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Safety of Low-Dose Aprotinin in Coronary Artery Bypass Graft Surgery

A Single-Centre Investigation in 2436 Patients in Germany

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Abstract

Background: The antifibrinolytic agent aprotinin is used to limit blood loss in cardiac surgery. In a recently performed multicentre observational study, the use of aprotinin was dose-dependently associated with a higher risk of renal failure and cardiovascular events.

Objective: Therefore, the aim of this study was to evaluate the impact of low-dose aprotinin (2 million kallikrein-inhibitor units) on safety variables in a large single-centre investigation in patients who underwent coronary artery bypass graft (CABG) surgery.

Methods: Clinical outcome variables such as renal failure, myocardial infarction, gastrointestinal failure, neurological complications and in-hospital mortality were assessed in 2436 CABG surgery patients, whereof 1162 patients received low-dose aprotinin perioperatively and 1274 patients did not receive aprotinin. Statistical analysis was performed using multivariable logistic regression.

Results: In patients receiving aprotinin, the odds ratios of experiencing one of the aforementioned adverse events were not significantly different from the patients who did not receive aprotinin ($p = 0.136–0.288$). Moreover, the need for rethoracotomy did not differ between the two groups ($p = 0.129$). However, the use of low-dose aprotinin reduced the risk of peri- and postoperative use of packed red blood cells by 39% and was associated with a mean reduction in postoperative blood loss of 201 mL compared with patients who did not receive aprotinin ($p < 0.001$). Mean total blood loss in the aprotinin group and the control group was 875 mL (standard deviation [SD]: 757 mL) and 1105 mL (SD: 867 mL), respectively ($p < 0.001$). In a sub-analysis in 2049 patients undergoing their first cardiac surgery and undergoing CABG using the internal mammary artery, efficacy and safety data of aprotinin were similar to the results of the entire study cohort of 2436 patients.

Conclusions: Our data indicate that low-dose aprotinin efficiently reduces blood loss and does not adversely affect relevant safety variables in CABG surgery.

Background

Antifibrinolytic therapy is used to limit postoperative blood loss in cardiac surgery. Prospective, randomized, placebo-controlled trials (RCTs) have demonstrated that the antifibrinolytic agent aprotinin reduces transfusion requirements in coronary artery bypass graft (CABG) surgery.[1] In addition, the use of aprotinin seems to be associated with a reduction in platelet transfusion in thoracic aortic surgery.[2] There is also evidence from a retrospective analysis of RCTs that aprotinin use may be associated with a lower risk of adverse cerebrovascular outcomes and a reduced need for the use of vasoactive drugs in coronary artery bypass surgery.[3] The regular aprotinin dose recommended by the manufacturer is 2 million kallikrein-inhibitor units (KIU) bolus, 2 million KIU in the pump prime and 500 000 KIU hourly via infusion. The safety of aprotinin has recently been questioned by some observational studies: Kincaid et al.[4] and Karkouti et al.[5] reported that aprotinin use was more often associated with renal dysfunction/failure in cardiac surgery compared with the antifibrinolytic agents aminocaproic acid or tranexamic acid. The very large observational multicentre study of Mangano et al.[6] also supports the assumption that aprotinin use may be related to renal events. In addition, in the study by Mangano et al.,[6] aprotinin use was associated with a higher risk of myocardial infarction or heart failure, and stroke or encephalopathy in primary surgery. Neither aminocaproic acid nor tranexamic acid was found to increase the risk of renal, cardiac or cerebral events. The same group also reported that aprotinin treatment was associated with a significant increase in 5-year mortality compared with a control group without use of antifibrinolytic agents, whereas neither aminocaproic acid nor tranexamic acid was associated with an increased mortality risk.[7]

However, the aforementioned retrospective data must be regarded as preliminary. In the study of Kincaid et al.,[4] the risk of renal failure was only significantly enhanced when combining the preoperative use of ACE inhibitors with intraoperative use of aprotinin. Karkouti et al.[5] themselves argued that several limitations in their study design cannot rule out a study bias in favour of tranexamic acid. Even the very large investigations of Mangano et al.,[6,7] have several limitations, such as the wide variation in the use of antifibrinolytic agents across surgeons, sites and countries.[8] Although a recently published retrospective study supports the safety concerns regarding aprotinin,[9] this study also suffers from several limitations, such as a relatively small number of patients in the aprotinin group and significant differences between the aprotinin and control groups with regard to various pre- and intraoperative parameters. Moreover, the adverse effects described in the aforementioned studies[4-6,9] have been observed with the regular aprotinin dose, also called high-dose aprotinin. Since low-dose aprotinin (2 million KIU in pump prime only) also reduces blood loss and transfusion requirements very effectively,[10,11] we exclusively used this dose at our institution. Therefore, we performed a single-centre study in a homogenous and large cohort of patients to investigate the effects of low-dose aprotinin use on safety variables in cardiac surgery.

Materials and Methods

Patients and Study Design

This report summarizes data obtained in 2436 cardiac surgery patients at our institution, Heart Center North-Rhine Westfalia, Ruhr University Bochum, Germany between August 2005 and July 2006. We screened all patients who underwent isolated CABG surgery. Between August 2005 and January 2006, 1062 patients (79.5%) received low-dose aprotinin (2 million KIU in pump prime; Bayer, Leverkusen, Germany) perioperatively, whereas 274 patients (20.5%) received no antifibrinolytic agent. Aprotinin was given in all internal mammary artery bypass surgeries and in all cardiac redo surgery. In addition, patients with platelet dysfunction (including patients with a prescription for clopidogrel or aspirin (acetylsalicylic acid) received aprotinin. The remaining 274 patients had their first cardiac surgery and did not receive an internal mammary artery bypass and therefore did not receive

aprotinin. Between February 2006 and July 2006 (after publication of Mangano's article in *The New England Journal of Medicine* in January 2006), 1000 patients (90.9%) received no antifibrinolytic agent, whereas 100 patients (9.1%) still received low-dose aprotinin (2 million KIU in pump prime) perioperatively. The majority of the 100 patients (58%) who still received aprotinin were operated on in February 2006. Since February 2006, aprotinin was not administered to specific patient groups. Moreover, it was the general strategy at our institution not to use higher dosages of aprotinin or other antifibrinolytic agents. In total, 1162 patients could be allocated to the aprotinin group. The 1274 patients not administered aprotinin comprised the control group. We used the electronic records of the patients to assess age, sex and anthropometric data. For haemoglobin and creatinine analysis, blood samples were collected 1–3 days before surgery. Creatinine and haemoglobin concentrations were also assessed at the intensive care unit (ICU). We measured creatinine by the autoanalyser Architect (Abbott, Wiesbaden, Germany) and haemoglobin by Abbott CellDyn 3500 haematology analyser (Abbott, Wiesbaden, Germany). At our institution, packed red blood cells (PRBCs) were given when haemoglobin levels were <9 g/dL or haemoglobin levels were between 9 g/dL and 11 g/dL and blood lactate levels were >2 mmol/L or mixed venous oxygen saturation (SvO_2) values were <70%. Fresh frozen plasma (FFP) was administered to bleeding patients (100 mL drain volume per hour) with prolongation of partial thromboplastin time and elevated international normalized ratio values (>1.5). Platelet concentrates (PCs) were administered to bleeding patients (100 mL drain volume per hour) with either low platelet counts (<80 000 per μL) or use of platelet aggregation inhibitors (e.g. aspirin or clopidogrel). Peri- and postoperative blood requirement was assessed using our blood bank records. The total number of PRBC included peri- and postoperative transfusions. We recorded the numbers of PRBCs, FFPs and PCs needed in each patient. We assessed peri-operative blood loss by measuring peri-operative suction volume before the patient reached the ICU. We measured postoperative blood loss within the first 2 postoperative days by collecting total drain volume during the stay at the ICU.

We also assessed clinical complications. Renal failure was defined as a new requirement for haemofiltration/dialysis or an increase in serum creatinine to >2.0 mg/dL and twice the baseline creatinine level. Intestinal failure was defined as a requirement for laparotomy. Myocardial infarction was defined as creatine kinase (CK) MB levels >10% of total CK. CK and its MB isoenzyme were measured every 4 hours on the day of surgery, three times a day on postoperative days 1–3 and daily thereafter until discharge. Myocardial infarction was verified by typical electrocardiogram changes. Neurological complications were defined as the occurrence of a stroke (central neurological deficit persisting for >72 hours) or a transient ischaemic attack (TIA; transient neurological deficit with recovery within 24 hours). A formal consultation by a neurologist was obtained for all neurological events. In-hospital mortality was assessed from the medical records.

Anaesthetic/Surgical Technique

Premedication consisted of lormetazepam 1–3 mg orally and morphine 10–15 mg subcutaneously (table I shows the manufacturer and manufacturer's location of drugs administered). Thereafter, anaesthesia was induced with etomidate 0.15–0.2 mg/kg, and fentanyl 2–3 μg/kg intravenously (IV) and pancuronium-bromide IV 0.1 mg/kg or rocuronium bromide IV 0.7 mg/kg. After tracheal intubation, anaesthesia was maintained with sevoflurane in oxygen/air.

Patients were cooled down to minimum blood and rectal temperatures of 27°C and 32°C, respectively. The left ventricle was vented via the right superior pulmonary vein. Ventricular fibrillation was induced either spontaneously or electrically. We cross-clamped the aorta intermittently while we performed distal anastomoses. Proximal anastomoses were sewn after cross clamp release using partial exclusion of the aorta by a side biting clamp.

Table I. Manufacturers of drugs used during the trial

Drug	Manufacturer and location
Lormetazepam	Schering, Berlin, Germany
Morphine	Ratiopharm, Ulm, Germany
Etomidate	B.Braun, Melsungen, Germany
Fentanyl	Janssen-Cilag, Neuss, Germany
Pancuronium-bromide	Delta-Select, Dreieich, Germany
Rocuronium bromide	Organon Technika, Oberschleißheim, Germany
Sevoflurane	Baxter, Unterschleißheim, Germany
Heparin	Roche, Grenzach-Wyhlen, Germany
Mannitol	B.Braun, Melsungen, Germany

Patients were perfused with a heparin-coated extracorporeal circulation (ECC)-set (HMT GmbH, Fürstenfeldbrück, Germany). The ECC-set operates with roller pumps in combination with an open coronary suction system. All components of the ECC-circuit are disposable. Intravenous heparin was administered in an initial dose of 300 IU/kg bodyweight. Intraoperatively, activated clotting time (ACT) was monitored at 20-minute intervals and was kept above 400 seconds. The ECC-system was primed with Ringer Lactate solution (1800 mL) in combination with 100 mL of 8.4% Na_2HCO_3. During rewarming, 2–3 mL/kg of 20% mannitol was added. Cannulas for ECC were placed in the ascending aorta, and venous drainage was installed via the superior and inferior caval veins. Nonpulsatile flow of 2.4 L/min × m was maintained. During weaning, inotropic support was only given if required to achieve haemodynamic stability. In order to achieve pre-ECC ACT values, we administered the same protamine dose after ECC weaning was finished compared with the heparin dose during ECC use. Residual volume from the ECC was infused as first choice fluid administration. Surgical/anaesthetic technique did not differ between the two study periods.

Statistics

Categorical variables are reported using the percentage of observations. Continuous variables are expressed as mean and standard deviation unless otherwise stated. We tested normal distribution of the data using the Kolmogorov-Smirnov test. Normal distribution was considered if p-values were >0.05. For comparative analyses between groups, we used Fisher's exact test, the unpaired student's t-test and the Mann-Whitney U test when appropriate. The associations between study groups and clinical outcomes were assessed by means of risk-adjusted multivariable logistic regression. We first conducted univariable analysis to examine the association between the occurrence of the endpoint of interest (renal failure, gastrointestinal failure, myocardial infarction, neurological complications, in-hospital mortality) and pre- and perioperative variables. All variables with a p-value <0.15 in the univariable analysis were entered into the multivariable regression model. These variables included aprotinin, sex, age, height, weight, diabetes mellitus, preoperative renal insufficiency, preoperative myocardial infarction, carotid stenosis, New York Heart Association (NYHA) functional class ≥III, preoperative haemoglobin, ACE inhibitors, nitrates, dopamine and adrenaline (epinephrine). We calculated the odds ratios (OR) and 95% CIs of having an event by aprotinin group with the control group being the reference group. We also performed multivariable logistic regression analysis in the subgroup of 2049 patients who had their first cardiac surgery and whose coronary artery bypass surgery was performed by using the internal mammary artery. This is a very homogenous group. In addition, this group also has a higher blood requirement than patients where other grafts are used, such as saphenous veins.[12]

Since treatment assignment was not based on random allocation and the aprotinin and control group were therefore not expected to be completely

comparable with regard to important covariates, we also analysed whether propensity score adjustments are necessary. We used 29 demographic and preoperative variables for each patient, using logistic regression. The propensity score ranged from a low of 0.00 to a high of 0.89. The discriminate power of the propensity score was quantified by measurement of the receiver operating characteristics area and was found to be 0.519 only. Therefore, we did not include the propensity score in overall multivariable logistic regression model. We used the statistical software package SPSS, version 14 (Chicago, IL, USA) to perform the analysis.

Results

Characteristics of the aprotinin group and control group are presented in table II. The two groups differed slightly with respect to some preoperative parameters. In detail, the aprotinin group was significantly younger and taller, less often required elective surgery, experienced renal insufficiency less often, had lower serum creatinine levels and needed ACE inhibitors less often than the control group. Cardiac surgery was more often a redo in the aprotinin group than in the control group. Few patients in either study group received preoperative antiplatelet medication.

Perioperative blood loss was 260 ± 217 mL in the aprotinin group and 288 ± 246 mL in the control group ($p < 0.001$). Postoperative blood loss of the two study groups is illustrated in figure 1. Mean blood loss was 201 mL lower in the aprotinin group than in the control group (615 mL vs 816 mL). Total (perioperative and postoperative) blood loss in the aprotinin group and the control group was 875 ± 757 mL and 1105 ± 867 mL, respectively ($p < 0.001$). Other outcome parameters of the two groups are presented in table III. As determined by multivariable regression analysis, aprotinin use reduced the risk of perioperative and postoperative PRBC transfusion by 39%, whereas the need for FFPs and PCs was not influenced by aprotinin use. The total number of transfused units of PRBC per patient was 2.64 ± 4.30 in the aprotinin group and 3.05 ± 4.75 in the control group ($p < 0.001$). Aprotinin use did not significantly affect the need for rethoracotomy. The use of aprotinin was not associated with an increased risk of adverse safety outcomes such as renal failure, myocardial infarction, intestinal failure, neurological complications and in-hospital death. Although ORs for some safety variables such as the need for rethoracotomy and neurological complications were <1.0, 95% CIs included 1.0, indicating no statistically significant beneficial effect of aprotinin use. Note that the total number of events influences the chance of achieving a statistically significant result with a small number of events leading to a lower probability of a significant result compared with a high number of events.

We additionally evaluated the effect of aprotinin use on renal dysfunction (postoperative creatinine increase >0.5 mg/dL). Again, no significant effect of aprotinin use was seen compared with controls (OR: 1.08; CI 0.87, 1.33; $p = 0.515$). As expected, age was an important risk factor for all adverse safety outcomes, with the exception of rethoracotomy. Each year of age increased the risk of an adverse event by 4% (myocardial infarction) to 9% (in-hospital death).

When only evaluating the 2049 patients undergoing their first cardiac surgery and having CABG using the internal mammary artery, decreases in the need for PRBCs, similar to those seen in the overall analysis, were observed (table IV). In this subgroup, aprotinin use was associated with a 228 mL lower blood loss than nonuse of aprotinin ($p < 0.001$). No other statistically significant differences between the aprotinin and the control group were seen.

Discussion

This large retrospective study in patients undergoing CABG surgery could demonstrate that the use of low-dose aprotinin is associated with a mean reduction in postoperative blood loss of 201 mL and a 39% lower risk for PRBC transfusion. However, data do not indicate that low-dose aprotinin use adversely affects relevant outcome parameters.

Our results on blood loss and red blood cell use are in line with data of a recently published meta-analysis of RCTs and a 2007 Cochrane update.[13,14]

Table II. Characteristics of the study groups[a]

Parameter	Aprotinin group (n = 1162)	Control group (n = 1274)	p-Value
Age (y)	66.8 ± 9.5	67.8 ± 9.1	0.005
Height (cm)	172 ± 9	171 ± 9	0.005
Weight (kg)	81.7 ± 13.6	81.5 ± 14.1	0.699
Body mass index (kg/m^2)	27.5 ± 3.8	27.7 ± 4.0	0.158
Sex distribution (% males)	80.1	77.1	0.075
Preoperative diagnoses (%)			
redo	7.3	4.1	0.001
myocardial infarction	43.6	41.1	0.218
carotid stenosis	8.3	9.5	0.319
PTCA	20.4	21.7	0.456
peripheral arterial occlusive disease	14.7	15.8	0.347
neurological disorders	12.3	12.0	0.852
diabetes mellitus[b]	29.3	28.9	0.858
liver insufficiency[c]	9.6	9.7	1.000
renal impairment[d]	18.8	22.8	0.014
Clinical and biochemical parameters			
elective surgery (%)	67.8	73.1	0.004
NYHA functional class III or intravenously (%)	61.1	60.2	0.230
creatinine (mg/dL)	1.13 ± 0.65	1.25 ± 1.4	0.007
haemoglobin (g/dL)	13.4 ± 1.5	13.4 ± 1.5	0.875
Medication until surgery (%)			
nitrates (intravenous)	7.5	5.8	0.103
anticoagulants, e.g. heparin, phenprocoumon	72.5	75.4	0.106
aspirin (acetylsalicylic acid)	1.3	1.2	0.855
ACE inhibitors	61.3	66.1	0.014
Intraoperative data			
operation time (min)	165 ± 35	160 ± 37	0.218
cardiopulmonary bypass time (min)	80 ± 69	90 ± 72	<0.001
IABP use (%)	1.3	1.3	1.000
dopamine use (%)	5.7	5.5	0.860
dobutamine use (%)	0.94	0.47	0.223
adrenaline (epinephrine) use (%)	1.3	0.4	0.022
noradrenaline (norepinephrine) use (%)	8.4	9.7	0.291

a Mean ± standard deviation unless otherwise specified.

b Insulin-dependent and orally treated diabetes mellitus.

c Bilirubin >2.0 mg/dL.

d Creatinine >1.5 mg/dL.

IABP = intra-aortic balloon pump; **NYHA** = New York Heart Association; **PTCA** = percutaneous transluminal coronary angioplasty.

The meta-analysis revealed a mean blood loss reduction of 226 mL with low-dose aprotonin and a relative risk (RR) for red blood cell transfusion of 0.76 compared with nonuse of aprotinin. Our data do not confirm the beneficial effects of aprotinin on platelet use that were observed in a relatively small case-control study of aortic surgery.[2] Moreover, our results do not confirm the safety concerns regarding aprotinin use, which are mainly based on recently published observational studies.[4,6,9] In the studies of Kincaid et al.[4] and Coleman et al.,[9] the use of high-dose aprotinin was associated with an increased risk of renal failure. In the study of Mangano et al.,[6] the effect of aprotinin on renal events

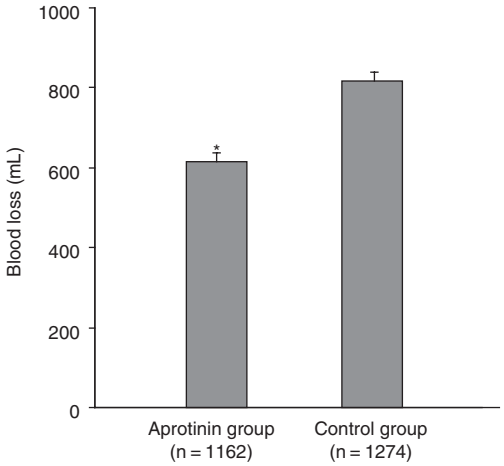

Fig. 1. Postoperative blood loss in coronary artery bypass graft surgery according to aprotinin use and nonuse (control group) [mean ± standard error of the mean]. * $p < 0.001$ vs control group.

was dose-dependent, with the highest incidence of events in the high-dose aprotinin group. Our results are in line with the aforementioned meta-analysis of RCTs.[13] This analysis demonstrates that high-dose aprotinin but not low-dose aprotinin increases the risk of renal failure compared with aprotinin nonuse. In a recently published very large observational multicentre study, the overall incidence of postoperative renal failure was significantly enhanced in the aprotinin subset. However, after risk adjustment with the addition of the highly significant transfused PRBC variable to the model, the purported independent effect of aprotinin on postoperative renal failure in cardiac surgery patients disappeared.[15]

The effects of aprotinin on neurological complications are inconclusive. A lower risk of adverse cerebrovascular outcomes has been observed in an earlier retrospective analysis of RCTs in patients receiving high-dose aprotinin.[3] Coleman et al.[9] reported that high-dose aprotinin use was associated with a lower risk of neurological complications. This result was mainly due to a decreased number of patients with delirium. Mangano et al.[6] reported a significant increase in the risk of stroke or encephalopathy with high-dose aprotinin compared with nonuse of aprotinin. In our investigation, the risk of neurological complications such as TIA and stroke was not affected by the use of aprotinin. Again, our results are in line with the aforementioned meta-analysis,[13] which demonstrated that neither low- nor high-dose aprotinin alters the incidence of stroke. With regard to myocardial infarction and mortality, our data are also in line with results of the meta-analysis of RCTs and the Cochrane update 2007.[13,14]

Our study has some strengths and limitations. The number of patients who received low-dose aprotinin or did not receive aprotinin in our investigation is comparable to or even higher than that in the multicentre observational study of Mangano et al.[6] or the meta-analysis of Brown et al.[13] Consequently, our investigation is the largest single-centre study on adverse effects of low-dose aprotinin in CABG surgery. An additional strength of our investigation is the short period of patient recruitment. This may limit sources of bias such as changes in surgical/anaesthetic procedures over time. The po-

Table III. Efficacy and safety of aprotinin as determined by multivariable logistic regression in 2436 cardiac surgery patients

Endpoint	Total number of events		Odds ratio (95% CI)	p-Value
	aprotinin group (n = 1162)	control group (n = 1274)		
Red blood cell use	642	808	0.61 (0.49, 0.76)	<0.001
Fresh frozen plasma use	135	175	0.89 (0.68, 1.16)	0.386
Platelet use	52	46	1.25 (0.79, 1.98)	0.350
Rethoracotomy	19	30	0.63 (0.35, 1.14)	0.129
Renal failure	70	70	1.43 (0.84, 2.44)	0.225
Myocardial infarction	48	45	1.32 (0.82, 2.13)	0.254
Intestinal failure	22	14	1.51 (0.74, 3.08)	0.256
Neurological complications	80	102	0.82 (0.59, 1.15)	0.258
In-hospital death	29	28	1.59 (0.86, 2.93)	0.136

Table IV. Efficacy and safety of aprotinin as determined by multivariable logistic regression in a sub group of 2049 patients undergoing their first cardiac surgery and having coronary artery bypass grafting using the internal mammary artery

Endpoint	Total number of events		Odds ratio (95% CI)	p-Value
	aprotinin group (n = 1057)	control group (n = 992)		
Red blood cell use	621	687	0.50 (0.37, 0.66)	<0.001
Fresh frozen plasma use	115	139	0.82 (0.60, 1.11)	0.200
Platelet use	36	36	0.88 (0.52, 1.48)	0.627
Rethoracotomy	17	21	0.84 (0.44, 1.61)	0.595
Renal failure	55	54	1.11 (0.74, 1.65)	0.618
Myocardial infarction	31	28	1.40 (0.78, 2.50)	0.257
Intestinal failure	21	9	1.65 (0.74, 3.69)	0.220
Neurological complications	61	84	0.75 (0.51, 1.10)	0.137
In-hospital death	20	17	1.40 (0.67, 2.93)	0.378

tential problem of a relatively healthy subgroup without aprotinin use in the pre-Mangano period, and a very sick subgroup with aprotinin use in the post-Mangano period, was largely avoided by the way we indicated aprotinin use and nonuse at our institution in the first and second study period (see materials and methods section). This resulted in two relatively homogenous study groups, which is also confirmed by the fact that a propensity score adjustment was not necessary. Moreover, our data are not influenced by site-level confounding, which is a characteristic of multicentre observational analyses. Note that site-level confounding is difficult to address with propensity analysis technique alone.[8] A limitation of our study is that myocardial infarction was assessed by analysis of CK and its MB isoenzyme only. Although we measured these parameters frequently, we cannot definitively rule out that we underestimated the postoperative incidence of myocardial infarction. However, this limitation would affect both study groups equally. Potential sources of bias includes the significantly lower prevalence of preoperative renal insufficiency, the less frequent use of ACE inhibitors, and the lower age in the aprotinin group compared with the control group. It is obvious that the risk of renal impairment is already higher in patients with a relatively high prevalence of preoperative renal insufficiency. Moreover, increased age and the preoperative use of ACE inhibitors along with intraoperative use of aprotinin have been identified as risk factors for renal impairment.[4] However, although statistically significant, the differences between the aprotinin and control group were rather small in our investigation. Moreover, our statistical model was designed to control for these factors. With regard to increased age, we were able to demonstrate that this was an important risk factor for all adverse safety outcomes.

The study of aprotinin by Mangano et al.[6] stands as an example of the importance of phase IV clinical trials. Observational studies are considered to permit the evaluation of drug safety in a large number of patients in a real-world setting. Although post-marketing, randomized controlled trials would provide robust data on drug safety, it has been argued that these studies may be subject to multiple sources of bias.[16] However, observational studies may not identify and measure all relevant covariates. Similar studies using a few different covariates may sometimes come to opposite conclusions.[16] Even in our two very similar study groups, we cannot definitively rule out that we did not consider all relevant covariates in the analysis. Fortunately, we were able to compare our efficacy and safety data with those of the recently published meta-analysis of RCTs by Brown et al.[13] Note that neither our data nor the meta-analysis of RCTs confirm the safety concerns of Mangano et al.[6] against aprotinin with regard to neurological complications and myocardial infarction, indicating that site-level confounding may indeed have played a role in the multicentre observational study of Mangano et al.[6]

Are there lessons we have to learn from the safety discussion on aprotinin? In 2004, 96 340 cardiac surgery procedures have been performed in the 79 cardiothoracic centres in Germany, of which 67 216 procedures have been CABG surgery.[17] Why should we not demand RCTs instead of observational phase IV studies for drugs that are frequently used perioperatively and where alternative strategies are available? Relevant in-hospital endpoints can easily be assessed. The design of our investigation indicates that such a demand is realistic. Much more than observational studies can do, large RCTs could provide important new safety information. Even if this safety information turns out to be incomplete, it could be very helpful in directing further scientific and regulatory actions if necessary. Therefore, independent RCTs in phase IV testing should be encouraged and supported. The BART (Blood Conservation using Anti-Fibrinolytics: A Randomized Trial) study is an independent, randomized controlled trial being conducted in 2970 cardiac surgery patients. Very recently, the BART study was halted after a planned periodic data analysis indicated an increase in all-cause mortality that almost reached statistical significance for 30-day mortality for patients in the aprotinin treatment arm compared with patients who received either aminocaproic acid or tranexamic acid.[18] Therefore, Bayer stopped sales of aprotinin globally. Patients of the BART study received the regular high-dose aprotinin dose (2 million KIU bolus, 2 million KIU in pump prime and 2 million KIU via infusion over 4 hours), which is much higher than the aprotinin dose our patients received. In the BART study, the RR of death from any cause at 30 days in the aprotinin group, compared with that in both groups receiving lysine analogues, was 1.53 (95% CI 1.06, 2.22). In our investigation, the OR of in-hospital death in the aprotinin group compared with the control group was of the same magnitude as 30-day mortality in the BART study, but did not achieve statistical significance (OR 1.59; 95% CI 0.86, 2.93). Given these new findings from the BART study, the safety of low-dose aprotinin must be documented by randomized controlled trials before this dosage can be recommended in CABG surgery. Together, our data and results of the BART study strengthen the general need for systematic drug studies with different dosages. Since the withdrawal of aprotinin, we do not use antifibrinolytic agents at our institution. At present, FFP, PCs, fibrinogen and factor VII concentrates are given in patients with a high bleeding risk, if necessary.

Conclusion

In summary, our data indicate that low-dose aprotinin reduces blood loss, but does not adversely affect relevant safety variables in cardiac surgery.

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