The Effect of Preoperative Anemia on the Outcome after Coronary Surgery

Tuomas Tauriainen,[1] Joni Koski-Vähälä,[1] Eeva-Maija Kinnunen,[1] and Fausto Biancari[1]

[1]Department of Surgery, Oulu University Hospital, Oulu, Finland

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For correspondence:
Prof. Fausto Biancari,
Department of Surgery,
Oulu University Hospital,
P.O. Box 21, 90029 Oulu, Finland.
Tel.: +358 40 7333 973;
Fax: + 358 8 315 2486;
E-mail: faustobiancari@yahoo.it

Abstract

Background: Preoperative anemia is associated with increased morbidity and mortality after cardiac surgery. Since anemia is ultimately treated with red blood cell (RBC) transfusions, we investigated the independent impact of anemia and transfusion on the outcome after coronary artery bypass grafting (CABG).

Methods: This study included 2761 consecutive patients who underwent isolated CABG. Anemia was defined as hemoglobin <12.0 g/dL in women and <13.0 g/dL in men. The main outcomes were 30-day and late mortality.

Results: Patients with preoperative anemia had an increased prevalence of significant comorbidities and were associated with higher unadjusted risk of early and late adverse events. Propensity score matching resulted in 560 pairs with similar baseline and operative characteristics. In these matched pairs, anemic patients had an increased risk of late all-cause death (P=0.047) and acute kidney injury (p<0.0001). However, when adjusted for the severity of perioperative bleeding, preoperative anemia was not associated with an increased mortality risk (HR 1.10, 95%CI 0.86-1.39). Instead, this regression model showed that the European CABG registry (E-CABG) bleeding classification was an independent predictor of late mortality (compared to grade 0: grade 1, HR 1.93, 95%CI 1.37-2.73, grade 2, HR 2.19, 95%CI 1.50-3.18, grade 3, HR 5.59, 95%CI 3.34-9.39, P<0.0001).

Conclusions: When adjusted for important baseline characteristics and operative factors as well as for the severity of perioperative bleeding and the amount of transfused blood products, anemia was not associated with an increased risk of adverse events. Increased exposure to blood transfusion among anemic patients may be the determinant of their poorer late survival.

Introduction

Anemia and exposure to red blood cell (RBC) transfusion are predictors of adverse events after cardiac and non-cardiac surgery [1-9]. Differentiating the negative effects of these two factors is difficult since preoperative anemia is itself associated with increased need of RBC transfusions [7,10,11,13-15]. On the other hand, preoperative anemia is relatively common in patients undergoing cardiac surgery [10] and is a result of multiple causes which in turn are risk factors for poor outcome in these patients [16]. The aim of the present study was to evaluate the independent effect of preoperative anemia on the outcome after coronary artery bypass grafting (CABG).

Materials and methods

Patients

The present study includes 2761 consecutive patients who underwent isolated CABG from June 2006 to December 2013 at the Oulu University Hospital, Finland. Complete data on pre-, intra- and postoperative variables were available in these patients. Data on the preoperative use of antithrombotics were retrospectively collected. Data on the types and amount of blood products such as RBCs, platelets and solvent/detergent-treated plasma (Octaplas; Octapharma AG, Lachen, Switzerland) were retrieved from a prospective electronic hospital registry. The amount of transfused blood products was estimated from the day of operation day until discharge or up to a maximum of 30 days after the operation. Data on the amount of chest drainage output at 12 hours after surgery were retrieved from a prospective electronic registry of the intensive care unit. Preoperative anemia was defined a hemoglobin level <12.0 g/dL in

women and <13.0 g/dL in men [17]. Clinical variables were defined according to the EuroSCORE II definition criteria [18]. The E-CABG classification of bleeding severity [19] was employed to stratify the severity of perioperative bleeding based on the type and amount of blood products transfused and the need of resternotomy for excessive bleeding. The E-CABG bleeding grades [19] are: Grade 0, no transfusion of blood products or transfusion of one unit of RBCs; Grade 1, transfusion of platelets, fresh frozen plasma/Octaplas and/or 2-4 units of RBCs; Grade 2, transfusion of 5-10 units of RBCs and/or reoperation for bleeding; Grade 3, transfusion of > 10 units of RBCs. Data on patients' death were provided up to January 31st, 2016 from the Finnish Population Registry Center, which collects the certificates of death of all inhabitants of Finland. We assume that there are no missing data on any immediate and late death of this study population.

Inclusion criteria

Patients who underwent any elective, urgent or emergency isolated CABG were included in this analysis.

Perioperative antithrombotic treatment

Aspirin was discontinued for seven days until 2012 and later on was continued until surgery. Warfarin was discontinued for 2 days before surgery. Enoxaparin was used preoperatively only in patients with acute coronary syndrome. Clopidogrel, prasugrel and ticagrelor were discontinued for at least 5 days when feasible.

Heparin (3.0 mg/kg) was administered intraoperatively to maintain an activated coagulation time of longer than 450 seconds and it was neutralized at the end of the procedure by protamine sulphate (3.0 mg/kg). Aprotinin was not used in any of these patients. Tranexamic acid was administered intraoperatively at discretion of the anesthesiologist. RBCs were transfused on the operation day if hemoglobin was less than 90 g/L. Later, RBCs were transfused if hemoglobin was less than 80 g/L. Octaplas as well as platelets were transfused according to the amount of intra- and postoperative bleeding, INR levels and platelet count.

Enoxaparin (40-80 mg once-a-day) was started on the evening of the operation day in those patients without excessive bleeding (<1000 mL). Aspirin 100 mg was restarted on the first postoperative day. Warfarin was restarted on the first postoperative day in patients on chronic oral anticoagulation unless excessive bleeding occurred. Warfarin was started *de novo* in case of persistent atrial fibrillation. Clopidogrel and ticagrelor were used postoperatively only in case of allergy to aspirin or recent percutaneous coronary intervention.

Operative techniques and management of chest drainages

Intermittent antegrade and retrograde cold blood cardioplegia was used during on-pump CABG. Epiaortic ultrasound was performed according to the surgeon's preference. Octopus stabilizer (Medtronic, Minneapolis, MN) as well as intracoronary shunts were routinely used in patients who underwent off-pump surgery. All blood lost during the operation was collected into a cell saver reservoir and washed. Salvaged red blood cells were transfused during or at the completion of the operation. Mediastinal/pleural blood was collected after surgery in a sterile collection chamber connected to 15 cm H_2O wall suction via an underwater seal and then

discarded.

Outcomes

The primary outcomes of this study were 30-day and late mortality. Secondary outcomes were the length of intensive care unit stay, stroke, atrial fibrillation, ventricular fibrillation or asystole, permanent pace-maker implantation, postoperative use of antibiotics, deep sternal wound infection, mediastinitis, low cardiac output syndrome, repeat revascularization, surgery for gastrointestinal complications, acute kidney injury according to the Kidney Disease: Improving Global Outcomes (KDIGO) criteria based on peak creatinine level during the in-hospital stay [20], nadir hemoglobin level during the postoperative period and chest drain output 12 hours after surgery. Low cardiac output syndrome was defined as postoperative cardiac index < 2.0 L/min/m^2 as measured at least twice. The other outcomes were defined according to the E-CABG definition criteria as previously reported [19].

Statistical analysis

Statistical analysis was performed using SPSS statistical software (version 23.0, IBM Corporation, New York, USA). No attempt to replace missing values was made. Continuous variables are reported as the mean and standard deviation. Nominal variables are reported as counts and percentages. Fisher's exact test, Chi-square test and Mann-Whitney tests were used for univariate analysis. Risk estimates are reported as beta coefficients, odds ratio (OR) and hazard rate (HR) with 95% confidence interval (95%CI). Observational studies do not provide randomization and therefore propensity score matching method was employed to select two groups of patients with and without preoperative anemia having similar baseline

and operative characteristics. The propensity score was estimated using a non-parsimonious logistic regression model with the preoperative anemia/non-anemia as the dependent variable. The following variables have been included as covariates: age, gender, body mass index, platelets count, eGFR, dialysis, pulmonary disease, diabetes, stroke, extracardiac arteriopathy, neurological dysfunction, atrial fibrillation, previous percutaneous coronary intervention, previous cardiac surgery, left ventricular ejection fraction ≤50%, recent myocardial infarction, critical preoperative status, preoperative intra-aortic balloon pump, recent ventricular arrhythmia, cardiac massage, urgency of the operation, off-pump surgery, epiaortic ultrasound, diseased ascending aorta, bilateral mammary artery grafts and radial artery graft. One-to-one propensity score matching was performed using a caliper width of 0.02 of the standard deviation of the logit of the propensity score. Analysis of the standardized differences after matching was used to assess the balance between the characteristics of propensity-matched pairs. The outcomes of matched groups were evaluated by the t-test for paired sample for continuous variables and the McNemar test for dichotomous variables. Difference in overall survival at 9 years was evaluated by the Kaplan-Meier method. Logistic regression, linear regression, ordinal regression and Cox proportional hazards analyses of propensity matched pairs were adjusted for the E-CABG bleeding grades in order to evaluate the impact of blood transfusion and resternotomy for excessive bleeding on the outcomes. In another regression model, preoperative anemia was adjusted for the number of transfused units of RBCs. All tests were two-sided with the alpha level set at 0.05 for statistical significance.

Results

Baseline and operative data

In this series, 662 patients (24.0%, 22.8% of men and 28.6% of women) had preoperative anemia. Baseline and operative characteristics of these patients are summarized in Tables 1 and 2. The prevalence of comorbidities was significantly higher among anemic patients. In particular, anemic patients were significantly older, had a higher prevalence of recent myocardial infarction and were operated mostly on urgent/emergency basis. Operative factors were similar between the study groups.

Outcomes in the overall series

Outcomes in overall series are summarized in Tables 3 and 4. In-hospital, 30-day and long-term mortalities were significantly increased in patients exposed to anemia ($P<0.0001$ in all). Unadjusted 8-year survival in non-anemic and anemic patients were 80.2% and 62.4% respectively.

Preoperative anemia was associated with a significantly increased risk of exposure to blood products (Tab. 3) and lower nadir haemoglobin values ($P<0.0001$), whereas blood loss at 12 hours was lower (484±416 vs. 509±388 ml, $P=0.029$) when compared to non-anemic patients.

In univariate analysis, preoperative anemia was associated with significantly longer stay in the intensive care unit, atrial fibrillation, ventricular fibrillation or asystole, postoperative use of antibiotics and acute kidney injury ($P<0.0001$ in all). The rates of postoperative stroke ($P=0.001$), low cardiac output syndrome ($P=0.003$) and surgery for gastrointestinal complications ($P=0.001$) were also significantly higher among anemic patients.

Propensity score matched analysis

Logistic regression (Hosmer-Lemeshow's test: P=0.248) provided a propensity score with an area under the receiver-operating characteristics curve of 0.773 (95%CI 0.753-0.793). Propensity-score matching (caliper width: 0.02) resulted in 560 patient pairs with similar baseline and operative covariates as confirmed by absolute standardized differences <10% in all baseline and operative covariates (Fig. 1).

In these propensity matched pairs, in-hospital (3.0% vs. 3.2%, P=1.00) and 30-day mortality rates (3.9% vs. 3.9%, P=1.00) were similar in non-anemics and anemics. However, Kaplan-Meier analysis showed a better survival among non-anemics at mid-term, but the difference somewhat decreased at long-term follow-up (at 8 years, 68.2% vs. 66.3, P=0.047, Tab. 4).

Exposure to RBC transfusion was significantly higher among anemic patients (Tab. 3). Similarly, nadir haemoglobin level was significantly lower among patients with preoperative anemia (mean, 7.6±0.9 vs. 8.3±1.1 g/dL, P<0.0001), but the amount of blood loss at 12 hours (mean, 477±414 vs. 494±376 mL, P=0.408) and rates of reoperation for bleeding (5.2% vs. 7.1%, P=0.222) were similar between the study groups.

In these propensity score matched pairs, preoperative anemia was associated with a significantly higher rate of acute kidney injury not requiring dialysis (26.3% vs. 15.9%, P<0.0001), without any increased risk of other early adverse events,

In view of the increased need of RBC transfusion among patients with preoperative anemia (Tab. 3), analyses in these propensity score matched pairs were further adjusted for the severity of perioperative bleeding/amount of transfusion as stratified by the E-CABG bleeding classification. These adjusted analyses showed that preoperative anemia was

associated only with an increased risk of acute kidney injury not requiring dialysis (OR 1.50, 95%CI 1.10-2.03), whereas other early outcomes were similar between anemics and non-anemics (Tab. 3).

Cox proportional hazards model in propensity matched pairs including preoperative anemia and the severity of preoperative bleeding stratified by the E-CABG bleeding classification showed that anemia (HR 1.10, 95%CI 0.86-1.39, Fig. 2) was not an independent predictor of late death. Instead, this regression model showed that the E-CABG bleeding classification was an independent predictor of mortality (compared to grade 0: grade 1, HR 1.93, 95%CI 1.37-2.73, grade 2, HR 2.19, 95%CI 1.50-3.18, grade 3, HR 5.59, 95%CI 3.34-9.39, P<0.0001). Similarly, anemia adjusted for the amount of transfused units of RBCs was not associated with poorer survival (HR 1.16, 95%CI 0.91-1.47), whereas the number of transfused RBCs was associated with increased risk of late death (per RBC unit: RR 1.06, 95%CI 1.04-1.08).

Discussion

The main finding of this study is that preoperative anemia is not associated with poorer survival when adjusted for baseline covariates and severity of perioperative bleeding.

Several studies showed that RBC transfusion is associated with increased mortality and morbidity after cardiac surgery [8,21,22]. In turn, anemic patients are more likely to receive transfusions [7,10,11,13-15] and preoperative anemia itself has been shown to be a risk factor for adverse events [4,23-25]. However, the interaction between the anemia status and the increased need of transfusion makes difficult to disentangle the individual prognostic impact

of these two factors. In their seminal contribution, Loor and colleagues [1] demonstrated the independent role of anemia and transfusion on the outcomes after cardiac surgery and concluded that both may have a significant and independent impact on adverse events. However, anemia and transfusion were assessed only intraoperatively and this prevented conclusive results on this issue. Indeed, using a different methodology and evaluating anemia, blood loss and transfusion during the entire postoperative period, preoperative anemia was not a risk factor for late mortality in propensity score matched pairs adjusted for exposure to blood products. The only adverse event associated with preoperative anemia was an increased risk of acute kidney injury. These findings were observed despite preoperative anemia was associated with significantly lower nadir haemoglobin levels without a difference in the amount of postoperative blood loss. However, some investigators consider anemia as a risk factor for increased bleeding because of its possible associated coagulopathy [26,27].

Since preoperative anemia is a modifiable condition, the hypothetical possibility to reverse its related risk of adverse events is intriguing. Evidence from previous studies suggests that the prevalence of preoperative anemia might be higher in cardiac surgery [4,5,10,23], than in the general population of similar age, from developed countries [28-30]. Increased comorbidities among patients requiring revascularization might explain the difference. Older age [23], lower baseline eGFR [20] and poor left ventricular ejection fraction [31] are associated with higher incidence of anemia. In addition to these factors, the present study identified recent myocardial infarction and critical preoperative status as significantly associated with preoperative anemia. We speculate that lower hemoglobin values observed in these two patient groups might be due, in some patients with critical conditions, to hemodilutional anemia secondary to substantial preoperative infusion of fluids.

However, the potential benefits of preoperative hemoglobin optimization are still unclear. Recent studies on the issue reported promising results. Preoperative treatment with EPO and/or intravenous iron is considered reasonable [32,33] and shown to reduce the need for RBC transfusion [34-36]. Hemoglobin optimization > 12g/dL was observed to improve the outcomes of Jehovah's witnesses undergoing cardiac surgery [37].

Our study has some limitations which should to be acknowledged. First, data collection was performed retrospectively. However, data on the amount of blood loss and use of blood products were recorded prospectively. This makes the estimation of perioperative bleeding and exposure to blood products rather reliable. Second, analysis limited to patients undergoing elective CABG would have enabled the exclusion of the impact of potential preoperative hemodilutional anemia, but it would have reduced the statistical power of this analysis. Importantly, propensity score matching provided pairs with similar prevalence of risk factors of critical prognostic importance. Third, this study does not address the possible multiple causes underlying preoperative anemia and some of them might have a prognostic impact which is left unrecognized. The strengths of the study are a relatively large database and a long follow-up with complete survival data.

Conclusions

In this study, preoperative anemia in patients undergoing CABG was associated with significant baseline comorbidities. When adjusted for important baseline characteristics and operative factors as well as for the severity of perioperative bleeding and the amount of transfused blood products, anemia was not associated with increased risk of adverse events. Increased exposure to blood transfusion among anemic patients may be the determinant of their poorer late survival.

Declaration of conflict of interests

None to declare.

Ethical approval details

This study was approved by the Institutional Review Board of the Oulu University Hospital.

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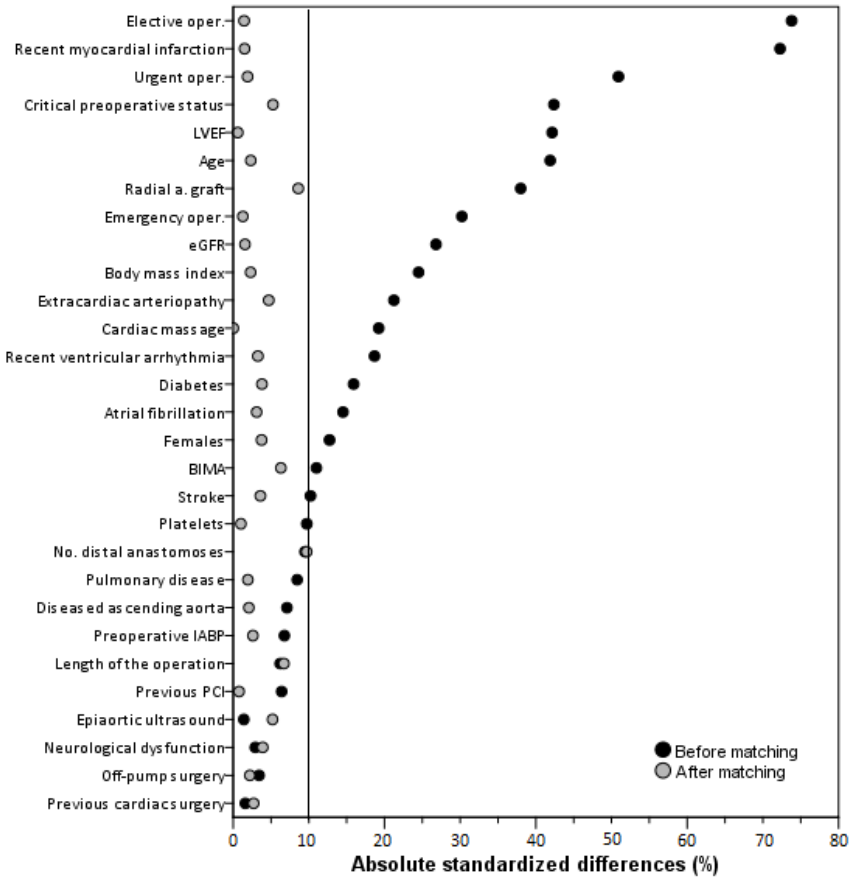

Figure 1. Absolute standardized difference before and after propensity score matching in the cohorts of patients with and without anemia.

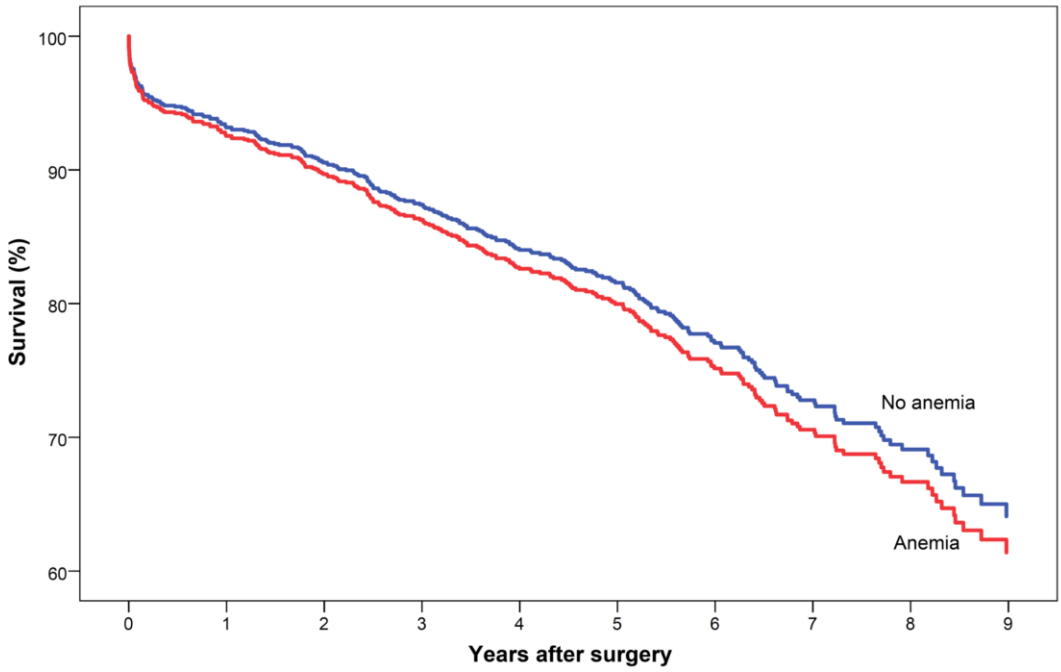

Figure 2. Cox proportional hazards estimate of survival in patients with and without anemia as adjusted by the E-CABG bleeding severity classification (HR, 1.10, 95%CI 0.86-1.39).

Table 1. Baseline characteristics.

	Overall series				*Propensity score matched pairs*		
Baseline variables	*Overall population No. 2761*	*No preop. anemia No. 2099*	*Preop. anemia No. 662*	*P-value*	*No preop. anemia No. 560*	*Preop. anemia No. 560*	*P-value*
Age (years)	66.6±9.1	66.2±9.1	69.9±8.6	<0.0001	69.5±8.7	69.7±8.5	0.566
Females	581 (21.0)	415 (19.8)	166 (25.1)	0.004	130 (23.2)	139 (24.8)	0.529
Body mass index	28.1±4.5	28.3±4.4	27.2±4.6	<0.0001	27.5±4.2	27.4±4.6	0.664
Hemoglobin (g/dL)	13.7±1.6	14.4±1.1	11.5±1.0	<0.0001	14.0±0.9	11.6±1.0	<0.0001
Platelets (10^9/L)	242±76	240±69	248±94	0.600	247±84.8	248±91	0.983
eGFR (mL/min/1.73 m^2)	86.1±25.2	87.8±22.9	80.5±31.0	<0.0001	82.8±23.9	83.2±27.4	0.359
Pulmonary disease	274 (9.9)	195 (9.3)	79 (11.9)	0.047	59 (10.5)	62 (11.1)	0.773
Diabetes	788 (28.5)	562 (26.8)	226 (34.1)	<0.0001	187 (33.4)	177 (31.6)	0.523
Stroke	95 (3.4)	62 (3.0)	33 (5.0)	0.012	20 (3.6)	24 (4.3)	0.538
Extracardiac arteriopathy	265 (9.6)	168 (8.0)	97 (14.7)	<0.0001	78 (13.9)	69 (12.3)	0.426
Neurological dysfunction	50 (1.8)	36 (1.7)	14 (2.1)	0.501	15 (2.7)	12 (2.1)	0.559
Atrial fibrillation	282 (10.2)	191 (9.1)	91 (13.7)	0.001	63 (11.3)	69 (12.3)	0.578
Previous PCI	199 (7.2)	143 (6.8)	56 (8.5)	0.153	40 (7.1)	41 (7.3)	0.908
Previous cardiac surgery	46 (1.7)	36 (1.7)	10 (1.5)	0.72	6 (1.1)	8 (1.4)	0.591
Left ventricular ejection fraction ≤50%	697 (26.2)	435 (21.6)	262 (40.7)	<0.0001	213 (38.0)	211 (37.7)	0.902
Recent myocardial infarction	1317 (47.7)	832 (39.6)	485 (73.3)	<0.0001	400 (71.4)	396 (70.7)	0.792
Critical preoperative status	217 (7.9)	99 (4.7)	118 (17.8)	<0.0001	71 (12.7)	81 (14.5)	0.383
Preoperative IABP	11 (0.4)	6 (0.3)	5 (0.8)	0.147	4 (0.7)	3 (0.5)	1.000
Inotropic support	67 (2.4)	25 (1.2)	42 (6.3)	<0.0001	17 (3.0)	22 (3.9)	0.415
Recent ventricular arrhythmia	83 (3.0)	45 (2.1)	38 (5.7)	<0.0001	25 (4.5)	29 (5.2)	0.577
Cardiac massage	43 (1.6)	18 (0.9)	25 (3.8)	<0.0001	14 (2.5)	14 (2.5)	1.000

Continuous variables are reported as mean and standard deviation. Categorical variables are reported as counts and percentages. PCI: percutaneous coronary intervention. IABP: intra-aortic balloon pump. eGFR: estimated glomerular filtration rate.

Table 2. Operative data.

	Overall series				*Propensity score matched pairs*		
Operative variables	*Overall population No. 2761*	*No preop. anemia No. 2099*	*Preop. anemia No. 662*	*P-value*	*No preop. anemia No. 560*	*Preop. anemia No. 560*	*P-value*
Urgency status				<0.0001			0.950
Elective	1259 (45.6)	1125 (53.6)	134 (20.2)		124 (22.1)	127 (22.7)	
Urgent	1306 (47.3)	869 (41.4)	437 (66.0)		375 (67.0)	370 (66.1)	
Emergency	196 (7.1)	105 (5.0)	91 (13.7)		61 (10.9)	63 (11.3)	
Off-pump surgery	1507 (54.6)	1137 (54.2)	370 (55.9)	0.438	315 (56.3)	309 (55.2)	0.718
Epiaortic ultrasound	1448 (52.4)	1097 (52.3)	351 (53.0)	0.733	311 (55.5)	296 (52.9)	0.368
Diseased ascending aorta	225 (8.1)	161 (7.7)	64 (9.7)	0.101	50 (8.9)	53 (9.5)	0.756
Number of distal anastomoses	4.0±1.1	4.0±1.1	3.9±1.1	0.510	4.0±1.0	3.9±1.0	0.977
Length of the operation (min)	249±69	249±71	246±62	0.324	248±54	244±56	0.569

Continuous variables are reported as mean and standard deviation. Categorical variables are reported as counts and percentages. CPB: cardiopulmonary bypass.

Table 3. Bleeding-related outcomes.

	Overall series				*Propensity score matched pairs*		
	Overall population No. 2761	*No preop. anemia No. 2099*	*Preop. anemia No. 662*	*P-value*	*No preop. anemia No. 560*	*Preop. anemia No. 560*	*P-value*
Nadir hemoglobin (g/dL)	8.3±1.2	8.5±1.2	7.6±0.9	<0.0001	8.3±1.1	7.6±0.9	<0.0001
Blood loss at 12 hours (mL)	504±394	509±388	484±416	0.029	494±376	477±414	0.408
RBC transfusion	1753 (63.5)	1160 (55.3)	593 (89.6)	<0.0001	393 (70.2)	497 (88.8)	<0.0001
RBC units transfused	2.5±3.4	1.9±2.8	4.5±4.2	<0.0001	2.7±3.7	3.9±3.5	<0.0001
Octaplas transfusion	737 (26.7)	514 (24.5)	223 (33.7)	<0.0001	174 (31.1)	175 (31.3)	1.000
Octaplas units transfused	1.2±2.4	1.0±2.1	1.7±3.3	<0.0001	1.3±2.4	1.3±2.6	0.546
Platelet transfusion	824 (29.8)	562 (26.8)	262 (39.6)	<0.0001	192 (34.3)	202 (36.1)	0.568
Platelet units transfused	3.0±6.1	2.5±5.0	4.5±8.6	<0.0001	3.4±6.1	3.4±6.1	0.178
Resternotomy for bleeding	180 (6.5)	139 (6.6)	41 (6.2)	0.697	40 (7.1)	29 (5.2)	0.222
Procedure of retained blood within 30 days	253 (9.2)	191 (9.1)	62 (9.4)	0.836	58 (10.4)	45 (8.0)	0.198
E-CABG bleeding grades				0.001			<0.0001
Grade 1	1116 (40.4)	819 (39.0)	297 (44.9)		257 (45.9)	259 (46.3)	
Grade 2	504 (18.3)	283 (13.5)	221 (33.4)		101 (18.0)	183 (32.7)	
Grade 3	68 (2.5)	27 (1.3)	41 (6.2)		15 (2.7)	25 (4.5)	

Continuous variables are reported as mean and standard deviation. Categorical variables are reported as counts and percentages. RBC: red blood cell.

Table 4. Outcomes in the overall series and in propensity score matched cohorts.

	Overall series				*Propensity score matched pairs*			
	Overall population No. 2761	*No preop. anemia No. 2099*	*Preop. anemia No. 662*	*Univariate analysis P-value*	*No preop. anemia No. 560*	*Preop. anemia No. 560*	*Univariate analysis P-value*	*Adjusted analysis Risk estimate (95%CI)*
In-hospital death	66 (2.4)	38 (1.8)	28 (4.2)	<0.0001	18 (3.2)	17 (3.0)	1.000	0.61, 0.31-1.23
30-day mortality	89 (3.2)	48 (2.3)	41 (6.2)	<0.0001	22 (3.9)	22 (3.9)	1.000	0.67, 0.36-1.26
ICU stay (days)	2.2±2.5	1.9±2.0	2.9±3.5	<0.0001	2.4±2.6	2.6±3.1	0.155	-0.29, -0.62-0.04
Stroke	58 (2.1)	33 (1.6)	25 (3.8)	0.001	14 (2.5)	17 (3.0)	0.719	0.93, 0.45-1.93
Atrial fibrillation	1185 (42.9)	848 (40.4)	337 (50.9)	<0.0001	276 (49.3)	278 (49.6)	0.951	0.95, 0.74-1.20
Ventricular fibrillation/asystole	48 (1.7)	24 (1.1)	24 (3.6)	<0.0001	11 (2.0)	18 (3.2)	0.265	1.13, 0.52-2.47
Permanent pace-maker implantation	18 (0.7)	11 (0.5)	7 (1.1)	0.163	4 (0.7)	6 (1.1)	0.754	1.39, 0.38-5.12
Low cardiac output syndrome	382 (13.8)	267 (12.7)	115 (17.4)	0.003	95 (17.0)	92 (16.4)	0.870	0.78, 0.54-1.05
Postop. intra-aortic balloon pump	16 (0.6)	11 (0.5)	5 (0.8)	0.556	6 (1.1)	4 (0.7)	0.754	0.46, 0.13-1.68
Repeat CABG or PCI	14 (0.5)	10 (0.5)	4 (0.6)	0.753	1 (0.2)	3 (0.5)	0.625	1.67, 0.17-16.24
Post-operative use of antibiotics	935 (33.9)	613 (29.2)	322 (48.6)	<0.0001	211 (37.7)	258 (46.1)	0.004	1.17, 0.91-1.50
Deep sternal wound infection	40 (1.4)	26 (1.2)	14 (2.1)	0.1	7 (1.3)	10 (1.8)	0.629	1.24, 0.46-3.35
Mediastinitis	43 (1.6)	29 (1.4)	14 (2.1)	0.184	10 (1.8)	10 (1.8)	0.181	0.88, 0.35-2.18
Surgery for gastrointest. compl.	32 (1.2)	16 (0.8)	16 (2.4)	0.001	6 (1.1)	10 (1.8)	0.454	1.03, 0.36-2.95
Acute kidney injury				<0.0001			<0.0001	**-0.31, -0.60- -0.01**
Grade 1	325 (12.0)	181 (8.7)	144 (23.0)		71 (12.9)	124 (22.4)		
Grade 2	71 (2.6)	40 (1.9)	31 (4.9)		17 (3.1)	25 (4.5)		
Grade 3	61 (2.3)	33 (1.6)	28 (4.5)		17 (3.1)	21 (3.8)		
New renal replacement therapy	51 (1.9)	28 (1.3)	23 (3.6)	<0.0001	16 (2.9)	17 (3.0)	1.000	0.61, 0.29-1.29
Acute kidney injury without dialysis	396 (14.3)	223 (10.6)	173 (26.1)	<0.0001	89 (15.9)	147 (26.3)	<0.0001	**1.50, 1.10-2.03**
Survival**				<0.0001			0.047	1.10, 0.86-1.39
1-year		96.0% (2015)	88.7% (587)		92.9% (520)	92.0% (515)		
5-year		88.4% (1287)	72.7% (319)		82.9% (315)	76.9% (280)		
8-year		80.2% (471)	62.4% (82)		68.2% (104)	66.3% (72)		

Continuous variables are reported as mean and standard deviation. Categorical variables are reported as counts and percentages. Risk estimates in bold indicate statistical significance in multivariate analysis; ICU: intensive care unit; CABG: coronary artery bypass grafting; PCI: percutaneous coronary intervention; Risk estimates are odds ratio or beta coefficient; 95%CI: 95% confidence interval; *: excluding bleeding-related outcomes; **: in parentheses are patients at risk.