Evaluating the safety implications of aprotinin use: The Retrospective Evaluation of Aprotinin in Cardio Thoracic Surgery (REACTS)

Craig I. Coleman, PharmD,^{a,c} Vera T. Rigali, PharmD,^c Jonathan Hammond, MD,^b Jeffrey Kluger, MD,^{a,d} Kenneth W. Jeleniowski, CCP,^b and C. Michael White, PharmD^{a,c}

Dr Coleman

From the Divisions of Cardiology^a and Cardiothoracic Surgery,^b Hartford Hospital, Hartford, Conn; and The University of Connecticut Schools of Pharmacy^c and Medicine,^d Storrs and Farmington, Conn

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Address for reprints: C. Michael White, PharmD, FCCP, FCP, Director, Cardiac Pharmacology Service, Hartford Hospital, 80 Seymour Street, Hartford, CT 06102-5037 (E-mail: cmwhite@hart Hosp.org).

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Objectives: Aprotinin is a drug used to reduce bleeding in patients undergoing cardiothoracic surgery with cardiopulmonary bypass. A recent cohort evaluation found elevated risks of renal, cardiovascular, and cerebrovascular events when aprotinin was used. We sought to determine the impact of aprotinin on safety variables among patients receiving cardiothoracic surgery with cardiopulmonary bypass from a single US hospital that reserves aprotinin for complex surgeries and Jehovah's Witnesses and does not utilize celite-based activated clotting time determinations.

Methods: We performed a cohort evaluation with multivariate logistic regression, including propensity score adjustment comprising patients from January 1, 2000 and December 31, 2005. We evaluated 3348 patients having cardiothoracic surgery in a single tertiary care medical center. We observed aprotinin use or lack of aprotinin in cardiothoracic surgery. The main outcome measures were odds (expressed as an odds ratio with 95% confidence interval) of developing myocardial infarction, cerebrovascular events, and renal dysfunction after cardiothoracic surgery between groups.

Results: Patients receiving aprotinin were less likely to experience a cerebrovascular event compared with control [0.65 (0.46–0.91)] and did not have an elevated odds of myocardial infarction [1.04 (0.53–2.04)] but were more likely to experience postoperative renal dysfunction [2.03 (1.37–3.01)].

Conclusions: Aprotinin was not associated with negative myocardial or cerebrovascular risks but did increase the risk of renal dysfunction. It is not known whether the renal dysfunction reflects renal damage or a transient reduction in glomerular filtration pressure.

Cardiothoracic surgery (CTS) with cardiopulmonary bypass (CPB) induces platelet dysfunction, thrombin production, and plasmin release.^{1,2} Bleeding during or shortly after CTS is a common complication, resulting in transfusion, reexploration, or tamponade.^{3,4} Cardiac operations account for 10% of the 11 million units of allogenic blood transfused in the United States annually and carry a real but small risk of blood transfusion infection.⁴

Abbreviations and Acronyms

ACT	= activated clotting time
CABG	= coronary artery bypass graft
CI	= confidence interval
CPB	= cardiopulmonary bypass
CTS	= cardiothoracic surgery
MI	= myocardial infarction
OR	= odds ratio
RR	= relative risk
TIA	= transient ischemic attack

Aprotinin is a serine protease inhibitor derived from bovine lung that attenuates thrombin generation, fibrinolysis, and inflammatory processes.^{3,4} In a multicenter, multinational (23 countries), observational study involving 4374 patients having CTS, aprotinin use was associated with an increased risk of renal dysfunction or renal failure among patients receiving primary (odds ratio [OR] 2.34; 95% confidence interval [CI] 1.27-4.31) and complex CTS (OR 2.59, 95% CI 1.36-4.95) as compared with patients receiving no treatment.⁵ The use of aprotinin was also associated with a significant increase in the risk of cardiovascular (OR 1.42, 95% CI 1.09-1.86) and cerebrovascular events (OR 2.15, 95% CI 1.14-4.06) among patients having primary CTS but not among patients having complex CTS.

These results are in contrast to those of a meta-analysis of randomized, placebo-controlled coronary artery bypass graft (CABG) trials from 1988 to 2001 where aprotinin (35 trials, 3887 subjects) did not increase the risk of myocardial infarction (MI; relative risk [RR] 0.85, 95% CI 0.63-1.14), renal failure (RR 1.01, 95% CI 0.55-1.83), or stroke (RR 0.53, 95% CI 0.31-0.90) versus controls.⁶ Most trials included in the meta-analysis were comprised of patients having complex CTS.

The observational study utilized data from 23 countries, and the meta-analysis was constituted mostly of trials conducted within the United States, which might account for the differences. In the International Multicenter Aprotinin Graft Patency Experience (IMAGE) trial, patients from 13 international sites were randomized to receive aprotinin (n = 436) or placebo (n = 434).⁷ Among 703 patients with assessable saphenous vein grafts, 15.4% of patients treated with aprotinin and 10.9% of patients treated with placebo had occlusions. However, in the United States, occlusions occurred in 9.4% of patients receiving aprotinin and 9.5% of patients receiving placebo ($P = .72$), and at Danish and Israeli sites, the occlusions occurred in 23.0% of patients receiving aprotinin and 12.4% patients receiving placebo ($P = .01$).^{7,8}

Neither the observational trial nor meta-analysis reported average doses of heparin between groups or what type of activated clotting time (ACT) test was being used. Aproti-

nin induces a drug-lab test interaction with diatomaceous earth-based ACTs (celite-ACT) resulting in abnormally high ACT values. Use of kaolin-based ACTs (kaolin-ACT) or "sonoclot aprotinin insensitive ACTs" do not have the same interaction.^{3,9} Studies have found underdosing of heparin when celite-ACTs are used with aprotinin, which may increase the risk of cardiovascular, cerebrovascular, and renal events versus control.^{3,10}

Given the dichotomous findings and limitations of the previous studies, we conducted a large cohort evaluation of aprotinin use for CTS from a single US hospital that does not use celite-ACT determinations.

Materials and Methods**Design and Population**

This was a cohort evaluation of all patients undergoing CTS at our institution between January 1, 2000 and December 31, 2005. The clinical data were collected prospectively and entered in the clinical database, but the aprotinin data and the analysis of the data occurred retrospectively. To be included in this evaluation, patients had to have undergone CABG surgery (either alone or with valve or other surgery) and utilized a CPB pump. Patients meeting the above criteria and using aprotinin comprised the treatment group, and those patients not utilizing aprotinin comprised the control group. Our institution's aprotinin protocol requires aprotinin to be dosed by either of the two Food and Drug Administration-approved regimens; however, the full-dose regimen is almost exclusively used. The Hartford Hospital Institutional Review Board approved this study with a waiver of informed consent.

Cardiopulmonary Bypass Pump Management

Anticoagulation was initiated with heparin 300 U/kg. The target kaolin-ACT before initiating the CPB pump was greater than 500 seconds for aprotinin-treated patients and greater than 450 seconds for non-aprotinin-treated patients. Kaolin-ACTs (Hemochron, ITC Corporation, Edison, NJ, and I-STAT, Abbott Point of Care, East Windsor, NJ) were taken at baseline, 5 minutes after initial heparinization, after heparin dosage adjustments, and after protamine reversal. During surgery, the threshold for transfusion was a hematocrit level below 18%. Pump flow rates ranged from 1.8 to 2.5 L/min/m² at 30°C to 32°C to 2.5 to 3.2 L/min/m² at 34°C to 37°C. In some patients, the depth of hypothermia was lowered to 20°C and determined via rectal probe. Cardioplegic solution for myocardial protection was a 4:1 blood to crystalloid mix with added insulin and procaine. There was a high and low potassium cardioplegic solution with both solutions containing lactated Ringer's, dextrose, sodium bicarbonate, and potassium chloride. Cardioplegic solution was given antegrade and/or retrograde and given either warm or cold.

Trial End Points and Definitions

For the purposes of this study, the following definitions were used: All end points were monitored for from the time of surgery until patient discharge. Renal dysfunction was defined as acute or worsening renal failure resulting in 1 or more of the following: (1) an increase in serum creatinine to >2.0 and twice the baseline creatinine level or (2) a new requirement for dialysis. MI was defined

as perioperative MI, diagnosed by finding two of the following criteria: (1) prolonged (>20 minutes) typical chest pain not relieved by rest and/or nitrates; (2) enzyme level elevation (either creatine kinase M monomer/B monomer isoenzyme > 5% of total creatine kinase, creatinine kinase greater than twice normal, lactate dehydrogenase subtype 1 > lactate dehydrogenase subtype 2, or troponin-T > 0.2 $\mu\text{g/mL}$); (3) new wall motion abnormalities; (4) serial electrocardiograph (at least 2) showing changes from baseline or serially in ST-T and/or Q waves that are 0.03 seconds in width and/or greater or plus one third of the total QRS complex in 2 or more contiguous leads. Stroke was defined as central neurologic deficit persisting for >72 hours. Transient ischemic attack (TIA) was defined as transient neurologic deficit with recovery within 24 hours. Delirium was defined as a definite state of confusion, agitation, or hallucination (auditory or visual) unrelated to narcotics or anesthesia. Patients with baseline delirium were only counted if their state markedly worsened post-CTS. Cerebrovascular event was defined as occurrence of stroke, TIA, or delirium. Death was defined as death prior to hospital discharge. Red blood cell requirement was defined as need for red blood cell transfusion. Reoperation due to bleeding was defined as operative reintervention required for bleeding or tamponade.

Subgroup analysis was conducted to determine the impact of surgical complexity on study safety and efficacy end points. In this analysis, only patients undergoing complex CTS (either repeat CTS or valvular involvement) were included in the analysis.

Statistical Analysis

Continuous variables are presented as means with standard deviations and were compared between groups using a Student *t* test. Dichotomous variables are presented as percentages and were compared between groups via χ^2 analysis.

As this was an observational study, the investigators had no control over which patients received aprotinin and which did not. As a result, significant differences on important observed demographic and pre- and perioperative variables were likely to occur, which could lead to a biased estimate of treatment effect. Therefore, we conducted multivariate logistic regression to control for potential confounders in our evaluation. We first conducted univariate analysis to examine the association between the occurrence of the end point of interest (dependant variable, renal failure, MI, and so on) and pre-, intra-, and postoperative variables (independent variables). All variables with a *P* value of $\leq .2$ in the univariate analysis were entered into a multivariate logistic regression model. In addition, the propensity score, or the conditional probability of being treated with aprotinin based upon an individual's characteristics, were calculated using 41 demographic and preoperative variables for each patient using logistic regression. The discriminate power of the propensity scores was quantified by measurement of the receiver operating characteristic area (the C-index) and was found to be 0.85.

Upon their calculation, the raw propensity score was included in overall multivariate logistic regression model in addition to variables qualifying for inclusion following univariate analysis. In the multivariate model, variables were selected by stepwise, backward elimination. Odds ratios and 95% CIs were calculated for all independent predictors. Statistical analysis was performed with

SPSS version 11.0 (SPSS, Chicago, Ill) and R version 1.8.1 (The R Foundation for Statistical Computing, Vienna, Austria).

Sample Size Calculation

Based upon the recent cohort analysis of aprotinin by Magano and colleagues,⁵ it was determined that a total of 1114 patients would be required to detect a 42% increase in patients' risk of postoperative MI using aprotinin compared with control, assuming a 13% incidence in the control group, an alpha of 0.05, and power of 80%. Moreover, based upon that same evaluation, it was determined that the above sample size should be sufficient to detect statistically significant increases in postoperative renal (increased by 134% in Magano et al⁵) and cerebrovascular (increased by 115% in Magano et al⁵) complications in patients receiving aprotinin compared with control, if they exist.

Results

Six thousand one hundred two patients undergoing CTS were evaluated for inclusion into this cohort analysis. Of these, 2754 patients had to be excluded from the analysis because they did not receive coronary artery bypass surgery (*n* = 1721) or because their surgeries were conducted without CPB (ie, off-pump surgery; *n* = 1033). Thus, 3348 patients were included in this evaluation, of which 362 patients received aprotinin during surgery (250 of the patients receiving aprotinin had complex surgeries) and 2986 patients did not.

Patients receiving aprotinin and not receiving aprotinin varied with respect to a number of important preoperative and perioperative characteristics (Table 1). Patients receiving aprotinin were older, more likely to be undergoing complex surgery, and were sicker as evidenced by a more significant history of left main disease, chronic obstructive pulmonary disease, hypertension, cerebrovascular disease, aortic stenosis, and preoperative renal dysfunction and an increased need for urgent or emergency surgery (*P* < .05 for all).

After multivariate logistic regression including propensity score adjustment, we found that patients receiving aprotinin were nearly twice as likely to experience postoperative renal dysfunction (*P* < .001) but nearly one third less likely to experience a neurologic complication compared with control (*P* = .01), although the decrease in neurologic complications with aprotinin was mainly a result in decreased delirium (Table 2). No additional differences in safety end points were noted between aprotinin and control (*P* > .53 for all comparisons). Patients receiving aprotinin were less likely to require a red blood cell transfusion or reoperation due to bleeding or tamponade compared with control (*P* < .001). Aprotinin's efficacy was mainly a result of decreased transfusion requirements (*P* < .001). In all of these multivariate analyses, propensity scores were included as a variable and were never found to be independent predictors.

TABLE 1. Pre- and intraoperative patient characteristics

	Aprotinin group (n = 362), n (%)	Control group (n = 2986), n (%)	P value
Age (y, mean $\pm$ SD)	70.7 $\pm$ 10.4	66.4 $\pm$ 10.7	<.001
Male	248 (68.5)	2226 (74.5)	.01
Race			
White	319 (88.1)	2672 (89.5)	.43
Black	4 (1.1)	67 (2.2)	.16
Hispanic	9 (2.5)	80 (2.7)	.83
Other	30 (8.3)	167 (5.6)	.04
Complex surgery	250 (69.1)	877 (29.4)	<.001
Valve surgery	172 (47.5)	689 (23.1)	<.001
Previous cardiothoracic surgery	126 (34.8)	278 (9.3)	<.001
Elective surgery	203 (56.1)	2107 (70.6)	<.001
Left main disease	92 (25.4)	624 (20.9)	.05
Number of diseased vessels (mean $\pm$ SD)	2.6 $\pm$ 0.75	2.7 $\pm$ 0.64	.007
Crossclamp time (min, mean $\pm$ SD)	104.9 $\pm$ 47.8	87.6 $\pm$ 40.7	<.001
Perfusion time (min, mean $\pm$ SD)	155.5 $\pm$ 67.7	127.0 $\pm$ 50.1	<.001
Catheterization during same admission	115 (31.8)	1382 (46.3)	<.001
History of diabetes mellitus	123 (34.0)	967 (32.4)	.54
History of chronic obstructive pulmonary disease	572 (19.9)	431 (14.4)	.006
History of hypertension	283 (78.2)	2115 (70.8)	.003
History of hyperlipidemia	256 (70.7)	2019 (67.6)	.23
History of aortic stenosis	107 (29.6)	317 (10.6)	<.001
Family history of coronary artery disease	60 (16.6)	712 (23.8)	.002
History of smoking (within 6 mo)	252 (69.6)	2016 (67.5)	.42
Morbidly obese	25 (6.9)	213 (7.1)	.87
History of peripheral vascular disease	62 (17.1)	430 (14.4)	.17
History of cerebrovascular disease	60 (16.6)	259 (8.7)	<.001
Preoperative renal dysfunction	32 (8.8)	102 (3.4)	<.001
Immunosuppression	1 (0.3)	10 (0.3)	>.99
Prior myocardial infarction	149 (41.2)	1152 (38.6)	.34
Cardiogenic shock	7 (1.9%)	47 (1.6)	.61
History of endocarditis	10 (2.8)	17 (0.6)	<.001
Preoperative aspirin use	237 (65.5)	2110 (70.7)	.04
Preoperative anticoagulation use	123 (34.0)	1043 (35.0)	.72
Preoperative digoxin use	35 (9.7)	229 (23.2)	.18
Preoperative beta-blocker use	277 (76.5)	2289 (76.7)	.95
Preoperative intravenous nitroglycerin	41 (11.3)	397 (13.3)	.29
Preoperative inotropes	9 (2.5)	48 (1.6)	.22
Preoperative steroid use	13 (3.6)	150 (5.0)	.23
Propensity score (mean $\pm$ SD)	0.30 $\pm$ 0.21	0.09 $\pm$ 0.12	<.001

When evaluating only patients undergoing complex CTS, increases in postoperative renal dysfunction and decreases in the need for red blood cell transfusions, similar to those seen in the overall analysis, were observed ($P < .024$ for both comparisons; Table 3). No other statistically significant differences between patients receiving aprotinin or control were seen in this subgroup analysis.

Discussion

Our study is unique because we utilized data from a US hospital where (1) the use of aprotinin was restricted predominantly to complex patients and Jehovah's Witnesses, (2) there was greater standardization of aprotinin dosing,

and (3) there was no use of celite-ACT determinations, which could interact with aprotinin.^{3,5,9,10} We were not able to discern elevated odds of developing MIs but found lower odds of cerebrovascular events and need for red blood cell transfusions. In contrast, the previously mentioned multicenter observational study found significantly elevated odds of both cardiac and cerebrovascular events among patients undergoing primary surgery.⁵ Although there were no significant elevations in the odds of cardiovascular and cerebrovascular events among those patients receiving complex surgery, the odds were about 30% higher for both end points in their study.⁵ The type of ACT testing performed in the previous observational study is not known, but if apprecia-

TABLE 2. Effect of aprotinin on efficacy and safety end points as determined by multivariate (propensity score adjusted) logistic regression in 3348 patients undergoing cardiothoracic surgery

End point	Total no. of events	P value	Odds ratio	95% confidence intervals
Red blood cell use or reoperation due to bleeding/tamponade	1887	<.001	0.41	0.31–0.53
Red blood cell use	1862	<.001	0.41	0.32–0.54
Renal dysfunction	182	<.001	2.03	1.37–3.01
Myocardial infarction	84	.92	1.04	0.53–2.04
Death or hospital readmission	391	.95	1.01	0.71–1.45
Death	202	.53	0.85	0.52–1.40
Stroke, TIA, or delirium	493	.01	0.65	0.46–0.91
Stroke	61	.69	0.83	0.33–2.09
TIA	8	.82	0.001	0.000–1.6E + 24
Delirium	444	.07	0.71	0.49–1.03

TIA, Transient ischemic attack. TIA occurred in 0/362 patients treated with aprotinin patients and 8/2986 control patients.

ble utilization of celite-ACTs occurred, this might help to explain the qualitative differences between our studies.⁵ In a single-center observational study conducted in Toronto, Canada comparing propensity score–matched patients receiving either aprotinin (n = 449) or tranexamic acid (n = 449), the investigators did not describe what type of ACT testing occurred but they did show a similar use of heparin among groups (50,000 ± 19,000 vs 52,000 ± 14,000 units, *P* = .10).¹¹ In that study, there was no difference in the occurrence of MI or stroke, which is similar to our present study. This suggests even more strongly that a celite-ACT aprotinin drug interaction leading to heparin underdosing might explain negative thrombotic results in the aforementioned multicenter observational study.

However, our study and the two previous observational studies found a significantly increased risk of renal dysfunction with aprotinin.^{5,11} All of our studies used renal dysfunction as an end point, which could include solely serum creatinine elevation.^{5,11} In contrast, the meta-analysis used a much more stringent definition of renal failure defined as anuria, kidney failure, acute kidney failure, kidney tubular necrosis, and uremia; which could be an explanation for

these findings.⁶ Although some drugs that increase serum creatinine do indeed increase the risk of renal failure and dialysis (amphotericin, radiocontrast dye), other drugs such as angiotensin-converting enzyme inhibitors and angiotensin receptor antagonists elevate serum creatinine but provide renal protection secondary to a reduction in glomerular filtration pressure.^{12,13}

Given the activity of aprotinin on the bradykinin system via direct inhibition of the serine protease kallikrein (the enzyme that converts kininogen to bradykinin),^{14,15} aprotinin may theoretically impact serum creatinine through a glomerular filtration pressure mechanism rather than by causing renal damage. In addition, aprotinin is primarily metabolized by the proximal convoluted tubule and could interfere with the reabsorption of other substrates.¹⁴ In a study by Fauli and colleagues,¹⁶ 60 consecutive patients with normal pre-CTS renal function underwent CTS with CPB. Patients were randomized to placebo, low-dose aprotinin, and high-dose aprotinin groups. In this study, the investigators looked at the renal elimination of alpha-1 microglobulin and beta-glucosaminidase post-CTS. Alpha-1 microglobulin is a small protein normally glomerularly filtered and then reabsorbed in the proximal convoluted tubule. Increases in alpha-1 microglobulin excretion represent subclinical renal tubular dysfunction without histologic damage. In contrast, beta-glucosaminidase is a sensitive marker of for lysosomal tubular damage indicating renal tubular injury. In the study, alpha-1 microglobulin concentrations were elevated versus placebo but beta-glucosaminidase levels were not.¹⁶ Clearly, further work on the mechanism of serum creatinine elevation with aprotinin is needed to determine whether it reflects an increased risk of kidney damage and need for dialysis or is just a laboratory anomaly.

Study Limitations

We acquired our clinical data from the hospital's CTS database. This database is used for quality control and is a part of the Society of Thoracic Surgery Database. The

TABLE 3. Effect of aprotinin on efficacy and safety end points as determined by multivariate (propensity score adjusted) logistic regression in 1127 patients undergoing complex cardiothoracic surgery

End point	Total no. of events	P value	Odds ratio	95% confidence intervals
Red blood cell use or reoperation due to bleeding/tamponade	792	<.001	0.38	0.27–0.53
Renal dysfunction	96	.02	1.76	1.08–2.88
Stroke, TIA, or delirium	221	.09	0.71	0.48–1.05
Myocardial infarction	36	.35	0.65	0.26–1.62

TIA, Transient ischemic attack.

definitions used were those specified by the Society of Thoracic Surgery and were collected using the standard data extraction form available at www.sts.org. Researchers were not involved in the determination of study end points, and the care of patients was at the discretion of their clinicians. Although this gave investigators less control over the definitions or data extraction, we were not able to introduce researcher bias into the trial, and we had prospectively collected data entered into the database from which to perform our data analysis.

In addition, investigators did not have a protocol delineating the standard use of sympathomimetics or the use of fluid resuscitation and could not ensure that the use was similar among groups.

Conclusions

In many patients undergoing complex CTS surgery without the use of celite-ACTs, our study suggests that aprotinin use is not associated with increased odds of cardiovascular or cerebrovascular events but does reduce the need for blood transfusion. Further work is needed to understand the implications of the renal dysfunction seen after CTS surgery.

References

- Desposit G, Avidan MS, Hogue CW. Mechanisms of hemostatic activation during extracorporeal circulation. *Ann Thorac Surg*. 2001; 72:1821-31.
- Kuitunen A, Hippala S, Vahtera E, Rasi V, Salmenpers M. The effects of aprotinin and tranexamic acid on thrombin generation and fibrinolytic response after cardiac surgery. *Acta Anaesthesiol Scand*. 2005; 49:1272-9.
- Serna DL, Thourani VH, Puskas JD. Antifibrinolytic agents in cardiac surgery: current controversies. *Semin Thorac Cardiovasc Surg*. 2005; 17:52-8.
- Bennet-Guerrero E, Sorohan JG, Gurevich ML, et al. Cost-benefit and efficacy of aprotinin compared with epsilon-aminocaproic acid in patients having repeat cardiac operations: a randomized, blinded clinical trial. *Anesthesiology*. 1997;87:1373-80.
- Mangano DT, Tudor IC, Dietzel C. The risk associated with aprotinin in cardiac surgery. *N Engl J Med*. 2006;354:353-65.
- Sedrakyan A, Treasure T, Elefteriades JA. Effect of aprotinin on clinical outcomes in coronary artery bypass graft surgery: a systematic review and meta-analysis of randomized clinical trials. *J Thorac Cardiovasc Surg*. 2004;128:442-8.
- Alderman E, Levy J, Rich J, et al. Analyses of coronary graft patency after aprotinin use: results from the International Multicenter Aprotinin Graft Patency Experience (IMAGE) trial. *J Thorac Cardiovasc Surg*. 1998;116:716-30.
- Levy JH. Safety of aprotinin in heparinized and nonheparinized patients. *J Cardiothorac Vasc Anesth*. 2004;18(Suppl):38s-42s.
- Ganter MT, Dalbert S, Graves K, Klaghofer R, Zollinger A, Hofer CK. Monitored activated clotting time for combined heparin and aprotinin application: an in vitro evaluation of a new aprotinin insensitive test using SONOCLOT. *Anesth Analg*. 2005;101: 308-14.
- Sundt TM, Kouchoukos NT, Saffitz JE, et al. Renal dysfunction and intravascular coagulation with aprotinin and hypothermic circulatory arrest. *Ann Thorac Surg*. 1993;55:1418-24.
- Karkouti K, Beattie WS, Dattilo KM, et al. A propensity score case-control comparison of aprotinin and tranexamic acid in high-transfusion-risk cardiac surgery. *Transfusion*. 2006;46:327-38.
- McEvoy GK, ed. AHFS Drug Information 2006. Bethesda, MD: American Society of Health-System Pharmacists, Inc.; 2006.
- Coyle JD, Gardner SF, White CM. The renal protective effects of angiotensin II receptor blockers in type 2 diabetes mellitus. *Ann Pharmacother*. 2004;38:1731-8.
- Porte RJ, Leebeek FW. Pharmacological strategies to decrease transfusion requirements in patients undergoing surgery. *Drugs*. 2002;62: 2193-211.
- White CM. Pharmacologic, pharmacokinetic and therapeutic differences among ACE inhibitors. *Pharmacother*. 1998;18:588-99.
- Fauli A, Gomar C, Campistol JM, Alvarez CL, Manig AM, Matute P. Kidney specific proteins in patients receiving aprotinin at high and low dose regimens during coronary artery bypass graft with cardiopulmonary bypass. *Eur J Anaesthesiol*. 2005;22:666-71.