April 2006
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28th Annual Meeting & Workshops

April 29 - May 3, 2006
San Diego, CA

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Society of Cardiovascular Anesthesiologists

P.O. Box 11086 • Richmond, Virginia 23230-1086

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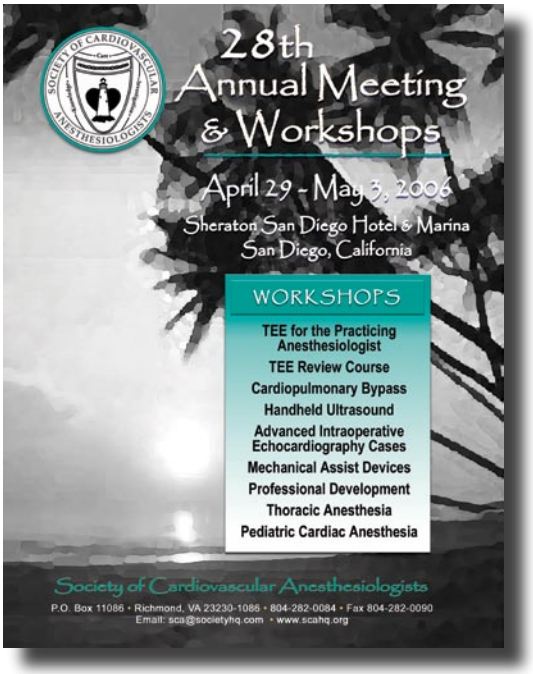

10th International Congress of Cardiothoracic and Vascular Anesthesia

Dear colleagues and friends:

It is our pleasure to invite you to participate in the 10th International Congress of Cardiothoracic and Vascular Anesthesia, to be held in Prague, Czech Republic, August 27-30, 2006.

The meeting will focus on cardiothoracic and vascular anesthesia, as well as perioperative and intensive care. New developments in clinical care, as well as new devices and technologies will be discussed by a faculty of more than 80 speakers from around the world. The scientific program of the meeting will be from Monday, August 28th to mid-day on Wednesday, August 30, 2006. There will be two parallel sessions of invited speakers, poster sessions, thoracic and TEE workshops.

Posters are welcome and will be exhibited during the congress. The deadline for abstract submission is May 31, 2006. All participants will receive a book of poster abstracts and a book of proceedings, consisting of a summary of all presentations by invited speakers. The official language of the Congress will be English.

Prague, the capital of the Czech Republic, is a vibrant city with a history spanning more than 1,000 years. It is an important cultural, architectural and educational center. First time visitors to the city will want to see the Prague Castle, Charles Bridge, the old Town Hall, the Jewish synagogues, the Brevnov Monastery and other superb baroque buildings.

Many activities and sightseeing opportunities will be offered to the congress participants and their accompanying persons. The Gala Dinner will be hosted in the Zofin Palace on one of the islands of Vltava river, offering a magnificent view of the Prague Castle and the ancient city skyline.

An important feature of this symposium is the unique opportunity to meet and interact with anesthesiologists from around the world.

We look forward to seeing you in Prague!

With best regards,

George Silvay, MD, PhD
New York, NY

Karel Cvachovec, MD
Prague, Czech Republic

James G.Ramsay, MD
Atlanta, GA

For more information:http://www.iccva2006.cz

SOCIETY OF CARDIOVASCULAR ANESTHESIOLOGISTS
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NEWSLETTER

P.O. Box 11086 • Richmond, VA 23230-1086 • (804)282-0084 • sca@societyhq.com April 2006

President's Message

Newsworthy Issues for SCA Members

Adult Cardiothoracic Anesthesiology as a Subspecialty

The extraordinary work over a number of years by many leaders in our society has culminated in the creation of a fourth subspecialty of anesthesiology. Our task force led by Alan Schwartz convinced the Anesthesiology Residency Review Committee (RRC) that cardiothoracic anesthesiology should join the other three accredited subspecialties of pain medicine, critical care medicine, and pediatric anesthesiology. The RRC collaborated with SCA task force members to refine the original draft program requirements, then at the February 14, 2006 meeting of the Accreditation Council for Graduate Medical Education (ACGME), the ACGME's Committee on Program Requirements reviewed the proposal and unanimously endorsed the RRC's recommendation. The new program requirements can be found at the ACGME's web site, http://www.acgme.org/acWebsite/RRC_040/040_printdex.asp.

The Anesthesiology RRC is currently developing the Program Information Form for the newly accredited fellowship. As soon as it is finalized this spring, the RRC will notify all department chairs and core program directors as well as the SCA leadership that the form is available. Programs may submit requests for accreditation of cardiothoracic fellowships any time thereafter.

Upcoming Meetings

This issue of the newsletter contains an invitation to SCA members from Karel Cvachovec, George Silvay, and me to the 10th International Congress of Cardiothoracic and Vascular Anesthesia to be held in Prague, Czech Republic August 27-30 this year. A number of SCA members have worked with Dr. Cvachovec and his organizing committee to put together an exciting program in this historic city. I encourage all of you to go to the SCA website and click on the meeting (under "Events"); the preliminary program will appear there very soon, and includes many well known speakers from North America. This is a great opportunity to meet anesthesiologists from all over the world, benefit from an excellent educational offering, and see this interesting and beautiful part of Europe. August is only five months away!

While at the website, scroll up from the International Congress and click on our Annual Meeting announcement to see the details for our meeting in San Diego, April 29 – May 3. This is only a few weeks away, and the deadline for reduced fee registration is April 20. Linda Shore-Lesserson and the Scientific Program Committee have put together an outstanding meeting, San Diego is a beautiful and interesting city and the Sheraton San Diego Hotel & Marina is conveniently situated near the airport and on the harbor. Plan to attend!

Certification in Perioperative Transesophageal Echocardiography (TEE)

Many of you are trying to understand the process for obtaining certification in Perioperative TEE. Although there is nothing "new" on this front, a brief recap is appropriate. The SCA and American Society of Echocardiography (ASE) collaborated to create an independent body called the National Board of Echocardiography (NBE). This independent body has no relationship to the American College of Graduate Medical Education (ACGME) and was created to develop standards for expertise in echocardiography and an ongoing examination and certification process. The NBE developed the requirements for certification in perioperative TEE including the training or experience requirements, and the examination of special competence (PTEeXAM). The website for the NBE is www.echoboards.org.

Any physician may apply to NBE and take the exam; passing the exam allows you to say you have achieved "testamur" status (passed the exam without applying for board certification). To obtain "board certification," in addition to passing the exam you must be licensed to practice medicine and have board certification by one of several boards (see details at the website), AND you must fulfill either training or experience criteria.

James G. Ramsay, MD
President, 2005-2007

Training criteria are "…a minimum of 12 months of clinical fellowship training dedicated to the perioperative care of surgical patients with cardiovascular disease." This cannot include core residency training, and must be obtained at an institution with an affiliation with an accredited anesthesiology residency program. The intent here is for the candidate to do a fellowship in cardiothoracic anesthesiology. This training must include "… study of 300 complete perioperative TEE examinations under appropriate supervision." Of these examinations 150 must be personally performed by the candidate. See the NBE website for the exact wording of these requirements and for documentation requirements.

Most SCA members are already in practice, and the training "pathway" to certification is not a realistic option. Until June 30, 2008, the "Practice Experience Pathway" is available to those of us in this situation. This pathway requires the applicant to perform at least 300 TEE exams within four years immediately preceding the application, with no less than 50 exams in any of those years. In addition, the applicant must have obtained at least 50 hours of AMA category 1 continuing medical education related to echocardiography during these four years. See the NBE website for exact wording and for documentation requirements. June 30, 2008 is only two and a half years away!

Continued on page 5

NEWSLETTER

SCA statement regarding the use of antifibrinolytic drugs

The following statement was composed by a task force of the Board of Directors, and endorsed by the entire Board.

Conflict of Interest Disclosure: Bayer, Inc., the maker of aprotinin ("Trasylol"), has been a supporter of SCA education efforts and research programs.

Bleeding is one of the primary challenges in caring for cardiac surgical patients. Clinical studies have documented the hazards of uncontrolled bleeding (e.g. severe hemodynamic instability, or emergent return to surgery for reopening of the chest with an increased risk of sternal and mediastinal infection) and transfusion of blood products (e.g. infectious complications of blood products and transfusion-related acute lung injury). For over a decade, anesthesiologists and surgeons have used antifibrinolytic agents for prophylaxis against the adverse effects of cardiopulmonary bypass on the coagulation system, particularly in patients undergoing repeat or complex cardiac surgery. These agents include the lysine analogs (epsilon aminocaproic acid and tranexemic acid) and the serine protease inhibitor, aprotinin. Many studies have been reported in the literature, including randomized controlled trials, observational studies, and several meta-analyses. This body of literature documents some degree of efficacy of each of these agents. Despite isolated reports of adverse safety events including thrombosis of coronary arterial grafts or other vessels and transient or even permanent deterioration in renal function, prior studies have not identified consistent statistically significant associations of these events with any of the currently used antifibrinolytics.

It is in this context that a widely publicized study by Mangano et al, on behalf of the Multicenter Study of Perioperative Ischemia (McSPI) Research Group, recently appeared in the *New England Journal of Medicine*. The published conclusions, that aprotinin use is associated with renal failure, myocardial infarction or heart failure, and stroke, is the subject of intense discussion among cardiovascular anesthesiologists and surgeons. This observational study of 4,374 patients at 69 centers in 17 countries is of particular interest to members of the Society of Cardiovascular Anesthesiologists (SCA), an international organization of over 5,000 anesthesiologists having a mission to promote excellence in patient care and safety as well as to promote and fund research in cardiovascular and thoracic anesthesiology. Many of our members collected data for the McSPI publications and have independently or collaboratively with McSPI published important clinical studies of perioperative transfusion related topics.

The strength of this observational cohort study is its large number of patients. However, the non-randomized design makes selection bias a potentially significant factor in the choice of an antifibrinolytic agent. A variety of statistical techniques, including propensity analysis, were used in an attempt to eliminate confounding factors and biases. Although the article states that multiple covariates were considered, these variables were not explicitly presented either in the text or in supplementary material (eg. internet supplement) and thus, it is unclear if the "correction" was sufficient to overcome the possibility that aprotinin may have been used in the sickest patients. Furthermore, no data were presented regarding variations in practices and outcomes among different centers and countries, factors that may require additional complex statistical adjustments. Current practice in many institutions reserves the use of aprotinin for complex valvular surgery, thoracic aortic surgery, reoperations, and patients with a bleeding diathesis, and it is unclear whether all of these were adequately considered in Mangano's definition of "complex surgery".

For these reasons, we believe the findings of Mangano's report may not be generalized to all patients, and the suggestion to immediately curtail all use of aprotinin is premature. We await further disclosure regarding the analysis of the data used for this study, an FDA analysis of previous trials, as well as additional clinical investigations to fully evaluate the issues raised by this study. Members of SCA continue to perform clinical research in this area. At our upcoming Annual Meeting in San Diego, important scientific information will be presented regarding the largest randomized clinical trial performed to date on this topic, which compares aprotinin to the lysine analogs in patients undergoing high risk cardiac surgery. Although this study is ongoing and all parties are blinded to the results, the trial's Data Safety and Monitoring Board has recommended that the trial continue after an interim analysis of 1,000 patients.

Until further data are made available, or until formal recommendations are issued by the Food and Drug Administration, the SCA suggests its members continue to carefully weigh the potential risks of aprotinin against the risks of bleeding associated with a planned cardiac operation. Consideration should be given to the individual patient's preexisting co-morbid conditions and factors impacting the coagulation system (e.g., preoperative administration of anti-platelet or anti-coagulant agents), and to the potential risks and benefits of the use of a lysine analogue. Anesthesiologists and surgeons share the responsibility for the decision to use one of these drugs. The SCA recognizes that individual patients may choose to address this issue with their surgeon or anesthesiologist and that such discussions should factor into decision making. As a leading international society dedicated to enhancing patient safety and minimizing adverse outcomes after cardiac surgery, we plan to continue to support scientific debate, educational efforts, funding of research grants, and collaborative efforts with other specialties to better clarify the risks and benefits of antifibrinolytic agents.

Literature Reviews

The risk associated with aprotinin in cardiac surgery.

Multicenter Study of Perioperative Ischemia Research Group and the Ischemia Research and Education Foundation. Mangano DT, Tudor IC, Dietzel C, *N Engl J Med* 354:353-365, 2006.

Mark A. Chaney, MD
University of Chicago

Bruce D. Spiess, MD, FAHA
Virginia Commonwealth University

Abstract Excerpt: The risk:benefit ratio of antifibrinolytic therapy in patients undergoing cardiac surgery remains somewhat controversial. In this observational study involving 4,374 patients undergoing revascularization, the authors prospectively assessed three agents (aprotinin [1,295 patients], aminocaproic acid [883 patients], and tranexamic acid [822 patients]) as compared with no agent (1,374 patients) with regard to serious outcomes by propensity and multivariable methods. In propensity-adjusted, multivariable logistic regression, use of aprotinin was associated with a doubling in the risk of renal failure requiring dialysis among patients undergoing complex coronary-artery surgery or primary surgery. Similarly, use of aprotinin in the latter group was associated with a 55 percent increase in the risk of myocardial infarction or heart failure and a 181 percent increase in the risk of stroke or encephalopathy. Neither aminocaproic acid nor tranexamic acid was associated with an increased risk of renal, cardiac, or cerebral events. Adjustment according to propensity score for the use of any one of the three agents as compared with no agent yielded nearly identical findings. All the agents reduced blood loss. The authors conclude that the association between aprotinin and serious end-organ damage indicates that continued use is not prudent and, in contrast, the less expensive generic medications aminocaproic acid and tranexamic acid are safe alternatives.

Comments (Mark A. Chaney, MD)

By the time this Newsletter is published, most (if not all) cardiac anesthesiologists will have at least heard of this manuscript. I would even venture to say that most of our readers by now have examined this clinical investigation in great detail. Since its publication in early February, much debate has occurred regarding interpretation of the data and how these findings should alter (if at all) clinical management. A large proportion of this debate has been colorfully impassioned (witness Bruce Spiess's Comments that follow). Furthermore, the very next day following publication, advertisements appeared on the Internet from lawyers soliciting fodder for potential litigation regarding the use of aprotinin. Thus, whether one agrees or disagrees with this study's conclusions, all cardiac anesthesiologists and cardiac surgeons need to re-evaluate their own personal philosophies regarding aprotinin use.

The strengths of this study include prospective design, a relatively large number of patients and data points, prespecified outcome events, and non-sponsor-supported status. The weaknesses of this study include observational design (lack of standardization regarding clinical decisions), an ill-defined patient population, and somewhat vague presentation of outcome events. Depending on who you talk to, the intense statistical analysis may be a strength or weakness.

What is concerning to me is the potential link between aprotinin use and generalized ischemic injury (brain, heart, kidney), along with an apparent dose-response relationship regarding these effects. What also struck me was the really clinically irrelevant (albeit statistically significant) effect all agents had on postoperative chest tube output (agents decreased mean output only 74 ml to 151 ml over the first 24 hours, when compared to controls).

I trained in the days prior to aprotinin availability. There is no doubt in my mind that aprotinin is a profound hemostatic agent that reduces blood loss associated with cardiac surgery. However, clot is a double-edged sword. Clots may be beneficial (reducing bleeding) and clot may be detrimental (causing ischemia). I have always wondered about potential systemic detrimental effects of microemboli with the use of aprotinin. Mangano's study perhaps reveals that this is a real clinical problem.

As with most "landmark" clinical investigations, more questions are raised than answered. At the present time, the potential risks and benefits of all three agents need to be thoughtfully reconsidered. Individual patient characteristics (age, medications, medical history, surgical history, proposed surgery, etc.) also should profoundly influence whether or not agents are used to decrease bleeding. During this time of increased scrutiny (from patients and no doubt lawyers), it is extremely important that the cardiac anesthesiologist and cardiac surgeon communicate effectively to formulate a plan (specific therapy or no therapy) that is best for each individual patient.

Comments (Bruce D. Spiess, MD, FAHA)

This article has created dramatic discussions within cardiac anesthesia. Re-examination of medical practice in light of any new scientific development is appropriate. However, scientific examination needs to be in depth, unbiased, based upon prior knowledge, and not fraught with emotion and/or panic. One single study in a literature containing over 1,500 articles does not by itself trump all others. Only prospective randomized trials prove cause and effect. We should not hastily abandon the results of well over 45 prospective randomized trials regarding aprotinin encompassing thousands of patients in which there was no connection between the drug and renal dysfunction.

This study acknowledges that the patients who received aprotinin were considerably more ill and at higher risk for bad outcomes. Notably, however, some very important preoperative factors are missing, such as data on medications (heparin, aminoglycosides). This commentator can think of another 30 risk factors that should have been included in such a preoperative risk analysis. The article does note that 97 different characteristics were originally assessed by univariate testing, but they are not listed. Perhaps the most scientifically appropriate way of approaching this risk assessment would have been to build from the already existing extensive literature on renal failure and cardiac surgery. In one such article (*Ann Thorac Surg* 80: 2148-2153, 2005), almost 3,000 patients at high risk for renal failure after heart surgery were analyzed and risks categorized. Three factors were found most important: diabetes, peripheral vascular disease, and decreased creatinine clearance. Creatinine clearance is far superior to a simplistic creatinine level. In Mangano's article, patients who received aprotinin had twice the amount of insulin dependent diabetes as compared to controls. The other two factors, creatinine clearance and peripheral vascular disease, were not entered into data analy-

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President's Message Continued from page 3

Antifibrinolytic Agents in Cardiac Surgery

Probably the most contentious issue in our specialty today is the conclusion by Dennis Mangano, in an article published in the *New England Journal of Medicine*, that continued use of aprotinin ("Trasylol") in cardiac surgery patients is "imprudent" due to significant risk of adverse events, especially renal failure. This conclusion was reached after analysis of data from 4,374 patients in an observational, multi-national database. In this issue of the Newsletter there is an SCA statement regarding the use of antifibrinolytic drugs in cardiac surgery, composed by a task force of the Board of Directors and approved by the entire Board. I encourage you to read this statement, and also to go the FDA website for a recently issued statement http://www.fda.gov/cder/drug/advisory/aprotinin.htm. The subject of antifibrinolytic drugs will be discussed at several sessions at our Annual Meeting at the end of April.

sis. The authors should have all the necessary data (age, weight, sex, and creatinine) for a calculation of creatinine clearance at baseline in order to segment patients within the aprotinin and other treatment groups for future development of renal failure. It is important to note that the *Ann Thorac Surg* article did not find any relationship between aprotinin (or any antifibrinolytic) and renal dysfunction.

Definitions of renal dysfunction in this study need to be clarified. In other clinical studies, not only is creatinine clearance followed, but delta creatinine as well. This study does follow a change in creatinine but time is not discussed. It is well known that aprotinin competes within the renal tubule for creatinine movement. In multiple prospective randomized trials it has been shown that creatinine can rise within 1-7 days after aprotinin yet this is transient. At 14 to 30 days, there is no difference. If this study queried for changes in creatinine from baseline up to day seven, values could be meaningless or could have skewed results for aprotinin. We don't know what was done because it is not outlined in the Methods. A combined renal event was assessed (not just increased creatinine, but dialysis as well). Such data should be presented separately. Was dialysis alone significant? Dialysis is what really matters, costs money, and creates suffering as well as increased death rate. This paper claims that dialysis was far more common in high risk patients who received aprotinin yet we need to know what was the patient's preoperative creatinine clearance. This article quotes literature regarding the effects of aprotinin upon rising creatinine. The studies cited were from the 1960's to the 1980's, a time prior to when the nature of the creatinine rise had been prospectively investigated. Indeed, only 10% of the entire references come from the last five years (an accepted time scale for currency with regards to scientific advance). These papers were also published prior to when aprotinin had undergone prospective randomized FDA trials. Furthermore, the article fails to quote a major article regarding hypothermic circulatory arrest and renal failure (*Circulation* 104: 276-281,2001). This study from Stanford showed that there was no relationship between aprotinin use and renal failure in 853 severely ill patients at very high risk for renal failure. What about dialysis, the ultimate renal failure? In this study, we have no data with respect to when dialysis was utilized. One might be tempted to conclude that any patient requiring dialysis had suffered significant renal injury. But if a cohort of severely ill patients existed within the database in which they already had a creatinine clearance of < 60 ml/min, a dramatic rise in dialysis and death should be expected. Only if those patients with aprotinin usage exceeded the expected published dialysis rate for their preoperative creatinine clearance cohort should one begin to investigate an independent association of aprotinin usage to dialysis dependence.

Therein lies the rub. The data as presented in this study simply is not detailed enough for the reader to understand the relative risks of patients who received aprotinin versus any other group. Data regarding time of CPB, blood transfusions, lowest HCT, ICU entry HCT, a wide number of other drugs (heparin, aminoglycosides), recent cardiac catheterization, and practice variations (national, regional) must all be reported.

Propensity analysis and multivariate logistic regressions are two statistical techniques employed when analyzing databased cohorts. Both of these techniques attempt to control for the potential effects of covariates or confounding factors. These statistical methods are only as good as the scientific thinking deciding which potential confounders are to be analyzed. A list of covariates analyzed by propensity analysis was not included in the paper. Therefore, we as readers cannot make the appropriate scientific decision about how the study was conducted. As a rough rule of thumb, an odds ratio of around two, or perhaps as high as three, can be due to a missed or unrecognized covariate. If an odds ratio is four or above, the likelihood of any relationship being cause and effect rises dramatically, but is still not proof. Odds ratios in this study for combined renal events fit well within that rule of thumb (a missed or unanalyzed covariate/s). Perhaps such an unnoticed covariate could actually be something not even recorded in the database. A perfect example that might have occurred in this investigation is heparin induced thrombocytopenia antibody formation. Patients with antibody formation have a 2-3 fold increased risk of death and other major thrombotic complications. Neither was such an antibody presence recorded in the database in question nor was a surrogate (heparin use, time in ICU preoperatively, platelet count, or delta platelet count) investigated. Suppose the patients who received aprotinin had a more frequent use of heparin preoperatively and therefore had a higher likelihood for heparin antibody formation. More severely ill patients would have been more likely to receive aprotinin. Once propensity testing was done, the results would show that aprotinin patients had more severe outcomes. Yet the heparin antibody may well have been the causative (though a covariate) agent. Thus, not only should all covariates tested be reported, readers should question whether the associations make sense. The propensity analysis showing that amicar had a lower death rate and a lower composite outcome event score as compared to aprotinin versus control fits with what we know. Amicar is utilized for the least ill patients. Any other conclusion with regards to the overall propensity scoring cannot be generated with the information presented in this paper. Full disclosure of all the raw data and how the propensity analysis was carried out should be presented to some unbiased third party (the U. S. FDA, for example).

This paper also makes sweeping and emotional claims regarding aprotinin usage. It claims that 11,050 patients would not require dialysis and that at least one billion dollars would be saved if aprotinin was not used. Such language is inflammatory, unscientific, and fully ungrounded. The call for a switch to amicar or tranexamic acid is not scientific. Neither drug is U.S. FDA indicated for any use during CPB. Neither drug has undergone randomized safety testing in large prospective blinded series in the setting of CPB. Indeed, data do exist that indicates amicar contributes to and increases the risk of renal failure during CPB. It certainly has in the past increased thrombotic risk with prostatic resection. The advocacy of a massive shift of therapy towards drugs with no safety testing and directly against the drug regulatory laws of the U.S. is unwise at best.

Renal failure occurs more frequently during CPB when patients have a low HCT. Furthermore, the use of transfusions to prevent or treat a low HCT further increases the risk of renal failure. There is no doubt that aprotinin dramatically reduces the need for transfusion. If the use of aprotinin is abandoned and patients receive more blood products, then it may be that the incidence of renal failure will rise. Also, risks of perioperative infection (particularly pneumonia), respiratory failure (transfusion-related acute lung injury), length of stay, and death all increase with more transfusion. No transfusion data are presented in this paper.

If the data from a study do not either fit the known biology or the results of prospective randomized trials, then as a scientist, one needs to examine them very carefully. The results could, of course, be correct and therefore represent a breakthrough in thinking. Unfortunately, this article neither fits what has been observed in previous prospective randomized trials or the known biology. Stroke, for instance, has been extensively accepted to be reduced by the use of aprotinin in randomized trials (cause and effect). This article does not show that effect (the patients receiving aprotinin were more ill at higher risk to begin with) but shows more stroke and encephalopathy in high risk patients.

So, what should the cardiac anesthesiologist conclude or do in light of this recent publication? This prospective databased association study should be digested into the overall 1,500 plus papers on cardiac surgery and aprotinin. Each member will have to read it carefully and in light of what data is present and what is missing ask him/herself whether he/she agrees or supports the conclusions. The FDA as well as others will review the data and perhaps the methods involved. That may take time but it is probably certain that some re-analysis will show whether the study is groundbreaking or flawed. As suggested earlier, in the interim, perhaps a large database could be followed examining any change in practice this one study causes and follow the outcomes of our patients. If this clinical investigation is incorrect and patients suffer increased transfusions, pneumonias, strokes, and death, what debt is owed to the public for such information? The lives of our patients are held in the balance.

Does the combination of aprotinin and angiotensin-converting enzyme inhibitor cause renal failure after cardiac surgery?

Kincaid EH, Ashburn DA, Hoyle JR, Reichert MG, Hammon JW, Kon ND. *Ann Thorac Surg*. 2005 Oct;80(4):1388-93.

Reviewer: Theodore A. Alston, MD, PhD
Assistant Professor
Harvard Medical School

Abstract: Cardiac surgery carries a low but dreaded risk of renal failure, and aprotinin is feared to increase the risk of that complication. There is conflicting evidence as to that potential effect of aprotinin. Kincaid et al retrospectively examined data collected over two years at Wake Forest. They find either aprotinin or else angiotensin-converting enzyme inhibitors (ACEIs) to be associated with postoperative renal insufficiency when used separately, although the statistical significance was low. However, the combination was associated with very significant nephrotoxicity.

"Hammersmith-dose" aprotinin was administered selectively to 420 of 1,209 adult patients felt to be at increased risk of bleeding during elective cardiac surgery requiring cardiopulmonary bypass. ACEI were continued up to surgery in 545 of the patients, with 195 patients receiving aprotinin and ACEI together. None of the patients had a past history of renal failure, and none exhibited preoperative serum creatinine levels of more than 1.5 mg/dL.

Within three days of the surgery, creatine levels increased to more than 2.0 mg/dL in 3.5% of the 1,209 patients. Hemodialysis was required by 57% of the high creatinine group, and the high-creatinine group suffered 48% mortality. The paper thus points out an ominous importance of a moderate increase in creatinine soon after cardiac surgery.

Patients with ACEIs continued up to surgery exhibited a 5.5% incidence of postoperative creatinine rise to more than 2.0 mg/dL. The aprotinin patients exhibited a 7.4% incidence, but, if the aprotinin was given with an ACEI, the incidence was 11.8%.

Comments: Aprotinin in higher-than-recommended doses was long known to carry nephrotoxicity. The drug is known to accumulate in proximal renal tubule cells and to potentially inhibit their function. However, renal impairment did not manifest in a statistically significant way during phase three studies leading to approval of aprotinin as a hemostatic aid to cardiac surgery. However, renal effects are implicated in this and other recent studies (for instance: The risk associated with aprotinin in cardiac surgery. Mangano DT, et al. *N Engl J Med*. 2006 Jan 26;354:353-65).

Kincaid et al find that renal danger of aprotinin may prove to be lessened by withholding ACEIs for a few days before cardiac surgery. They plausibly hypothesize that the combination of ACEIs with aprotinin may impair glomerular perfusion pressure.

A limitation of the Kincaid study is that aprotinin was selectively administered to patients felt to be at increased risk for complications. Ironically, aprotinin is expected to reduce the need for blood transfusion, and the need for blood transfusion was also associated with postoperative renal impairment in this retrospective study.

It seems prudent to hold ACEIs before anticipated use of aprotinin. Perhaps other pharmacological strategies will also be found to improve the safety of aprotinin. For instance, a drug to block the renal tubular uptake of aprotinin would be of interest.

Thromboembolic adverse events after use of recombinant human coagulation factor VIIa.

O'Connell KA, Wood JJ, Wise RP, Lozier JN, Braun MM. *JAMA* 2006;295(1):293-298.

Reviewer: Michael H. Wall, MD
University of Texas Southwestern Medical Center at Dallas
Dallas, TX

Abstract Excerpt: O'Connell et al, from the Food and Drug Administration (FDA), set out to review serious thromboembolic adverse events (AEs) reported to the FDA's Adverse Events Reporting System (AERS) between March 25, 1999 and December 31, 2004 in patients who received recombinant human coagulation factor VIIa (rFVIIa).[1] The database includes AE reports from approved (bleeding in patients with hemophilia A or B and inhibitors to factors VIII or IX) and off-label use. Reporting to the AERS is mandatory for drug manufacturers – but voluntary for health care professionals (and consumers). Because of this the number of AE's reported underestimates the true incidence of AE's. Also, the database (being uncontrolled and retrospective) can not prove a causal relationship.

The use of rFVIIa increased from 349 patients in 2000 to 4,520 patients in 2004. From March 25, 1999 to December 31, 2004 there were 168 reports describing 185 thromboembolic AE's. Fifty-nine of the reports involved patients in post-licensure trials. All of these reports were in patients without hemophilia, where rFVIIa was used off-label, most commonly for active bleeding in surgical patients. Eighty-four percent of the voluntary AE reports were from patients without hemophilia where rFVIIa was used off label for active bleeding in surgical patients. Fifty-four percent of the thromboembolic AE's were arterial (with cerebral and acute myocardial infarction being the most common); 40% were venous (with "other venous" and pulmonary emboli being the most common); 6% were device occlusion (LVAD, dialysis, etc.). There were 50 reported deaths and the thromboembolic event was the probable cause of death in 72% of these cases.

The median time period from the last dose of rFVIIa and the thromboembolic AE was 24 hours. Twenty percent of all thromboembolic AE occurred within the first two hours. Additional hemostatic agents (cryoprecipitate, fresh-frozen plasma, platelets, ϵ-aminocaproic acid, etc.) were used in 38% of these cases.

In an addendum – the authors briefly report on an additional 52 patients with a thromboembolic AE that were reported over 10 months from January 1, 2005 to November 1, 2005. These reports were similar to those detailed already. The authors point out this case series is most useful for generating hypothesis for future studies of rFVIIa use in other diseases and indications.

Comments: This paper raises concerns about an association of the off-label use of rFVIIa and serious thromboembolic AE's. However, massive blood loss following cardiac surgery is an important clinical problem and its treatment (massive volumes of blood and blood products) also has significant risks. In an effort to treat massive blood loss after cardiac surgery some centers are using rFVIIa – usually after traditional treatment with component therapy has failed. Karkouti et al[2] report a case control series of patients treated with and without rFVIIa. rFVIIa was associated with decreased blood loss and transfusion requirements, but the rFVIIa patients also had a longer ICU and hospital length of stay and a higher incidence of acute renal dysfunction. These findings, together with the recent report by Mangano et al showing increased risk of renal failure, myocardial infarction and stroke associated with aprotinin[3] emphasize the delicate balance between bleeding, fibrinolysis, anti-fibrinolytics, transfusion therapy and new novel hemostatic agents.

Prospective randomized trials of rFVIIa in cardiac surgery and other off-label indications need to be done.

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Drug & Innovation Updates

Dexmedetomidine: A review of its benefits and applications

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Dexmedetomidine (DEX; Precedex) and clonidine are α2 agonists, which provide analgesia, anxiolysis, sedation, and, like β-blockers, reduce sympathetic outflow. In 1999, the Federal Drug Administration approved DEX for 24 hours of intravenous sedation for ventilated patients in the intensive care unit.[1] However, over the last 5-10 years, DEX has been administered to a variety of patients in a wide range of clinical scenarios in and out of the operating room.[2]

Compared to clonidine, DEX is significantly more selective for the α2 receptor (α2:α1- 1600:1 vs. 300:1). Its lipid solubility results in an initial rapid redistribution phase (6 minutes) followed by a slower (2-3 hour) elimination phase, allowing DEX to be titrated to a desired effect. Although usually administered intravenously, intramuscular and buccal administration result in 100%, and 82% bioavailability respectively,[3] and can be administered 45 minutes prior to surgery to reduce patient anxiety.[4-5] The major metabolic pathway involves hepatic biotransformation. While patients with liver failure are expected to have impaired metabolism, the presence of renal dysfunction does not effect ts clearance.

Dosing of DEX is initiated with a 0.5 to 1.0 ug/kg load over 10-15 minutes followed by an infusion of 0.2 to 0.7 ug/kg/hr. These doses vary depending on the patient and clinical scenario with infusions as high as 5-10 ug/kg/hr when used as the sole anesthetic. For patients immediately after cardiac surgery the loading dose may be omitted.

Pre- and post-junctional α2 receptors mediate different physiologic responses, depending on receptor sub-type and location.[6-8] Stimulation of pre-junctional α2 adrenergic receptors inhibits norepinephrine release, and also contributes to increased secretion of GABA from the locus ceruleus in the brainstem, resulting in anxiolysis, sedation and a 'natural' sleep state.[9] Stimulation of α2 receptors of the intermediolateral and substantia gelatinosa of the spinal cord inhibits the release of substance P resulting in analgesia. In the airway, α2 stimulation may result in bronchodilation and decreased salivation. While pre-junctional α2 receptors result in bradycardia and vasodilation, post-junctional α2-b receptors results in vasoconstriction, the more dominant response with higher dose regimens (>1 ug/kg/min).

Dose dependent reduction in catecholamine secretion during DEX infusion has cardioprotective effects, in part, by reducing heart rate and improving myocardial oxygen balance.[10-15] In a model of cardiac ischemia, 1-3 ug/kg of DEX preserved coronary blood flow to ischemic regions while reducing flow to non-ischemic.[13] This was coupled with a reduction in myocardial demand without a reduction in oxygen consumption, resulting in improved balance for the ischemic tissues, while not compromising non-ischemic regions. [13]

Dexmedetomidine may also exert neuroprotective effects in models of cerebral ischemia due to embolic events.[16,17] Although these animal models demonstrate that post ischemic administration of DEX reduced injury area, it did so at relative large doses (10-100 ug/kg).

The reported benefits of DEX during cardiac surgical procedures are mixed, being complicated by significant hemodynamic compromise.[18-20] However, for the hypertensive and tachycardiac patient, DEX may be of significant benefit by reducing sympathetic outflow and improving hemodynamics. Although intraoperative benefits are not clear, individual patients may benefit especially during the postoperative period. Administration in the intensive care unit reduces the need for supplemental medications such as morphine, benzodiazepines, and propofol.[21] Early after heart surgery a loading dose may not be necessary, as initiation of an infusion may suffice, which minimizes unwanted reductions in blood pressure and heart rate.[22-25] Data also demonstrates improved cooperation and tolerance of patients during and after weaning from mechanical ventilation.[26,27] While other agents may provide similar sedation, anxiolysis, and analgesia, the lack of significant respiratory depression found with DEX is unique.[6,7,10,28,29] These properties make DEX a unique agent during weaning from mechanical ventilation.

Further application of α-2 agonists to prevent or treat withdrawal from alcohol, narcotics, other 'recreational' drugs, and from benzodiazepines and narcotics administered during hospitalizations, has been described.[30-34] When compared to benzodiazepines, the occurrence and severity of withdrawal was less during administration of α2 agonists.[34] Administration of DEX to an 8 month-old, displaying withdrawal symptoms from midazolam and fentanyl, allowing successful detoxification.[35] Proposed mechanism includes a more favorable balance between sympathetic and parasympathetic outputs form the central and peripheral nervous systems as well as an increase in GABA activity.

Favorable hemodynamic and adrenergic responses during infusions of DEX have been reported in patients undergoing major vascular surgery.[12-15] Patients undergoing CEA had lower serum catecholamines, received less additional sedating medications, and were more alert at the conclusion of surgery.[15] Although an increased use of vasopressor was reported, greater hemodynamic stability was described during infusion of DEX.

For awake procedures such as difficult intubations,[36] radiology procedures in pediatric patients[37] transesophageal echocardiography (personal experience), and awake craniotomies[38,39] DEX has been effectively used as an adjunct or the sole means of sedation. Application of DEX for sedation during awake electrophysiology procedures has been similarly effective.[40] Higher infusion rates (> 1-2 ug/kg/hr) provided excellent sedation while maintaining hemodynamic stability for patients with significant cardiovascular dysfunction.[40] As reported elsewhere, respiratory function was preserved.[6,7,10,28,29,40]

Ramsay et al reported on DEX as the sole intravenous anesthetic for three spontaneously breathing patients undergoing airway surgery.[41] This technique reduced the need for supplemental oxygen and any issues surrounding the use of electrocautery and fire hazards. After a loading dose of 1 ug/kg, high infusion rates (5-10 ug/kg/hr) were required for the patient to be cooperative and stable. Patients were easy to arouse, cooperative, and fully alert within 2-3 hours after discontinuation of DEX. Despite higher infusion rates there was minimal respiratory depression, and only small reductions in heart rate and blood pressure.

We have found DEX to be useful during major spine surgeries, during which somatosensory and motor evoked potential are recorded. Not only does DEX not interfere with neuromonitoring, but has facilitated the intraoperative 'wake up' test.

Pharmacoeconomic benefits of using dexmedetomidine exist despite the greater acquisition costs ($57.20 for each 2 milliliter vial). This demonstrates the greater impact on total expenses beyond the direct pharmaceutical costs, especially in the intensive care unit.[42,43]

Adverse hemodynamic reactions, which are primarily dose-dependant, include bradycardia and hypotension.[44] Other less frequent adverse effects include dry mouth, nausea, confusion, and dizziness.

In conclusion, DEX possesses an array of beneficial effects compared to more traditional anesthetic and sedating medications. By providing sedation, anxiolysis, and analgesia without significant respiratory depression, DEX is a unique medication, which is likely to see greater clinical application.

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Literature Reviews on the Web

Donation after Cardiac death. The University of Wisconsin experience with liver tansplantation.

Foley DP, Fernandez LA, Leverson G, et al.
Annals of Surgery 2005; 242(5):724-731.

Reviewer: Michael H. Wall, M.D.
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Abstract: The authors of this interesting paper report on the outcomes of 36 liver transplants (LTx) from organs donated after cardiac death (DCD) (formally known as nonheart-beating donors) with 553 LTx's from donated after brain death (DBD).[1]

The authors comment that, LTx is the standard of care for patients with end-stage liver disease; however transplantation continues to be limited by a shortage of donor organs. Using organs from nonheart-beating donors is one way to expand the donor pool. The authors describe two types of DCD. Uncontrolled DCD, patients usually undergo cardiac arrest and cardio pulmonary resuscitation prior to donation. Despite the use of cardiopulmonary bypass in some centers, the organs after uncontrolled DCD suffer ischemic damage, and as a result one-year graft survival rates are less than 20%, compared to > 80% in DBD. In *controlled* DCD, after consent is obtained, the patient is taken to the operating room and fully supported. Femoral arterial and venous cannulas are placed under local anesthesia, 10,000 to 20,000 units of heparin and 10 to 20 mg of phentolamine are given. Then the patients physician of record (who is not on the transplant team) extubates the patient, stops all vasoactive drugs, and makes the cardiopulmonary declaration of death. After an additional five minutes elapse [as described in the Institute of Medicine Guidelines][2] cold organ preservation solutions are administered and organ procurement and preservation is done.

In this series, warm ischemic time (time from extubation to perfusion of cold organ preservation solution) was 17.8 ±10.6 min, and cold ischemic time (time from infusion of cold solution to recipient reperfusion) was 8.2±1.9 hours, which was not different from cold ischemic time in DBD LTx recipients. Patient survival at one and three years was significantly less in the DCD group (1 yr: DCD 80% vs. DBD 91%; 3 yr: DCD 68% vs. DBD 84%). Similarly, one and three year graft survival was significantly less in the DCD group, and there was a higher rate of biliary strictures, hepatic artery stenosis, hepatic abscess and biloma in the DCD group.

In a comprehensive discussion, the authors conclude that although LTx after DCD results in worse graft and patient survival when compared to DBD, the results of LTx after DCD are encouraging and with further research and improvements in technique outcomes may improve.

Comments: This paper should be required reading for those involved with nonbeating-heart donors and transplantation anesthesiologists. The discussion thoroughly reviews the LTx after DCD literature and comments on DCD transplantation of kidney and kidney-pancreas. The authors note that there is no difference in patient or graft survival at five, 10 and 15 years after renal transplantation with DCD vs. DBD! The authors report similar success rates in kidney-pancreas transplantation using nonbeating-heart donors.

Finally, the authors comment that the use of nonheart-beating donors may increase the number of organ donors by 15-25%. So, if your center is not doing DCD now you may be in the future, and this is a great article to learn about this interesting and expanding method to address the organ shortage crisis.

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Aprotinin inhibits proinflammatory activation of endothelial cells by thrombin through the protease-activated receptor 1.

Day JRS, Taylor KM, Lidington EA, Mason JC, Haskard DO, Randi AM, Landis RC.
J Thorac Cardiovasc Surg. 2006 Jan;131(1):21-7.

Reviewer: Theodore A. Alston, MD, PhD
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Abstract: Aprotinin has been previously shown to inhibit the activation of platelets by thrombin while preserving platelet responsiveness to other aggregation stimuli. The thrombin receptor on platelets is a membrane-spanning protein called protease-activated receptor 1 (PAR1), and thrombin activates PAR1 proteolytically.

PAR1 is also present on endothelial cells, and the Hammersmith researchers now report that aprotinin protects endothelial PAR1 from thrombin. Endothelial cells were cultured from human umbilical vein. An antibody was used to assay cleavage of endothelial PAR1 by thrombin. Aprotinin (200 KIU/mL) protected PAR1 from proteolysis by thrombin.

Cleavage of PAR1 by thrombin results in a calcium ion influx into endothelial cells, and that influx can monitored by loading the cells with a calcium-sensitive fluorescent molecule. Aprotinin (1600 KIU/mL) completely blocked the ability of thrombin to cause calcium influx. A small peptide is able to activate PAR1 without the need for thrombin, and the peptide elicited calcium influx that was not blocked by aprotinin.

Proteolytic activation of PAR1 by thrombin activated an endothelial protein kinase, increased expression of a protein-synthesis transcription factor, and increased endothelial secretion of interleukin-6. Aprotinin (1600 KIU/mL) blocked those actions of thrombin.

Comments: The mechanism by which aprotinin reduces microvascular bleeding is incompletely understood and is probably multifactorial. It may well prove to be that PAR1 of endothelial cells is a pharmacologically important target of the drug. Of course, endothelial effects of aprotinin would not manifest in routine coagulation experiments performed outside of blood vessels. This consideration also applies to at least one other aprotinin-endothelium interaction. That is, aprotinin inhibits activated protein C in clinically achieved concentrations of drug. However, the conversion of protein C to activated protein C is effected by thrombin bound to endothelial thrombomodulin. Therefore, the procoagulant effect of aprotinin on activated protein C is not seen in ordinary endothelium-free blood coagulation tests in vitro.

Most of the present experiments with cultured and dispersed endothelial cells involve a high concentration of aprotinin. The clinically targeted and roughly achieved plasma concentration of aprotinin is about 200 KIU/mL. Therefore, effects reported in isolated endothelial cells exposed to 1600 KIU/mL drug are obtained under forcing experimental conditions. Furthermore, it is difficult to know what would constitute a "physiological" concentration of thrombin to be used in experiments in vitro.

However, these first experiments with aprotinin and endothelial PAR1 may prove to be seminal. Experiments with blood vessels might reveal that endothelial PAR1 is significantly responsible for the inhibition of bleeding by aprotinin. The authors plausibly propose that endothelial PAR1 mediates anti-inflammatory properties of aprotinin.

Perioperative magnesium supplementation to prevent atrial fibrillation after off-pump coronary artery surgery: a randomized controlled study.

Zangrillo A, Landoni G, Sparicio D, Pappalardo F, Bove T, Cerchierini E, Sottocorna O, Aletti G, Crescenzi G. Department of Cardiothoracic and Vascular Anesthesia, Vita-Salute University of Milano, Milan, Italy. *J Cardiothorac Vasc Anesth.* 2005 Dec;19(6):723-8.

Reviewer: Mohammed M. Minhaj, MD
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Abstract: Atrial fibrillation (AF) remains a common perioperative complication in cardiac surgical patients. Electrolyte disturbances have been known to be a potential contributory cause for developing AF. Magnesium replacement has been advocated as a means of reducing perioperative arrhythmias. In this randomized, blinded, controlled study, One hundred and sixty patients scheduled for off-pump coronary artery bypass graft (OPCABG) surgery were administered either 2.5 grams of magnesium sulfate or placebo over 30 minutes in the operating room. Postoperative AF occurred in 16/80 patients in the magnesium group and 18/80 patients in the placebo group with no significant difference. The authors contend that prophylactic intraoperative administration of magnesium is of no benefit in patients undergoing OPCABG to reduce AF.

Comments: Despite many studies in the literature attempting to identify causes and preventative measures for perioperative AF, it remains the most common complication of cardiac surgery. Postoperative AF has repeatedly been demonstrated to prolong hospital/ICU stays, increase economic costs, increase morbidity (including stroke) and potentially mortality. Given that postoperative AF has been reported in over 50% of patients in some studies, its importance cannot be overstated.

For OPCABG surgery, it was initially thought that the avoidance of cardiopulmonary bypass (CPB) would decrease the incidence of postoperative AF. This unfortunately has not been borne out by the literature. This study attempted to identify if routine, prophylactic magnesium administration would be beneficial.

Magnesium is important in maintaining cellular function, coronary vasodilation and may actually improve cardiac output by reducing systemic vascular resistance and increasing diastolic relaxation. Its benefit as an antiarrhythmic agent was demonstrated in a recent meta-analysis where it was associated with a 23% reduction in postoperative AF in patients undergoing cardiac surgery with CPB.

The results however of this study were not in agreement. They found no difference in the two groups of patients, either treated with placebo or magnesium intraoperatively. There was increased AF in older patients, in concordance with multiple earlier studies. Both patient groups were similar with respect to age, gender, past medical history (there could be no previous history of arrhythmia) and surgical grafts. Additionally, potassium levels were always maintained above 4 mEq/mL.

While interesting, there were several limitations within the study. First, there was no measurement of randomization of patients based on left atrial size or diastolic left ventricular (LV) function; both large atrial size and diastolic dysfunction have been implicated in the development of postoperative AF. Additionally, postoperative magnesium levels were not followed, hypomagnesemia is known to be quite common in the postoperative period and perhaps therapy throughout the perioperative period is actually warranted. Additionally, all patients, both in the treatment and placebo groups received 2.5 gm magnesium postoperatively in the ICU within 24 hours. Since all patients received some magnesium, irrespective of postoperative levels, the comparison may be between receiving 2.5 or 5 gm, not just between receiving an intraoperative dose or not.

Many institutions have routine postoperative orders to maintain certain electrolyte levels. While potassium levels were followed in these patients, magnesium levels were not. While difficult to design perhaps, preexisting and postoperative magnesium levels would be important predictive factors that if controlled for would have either further validated the results or altered them.

In conclusion, given the drawbacks of AF, with its increased morbidity, hospital costs, etc, the search for a potential solution continues. Prophylactic magnesium administration may yet play a role in OPCABG, and this study does not decisively argue against it.

The risk associated with aprotinin in cardiac surgery

Mangano DT, Tudor JC, & Dietzel C for the Multicenter Study of Perioperative Ischemia Research Group and the Ischemia Research and Education Foundation. *N Engl J Med* 2006; 354:353-65

Reviewer: KW Tim Park, MD
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Introduction: Whereas antiplatelet and fibrinolytic agents play an important role in medical therapy for patients with an acute coronary syndrome, not only are these agents not used in any surgical therapy that may follow because of concerns regarding excessive bleeding, but also antifibrinolytic agents are often utilized to reduce bleeding. The antifibrinolytic agents include lysine analogues (aminocaproic acid and tranexamic acid) and the serine protease inhibitor aprotinin. Prior case reports and small single-center studies have raised questions regarding the safety of the antifibrinolytic agents – specifically whether they increase the incidence of graft thrombosis and renal dysfunction. The present study is the first to address these safety concerns in a multi-institutional, prospective, non-sponsor-supported study that is adequately powered to answer the questions regarding all three agents simultaneously.

Methods: Patients, at least 18 in age, scheduled for coronary artery bypass surgery using cardiopulmonary bypass were enrolled at 69 centers around the world, each center enrolling approximately 50 patients per year. Patients could be undergoing primary surgery (revascularization only) or complex surgery (concurrent valve surgery). Clinical decisions, even involving the use or non-use of an antifibrinolytic, were not controlled by the study protocol. Rather, patient characteristics amounting to about 7,500 data fields were collected and selection bias was controlled by multivariable logistic regression and propensity-score adjustment. Prespecified outcome events were cardiovascular (myocardial infarction (MI) or heart failure), cerebrovascular (stroke, encephalopathy, or coma), or renal (dysfunction or failure) as well as death. In addition, blood loss was measured as chest-tube output during the first 24 hours after surgery.

Results: Overall, 1,295 patients received aprotinin, 883 aminocaproic acid, 822 tranexamic acid, and 1,374 none of the three. Baseline characteristics of the four groups of patients differed significantly, with the aprotinin group being less educated, less likely to have an urgent surgery, more likely to have a history of heart failure, heart block, carotid disease, liver disease, renal disease, prior CABG, valve disease & prior valve surgery, and more likely to be undergoing a complex surgery during the study. These differences were adjusted for with the propensity scores. Overall, the use of aprotinin was associated with an increased risk of renal and nonrenal events when compared to the other three groups. Among the 3,013 patients undergoing primary surgery, aprotinin, compared to control, was associated with 2.34 fold increase in renal events (P = 0.006), 1.42 fold increase in cardiovascular events (P = 0.01), and 2.15 fold increase in cerebrovascular events (P = 0.02), after propensity score adjustments. Mortality was not increased significantly, however. Among the 1,361 patients undergoing complex surgery, aprotinin was associated 2.59 fold increase in renal events (P = 0.004) compared to controls, after propensity score adjustments. The other two antifibrinolytics were not associated with any increased risk of adverse events. Rather, in patients undergoing complex surgery, aminocaproic acid was associated with a four-fold reduction in mortality (P = 0.01). Furthermore, a dose-response relationship was found for aprotinin with respect to renal, cardiovascular and composite outcomes. All three antifibrinolytics decreased surgical bleeding compared to control, but aprotinin was not more efficacious than the other two agents.

Discussion and Comments: This study raises serious questions on continued advisability of using aprotinin to reduce surgical bleeding in cardiac surgery. Aprotinin appears associated with an increased risk of renal adverse events in both primary and complex surgery, in a dose-dependent manner. Although the reason for this association is not clear, potential mechanisms the

authors suggest include inhibition of renal tubule protease secretion (kallikrein and kinin), prostaglandin and rennin synthesis, prostasin secretion, and bradykinin release; dose-dependent renal afferent vasoconstriction; and interference with the synthesis and release of endothelial nitric oxide. In addition, in primary revascularization surgery, aprotinin appears associated with an increased risk of cardiovascular and cerebrovascular events. This association may be due to inhibition of soluble proteases such as kallikrein, plasmin, and trypsin; inhibition of activated protein C; preservation of platelet adhesive and aggregatory properties; and impairment of vascular endothelial function in conjunction with inhibition of nitric oxide synthesis and release. These adverse effects were observed in the absence of superior blood-conserving effect of aprotinin over the lysine analogues, which were not associated with adverse renal, cardiovascular, or cerebrovascular events. Switching from aprotinin to the lysine analogues would result in direct savings in drug costs as well as indirect savings from reduction in adverse events.