Aprotinin revisited

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In 2008, we saw the withdrawal of aprotinin from the US markets after preliminary results from a large, randomized clinical trial in Canada. This drug, a potent antifibrinolytic, was used primarily in complex and/or redo cardiac surgery as an adjunct to decrease postoperative bleeding and complications. The Canadian study raised questions previously brought up in similar studies—does aprotinin increase the risk of mortality and renal failure after cardiac surgery? Recently, a re-review of the Canadian data noted flaws in the study, as well as in the interpretation of the results. The present review revisits the aprotinin controversy. (*J Thorac Cardiovasc Surg* 2012;144:998-1002)

In May of 2008, the results of the Blood Conservation Using Antifibrinolytics in a Randomized Trial (BART) were published,¹ although the results and corresponding data had been a matter of speculation for months before publication.²⁻⁴ BART was a multicenter, blinded, randomized trial of 2331 high-risk cardiac surgery patients comparing aprotinin (Trasylol; Bayer Pharmaceuticals Corp, West Haven, Conn) with 2 lysine analogs, tranexamic acid (Cyklokapron; Pfizer Inc, New York, NY) and epsilon-aminocaproic acid (Amicar; Xanodyne Pharmaceuticals, Inc, Newport, Ky). The study was prompted in part by a continuing controversy of the risk/benefit profile of aprotinin, with this concern increasing during the study by observational studies questioning the safety of aprotinin.⁵⁻⁷ This controversy seemed to have no end, and despite literally thousands of publications, no clear answer could be found, in part, perhaps, because of the statistical machinations performed to try and match 2 or more groups of patients (and treatments) to test a hypothesis.⁸ Even the well-thought out, well-planned BART was not immune from questions regarding the study design and analysis.⁹ Subsequently, enrollment into the aprotinin treatment arm of the BART was halted because of concerns presented to the drug safety monitoring board that there was an apparent increase in mortality associated with the drug.

Even while the BART was progressing, other centers were reporting their own results comparing aprotinin with the other 2 antifibrinolytic agents. Pagano and colleagues¹⁰ retrospectively compared 3481 patients who had undergone cardiac procedures using aprotinin with 4355 patients who had not received the drug. They found no increase in either all-cause mortality or renal failure.¹⁰ One potentially

significant aspect of their study was that it included patients undergoing primary coronary artery bypass grafting, the indication for which the drug was approved. A similar finding was seen for patients undergoing off-pump coronary artery bypass grafting.¹¹ Furnary and colleagues¹² retrospectively analyzed prospectively collected data from more than 15,000 patients from 12 centers contributing to the Merged Cardiac Registry. They found that when the use of transfused packed red blood cells was accounted for in their risk model, the risk of renal failure in the face of transfusion was significant ($P < .0001$; odds ratio [OR], 1.23/transfused packed red blood cells) and that the addition of the transfusion variable to the risk model attenuated the "...purported independent [e]ffect of aprotinin ($P = .231$) on ARF [acute renal failure]."¹² They concluded that aprotinin use did not independently increase the risk of renal failure in cardiac surgery patients.¹² In contrast, Schloss and colleagues¹³ reported that although aprotinin's negative effect was independent of baseline renal function, a negative effect on mortality was still present.

Before the publication of the BART results and based on preliminary data, Health Canada requested Bayer, Inc. to suspend marketing of the drug in Canada. Health Canada was followed shortly thereafter by the European Medicines Agency, which cited the BART in determining that the benefits of the drug no longer outweighed the risks. Subsequently, worldwide marketing of aprotinin was frozen by Bayer. In Canada, a limited access program was put into place to make aprotinin available to physicians on a case-by-case basis in situations in which the benefits outweighed the risks, especially because no other equivalent product was authorized in Canada. In the United States, the drug was voluntarily removed from clinical access in 2008, although technically it remained approved by the Food and Drug Administration (FDA) and, as was the case in Canada, was theoretically available on a compassionate use basis. The withdrawal of this drug from the routine armamentarium of cardiac surgeons and anesthesiologists was met with mixed reactions. Those who had considered this to be a dangerous drug had some level of vindication by the results of BART, but others who believed the drug played a significant role in reducing blood loss were left searching for alternatives. The alternatives were obvious—switch to

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Abbreviations and Acronyms

BART	= Blood Conservation Using Antifibrinolytics in a Randomized Trial
FDA	= Food and Drug Administration
OR	= odds ratio
TXA	= tranexamic acid

(or continue using) Amicar (Xanodyne Pharmaceuticals, Inc) or tranexamic acid (TXA), or use nothing at all.

As surgeons began switching, reports started to trickle in relating to the benefit (or risk) of these alternatives. Martin and colleagues¹⁴ found, in neonatal cardiac surgery, that the conversion from aprotinin to Amicar led to a significant increase in postoperative blood loss, although no differences were seen in the transfusion requirements or major clinical outcomes. The use of TXA also came under scrutiny, with its relationship to seizures, including in patients undergoing hypothermic arrest.¹⁵⁻¹⁸ A meta-analysis by Ngaage and Bland¹⁹ suggested that “Given the potential for increase [d] neurological complications, the current trend towards indiscriminate use of tranexamic acid for all cardiac patients needs to be re-evaluated.” Likewise, the purported downside of using aprotinin did not disappear with the loss of this drug. One strong advocate for the withdrawal of the drug stated on the *60 Minutes* news show that by his calculations, 1000 lives were lost per month because of this drug; however, after the drug was pulled from the market, there did not appear to be an improvement in the Society of Thoracic Surgeons mortality data. One thousand US cardiac deaths each month would be difficult to hide. What was seen by some was an increase in blood use without an effect on renal failure or early mortality,^{20,21} as well as an increase in off-label use of recombinant factor VIIa.²² No evidence was seen of an improvement in mortality by the lack of the use of aprotinin.

There remained patient populations outside of BART for whom aprotinin was thought by some to have a beneficial effect. Pasquali and colleagues²³ compared aprotinin with Amicar, TXA, and no antifibrinolytic agent in 22,258 pediatric cardiac surgery patients and found that compared with no drug, aprotinin was associated with a significant reduction in combined hospital mortality/bleeding requiring surgical intervention (OR, 0.81), with this finding more pronounced in the redo sternotomy subgroup (OR, 0.57). A comparative analysis with the antifibrinolytic agents showed efficacy similar to that of Amicar and improved outcomes compared with TXA,²³ a finding the investigators also reported in a larger study.²⁴ Similar findings were reported by Wilder and colleagues²⁵ in their study of 423 neonates, despite the patients in the aprotinin group having a greater baseline creatinine. The conflicting results

continued with a smaller retrospective study showing a detrimental effect on renal function (compared with Amicar) in children but an increase in platelet and fresh-frozen plasma usage with nonaprotinin treatment.²⁶ Manrique and colleagues²⁷ proposed that when the preoperative risk factors were taken into account, there did not appear to be an increased risk of renal failure in the pediatric cardiac surgery population. Another study showed no difference in outcomes between aprotinin and TXA in the pediatric population.²⁸ Other beneficial effects of aprotinin were noted in patients undergoing the Fontan procedure, specifically an anti-inflammatory, protective role,²⁹ a finding suggested to result from attenuation of tumor necrosis factor- α , interleukin-10, matrix metalloproteinase-8, and matrix metalloproteinase-9 in aprotinin patients compared with TXA patients.³⁰

For high-risk patients, Karkouti and colleagues³¹ retrospectively evaluated 15,365 cardiac patients, 1017 of whom received aprotinin, and created a matched-pair cohort of 1544 for propensity scoring. Aprotinin was associated with increased acute renal dysfunction; however, when patient risk status was included, aprotinin significantly lowered mortality (OR, 0.6) and massive blood loss (OR, 0.7) and had a nonsignificant effect on renal injury (OR, 1.1, 95% confidence interval, 0.7-1.7).³¹

After the BART, similar studies continued to suggest an effect on long-term mortality associated with aprotinin. Stamou and colleagues³² used propensity matching to compare aprotinin with Amicar. They found that although aprotinin did decrease the rate of blood product usage and re-exploration, an increase occurred in in-hospital cardiac arrest and late mortality.³² Another propensity-matched study did not show a benefit in terms of blood product usage (compared with TXA) or short-term mortality but found an increase in the risk of postoperative dialysis.³³ Additionally, previous meta-analyses were revisited because of the BART outcomes. An earlier Cochrane analysis in 2007 had demonstrated the positive aspects of antifibrinolytic therapy, including a reduction in blood loss and the need for transfusion. The benefit of aprotinin compared with TXA appeared to be increased for high-risk patients.³⁴ After the BART, there appeared to be a significant risk of death (relative risk, 1.39) with most of the data contributing to the added risk coming from the BART.³⁵ Before the Cochrane revision, Rosén³⁶ criticized the 2007 analysis because of the inclusion of small studies in the meta-analysis, especially if the specified outcome was not a part of the original study design. A similar update on a previously published blood conservation guideline by the Society of Thoracic Surgeons and Society of Cardiovascular Anesthesiologists also required revision to reflect the findings of BART.^{37,38}

In a survey of cardiac surgeons in Great Britain, 33% of those responding believed that the withdrawal of aprotinin had hurt their patients; most respondents did not perceive

a change. Notably, not a single physician had remarked that the withdrawal of the drug had made their patients better.³⁹ In a large series from China comparing 1700 patients before the cessation and 2200 patients after the cessation of aprotinin availability, the use of blood products increased significantly.⁴⁰ For patients undergoing coronary artery bypass grafting, the same group showed no effect of aprotinin on mortality ($P = .45$), long-term mortality ($P = .21$), or major adverse cardiac/cerebrovascular events ($P = .82$).⁴¹ Interestingly, the increased use of blood products itself was associated with a greater incidence of renal dysfunction, not less, such as would have been predicted by those believing that aprotinin was a major contributor to postoperative renal failure. The increased use of blood products after aprotinin withdrawal also correlated with the increased duration of mechanical ventilation and an overall decrease in arteriolar/alveolar oxygenation.⁴⁰ This follows what has been published relating the risks of blood transfusion and transfusion-related acute lung injury. Single-center experiences from Emory University, the University of Chicago, and Wake Forest University have all noted an increase in blood usage after the cessation of aprotinin.⁴²⁻⁴⁴ Clearly, no drug is without risks, and we, as a profession, must be very careful how we review and interpret the published data, science, and evolving technologies. As noted by Sundt,⁴ the repercussions of BART went beyond the withdrawal of a single drug; this event served as a notice as to how we, as surgeons, worked with industry, as well as the often preconceived notions (both pro and con) that influence how we practice our trade.

Recently, an extensive review of the BART data by Health Canada determined that the withdrawal had been premature. This analysis (available from: http://www.hc-sc.gc.ca/dhp-mps/medeff/eacvhp-ccvrps/eap-gce_trasylol/final_rep-rap-eng.php) found disagreement with the published conclusions (and global reaction) of the BART data. First, an extensive review of multiple clinical trials and postmarket studies supported the benefits of aprotinin when used appropriately and “on-label” (ie, for routine coronary artery bypass grafting). Few clinical trials for higher risk patients were available, although epidemiologic studies demonstrated that this was the population that the drug was being primarily used for, including in the BART. Second, the reviewers noted that compared with the 2 other antifibrinolytics in the BART, aprotinin unexplainably prolonged the partial thromboplastin time. This resulted in lower doses of heparin in the aprotinin arm of the study. The impact of this lower dose on the outcomes is not immediately known but it might mirror the initial concerns with aprotinin monitoring during cardiopulmonary bypass using the activated clotting time versus the ecarin clotting time. Third, Health Canada concluded that the study had not been designed to reliably determine the risk of death relative to the 2 other drugs in the study and that the increase in deaths in the

aprotinin arm could have been due to chance. From these conclusions, Health Canada determined that the risk profile of aprotinin remained favorable when used appropriately. Furthermore, they approved lifting the previous withdrawal notification, with the caveat that additional package warnings regarding renal risks, abnormal activated partial thromboplastin time measurements, the risk of underanticoagulation with heparin, and the risk of death when used outside of approved indications be added.

Since Health Canada’s action, on February 12, 2012, the European Medicines Agency recommended lifting the ban on aprotinin.⁴⁵ The findings of the European Medicines Agency mirrored those of Health Canada, finding fault with the heparin dosing disparities, inappropriate monitoring of anticoagulation, and exclusion of selective patient data from the initial analysis. Whether the drug is ever marketed again in the United States might reflect more the tort environment than the desire of surgeons to revisit this drug. After 6 or more years of controversy, a number of reports supporting renal dysfunction/failure, and larger ones demonstrating no such effect, we have been left with an uncontrolled human experiment brought on by the withdrawal of a drug from the market. It appears that such human experimentation has not proved that lives are saved by not having the drug. Rather it seems that blood usage has increased, and perhaps some harm has been done. We need to learn a number of collective lessons from this series of events.

Returning to the observation of Sundt⁴—can we envision other parts of our practice in which we are creating new aprotinin controversies for the future? Every time we use recombinant factor VIIa (NovoSeven, Novo Nordisk Inc., Princeton, NJ), do we consider what the FDA approved the drug for? Every time we stent an aortic dissection, do we stop and think about what the devices are approved for? Probably not, because in our own mental map, we know that when someone is bleeding to death, using factor VIIa might be all that is left to try. The newest available proteins for thrombosis treatment include fibrinogen concentrates and prothrombin concentrates. The use of these agents to stop bleeding will certainly create a hypercoagulable state in some patients. Is it the medication’s “fault”—or a lack of understanding by physicians of the dynamic process, as well as an inability to highly individualize therapy? When the motor vehicle accident patient presents to the emergency room with bleeding transaction, thoracic endovascular stent grafting can usually be done safely and expediently, especially when the open expertise might not be available.⁴⁶ Thus, the dilemma for our profession—how do we, or can we, expand the indications for current technology and therapeutics without losing sight of the continuing need for rigorous, evidence-based practice? Clearly, industry will not support randomized trials for every indication we, as surgical teams, believe are reasonable. These companies are driven by business opportunity costs. To limit our practice

to just FDA-approved indications is not right either. Most drugs are never indicated by the FDA approval for pediatric usage. However a “band wagon” mentality of following certain parts of the published data yet dispensing with refuting data means we are not providing our patients with the best service. Human trials should not be conducted by withdrawal of useful agents from the market place, allowing us an eventual look back to determine whether the dire predictions came true or whether new complications arose in certain populations. Our professional societies should continue to play an active role in defining guidelines without reflexively altering our practice in response to the fear of litigation. Each of us as physicians needs to critically read the published data and weigh the pros and cons for our patients regarding the available therapeutic options. That is the practice of medicine.

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