

EDITORIAL



The Aprotinin Story — Is BART the Final Chapter?

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The aprotinin story began in 1987, when investigators reported that the use of the drug in patients undergoing repeat open-heart surgery decreased the need for blood transfusion by a factor of 8.¹ In 1993, the Food and Drug Administration (FDA) approved the use of aprotinin to reduce blood loss during coronary-artery bypass grafting, and the drug became widely used in cardiac surgery. In 2006, the use of aprotinin became controversial when the drug was associated with an increased risk of renal failure, myocardial infarction, stroke, and death in a large observational study.^{2,3} Two subsequent cohort studies also linked aprotinin to an increased risk of death.^{4,5} In contrast, an increase in such adverse events was not associated with the lysine analogue antifibrinolytic agents (e.g., aminocaproic acid and tranexamic acid). The controversy and uncertainty increased when an updated meta-analysis of clinical trials showed no increased risk of myocardial infarction, stroke, or death in patients receiving aprotinin.^{6,7}

In this issue of the *Journal*, the aprotinin saga continues with a report from the Blood Conservation Using Antifibrinolytics in a Randomized Trial (BART) study (Current Controlled Trials number, ISRCTN15166455),⁸ which compared aprotinin with the lysine analogues in patients undergoing high-risk cardiac surgery. BART set a high standard for future trials of antifibrinolytic drugs: its design and conduct were fully transparent, the most clinically relevant alternatives were compared in a double-blind fashion, and a prespecified end point was any death within 30 days after surgery. BART provided modest evidence that aprotinin was the more effective hemostatic agent, since patients who received it had a reduced risk of massive postoperative bleeding (relative risk, 0.79; 95% confidence interval [CI],

0.61 to 1.01), although the difference was of borderline statistical significance. The patients receiving aprotinin also had a reduced need for postsurgical administration of blood products. These findings were consistent with those of a Cochrane meta-analysis,⁷ which showed that patients receiving aprotinin were less likely to have red-cell transfusions than were those receiving lysine analogues (relative risk, 0.83; 95% CI, 0.69 to 0.99). However, at 30 days, patients who were receiving aprotinin in BART had an increased risk of death of more than 50% (relative risk, 1.53; 95% CI, 1.06 to 2.22), an outcome that led trial investigators to conclude that aprotinin should no longer be used in patients undergoing high-risk cardiac surgery.⁸

Readers of the BART report are likely to have several questions. Why do the mortality findings differ from those of meta-analyses of previous trials? Why does better prevention of blood loss not translate into improved clinical outcomes? Are there surgical patients for whom aprotinin might continue to be indicated? What lessons are there in this lengthy saga for future testing of hemostatic agents?

Before BART, meta-analyses of clinical trials had given no indication of an excess risk of death associated with aprotinin, findings that played an important role in the FDA's decision in 2006 not to add a black-box warning to the aprotinin label.⁹ The updated Cochrane review⁷ reported a relative risk for death of 0.90 (95% CI, 0.67 to 1.20) for aprotinin as compared with placebo and showed no evidence of increased risk for aprotinin as compared with the lysine analogues.

One possible explanation for these seemingly discrepant findings is that lysine analogues reduce the risk of death as compared with placebo,

a benefit that might not have been detected in the meta-analyses because of the very limited mortality data available for these drugs. It seems more probable that the meta-analyses did not detect an increased risk of death for aprotinin because of the intrinsic limitations of pooling data from many small trials that were not designed to study mortality. Factors that would favor the null hypothesis and provide a false sense of security regarding the safety of aprotinin included the small size of numerous trials with no reported deaths in either study group, the high proportion of data from trials with low or moderate quality, the inclusion of a mixture of both high-risk and low-risk patients, and the frequent failure to ascertain the deaths of patients after hospital discharge. Thus, the finding from the meta-analysis that aprotinin did not increase mortality as compared with placebo should have been interpreted very cautiously, particularly given the contradictory findings from some epidemiologic studies.

There are several potential explanations for why an effective hemostatic agent such as aprotinin could increase mortality. High-risk cardiac surgeries involve the use of medications with both procoagulatory and anticoagulatory effects, and the optimum balance between these poles is incompletely understood. Thus, aprotinin may have increased mortality because it is the more effective antifibrinolytic agent. If correct, this hypothesis has important implications for dose selection in the development of more potent antifibrinolytic agents. Alternatively, because aprotinin is a nonspecific serine protease inhibitor, it not only inhibits the fibrinolytic enzyme plasmin but also affects many biologic mediators, including kallikrein, protease-activated receptor 1, and complement.¹⁰ Thus, the inhibition of kallikrein, for example, would be expected to reduce bradykinin production, with potential effects on vasodilation, inflammation, and responses to angiotensin-converting-enzyme inhibitors. Adverse outcomes that are related to such off-target effects could outweigh the benefits of the prevention of blood loss.

Are there patients for whom aprotinin should continue to be used during cardiac surgery? The conventional wisdom has been that aprotinin was most beneficial in high-risk surgeries that were likely to cause increased blood loss.¹¹ It is precisely in this population that BART provides convincing evidence as to the superiority of the lysine

analogues. Thus, although the existence of a class of patients who would benefit from aprotinin is not impossible, it seems highly unlikely. If such a subgroup existed, the benefits of aprotinin with regard to clinical end points would need to be confirmed by an adequately powered clinical trial before further unrestricted use of the drug.

Thus, in all likelihood, this is the end of the aprotinin story. What are the lessons we can learn with regard to future testing of hemostatic agents? First, there must be less emphasis on comparisons of new agents with placebo and more emphasis on adequately powered, head-to-head comparisons with other available drugs.⁶ Second, although blood loss in the setting of cardiac surgery is of undisputed clinical importance, it has some of the characteristics of a surrogate end point. Just as is the case for antidiabetic agents, nonsteroidal antiinflammatory drugs, weight-loss drugs, and therapies to prevent reocclusion of coronary arteries, antifibrinolytic drugs cannot be judged solely by their effects on the primary physiological target. Evaluation of future agents for preventing blood loss in cardiac surgery must include effects on mortality and other clinical end points.

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