ORIGINAL RESEARCH

Safety of Perioperative Aprotinin Administration During Isolated Coronary Artery Bypass Graft Surgery: Insights From the ART (Arterial Revascularization Trial)

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***Background*—**There is still uncertainty about the safety of aprotinin for coronary artery bypass graft surgery. The ART (Arterial Revascularization Trial) was designed to compare survival after bilateral versus single internal thoracic artery grafting. Many of the ART patients (≈30%) received perioperative aprotinin. We investigated the association between perioperative aprotinin administration and short-term (in-hospital) and long-term outcomes by performing a post hoc analysis of the ART.

***Methods and Results*—**Among patients enrolled in the ART (n=3102) from 2004 to 2007, we excluded those who did not undergo surgery (n=18) and those with no information about use of perioperative aprotinin (n=9). Finally, 836 of 3076 patients (27%) received aprotinin. Propensity matching was used to select 536 pairs for final comparison. Aprotinin was also associated with an increased risk of hospital mortality (9 [1.7%] versus 1 [0.2%]; odds ratio, 9.12; 95% confidence interval [CI], 1.15–72.2; *P*=0.03), intra-aortic balloon pump insertion (37 [6.9%] versus 17 [3.2%]; odds ratio, 2.26; 95% CI, 1.26–4.07; *P*=0.006), and acute kidney injury (102 [19.0%] versus 76 [14.2%]; odds ratio, 1.42; 95% CI, 1.03–1.97; *P*=0.03). Aprotinin was not associated with a lower incidence of transfusion (37 [6.9%] versus 28 [5.2%]; odds ratio, 1.34; 95% CI, 0.81–2.23; *P*=0.25) and reexploration (26 [4.9%] versus 19 [3.5%]; hazard ratio, 1.39; 95% CI, 0.76–2.53; *P*=0.28). At 5 years, all-cause mortality was significantly increased in the aprotinin group (56 [10.6%] versus 38 [7.3%]; hazard ratio, 1.51; 95% CI, 1.0–2.28; *P*=0.045).

***Conclusions*—**In the present post hoc ART analysis, aprotinin was associated with a significantly increased risk of early and late mortality.

***Clinical Trial Registration*—**URL: http://www.isrctn.com. Unique identifier: ISRCTN46552265. **(*J Am Heart Assoc*. 2018;7: e007570. DOI: 10.1161/JAHA.117.007570.)**

Key Words: aprotinin • coronary artery bypass graft surgery • outcomes • propensity score matching • Surgery

Bleeding remains a major complication after coronary artery bypass graft (CABG) surgery and is associated with poorer short- and long-term outcomes.[1] Aprotinin is the most studied antifibrinolytic agent to limit blood loss in cardiac surgery. However, concerns have been expressed over its potential detrimental effect on short-term outcomes, including renal dysfunction, graft occlusion, and stroke,[2–5] as well as late mortality.[6] Aprotinin was taken off the market in November 2007 because of safety concerns expressed in 4 studies in *The New England Journal of Medicine*.[2–5] Ten years later, aprotinin is being reintroduced, but without any new clinical trials on safety. The regulatory authorities, including

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Accompanying Tables S1 through S3 and Figure S1 are available at http://jaha.ahajournals.org/content/7/4/e007570/DC1/embed/inline-supplementary-material-1.pdf

*A complete list of the ART (Arterial Revascularization Trial) Investigators can be found in the Appendix at the end of the article.

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Clinical Perspective

What Is New?

- Aprotinin is currently being reestablished into clinical practice in Europe and Canada for adult patients undergoing isolated coronary bypass surgery without any new clinical trials on safety in this subgroup.
- The present analysis on a selected low-risk coronary bypass surgery population supports the association between aprotinin administration and adverse hospital outcomes and long-term survival.

What Are the Clinical Implications?

- On the basis of the present findings, a word of caution should be exercised by local authorities on the liberal use of aprotinin before further investigations will clarify the potential risks related to its perioperative administration.

Health Canada and the European Medicines Agency, revisited the previously available data, and after highlighting several methodological limitations, they concluded that no firm assumption could be made on mortality.[7] Consequently, aprotinin is currently being reestablished into clinical practice in Europe and Canada for adult patients undergoing isolated CABG who are at high risk of major blood loss.[8]

The ART (Arterial Revascularization Trial) is designed to compare 10-year survival after bilateral internal thoracic artery versus single left internal thoracic artery grafting, and an interim report at 5 years has not shown any clear difference between the 2 groups.[9] Approximately 30% of patients enrolled in the ART received perioperative aprotinin. We investigated the association between perioperative aprotinin administration and short- and long-term outcomes in patients undergoing isolated CABG by conducting a post hoc analysis on high-quality data from the ART.

Methods

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure. A post hoc analysis of the ART was conducted. This research adheres to the principles set forth in the Declaration of Helsinki. In ART, aprotinin was the only antifibrinolytic agent administered perioperatively, and its use was based on surgeon discretion/local policies. For the present analysis, among patients enrolled in the ART (n=3102) from 2004 to 2007, we excluded those who did not undergo surgery (n=18) and those with no information about use of perioperative aprotinin (n=9). Perioperative aprotinin was administered to 836 of 3076 patients (27.1%, aprotinin group) included in the present analysis. The baseline characteristics in the aprotinin and no aprotinin groups are reported in Table S1. There was a large variation in aprotinin use across different centers. Unadjusted hospital and long-term outcomes in the 2 groups are reported in Tables S2 and S3.

Patient Involvement

Because the present study represents a post hoc observational analysis of the ART, there was no patient involvement.

Trial Design

The ART was approved by the institutional review board of all participating centers, and informed consent was obtained from each participant. The protocol for the ART has been published.[10] Briefly, the ART is a 2-arm, randomized, multicenter trial conducted in 28 hospitals in 7 countries, with patients being randomized equally to single left internal thoracic artery or bilateral internal thoracic artery grafts. Eligible patients were those with multivessel coronary artery disease undergoing CABG, including urgent patients. Only emergency patients (refractory myocardial ischemia/cardiogenic shock) and those requiring single grafts or redo CABG were excluded.

Follow-Up

Questionnaires were sent to study participants by post every year after surgery. No clinic visits were planned apart from the routine clinical 6-week postoperative visit. Participants were sent stamped addressed envelopes to improve the return rates of postal questionnaires. Study coordinators contacted participants by telephone to alert them to the questionnaire's arrival and to ask them about medications, adverse events, and health services resource use.

Study Outcomes

Primary outcomes were hospital outcomes, which included hospital death, myocardial infarction (MI), cerebrovascular accident, need for repeated revascularization, postoperative atrial fibrillation, need for intra-aortic balloon pump insertion, postoperative renal replacement therapy, acute kidney injury (AKI), sternal wound infection, red blood cell transfusion, and reexploration for bleeding. We also investigated the association between perioperative aprotinin administration and 5-year mortality (including all-cause and cardiovascular mortality), nonfatal MI, cerebrovascular accident, and repeated revascularization.

Outcome Definitions

Death was classified into cardiovascular and noncardiovascular, where possible, using autopsy reports and death certificates. Congestive heart failure, arrhythmia or MI, pulmonary embolus, and dissection were considered cardiovascular causes of death.

MI was diagnosed when 2 of the following 3 criteria were present: (1) unequivocal ECG changes, (2) elevation of cardiac enzyme(s) above twice the upper limit of normal or diagnostic troponin increases, and (3) chest pain typical for acute MI, which lasted >20 minutes. Cerebrovascular accident was defined as new neurological deficit evidenced by clinical signs of paresis, plegia, or new cognitive dysfunction, including any mental status alteration lasting >24 hours and/or evidence on computed tomographic or magnetic resonance imaging scan of a recent brain infarct (<6 months). Repeated revascularization was defined as coronary bypass surgery or percutaneous coronary intervention performed after the trial procedure. AKI was defined as a 0.3-mg/dL (≥26.5-mmol/L) creatinine increase from baseline within 48 hours of surgery.[11]

Statistical Analysis

Multiple imputation (m=10) was used to address missing data (Figure S1). The method of Rubin[12] was used to combine results from each of the imputed data sets (Amelia R package). Because use of aprotinin was not based on randomization, a propensity score (PS) was generated for each patient from a multivariable logistic regression model on the basis of baseline and intraoperative covariates as independent variables, with aprotinin versus no aprotinin as a binary dependent variable.[13] Because a large variation in aprotinin use was found among recruiting centers, individual centers were also included into the PS model to adjust for potential confounding related to different practice patterns. Pairs of patients were derived using greedy 1:1 matching, with a caliper of width of 0.2 SDs of the logit of the PS (MatchIt R package). The quality of the match was assessed by graphical visualization of PS distribution overlapping. Selected pretreatment variables in PS–matched groups were compared using the absolute standardized mean difference, with a value >0.10 taken to represent meaningful covariate imbalance. For outcomes analysis, conditional logistic and Cox regression models stratified for matched pairs with robust standard error estimation were used to investigate the treatment effect on short- and long-term outcomes, respectively. For competing risks, a model for the subdistribution hazard of the cumulative incidence function, proposed by Fine and Gray, was used[14] (riskRegression R packages). The effect of aprotinin on long-term mortality was also adjusted for medications prescribed at discharge. $P<0.05$ was considered statistically significant. All statistical analysis was performed using R Statistical Software (version 3.2.3; R Foundation for Statistical Computing, Vienna, Austria).

Results

PS Matching

Table S2 summarizes baseline characteristics of patients in the original aprotinin and no aprotinin groups. Patients who received aprotinin were more likely to be white, to be older, and to have an advanced New York Heart Association functional class. The use of aprotinin was also associated with a higher rate of preoperative dual-antiplatelet administration and use of cardiopulmonary bypass and saphenous vein grafts. Patients who did not receive aprotinin were more likely to be diabetic and to receive preoperative angiotensin-converting enzyme inhibitors/receptor blockers. There were also a few centers where the aprotinin administration rate was extremely high (eg, Edinburgh Royal Infirmary) and others where the aprotinin administration rate was extremely low (eg, Papworth Hospital and Austin Repatriation Medical Centre). PS matching selected 536 matched pairs with similar distribution of covariates and recruiting centers (all standardized mean differences, <0.10), as shown in Table 1, and comparable PS distribution (Figure 1).

Hospital Outcomes

Hospital outcomes in the matched sample are summarized in Table 2. Hospital mortality was significantly higher in the aprotinin group (9 [1.7%] versus 1 [0.2%]; odds ratio [OR], 9.12; 95% confidence interval [CI], 1.15–72.2; $P=0.03$). Aprotinin was also associated with an increased risk of intra-aortic balloon pump insertion (37 [6.9%] versus 17 [3.2%]; OR, 2.26; 95% CI, 1.26–4.07; $P=0.006$) and AKI (102 [19.0%] versus 76 [14.2%]; OR, 1.42; 95% CI, 1.03–1.97; $P=0.03$), although the increased risk of renal replacement therapy in the aprotinin group did not reach statistical significance (25 [4.7%] versus 18 [3.4%]; OR, 1.41; 95% CI, 0.75–2.61; $P=0.27$). We also found a nonsignificant trend toward increased risk of in-hospital repeated revascularization in the aprotinin group (7 [1.3%] versus 2 [0.4%]; OR, 3.53; 95% CI, 0.73–17.1; $P=0.1$). Aprotinin was not associated with a lower incidence of red blood cell transfusion (37 [6.9%] versus 28 [5.2%]; OR, 1.34; 95% CI, 0.81–2.23; $P=0.25$) or reexploration for bleeding (26 [4.9%] versus 19 [3.5%]; OR, 1.39; 95% CI, 0.76–2.53; $P=0.28$).

Five-Year Outcomes

Five-year outcomes are summarized in Table 3 and Figures 2 and 3. All-cause mortality was significantly increased in the aprotinin group (56 [10.6%] versus 38 [7.3%]; hazard

Table 1. Baseline Characteristics of Patients in the Aprotinin and No Aprotinin Groups (Matched Sample)

Characteristics	Aprotinin Group (n=536)	No Aprotinin Group (n=536)	SMD
Ethnicity			0.221
White	518 (96.6)	522 (97.4)	
East Asian	3 (0.6)	0 (0.0)	
South Asian	15 (2.8)	7 (1.3)	
Afro-Caribbean	0 (0.0)	0 (0.0)	
African	0 (0.0)	1 (0.2)	
Other	0 (0.0)	6 (1.1)	
Age, mean (SD), y	64.76 (9.15)	64.51 (8.56)	0.028
Female sex	81 (15.1)	71 (13.2)	0.054
BMI, mean (SD), kg/m^2	28.10 (3.99)	28.24 (4.06)	0.034
Creatinine, mean (SD), mmol/L	96.28 (21.86)	95.84 (21.46)	0.020
NYHA class III/IV	103 (19.2)	98 (18.3)	0.024
Unstable angina	40 (7.5)	39 (7.3)	0.007
Diabetes mellitus			0.042
No history of diabetes mellitus	426 (79.5)	417 (77.8)	
Insulin-dependent diabetes mellitus	23 (4.3)	26 (4.9)	
Non–insulin-dependent diabetes mellitus	87 (16.2)	93 (17.4)	
Smoking			0.100
Current smoker	91 (17.0)	87 (16.2)	
Ex-smoker	294 (54.9)	319 (59.5)	
Never smoked	151 (28.2)	130 (24.3)	
COPD/asthma	37 (6.9)	34 (6.3)	0.023
PVD	35 (6.5)	41 (7.6)	0.044
CVA	19 (3.5)	19 (3.5)	<0.001
MI	242 (45.1)	243 (45.3)	0.004
PCI	95 (17.7)	92 (17.2)	0.015
AF	10 (1.9)	9 (1.7)	0.014
LVEF			0.031
Good (≥50%)	423 (78.9)	418 (78.0)	
Moderate (31%–49%)	104 (19.4)	110 (20.5)	
Poor (≤30%)	9 (1.7)	8 (1.5)	
Antiplatelet regimen			0.038
None	78 (14.6)	76 (14.2)	
Aspirin only	313 (58.4)	321 (59.9)	
Aspirin plus clopidogrel	124 (23.1)	121 (22.6)	
Clopidogrel only	21 (3.9)	18 (3.4)	
Antiplatelet within 3 d	116 (21.6)	117 (21.8)	0.005
Warfarin	10 (1.9)	10 (1.9)	<0.001
β-Blockers	443 (82.6)	448 (83.6)	0.025
Statins	510 (95.1)	515 (96.1)	0.046
ACEI/ARB	358 (66.8)	346 (64.6)	0.047
Off-pump surgery	173 (32.3)	188 (35.1)	0.059

Continued

Table 1. Continued

Characteristics	Aprotinin Group (n=536)	No Aprotinin Group (n=536)	SMD
Use of saphenous vein graft	439 (81.9)	448 (83.6)	0.044
No. of grafts, mean (SD)	3.17 (0.81)	3.20 (0.81)	0.030
Hospital			0.08
First Department of Cardiac Surgery	66 (12.3)	68 (12.7)	
Second Department of Cardiac Surgery	46 (8.6)	44 (8.2)	
Austin Repatriation Medical Centre	10 (1.9)	7 (1.3)	
Bydgoszcz Szpital Uniwersytecki	0 (0.0)	0 (0.0)	
Care Hospital	0 (0.0)	1 (0.2)	
Castle Hill Hospital	39 (7.3)	34 (6.3)	
Edinburgh Royal Infirmary	30 (5.6)	22 (4.1)	
Escorts Heart Institute	0 (0.0)	0 (0.0)	
Freeman Hospital	0 (0.0)	1 (0.2)	
Glenfield Hospital	38 (7.1)	38 (7.1)	
Harefield Hospital	28 (5.2)	25 (4.7)	
Heart Institute of Pernambuco	0 (0.0)	2 (0.4)	
John Paul Hospital	0 (0.0)	1 (0.2)	
John Radcliffe Hospital	100 (18.7)	113 (21.1)	
King's College Hospital	0 (0.0)	0 (0.0)	
Landesklinikum St Polten	6 (1.1)	2 (0.4)	
Manchester Royal Infirmary	23 (4.3)	31 (5.8)	
Medical University of Gdansk	3 (0.6)	3 (0.6)	
Northern General Hospital	10 (1.9)	10 (1.9)	
Ospedale Mauriziano	0 (0.0)	0 (0.0)	
Papworth Hospital	2 (0.4)	4 (0.7)	
Royal Brompton Hospital	25 (4.7)	24 (4.5)	
Royal Sussex County Hospital	50 (9.3)	58 (10.8)	
Rzeszow Szpital Wojewodzki 2	2 (0.4)	2 (0.4)	
Silesian Centre for Heart Disease	0 (0.0)	0 (0.0)	
St George's Hospital	0 (0.0)	1 (0.2)	
The Cardiothoracic Centre	0 (0.0)	0 (0.0)	
University Hospital of Wales	58 (10.8)	45 (8.4)	

Data are given as number (percentage) unless otherwise indicated. ACEI/ARB indicates angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; AF, atrial fibrillation; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; and SMD, standardized mean difference.

ratio, 1.51; 95% CI, 1.0–2.28; P=0.045). We found an excess of cardiovascular deaths, MIs, and repeated revascularizations in the aprotinin group, although these differences did not reach statistical significance. Medications at discharge were comparable between the 2 groups (Table 4). After controlling for medication at discharge, aprotinin remained associated with a significantly increased risk of late death (hazard ratio, 1.54; 95% CI, 1.02–2.33; P=0.04).

Discussion

The present post hoc ART analysis found that, in patients undergoing isolated CABG, aprotinin administration was associated with a higher risk of in-hospital mortality, intra-aortic balloon pump insertion, and AKI. We also found a nonstatistically significant increased risk of early reintervention. At 5 years, perioperative aprotinin administration was associated with significantly higher mortality.

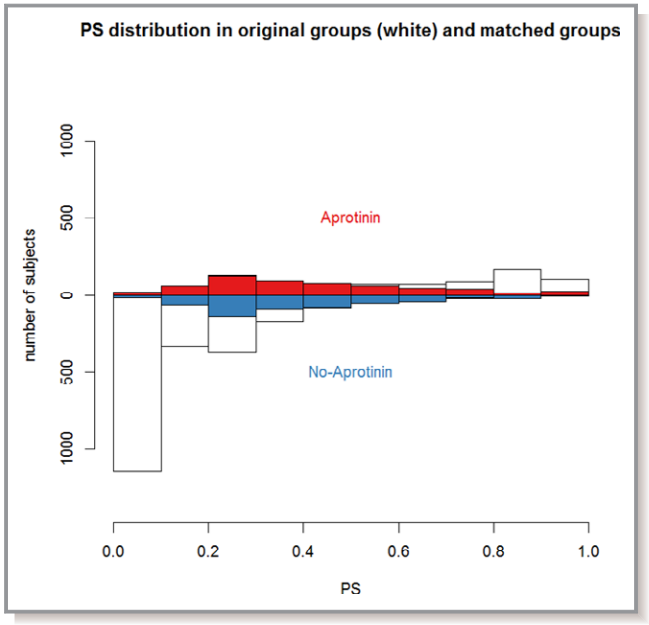

Figure 1. Mirrored histogram showing propensity score (PS) distribution in the 2 groups before (white) and after (red and blue) matching.

Aprotinin has been shown to effectively reduce blood loss and the need for transfusion associated with heart surgery[15]; currently, Health Canada and the European Medicines Agency believe the accumulated evidence on the benefits of aprotinin outweighs its risks in isolated CABG surgery.[7,8] In a prospective cohort study in 2006, Mangano and colleagues[2] reported that aprotinin was associated with an increased risk of renal failure, MI, heart failure, stroke, encephalopathy, and mortality (2.8% versus 1.3%; *P*=0.02). Consequently, in 2006, the Food and Drug Administration listed renal dysfunction, along with anaphylaxis, graft occlusion, and stroke, among the drug's safety concerns.[16] However, the association between aprotinin and renal failure was disputed by Furnary and colleagues in 2007, who suggested that this was a confounding variable because renal impairment was also related to an increased packed red cell transfusion in the setting of cardiac surgery.[17] In 2007, Mangano and colleagues reanalyzed the 2006 data and reported that aprotinin was independently predictive of 5-year mortality.[6] A possible limitation of this analysis was that the authors failed to report whether the surgery was on or off pump, and this variable may have influenced not only the choice of antifibrinolytic agent but also clinical outcomes. The Cardiovascular and Renal Drugs Advisory Committee of the Food and Drug Administration reviewed the evidence from these studies; the committee could not endorse the findings after questions about the methods used, and because the data had not been independently reviewed by the Food and Drug Administration.[18]

Another source of concern about aprotinin's safety was a preliminary report in 2006, from the manufacturer's own database, that showed a higher risk of death and acute renal failure in patients undergoing CABG who received aprotinin compared with patients who had received other antifibrinolytics.[19] This study was limited by its inability to account for the proportion of patients undergoing long-term dialysis when assessing the need for postoperative dialysis. The BART (Blood Conservation Using Antifibrinolytics in a Randomized Trial), published in 2008,[5] was a blinded randomized controlled trial comparing aprotinin, tranexamic acid, and aminocaproic acid in patients undergoing high-risk cardiac surgery. The trial was terminated early on the advice of the

Table 2. Hospital Outcomes in the Matched Sample

Outcomes	Aprotinin Group (n=536)	No Aprotinin Group (n=536)	*P* Value	OR (95% CI)
Mortality	9 (1.7)	1 (0.2)	0.03	9.12 (1.15–72.2)
MI	12 (2.2)	9 (1.7)	0.51	1.34 (0.56–3.21)
CVA	8 (1.5)	8 (1.5)	1.00	1 (0.37–2.68)
Repeated revascularization	7 (1.3)	2 (0.4)	0.11	3.53 (0.73–17.1)
POAF	143 (26.7)	169 (31.5)	0.09	0.79 (0.61–1.03)
IABP insertion	37 (6.9)	17 (3.2)	0.006	2.26 (1.26–4.07)
RRT	25 (4.7)	18 (3.4)	0.27	1.41 (0.75–2.61)
AKI	102 (19.0)	76 (14.2)	0.03	1.42 (1.03–1.97)
Sternal wound infection	25 (4.7)	19 (3.5)	0.35	1.33 (0.72–2.44)
RBC transfusion	37 (6.9)	28 (5.2)	0.25	1.34 (0.81–2.23)
Reexploration	26 (4.9)	19 (3.5)	0.28	1.39 (0.76–2.53)

Data are given as number (percentage) unless otherwise indicated. AKI indicates acute kidney injury; CI, confidence interval; CVA, cerebrovascular accident; IABP, intra-aortic balloon pump; MI, myocardial infarction; OR, odds radio; POAF, postoperative atrial fibrillation; RBC, red blood cell; and RRT, renal replacement therapy.

Table 3. Five-Year Outcomes in the Matched Sample

Outcomes	Aprotinin Group (n=536)	No Aprotinin Group (n=536)	*P* Value	HR (95% CI)
Cardiovascular mortality	22 (4.1)	18 (3.4)	0.48	1.25 (0.67–2.33)
MI	18 (3.4)	15 (2.8)	0.58	1.21 (0.61–2.4)
CVA	12 (2.3)	19 (3.6)	0.23	0.64 (0.31–1.32)
Repeated revascularization	37 (7.0)	32 (6.1)	0.49	1.18 (0.74–1.9)
All-cause mortality	56 (10.6)	38 (7.3)	0.045	1.51 (1.0–2.28)

Data are given as number (percentage) unless otherwise indicated. CI indicates confidence interval; CVA, cerebrovascular accident; HR, hazard ratio; and MI, myocardial infarction.

safety committee because of a nonsignificant increase in mortality associated with aprotinin. Although the BART had the benefit of being a blinded randomized controlled trial, several limitations were identified in its conduct, in particular the unexplained exclusion of 137 patients from the analysis after randomization.[20] In view of conflicting findings reported, further analyses based on high-quality data are warranted to provide further evidence on the safety of perioperative aprotinin administration.

The present post hoc ART analysis found that aprotinin administration was significantly associated with an increased risk of hospital death, AKI, and need for intra-aortic balloon pump insertion postoperatively, thus supporting previous reports. We could not demonstrate a definitive association between aprotinin administration and need for renal replacement therapy, but this might be partially attributed to the relatively low baseline renal risk of the present population. We also found that aprotinin administration was associated with a significantly increased risk of late mortality. Although aprotinin administration was associated with reduced incidence of red blood cell transfusion in the original sample (Table S2), this association was no longer present after matching, which also accounted for participating centers. This observation suggests that in the ART, different transfusion policies, rather than aprotinin itself, might have influenced red blood cell transfusion exposure.

The main limitations of the present analyses are obviously the nonrandomized comparison (despite the close matching in the propensity-scored patients) and the few outcome events, with consequently wide CIs. Despite PS modeling, we cannot exclude a residual selection bias based on unmeasured or unmeasurable characteristics. Another limitation is that the exact dose of aprotinin administered was not collected and, therefore, a dose-response association cannot be excluded. However, a previous meta-analysis did not find any association between dose and adverse events.[21]

In conclusion, we found that the use of aprotinin was associated with an excess of early death and this also translated into an increased cardiac-related mortality at 5 years. Aprotinin is currently offered to many patients undergoing CABG, and the present analysis supports the hypothesis that aprotinin use might be associated with an increase in avoidable deaths. Therefore, a word of caution should be exercised by local authorities on the liberal use of aprotinin during isolated CABG before stronger evidence of its safety profile will be available.

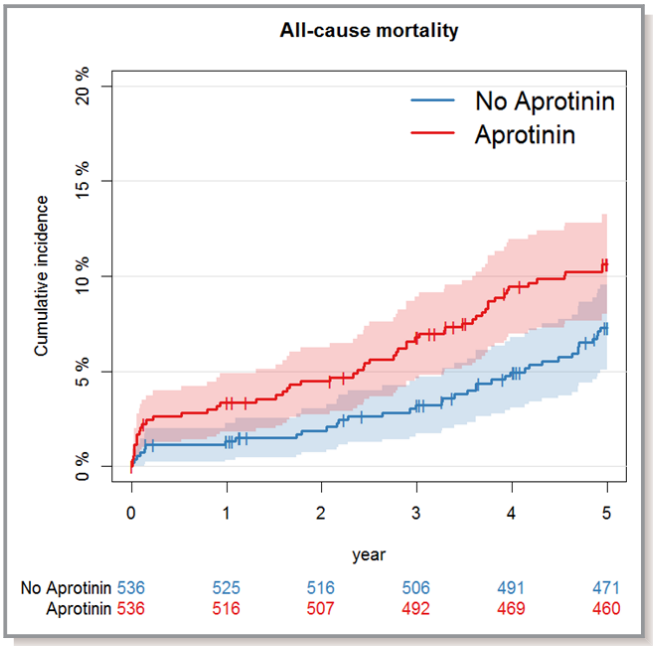

Figure 2. Five-year cumulative incidence of all-cause mortality in the matched groups.

Appendix

ART (Arterial Revascularization Trial) Contributors

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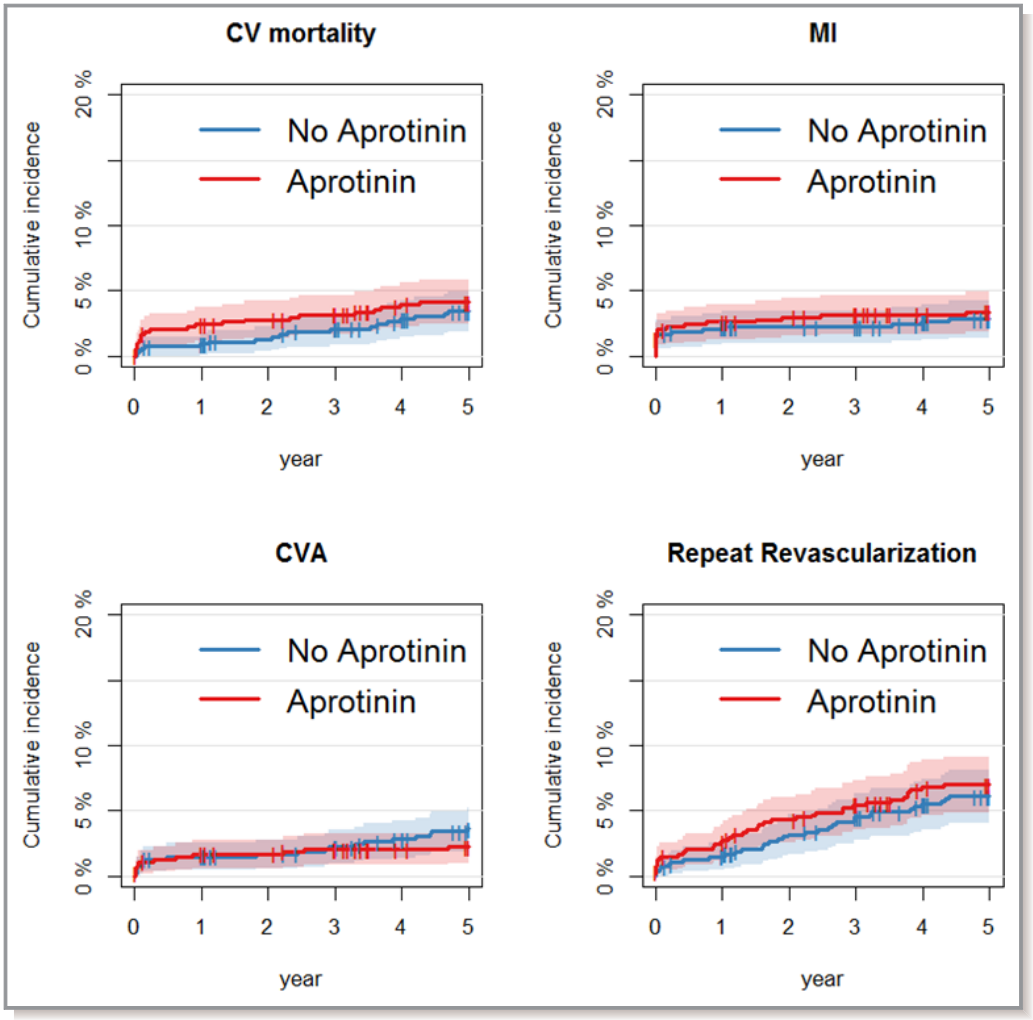

Figure 3. Five-year cumulative incidence of cardiovascular (CV) death, myocardial infarction (MI), cerebrovascular accident (CVA), and repeated revascularization in the matched groups.

V. Atkinson, A. Newcomb, P. Polidano, R. Pana, S. Gerbo, P. O'Keefe, U. von Oppell, D. Mehta, A. Azzu, A. Szafranek, E. Kulatilake, J. Evans, N. Martin, D. Banner, U. Trivedi, A. Forsyth, J. Hyde, A. Cohen, M. Lewis, E. Gardner, A. MacKenzie, N. Cooter, E. Joyce, J. Parker, F. Champney, S. Clark, J. Dark, K. Tocewicz, T. Pillay, S. Rowling, J. Adams-Hall, A. Bochenek, M. Cisowski, M. Bolkowski, W. Morawski, M. Guc, M. Krejca, M. Wilczynski, A. Duralek, W. Gerber, J. Skarysz, R. Shrestha, W. Swiech, P. Szmagala, L. Krzych, A. Pawlak, K. Kepa, R. Hasan, D. Keenan, B. Prendergast, N. Odom, K. McLaughlin, G. Cummings-Fosong, C. Mathew, H. Iles-Smith, A. Oomen, J. Desai, A. El-Gamel, L. John, O. Wendler, M. Andrews, K. Rance, R. Williams, V. Hogervorst, J. Gregory, J. Jessup, A. Knighton, A. Hoare, A. Ritchie, C. Choong, S. Nair, D. Jenkins, S. Large, C. Sudarshan, M. Barman, K. Dhital, T. Routledge, B. Rosengard, H. Munday, K. Rintoul, E. Jarrett, S. Lao-Sirieix, A. Wilkinson, L. Garner, J. Osmond, H. Holcombe, A. Cale, S. Griffin, J. Dickson, T. Spyt, M. Hickey, A. Sosnowski, G. Peek, J. Szostek, L. Hadjinikalaou, E. Logtens, M. Oakley, S. Leji, J. Gaer, M. Amrani, G. Dreyfus, T. Bahrami, F. de Robertis, K. Baig, G. Asimakopoulos, H. Vohra, V. Pai, S. Tadjkarimi, B. Soleimani, G. Stavri, G. Bull, H.

Table 4. Medication at Discharge in the Matched Sample

Medications	Aprotinin Group (n=536)	No Aprotinin Group (n=536)	*P* Value
β-Blocker	462 (86.2)	450 (84.0)	0.34
Statins	509 (95.0)	514 (95.9)	0.55
ACEI/ARB	307 (57.3)	296 (55.2)	0.53
Antiplatelet regimen			0.67
None	8 (1.5)	11 (2.1)	
Aspirin only	416 (77.6)	417 (77.8)	
Aspirin plus clopidogrel	92 (17.2)	94 (17.5)	
Clopidogrel only	20 (3.7)	14 (2.6)	
Warfarin	18 (3.4)	23 (4.3)	0.52

Data are given as number (percentage) unless otherwise indicated. ACEI/ARB indicates angiotensin-converting enzyme inhibitor/angiotensin receptor blocker.

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Disclosures

None.

References

1. Kuduvalli M, Oo AY, Newall N, Grayson AD, Jackson M, Desmond MJ, Fabri BM, Rashid A. Effect of peri-operative red blood cell transfusion on 30-day and 1-year mortality following coronary artery bypass surgery. *Eur J Cardiothorac Surg*. 2005;27:592–598.
2. Mangano DT, Tudor IC, Dietzel C; Multicenter Study of Perioperative Ischemia Research Group, Ischemia Research and Education Foundation. The risk associated with aprotinin in cardiac surgery. *N Engl J Med*. 2006;354:353–365.
3. Schneeweiss S, Seeger JD, Landon J, Walker AM. Aprotinin during coronary artery bypass grafting and risk of death. *N Engl J Med*. 2008;358:771–783.
4. Shaw AD, Stafford-Smith M, White WD, Phillips-Bute B, Swaminathan M, Milano C, Welsby IJ, Aronson S, Mathew JP, Peterson ED, Newman MF. The effect of aprotinin on outcome after coronary-artery bypass grafting. *N Engl J Med*. 2008;358:784–793.
5. Fergusson DA, Hébert PC, Mazer CD, Fremes S, MacAdams C, Murkin JM, Teoh K, Duke PC, Arellano R, Blajchman MA, Bussières JS, Côté D, Karski J, Martineau R, Robblee JA, Rodger M, Wells G, Clinch J, Pretorius R. A comparison of aprotinin and lysine analogues in high-risk cardiac surgery. *N Engl J Med*. 2008;358:2319–2331.
6. Mangano DT, Miao Y, Vuylsteke A, Tudor IC, Juneja R, Filipescu D, Hoeft A, Fontes ML, Hillel Z, Ott E, Titov T, Dietzel C, Levin J. Mortality associated with aprotinin during 5 years following coronary artery bypass graft surgery. *JAMA*. 2007;297:471–479.
7. European Medicines Agency. 2013. http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Antifibrinolytic_medicines/WC500122922.pdf. Accessed September 18, 2013.
8. European Medicines Agency. 2013. http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Antifibrinolytic_medicines/WC500122924.pdf. Accessed September 18, 2013.
9. Taggart DP, Altman DG, Gray AM, Lees B, Gerry S, Benedetto U, Flather M. Randomized trial of bilateral versus single internal-thoracic-artery grafts. *N Engl J Med*. 2016;375:2540–2549.
10. Taggart DP, Lees B, Gray A, Altman DG, Flather M, Channon K. Protocol for the Arterial Revascularisation Trial (ART): a randomised trial to compare survival following bilateral versus single internal mammary grafting in coronary revascularisation [ISRCTN46552265]. *Trials*. 2006;7:7.
11. Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. *Nephron Clin Pract*. 2012;120:c179–c184.
12. Rubin DB. *Multiple Imputation for Nonresponse in Surveys*. New York, NY: J Wiley & Sons; 1987.
13. Austin PC. A tutorial and case study in propensity score analysis: an application to estimating the effect of in-hospital smoking cessation counseling on mortality. *Multivariate Behav Res*. 2011;46:119–151.
14. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc*. 1999;94:496–509.
15. Howell N, Senanayake E, Freemantle N, Pagano D. Putting the record straight on aprotinin as safe and effective: results from a mixed treatment meta-analysis of trials of aprotinin. *J Thorac Cardiovasc Surg*. 2012;145:234–240.
16. US Food and Drug Administration. Information for healthcare professionals: aprotinin injection (marketed as trasylol) 2010. Available at: https://www.fda.gov/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/ucm142720.htm. Accessed May 4, 2012.
17. Furnary AP, Wu YX, Hiratzka LF, Grunkemeier GL, Page US. Aprotinin does not increase the risk of renal failure in cardiac surgery patients. *Circulation*. 2007;116:I-127–I-133.
18. FDA Cardiology and Renal Drugs Advisory Committee. Trasylol (aprotinin injection) risk benefit review 2006. Available at: https://www.fda.gov/ohrms/dockets/ac/06/slides/2006-4234S3-01-Bayer.pdf Accessed August 18, 2012.
19. Trasylolw (aprotinin injection) briefing document 2007. Available at: https://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4316b1-03-BAYER.pdf Accessed August 18, 2012.
20. Health Canada. Final report—expert advisory panel on Trasylol (aprotinin) 2011. http://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2011/13544a-eng.php. Accessed July 8, 2012.
21. 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;128:442–448.

Supplemental Material

Table S1. Baseline characteristics of patients in the aprotinin and no-aprotinin groups in the original sample.

	Aprotinin	No Aprotinin	SMD
n	836	2240	
Ethnicity (\%)			0.354
Caucasian	813 (97.2)	2012 (89.8)	
East Asian	3 (0.4)	3 (0.1)	
South Asian	20 (2.4)	129 (5.8)	
Afro-Carribean	0 (0.0)	2 (0.1)	
African	0 (0.0)	5 (0.2)	
Other	0 (0.0)	89 (4.0)	
Age (years), mean (sd))	64.84 (8.95)	63.17 (8.89)	0.187
Female n(%)	125 (15.0)	314 (14.0)	0.027
BMI (mean (sd))	28.25 (3.99)	28.20 (4.01)	0.014
Creatinine (mmol/l), mean (sd)	97.18 (22.55)	96.56 (21.77)	0.028
NYHA class III/IV n(%)	205 (24.5)	452 (20.2)	0.104
Unstable Angina n(%)	73 (8.7)	165 (7.4)	0.050
Diabetes n(%)			0.102
No history of diabetes	664 (79.4)	1684 (75.2)	
Insulin dependent diabetes	39 (4.7)	132 (5.9)	
Non-insulin dependent diabetes	133 (15.9)	424 (18.9)	
Smoking n(%)			0.085
Current smoker	138 (16.5)	304 (13.6)	
Ex-smoker	462 (55.3)	1259 (56.2)	
Never smoked	236 (28.2)	677 (30.2)	
COPD/Asthma n(%)	66 (7.9)	133 (5.9)	0.077
PVD n(%)	66 (7.9)	151 (6.7)	0.044
CVA n(%)	25 (3.0)	65 (2.9)	0.005
MI n(%)	369 (44.1)	919 (41.0)	0.063
PCI n(%)	136 (16.3)	349 (15.6)	0.019
AF n(%)	15 (1.8)	31 (1.4)	0.033
LVEF (\%)			0.047
Good (≥50%)	633 (75.7)	1687 (75.3)	
Moderate (31-49%)	181 (21.7)	508 (22.7)	
Poor (≤30%)	22 (2.6)	45 (2.0)	
Antiplatelet regime			0.123
None	88 (10.5)	288 (12.9)	
Aspirin only	506 (60.5)	1412 (63.0)	
Aspirin plus clopidogrel	207 (24.8)	471 (21.0)	
Clopidogrel only	35 (4.2)	69 (3.1)	
Antiplatelet within 3 days n(%)	159 (19.0)	353 (15.8)	0.086
Warfarin n(%)	17 (2.0)	43 (1.9)	0.008
Beta-blockers n(%)	688 (82.3)	1844 (82.3)	0.001
Statins n(%)	795 (95.1)	2088 (93.2)	0.080

ACEI/ARB n(%)	526 (62.9)	1531 (68.3)	0.115
Off-pump surgery n(%)	309 (37.0)	950 (42.4)	0.112
Use of saphenous vein graft n(%)	676 (80.9)	1699 (75.8)	0.122
Number of grafts, mean (sd)	3.19 (0.82)	3.18 (0.80)	0.003
Hospital n(%)			0.61
1st Department Of Cardiac Surgery	70 (8.4)	74 (3.3)	
2nd Department Of Cardiac Surgery	46 (5.5)	209 (9.3)	
Austin Repatriation Medical Centre	176 (7.9)	10 (1.2)	
Bydgoszcz Szpital Uniwersytecki	0 (0.0)	23 (1.0)	
Care Hospital	0 (0.0)	69 (3.1)	
Castle Hill Hospital	61 (7.3)	35 (1.6)	
Edinburgh Royal Infirmary	191 (22.8)	22 (1.0)	
Escorts Heart Institute	0 (0.0)	19 (0.8)	
Freeman Hospital	0 (0.0)	152 (6.8)	
Glenfield Hospital	38 (4.5)	56 (2.5)	
Harefield Hospital	36 (4.3)	56 (2.5)	
Heart Institute Of Pernambuco	0 (0.0)	82 (3.7)	
John Paul Hospital	0 (0.0)	92 (4.1)	
John Radcliffe Hospital	102 (12.2)	324 (14.5)	
King's College Hospital	0 (0.0)	114 (5.1)	
Landesklinikum St Polten	17 (2.0)	2 (0.1)	
Manchester Royal Infirmary	71 (8.5)	44 (2.0)	
Medical University Of Gdansk	3 (0.4)	71 (3.2)	
Northern General Hospital	10 (1.2)	53 (2.4)	
Ospedale Mauriziano	0 (0.0)	61 (2.7)	
Papworth Hospital	2 (0.2)	98 (4.4)	
Royal Brompton Hospital	25 (3.0)	56 (2.5)	
Royal Sussex County Hospital	51 (6.1)	128 (5.7)	
Rzeszow Szpital Wojewodzki 2	2 (0.2)	4 (0.2)	
Silesian Centre For Heart Disease	0 (0.0)	10 (0.4)	
St. George's Hospital	0 (0.0)	77 (3.4)	
The Cardiothoracic Centre	0 (0.0)	49 (2.2)	
University Hospital of Wales	101 (12.1)	84 (3.8)	

SMD: standardized mean difference; BMI: body mass index; NYHA: New York Heart Association; COPD: Chronic obstructive pulmonary disease; PVD: peripheral vascular disease; CVA: cerebrovascular accident; MI: myocardial infarction; PCI: percutaneous coronary intervention; AF: atrial fibrillation; LVEF: left ventricular ejection fraction; ACEI/ARB: angiotensin converting enzyme inhibitor/angiotensin receptor blocker

Table S2. Hospital outcomes in the original sample.

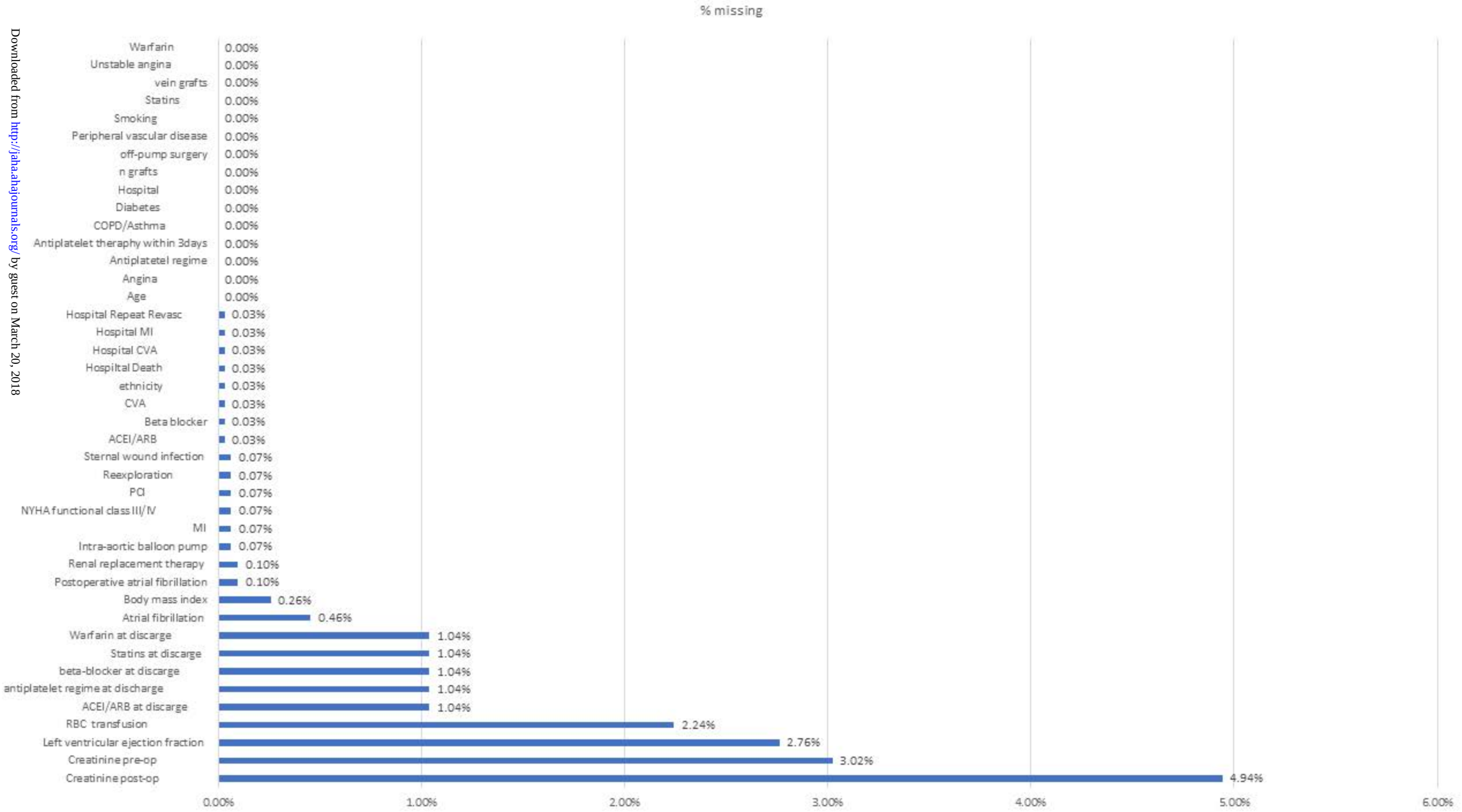
	Aprotinin	No Aprotinin
n	836	2240
Mortality n(%)	14 (1.7)	18 (0.8)
MI n(%)	13 (1.6)	41 (1.8)
CVA n(%)	8 (1.0)	32 (1.4)
Repeat Revascularization n(%)	8 (1.0)	7 (0.3)
POAF n(%)	211 (25.2)	551 (24.6)
IABP insertion n(%)	52 (6.2)	74 (3.3)
RRT n(%)	39 (4.7)	122 (5.4)
AKI n(%)	146 (17.5)	396 (17.7)
Sternal wound infection n(%)	38 (4.5)	72 (3.2)
RBC transfusion n(%)	61 (7.3)	315 (14.1)
Re-exploration n(%)	33 (3.9)	70 (3.1)

MI: myocardial infarction; CVA: cerebrovascular accident; POAF: postoperative atrial fibrillation; IABP intra-aortic balloon pump; RRT: renal replacement therapy; AKI: acute kidney injury; RBC: red blood cells

Table S3. Five-year outcomes in the original sample.

	Aprotinin	No Aprotinin
n	836	2240
Cardiovascular mortality	35(4.2)	71(3.2)
MI	25(3.0)	79(3.6)
CVA	21(2.5)	65(2.9)
Repeat Revascularization	55(6.6)	147(6.7)
All-cause mortality	82(9.9)	178(8.1)

MI: myocardial infarction; CVA: cerebrovascular accident



Safety of Perioperative Aprotinin Administration During Isolated Coronary Artery Bypass Graft Surgery: Insights From the ART (Arterial Revascularization Trial)

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