Journal of Cardiothoracic and Vascular Anesthesia 36 (2022) 3057–3064

Contents lists available at ScienceDirect

Journal of Cardiothoracic and Vascular Anesthesia

journal homepage: www.jcvaonline.com

Original Article

Perioperative Bleeding Requiring Blood Transfusions is Associated With Increased Risk of Stroke After Transcatheter and Surgical Aortic Valve Replacement

Tuomas Tauriainen, MD, PhD[*,1], Tatu Juvonen, MD, PhD[*,†], Vesa Anttila, MD, PhD[‡], Pasi Maaranen, MD[§], Matti Niemelä, MD, PhD[‖], Markku Eskola, MD, PhD[§], Tuomas Ahvenvaara, MD[*], Annastiina Husso, MD, PhD[¶], Marko P.O. Virtanen, MD, PhD[§], Eeva-Maija Kinnunen, MD, PhD[†], Sebastian Dahlbacka, MD, PhD[†], Maina Jalava, MD, PhD[‡], Mika Laine, MD, PhD[†], Antti Valtola, MD, PhD[¶], Peter Raivio, MD, PhD[†], Antti Vento, MD, PhD[†], Juhani Airaksinen, MD, PhD[§], Timo Mäkikallio, MD, PhD[‖], Fausto Biancari, MD, PhD[†,**]

[*]*Research Unit of Surgery, Anesthesia and Intensive Care, Faculty of Medicine, University of Oulu, Oulu, Finland*

[†]*Heart and Lung Center, Helsinki University Hospital, University of Helsinki, Helsinki, Finland*

[‡]*Heart Center, Department of Surgery, University of Turku, Turku University Hospital, Turku, Finland*

[§]*Heart Hospital, Tampere University Hospital and Faculty of Medicine and Health Technology, University of Tampere, Tampere, Finland*

[‖]*Department of Internal Medicine, Oulu University Hospital, Oulu, Finland*

[¶]*Heart Center, Kuopio University Hospital, Kuopio, Finland*

[**]*Clinica Montevergine, GVM Care and Research, Mercogliano, Italy*

Objectives: The authors aimed to investigate the impact of severe bleeding and use of red blood cell (RBC) transfusion on the development of postoperative stroke after surgical (SAVR) and transcatheter aortic valve replacement (TAVR), taken from the FinnValve registry.

Design: Nationwide, retrospective observational study.

Setting: Five Finnish university hospitals participated in the registry.

Participants: A total of 6,463 patients who underwent SAVR (n = 4,333) or TAVR (n = 2,130).

Interventions: Patients who underwent TAVR or SAVR with a bioprosthesis with or without coronary revascularization.

Measurements and Main Results: The incidence of postoperative stroke after SAVR was 3.8%. In multivariate analysis, the number of transfused RBC units (odds ratio [OR], 1.098; 95% confidence interval [CI], 1.064-1.133) was one of the independent predictors of postoperative stroke. The incidence of stroke increased, along with the severity of perioperative bleeding, according to the European Coronary Artery Bypass Grafting (E-CABG) bleeding grades were as follows: grade 0, 2.2% (reference group); grade 1, 3.4% (adjusted OR, 1.841; 95% CI, 1.105-3.066); grade 2, 5.5% (adjusted OR, 3.282; 95% CI, 1.948-5.529); and grade 3, 14.8% (adjusted OR, 7.103; 95% CI, 3.612-13.966). The incidence of postoperative stroke after TAVR was 2.5%. The number of transfused RBC units was an independent predictor of stroke after TAVR (adjusted OR, 1.155; 95% CI, 1.058-1.261). The incidence of postoperative stroke increased, along with the severity of perioperative bleeding, as stratified by the E-CABG bleeding grades: E-CABG grade 0, 1.7%; grade 1, 5.3% (adjusted OR, 1.270; 95% CI, 0.532-3.035); grade 2, 10.0% (adjusted OR, 2.898; 95% CI, 1.101-7.627); and grade 3, 30.0% (adjusted OR, 10.706; 95% CI, 2.389-47.987).

[1]Corresponding author: Kajaanintie 50, 90220, Oulu, Finland.
E-mail address: tuomas.ttau@gmail.com (T. Tauriainen).

https://doi.org/10.1053/j.jvca.2022.04.029

Conclusions: Perioperative bleeding requiring RBC transfusion and/or reoperation for intrathoracic bleeding is associated with an increased risk of postoperative stroke after SAVR and TAVR. Patient blood management and meticulous preprocedural planning and operative technique aiming to avoid significant perioperative bleeding may reduce the risk of cerebrovascular complications.

Keywords: Aortic valve replacement; SAVR; Transfusion; Bleeding; Stroke

POSTOPERATIVE STROKE is a severe complication of cardiovascular interventions. Blood transfusion is suspected to increase the risk of stroke,[1-8] still prior studies lacked a stratification of the severity of periprocedural bleeding.[5] Preoperative anemia,[9] prior stroke,[3,10-12] intraoperative hypotension, and low hemoglobin/hematocrit levels during cardiopulmonary bypass,[3,13] in addition to iatrogenic debris embolization during manipulation of the aorta and/or calcified valves,[14-17] have been identified as some of the main risk factors for postprocedural stroke. Therefore, it is not clear if perioperative bleeding and the use of blood products may have an effect on the development of cerebrovascular complication independently of the above-mentioned risk factors. In this study, the authors aimed to investigate the effects of perioperative bleeding and blood transfusions on the development of postoperative stroke after surgical (SAVR) and transcatheter aortic valve replacement (TAVR), taken from a nationwide registry.

Methods

The FinnValve registry included 6463 patients from a Finnish nationwide cohort (ClinicalTrials.gov Identifier: NCT03385915), which collected retrospective data from consecutive patients undergoing SAVR or TAVR with a bioprosthesis for significant aortic valve stenosis in all 5 Finnish university hospitals (Oulu, Kuopio, Tampere, Turku, and Helsinki) between January 2008 and November 2017. The main purpose of this database was to compare the outcomes after SAVR and TAVR. For this reason, mechanical valve prostheses were excluded from this registry. There were 4333 patients treated with SAVR and 2130 patients treated with TAVR. An approval for the study, in addition to a waiver for the requirement for informed consent, were acquired from the institutional review boards of all participating hospitals.

The inclusion criteria of this study were (1) presence of aortic valve stenosis with or without aortic valve regurgitation; (2) patient's age $\geq$18 years; and (3) primary SAVR or TAVR with a bioprosthesis, with or without concomitant coronary revascularization. The exclusion criteria were (1) any prior surgical or catheter-based intervention on the aortic valve; (2) concomitant major cardiac procedure on other valves/cardiac structures including the ascending aorta; (3) procedure for isolated aortic valve regurgitation; (4) procedure for endocarditis; and (5) SAVR with a mechanical prosthesis. The baseline variables were defined according to the EuroSCORE II criteria.[18] Anemia was defined according to a hemoglobin cutoff value of $<$130 g/L in men and $<$120 g/L in women, as suggested by the World Health Organization.[19]

The primary outcome endpoint of the present analysis was any focal or global neurologic deficiency lasting $>$24 h during the postoperative in-hospital period. The diagnosis of stroke was made using computed tomography/magnetic resonance imaging and confirmed by a neurologist. Symptoms persisting beyond hospital discharge defined permanent stroke; otherwise, it was classified as temporary. Disabling stroke was defined as a major neurophysiologic deficit without significant recovery at discharge. The severity of perioperative bleeding was stratified according to a modified version of the European Coronary Artery Bypass Grafting (E-CABG) bleeding severity criteria,[20] which are the following: grade 0, no need of blood products with the exception of 1 unit of red blood cells (RBC); grade 1, transfusion of 2 to 4 units of RBC; grade 2, transfusion of 5 to 10 units of RBC or reoperation for intrathoracic bleeding, or both; and grade 3, transfusion of $>$10 units of RBC.

Statistical analyses

Statistical analyses were performed using SPSS v. 25.0 statistical software (IBM Corporation, New York). Categorical variables are presented as counts and percentages, whereas continuous variables are presented as mean and standard deviation. χ^2 test, Fischer's exact test, and Mann-Whitney U tests were used in univariate analysis. Multivariate analysis was performed using logistic regression. The results are presented as odds ratios and their 95% confidence intervals. No attempt to replace missing values was made. Risk factors for stroke were identified using logistic regression with backward selection. Variables with a p value < 0.05 and < 0.20 in the univariate analysis were included in the regression models of the SAVR and TAVR cohorts, respectively, to avoid model overfitting and multicollinearity. Hosmer-Lemeshow's goodness-of-fit test and the receiver operating characteristics (ROC) curve were used to assess the calibration and discrimination of the regression model. The following variables were included into the regression model of the SAVR cohort: age, anemia, preoperative creatinine, use of clopidogrel, ticagrelor or prasugrel, use of direct oral anticoagulation, extracardiac arteriopathy, prior transient ischemic attack or stroke, prior cardiac surgery, urgent/emergent/salvage surgery, EuroSCORE II, preoperative aortic valve maximum gradient, cardiopulmonary bypass duration, concomitant CABG, postoperative nadir hemoglobin level, postoperative intra-aortic balloon pump,

postoperative extracorporeal membrane oxygenation, reoperation for intrathoracic bleeding, and the number of transfused RBC units. The regression model for the TAVR cohort included sex, chronic kidney disease class 4 or 5, prior transient ischemic attack or stroke, extracardiac arteriopathy, urgency, the use of inotropes at anesthesia induction, size of the TAVR prosthesis, balloon aortic valvuloplasty before prosthesis positioning, concomitant unplanned percutaneous coronary intervention during TAVR, balloon dilatation, resternotomy/rethoracotomy for bleeding, nadir hemoglobin, and the number of transfused RBC units. The regression models were further adjusted for the E-CABG bleeding grades by excluding resternotomy for bleeding and the number of transfused RBCs from the independent variable list. All tests were two-sided, and a $p < 0.05$ was set for statistical significance.

Results

SAVR cohort

Overall, 4,333 patients underwent SAVR, and their incidence of postoperative stroke was 3.8% (n = 165). The proportion of disabling stroke was 53.9% (n = 89). The majority of the postoperative strokes were classified as ischemic (n = 148, 89.7%). One patient was diagnosed with hemorrhagic stroke (0.6%) and 2 patients had ischemic stroke with associated hemorrhage (1.2%). The remainder of the postoperative strokes could not be classified in the aforementioned categories (n = 14, 8.5%).

Baseline characteristics, operative variables, and outcomes of patients who underwent SAVR are summarized in Tables 1 and 2.

Table 1
Baseline characteristics of patients with and without postprocedural stroke who underwent surgical aortic valve replacement.

Baseline Variables	Overall SAVR Population n = 4,333	No Stroke n = 4,168	Stroke n = 165	*p* Value
Age (y)	75.1 ± 6.5	75.0 ± 6.6	76.3 ± 5.9	0.024
Female	2,026 (46.8)	1,961 (47.0)	65 (39.4)	0.053
BMI (kg/m^2)	27.7 ± 4.8	27.7 ± 4.8	27.9 ± 4.4	0.336
Hemoglobin (g/L)	132.2 ± 14.8	132.3 ± 14.7	130.0 ± 15.8	0.098
Anemia WHO	1192 (27.5)	1130 (27.1)	62 (37.6)	0.003
eGFR MDRD (mL/min/1.73 m^2)	75.8 ± 21.6	75.9 ± 21.6	72.0 ± 22.7	0.014
CKD Classes 4 or 5	52 (1.2)	48 (1.2)	4 (2.4)	0.135
Diabetes	1,154 (26.6)	1,102 (26.4)	52 (31.5)	0.148
Prior TIA or stroke	497 (11.5)	467 (11.2)	30 (18.2)	0.006
Pulmonary disease	642 (14.8)	612 (14.7)	30 (18.2)	0.215
Preoperative atrial fibrillation	955 (22.0)	916 (22.0)	39 (23.6)	0.614
Extracardiac arteriopathy	539 (12.4)	509 (12.2)	30 (18.2)	0.023
Coronary artery disease	1,995 (46.0)	1,898 (45.5)	97 (58.8)	0.001
Malignancy	547 (12.6)	531 (12.7)	16 (9.7)	0.248
Active malignancy	60 (1.4)	55 (1.3)	5 (3.0)	0.077
Antithrombotic drugs				
Preoperative NOACs	43 (1.0)	38 (0.9)	5 (3.0)	0.023
Preoperative warfarin	752 (17.4)	726 (17.4)	26 (15.8)	0.581
Preoperative P2Y12 blocker	189 (4.4)	175 (4.2)	14 (8.5)	0.008
NYHA class				
I	58 (1.3)	57 (1.4)	1 (0.6)	
II	1632 (37.8)	1590 (38.1)	47 (28.5)	
III	2185 (50.4)	2089 (50.1)	96 (58.2)	
IV	453 (10.5)	432 (12.7)	21 (12.7)	0.057
LVEF				
>50%	3,420 (79.0)	3,296 (79.1)	124 (75.6)	
30%-50%	791 (18.3)	753 (18.1)	38 (23.2)	
21%-39%	94 (2.2)	93 (2.2)	1 (0.6)	
<21%	24 (0.6)	23 (0.6)	1 (0.6)	0.220
Prior cardiac surgery	97 (2.2)	88 (2.1)	9 (5.5)	0.011
Prior PCI	405 (9.3)	381 (9.1)	24 (14.5)	0.019
Critical preoperative state	113 (2.6)	106 (2.5)	7 (4.2)	0.203
EuroSCORE II (%)	4.2 ± 5.5	4.2 ± 5.4	5.5 ± 6.2	< 0.0001
Aortic valve characteristics				
Isolated stenosis	2,908 (67.1)	2,795 (67.1)	113 (68.5)	0.702
Max. gradient (mmHg)	77.7 ± 22.5	77.8 ± 22.4	73.8 ± 24.4	0.010
Bicuspid valve	920 (21.2)	888 (21.3)	32 (19.4)	0.556

NOTE. Continuous variables are reported as mean and standard deviation. Categorical variables are reported as count and percentage. *p* values are from univariate analysis.

Abbreviations: BMI, body mass index; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; MDRD, Modification of Diet in Renal Disease; NOAC, novel oral anticoagulant; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; SAVR, surgical aortic valve replacement; TIA, transient ischemic attack; WHO, World Health Organization.

Table 2
Intra- and postoperative variables of patients with and without postprocedural stroke who underwent surgical aortic valve replacement.

Intra- and Postoperative Variables	Overall SAVR Populationn = 4,333	No Stroken = 4,168	Stroken = 165	*p* Value
Urgent/emergent operation	588 (13.6)	556 (13.3)	32 (19.4)	0.026
Associated CABG	1,834 (42.3)	1,744 (41.8)	90 (54.5)	0.001
Cardiopulmonary bypass time (min)	129.0 ± 45.3	128.0 ± 44.3	153.9 ± 61.6	< 0.0001
Postoperative atrial fibrillation	2,454 (56.6)	2,349 (56.4)	105 (63.6)	0.064
RBC transfusion	3,010 (70.4)	2,874 (69.9)	136 (83.4)	< 0.0001
RBC transfused units	3.0 ± 3.8	2.9 ± 3.5	6.1 ± 8.6	< 0.0001
Reoperation for intrathoracic bleeding	351 (8.1)	325 (7.8)	26 (15.8)	< 0.0001
Nadir hemoglobin (g/L)	86.7 ± 11.8	86.8 ± 11.9	83.4 ± 9.6	0.001
Delta hemoglobin (g/L)	45.5 ± 16.3	45.5 ± 16.2	46.6 ± 17.1	0.482
E-CABG bleeding grades				< 0.0001
Grade 0	1,577 (36.9)	1,543 (37.5)	34 (20.9)	
Grade 1	1,669 (39.0)	1,613 (39.2)	56 (34.4)	
Grade 2	856 (20.0)	809 (19.7)	47 (28.8)	
Grade 3	176 (4.1)	150 (3.6)	26 (16.0)	
E-CABG bleeding grades 2-3*	1032 (24.1)	959 (23.3)	73 (44.8)	< 0.0001
VARC 2 bleeding grades				0.001
VARC 2 major bleeding	1564 (36.2)	1525 (36.6)	39 (23.6)	
VARC 2 life-threatening bleeding	2597 (60.0)	2475 (59.5)	122 (73.9)	
Postoperative IABP	73 (1.7)	64 (1.5)	9 (5.5)	0.002
ICU stay (d)	2.2 ± 2.8	5.3 ± 6.2	2.1 ± 2.5	< 0.0001
In-hospital stay (d)	8.3 ± 6.4	12.7 ± 9.2	8.1 ± 6.2	< 0.0001
In-hospital death	130 (3.0)	25 (15.2)	105 (2.5)	< 0.0001
30-day death	158 (3.6)	28 (17.1)	130 (3.1)	< 0.0001

NOTE. Continuous variables are reported as mean and standard deviation. Categorical variables are reported as count and percentage.
Abbreviations: CABG, coronary artery bypass grafting; IABP, intra-aortic balloon pump; ICU, intensive care unit; RBC, red blood cell; SAVR, surgical aortic valve replacement; VARC, Valve Academy Research Consortium.
* Excludes peripheral vascular bleeding.

Logistic regression (Hosmer-Lemeshow's test p = 0.904; area under the ROC curve 0.704; 95% CI, 0.655-0.753) identified prior cardiac surgery (OR, 2.449; 95% CI, 1.113-5.387), preoperative use of direct oral anticoagulants (OR, 5.386; 95% CI, 1.994-14.548), cardiopulmonary bypass time (OR, 1.005; 95% CI, 1.002-1.009), and the number of transfused RBC units (OR, 1.098; 95% CI, 1.064-1.133) as independent predictors of postoperative stroke after SAVR (Table 3).

The incidence of stroke increased with the severity of perioperative bleeding according to the E-CABG bleeding grades: grade 0, 2.2% (reference group); grade 1, 3.4% (adjusted OR, 1.841; 95% CI, 1.105-3.066); grade 2, 5.5% (adjusted OR, 3.282; 95% CI, 1.948-5.529); and grade 3, 14.8% (adjusted OR, 7.103; 95% CI, 3.612-13.966; p < 0.0001) (Fig. 1).

TAVR cohort

Overall, 2310 patients underwent TAVR, and their characteristics, operative variables, and outcomes are summarized in Tables 4 and 5. The incidence of postoperative stroke after TAVR was 3.8% (n = 54), and the proportion of disabling stroke was 35.2% (n = 19). The majority of the postoperative strokes were classified as ischemic (n = 44, 81.5%). Three patients were diagnosed with hemorrhagic stroke (5.5%), and 2 patients had ischemic stroke with associated hemorrhage (3.8%). The remainder of the postoperative strokes could not be classified in the aforementioned categories (n = 13, 24.1%).

Table 3
Independent predictors of postprocedural stroke in the surgical and transcatheter aortic valve replacement cohorts.

Predictors of Stroke in Multivariate Analysis	SAVR Cohort	TAVR Cohort
Age	1.028, 0.997-1.059	-
Female	-	0.493, 0.274-0.889
NOACs	5.386, 1.994-14.548	-
Prior TIA or stroke	1.578, 0.978-2.547	-
Prior cardiac surgery	2.499, 1.113-5.387	-
Aortic valve max gradient	0.993, 0.985-1.001	-
Cardiopulmonary bypass time	1.005, 1.002-1.009	-
RBC transfused units	1.098, 1.064-1.133	1.155, 1.058-1.261
Nadir hemoglobin	-	0.963, 0.942-0.984
Adjusted analysis		
E-CABG bleeding grades		
Grade 0	-	-
Grade 1	1.841, 1.105-3.066	1.270, 0.532-3.035
Grade 2	3.282, 1.948-5.529	2.898, 1.101-7.627
Grade 3	7.103, 3.612-13.966	10.706, 2.389-47.987
E-CABG bleeding grade 2 to 3 (it excludes peripheral vascular bleeding)	2.137, 1.414-3.228	2.949, 1.093-7.957

NOTE. Risk estimates are from multivariate analysis and they are reported as odds ratios with their 95% confidence intervals.
Abbreviations: E-CABG, European coronary artery bypass grafting; NOAC, novel oral anticoagulant; RBC, red blood cell; SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement; TIA, transient ischemic attack.

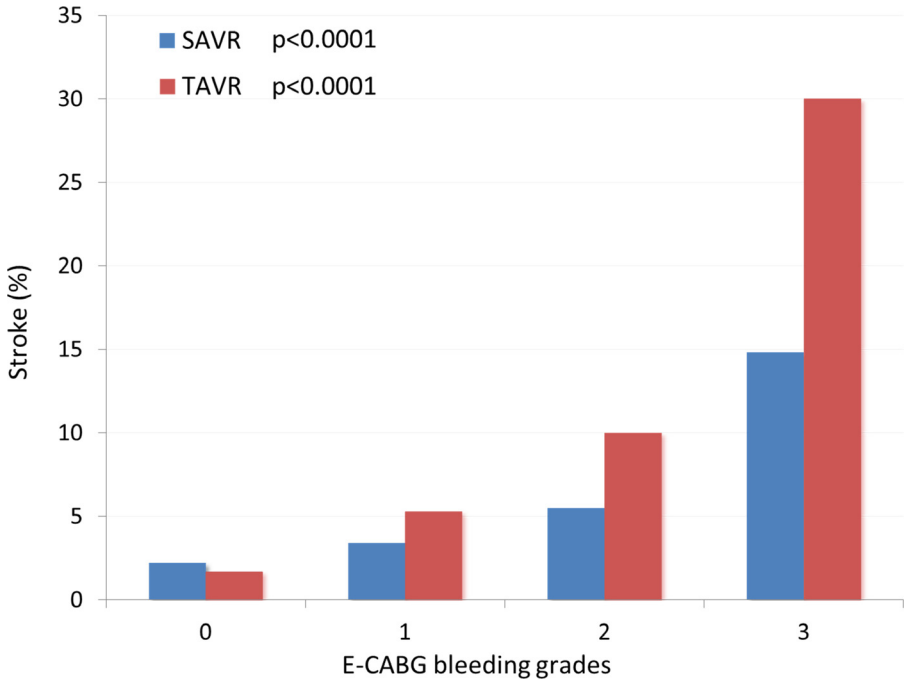

Fig 1. The incidence of stroke in surgical aortic valve replacement and transcatheter aortic valve replacement cohorts according to the European Coronary Artery Bypass Grafting bleeding severity grading. E-CABG, European Coronary Artery Bypass Grafting; SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement.

Table 4
Baseline characteristics of patients with and without postprocedural stroke who underwent transcatheter aortic valve replacement.

Baseline variables	Overall TAVR n = 2130	No stroke n = 2076	Stroke n = 54	*p* Value
Age (y)	81.2 ± 6.6	81.2 ± 6.6	81.8 ± 5.3	0.827
Female	1,172 (55.0)	1,148 (55.3)	24 (44.4)	0.113
BMI (kg/m^2)	27.1 ± 4.8	27.2 ± 4.8	26.4 ± 4.8	0.437
Hemoglobin (g/L)	124.9 ± 15.5	125.0 ± 15.5	123.1 ± 16.2	0.250
Anemia WHO	995 (46.7)	967 (46.6)	28 (51.9)	0.445
eGFR MDRD (mL/min/1.73 m^2)	65.4 ± 23.0	65.5 ± 23.1	62.8 ± 22.8	0.574
CKD Classes 4 or 5	83 (3.9)	78 (3.8)	5 (9.3)	0.056
Diabetes	605 (28.4)	586 (28.2)	19 (35.2)	0.263
Prior TIA or stroke	384 (18.0)	370 (17.8)	14 (25.9)	0.126
Pulmonary disease	456 (21.4)	446 (21.5)	10 (18.5)	0.600
Preoperative atrial fibrillation	932 (43.8)	910 (43.8)	22 (40.7)	0.651
Extracardiac arteriopathy	412 (19.3)	397 (19.1)	15 (27.8)	0.112
Coronary artery disease	603 (28.3)	583 (28.1)	20 (37.0)	0.149
Malignancy	124 (5.8)	122 (5.9)	2 (3.7)	0.767
Active malignancy	431 (20.2)	319 (20.2)	12 (22.2)	0.713
Antithrombotic drugs	84 (3.9)	81 (3.9)	3 (5.6)	0.470
Preoperative NOACs	87 (4.1)	84 (4.0)	3 (5.6)	0.483
Preoperative warfarin	792 (37.2)	773 (37.2)	19 (35.2)	0.758
Preoperative P2Y12 blocker	304 (14.3)	297 (14.3)	7 (13.0)	0.781
NYHA class				0.266
I	17 (0.8)	17 (0.8)	0 (0)	
II	346 (16.2)	342 (16.5)	4 (7.4)	
III	1,523 (71.5)	1,481 (71.3)	42 (77.8)	
IV	244 (11.5)	236 (11.4)	8 (14.8)	
LVEF				0.680
>50%	1,530 (72.0)	1,492 (72.0)	38 (70.4)	
30%-50%	506 (23.8)	494 (23.8)	12 (22.2)	
21%-39%	72 (3.4)	69 (3.3)	3 (5.6)	
<21%	18 (0.8)	17 (0.8)	1 (1.9)	
Prior cardiac surgery	431 (20.2)	420 (20.2)	11 (20.4)	0.980

(*continued*)

Table 4 (*continued*)

Baseline variables	Overall TAVR n = 2130	No stroke n = 2076	Stroke n = 54	*p* Value
Prior PCI	467 (21.9)	454 (21.9)	13 (24.1)	0.699
Critical preoperative state	48 (2.3)	47 (2.3)	1 (1.9)	1.000
EuroSCORE II (%)	7.2 ± 7.4	7.2 ± 7.3	9.0 ± 12.4	0.620
Aortic valve characteristics				
Isolated stenosis	1,464 (68.7)	1,430 (68.9)	34 (63.0)	0.354
Max. gradient (mmHg)	78.2 ± 21.8	78.3 ± 21.8	74.5 ± 18.1	0.337
Bicuspid valve	114 (5.4)	111 (5.3)	3 (5.6)	0.764

NOTE. Continuous variables are reported as mean and standard deviation. Categorical variables are reported as count and percentage; *p* values are from univariate analysis.

Abbreviations: BMI, body mass index; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; MDRD, Modification of Diet in Renal Disease; NOAC, novel oral anticoagulant; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; TAVR, transcatheter aortic valve replacement; TIA, transient ischemic attack; WHO, World Health Organization.

Logistic regression (Hosmer-Lemeshow's test p = 0.646 and area under the ROC curve 0.725; 95% CI, 0.656-0.793) showed that the number of transfused RBCs was as an independent predictor of stroke (OR, 1.155; 95% CI, 1.058-1.261) (Table 3). Low nadir hemoglobin levels (OR, 0.963; 95% CI, 0.942-0.984) and male sex were independently associated with increased risk of postoperative stroke (OR, 0.493; 95% CI, 0.274-0.889) as well. The incidence of postoperative stroke increased, along with the severity of perioperative bleeding, as stratified by the E-CABG bleeding grades: E-CABG grade 0, 1.7%; grade 1, 5.3% (adjusted OR, 1.270; 95% CI, 0.532-3.035); grade 2, 10.0% (adjusted OR, 2.898; 95% CI, 1.101-7.627); and grade 3, 30.0% (adjusted OR, 10.706; 95% CI, 2.389-47.987) (p < 0.0001) (Fig. 1).

Table 5
Intra- and postoperative variables of patients with and without postprocedural stroke who underwent transcatheter aortic valve replacement.

Intra-and Postoperative Variables	Overall TAVR Cohort n = 2,130	No stroke n = 2,076	Stroke N = 54	*p* Value
Urgent/emergent/salvage operation	158 (7.4)	151 (7.3)	7 (13.0)	0.115
Size of TAVR prosthesis (mm)	26.3 ± 2.5	26.3 ± 2.5	26.6 ± 2.2	0.178
Balloon valvuloplasty before TAVR valve positioning	1,159 (54.4)	1,123 (54.1)	36 (66.7)	0.067
PCI immediately before TAVR	109 (5.1)	107)5.2)	2 (3.7)	1.000
PCI during TAVR	13 (0.6)	12 (0.6)	1 (1.9)	0.285
Unplanned PCI during TAVR	4 (0.2)	3 (0.1)	1 (1.9)	0.098
Postoperative atrial fibrillation	866 (40.7)	842 (40.6)	24 (44.4)	0.566
RBC transfusion	403 (19.2)	378 (18.5)	25 (46.3)	< 0.0001
RBC transfused units	0.6 ± 1.7	0.6 ± 1.6	2.3 ± 3.9	< 0.0001
Reoperation for intrathoracic bleeding	33 (1.5)	29 (1.4)	4 (7.4)	0.009
Nadir hemoglobin (g/L)	101.8 ± 16.2	102.0 ± 16.2	90.8 ± 13.5	< 0.0001
Delta hemoglobin (g/L)	23.2 ± 14.0	22.9 ± 13.8	32.3 ± 19.5	< 0.0001
E-CABG bleeding grades				< 0.0001
Grade 0	1,780 (85.0)	1,749 (85.7)	31 (57.4)	
Grade 1	225 (10.7)	213 (10.4)	12 (22.2)	
Grade 2	80 (3.8)	72 (3.5)	8 (5.6)	
Grade 3	10 (0.5)	7 (0.3)	3 (5.6)	
E-CABG bleeding grades 2-3	90 (4.3)	79 (3.9)	11 (20.4)	< 0.0001
VARC 2 bleeding grades				< 0.0001
VARC 2 major bleeding	567 (26.7)	547 (26.5)	20 (37.0)	
VARC 2 life threatening bleeding	167 (7.9)	152 (7.4)	15 (27.8)	
Postoperative IABP	4 (0.2)	4 (0.2)	0 (0)	1.000
ICU stay (d)	0.7 ± 1.5	2.4 ± 3.2	0.7 ± 1.4	< 0.0001
In-hospital stay (d)	5.5 ± 5.0	9.0 ± 6.7	5.4 ± 5.0	< 0.0001
In-hospital death	48 (2.3)	7 (13.0)	41 (2.0)	< 0.0001
30-day death	62 (2.9)	53 (2.6)	9 (16.7)	< 0.0001

NOTE. Continuous variables are reported as mean and standard deviation. Categorical variables are reported as count and percentage. *p* values are from univariate analysis.

Abbreviations: E-CABG, European coronary artery bypass grafting; IABP, intra-aortic balloon pump; ICU, intensive care unit; RBC, red blood cell; TAVR, transcatheter aortic valve replacement; VARC, Valve Academy Research Consortium.

*Excludes peripheral vascular bleeding.

Discussion

The present findings suggested that perioperative bleeding measured using RBC transfusions is associated with increased risk of postprocedural stroke after both SAVR and TAVR. The results remained significant after adjusting for other risk factors for stroke. In the literature, there are multiple potential mechanisms underlying the development of stroke in patients undergoing cardiovascular interventions.[21] Most of the periprocedural acute strokes are believed to be mostly secondary to embolization of atheromatous debris from the aortic wall or the diseased aortic valve during manipulation of the aorta and the calcified aortic valve.[14-17]

Severe perioperative bleeding and associated hypotensive episodes, in addition to decreased hemoglobin/hematocrit levels, also are possible causes of intraoperative stroke. Bahrainwala et al. and Karkouti et al. reported that low hemoglobin and hematocrit values during cardiopulmonary bypass were independent predictors of stroke in cardiac surgery.[3,13] The association between increased stroke risk and preoperative anemia also has been observed.[9] In patients undergoing TAVR, a sudden loss of perfusion pressure due to balloon valvuloplasty or rapid pacing during valve positioning have been speculated to predispose to an increased risk of periprocedural stroke.[21,22] These findings might be worsened by underlying conditions such as carotid artery stenosis. Prior stroke has been reported to predict postoperative stroke in both cardiac surgery and interventional cardiology.[3,10-12] Moreover, another major contributing factor shown to increase the risk of postoperative stroke is atrial fibrillation.[22-24]

In the present analysis, in addition to bleeding measured using RBC transfusions, advanced age, use of new oral anticoagulants, prior transient ischemic attack or stroke, prior cardiac surgery, and prolonged cardiopulmonary bypass duration were independent predictors of perioperative stroke after SAVR. Notably, new oral anticoagulants, prior cardiac surgery, and prolonged cardiopulmonary bypass duration are known to increase the risk of perioperative bleeding. Less evident was the impact of such comorbidities after TAVR. Indeed, male sex, RBC transfusion, and nadir hemoglobin level were predictive of stroke after TAVR. This finding suggested that the mechanisms underlying the development of stroke after TAVR and SAVR may be different; still, perioperative anemia and bleeding requiring the use of blood products may contribute to stroke after both procedures.

The present findings might have been biased by a few limitations of the study methodology. First, the retrospective nature of the study was the main limitation of this analysis. Second, the authors did not have data on the presence and severity of carotid artery stenosis, the occurrence of intraoperative hypotensive episodes, the coexistence and severity of aortic atherosclerosis, and the number of other transfused blood products other than RBCs. Finally, interinstitutional differences in patient perioperative management might be a confounding factor, the effect of which is hard to be defined because of the limited number of cerebrovascular events in each participating center. Although the data were gathered from a national database, there also might have been potential variability in the diagnosis and subsequent interventions of the neurologic deficits.

Conclusions

Perioperative bleeding requiring RBC transfusion/reoperation for intrathoracic bleeding is associated with an increased risk of postoperative stroke after SAVR and TAVR. Patient blood management and meticulous preprocedural planning and operative technique aiming to avoid significant perioperative bleeding may reduce the risk of cerebrovascular complications.

However, prospective studies are needed to address the aforementioned limitations of the present study and produce more conclusive evidence on a potential causal effect of perioperative bleeding/blood transfusion on postoperative stroke.

Declaration of Competing Interest

K.E. Juhani Airaksinen reports research grants from The Finnish Foundation for Cardiovascular Research; the status of speaker for Bayer, Pfizer, and Boehringer-Ingelheim; and status as a member in the advisory boards for Bayer, Pfizer, Astra-Zeneca. Other authors have no conflict of interests to declare.

References

1 Biancari F, Tauriainen T, Perrotti A, et al. Bleeding transfusion and the risk of stroke after coronary surgery: a prospective cohort study of 2357 patients. Int J Surg 2016;32:50–7.

2 Brascia D, Garcia-Medina N, Kinnunen EM, et al. Impact of transfusion on stroke after cardiovascular interventions: meta-analysis of comparative studies. J Crit Care 2016;38:157–63.

3 Bahrainwala Z, Grega M, Hogue C, et al. Intraoperative hemoglobin levels and transfusion independently predict stroke after cardiac operations. Ann Thorac Surg 2011;4:1113–8.

4 Kinnunen EM, Juvonen T, Biancari. Use of blood products and diseased ascending aorta are determinants of stroke after off-pump coronary artery bypass grafting. J Cardiothorac Vasc Anesth 2015;5:1180–6.

5 Tchetche D, Van der Boon R, Dumonteil N, et al. Adverse impact of bleeding and transfusion on the outcome post-transcatheter aortic valve implantation: insights from the Pooled-RotterdAm-Milano-Toulose in collaboration plus (PRAGMATIC Plus) initiative. Am Heart J 2012;3:402–9.

6 Seiffert M, Conradi L, Terstesse A, et al. Blood transfusion is associated with impaired outcome after transcatheter aortic valve implantation. Catheter Cardiovasc Interv 2015;3:460–7.

7 Apostolidou E, Aronow H, Beale C, et al. Association between red blood cell transfusion and clinical outcomes among patients undergoing transcatheter aortic valve replacement. Ann Thorac Surg 2019;6:1791–8.

8 Kolte D, Beale C, Aronow H, et al. Trends and outcomes of red blood cell transfusion in patients undergoing transcatheter aortic valve replacement in the United States. J Thorac Cardiovasc Surg 2019;19:30717–22.

9 Ranucci M, Di Dedda U, Castelvecchio S, et al. Impact of preoperative anemia on outcome in adult cardiac surgery: a propensity matched analysis. Ann Thorac Surg 2012;4:1134–41.

10 Werner N, Zeymer U, Schneider S, et al. Incidence and clinical impact of stroke complicating transcatheter aortic valve implantation: results from the German TAVI registry. Catheter Cardiovasc Interv 2016;4:644–53.

11 Vlastra W, Jimenez-Quevedo P, Tchethce D, et al. Predictors, incidence, and outcomes of patients undergoing transfemoral transcatheter aortic valve implantation complicated by stroke. Circ Cardiovasc Interv 2019;12:e007546.
12 Didier R, Koifman E, Kiramijyan S, et al. The impact of prior stroke on the outcome of patients with severe aortic stenosis undergoing transcatheter aortic valve replacement. Cardiovasc Revasc Med 2016;5:322–7.
13 Karkouti K, Djaiani G, Borger M, et al. Low hematocrit during cardiopulmonary bypass is associated with increased risk of perioperative stroke in cardiac surgery. Ann Thorac Surg 2015;80:1381–7.
14 Van Mieghem N, Faquir N, Rahhab Z, et al. Incidence and predictors of debris embolizing to the brain during transcatheter aortic valve implantation. JACC Cardiovasc Interv 2015;5:718–24.
15 Doerner J, Kupczyk P, Wilsing M, et al. Cerebral white matter lesion burden is associated with the degree of aortic valve calcification and predicts peri-procedural cerebrovascular events in patients undergoing transcatheter aortic valve implantation (TAVI). Catheter Cardiovasc Interv 2018;4:774–82.
16 Grabert S, Lange R, Bleiziffer S. Incidence and causes of silent and symptomatic stroke following surgical and transcatheter aortic valve replacement: a comprehensive review. Int Cardiovasc Thorac Surg 2016;3:469–76.
17 Alassar A, Roy D, Valencia O, et al. Cerebral embolization during transcatheter aortic valve implantation compared with surgical aortic valve replacement. Interact Cardiovasc Thorac Surg 2013;17(suppl 2):134–5.
18 Nashef S, Roques F, Sharples L, et al. Euroscore II. Eur J Cardiothorac Surg 2012;4:734–44.
19 World Health Organization. Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity. Available at: https://apps.who.int/iris/bitstream/handle/10665/85839/WHO_NMH_NHD_MNM_11.1_eng.pdf?sequence=22&isAllowed=y. Accessed January 6, 2022.
20 Biancari F, Ruggieri V, Perrotti A, et al. European multicenter study on coronary artery bypass grafting (E-CABG registry): study protocol for a prospective clinical registry and proposal of classification of postoperative complications. J Cardiothorac Surg 2015;10:90.
21 Patel P, Patel S, Feinman J, et al. Stroke after transcatheter aortic valve replacement: Incidence, definitions, etiologies and management options. J Cardiothorac Vasc Anesth 2018;2:968–81.
22 Davroulos P, Mplani V, Koniari I, et al. Transcatheter aortic valve replacement and stroke: a comprehensive review. J Geriatric Cardiol 2018;1:95–104.
23 Murdock D, Rengel L, Schlund A, et al. Stroke and atrial fibrillation following cardiac surgery. WMJ 2003;4:26–30.
24 Horwich P, Buth K, Legare JF. New onset postoperative atrial fibrillation is associated with a long-term risk for stroke and death following cardiac surgery. J Card Surg 2013;1:8–13.