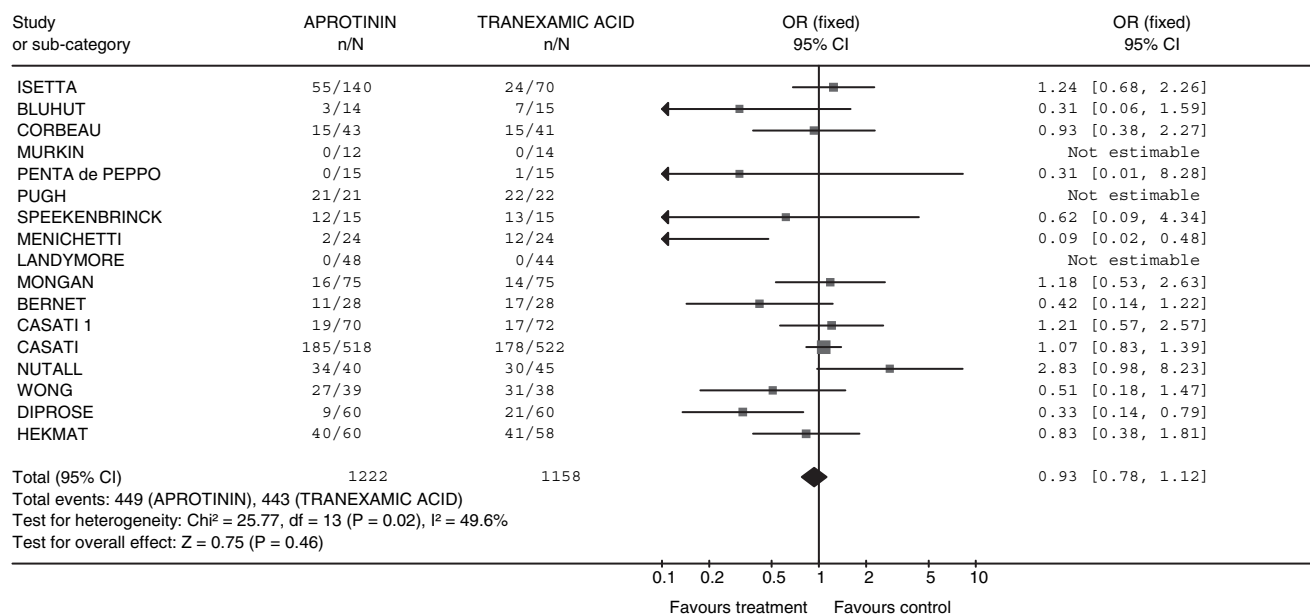


Figure 1. Systematic analysis of the blood-conserving properties of aprotinin versus tranexamic acid in cardiac surgery. In all studies the odds ratio for the risk of a blood transfusion was 0.93 95% (CI 0.78–1.12) $P = 0.46$. There is significant heterogeneity ($I^2 = 50\%$). The studies showing the best blood-conserving properties (Menichetti, Diprose, and Bernet) all had higher preoperative hemoglobin levels (details are in the on-line Appendix). When these three studies are eliminated from the analysis, the odds ratio for the risk of transfusion is 1.06 (95% CI 0.87–1.28) $P = 0.56$. Furthermore, there is no heterogeneity. Regression analysis also suggests that in these studies, the need for transfusion is driven by the preoperative hemoglobin level.

compelling that an antifibrinolytic drug should be used in all patients undergoing cardiac surgery with CPB to decrease blood loss, and there seems to be a general consensus on this point. Two issues remain controversial. The first is whether aprotinin has a better balance of benefit and harm than the less expensive lysine analogues. The second is a philosophical issue as to why the less expensive, older, equally effective, lysine analogues have not been registered and approved for cardiac surgery by the Food and Drug Administration (FDA) (this later issue is best debated in a separate forum).

WHAT ARE THE RELATIVE BENEFITS OF ANTIFIBRINOLYTIC DRUGS?

Debates such as this require a full evaluation of the evidence. In medicine, there is a hierarchy of the evidence where the double-blind randomized trial occupies the highest echelon. The existing randomized head-to-head comparisons of different antifibrinolytic therapies are not optimal and are influenced by numerous factors, including the degree of blinding and the size of the trial (7). Nevertheless, these studies provide valuable information when their results are pooled together by meta-analytic techniques to overcome their small sample sizes.

In one recent meta-analysis, 13 head-to-head studies comparing aprotinin with tranexamic acid were identified and their results pooled (8). For the purpose

of the present evaluation, we have updated this meta-analysis by identifying and adding four studies published or identified in the intervening period (9–11)¹ (details of each of these studies can be viewed in on-line Appendix Table 1). Altogether, the results of 17 comparative studies that included more than 2900 patients were pooled. The relative blood-conserving effects of the drugs have been evaluated in three ways: 1) the proportion of patients exposed to allogeneic blood; 2) the number of units of RBC transfused; and 3) the incidence of re-exploration.

These evaluations found that aprotinin was associated with a slight, but insignificant decrease in the proportion of patients transfused and the number of units of RBC transfused (Fig. 1). The reliability of the finding was complicated by the presence of significant heterogeneity among the studies' results. The lack of homogeneity in these studies is because of the failure of randomization in some of the smaller studies to balance the study groups on important baseline variables. For example, in three of the studies that found aprotinin to be superior to tranexamic acid, the average preoperative hemoglobin concentration was notably

¹ Murkin JM, McKenzie FN, et al. A comparison of complications of different antifibrinolytic s in cardiac surgical patients undergoing repeat median sternotomy [abstract]. *Anesth Analg* 1995;80: SCA132.

higher in the aprotinin group (these studies are references 10, 12, and 15 in Table 1 of the on-line Appendix). After either eliminating these studies from the analysis or by adjusting for the differences using regression analysis, there is no difference in the blood-conserving properties between aprotinin and tranexamic acid. Furthermore, there is also evidence of publication bias in favor of aprotinin (on-line Appendix Fig. 3). On the basis of these findings, it is our contention that the available comparisons are biased in favor of aprotinin. However, it is evident that, in the context of these studies, even with these apparent biases, aprotinin is not a superior blood-conserving drug. This evidence is a powerful and logical rejection of the hypothesis that aprotinin is a superior blood-sparing drug. This ought to be sufficient to lay to rest the controversy on antifibrinolytic drug choice. The safety concerns about aprotinin only serve to put the proverbial "final nail in the coffin" for routine use of aprotinin.

WHAT IS THE RELATIVE SAFETY OF ANTIFIBRINOLYTIC DRUGS?

To properly assess the relative safety profile of antifibrinolytic drugs, it is necessary to consider both the results of systematic reviews of placebo-controlled randomized, controlled trials (RCTs) and the results of large observational studies. Available head-to-head RCTs are of little additional value, for they provide scant information on adverse events. When considering the placebo-controlled RCTs, it is important to remember that many adverse events such as stroke, renal failure, myocardial infarction, and death are directly related to excessive bleeding. Because antifibrinolytic drugs decrease excessive bleeding, they should be associated with reduced adverse event rates in placebo-controlled studies. Reassuringly, systematic reviews of these studies found that, when compared with placebo, the point estimates for adverse event rates were, for the most part, decreased by both classes of drugs (5,6). Notably, the meta-analysis of the placebo-controlled trials found no reduction in renal failure or myocardial infarction, despite a 30% reduction in transfusion, when aprotinin was used as an antifibrinolytic! This was an important finding and has not been emphasized. If, as the aprotinin protagonists insist, there is not renal toxicity; one would have expected a commensurate reduction in renal failure. Moreover, the recent spate of Letters to the Editor on the subject has shown that aprotinin was, in fact, associated with postoperative renal dysfunction (5,9). Finally, these results, (i.e., no blood-conserving benefit and renal dysfunction) are consistent with those of recently published observational studies (1,2).

At this point we wish to reiterate that although methodologically pristine RCTs occupy the highest echelon in the hierarchy of medical evidence for measuring the efficacy of a drug, they are not necessarily the best means for identifying drug toxicity.

This is particularly true if the associated harms are rare, delayed, or unrelated to the therapeutic indication of the drug. Large observational studies, with appropriate multivariable risk-adjusted analysis to control for the known confounding factors, may be better suited for detecting such drug side effects (12). These large databases have the advantage of representing both the true clinical scenario and the entire population. However, many commentators heap scorn on the lowly nonrandomized trial even going as far as dismissing the results and we think this is unwise.

In the recent observational studies (1,2), data from large, comprehensive clinical databases were used to assess the relative benefits and harms of antifibrinolytic drugs by comparing the outcomes of patients who received aprotinin with those who received lysine analogues, using propensity score methods to adjust for baseline differences between the treatment groups. These studies had similar results, in that neither found aprotinin to have superior blood-sparing effects. This finding is consistent with the findings of the systematic reviews of head-to-head RCTs and both nonrandomized trials found aprotinin to be associated with increased renal dysfunction. Again, this finding is consistent with the findings of the systematic reviews of placebo-controlled RCTs. Both the Mangano et al. (1) report and our study (2) have important limitations, as do the RCTs. The limitations of the study by Mangano et al. have been clearly highlighted in a currently published Letter to the Editor (13). Our major criticism of the Mangano et al. article is the lack of clarity in the methodology. There is no description of how the propensity scores were derived or which factors were included in the propensity score model. Particularly, we are unsure of the degree to which the results from different hospitals in different countries and continents were controlled for. This can be a difficult problem to balance, for if in one hospital, aprotinin is used on every patient and in a second hospital, only the very high risk patients get aprotinin, the final model may have important biases. The study by Karkouti et al. has received considerably less notoriety; yet, with no collaboration, the results are remarkably similar to that of Mangano et al. This was a large single-center study with all the methodology clearly delineated. After all the evidence is considered, no one can deny that aprotinin is more expensive. There is little doubt that aprotinin has not been shown to have better blood-conserving properties than the lysine analogues. Even the studies conducted to register aprotinin with the FDA suggested that aprotinin is associated with increased toxicity. Our position is these recent nonrandomized trials only serve to strengthen the argument against the routine use of aprotinin in cardiac surgery.

IS RENAL DYSFUNCTION AN IMPORTANT OUTCOME?

Postoperative renal dysfunction or, more precisely, the postoperative increase in creatinine is a surrogate outcome for postoperative dialysis. Many have argued that renal dysfunction has little clinical relevance. Moreover, it is true that neither Mangano et al.'s study (1) nor ours demonstrated an increased rate of dialysis after the use of aprotinin. In the Karkouti et al. (2) article, in 898 propensity-matched patients, the rate of dialysis after aprotinin administration was 5.6%, whereas dialysis occurred in 3.1% of the tranexamic population. This difference was not found to be statistically significant. Postoperative dialysis is relatively rare; the need for dialysis after cardiac surgery increases the length of hospital stay, hospital costs, decreases quality of life, and is associated with a doubling of mortality. As it is a rare occurrence, an adequately powered trial would require several thousand patients in each arm to demonstrate a difference in the effect of aprotinin. Obviously, that trial has not been conducted and, given the size of the ongoing BART trial sponsored by the Canadian Institute of Health Research, it is also under-powered to answer this particular question. It is also of note that no trial to date has been adequately powered to adequately investigate *any* renal-protective strategy. Therefore, we have been forced to use surrogate measures of renal failure.

The postoperative increase in creatinine, (and the decrease in calculated creatinine clearance) has been used as just such a surrogate outcome. This measure is admittedly less than perfect, but it has been validated. Wijeyesundera et al. (14) demonstrated that for every 10% increase in postoperative serum creatinine 72 h postoperatively, the odds of postoperative mortality were increased 1.17 times, and the odds of dialysis were increased 1.42 times. In our report about aprotinin, our definition of renal dysfunction was a 50% increase in postoperative creatinine. The data from placebo-controlled RCTs (15) and nonrandomized trials are consistent in showing that aprotinin is associated with increased serum creatinine in the immediate postoperative period. The lysine analogues are not. Why should any clinician assume this potential risk, given that there is no demonstrable difference in blood conservation?

ARE THERE OTHER RELEVANT ISSUES?

Any discussion of aprotinin would be incomplete without noting its proclivity for causing anaphylaxis upon re-exposure. It is telling that the FDA, in approving aprotinin, recommended against its routine use owing to its risk of severe allergic reactions and kidney toxicity (<http://www.fda.gov/bbs/topics/NEWS/NEW00453.html>).

Still other proponents will argue that aprotinin has benefits beyond blood conservation, such as offering neurological protection owing to its action on protease-activated receptors (13). There is, however, no clinical

evidence that aprotinin reduces the risk of stroke, and other adverse events beyond those that can be explained by reduction of blood loss. Thus, until the organ-protective effects of aprotinin are demonstrated in studies that compare aprotinin with other antifibrinolytic drugs, this argument has no merit.

WHERE DO WE GO FROM HERE?

Important questions remain about the use of antifibrinolytic drugs. Which of the drugs is most effective in avoiding massive blood loss? Which of them is more effective in the truly high-risk cases, few studies have included high-risk patients. On this point, readers should note that our study (2) did not, or could not, match 134 patients who received aprotinin. This unmatched portion had an excessive number of patients (60%), who needed more than 5 U of blood and 30% required more than 10 U. We are unaware of any studies in which this very high transfusion risk population has been adequately studied. Finally, do any of the antifibrinolytic drugs offer benefits beyond limiting blood loss? To answer these and other questions, well-designed, head-to-head, clinical trials are required. Until that time, the routine use of aprotinin in patients undergoing cardiac surgery with CPB cannot be recommended outside of the experimental setting. It is clear that the antifibrinolytic of choice today should be a lysine analog. We keenly await the blood conservation results of the BART trial (16).

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