Bleeding and transfusion in cardiac surgery are associated with serious adverse events, including an increased length of hospital stay, infection, return to the operating room, length of ventilation/respiratory failure, atrial fibrillation, myocardial infarction, renal failure (RF), and short-term and long-term mortality. Strategies to reduce transfusion have been advantageous. Prophylactic pharmacologic agents focused on reducing transfusion were introduced very early on in cardiac surgery. Antifibrinolytic agents, lysine analog agents (epsilon-aminocaproic acid [EACA] and tranexamic acid [TA]) and the serine protease inhibitor, aprotinin (Bayer Pharmaceuticals Inc, West Haven, CT) were used from the mid-90s to 2007. On November 5, 2007, after consultation with health regulatory authorities, Bayer announced it had suspended marketing of aprotinin.

Aprotinin was effective in decreasing bleeding as well as the demand/usage of perioperative transfusion. Academic arguments have raged as to whether aprotinin was more effective than the lysine analogs, especially for high-risk bleeding groups. Three retrospective studies called into question the safety of aprotinin with regards to renal dysfunction (transient groups. Three retrospective studies called into question the safety of aprotinin with regards to renal dysfunction (transient creatinine increase)/dialysis and long-term mortality. Strategies to reduce transfusion have been advantageous. Prophylactic pharmacologic agents focused on reducing transfusion were introduced very early on in cardiac surgery. Antifibrinolytic agents, lysine analog agents (epsilon-aminocaproic acid [EACA] and tranexamic acid [TA]) and the serine protease inhibitor, aprotinin (Bayer Pharmaceuticals Inc, West Haven, CT) were used from the mid-90s to 2007. On November 5, 2007, after consultation with health regulatory authorities, Bayer announced it had suspended marketing of aprotinin.

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This synopsis is not news to any practicing cardiac anesthesiologist. The following assertions had been made by Mangano et al and McSPI: “The association between aprotinin and serious end-organ damage indicates that continued use is not prudent. In contrast, the less expensive generic medications aminocaproic acid and tranexamic acid are safe.” Assertions went on that the withdrawal of aprotinin would reduce renal failure/cost and “… prevent renal failure in 11,050 patients per year, yielding an indirect savings (from the saved costs of dialysis) of more than $1 billion per year in addition to direct savings (from reduced drug costs) of nearly $250 million per year.” Also, McSPI said “replacement of aprotinin with tranexamic acid would prevent 9790 complications necessitating dialysis each year, yielding similar direct and indirect savings.”

It is now approximately 2.5 years after the withdrawal of aprotinin. Have the predictions of improved patient outcome come true, are costs down, or has there been a change in cardiac anesthesia? McSPI investigators stated publicly that TA and EACA are safe and are equivalent to aprotinin in blood-sparing efficacy, and, therefore, the withdrawal of aprotinin would enhance the practice (be it of perceived benefit) of cardiac anesthesia or at least not make a big difference. The BART investigators and others involved in retrospective analysis studies made no predictions.

Other important impressive (in numbers) retrospective articles were published contemporary to the McSPI and Karkouti et al articles. The day before the first Food and Drug Administration (FDA) advisory panel (2006), a large (>12,000 cases) retrospective data-based analysis came from the Providence Health Care System. Furnary et al concluded that by univariate analysis aprotinin was associated with an increase in renal dysfunction, but that once a careful control for the use of transfusion was taken into account it was the use of blood that had driven the adverse events, not the use of aprotinin alone. In that database, aprotinin was administered to those patients who were more ill than those who received lysine analogs; that was physician channeling. It was the risk of bleeding coupled with the physician reaction to the use of aprotinin and transfusion that drove the adverse outcomes. That paper, although it was presented in person to the FDA panel by Dr Furnary, went largely unheard.

Pagano et al reviewed 7,836 patients in a single-centered study of cardiac surgery between 1998 and 2006. In contrast to the McSPI and BART studies, there was no evidence of increased short- or long-term mortality because of aprotinin.
usage, renal dysfunction, or RF. Pagano et al agreed with BART and Furnary et al in that blood transfusion and reoperation for bleeding was significantly reduced by the use of aprotinin. 

In 2008, the German Heart Center reported on more than 1,100 patients, noting that aprotinin seemed riskier in routine coronary artery bypass graft surgery, but that TA was associated with increased seizures and produced worse outcomes in valve surgery. Of note, actually atrial fibrillation (AF) and RF were higher in the group who received TA (a contradiction to the McSPI conclusions). In high-risk surgery, the mortality was higher with aprotinin. They concluded that both drugs have significant side effects.

The use of fresh frozen plasma (FFP) has the same association with renal failure as does aprotinin as reported in the first McSPI aprotinin paper. The usage of red cells also has the same statistical p value relationship to renal dysfunction/failure. There was no mention in the original McSPI papers presented to the FDA that transfusion had such equal relationships to renal dysfunction/failure. It can only be concluded from all the papers together that the usage of transfusion and the usage of aprotinin are closely intertwined, meaning that the ability to separate them as true cause and effect by retrospective analysis is at best a statistical three-ring circus.

A review of all the published articles by McSPI from the single database (EPI-II data) regarding aprotinin, renal failure, and transfusion showed that dramatically conflicting and inconsistent messages exist. Some articles blame aprotinin, others do not mention aprotinin, and still others note that the cause of RF is transfusion itself. One McSPI article noted that there are large differences in site, country, and practice patterns. Work from Wake Forrest University shortly after the change in aprotinin usage found dramatic increases in overall transfusion, red cells, FFP, and excessive bleeding requiring re-exploration. From the University of Chicago, a preliminary report noted no increase in red cell usage after their center stopped using aprotinin. However, 1 year later, that same group published a different message. In that second publication, they noted that although red cell transfusions intraoperatively had not changed, their center had experienced a statistically significant increase in the use of FFP. Moreover, they noted a disturbing trend toward more reoperations for bleeding, which they had not seen in the aprotinin era.

The single largest report to date regarding a change in practice and patient outcomes is from a single center in China. This is not a randomized controlled study; however, the report summarizes a dichotomous dramatic change in practice. For 6 months (n = 1,699) before and 6 months (n = 2,225) after the withdrawal of aprotinin, data were examined on all cardiac surgery patients at this center. During the 6 months in which aprotinin was used, all patients received the drug, and afterwards no antifibrinolytics were given. Not surprisingly, without the use of EACA or TA the blood loss, reoperation for bleeding, and overall transfusion of coagulation products took a dramatic rise. However, with the nonuse of aprotinin, there was no change in renal failure (p = 0.46) and a nonstatistical trend (p = 0.09) toward less renal dysfunction without aprotinin (eg, increased use of blood products). There was, consistent with the increased use of FFP, platelets, and other blood products, a rise in mechanical ventilation time and prolonged mechanical ventilation. The Chinese study examined PaO2/FiO2 ratios. The aprotinin group had a significantly better ratio (353.2 v 505.8, p < 0.001). TRALI is a diagnosis of exclusion as well as a worst-case scenario. Some recent opinions have stated that it is possible to have “a touch of TRALI” (A-a ratio change). In a review of lung dysfunction after cardiac surgery, looking only until 2006, Koch et al found that blood transfusion was not less proven otherwise. Is there an unexplored HiTT-aprotinin interaction? Neither of the databases (McSPI and Karkouti) had any ability to follow HiTT as a potential confounder, nor did they consider it an option/confounder. Also noted to the FDA were this author’s predictions that there would be an increased usage of transfusion if aprotinin was withdrawn. Furthermore, it was the present author’s assertion that mechanical ventilation (a manifestation of transfusion-related acute lung injury [TRALI]) would increase in the cardiac surgery population.

Now, some 29 months later, those predictions may be coming true. The previously quoted data-based retrospective reviews have shown that the conclusions of McSPI were premature, incomplete, variable, and inconsistent and that the usage of aprotinin was inextricably intertwined between dramatically ill patients who required excess blood products.
independently associated in cardiac surgery with TRALI. However, that review used the international worse-case definition, not examining individual arterial/alveolar oxygen gradients, and it was looking at patients during the period when aprotinin was widely used. The reader should remember that aprotinin was first tried as a way to decrease lung dysfunction after surgery.

In the most recent report of change in practice after the withdrawal of aprotinin, investigators from Emory University noted that the use of FFP, cryoprecipitate, platelethpheresis packs, and red blood cell transfusions were significantly higher when they changed from aprotinin to TA.17 The preoperative demographics of these 160 patients were almost identical. The re-exploration rate was 11.5% for those receiving TA versus 2.4% for those receiving aprotinin (p < 0.05). There were no seizures in the group receiving aprotinin, but there were 2 in the TA group (p = 0.02). Although aprotinin costs $1,000.00 more than TA, the increased use of blood products offset that cost differential by more than $3,000.00. The factor VIIa use was not included in the cost analysis of the Emory study. The use of factor VIIa is evolving/increasing throughout cardiac surgery, in part because of the withdrawal of aprotinin.

There is no doubt that factor VIIa is a potent prothrombotic agent. Other reports of seizures arising from TA have been forthcoming in the literature as well, so it is not just isolated. TA is well known in neurosurgery to be associated with seizures and coming in the literature as well, so it is not just isolated. TA is a potent prothrombotic agent.

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In summary, the practice of cardiac surgery/anesthesia has profoundly changed with the withdrawal of aprotinin. The large retrospective analyses that were published shortly after the McSPI, Karkouti et al., and BART studies have not supported these earlier articles. The BART study actually negates the first McSPI renal paper and does show differences in blood usage and reoperation rate. The other retrospective studies have shown that the literature is muddy, inconclusive, and fraught with confusion regarding patient risk, transfusion, and drug usage. Essentially, the only thing that can be concluded from the data-based studies is that there still is no single clearly guiding randomized controlled study of aprotinin versus EACA and TA. The assertions by McSPI that TA and EACA are safe and equally effective in reducing bleeding/transfusion are becoming ever more wrong. Bleeding and transfusion usages are increasing since the withdrawal of aprotinin. This is now documented.

The withdrawal of aprotinin has translated to pulmonary dysfunction and an increased length of stay in intensive care units. Reoperations for bleeding have been documented to be increased as well. Costs have dramatically increased in both drug usage (more factor VIIa) as well as through the increased usage of blood products, intensive care unit time, and so on. Perhaps what speaks the loudest in this debate is the lack of reporting of improved patient outcome, lowered cost, or general patient improvement with the withdrawal of aprotinin. Where are those reports?

All of medicine could learn from the lessons of the last few years. Several wonderful editorials have drawn clinicians’ attention to the folly (by all), the lack of responsible medical shepherding in both aprotinin’s usage (its near-universal application), and its ultimate withdrawal.28,29 Physicians have taken emotional sides on the issue. From a review of the literature, there is no definitive study supporting this level of passion on either side. Now, several years after the meetings of the FDA and Health Canada, there is no conclusive ruling by the regulatory agencies. The aprotinin drug withdrawal was driven by media attention, lay pressure, emotion, and fear of legal actions, which strikes this scientist as not in the public’s best interest. Science today does not support the conclusions of the McSPI papers of several years ago. Karkouti et al has published new data showing that aprotinin may well improve outcome in some high-risk patients, stating that “aprotinin tends to have a better risk-benefit profile than tranexamic acid in high-risk, but not low-to-moderate risk patients. Its use in high-risk cases may therefore be warranted.”30

The entire series of events have been most unfortunate in that they were not driven by science, level I evidence, and cool heads. Today, clinicians are part way through a pharmaceutical/societal experiment (with no control and no protocol) wherein a highly effective drug with incompletely investigated (in specific subgroups) effects on outcome as compared with other competition has been withdrawn. It would be wonderful to be able to conclude what morbidity/mortality exists now in its absence. However, this clinician suspects that drama and opinion will still rule the day rather than objective science once the present-day uncontrolled withdrawal experiment is finished. Perhaps a very pertinent quote to this entire aprotinin controversy was prophetically uttered by Winston Churchill under different circumstances when he said, “These, gentlemen, are the opinions upon which I base my facts.”

REFERENCES


