Original research

Bleeding, transfusion and the risk of stroke after coronary surgery: A prospective cohort study of 2357 patients

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HIGHLIGHTS

- The mechanisms underlying stroke after cardiac surgery are not fully understood.
- Bleeding and blood transfusion independently increase the risk of stroke after coronary surgery.
- The risk of postoperative stroke is highest in case of severe postoperative bleeding.

ARTICLE INFO

ABSTRACT

Introduction: This study was planned to investigate the impact of severe bleeding and blood transfusion on the development of stroke after coronary surgery.
Methods: This cohort study includes 2357 patients undergoing isolated CABG from the prospective European Coronary Artery Bypass Grafting (E-CABG) registry. Severity of bleeding was categorized according to the Universal Definition of Perioperative Bleeding (UDPB), E-CABG and PLATO definitions.

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Results: Thirty patients (1.3%) suffered postoperative stroke. The amount of transfused red blood cell (RBC) (OR 1.10, 95%CI 1.03—1.18), preoperative use of unfractioned heparin (OR 4.49, 95%CI 1.91—10.60), emergency operation (OR 3.97, 95%CI 1.47—10.74), diseased ascending aorta (OR 4.62, 95%CI 1.37—15.65) and use of cardiopulmonary bypass (p = 0.043, OR 4.85, 95%CI 1.05—22.36) were independent predictors of postoperative stroke. Adjusted analysis showed that UDPB classes 3—4 (crude rate: 3.6% vs. 1.0%; adjusted OR 2.66, 95%CI 1.05—6.73), E-CABG bleeding grades 2—3 (crudes rate: 6.3% vs. 0.9%; adjusted OR 5.91, 95%CI 2.43—14.36), and PLATO life-threatening bleeding (crude rate: 2.5% vs. 0.6%, adjusted OR 3.70, 95%CI 1.59—8.64) were associated with an increased risk of stroke compared with no or moderate bleeding.
Conclusions: Bleeding and blood transfusion are associated with an increased risk of stroke after CABG, which is highest in patients with severe bleeding.

1. Introduction

Postoperative stroke is one of the most severe complications after cardiac surgery. Recent studies reported on a possible association between blood transfusions and the development of postoperative stroke [1–6]. However, investigation of the mechanistic role of excessive bleeding requiring transfusion in the pathogenesis of postoperative neurological complications is made difficult by the multifactorial causation of postoperative stroke [7–10], the lack of adequate stratification methods of the severity of bleeding, and of prospective data. The on-going European multicenter registry E-CABG [11] collects prospectively a number of variables on the amount of bleeding, severity of anemia, and use of any blood products in patients undergoing isolated coronary artery bypass grafting (CABG). This allows a stratification of the severity of bleeding according to the E-CABG bleeding severity definition [11], the Universal Definition of Perioperative Bleeding (UDPB) [12], and Platelet Inhibition and Patient Outcomes (PLATO) bleeding definition for major hemorrhage [13]. The prospective E-CABG registry was used to investigate the impact of increasing severity of bleeding and use of blood products on the development of stroke after isolated CABG.

2. Methods

The E-CABG registry is a prospective, multicenter study enrolling patients undergoing isolated CABG at 15 European cardiac surgery centers (Besançon, France; Catanzaro, Italy; Genoa, Italy; Hamburg, Germany; Milan, Italy; Nuremberg, Germany; Naples, Italy; Oulu, Finland; Parma, Italy; Pedara, Italy; Rennes, France; Rome, Italy; Stockholm, Sweden; Trieste, Italy; Verona, Italy). This study is registered in Clinicaltrials.gov (Identifier: NCT02319083) and its study protocol and definition criteria are reported in detail elsewhere [11]. For the purpose of the present analysis, we included a consecutive series of patients with coronary artery disease undergoing isolated CABG from January 2015 to September 2015. This analysis was planned before starting the E-CABG project. Patients undergoing carotid angioplasty or endarterectomy immediately before CABG (n = 97) and those with missing data (n = 28) were excluded from this analysis. Data on preoperative antithrombotics, postoperative blood loss, anemia, and use of any type of blood products were collected prospectively in order to stratify the severity of bleeding according to the E-CABG bleeding severity definition [11], UDPB criteria [12], and PLATO major and life-threatening bleeding criteria [13]. Preoperative anemia was defined as hemoglobin <12 gr/dL in women and <13 gr/dL in men. Data on preoperative ultrasound screening of the status of carotid arteries and intraoperative use of epiaortic ultrasound were available according to institutional policies and were considered as covariates in multivariate analyses.

The main outcome measure of this study was any temporary or permanent ischemic stroke occurring during the in-hospital stay after CABG. Stroke was defined as any focal or global neurological syndrome occurring during the in-hospital stay caused by ischemia not resolving within 24 h. The diagnosis and nature of stroke was made on the basis of findings at computed tomography and/or magnetic resonance imaging of the brain and confirmed by a neurologist. When neurological signs and symptoms disappeared before discharge, stroke was defined temporary, otherwise it was defined as permanent.

3. Statistical analysis

Summary statistics are presented as means ± standard deviation for continuous variables and as counts and percentages for categorical variables. Odds ratios (ORs) and 95% confidence interval (CIs) are reported. No attempt to replace missing values was made. Fisher exact test, Chi-square test and Mann-Whitney tests were used for univariate analysis. Logistic regression with backward selection was used to identify risk factors associated with postoperative stroke. Since the incidence of stroke was less than 2%, we included in the regression models only variables with a p < 0.05 in univariate analysis in order to avoid model overfitting. The fit of the final multivariate logistic regression analysis was assessed using the Hosmer-Lemeshow goodness-of-fit test and the discriminatory power was quantified by C-statistics. In a subsequent analysis, a logistic regression model was conducted to adjust the risk of stroke associated with increasing UDPB classes, E-CABG bleeding grades and PLATO bleeding classes for any baseline, operative and postoperative covariate potentially associated with the development of stroke as defined by a p < 0.05. According to this criterion, critical preoperative state, emergency operation, preoperative use of unfractioned heparin, diseased ascending aorta, use of cardiopulmonary bypass, amount of chest tube output 12 h after surgery, units of transfused RBC, administration of fibrinogen and of prothrombin complex were included in to the regression model for prediction of stroke. Along with these variables, also postoperative atrial fibrillation (p = 0.054), prolonged use of inotropics after surgery (p = 0.029), use of intra-aortic balloon pump (p = 0.126), and use of extracorporeal mechanical oxygenation (p = 0.008) were included in to the regression models because of their potential causative role in the development of postoperative stroke. Furthermore, participating centers, baseline and nadir levels of hemoglobin, and hematocrit on the operation day were forced in to this regression models. All tests were two-sided with the alpha level set at 0.05 for statistical significance. All statistical analysis

were performed using the SPSS v. 23.0 statistical software (IBM Corporation, 1 New Orchard Road Armonk, New York 10504-1722, United States).

4. Results

The present analysis includes 2357 patients who underwent isolated CABG from the E-CABG registry. Patients' characteristics and operative data are summarized in Tables 1 and 2. Bleeding outcome endpoints are reported in Table 3.

Thirty-six patients (1.5%) died during the in-hospital stay. Thirty patients (1.3%) suffered stroke after surgery. Stroke was permanent in 22 patients (0.9%). Stroke occurred during the operation day or the first postoperative day in 12 patients, during the second or third postoperative day in 10 patients, and later on in eight patients.

Predictors of stroke in univariate analysis are listed in Tables 1–3.

Regression analysis (2324 patients included in the analysis, Hosmer-Lemeshow's test, p = 0.305, area under the ROC curve 0.824, 95%CI 0.757–0.891) including covariates with p < 0.05 in univariate analysis showed that the amount of RBC units transfused during and after surgery (p = 0.003, OR 1.10, 95%CI 1.03–1.18), preoperative use of unfractioned heparin (p = 0.001, OR 4.49, 95%CI 1.91–10.60), emergency operation (p = 0.007, OR 3.97, 95%CI 1.47–10.74), atherosclerosis of the ascending aorta (p = 0.014, OR 4.62, 95%CI 1.37–15.65) and use of cardiopulmonary bypass (p = 0.043, OR 4.85, 95%CI 1.05–22.36) were independent predictors of postoperative stroke (Tables 1–3). When the amount of RBC units transfused during surgery was included in this model, this was an independent predictor of stroke (p = 0.022, OR 1.09, 95%CI 1.01–1.17).

Table 1
Baseline characteristics of 2357 patients undergoing coronary surgery and predictors of postoperative stroke at univariate and multivariate analysis.

Clinical variables	Overall population n = 2357	No stroke n = 2327	Stroke n = 30	Univariate analysis p-value	Multivariate analysis (odds ratio, 95%CI)
Age (years)	67.0 ± 9.3	67.0 ± 9.3	66.0 ± 9.9	0.744	–
Females	375 (15.9)	370 (15.9)	5 (16.7)	0.805	–
Body mass index	27.6 ± 4.2	27.6 ± 4.2	27.4 ± 4.8	0.588	–
Hemoglobin (g/L)	137 ± 16	137 ± 16	141 ± 16	0.275	–
Hematocrit (%)	40 ± 4	40 ± 5	41 ± 4	0.297	–
Platelets (10^9/L)	226 ± 66	226 ± 66	218 ± 63	0.531	–
eGFR (mL/min/1.73 m^2)	81 ± 26	81 ± 34	79 ± 29	0.749	–
Dialysis	29 (1.2)	29 (1.2)	0	1.000	–
Functioning kidney transplant	7 (0.3)	7 (0.3)	0	1.000	–
Pulmonary disease	208 (8.8)	204 (8.8)	4 (13.3)	0.331	–
Diabetes	729 (30.9)	722 (31.0)	7 (23.3)	0.365	–
Insulin dependent diabetes	311 (13.2)	309 (13.3)	2 (6.7)	0.417	–
Preop. carotid ultrasound	841 (35.7)	831 (35.7)	10 (33.3)	0.850	–
Transient ischemic attack	48 (2.0)	47 (2.0)	1 (3.3)	0.463	–
Stroke	96 (4.1)	94 (4.0)	2 (6.7)	0.347	–
Poor mobility	58 (2.5)	58 (2.5)	0	1.000	–
Extracardiac arteriopathy	451 (19.1)	442 (19.0)	9 (30.0)	0.128	–
Hypertension	1864 (79.1)	1836 (78.9)	28 (93.3)	0.068	–
Atrial fibrillation	179 (7.6)	175 (7.6)	4813.3)	0.283	–
Prior percutaneous coronary int.	495 (21.0)	486 (20.9)	9 (30.0)	0.223	–
Prior cardiac surgery	22 (0.9)	22 (0.9)	0	1.000	–
Left ventricular ejection fraction				0.445	–
31–50%	569 (24.2)	558 (24.0)	11 (36.7)		
21–30%	94 (4.0)	93 (4.0)	1 (3.3)		
<21%	10 (0.4)	10 (0.4)	0		
Diagnosis				0.515	–
Unstable angina	419 (17.8)	414 (17.8)	5 (6.5)		
NSTEMI	541 (23.0)	535 (23.0)	6 (20.0)		
STEMI	155 (6.6)	151 (6.5)	4 (13.3)		
Critical preoperative status	83 (3.5)	79 (3.4)	4 (13.3)	0.019	–
Preoperative IABP	72 (3.1)	71 (3.1)	1 (3.3)	0.608	–
Ventricular arrhythmias	43 (1.8)	43 (1.8)	0	1.000	–
Out-of-hospital cardiac arrest	21 (0.9)	21 (0.9)	0	1.000	–
Medical treatment before surgery					
Aspirin	2110 (89.5)	2082 (89.5)	28 (93.3)	0.763	–
Statin	1748 (74.2)	1727 (74.2)	21 (70.0)	0.600	–
Clopidogrel	457 (19.4)	452 (19.4)	5 (16.7)	0.820	–
Ticagrelor	346 (14.7)	343 (14.7)	3 (10.0)	0.609	–
Prasugrel	25 (1.1)	24 (1.0)	1 (3.3)	0.275	–
Warfarin/coumadin	59 (2.5)	58 (2.5)	1 (3.3)	0.770	–
New oral anticoagulants	23 (1.0)	22 (0.9)	1 (3.3)	0.256	–
Ticlopidin	9 (0.4)	9 (0.4)	0	1.000	–
Fondaparinux	106 (4.5)	106 (4.6)	0	0.643	–
Low molecular weight heparin	808 (34.3)	798 (34.3)	10 (34.5)	0.983	–
Unfractioned heparin	226 (9.6)	217 (9.3)	9 (30.0)	0.001	4.49, 1.91–10.60
Glycoprotein IIb/IIIa inhibitors	23 (1.0)	23 (1.0)	0	1.000	–
CRUSADE bleeding score	25 ± 13	25 ± 13	27 ± 12	0.446	–
Papworth bleeding score	0.9 ± 0.8	0.9 ± 0.8	1.0 ± 0.8	0.578	–
GRACE score	121 ± 31	121 ± 31	124 ± 29	0.525	–
EuroSCORE II (%)	2.5 ± 3.7	2.5 ± 3.7	3.2 ± 2.8	0.061	–

Continuous variables are reported as mean and standard deviation. Categorical variables are reported as absolute number and percentages. Clinical variables are reported according to the EuroSCORE II definition criteria. eGFR: estimated glomerular filtration; NSTEMI: non ST-elevation myocardial infarction; STEMI: ST-elevation myocardial infarction; IABP: intra-aortic balloon pump; CRUSADE: Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines?; GRACE: Global Registry of Acute Coronary Events.

Table 2
Operative data of 2357 patients undergoing coronary surgery.

Operative variables	Overall population n = 2357	No stroke n = 2327	Stroke n = 30	Univariate analysis p-value	Multivariate analysis (odds ratio, 95%CI)
Urgency status				<0.0001	
Elective	1340 (56.9)	1325 (56.9)	15 (50.0)		–
Urgent	921 (39.1)	913 (39.2)	8 (26.7)		–
Emergency	96 (4.1)	89 (3.8)	7 (23.3)	<0.0001	3.97, 1.47—10.74
Epiaortic ultrasound	247 (10.4)	246 (10.6)	1 (3.3)	0.361	–
Diseased ascending aorta	85 (3.6)	81 (3.5)	4 (13.3)	0.021	4.62, 1.37—15.65
Use of cardiopulmonary bypass	1849 (78.4)	1821 (78.3)	28 (93.3)	0.045	4.85, 1.05—22.36
Aorta left untouched	356 (15.1)	355 (15.3)	1 (3.3)	0.074	–
Bilateral mammary artery graft	923 (39.2)	909 (39.1)	14 (46.7)	0.397	–
Radial artery graft	27 (1.1)	27 (1.2)	0	1.000	–
Number of distal anastomoses	2.7 ± 0.9	2.7 ± 0.9	2.7 ± 0.8	0.888	–
Cross-clamping time (min)	59 ± 33	59 ± 33	70 ± 53	0.511	–
Cardiopulmonary bypass time (min)	84 ± 36	84 ± 36	101 ± 43	0.033	–
Length of the operation (min)	224 ± 84	223 ± 83	241 ± 109	0.885	–

Continuous variables are reported as mean and standard deviation. Categorical variables are reported as absolute number and percentages.

Table 3
Bleeding outcome end-points and their association with postoperative stroke.

Bleeding-related variables	Overall population n = 2357	No stroke n = 2327	Stroke n = 30	Univariate analysis p-value	Multivariate analysis (odds ratio, 95%CI)
Nadir hematocrit (%)	30 ± 9	30 ± 10	30 ± 5	0.994	–
Nadir hemoglobin (g/L)	98 ± 16	98 ± 13	97 ± 16	0.823	–
Chest tube output at 12 h (mL)	442 ± 281	440 ± 279	632 ± 419	0.001	–
Use of blood products	992 (42.1)	975 (41.9)	17 (56.7)	0.070	–
Transfused RBC	927 (39.3)	910 (39.1)	17 (56.7)	0.060	–
Transfused RBC units intraoperatively	0.3 ± 0.8	0.3 ± 0.8	0.9 ± 1.6	0.010	–
Transfused RBC units intra- and postoperatively	1.1 ± 2.4	1.1 ± 2.3	3.7 ± 5.3	0.001	1.10, 1.03—1.18
Transfused fresh frozen plasma	141 (6.0)	137 (5.9)	4 (13.3)	0.100	–
Transfused fresh frozen plasma units	0.2 ± 1.4	0.2 ± 1.1	0.4 ± 1.3	0.087	–
Transfused platelets	168 (7.1)	164 (7.0)	4 (13.3)	0.161	–
Transfused plateletes units	0.3 ± 2.0	0.3 ± 2.0	1.3 ± 5.3	0.164	–
rFVII	2 (0.1)	2 (0.1)	0	1.000	–
Cryoprecipitate	7 (0.3)	6 (0.3)	1 (3.3)	0.086	–
Fibrinogen	61 (2.6)	58 (2.5)	3 (10.0)	0.041	–
Prothrombin complex	39 (1.6)	36 (1.5)	3 (10.0)	0.012	–
Resternotomy for bleeding	66 (2.8)	64 (2.8)	2 (6.7)	0.206	–
UDPB classes				0.001	–
0	1315 (55.8)	1305 (56.1)	10 (33.3)		
1	288 (12.2)	284 (12.2)	4 (13.3		
2	534 (22.7)	526 (22.6)	8 (26.7)		
3	197 (8.4)	191 (8.2)	6 (20.0)		
4	23 (1.0)	21 (0.9)	2 (6.7)		
E-CABG bleeding grades				<0.0001	–
0	1571 (66.7)	1556 (66.9)	15 (50.0)		
1	627 (26.6)	622 (26.7)	5 (16.7)		
2	140 (5.9)	132 (5.7)	8 (26.7)		
3	19 (0.8)	17 (0.7)	2 (6.7)		
PLATO bleeding grades				<0.0001	–
No significant bleeding	380 (16.2)	379 (16.3)	1 (3.3)		
Major bleeding	1120 (47.6)	1112 (47.9)	8 (26.7)		
Life-threatening bleeding	851 (36.2)	830 (35.8)	21 (70.0)		

Continuous variables are reported as mean and standard deviation. Categorical variables are reported as absolute number and percentages; RBC: red blood cell; rFVII: re-combinant human coagulation factor VII; UDPB: Universal Definition of Perioperative Bleeding; PLATO: Platelet Inhibition and Patient Outcomes study.

The status of the internal carotid artery was investigated pre-operatively in 902 patients (35.8%). When the highest degree of stenosis of the internal carotid artery was considered in a regression model including the above mentioned predictors of stroke, the amount of transfused RBC units (p < 0.0001, OR 1.29, 95%CI 1.13—1.46) was the only independent predictor of this neurological complication. Similar results were observed when the amount of transfused RBC was adjusted for the presence of bilateral stenosis >50%.

The severity of bleeding and amounts of blood products as defined by UDPB (p = 0.001), E-CABG (p < 0.0001), and PLATO (p < 0.0001) classifications were predictive of postoperative stroke at univariate analysis (Fig. 1). Since the risk of stroke was highest in patients with UDPB classes 3 and 4, E-CABG bleeding grades 2 and 3 as well as in PLATO life-threatening bleeding (Fig. 1), these were considered for adjusted analyses.

Risk estimates of stroke according to severe bleeding as defined by the UDPB, E-CABG, and PLATO criteria were separately calculated by adjusting for the independent predictive covariates, but the amount of transfused RBCs. These analyses showed that UDPB classes 3—4 (crude rate: 3.6% vs. 1.0%; adjusted OR 2.66, 95%CI 1.05—6.73), E-CABG bleeding grades 2—3 (crudes rate: 6.3% vs. 0.9%; adjusted OR 5.91, 95%CI 2.43—14.36), and PLATO life-threatening bleeding (crude rate: 2.5% vs. 0.6%,
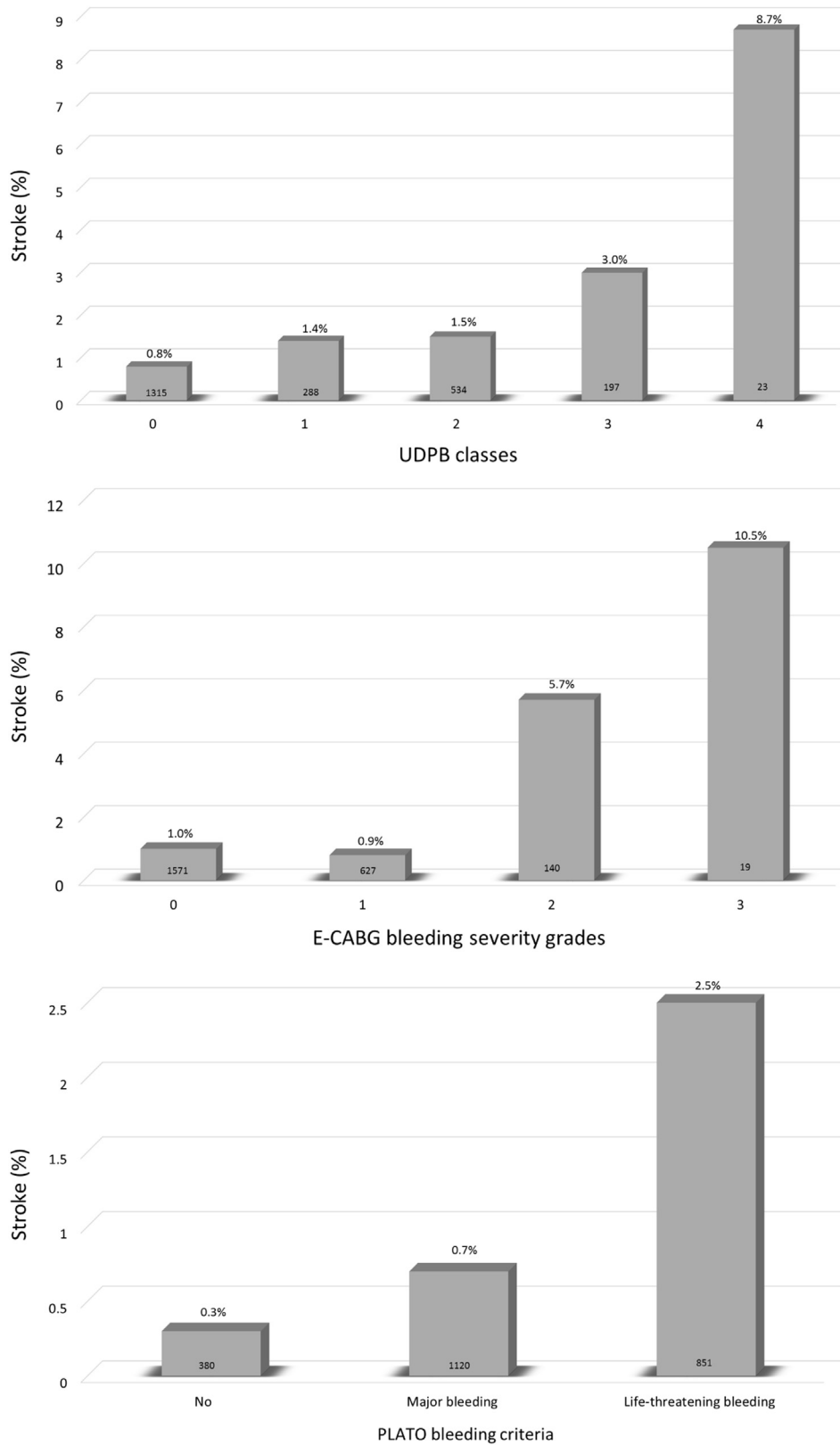
Fig. 1. Incidence of postoperative stroke according to increasing severity of bleeding defined according to the UDPB (p < 0.0001), E-CABG (p < 0.0001), and PLATO (p < 0.0001) bleeding criteria.

adjusted OR 3.70, 95%CI 1.59—8.64) were associated with an increased risk of stroke compared with no or moderate bleeding (Table 4).

5. Discussion

The present results suggest that bleeding requiring blood

Table 4
Adjusted risk estimates of postoperative stroke in patients with severe bleeding.

Bleeding classification methods	Reference category	Severe bleeding (OR, 95%CI)
UDPB classes	0—2	3—4
Crude estimate	—	3.63, 1.60—8.25
Adjusted estimate	—	2.66, 1.05—6.73
E-CABG bleeding grades	0—1	2—3
Crude estimate	—	7.31, 3.36—15.90
Adjusted estimate	—	5.91, 2.43—14.36
PLATO bleeding grades	No or major bleeding	Life-threatening bleeding
Crude estimate	—	4.19, 1.91—9.19)
Adjusted estimate	—	3.70, 1.59—8.64

Values are odds ratio and 95% confidence interval; UDPB: Universal Definition of Perioperative Bleeding; PLATO: Platelet Inhibition and Patient Outcomes study.

transfusion is associated with a significantly increased risk of postoperative stroke. The negative prognostic effect of bleeding/ blood transfusion was investigated in several multivariate analyses adjusted for a number of possible confounders. The role of RBC transfusion seems to be independent of other well-recognized causative factors such as atherosclerosis of the ascending aorta and use of cardiopulmonary bypass. Cannulation and clamping of a diseased ascending aorta may be a source of embolism during cardiac surgery [10,14], whereas cardiopulmonary bypass may contribute to major derangements in cerebral circulation secondary to severe hemodilution, inadequate coupling of pump flow and temperature as well as low perfusion pressure [15]. The risk of stroke has been shown to be increased by prolonged cardiopulmonary bypass duration [16].

We observed that preoperative administration of unfractioned heparin and emergency operation were other independent risk factors for stroke, both carrying a substantially increased risk of major bleeding related to the use of potent antithrombotics immediately before surgery. Similarly, also using cardiopulmonary bypass in coronary surgery has been shown to increase the risk of bleeding [17]. In turn, we speculate that off-pump surgery may be associated with a lower risk of stroke also by its recognized benefits in reducing blood loss and need of blood transfusion.

The present findings confirm those of a few previous retrospective studies reporting on the increased risk of stroke associated with exposure to RBC and/or fresh frozen plasma/Octaplas and platelets [1,3—5]. However, previous studies did not investigate the risk of neurological complications related with increasing severity of perioperative bleeding because the UDPB, E-CABG and PLATO bleeding definitions were not available at that time. The present analysis showed that the risk of stroke is substantial only in those patients with severe bleeding as defined by three perioperative bleeding stratification methods. This means that the risk of cerebrovascular events is higher in patients with significant blood loss requiring large amount of blood transfusion. It is worth noting that the risk of stroke was lowest (0.3%) in patients without major bleeding as defined by the PLATO criteria. This finding suggests that conditions requiring transfusion of >1 unit of RBC and a significant drop in hemoglobin level are those posing the patients at high risk of stroke.

In absence of data on intra- and postoperative hemodynamics, we may speculate that transient bleeding-related hypotension and anemia might be responsible for the development of stroke. Indeed, a number of studies demonstrated that both preoperative and post-cardiopulmonary bypass anemia is associated with a higher risk of stroke [3,18]. A recent meta-analysis by Fowler et al. [19] showed that anemia before cardiac surgery is associated with a significantly increased risk of stroke (OR 1.28, 95%CI 1.06—1.55). These findings suggest that reduced oxygen delivery secondary to pre-existent or transient anemia as well as hypotension secondary to significant

bleeding may result in cerebral ischemia in presence of intracranial atherosclerosis or the expansion of small brain infarcts secondary to embolism. However, in this scenario, we cannot entirely disentangle the role of transfusion of blood products on the development of stroke. Transfusion of even a single unit of RBC has been shown to increase the risk of stroke and/or myocardial infarction [2], whilst in this study the risk of neurological complications was most evident in patients with severe bleeding requiring transfusion of large amounts of RBC units. Furthermore, retrospective data suggest that administration of solvent/detergent-treated plasma (Octaplas®) and platelets may result in an even higher risk of stroke than RBC transfusion [4,5]. Therefore, a possible thrombogenic potential of these blood products cannot be excluded.

A number of limitations related with this study should be acknowledged. First, the present study was ideated at the time of planning of this prospective, multicenter registry. Therefore, we collected detailed information on blood products transfused during and after surgery as well as on nadir levels of hemoglobin and hematocrit on the operation day. However, we did not plan to collect data on hypotensive episodes occurring during and after surgery because of anticipated difficulties to retrieve data on arterial pressure during the intra- and postoperative period. Analyses were adjusted for severe hypotensive events requiring prolonged use of inotropics after surgery, use of intra-aortic balloon pump and/or extracorporeal mechanical oxygenation, but even a less pronounced hypotensive state might have had an impact on the development of stroke. Second, epiaortic ultrasound was performed only in 10% of patients. Therefore, identification of atherosclerotic ascending aorta as well as strategy of avoiding aortic manipulation when indicated were suboptimal. We may expect that patients with diseased ascending aorta were, in most of cases, those with atherosclerosis lesions identified at palpation. Third, preoperative ultrasound examination of the carotid arteries was performed in 36% of patients. However, subanalysis of this subset of patients showed that transfusion of RBC was the only independent predictor of stroke even when adjusted for the severity of stenosis of the internal carotid arteries. Finally, the main end-point of this study was any clinically evident stroke, but its incidence has been shown to be much lower than brain ischemic lesions detected at magnetic resonance imaging after cardiac surgery [20,21]. Although most of brain infarcts are silent and without any significant impact on the prognosis of these patients [20], a thoroughly evaluation of such ischemic lesions may provide more reliable information on the causative role of bleeding and blood transfusion on the development of postoperative stroke.

6. Conclusions

The results from this prospective study provide evidence on the impact of bleeding and/or blood transfusion on the development of

stroke after CABG. Such a risk is highest in patients with severe bleeding. These findings suggest that optimization of preoperative level of hemoglobin and reduction of blood loss may decrease the need of blood transfusion and, in turn, the risk of neurological complications after coronary surgery.

Ethical approval

The study was approved by the local regional or institutional review board according to national guidelines for approval of registry studies. Informed consent was collected in institutions where it was required by the review board.

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Author contribution

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Conflicts of interest

None of the authors do have any conflicts of interest.

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