EDITORIAL

Aprotinin and Cardiac Surgery

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"These, Gentlemen, are the opinions upon which I base my facts."
— Sir Winston Churchill

Of the recent issues affecting the practice of cardiothoracic surgery, perhaps none has affected or evoked more passionate debate (and angst) than the controversy surrounding the use of the antifibrinolytic aprotinin (Trasylol, Bayer Pharmaceuticals, West Haven, Conn). Aprotinin first appeared as a potent therapy for pancreatitis; it soon became apparent that the antifibrinolytic properties of this serine proteinase inhibitor could have a beneficial effect on postoperative bleeding in patients after cardiopulmonary bypass surgery. Cosgrove and colleagues,[1] in a small, randomized trial, confirmed the benefits of aprotinin in reducing postoperative chest tube output and transfusion requirements, but they also noted a statistically nonsignificant increase in Q-wave myocardial infarction (and in some cases graft thrombosis) in the low-dose and high-dose aprotinin arms of their study. In 1993, the Food and Drug Administration (FDA) approved aprotinin for use in patients undergoing coronary artery bypass grafting (CABG), with subsequent changes in labeling in 1994 and 1998.

In 2006, Mangano and colleagues[2] and Karkouti and colleagues[3] published studies that generated much controversy and prompted the FDA to convene an advisory committee meeting in September of 2006. Both studies were observational analyses of prospectively collected data, and both used a statistical technique of propensity matching. The expressed purpose of the advisory meeting was to elicit advice in response to the studies' findings that the use of aprotinin was associated with an increased risk of adverse cardiovascular and renal events. In addition, the panel wanted to reexamine data on anaphylactic reactions seen with the re-dosing of aprotinin. At the close of the meeting, the Committee provided the FDA with their conclusions and recommendations (summarized in Table 1). The FDA then modified aprotinin labeling in December of 2006, changing the approved indication for use only in patients who are at increased risk for blood loss and blood transfusion in association with cardiopulmonary bypass and CABG. In addition, changes were made in labeling to handle the anaphylaxis issues.

The dust had barely settled when two pertinent events occurred. First, Mangano and colleagues[4] followed up with a second study, this one looking at long-term mortality. Second, it was revealed that Bayer had not shared preliminary data from its own observational clinical study (the so-called i3 Drug Safety Study) with the FDA before the advisory committee meeting. The FDA reacted by convening a second advisory committee meeting to review the data from the i3 Drug Safety Study and Mangano and colleagues' study. Before this meeting, FDA statisticians reviewed (for accuracy) the datasets and results described by Mangano and colleagues, Karkouti and colleagues, and i3. At the completion of testimony and review of the data submitted, the committee took 3 votes. In summary, the committee recommended 1) continued marketing authorization (16 yes votes, 1 no, and 1 abstention); 2) that the findings of i3 and Mangano and colleagues[2,4] need not be described in product labeling (6 in favor of including, 11 against, and 1 abstention); 3) additional clinical studies need to be performed as a prerequisite of continued market authorization (unanimous).

In the meantime, investigators in Canada were reviewing their prospective data from the BART (**B**lood conservation using **a**ntifibrinolytics: A **r**andomized **t**rial) study. This study, overseen by the Ottawa Health Research Institute, involved 19

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TABLE 1. Conclusions and recommendations from September 2006 Advisory Committee

- Trasylol increases the risk for renal dysfunction, but the data do not establish an increased risk for renal failure requiring dialysis.
- Hypersensitivity/anaphylactic reactions are known serious complications of the administration of aprotinin, and methods should be sought to reduce their frequency and impact.
- Reduction in the frequency and amount of blood transfusion during CABG surgery remains an important benefit of the use of aprotinin.
- The benefit/risk ratio of aprotinin seems to be greatest in patients undergoing complex surgery or who have other risk factors for bleeding.
- The population in whom aprotinin is used should be more restrictive than currently approved.

CABG, Coronary artery bypass grafting.

cardiac centers, with an expected enrollment of 2970 patients. There were 3 arms to this study; aprotinin and two 2 lysine analogs: tranexamic acid (Cyklokapron, Pharmacia & UpJohn Inc, Somerset County, NJ) and epsilon-aminocaproic acid (Amicar, Xanodyne Pharmaceuticals, Newport, Ky). The express purpose of this trial was to "definitively determine if aprotinin" was superior to the other 2 antifibrinolytics in terms of decreasing postoperative bleeding, decreasing blood and blood product use, and decreasing postoperative morbidity and mortality. A review by the Data Safety Monitoring Board (DSMB) after enrollment of 2163 patients revealed a nonstatistically significant trend toward increased mortality in the aprotinin arm. Although no further specific information is available at this time, it was noted that the increase in mortality was approximately 2 per 100 patients, and that although aprotinin did decrease the amount of serious bleeding, it was paradoxically associated with more deaths due to hemorrhage. Bayer and the FDA were notified by the DSMB, a clinical advisory was issued, and subsequently on November 5, 2007, Bayer announced a moratorium on further marketing of aprotinin pending review of the BART data.

In this issue, Pagano and colleagues[5] add further data to the ongoing debate. In summary, the authors find what has always been the mainstay of aprotinin: significant reductions in reoperation for bleeding and in transfusion requirements. Where the data vary from Mangano and colleagues' is in the survival data. In the total group of patients receiving aprotinin, in-hospital mortality was not significantly different from the control group (4.0% vs 3.5%), whereas the EuroSCORE in the aprotinin group was significantly higher. Renal dysfunction also did not significantly differ between the 2 groups.

The current study shares many of the same characteristics with the BART study. Both studies were free from industry support. The inclusion criteria were similar; BART included reoperations for either CABG or aortic valve replacement with a CABG, any mitral valve or multiple valve replacement (including with CABG), aortic root replacements, and reoperations for adult congenital heart procedures. Unique exclusion criteria in BART included patients unable to receive blood products and those with previous exposure to aprotinin. Pagano and colleagues[5] considered all adult patients undergoing cardiac procedures (including primary revascularization), excluding those requiring circulatory arrest, transplantation, distal aortic surgery, and adult congenital surgery. The number of patients in each study differed; BART was designed to enroll 990 patients in each of the 3 arms, Pagano and colleagues reviewed a total of 7836 patients (during a 9-year period), of whom 3481 received aprotinin. In deference to Mangano and colleagues' reports,[2,4] the authors used the same criteria for renal failure.

There are, however, potentially significant differences other than study design (ie, randomized prospective multicenter trial [BART] vs retrospective review of prospectively acquired data from a single center). First, there seems to be a difference in the administration of the aprotinin. The full-dose Hammersmith protocol provides for a 2 million kallikrein inhibitor unit (KIU) bolus, 2 million KIU in the pump prime, and 500,000 KIU/h infusion until chest closure. Pagano and colleagues[5] describe a similar dosing except for the pump prime; they unexplainably used 1 million units. BART described the infusion of 2 million units for 4 hours, which matches the Hammersmith protocol during these 4 hours.

Second, as already alluded to, the inclusion criteria were similar, but Pagano and colleagues[5] also include primary CABG. This can alter to some degree the risk stratification, and therefore the post hoc analysis of risk. As seen in their Table 1, this has the effect of altering the profile of the patients in each group. For example, the Canadian Cardiovascular Society class in the aprotinin group is lower, but the New York Heart Association class is higher, reflecting that patients undergoing routine CABG did not necessarily receive aprotinin (3391/4355 patients [78%] who did not receive aprotinin underwent CABG compared with 1921/3481 patients [55%] who received aprotinin). Prediction of risk in the study used the EuroSCORE, appropriate in this circumstance both for the robustness of the tool and for the patient population. The multivariate analysis ultimately included the variable EuroSCORE, along with diabetes, the year of surgery, and the use of aprotinin. As the model was being fitted, it seemed necessary to perform a log-transformation of the score. As the authors point out, this can be statistically justified using the Akaike Information Criterion. This criterion takes into account both the goodness of fit and the number of parameters that have to be estimated to achieve this particular degree of fit by imposing a "penalty" for

increasing the number of parameters. By using this approach, when the log EuroSCORE is taken into account, there does not appear to be an increase risk of renal dysfunction, need for dialysis, or mortality associated with the use of aprotinin.

What happens if you move away from the model and look at just the raw data? In Table 2, under "Other Cardiac Surgery," the patient mix now approaches that of BART, although the patients were not randomized. The mortality rates then appear equivalent (6.5% in the aprotinin group and 6% in the non-aprotinin group). What is remarkable is that, by report, the mortality rate in the aprotinin group is approximately that seen in the BART aprotinin arm.

How then to judge this latest study in the face of BART? We must first begin with facts. The Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists, in a Joint Task Force, looked at the issue of blood transfusion and cardiac surgery.[6] Aprotinin itself was not the subject of the clinical guideline, but the panel members were acutely aware of issues brought up by the first FDA advisory committee. Despite the studies by Mangano and colleagues[2,4] and Karkouti and colleagues,[3] the panel endorsed the use of aprotinin (as well as the other antifibrinolytics) with a Class I recommendation (level of evidence A). From an evidence-based point of view, neither the BART study nor this current study would seem to alter that recommendation, the former because (at least at this point) statistical significance was not achieved, the latter because the findings are similar to previous studies. Most would agree that aprotinin does reduce the need for transfusion, perhaps more so than the other antifibrinolytics. Mounting evidence suggests that transfusion itself can lead to a decrease survival in patients with cardiac disease,[7] as well as contribute to the development of renal failure.[8] The use of aprotinin in cardiac surgery is not a minor issue. In the United States approximately 110,000 patients were exposed to this drug in 2006, and 4.77 million exposures have occurred worldwide since 1985. Alternatives do exist; the lysine analogues have their proponents. Other alternatives, such as recombinant Factor VIIa (NovoSeven, Novo Nordisk, Bagsvaerd, Denmark), prothrombotic by definition, may not be as palatable from an economic or side effect point of view.

Controversy will always exist within the medical and scientific community. This particular controversy has placed some surgeons in a precarious situation: Do we stop using aprotinin in high-risk cases (eg, the Jehovah Witness, left ventricular assist device implantation, complex aortic surgery) knowing that bleeding may be a problem? Similarly, do we continue using aprotinin for the same patients knowing that there may be added risk? Do we wait for the results of a single study (ie, BART) despite the volume of studies preceding BART? And if the BART results prove to be inconclusive, do we resume using aprotinin until the next negative study appears? In the face of conflicting "facts" and numerous opinions, it seems that the best course of action remains to adhere to individual responsibilities. The DSMB should continue to be vigilant in attempting to detect thresholds of differences in blinded studies; investigators should continue to try and dissect differences that appear in trials; and clinicians should continue to offer what they consider the standard of care to their patients.

References

1. Cosgrove DM, Heric B, Lytle BW, Taylor PC, Novoa R, Golding LA, et al. Aprotinin therapy for reoperative myocardial revascularization: a placebo-controlled study. *Ann Thorac Surg*. 1992;54:1031-6.
2. Mangano DT, Tudor IC, Dietzel C. The risk associated with aprotinin in cardiac surgery. *N Engl J Med*. 2006;354:353-65.
3. Karkouti K, Beattie WS, Dattilo KM, McCluskey SA, Ghannam M, Hamdy A, et al. A propensity score case-control comparison of aprotinin and tranexamic acid in high-transfusion-risk cardiac surgery. *Transfusion*. 2006;46:327-38.
4. Mangano DT, Miao Y, Vuylsteke A, Tudor IC, Juneja R, Filipescu D, et al. Mortality associated with aprotinin during 5 years following coronary artery bypass graft surgery. *JAMA*. 2007;297:471-9.
5. Pagano D, Howell NJ, Freemantle N, Cunningham D, Bonser RS, Graham TR, et al. Bleeding in cardiac surgery: the use of aprotinin does not affect survival. *J Thorac Cardiovasc Surg*. 2008;135:495-502.
6. Society of Thoracic Surgeons Blood Conservation Guideline Task Force, Ferraris VA, Ferraris SP, Saha SP, Hessel EA 2nd, Haan CK, Royston BD, et al; Society of Cardiovascular Anesthesiologists Special Task Force on Blood Transfusion, Spiess BD, Shore-Lesserson L, Stafford-Smith M, Mazer CD, Bennett-Guerrero E, Hill SE, et al. Preioperative blood transfusion and blood conservation in cardiac surgery: the Society of Thoracic Surgeons and The Society of Cardiovascular Anesthesiologists clinical practice guideline. *Ann Thorac Surg*. 2007;83:S27–86.
7. Koch CG, Liang L, Duncan AI, Mihaljevic T, Loop FD, Starr NJ, et al. Transfusion in coronary artery bypass grafting is associated with reduced long-term survival. *Ann Thorac Surg*. 2006;81:1650-7.
8. Furnary AP, Wu Y, Hiratzka LF, Grunkemeier GL, Page US. Aprotinin does not increase the risk of renal failure in cardiac surgery patients. *Circulation*. 2007;116(II Suppl):I127-33.