

EDITORIAL



Learning from Aprotinin — Mandatory Trials of Comparative Efficacy and Safety Needed

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Aprotinin, a hemostatic agent that inhibits the fibrinolytic enzyme plasmin,¹ was approved by the Food and Drug Administration (FDA) in 1993 for reducing blood loss during coronary-artery bypass grafting (CABG). By 2006, aprotinin was prescribed for approximately 200,000 patients undergoing cardiac surgery worldwide.² Aminocaproic acid and tranexamic acid are lysine analogues that inhibit the binding of fibrin to plasminogen and also reduce blood loss, but a specific indication for bypass grafting is not included on their labels.¹ The safety of aprotinin was called into question in 2006 and 2007, when the results of an international cohort study by Mangano et al. of patients undergoing CABG were published. The findings included increased risks of renal failure, myocardial infarction, and stroke and increased 5-year mortality with aprotinin but not with the lysine analogues.^{2,3} Two additional cohort studies in this issue of the *Journal* show that patients undergoing CABG who received aprotinin had greater mortality — in the short term, as reported by Schneeweiss et al.,⁴ and in the long term, as reported by Shaw et al.⁵ — than did those who received aminocaproic acid.

In October 2007, the data and safety monitoring board stopped the enrollment of patients into a large Canadian study of the use of aprotinin, as compared with aminocaproic acid or tranexamic acid, during cardiac surgery (Blood Conservation using Antifibrinolytics: A Randomized Trial in a Cardiac Surgery Population [BART]; ISRCTN no. 15166455).⁶ An interim analysis of more than 2000 patients found increased 30-day mortality in the aprotinin group. Subsequently, the manufacturer temporarily suspended the worldwide marketing of aprotinin, pending a full re-

view of the trial data, thus limiting its use to that by physicians participating in a restricted, special-access protocol. Although the findings from BART, which included patients undergoing both CABG and valve surgery, are preliminary and are reported to have borderline statistical significance, the future for aprotinin now appears very cloudy. The recommendation of the data and safety monitoring board to halt BART, coupled with the increased mortality associated with aprotinin use in three independent cohort studies, will make it difficult, in the absence of convincing new data, to prescribe this drug, except perhaps in limited circumstances.

What can we learn from the saga of aprotinin, a drug that apparently confers less overall benefit than cheaper alternatives yet has remained on the market for more than 14 years and become the recommended hemostatic agent for high-risk cardiac surgeries?¹ Aprotinin was approved for cardiac surgery on the basis of premarketing randomized, controlled trials that showed reduced blood loss with aprotinin as compared with placebo. Even around the time of its introduction, concerns were raised about adverse prothrombotic and renal effects, and some experts suggested that aminocaproic acid was a better therapeutic choice.⁷ Nevertheless, there was no requirement for more definitive information on infrequent but serious complications, survival after surgery, and performance relative to then-available alternatives. The lack of critical clinical information about newly licensed medications reflects the balancing of the need for these data against the need for timely drug availability.⁸

The safety of aprotinin ultimately was challenged by the results of observational studies, in

which routine clinical practice determines the therapy patients receive. Despite sophisticated statistical techniques used to compensate for potential imbalances among treatment groups, there is always concern that unmeasured factors bias the results. Indeed, many thought that the findings of Mangano et al. reflected this type of confounding.^{9,10} Aprotinin clearly reduced the need for blood transfusions¹ and thus was more likely to be prescribed for patients with greater anticipated perioperative blood loss. An increased risk of adverse events would be expected for these higher-risk cases, which the investigators' data might not have identified as such. The studies of Schneeweiss et al. and Shaw et al. reinforce this concern: the cases in which aprotinin was given were more complicated than those in which another (or no) agent was given, and the relative-risk estimates decreased after adjustment for measured covariates. Although the instrumental-variable analysis by Schneeweiss et al. allays some of these concerns, the study was also observational and thus potentially susceptible to bias from unmeasured characteristics associated with surgeons' preference for aprotinin.

The conclusion that confounding influenced the findings of Mangano et al. was buttressed by meta-analyses of numerous, relatively small randomized, controlled trials. A pooled analysis of the clinical-trial database of the manufacturer of aprotinin found no significantly increased risk of renal failure, myocardial infarction, stroke, or death from any cause for aprotinin users. This apparently played an important role in the recommendation by the Cardiovascular and Renal Drugs Advisory Committee of the FDA not to require additional warnings on the label for aprotinin.⁹ A Cochrane Collaboration meta-analysis of data from 211 randomized, controlled trials involving a total of 20,781 patients had similar findings.¹¹

The apparent discrepancy between BART and the meta-analyses highlights the insufficiently appreciated pitfalls of pooling data from many small trials to establish drug safety.¹² Meta-analyses of end points that the original trials were not designed or powered to study have methodologic limitations that may obscure safety problems. These limitations include the heterogeneity of patient populations and surgical procedures, the short duration of follow-up, and limited or incomplete information on the end points. In the Cochrane analysis of blood transfusion in 98 trials

of aprotinin with no alternative hemostatic agent,¹¹ mortality data were reported in only 52. Even fewer aprotinin trials had mortality data for the crucial comparisons with the lysine analogues: 14 trials for tranexamic acid and 3 trials for aminocaproic acid.

The history of aprotinin thus exemplifies the intrinsic limitations of current approaches to evaluation of the comparative efficacy and safety of new medications. Premarketing testing leaves many important questions unanswered because of the frequent reliance on comparison with placebo and the limited numbers of patients studied.⁸ Although observational studies provide the opportunity to conduct comparative studies of large numbers of patients, the aprotinin story shows how concerns about residual bias limit the utility of nonrandomized studies — concerns that are reinforced by high-profile discrepancies between observational studies and randomized, controlled trials. Meta-analyses of randomized, controlled trials have many limitations that may bias the results toward showing no difference between the treatment groups for end points the original trials were not designed to study. The coxibs are another case in point. Meta-analyses that compared these drugs with placebo reported no increased risk of serious cardiovascular disease, whereas subsequent large, randomized, controlled trials found that such risk was increased by a factor of 2 to 3.^{13,14}

Thus, the key lesson from the aprotinin story is that when a new drug has alternatives, as is the case for aprotinin, head-to-head comparative trials powered for important clinical end points are needed before the drug is routinely prescribed for large numbers of patients.⁸ These randomized trials are the best way to define relative efficacy and safety, the most critical information for patients and physicians. If, as is often the case, these trials are not part of the premarketing testing, then they should be conducted as soon as possible after licensing. The manufacturer cannot be relied on to perform these studies voluntarily, because they frequently serve no commercial purpose. Indeed, several observers noted the dearth of trials comparing aprotinin with the lysine analogues^{1,10,11} and commented on the economic disincentives for direct comparisons of competing therapies.¹⁰ Thus, when indicated, postmarketing comparative efficacy and safety trials, supervised by the FDA, should be mandatory.⁸ To limit the

risk for patients, distribution of new drugs should be restricted while these trials are being conducted, with selective extension of patents to reduce the economic burden on the manufacturer.^{8,15}

The FDA Amendments Act of 2007 gives the agency new authority to require postmarketing studies and to place restrictions on drug distribution or use.¹⁶ Thus, depending on how the regulations for this legislation are written and interpreted, this reform may facilitate comparative efficacy and safety trials and allow for the phased release of new drugs. If it ultimately does not, the legislation should be amended appropriately. Otherwise, we will continue to repeat the unfortunate history of aprotinin, in which large numbers of patients received a therapy that apparently was suboptimal.

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