

Aprotinin Use in Adult Cardiac Surgery: A Recommendation Statement from the University of Pennsylvania Health System Center for Evidence-based Practice

***Note: This guideline was originally released on September 19, 2006. An FDA Statement regarding new aprotinin data was released on September 29, 2006, and was attached to this guideline on October 2, 2006. The FDA is reviewing the new aprotinin data at this time, and our original guideline will be modified as needed once that information becomes available. Please review the FDA statement before consulting the guideline.**

University of Pennsylvania Health System Aprotinin Task Force

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FDA Statement (September 29, 2006)

Since January, 2006, the Food and Drug Administration (FDA) has been conducting a safety review of Trasylol (aprotinin injection). The review was triggered by the results of two published research studies: one that reported an increase in the chance of kidney failure, heart attack and stroke in patients treated with Trasylol compared to those treated with other similar drugs, and the other that reported an increase in kidney dysfunction compared to another drug. On September 21, 2006, FDA held a public meeting of the Cardiovascular and Renal Drugs Advisory Committee to discuss the safety and overall risk-benefit profile for Trasylol. At that meeting, the committee discussed the findings from the two published observational studies, the Bayer worldwide safety review, and the FDA review of its own post-marketing database.

On September 27, 2006, Bayer Pharmaceuticals told FDA that it had conducted an additional safety study of Trasylol. The preliminary findings from this new observational study of patients from a hospital database reported that use of Trasylol may increase the chance for death, serious kidney damage, congestive heart failure and strokes. FDA was not aware of these new data when it held the September 21, 2006, Advisory Committee meeting on Trasylol safety. FDA is actively evaluating these new data and their implications for appropriate use of the drug.

While FDA conducts its evaluation of this new safety study, we recommend the following to healthcare providers:

- * Physicians who use Trasylol should carefully monitor patients for the occurrence of toxicity, particularly to the kidneys, heart, or brain, and promptly report observed adverse event information to Bayer Pharmaceuticals, the drug manufacturer, or to the FDA MedWatch program, by phone (1-800-FDA-1088), by fax (1-800-FDA-0178), or by the Internet at <http://www.fda.gov/medwatch/index.html>.

- * Physicians should consider limiting Trasylol use to those situations where the clinical benefit of reduced blood loss is essential to medical management of the patient and outweighs the potential risks.

These recommendations are similar to those provided in a February 8, 2006, FDA Public Health Advisory and information sheets for health care professionals and patients which were based on the published studies mentioned above.

See <http://www.fda.gov/cder/drug/infopage/aprotinin/default.htm>

Trasylol works to slow or prevent bleeding, and is used to reduce blood loss and the need for blood transfusion during some types of heart surgeries. Trasylol is made from the lung tissue of cattle.

In the published studies and the recently supplied Bayer study, patients were not assigned at random to receive various treatments, but rather had their treatment chosen by their physician as part of their standard medical care. Consequently, in these safety studies, patients receiving Trasylol may have had a higher chance for serious complications to begin with as compared to patients receiving no treatment or treatment with another drug intended to decrease bleeding.

This possibility complicates the assessment of whether the available studies show that Trasyolol treatment, rather than other factors, increased the chance for serious kidney or heart complications.

The new study was done for Bayer by a contract research organization. Existing hospital data from 67,000 records of patients undergoing coronary artery bypass graft surgery were examined. 30,000 of the patients were treated with Trasyolol and 37,000 were treated with alternate products. Using complex epidemiological and statistical methods, the report suggested that patients receiving Trasyolol were at increased risk for death, kidney failure, congestive heart failure and stroke.

Healthcare providers and patients are encouraged to report adverse event information to FDA via the MedWatch program by phone (1-800-FDA-1088), by fax (1-800-FDA-0178), or by the Internet at <http://www.fda.gov/medwatch/index.html>.

Recommendations (September 19, 2006)*

1. We recommend that aprotinin remain on drug formulary.
2. As the evidence does not demonstrate a significant association between aprotinin use and decreased mortality, we recommend that aprotinin use be judicious, not routine.
3. We support the targeted use of aprotinin in adult cardiac surgery patients considered at high risk for intra-operative or post-operative bleeding, and coronary artery bypass graft surgery patients considered at high risk for cerebrovascular accidents.
4. We discourage the use of aprotinin in patients considered at high risk for renal dysfunction.
5. Although less high quality efficacy and safety data are available for pharmacologic alternatives to aprotinin, we support the targeted use of aminocaproic acid as a lower priced yet efficacious alternative to aprotinin in patients considered at high risk for intra-operative bleeding.

*This recommendation is based on high quality evidence and an assessment of the important trade-offs between the potential benefits and harms of aprotinin use, and is a guideline that should inform, but not replace, expert clinical judgment.

Introduction

The University of Pennsylvania Health System Center for Evidence-based Practice convened the Aprotinin Task Force in April 2006 in response to concerns about the safety of aprotinin use in adult cardiac surgery. These concerns were prompted by the Mangano and Karkouti studies published in the New England Journal of Medicine and Transfusion, respectively, and the subsequent Public Health Advisory issued by the US Food and Drug Administration.¹⁻³ The purpose of the Task Force was to develop a guideline for the use of aprotinin by cardiac anesthesiologists and surgeons in adult cardiac surgery.

Methods

The guideline was developed based on methods previously described by the GRADE Working Group.⁴ In summary, an initial meeting was held to define the patients, interventions, comparators and outcomes of concern. Physicians from cardiothoracic surgery, cardiac anesthesiology, nephrology and hematology from the Hospital of the University of Pennsylvania, Penn Presbyterian Medical Center, and Pennsylvania Hospital were invited to attend, and five anesthesiologists and one hematologist joined the Task Force, along with the Chief Medical Officer (CMO) of the University of Pennsylvania Health System (UPHS) and the Director and Co-Director of the Center for Evidence-based Practice (CEP). Voting members of the Task Force were free of financial conflicts of interest. Two of the nine members abstained from voting secondary to potential financial conflicts of interest, but fully participated in the Task Force discussions.

The Task Force agreed to perform a systematic review of the association of aprotinin and its pharmacologic alternatives epsilon-aminocaproic acid (ACA) and tranexamic acid (TXA) with the outcomes of transfusion, reoperation for bleeding, renal dysfunction, mortality, myocardial infarction, cerebrovascular accident, cognitive dysfunction, thrombosis, graft closure, fatal thrombosis, lung injury, hypersensitivity reaction, and cost. The systematic review was designed to identify "high quality evidence" as defined by GRADE for the exposures and outcomes listed. As a result, we initially identified systematic reviews (SRs), and then supplemented those reviews with randomized controlled trials (RCTs) published after the most recent SR for a given outcome. Our search of PubMed and the Cochrane Database of Systematic Reviews using the MeSH terms "aprotinin", "aminocaproic acids" and "tranexamic acid" ultimately identified seventy-nine studies that we used in our review. Following the systematic review, meta-analyses were conducted by CEP when appropriate, and the results were reviewed with Task Force members. Input was also received from Bayer (the manufacturer of aprotinin) as well as an author of the Society of Thoracic Surgeons most recent guideline addressing aprotinin use. This guideline was developed through consensus, and underwent review by the CMO of each hospital in the UPHS.

"High quality" data or evidence refers to data or evidence extracted from randomized controlled trials (RCTs) or systematic reviews of RCTs. By definition, further research is very unlikely to change our confidence in the estimates of effect reported by "high quality" sources of data.⁴ "Coronary artery bypass graft surgeries" (CABGs) include primary, redo, and complex CABGs unless otherwise specified. The term "significant" refers to associations that are clinically and statistically significant.

The current state of the evidence

The majority of the data on hemostatic agents available for this review was high quality data examining aprotinin use in cardiac surgery. High quality data examining the association between tranexamic acid (TXA) or aminocaproic acid (ACA) and bleeding in cardiac surgery was less common, with ACA being the least commonly studied. High quality data examining the potential harms of aprotinin was common, but high quality data examining the potential harms of TXA and ACA were rare, with ACA being the least commonly studied. Specifically, high quality studies examining the association between TXA or ACA and mortality, reoperations for bleeding, myocardial infarctions, cerebrovascular accidents and renal dysfunction were rare, and high quality studies examining the association between ACA and renal dysfunction are not currently available. Moreover, high quality data comparing aprotinin to TXA or ACA only exists for the outcome of transfusion. Lastly, data comparing the incremental cost-effectiveness of aprotinin to TXA or ACA is not currently available.

Benefits and risks of aprotinin use

The benefits of aprotinin when compared to placebo include a significant reduction in blood transfusions in all surgeries (approximately 45% relative risk reduction or 20% absolute risk reduction, from approximately 65% with placebo to 45% with aprotinin), a significant reduction in reoperations for bleeding in all surgeries (approximately 60% relative risk reduction or 3.5% absolute risk reduction, from approximately 5% with placebo to 1.5% with aprotinin), a

significant reduction in cerebrovascular accidents in coronary artery bypass graft surgeries (approximately 50% relative risk reduction or 1% absolute risk reduction, from approximately 2% with placebo to 1% with aprotinin), and a significant reduction in cognitive dysfunction post-cardiac surgery (approximately 40% relative risk reduction or 35% absolute risk reduction, from approximately 95% with placebo to 60% with aprotinin), although this benefit did not remain significant at 6 weeks of follow-up.

The risks of aprotinin when compared with placebo include a significant increase in renal dysfunction (approximately 50% relative risk increase or 4.5% absolute risk increase, from approximately 8.5% with placebo to 13% with aprotinin). Here, renal dysfunction is defined as a post-operative creatinine increase ≥ 0.5 mg/dL above baseline. Aprotinin use was not associated with renal failure, defined as a post-operative creatinine increase ≥ 2 mg/dL above baseline or hemodialysis.

Aprotinin use was not associated with increased or decreased mortality, myocardial infarction, pulmonary artery or deep vein thromboses, or graft closure.

Evidence review of aprotinin use in the context of pharmacologic alternatives, organized by outcome

Transfusion - The evidence demonstrates that full dose aprotinin when compared with placebo significantly reduced blood transfusions in all surgeries (approximately 45% relative risk reduction or 20% absolute risk reduction, from approximately 65% with placebo to 45% with aprotinin) and off-pump cardiac surgeries (approximately 75% relative risk reduction or 15% absolute risk reduction, from approximately 25% with placebo to 10% with aprotinin), as well as in patients receiving clopidogrel less than 5 days before cardiac surgeries (approximately 40% relative risk reduction or 25% absolute risk reduction, from approximately 80% with placebo to 55% with aprotinin). Tranexamic acid (TXA) also significantly reduced blood transfusions in our systematic review of all surgeries (approximately 40% relative risk reduction or 20% absolute risk reduction, from approximately 50% with placebo to 30% with TXA), but did not significantly reduce blood transfusions in our systematic review of off-pump cardiac surgeries. Aminocaproic acid (ACA) reduced blood transfusions in a systematic review of all surgeries (approximately 45% relative risk reduction or 20% absolute risk reduction, from approximately 50% with placebo to 30% with ACA), but did not significantly reduce blood transfusions in a randomized controlled trial (RCT) of primary coronary artery bypass graft surgeries. There is no evidence to suggest that one hemostatic agent is superior to another in head-to-head comparisons.

Reoperation for bleeding - The evidence demonstrates that full dose aprotinin when compared with placebo significantly reduces reoperations for bleeding in all surgeries (approximately 60% relative risk reduction or 3.5% absolute risk reduction, from approximately 5% with placebo to 1.5% with aprotinin). TXA and ACA when compared with placebo were not significantly associated with increased or decreased reoperations for bleeding, although the current data may be inadequate to detect significant associations.

Cerebrovascular accidents (CVAs) - The evidence demonstrates that full dose aprotinin when compared with placebo significantly reduces the risk of CVAs in a systematic review of coronary artery bypass graft surgeries (CABGs) (approximately 50% relative risk reduction or 1% absolute risk reduction, from approximately 2% with placebo to 1% with aprotinin), but did not significantly reduce CVAs in a systematic review of all surgeries. TXA and ACA were not significantly associated with increased or decreased CVAs in a systematic review of all surgeries, although the current data may be inadequate to detect significant associations.

Cognitive dysfunction - The evidence demonstrates that full dose aprotinin when compared with placebo significantly reduces cognitive dysfunction post-cardiac surgery (approximately 40% relative risk reduction or 35% absolute risk reduction, from approximately 95% with placebo to 60% with aprotinin), but this benefit did not remain significant at 6 weeks of follow-up. Data from RCTs examining the association of ACA or TXA with cognitive dysfunction are not currently available.

Renal dysfunction/failure - The evidence demonstrates that full dose aprotinin when compared with placebo significantly increases the risk of renal dysfunction (approximately 50% relative risk increase or 4.5% absolute risk increase, from approximately 8.5% with placebo to 13% with aprotinin). Here, renal dysfunction is defined as a post-operative creatinine increase ≥ 0.5 mg/dL above baseline. Aprotinin use was not associated with renal failure, defined as a post-operative creatinine increase ≥ 2 mg/dL above baseline or hemodialysis. TXA use was not significantly associated with renal dysfunction or failure in a systematic review of all surgeries, although the current data may be inadequate to detect significant associations. Data from RCTs examining the association of ACA with renal dysfunction or failure are not currently available.

Mortality, Myocardial infarction (MI), Thromboses, Graft Closure - The evidence demonstrates that full dose aprotinin when compared with placebo is not significantly associated with increased or decreased risks of mortality or MIs in systematic reviews of CABGs and all surgeries, deep vein or pulmonary thromboses in a systematic review of all surgeries, or graft closure in a systematic review of CABGs, although the current data may be inadequate to detect significant associations. TXA or ACA was not associated with mortality, MIs, or deep vein or pulmonary thromboses in systematic reviews of all surgeries, although the current data may be inadequate to detect significant associations. Data from RCTs examining the association of ACA or TXA with graft closure are not currently available.

Hypersensitivity reactions - Case reports have documented the occurrence of hypersensitivity reactions with the use of aprotinin in cardiac surgery. The incidence of hypersensitivity reactions to aprotinin is approximately 2.5% in those who are reexposed. Documentation of hypersensitivity reactions with ACA or TXA is not currently available.

Fatal thromboses - Case reports have documented the occurrence of fatal thromboses with the use of aprotinin and ACA in cardiac surgery. Documentation of fatal thromboses with TXA is not currently available. Data from RCTs examining the association of aprotinin or ACA with fatal thromboses are not currently available.

Cost - The cost of aprotinin in a full dose 4 hour procedure at the Hospital of the University of Pennsylvania (HUP) is approximately \$1,465.56, and the cost of ACA in a maximum dose 4 hour procedure at HUP is approximately \$3.71. These costs are the direct pharmacy costs for the drugs, and do not consider short and long term cost savings or spending that may result from drug use, such as savings resulting from decreased blood transfusions, reoperations for bleeding, or CVAs, or spending resulting from increased renal dysfunction. Cost identification analyses comparing costs of aprotinin to those of ACA and placebo suggest that ACA and placebo use may offer greater cost savings when drug, blood product, and operating room time costs are considered in the 24 hour post-operative time period, and that aprotinin may offer cost savings over placebo and may approximate the cost of ACA in the time period from post-operation to discharge. The reported differences in costs between aprotinin, ACA, TXA and placebo use in this context are on the scale of hundreds of dollars per patient. Comprehensive cost-effectiveness analyses comparing aprotinin, ACA and TXA to placebo are not currently available.

Examples of patients in whom aprotinin or aminocaproic acid use may or may not be indicated

A complex cardiac surgery patient actively on clopidogrel (considered a high risk for intra-operative or post-operative bleeding) with a serum creatinine in the normal range may be a reasonable candidate for aprotinin use.

A complex coronary artery bypass graft surgery (CABG) patient with a previous cerebrovascular accident (CVA) who is considered a high risk for intra-operative or post-operative bleeding or another CVA may be a reasonable candidate for aprotinin use.

A complex cardiac surgery patient with advanced stage chronic kidney disease who is considered a high risk for intra-operative bleeding may be a reasonable candidate for aminocaproic acid (ACA) use.

A complex cardiac surgery patient with a serum creatinine in the normal range who is considered a high risk for intra-operative bleeding and who has been exposed to aprotinin in the last 6 months may be a reasonable candidate for ACA use.

A primary CABG patient with a serum creatinine in the normal range who is not considered a high risk for intra-operative or post-operative bleeding may be a reasonable candidate for no hemostatic agent use.

A primary CABG patient with a serum creatinine above the normal range who is not considered a high risk for intra-operative or post-operative bleeding may be a reasonable candidate for no hemostatic agent use.

Suggestions for future research

Given the current state of the evidence, we suggest further research into the potential harms of aminocaproic acid (ACA) and tranexamic acid (TXA), and into the potential benefits and harms of ACA and TXA as compared to aprotinin and placebo. An essential piece of such studies should be cost-effectiveness analyses comparing the incremental cost-effectiveness of these three hemostatic agents.

All of the members of the Aprotinin Task Force contributed to the development of this guideline, participated in at least two of the four meetings, and had the opportunity to review and comment on drafts of this guideline. CAU and KW of the University of Pennsylvania Health System (UPHS) Center for Evidence-based Practice led the process. KW performed the systematic review. CAU prepared the evidence tables, performed the meta-analyses and wrote the initial draft of the guideline.

We are indebted to David Fisman, MD, MPH for his assistance in using STATA to perform meta-analyses; to Adam Lessler for his review of the cost data and preparation of the cost table; to Michael Mercincavage for his review of hemostatic agent use at the UPHS; and to Alicia Salvatore for her coordination of the Task Force meetings.

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BAK and WJV report having received honoraria from Bayer, the manufacturer of aprotinin, and abstained from voting on the final guideline. No other potential financial conflicts of interest relevant to this guideline were reported.

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