NOTHING QUITE RAISES the ire or brings out the torches and the pitchforks in the cardiothoracic anesthesia circles more than a discussion about aprotinin. Much has been discussed and published regarding the broad-acting serine protease inhibitor. Keen interest in aprotinin began with Royston et al’s published report showing that the use of the drug resulted in an 8-fold decrease in the need for blood transfusion in patients undergoing repeat cardiac surgery. Aprotinin came into routine use for repeat coronary artery bypass graft (CABG) surgery after Food and Drug Administration (FDA) approval in 1993 as a means to curtail perioperative bleeding. It was later approved for first-time CABG surgery in 1998 for the same indication. In the wake of its generally warm reception, aprotinin was plagued by concerns regarding thrombosis of venous conduit and arterial coronary grafts as well as native coronary thrombosis.\(^2,3\) Additional concerns regarding cardiovascular collapse because of anaphylaxis, catastrophic systemic thrombosis, and renal insufficiency/failure in the setting of deep hypothermic circulatory arrest also had come to light.\(^4\)

The FDA had been keeping a watchful eye as the developments unfolded, but issues were brought to a head with the Mangan et al study published in the *New England Journal of Medicine* in January 2006. This observational, retrospective, multicenter study of 4,374 patients compared aprotinin (full or half-dose) with no agent, tranexamic acid (TA), and epsilon aminocaproic acid (EACA) in primary or complex CABG surgery performed with cardiopulmonary bypass (CPB). Primary CABG surgery (\(n = 3013\)) was defined as elective CABG surgery or angioplasty without prior cardiac or vascular surgery. Complex surgery (\(n = 1,361\)) was defined as CABG surgery with valvular or other cardiac procedure and any repeat cardiovascular procedure. The investigators found a doubling in the risk of renal failure requiring dialysis in the primary and complex CABG surgery groups treated with aprotinin. Only in the primary CABG surgery group was aprotinin associated with an increased risk of myocardial infarction or heart failure (\(p < 0.001\)), an increased risk of stroke or encephalopathy (\(p < 0.001\)), and increased mortality (\(p = 0.02\)). Aprotinin showed a dose-response relationship regarding renal, cardiovascular, and composite outcomes. Despite the fact that the study’s findings were seen predominantly in the primary surgery cohort, the investigators broadly concluded that aprotinin use was not prudent and suggested that other lysine analogs should be used. This brought about widespread concern, and numerous cardiac surgical groups altered their administration of aprotinin based on this study. Amid criticism that this study was an observational, retrospective study, the Blood Conservation Using Antifibrinolytics in a Randomized Controlled Trial (BART) was already underway. Meta-analyses of clinical trials had given no indication of excess risk of death caused by aprotinin, so in 2006 the FDA decided not to add a black-box warning to the aprotinin label. The BART study was a multicenter, double-blinded study comparing full-dose aprotinin with standard-dose EACA or TA in high-risk cardiac surgery (defined as twice the average mortality for isolated primary CABG surgery and a risk for repeat surgery exceeding 5%).\(^5\) Although the study design called for the enrollment of 2,970 patients, it was halted at 2,331 patients because of a higher rate of death in patients receiving aprotinin. Aprotinin had shown a modest reduction in the risk of massive bleeding (relative risk = 0.79; 95% confidence interval, 0.59-1.05); however, the relative risk of death was 1.53 (95% confidence interval, 1.06-2.22). Bayer voluntarily removed aprotinin from the market in response to an FDA request in November 2007; and, subsequently, remaining supplies were removed from warehouses upon online publication of the BART study in May 2008.

As mentioned, before the withdrawal of aprotinin, the Mangano et al study prompted some cardiac surgical groups to alter their use of aprotinin. Strouch et al conducted a retrospective study to evaluate the effect of the Mangano et al study on a single institution’s (University of Chicago) use of aprotinin (full- and half-dose) on blood product use during CPB and the frequency of reoperation for excessive bleeding. The study examined 499 total patients for cardiac surgery from February 2005 to January 2006 (group 1) and from February 2006 to January 2007 (group 2). Strouch et al showed a decrease in aprotinin use from 58% to 17% (\(p < 0.001\)), the nonuse of aprotinin increased from 18% to 47% (\(p < 0.001\)), and fresh frozen plasma (FFP) increased from 24% to 36% (\(p = 0.004\)); whereas packed red blood cell (PRBC) transfusion rate remained stable. PRBCs were administered to maintain the on-CPB hemoglobin at 9 to 10 g/dL, and FFP was given for every 4 units of PRBCs. The administration of FFP to maintain a therapeutic activated coagulation time, in the setting of antithrombin III deficiency, was not documented. There was a trend toward reoperation that was not statistically significant. Although it is interesting to track findings before and after the publication of a pivotal study, only the CPB period was evaluated, and postoperative blood loss necessitating reoperation was not shown.

Now that aprotinin is no longer available for clinical use, what has changed? Certainly, most individuals in the cardiac surgical arena have an opinion about the topic. Investigators from the United Kingdom polled the opinions of cardiac anesthesiologist and surgeon members of the Association of Cardiothoracic Anesthesiologists and the Society for Cardiothoracic Surgery in Great Britain and Ireland, respectively, using a mailed survey approximately 1 year after the withdrawal of aprotinin.\(^6\) Five hundred forty-six surveys were mailed; 285

Con: The Practice of Cardiac Anesthesia Has Not Significantly Changed After the Withdrawal of Aprotinin

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were returned (52% response rate). Seventy-five percent of the surveys were completed by anesthesiologists, with 25% completed by cardiac surgeons; yet there was no significant difference in responses between the 2 groups. Their responses showed that 61% of respondents believed the withdrawal of aprotinin had no effect, 29% believed it had a detrimental effect, and 2% believed it had an extremely detrimental effect on patient care. Eight percent responded that it had a beneficial effect. The majority of respondents reported no change in the use of PRBCs (66%), blood products (53%), mechanical cell salvage (84%), factor VIIa (79%), or frequency of reoperation for bleeding (65%). While 32%, 45%, 24%, and 20% of respondents, respectively, reported a perceived increase in the use of these products, 30% reported an increase in reoperation for bleeding. It is conceivable that those who did not perceive that the withdrawal of aprotinin had a significant impact answered “no impact” to the blood/factor and reoperation questions. Conversely, the “detrimental” and “extremely detrimental” respondents likely answered that blood/factor use and reoperations increased. As a survey, these results are subjective and are not a true measure of changes, yet they do gauge perception. Although the goal is to practice in an evidence-based manner, when evidence is limited or conflicting, opinions and are not a true measure of changes, yet they do gauge perception. Although the goal is to practice in an evidence-based manner, when evidence is limited or conflicting, opinions may be the deciding factor. Opinions have changed, and this can drive changes in practice.

Results of the withdrawal of aprotinin are just beginning to appear in the literature. A Chinese group conducted an observational, case-control study evaluating 1,699 cardiac surgical patients from June 2007 to December 18, 2007 receiving aprotinin compared with 2,225 similar patients from December 19, 2007 to June 2008 receiving no antifibrinolytic (comparing before and after aprotinin withdrawal). This institution changed from all cardiac surgical patients receiving aprotinin to no patient receiving an antifibrinolytic. Only pediatric cases were excluded; otherwise, all cardiac cases were included. The aprotinin group showed less postoperative blood loss (first 24 hours, 405 mL vs 628 mL, \( p < 0.001 \)), fewer units of PRBCs (2.6 vs 3.2, \( p < 0.002 \)), a lower volume of FFP transfused (317 vs 401, \( p < 0.001 \)), and a lower rate of reoperation for bleeding (2% vs 3.7%, \( p < 0.002 \)). Without a clearly defined transfusion trigger or protocol, as well as the lack of trigger indicated for surgical re-exploration, it is difficult to draw a conclusion as to what caused the findings in this population. With the withdrawal of any antifibrinolytic, the expected outcome would be that increased bleeding would be encountered, yet there was not an identified change in practice to deal with this expectation. Also, the practitioner’s own threshold for transfusion and surgical re-exploration could have been lowered in the upheaval after the withdrawal of aprotinin. Is it surprising that the reported difference in postoperative blood loss of 250 to 300 mL prompted re-exploration? Interestingly, this group did not find an increased risk of in-hospital mortality or adverse renal, cardiac, or neurologic events in the aprotinin group. Instead, they found that the aprotinin group had a shorter mechanical ventilation time and a higher arterial oxygen tension/inspired oxygen fraction ratio, indicating a potential protective effect of aprotinin or the benefit of a lower volume of blood product transfusion.

Additional information is being compiled regarding the impact of the withdrawal of aprotinin. Sniecinski et al conducted a retrospective, observational study examining the change from full-dose aprotinin to TA at a single institution (Emory University) for procedures requiring deep hypothermic arrest (DHCA). One hundred sixty consecutive DHCA cases were evaluated from January 2006 through November 2008 (aprotinin use stopped November 15, 2007; aprotinin, \( n = 82 \); TA, \( n = 78 \)). Patients receiving TA received more FFP (2.5 \( U, p < 0.001 \)), platelets (0.5 \( U, p < 0.01 \)), cryoprecipitate (25 \( U, p < 0.001 \)), had a higher need for factor VIIa rescue (34.6% vs 12.2%, \( p < 0.01 \)), and a trend toward a lower re-exploration rate (11.5% vs 2.4%, \( p = 0.05 \)). The transfusion of hemostatic blood products (FFP, platelets, and cryoprecipitate) in the operating room was dictated by an ongoing blood loss of 200 mL/h without obvious surgical bleeding at the discretion of the anesthesiologist. Factor VIIa was given with the input of a hematologist to treat microvascular bleeding after 4 \( U \) of FFP, 2 \( U \) of platelets, and 20 \( U \) of cryoprecipitate had been administered. In the postoperative setting platelets and FFP were administered according to laboratory studies (platelet count <100,000, fibrinogen <150 mg/dL, respectively), whereas PRBCs were at the discretion of the intensivist. With the lack of intraoperative laboratory results and transfusion of PRBCs at the discretion of the practitioner, results will vary based on the individual’s medical opinion. A point of interest was a noted increased incidence of seizure in the TA group (5 vs none in the aprotinin group). DHCA duration greater than 40 minutes is associated with seizures, yet the TA group had DHCA times of only 15 to 35 minutes. Presumably, the proconvulsant effect of TA is believed to be mediated by y-aminobutyric acid-receptor antagonism. This proconvulsant effect was noted in separate investigations by Martin et al and Breuer et al, and a meta-analysis of TA use in cardiac surgery cautions against indiscriminate use because of a tendency toward an increased risk of postoperative neurologic events.

The challenge is to determine the value of this evolving literature. In the setting of multiple, retrospective, observational studies, it can be said that the events preceding and following the withdrawal of aprotinin have been documented. Yet, a direct cause and effect relationship cannot be drawn between whether the lack of aprotinin administration caused the multitude of outcomes that were noted. There also arises the possibility that some of the results that will be encountered are a result of the transfusion of blood products. The transfusion of PRBCs has been associated with myocardial infarction, renal dysfunction, renal failure requiring dialysis, wound infection, prolonged length of stay, low-output heart failure, and long-term mortality. These are some of the same complications that have been cited as the rationale for the abandonment of aprotinin. Additionally, thrombotic complications attributed to the use of factor VIIa and neurologic complications seen in association with TA may be undesirable resultant effects. It remains to be seen whether patient outcomes improve without the use of aprotinin, as would be expected based on the conclusions of the Mangano and Bart studies.

The question remains whether the practice of cardiac anesthesia has changed. Other than the lack of antifibrinolytic use or the change to an alternative antifibrinolytic, are clinicians proactively doing anything different? Most of the studies men-
tioned previously did not have robust transfusion triggers or protocols. The immediate period after the withdrawal of aprotinin should have fostered a hardy response to reform transfusion practices. The Society of Thoracic Surgeons (STS) Workforce on Evidence Based Surgery, in conjunction with the Society of Cardiovascular Anesthesiologists (SCA), established guidelines for perioperative blood transfusion in 2007. This document collated peer-reviewed literature and made recommendations based on the class and level of evidence available for an evidence-based approach to blood conservation. This was a multimodality approach that included the use of red-cell-saving devices, transfusion triggers, antifibrinolytics, comments on the need to discontinue antiplatelet and thienopyridines, human erythropoietin, predonation of blood, off-pump coronary artery bypass, and patient risk stratification. In a yet-to-be-published report (in press 2010), Likosky et al surveyed the effect of the STS/SCA guidelines upon cardiac surgical practice. Of the 5,719 emails sent, 1,828 surveys were returned (response rate of 32%), with 886 anesthesiologists and 516 perfusionists responding, predominantly from the United States and Canada. There were no surgeon respondents in the STS who declined to participate in the study. Of note, the guidelines were established and promulgated during the time when aprotinin was withdrawn from the market and the survey was conducted between February 2009 and April 2009 (the period after aprotinin withdrawal). With 78% of the anesthesiologists and 67% of the perfusionists reporting having read all or part of the guidelines, only 20% of all respondents reported having had an institutional discussion. Only 4 of the 38 guideline recommendations were reported by 5% of respondents as having been adopted. The 4 guidelines adopted included reduced hemoglobin level transfusion trigger, the use of leukocyte-reduced PRBCs, the use of leukocyte-reduced platelets or coagulation factors, and the use of factor VIIa as a rescue therapy. With the majority of respondents being anesthesiologists, this is evidence that supports that the withdrawal of aprotinin did not significantly change the practice of cardiac anesthesia. Only 15% of the respondents reported having conducted an institutional examination regarding the use of aprotinin. Limitations of the study are those similar to any survey conducted an institutional examination regarding the use of aprotinin. The immediate period after the withdrawal of aprotinin was suspended in cardiac surgery: Different results in the real post-aprotinin era.

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The aftermath of the withdrawal of aprotinin would have been an opportune time to make the strongest argument for the use of point-of-care (POC) testing to advance the practice of perioperative cardiac surgical care. Rather than rely on the clinician’s empiric administration of blood products because of long turnaround times of laboratory-based coagulation tests, POC devices would provide rapid perioperative assessment to direct the appropriate targeted therapy. There are numerous POC testing devices that are currently available, such as platelet function analyzers, viscoelastic clot analyzers, modified thromboelastographs, and heparin effect monitors. The limitations to the use of POC testing are primarily related to the expense, training, and maintenance of the systems. More importantly, the application of a transfusion algorithm with POC testing repeatedly has shown reductions of blood loss and transfusion requirements in cardiac surgical patients. Solely adopting a multidisciplinary blood-conservation program (without POC testing) has been shown to lower the use of allogeneic RBC transfusions. Brevig et al adopted a blood-conservation initiative from 2003 to 2007 treating 2,531 patients. Although there was not an identified transfusion target, measures enacted included providing a blood-conservation coordinator, reduced CPB tubing lengths and prime volume, normothermia (except in cases of DHCA), and permissive anemia. In the postoperative period, PRBCs were transfused based on clinical findings of anemia associated with persistent hypotension, orthostatic hypotension, tachycardia, and the inability to rehabilitate. Over the 5-year period, the authors noted a decrease in PRBC transfusion from 43% in 2003 to 18% in 2007. They also noted decreases in new renal insufficiency, units of PRBCs transfused per patient, and time to extubate, and they found no change in mortality. The investigators noted that the biggest barriers to the adoption of the initiative were the attitudes and culture of the patient care team. Evidence supports that POC testing and blood-conservation protocols have a significant positive effect on patient outcomes. It is time to stop practicing as if clinicians are stuck in the dark ages and advance cardiac surgical and anesthetic practice by providing definitive therapy and an organized approach, especially in the post-aprotinin era.


