The use of antifibrinolytic therapy is commonplace in coronary artery revascularization procedures. Cardiac surgery accounts for more than 700,000 surgeries per year, with approximately 70% of these cases requiring antifibrinolytic therapy for coronary artery bypass graft (CABG) procedures. Two main classes of antifibrinolytics are used in CABG procedures: synthetic lysine analogues and serine protease inhibitors. Both classes of antifibrinolytics have been shown to decrease the incidence of blood transfusions. However, new data have emerged regarding an increase in adverse outcomes associated with serine protease inhibitors. The purpose of this review article is to describe the clinical significance of antifibrinolytic therapy and the current implications associated with its use.

Keywords: Antifibrinolytics, aprotinin, cardiac bypass, hemostasis, transfusion.
medical or nursing journal and/or text, and (3) discussed coronary artery revascularization procedures or explained the action of antifibrinolytic agents.

**Lysine Analogues**

EACA and TXA are synthetic lysine analogues. EACA is a synthetic chemical analog of the amino acid lysine. It acts by binding to the lysine-binding sites of plasminogen and plasmin. Once bound, EACA displaces plasminogen from fibrin, resulting in inhibition of the natural tendency of plasminogen to split fibrinogen. A secondary proposed action of EACA is the ability to bind to fibrin and protect it from plasmin degradation. The mechanism of action of TXA is identical to that of EACA; however, it is roughly 10 times more potent per unit dose than EACA. In addition, EACA and TXA inhibit the transformation of plasminogen to plasmin by clot-bound tissue plasminogen activator (tPA) vs circulating tPA. Consequently, TXA and EACA may not be as effective as a serine protease inhibitor in preventing systemic fibrinolysis when elevated levels of tPA elicit a systemic increase in circulating plasmin and, eventually, increased bleeding times associated with elevated fibrinogen degradation products.

Several studies have evaluated the clinical implications associated with EACA and TXA in reducing blood loss during and after cardiac surgery. These studies showed that TXA and EACA can reduce blood loss after cardiac surgery. EACA and TXA have been extensively studied and shown to have an excellent safety margin in cardiac procedures with fewer than 1% of cases demonstrating potential complications. Severe complications associated with synthetic lysine analogues administration include seizures, renal failure, and rhabdomyolysis.

**Serine Protease Inhibitor**

The mechanism of action of aprotinin differs from the previously discussed lysine analogues. As a nonspecific serine protease enzyme inhibitor, aprotinin helps modulate the systemic inflammatory response associated with CPB through its effects on kallikrein and plasmin inhibition. Inhibiting plasmin preserves the insoluble clot. Kallikrein serves an important role in accelerating the systemic inflammatory response. Kallikrein accelerates factor XII formation, initiates complement systems, and promotes fibrinolysis and renin formation. It also promotes bradykinin release, which increases vascular permeability and tPA formation.

Aprotinin is associated with preventing fibrin degradation by inhibiting plasmin and kallikrein formation. Fibrin degradation products (FDPs) have a high affinity for platelets, making them nonfunctional. The FDPs also increase the release and synthesis of monocyte-macrophage–derived interleukins 1 and 6, which induce further endothelial and end-organ damage. Finally, FDPs weaken the ability of factor XIII to form a strong fibrin clot. By preventing kallikrein and plasmin activation and decreasing FDPs, aprotinin assists with blood preservation during CPB. In a thorough meta-analysis of aprotinin, large and small doses decreased the proportion of patients undergoing cardiac surgery patients who required blood products.

In addition to blood conservation, aprotinin preserves platelet function. Although the direct mechanism of action of platelet preservation is unknown, a potential explanation is that aprotinin selectively protects platelets from desensitization that occurs throughout extracorporeal circulation time. This desensitization would decrease the degranulation and consumption of platelets that occurs with thrombin formation. A thorough meta-analysis of aprotinin reported that the preservation of glycoprotein 1b occurred with aprotinin use. Glycoprotein 1b assists with platelet adhesion to vascular endothelium. Proponents of aprotinin also cite neutrophil activation and reduction of atrial fibrillation as additional benefits.

An increase in anaphylactic and anaphylactoid reactions has been reported with aprotinin. Despite decreasing blood product use, institutions may choose other options owing to immunogenicity, the higher cost, and other possible side effects associated with its use.

**Comparison of Lysine Analogues and Serine Protease Inhibitors**

Meta-analyses comparing EACA, TXA, and aprotinin concluded that all 3 agents, when used in conjunction with extracorporeal circulation, reduced blood loss and additional use of allogeneic blood products. Aprotinin is an expensive drug, and its immunogenicity, which can potentially cause an allergic response with reexposure, has led to the comparison, in multiple studies, of the cheaper lysine-analog antifibrinolytic drugs for efficacy. It is important to note that these studies had limited size, were often not blinded clinical trials, and did not incorporate redo surgical procedures. The mean ± SD costs for pharmacological and transfusional treatments were significantly lower for TXA ($58.10 ± $105.10) vs EACA ($100.70 ± $158.60) vs aprotinin ($432.60 ± $118.70). An additional prospective randomized, partially blinded study compared the costs of lysine analogues and serine protease inhibitors with the cost of allogeneic blood requirements. The study concluded that TXA was less costly than aprotinin and achieved a comparable benefit. These results are similar to those previously published comparing aprotinin with EACA and TXA. The cost-effective advantage of the lysine analogues with similar end results has led to their use at many institutions.

Perhaps the most conclusive literature that promotes use of lysine analogues over aprotinin is a recent article that reported an association of aprotinin with renal toxic effects and ischemic events in patients undergoing CABG.
surgery.\textsuperscript{23} Among patients undergoing complex coronary-artery surgery, the use of aprotinin was associated with a 2-fold increase in renal failure requiring dialysis a 55% increase in myocardial infarction or heart failure, and a 181% increase in stroke or encephalopathy.\textsuperscript{23} The study, which included 4,373 patients undergoing coronary revascularization, at more than 69 hospitals, concluded that neither EACA nor TXA was associated with an increase risk in renal, cerebral, or cardiac events.

The study used statistical procedures to adjust for the known differences between the treatment groups. The descriptive observational study does not demonstrate cause and effect and did not randomly assign patients to aprotinin, TXA, EACA, or no medical intervention groups. The patients had imbalances in baseline characteristics, and patients treated with aprotinin had a higher propensity for multiple morbidities than did patients receiving different antifibrinolytic therapy.\textsuperscript{23} To adjust for these imbalances, complex statistical methods involving propensity scores was used. Despite the complexity adjustment, aprotinin, in low and high doses, showed an increase in morbidity and mortality.\textsuperscript{23} Although all 3 agents decreased blood loss, the propensity of end-organ damage, specifically the kidney, heart, and brain, was associated only with aprotinin.

Aprotinin was associated with adverse outcomes in another observational study of 898 patients, half of whom were treated with aprotinin and the other half with TXA, undergoing CABG with CPB. Baseline characteristics among participants were similar.\textsuperscript{30} Although the rates of adverse events were similar between groups, there was a noticeable rate of renal dysfunction in the aprotinin group, especially in patients with preexisting renal dysfunction.\textsuperscript{30} Allogeneic blood transfusion requirements were similar for both groups.\textsuperscript{30}

The US Food and Drug Administration (FDA) issued an alert in relation to the recently published reports of serious renal and cardiovascular toxic effects following aprotinin administration to patients undergoing CABG surgery.\textsuperscript{30} On September 27, 2006, Bayer Pharmaceuticals told the Food and Drug Administration that it had conducted an additional safety study of aprotinin. The preliminary findings from this new observational study of patients from a hospital database showed that use of aprotinin may increase the chance of death, serious kidney damage, congestive heart failure, and stroke. The worldwide study funded by Bayer, the maker of aprotinin, supported the data from the 2 previous observational studies.\textsuperscript{31} When using aprotinin, providers should carefully monitor the occurrence of toxic effects, in particular focusing on the kidneys, heart, and brain.\textsuperscript{30} Aprotinin should be used only when blood conservation clearly outweighs the potential side effects.\textsuperscript{30} There are ongoing studies evaluating the risks and benefits of aprotinin, and additional research is needed to determine its future use in antifibrinolytic therapy.

Conclusion
There are 2 main pharmacologic options for antifibrinolytic therapy for patients undergoing CPB. Lysine analogues and serine protease inhibitors have been shown to decrease the allogeneic blood transfusion requirements that are customary with extracorporeal circulation. Anesthetists need to understand the pharmacokinetics and pharmacodynamics of each class of drug. Despite the blood-salvaging benefit of these drugs, they come with known risks. As new information is revealed about these classes of drugs, anesthesia providers should be aware of the risks associated with lysine analogues and serine protease inhibitors.

As of November 5, 2007, Bayer Pharmaceuticals has suspended the marketing of aprotinin due to patient safety concerns. Initial results from a Canadian study suggest that patients administered aprotinin have a greater risk of death than patients taking other antifibrinolytic drugs. Sales of aprotinin have been suspended until the FDA can conduct further studies into the risks and benefits of the drug. The FDA and Bayer are working together to phase aprotinin out of the workplace and prevent potential shortages of other antifibrinolytics.\textsuperscript{33,34}

REFERENCES

12. Brown R, Thiawate B, Mongan P. Tranexamic acid is effective in decreasing postoperative bleeding and transfusion in primary coro-


**AUTHORS**

Jason Trudell, CRNA, MSN, is a nurse anesthetist for Anesthesia Group of Onodaga, PC, Syracuse, New York. Email: jasontrudell58@hotmail.com.

Nicholas McMurdy, CRNA, MSN, is a nurse anesthetist at Fairfax Anesthesia Associates, Inc, Fairfax, Virginia.

* The authors were students at the University of Pittsburgh School of Nursing Nurse Anesthesia Program, Pittsburgh, Pennsylvania, when this article was written.