Bleeding in cardiac surgery: The use of aprotinin does not affect survival

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Objective: The antifibrinolytic drug aprotinin has been the most widely used agent to reduce bleeding and its complications in cardiac surgery. Several randomized trials and meta-analyses have demonstrated it to be effective and safe. However, 2 recent reports from a single database have implicated the use of aprotinin as a risk for postoperative complications and reduced long-term survival.

Methods: In this single-institution observational study involving 7836 consecutive patients (1998–2006), we assessed the safety of using aprotinin in risk reduction strategy for postoperative bleeding.

Results: Aprotinin was used in 44% of patients. Multivariate analysis identified aprotinin use in risk reduction for reoperation for bleeding (odds ratio, 0.51; 95% confidence interval, 0.36–0.72; $P = .001$) and need for blood transfusion postoperatively (odds ratio, 0.67; 95% confidence interval, 0.57–0.79; $P = .0002$). The use of aprotinin did not affect in-hospital mortality (odds ratio, 1.03; 95% confidence interval, 0.71–1.49; $P = 0.73$), intermediate-term survival (median follow-up, 3.4 years; range, 0–8.9 years; hazard ratio, 1.09; 95% confidence interval, 0.93–1.28; $P = .30$), incidence of postoperative hemodialysis (odds ratio, 1.16; 95% confidence interval, 0.73–1.85; $P = .49$), and incidence of postoperative renal dysfunction (odds ratio, 0.78; 95% confidence interval, 0.59–1.03; $P = .07$).

Conclusion: This study demonstrates that aprotinin is effective in reducing bleeding after cardiac surgery, is safe, and does not affect short- or medium-term survival.

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Excessive postoperative bleeding during cardiac surgery occurs in 3.6% of patients undergoing coronary artery bypass grafting (CABG) and increases to 11% in those requiring more complex operations. Reoperation for bleeding increases hospital mortality 3- to 4-fold, substantially increases postoperative hospital stay, and has a sizeable effect on health care costs.[1,2] Even without the requirement for reoperation, blood loss frequently leads to transfusion of allogeneic blood products, which exposes patients to the risk of transfusion-related adverse effects, including allergic reactions, transfusion errors, and blood-borne infections. Concerns about transfusion safety, particularly in the United Kingdom, where there is the potential added risk of variant Creutzfeldt–Jakob disease, blood product shortages and increasing blood bank costs have generated an increasing interest in adopting risk-reducing strategies for postoperative bleeding. In this context the most effective and widely

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Abbreviations and Acronyms
CABG = coronary artery bypass grafting
CI = confidence interval
GFR = glomerular filtration rate
KIU = kallikrein inhibitor units

used prophylactic pharmacologic agent for reducing postoperative bleeding and bleeding complications is the antifibrinolytic drug aprotinin.[3,4]

The efficacy and safety of this drug have been reported in several systematic reviews of randomized trials,[3,5,6] but data on midterm outcomes of patients treated with aprotinin are not widely available. Two recently published and highly publicized reports from a single database[7,8] have implicated the use of aprotinin in increased short- and long-term adverse outcomes for patients undergoing cardiac surgery. This has led to a wave of adverse publicity in North America and Europe, which is threatening to alter risk reduction strategies widely used in cardiac surgery and has prompted regulatory authorities to review the safety of this drug.

The aim of our study was to review the effects and the safety of aprotinin with regard to short-term and midterm outcomes from our unit and to interpret the results in the context of the previously published reports.

Materials and Methods

Patient Population

We reviewed data from the cardiac surgical database, which holds prospectively collected clinical information on all patients undergoing cardiac surgery at our unit. The data are acquired prospectively as part of the patients' pathways and are based on the minimal dataset defined by the Society for Cardiothoracic Surgery in Great Britain and Ireland[2] with some customized additions. For the purpose of this study, we excluded patients undergoing operations requiring circulatory arrest, distal aortic surgery, transplantation, surgical intervention for thoracic trauma, and adult congenital surgery.

Data Completion

We analyzed data from January 1, 1998, to December 12, 2006. Data on aprotinin use were available on 7836 (98%) of the 7997 eligible patients, and this constitutes the population for this study (Figure 1). Data on blood product transfusion requirements were available on 7693 (98.2%) of the 7836 patients, data for need of new postoperative hemodialysis requirement were available on 7703 (98.3%) of 7836 patients, and preoperative and postoperative complete renal function data were available on 7503 (95.8%) of 7836 patients.

Study End Points

In-hospital mortality was tracked from our database, and postdischarge survival data were obtained from the National Central Cardiac Audit Database, which is linked to the Office of National Statistics (census date, January 12, 2006). In-hospital mortality was defined as death within 30 days from the operation or at any time within the same hospital admission. To enable comparison with the Mangano reports, renal dysfunction was defined as a postoperative serum creatinine level of 177 μmol/L with an increase over the preoperative baseline level of at least 62 μmol/L.[7] Percentage change in serum creatinine (% Δ Cr) level was calculated as follows: $([\textit{Highest postoperative creatinine}]/[\textit{Preoperative creatinine}]-1)\times 100\%$. The glomerular filtration rate (GFR) was estimated by using the Cockroft–Gault formula[9] and adjusted for each 1.73 m^2 of body surface area. Percentage decrease in GFR was calculated by using the following formula: $([\textit{Lowest postoperative GFR}]/[\textit{Preoperative GFR}]-1)\times 100\%$. Data on blood product transfusion is expressed as the number of patients requiring at least 1 unit of blood product. Aprotinin was administered as one million kallikrein inhibitor units (KIU) in the cardiopulmonary bypass reservoir, 2 million KIU to the patient as a loading dose, and a half million KIU/h to the patient until return to Intensive Therapy Unit (full-dose regimen).

In our institution the use of aprotinin was mainly based on surgeon choice and reserved for "high-risk" patients from 1997 through 2001. From 2002, this drug was used in an increasing numbers of patients, irrespective of their risk. Data are described for the

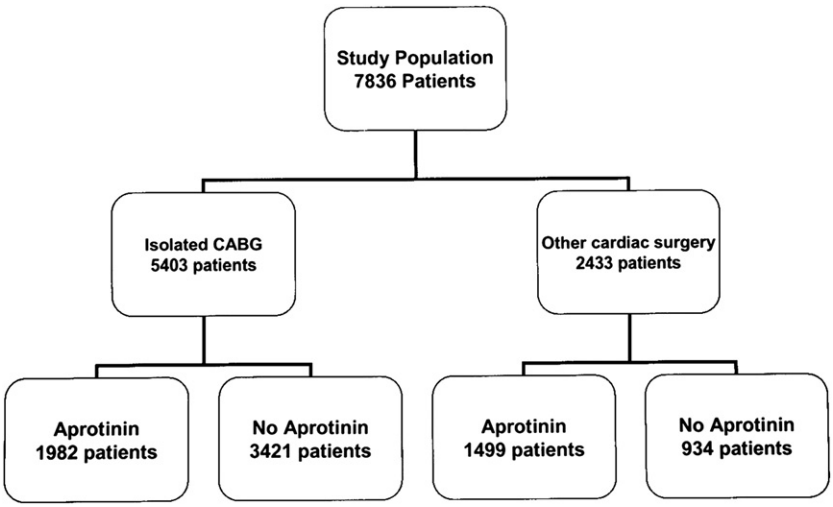

Figure 1. Flow chart of the study population. *CABG*, Coronary artery bypass grafting.

entire group, and a subanalysis of patients undergoing isolated CABG was done.

Statistical Analysis

Descriptive data are expressed as the mean ± 1 standard deviation. The level of statistical significance (α) was set at .05 (two-sided).

The risk profile in cardiac surgery is commonly assessed by using the EuroSCORE, which contains variables known to influence outcomes like age, sex, and ventricular function.[10] We developed prognostic models to examine whether there was an additional effect of aprotinin on the incidence of postoperative renal dysfunction, need for new hemodialysis, all-cause in-hospital mortality, and post-discharge survival. In these models we included the EuroSCORE value as a patient-level covariate, year of operation, diabetes, and surgeon as a random effect. For the end point of renal dysfunction and renal dialysis, we added the preoperative GFR as a patient-level covariate in the model, a known predictor of outcome even when mildly deranged.[11] The EuroSCORE was log transformed (log Euroscore) because this achieved a substantial improvement in model fit, as judged by using the Aikeke information criterion. Categorical models were conducted with PROC NLMIXED in SAS 9.1 (SAS Institute, Cary, NC). Time-to-event analyses were conducted by using approximate frailty models in the statistical package R.[12]

Results

Summary patient demographics, type of operation performed, and use of aprotinin is illustrated in Tables 1 and 2 and Figure 1. Aprotinin was used in 44.4% (3481/7836) of patients. Patients receiving aprotinin had a higher risk profile, including more severe heart failure; a higher prevalence of type II diabetes, hypertension, and peripheral vascular disease; and a higher EuroSCORE (Table 1). In addition, aprotinin patients were also more likely to undergo more complex operations (Table 1).

The overall in-hospital mortality was 3.7% (299/7836). The incidence of reoperation for bleeding was 4.9% (385/7836), and the use of aprotinin was associated with a significant risk reduction for this end point (odds ratio, 0.51; 95% confidence interval [CI], 0.36–0.72; $P = .001$; Table 3).

Patients requiring reoperation for bleeding had a significantly longer postoperative hospital stay (16 ± 17 vs 11 ± 11 days, $P < .0001$). Transfusion of blood products was required in 43% (3737/7693) of patients.

In the multivariate analysis the use of aprotinin was associated with a reduction for transfusion requirements (odds ratio, 0.67; 95% CI, 0.57–0.79; $P = .0002$).

Aprotinin and Survival

In-hospital mortality was 4.0% (139/3481) for the aprotinin group and 3.5% (154/4355) for the nonaprotinin group.

The preoperative log EuroSCORE was the strongest predictor of in-hospital mortality, whereas the use of aprotinin was not associated with an increased risk for this end point (odds ratio, 1.03; 95% CI, 0.71–1.49; $P = .85$; Table 4).

TABLE 1. Demographics in patients treated with and without aprotinin

	No aprotinin (n = 4355)	Aprotinin (n = 3481)	*P* value
Age (y)	63.8 ± 9.8	64.8 ± 11	<.0001
Female sex	1058 (24.3)	78 (28.1)	.0005
CCS class			
I	633 (14.5)	59 (27.6)	.0001
II	1422 (32.7)	123 (32.3)	
III	1037 (23.8)	821 (23.6)	
IV	1263 (29.0)	573 (16.5)	
NYHA class			
I	1387 (31.9)	825 (23.8)	<.0001
II	1864 (42.8)	1533 (44.1)	
III	832 (19.1)	799 (23.0)	
IV	271 (6.2)	316 (9.1)	
Diabetes			
Type I	284 (6.5)	219 (6.3)	<.0001
Type II (oral therapy)	351 (8.1)	407 (11.7)	
Type II (diet)	153 (3.5)	124 (3.6)	
Hypertension	2401 (55.1)	2204 (63.3)	<.0001
Peripheral vascular disease	446 (10.2)	432 (12.4)	.003
LV function			
Good (EF >50%)	2754 (63.2)	2161 (62.1)	.071
Moderate (EF 30%–49%)	1281 (29.4)	1098 (31.5)	
Poor (EF <30%)	315 (7.2)	216 (6.2)	
Previous MI	1957 (44.9)	1127 (32.3)	<.0001
EUROScore	3.8 ± 2.8	5 ± 3.4	<.0001
Urgent/emergency procedure	1507 (34.6)	1120 (32.1)	<.0001
Procedure			
CABG only	3421 (78.6)	1982 (56.9)	<.0001
Valve only	532 (12.2)	817 (23.5)	
CABG + valve	314 (7.2)	456 (13.1)	
Valve + other	16 (0.4)	103 (3)	
CABG + other	66 (1.5)	74 (2.1)	
Other cardiac surgery	6 (0.1)	49 (1.4)	

Values shown in parentheses are percentages. *CCS*, Canadian Cardiovascular Society; *NYHA*, New York Heart Association (5 missing data for the aprotinin group); *LV*, left ventricle (5 not measured in the no Aprotinin group and 6 not measured in the aprotinin group); *EF*, ejection fraction.

The lack of effect of aprotinin on in-hospital survival was independent of the preoperative EuroSCORE or the type of operation (Figure 2, *A*). Postdischarge survival data were available on 100% discharged patients. The median follow-up time was 3.4 years (0–8.9 years). The 5-year unadjusted survival was 85.2% for the nonaprotinin group and 80.8% for the aprotinin group, a difference that was highly statistically significant ($P < .0001$). However, the preoperative log EuroSCORE was the strongest independent predictor of

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TABLE 2. Surgical characteristics

	No aprotinin (n = 4355)	Aprotinin (n = 3481)	*P* value
CABG only			
EUROScore (mean ± SD)	3.2 ± 2.5	3.6 ± 2.7	<.0001
Priority (no. of patients)			
Elective	2196 (64.8)	1296 (67.5)	.19
Urgent	1159 (34.2)	602 (31.3)	
Emergency	36 (1)	23 (1.2)	
Triple-vessel disease (no. of patients)	2676 (78.9)	1559 (81.2)	.05
LMS (no patients)	653 (19.3)	560 (29.2)	<.0001
No. of CABG (mean ± SD)	2.8 ± 0.8	3.0 ± 0.9	.001
Clamp time (mean min ± SD)	45 ± 20	52 ± 21	<.0001
Bypass time (mean min ± SD)	80 ± 31	91 ± 33	<.0001
LCOS (no. of patients)	1183 (34.9)	571 (29.7)	<.0001
Reoperation (no. of patients)	176 (5.3)	56 (2.9)	<.0001
In-hospital mortality (no. of patients)	94 (2.8)	35 (1.8)	.18
Other cardiac surgery			
EUROScore (mean ± SD)	6.0 ± 2.7	6.8 ± 3.3	<.0001
Priority (no. of patients)			
Elective	649 (67.3)	1061 (68)	.001
Urgent	298 (30.9)	430 (27.6)	
Emergency	17 (1.8)	69 (4.4)	
Triple-vessel disease (no. of patients)	218 (22.7)	335 (21.5)	.052
LMS (no. of patients)	52 (5.4)	126 (8.1)	.001
No. of distals (no. of patients)	0.9 ± 1.2	0.9 ± 1.3	.91
Clamp time (mean min ± SD)	75 ± 33	91 ± 42	<.0001
Bypass time (mean min ± SD)	103 ± 46	128 ± 56	<.0001
LCOS (no. of patients)	449 (46.5)	770 (49.4)	.4
Reoperation (no. of patients)	73 (7.7)	80 (5.2)	<.0001
In-hospital mortality (no. of patients)	58 (6)	102 (6.5)	.779

Values in parentheses are percentages. *CABG*, Coronary artery bypass grafting; *SD*, standard deviation; *LMS*, left main stem; *LCOS*, low cardiac output syndrome (combined end point of use of inotropic agents, intra-operative balloon pump, or both).

long-term survival (hazard ratio, 3.51; 95% CI, 3.12–3.93; $P < .0001$). The use of aprotinin was not associated with reduced survival when accounting for log EuroSCORE, year of operation, diabetes, and surgeon as a random effect (hazard ratio, 1.09; 95% CI, 0.93–1.28; $P = .30$, Table 5). The lack of influence of aprotinin on long-term survival was independent of the preoperative EuroSCORE or the type of operation (Figure 2, *B*).

Aprotinin and Renal Function

Detailed renal function data were available on 96% (3349/3481) of patients in the aprotinin group and 95% (4154/4355) in the nonaprotinin group. The overall incidence of new postoperative hemodialysis was 2.4% (186/7703). Hemodialysis was required in 1.5% (81/5238) of the patients undergoing CABG and in 4.3% (105/2465) of the patients undergoing other cardiac operations. The incidence of new hemodialysis in patients undergoing CABG was 1.7% (33/1912) for the aprotinin group and 1.4% (48/3326) for the nonaprotinin group, and that for patients undergoing other cardiac surgery was 4.9% (75/1526) in the aprotinin group and 3.2% (30/939) in the nonaprotinin group.

In the multivariate analysis the use of aprotinin was not associated with an increased risk of requiring postoperative hemodialysis (odds ratio, 1.16; 95% CI, 0.73–1.85; $P = .49$).

TABLE 3. Multivariate analysis of risk factors for reoperation for bleeding

	Odds ratio	95% CI	*P* value
Log EuroSCORE	1.71	1.40–2.10	.0001
Diabetes	0.76	0.55–1.04	.0832
Year of operation			
1998	0.35	0.19–0.67	.0041
1999	0.85	0.49–1.47	.5344
2000	1.00	0.58–1.71	.9986
2001	1.51	0.93–2.57	.096
2002	1.11	0.68–1.81	.6503
2003	1.08	0.66–1.77	.739
2004	1.10	0.69–1.75	.6671
2005/2006	0	0–0	
Aprotinin	0.51	0.36–0.72	.0012

95% CI, 95% Confidence interval.

TABLE 4. Multivariate analysis of risk factors for in-hospital mortality

	Odds ratio	95% CI	*P* value
Log EuroSCORE	7.36	5.46–9.94	<.0001
Diabetes	1.49	1.08–2.04	.0184
Year of operation			
1998	2.29	1.30–4.06	.0084
1999	1.91	1.06–3.45	.0348
2000	2.28	1.29–4.04	.009
2001	2.41	1.35–4.31	.0065
2002	1.67	0.95–2.93	.0714
2003	1.43	0.82–2.49	.1884
2004	1.01	0.58–1.75	.9729
2005/2006	0	0–0	
Aprotinin	1.03	0.71–1.49	.851

95% CI, 95% Confidence interval.

Renal dysfunction, as defined by Mangano,[13] occurred in 3.5% of patients receiving aprotinin and 4.9% of those not treated with aprotinin. The use of aprotinin was not associated with an increase in this end point (odds ratio, 0.78; 95% CI, 0.59–1.03; $P = .07$). We subdivided patients in quartiles of renal dysfunction based on the relative changes in GFR or creatinine values after surgical intervention. Aprotinin had no effect on these end points (Table 6).

In the multivariate analysis the use of aprotinin had no significant effect on serum creatinine values postoperatively (mean change from preoperative, 3.3 μmol/L; 95% CI, −0.83 to 7.52 μmol/L; $P = .12$) or GFR postoperatively (mean change from preoperative, −0.19 mL/min per 1.73 m^2; 95% CI, −1.26 to 0.87; $P = .72$).

Discussion

The role of aprotinin in cardiac surgery has been studied in 64 prospective randomized trials, and the evidence that this drug is effective in reducing bleeding and its complications was clearly established since the 12th trial in 1992.[5,14] With regard to the safety of aprotinin, concerns have been raised since its phase II trials that it might be associated with cerebral, myocardial, and renal adverse events.[15] A recent meta-analysis of 35 randomized trials including 3879 patients undergoing CABG showed no increase in the rates of myocardial infarction, renal failure, or mortality with aprotinin but indicated a reduced stroke rate in the treatment group.[3] A larger systematic review of randomized studies that included patients undergoing CABG, other cardiac surgery, or both confirmed the safety of aprotinin with regard to operative mortality, stroke, myocardial infarction, or renal failure, but there was an increased risk of renal dysfunction in the treatment group.[6] There are no large-scale randomized studies or meta-analyses to address the effect of aprotinin on long-term survival.

In our study the use of aprotinin was associated with a significant reduction in reoperation for bleeding and need for blood transfusions. Reduction in reoperation for bleeding has been associated with a reduction in mortality, morbidity, and resource use,[1,2] whereas blood transfusions are known to confer immediate[16] and long-term risks to the patient.[17,18]

Aprotinin and Survival

Midterm and long-term survival after cardiac surgery depends on many factors, including the patients' preoperative risk profiles, the type of operation, and the postoperative complications. Aprotinin is usually administered to patients with a higher risk profile or to those undergoing more

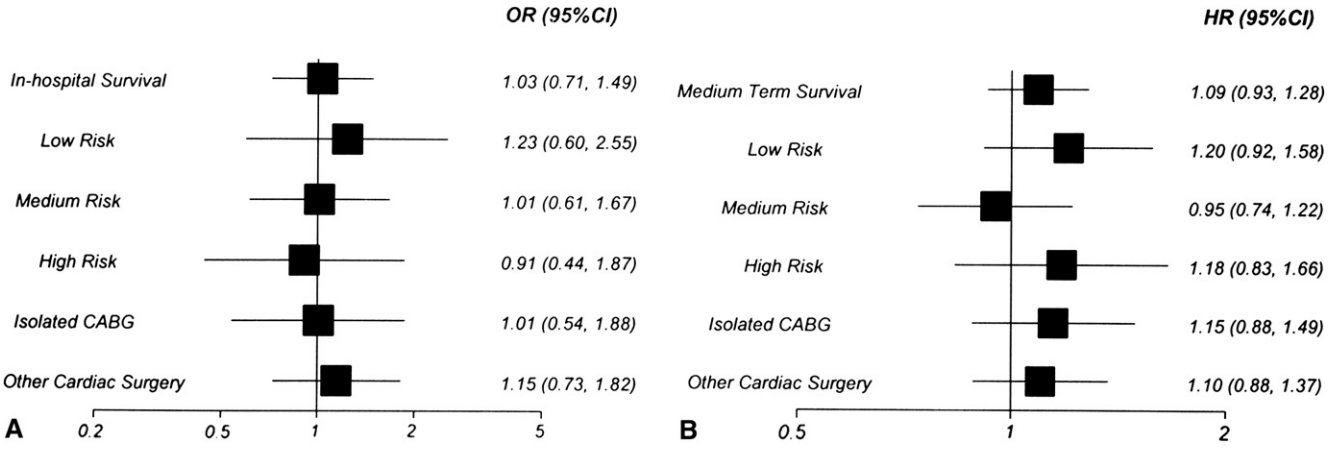

Figure 2. Forest plots illustrating the effects of aprotinin on in-hospital mortality (A) and long-term survival (B) for the entire study population and for patients with low (Euroscore 0-5), medium (Euroscore 6-9), and high (Euroscore ≥10) risk. Data also illustrate the effects of aprotinin on patients undergoing isolated coronary artery bypass grafting *(CABG)* or other cardiac surgery. *OR*, Odds ratio; *HR*, hazard ratio; *95% CI*, 95% confidence interval.

TABLE 5. Multivariate analysis of risk factors for medium-term survival

	Hazard ratio	95% CI	*P* value
Log EuroSCORE	3.51	3.12–3.93	<.0001
Diabetes	1.22	1.05–1.42	.008
Year of operation			
1998	1.58	1.17–2.13	.0031
1999	1.50	1.11–2.03	.008
2000	1.37	1.00–1.86	.048
2001	1.46	1.06–2.00	.02
2002	1.29	0.95–1.74	.10
2003	1.17	0.86–1.58	.33
2004	0.93	0.68–1.27	.65
2005/2006	0.00	0–0	
Aprotinin	1.09	0.93–1.28	.30

95% CI, 95% Confidence interval.

TABLE 6. Renal dysfunction by aprotinin group

	No aprotinin (n = 4154)	Aprotinin (n = 3349)	*P* value
Preoperative creatinine (μmol/L)	114 ± 52	115 ± 67	.0080
Peak Postoperative creatinine (μmol/L)	138 ± 84	140 ± 93	.1166
Mean increase in creatinine (μmol/L)	27 ± 60	25 ± 64	.1166
Preoperative renal impairment (no. of patients)	78 (2.1%)	103 (3.3%)	.0046
Increase in creatinine from preoperative value (no. of patients)			
<25%	3072	2449	.32
25%–<50%	536	446	
50%–<100%	296	258	
≥100%	251	196	
Decrease in GFR from preoperative value (no. of patients)			
<25%	3320	2640	.18
25%–<50%	577	511	
50%–<75%	230	182	
≥75%	18	11	
Renal dysfunction†	440	359	.45

Approximately adjusted for log Euroscore, diabetes, year of operation, and surgeon as random effects and preoperative creatinine score for postoperative measures. *GFR*, Glomerular filtration rate. *Preoperative creatinine ≥ 200 μmol/L. †According to definition used by Mangano and associates.[13]

complex operations. This constitutes a bias that needs to be addressed when analyzing observational studies. The most significant factor influencing postdischarge survival in our study was the patients' EuroSCOREs, which is in accordance with previous reports.[19-21] This finding is not surprising given that the EuroSCORE is comprised of variables, such as age, left ventricular function, pulmonary disease, and peripheral vascular disease, which are known to influence long-term survival. When accounting for these prognostic indicators, the use of aprotinin had no adverse effect on in-hospital mortality or midterm postdischarge survival in our study. These findings were at odds with the study by Mangano and colleagues.[8] In that study aprotinin was used in patients with a more adverse risk profile, among whom there was a 21% greater incidence of congestive heart failure than in the control group, 37% more pulmonary disease, 32% more renal disease, 50% more carotid disease, and 2-fold more concomitant valvular disease, all factors well known to influence survival. Propensity scores were used to handle selection bias in their observational study. However, it is known that if the number of variables for which to match is increased, matching is not practical. In our study, although patients receiving aprotinin have a worse preoperative risk profile, the overall risk spread appears more balanced (Table 1) than in the report by Mangano and colleagues.[8] This is possibly due to the fact that since 2002, there was an increasing use of aprotinin in most patients, irrespective of their preoperative risk (Figure 3). The study by Mangano and colleagues reports the long-term outcomes of patients undergoing CABG, and our findings extend to other common cardiac surgical operations.

Aprotinin and Renal Complications

A deterioration in postoperative renal function, particularly when leading to hemodialysis, is associated with increased in-hospital mortality and a decreased postdischarge survival.[13] The reported incidence of renal dysfunction after cardiac surgery is dependent on the definition used and ranges between 0.9% and 29%.[22-24] In addition, postoperative renal function is influenced by many preoperative and intraoperative risk factors.[13,25] Previous studies have suggested an association between the use of aprotinin and a transient increase in postoperative serum creatinine levels.[26] A meta-analysis including only patients undergoing CABG showed no difference in the incidence of postoperative renal complications between aprotinin and placebo.[3] A recent meta-analysis that included patients undergoing valvular heart surgery has shown that aprotinin is associated with an increased risk for postoperative renal dysfunction.[6] In this study renal dysfunction was defined as an increase in postoperative creatinine value of 40 μmol/L from the preoperative value. In our study we used 2 different definitions to identify renal dysfunction: an absolute change in postoperative creatinine value, as reported by Mangano and colleagues,[7] to allow direct comparison with their study and a relative change in either creatinine or GFR after the operation, which is known to be more accurate in predicting outcome.[27] We found that the use of aprotinin was not associated with a change in serum creatinine

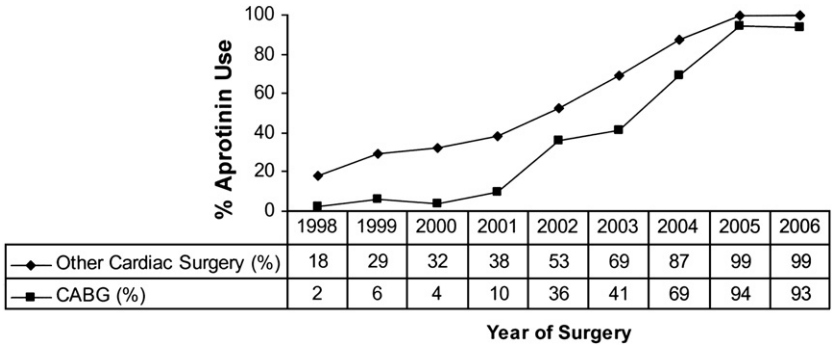

Figure 3. Graph illustrating the percentage of patients undergoing coronary artery bypass grafting *(CABG)* and those undergoing other cardiac operations in which aprotinin had been used at out institution.

values or in estimated GFR postoperatively. Our findings were at odds with the report from Mangano and colleagues.[7] In their study patients receiving aprotinin had a significantly higher incidence of risk factors known to increase the risk of renal dysfunction after surgical intervention.[14] In our analysis we have attempted to adjust for factors like preoperative EuroSCORE, GFR, age, diabetes, and year of operation. Mangano and colleagues[7] do not report data on patient age, cardiopulmonary bypass time, and use of aspirin, factors well known to influence postoperative renal function, as reported by the same authors in other publications.[28] In one study by Mangano and colleagues[7] the incidence of renal dysfunction was 2% in the control group. This is lower than the 7.7% incidence previously reported by the same group, apparently using the same database of patients, and among the lowest reported in the literature.[13] In our study, when using the same definition as the study by Mangano and colleagues,[7] renal dysfunction occurred in 4.9% of patients without aprotinin, and this finding is in accordance with a number of previous reports.[13,22,29,30] Furthermore, the incidence of renal dysfunction in our aprotinin group was lower than that in the aprotinin group in the study by Mangano and colleagues (3.5% vs 5%).[7] Changes of serum creatinine values from the preoperative value predict outcome more accurately.[27] A postoperative increase in serum creatinine value of 50% or greater from its preoperative value is clinically significant and affects in-hospital and long-term outcome.[27] When using this threshold, the use of aprotinin was not associated with an increase in the incidence of this end point in our study. This was the case across all ranges of preoperative creatinine values (data not shown).

Finally, there was no difference in the incidence of new hemodialysis between the aprotinin and nonaprotinin groups, and this is in accordance with all randomized studies.[3,6]

Study Limitations

The first limitation of our study is inherent in its observational nature. Statistical modeling might go some way toward accounting for differences in risk between subjects but provides imperfect adjustment and remains open to residual confounding. In a study examining the risk associated with the use of aprotinin, it appears likely that a latent risk is described simply by the choice of the clinician to use or not to use the agent in subjects who appear otherwise at the same apparent risk. The use of aprotinin in the early years of our study was reserved for patients with a higher risk profile, which introduces an inherent bias against aprotinin. The changing selection criteria for aprotinin use over time is a strength of the study because this changing selection bias could be conditioned for by including year of intervention as a patient level factor in the analysis. Our study is based on a single-center experience that encompasses the data from only 8 surgeons. Although this can be seen as a potential limitation, it eliminates institutional influences inherent in studies in which data are derived from a mixture of small-volume institutions, which might be important when nonrandomized studies are reported.

Our dataset was not intended to study the effects of aprotinin, and therefore we do not have data on the incidence of postoperative new myocardial infarction. The incidence of low cardiac output syndrome, however, a combined end point of use of an intra-aortic balloon pump, inotropic support, or both, was not increased in the aprotinin group (Table 2).

In summary, with all the limitations of reporting observational studies involving an agent that is normally administered to patients with a higher risk profile, our study indicates that the use of aprotinin, although beneficial in reducing the risk of bleeding and the need for blood transfusion, is not associated with adverse effects on renal function or postdischarge survival. Based on the presented evidence, the withdrawal of aprotinin from cardiac surgeons' risk reduction armamentarium will seriously threaten patient safety for no perceptible gain and might cost lives.

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