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September 12, 2006

LCDR Cathy Groupe

U.S. Public Health Service

Health Service Science Administrator

FDA Advisors and Consultants Staff

5630 Fishers Lane, HFD-21

Rockville, Maryland 20857

Dear Commander Groupe:

Thank you for the information with regards to the September 21, 2006 meeting of the Cardiovascular and Renal Drugs Advisory Committee of the FDA, scheduled to discuss aprotinin. I will speak during the public session and for that session I would appreciate it if you could distribute to the committee the enclosed papers. They consist of:

1. Spiess BD. Blood transfusion: The silent epidemic. *Ann Thorac Surg* 2001; 72:S1832-7.
2. Spiess BD. Choose one: Damned if you do/damned if you don't! *Crit Care Med* 2005; 33:1871-1874.
3. SCA Editorial Commentary: Have we got it right? We cannot afford to be wrong! *Society of Cardiovascular Anesthesiologists Newsletter*. April 2006 Volume 5, #2, pages 5-7. Web link [www. SCAHQ.org](http://www.SCAHQ.org).

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FDA Advisory Panel: Aprotinin
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9-21-06

Bruce D. Spiess, MD, FAHA

Thank you to the entire advisory panel for your time and the opportunity to address this group. Thank you also to Cathy Groupe for the instructions regarding today's proceedings and for distribution of the materials that I sent. By way of full disclosure, in an effort for transparency, let it be known that I have received research support from Bayer Pharmaceuticals as well as consulting and honoraria for specific projects. I am here today, however on my own. Also, by way of disclosure, I have been intimately involved in the past with McSPI and published extensively from their prior databases. Indeed, for a number of years I was the director of the hematology study section within McSPI, the peer review group who should have been responsible for such manuscripts as this aprotinin paper.

I have three points to address. First, my opinions with regards to the scientific merit of the New England Journal of Medicine article regarding aprotinin are summarized in the editorial of April 6, 2006 published in the newsletter of the Society of Cardiovascular Anesthesiologists. Physician channeling of more ill patients toward the more effective drug aprotinin and the employed statistical methods utilized for eliminating bias are of particular concern to me. A point I wish to stress, also present in my editorial, is the likely possibility that some covariate or confounding variable does exist that was not only not included in the multivariate statistical analysis but that was not even captured in the McSPI data base. Specifically I am referring to a potentially serious unrecognized confounder, the presence of heparin-platelet factor 4 antibodies or the so

called HIT syndrome. Recent research has found not only that the full blown clinical picture of HIT is quite pro-thrombotic, but that the presence of HPF-4 antibodies alone, have serious implications. Without antibodies present the risk of serious adverse events in a study of over 300 CABG patients was 5%. With moderate levels of antibody present the incidence of death, MI, stroke and other events went to 12.5%. A high level of antibody was associated with 31.3% of patients having severe outcomes. Unfortunately there was no HPF-4 antibody collected in the McSPI data base. But, also unfortunate is the fact that there was no surrogate such as pre-operative heparin usage, length of time in the cardiology ICU pre-operatively, multiple dosing of heparin etc. included either in analysis or the data base. A case report of sudden right and left heart thrombosis has been published in the Canadian literature in which a patient undergoing open heart surgery clotted extensively after heparin was reversed with protamine. This patient had HIT antibodies and did not receive aprotinin. My point is this, HIT antibodies may well have occurred more often in the aprotinin treated patients due to a selection bias by the physicians channeling treatment for these more ill patients. Without testing for HIT, collecting data regarding HIT or even examining HIT surrogates one cannot eliminate that single and now very important biologic cause for severe adverse events.

In my editorial, I call for an unbiased third party such as the FDA to examine not only the conclusions but the raw data, how the analysis was performed and ultimately the conclusions drawn. I commend you for undertaking this huge task. My point with regards to HITT is that experts in cardiovascular surgery, anesthesiology and transfusion/hematology should have open access to viewing the raw data so that incomplete or inaccurate associations are not left being interpreted as cause and effect. I

stressed in my editorial that our patients deserve the correct answer. Already patients are suffering.

The second point I would like to stress is the effects of blood transfusion upon outcome after heart surgery. That particular subject is one in which I feel that I am qualified as an expert. Indeed I have lectured more than 50 times on the subject in the last year throughout the world. Most physicians view our blood supply today to be the safest it has ever been. At least with respect to the risks of AIDS, hepatitis and West Nile Virus the statement is absolutely true. But, since these viruses have been largely eliminated from our risk radar, research has been refocused upon immune modulation, TRALI, and ultimately adverse events with and without transfusion. The body of literature showing associations between transfusion and severe adverse events is large and growing. Within the last three months several important studies have been added in cardiac surgery, some with data bases in excess of 12,000 patients. These data bases have shown that patients who received more transfusion have a dramatically higher mortality rate, more renal failure, longer hospital stay as well as a number of other severe outcomes. Importantly two studies, Engoren et al. and recently Koch et al. have shown that patients who are transfused more have a higher mortality rate even out to five years after surgery and those that are transfused more have a worse quality of life. That includes their abilities to perform activities of daily living. Multivariate models and propensity analysis in these studies have been employed with appropriate control for confounders and the associations stand.

January 16, 2006 I was invited to participate in the Duke University Clinical Research Institute's sponsored meeting entitled "Bleeding and Transfusion in

Cardiovascular Disease: a Think Tank” in Arlington , Virginia. In attendance were 41 physicians and industrial leaders for this provocative discussion of recent data. Present for the FDA were: Ann Ferriter : Acting Branch Chief, Circulatory Support and Prosthetics Branch Division of Cardiovascular Devices, James Hung, PhD, Office of Biostatistics of the FDA, Donna Lochner, PhD, Deputy Director of the Division of Cardiovascular Devices, Wolf Sapirstein MB, ChB, MPH Associate Director/ Senior Medical Officer Division of Cardiovascular Devices, Norma Stockbridge MD, PhD Acting Division Director Division of Cardiovascular and Renal Products, as well as Bram Zuckerman, MD. From the National Institutes of Health were George Nemo, PhD Acting Director, Blood Resources Program, NHLBI, and Kieth Horvath, MD, Cardiothoracic Surgery Branch of NHLBI. In the opening statement for the program Dr Robert Califf, MD, Vice Chancellor for Clinical Research and Director of Duke Clinical Research reviewed recent data regarding blood transfusion and its association with increased mortality in patients undergoing PCI- cath lab interventions as well as cardiac surgery. He showed a number of papers including data from the Cochrane data base and then concluded with the statement: “Blood transfusion is the fourth largest killer of patients within the United States.” I would urge you to contact his office for a transcript of that meeting if you have any doubts with regards to the risks of transfusion and outcome in heart surgery.

I am an outspoken advocate for us reducing our use of allogeneic transfusion in heart surgery. I believe the data is strongly present to show that transfusion of allogeneic blood is associated with worse outcomes. In our center, Virginia Commonwealth University Health System, we have reduced transfusion rates (all comers) for heart

surgery from greater than 70% to below 12-18% through an aggressive blood conservation program. Aprotinin has been a major part of that program. Our patients are doing better, with less time on ventilators, less renal dysfunction and less congestive heart failure than when we more liberally transfused.

The American Association of Blood Bankers, just recently noted that the so called TRICC study by Paul Hébert et al. is the single most important study in the history of transfusion. Every member of this advisory board should read that study as it is the only large randomized prospective trial of blood transfusion. It found that patients transfused less always did as well as or better than those patients transfused more. In severely ill medical ICU patients with the best practice, the mortality rate was 28.1% in hospital. Withholding blood transfusion to a hemoglobin of 7gm/dl improved in hospital mortality by 25% overall to a rate of 21%. When was the last time a drug was approved by the FDA when its non usage improved outcome by 25%?

Transfusion has never undergone safety and efficacy testing by the FDA. I gave you my editorial from Critical Care Medicine about transfusion and renal failure. Habib's work has shown that low hematocrit has an association with increased renal dysfunction but that transfusing either in response to the low hematocrit or as an effort to prevent it multiplies and worsens the risk of renal failure. Physicians in the United States transfuse based upon lore, convention and belief. The act, to transfuse is in the end analysis an emotion driven prophylactic event. Only today are we beginning to find the astounding associations between transfusion utilization and worse outcomes. Truly in the case of cardiac surgery less is more.

The New England Journal of Medicine paper has caused many cardiac surgery programs to change their practice. When I speak at individual hospitals their lead cardiac surgeons and anesthesiologists talk to me. For example at Loma Linda University they stopped using aprotinin after the paper was published. But they noticed such a large increase in bleeding and re-operation that within several months they began using the drug once again. Most often, when physicians have changed their practice they tell me they don't believe the results of the article but they are so scared of the litigation climate that has been created as a result of the article that they are fearful they will be sued if anything happens to one of their patients. In Europe, the New England Journal of Medicine article was largely ignored, but it was the act of the FDA publishing an official statement, albeit cautionary and non committal, that lent validity and caused some to change. My plea is this. Please realize that blood transfusion is not necessarily life saving, it can be deadly. Indeed there is good data to suggest and support Rob Califf's allegations. Any decision made by this important deliberative body will affect the lives of many people worldwide. It already has.

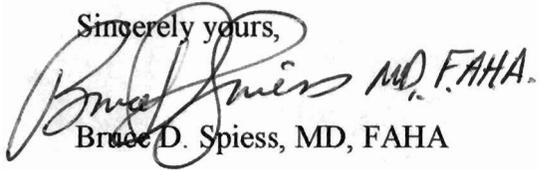
The third point is to make the committee aware of a document that you may wish to obtain. The Society of Thoracic Surgeons (STS) and the Society of Cardiovascular Anesthesiologists are about to publish: "Peri-operative Blood Transfusion & Blood Conservation in Cardiac Surgery: The Society of Thoracic Surgeons and The Society of Cardiovascular Anesthesiologists Practice Guideline Series. Dr Victor Ferraris from the University of Kentucky led a group of 8 physicians from STS and I led 7 physicians from SCA in co-jointly creating the guidelines for practice. This document is an evidence based review with citations in excess of 750 references outlining where the societies will

steer practice. I am not authorized by either society to pass on publicly a copy of the guidelines nor do I feel it appropriate that I summarize them for you now. However, as a private citizen I think the FDA should be aware that such a document exists, and will be published later this fall. I am equally sure with an enquiry from this advisory panel a rapid response with the guidelines would be forthcoming from either or both societies. I can assure this group that the question of not only efficacy but also safety of aprotinin as well as the lysine analogues was carefully considered and an extensive evidenced based literature review was completed. Both the Karkhouthi and the Mangano papers were evaluated, cited and considered when the guidelines were crafted.

In summary, I thank you for your time and consideration. I do believe the Mangano article infers cause and effect rather than simple association, a dangerous and scientifically unfounded conclusion especially when some key confounders have neither been collected nor tested. It calls for the use of drugs that are not FDA approved for usage and ones that have little or no safety data. Furthermore, blood transfusion itself is a major risk hazard for adverse outcome, particularly renal failure. That key ingredient in the risk benefit equation with which you are struggling, blood transfusion utilization, was not even tested in the Mangano article. Ignoring that key confounder alone, as a hematology expert, makes me wonder what peer review input this manuscript had during its inception, analysis and publication. Lastly and most importantly, whatever is decided here, will affect the survival and quality of life for a large number of people with cardiovascular disease not just in the United States but worldwide.

I will make three points both from these enclosed pages and with regards to national guidelines for transfusion in cardiac surgery. Thank you again and I look forward to addressing the FDA advisory panel.

Sincerely yours,

A handwritten signature in black ink, appearing to read "Bruce D. Spiess MD, FAHA". The signature is written in a cursive style with a large initial "B".

Bruce D. Spiess, MD, FAHA

SCA Newsletter Commentary

Have we got it right? We Cannot Afford to be Wrong!

Bruce D. Spiess, MD, FAHA

The recent article in *New England Journal of Medicine* (2006;354: 353-365) by D. Mangano entitled "The Risk Associated with Aprotinin in Cardiac Surgery, has created dramatic discussions within cardiac anesthesia. Physicians are examining their practices. Re-examination of medical practice in light of any new scientific development is prudent and 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 well over 1500 articles does not by itself trump all other literature no matter how many patients it contains. Especially, when the study in question, is a data based observational retrospective analysis. At best, the only conclusions that can be drawn from such data based studies are associations. Only prospective randomized trials prove cause and effect. We should not hastily abandon the results of well over 45 prospective randomized trials of aprotinin encompassing thousands of patients in which there was no connection between aprotinin's use and renal dysfunction. Evidence based medicine always favors that prospective, randomized, double blinded studies are of superior value to even the best statistically analyzed retrospective evaluations.

The *NEJM* article acknowledges that the patients who received aprotinin were considerably more ill and at higher risk for bad outcomes. Table 1 lists and segments 27 different pre-operative characteristics. Notably some very important factors are missing. Others reported are of questionable relation to the study. Data on medication usage are missing (i.e. heparin usage, aminoglycosides) whereas college education level is included. This commentator could well think of another 30 risk factors that should have been included in such a pre-operative risk analysis. The article does note that 97 different characteristics were originally tested 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. An important article regarding such risks is: Chukwuemeka A. et al. "Renal dysfunction on high-risk patients after on-pump and off-pump coronary artery bypass surgery: A propensity score analysis. *Annals Thoracic Surgery* 2005;80: 2148-2153. In that article almost 3000 patients at high risk for renal failure after heart surgery were analyzed and risks categorized. Three factors were most important: diabetes, peripheral vascular disease and decreased creatinine clearance. Creatinine clearance (even calculated) is far superior to a simplistic creatinine level. In the *NEJM* article the patients who received aprotinin had twice the amount of insulin dependent diabetes as compared to the control. But the other two major risks, creatinine clearance and peripheral vascular disease, were not entered in the data analysis. The *NEJM* must have all the necessary data (age, weight, sex, and creatinine) for a calculation of creatinine clearance at baseline. One suggestion would be to go back and do that calculation, then to segment patients within the aprotinin and other treatment groups by creatinine clearance risks for future development of true renal failure. It is important to note that article by

Chuckwuemka et al. did not find any relationship between aprotinin or any antifibrinolytic and renal failure dysfunction. If creatinine clearance is below 60cc/min in Chuckwuemeka's article then renal dialysis may well exceed 25%. In some severe sub-groups the dialysis post CPB may be above 85%.

The basic definitions of renal failure and dysfunction in the *NEJM* need to be clarified or questioned. In Chuckwuememka et al. and in Habib et al. (Hemodilutional anemia and transfusion during cardiopulmonary bypass in renal injury after coronary artery revascularization: Implications on operative outcome. *Crit Care Med* 2005;33:1749-54.), not only are creatinine clearance followed but delta creatinine is important. The *NEJM* article 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 but that this is transient. By return to follow up at 14 to 30 days there is no difference in creatinine in prospective trials (thousands of patients). If the *NEJM* article queried for changes of creatinine (either a 177umol per liter- 2mg/dl or 62 umol per liter- .66mg/dl increase) from baseline up to day 7 those delta creatinine values could be meaningless or have skewed the renal dysfunction results for aprotinin. We don't know what was done because it is not outlined in the methods.

A combined renal event was utilized. So it was not just increased creatinine but that finding combined with the number of patients who underwent dialysis. The data really needs to be presented separately for dialysis as well as for delta creatinine, again with the recognition that delta creatinine changes prior to day 7-14 might be of less meaning. Was dialysis alone significant? Dialysis is what really matters, costs money and creates suffering as well as increased death rate. The *NEJM* paper claims that dialysis was far more common in high risk patients who received aprotinin but then it needs to be asked what was the patient's preoperative creatinine clearance? If we would have expected a very high rate of dialysis in these patients then creatinine clearance coming in would have been very important.

The *NEJM* article quotes literature with regards to the effect 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, in the entire *NEJM* paper only 10% of the entire references come from the last 5 years (an accepted time scale for currency with regards to scientific advance). These papers were also prior to when aprotinin had undergone prospective randomized FDA trials. Cellular effects of aprotinin upon renal cells in rats tested of course without cardiopulmonary bypass or anticoagulation in the 1960-1980's may have little relevance to the contemporary argument at hand. The *NEJM* article fails to quote a major article regarding hypothermic circulatory arrest and renal failure (Mora-Mongano CT et al. Aprotinin, blood loss and renal dysfunction in deep hypothermic circulatory arrest. *Circulation* 2001;104: I276-81.) That article, arising from Stanford University, 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? That should be a hard end point of which there is no controversy. In the *NEJM* article we have no data with respect to when dialysis was utilized. Was it immediately post-operatively, discharge dialysis or just at any time, for just a short period of time? 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 data base in which they already had a creatinine clearance of <60ml/min a dramatic rise in dialysis and death has been shown to be expected (Chuckwemeka et al.). Only if those patients with aprotinin usage exceeded the expected published dialysis rate for their pre-operative 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 present *NEJM* article 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 bypass, blood transfusions, lowest hematocrits, ICU entry hematocrits, a wide number of other drugs such as aminoglycoside antibiotics, recent cardiac catheterization, and extremely importantly center (national practice and regional practice variations) must all be reported.

Propensity analysis and multivariate logistic regressions are two statistical techniques employed when analyzing data based 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 2 or perhaps as high as 3 can be due to a missed or unrecognized covariate. If an odds ratio is 4 or above the likelihood of any relationship being cause and effect rises dramatically, but is still not proof. Odds ratios in the *NEJM* article 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 data base. A perfect example that might well have occurred in this investigation is heparin induced thrombocytopenia antibody formation. It has now been demonstrated that 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 data base in question nor was a surrogate (heparin use pre-op, length of time in ICU pre-op, platelet count pre-op or delta platelet count from pre-op to day 7 post op) investigated. Suppose the patients who received aprotinin had a more frequent use of heparin pre-op and therefore had a higher likelihood for heparin antibody formation. In accordance with the observational study such more severely ill patients would have been more likely to receive aprotinin. Once propensity testing was done the results of such testing would show that aprotinin had more likely severe outcomes. Yet it, the heparin antibody, may well have been the causative biologic (though a covariate) agent. It is therefore not only of extreme importance that all covariates tested be reported but that those reading such data based articles ask themselves whether the associations make sense.

The propensity analysis showing that amicar has a lower death rate and a lower composite outcome event score as compared to aprotinin versus control actually fits with what we know. Amicar is utilized for the least ill patients (in the United States). Any other conclusion with regards to the overall propensity scoring cannot be concluded with the information presented in the *NEJM* paper. Full disclosure of all the raw data and how the propensity analysis was carried out needs to be presented to some unbiased third party (The United States Food and Drug Association for example).

The *NEJM* paper makes sweeping and emotional claims regarding aprotinin usage. It claims that 11,050 patients would not require dialysis and that at least 1 billion dollars would be saved if aprotinin was not used in surgery. Such language is inflammatory, unscientific and fully ungrounded based upon the fact that even with perfect propensity statistics only an association (not cause and effect) can be concluded from this retrospective data base. The call for a switch to amicar or tranexamic acid is not scientific. Neither drug is US FDA indicated for any use in CPB. Neither drug has undergone randomized safety testing in large prospective blinded series in the setting of CPB. Indeed data do exist that amicar contributes to and increases the risk of renal failure in CPB. It certainly has in the past caused thrombotic risks 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 United States is unwise at best.

Renal failure occurs more frequently within CPB when patients have a low Hct. on bypass (Habib et al.). A recent land mark article found that we are damned if we do and damned if we don't in that the use of transfusions to prevent or treat such a low Hct. further worsens the risks of renal failure. There is no doubt that aprotinin dramatically reduces the need for transfusion in heart surgery. If the use of aprotinin is abandoned and patients receive more blood products then it may well be, according to Habib et al, that the renal failure risks will rise. Furthermore, it is well known today that the risks of perioperative infection (particularly pneumonia), respiratory failure (transfusion related acute lung injury), length of stay and death all worsen with more transfusion. No transfusion data are presented in the *NEJM* paper. If you personally change your practice because of this one paper keep very close records of transfusion, re-operation for bleeding, pneumonia, stroke, cost, length of stay and death rates in your patients. You may well prove to yourself the truth of the literature.

If the data from a study do not either fit the biology known or the prospective randomized trials then as a scientist one needs to examine them very carefully. They could, of course be correct and therefore represent a breakthrough in thinking. Unfortunately, the *NEJM* article neither fits what has been seen in the prospective randomized trials or the biology. Stroke for instance has been extensively accepted to be reduced by the use of aprotinin in randomized trials (cause and effect). The *NEJM* 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 data based association study should be digested into the overall 1500 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 well take time but it is probably certain that some reanalysis will show whether the study is groundbreaking or flawed. As suggested earlier, in the interim perhaps a large data base could be followed examining any change in practice this one study causes and follows the outcomes of our patients. If the *NEJM* 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.

