Performance of CHA_2DS_2-VASc score for stroke prediction after surgical aortic valve replacement

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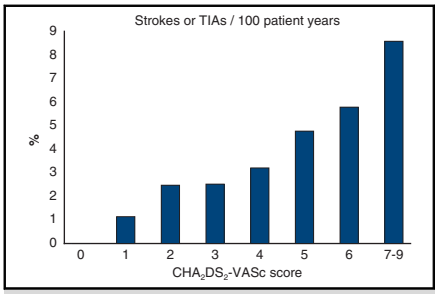
ABSTRACT

Objective: Stroke is a frequent complication occurring early and late after surgical aortic valve replacement. There is an unmet clinical need for simple tools to assess postoperative stroke risk. We sought to assess the predictive performance of Congestive heart failure; Hypertension; Age ≥75 (doubled); Diabetes mellitus; prior Stroke, transient ischemic attack or thromboembolism (doubled); Vascular disease; Age 65 to 74; Sex category (female) (CHA_2DS_2-VASc) score in patients undergoing surgical aortic valve replacement with a bioprosthesis.

Methods: Seven hundred fourteen patients undergoing isolated surgical aortic valve replacement with a bioprosthesis at 4 university hospitals were included. Data were collected retrospectively from patient records and monitored by an independent party.

Results: Median follow-up time was 4.8 years. Mean CHA_2DS_2-VASc score was 4.1 ± 1.6. Low (scores, 0-1), high (scores, 2-4), and very high (scores, 5-9) CHA_2DS_2-VASc scores were observed in 39 (5.5%), 400 (56.0%), and 262 (38.5%) patients, respectively. Incidences of stroke or transient ischemic attack at 1 year were 2.6%, 4.8%, and 10.7%; at 5 years incidences were 5.2%, 14.0%, and 21.9%; and at 10 years incidence were 5.2%, 20.7%, and 37.9% for patients in low, high, and very high scores, respectively. Incidences of major bleeds at 1 year were 0%, 1.8%, and 2.7%; at 5 years incidences were 0%, 5.4%, and 8.7%; and at 10 years incidences were 0%, 9.0%, and 27.1%, respectively. Competing risk analysis showed that patients with CHA_2DS_2-VASc score of 5 through 9 had a significantly increased risk of stroke or transient ischemic attack (hazard ratio, 4.75; 95% confidence interval, 1.09-20.6; $P = .037$) irrespective of preoperative or new-onset in-hospital atrial fibrillation compared with low-risk patients.

Conclusions: CHA_2DS_2-VASc is a valuable tool to identify patients with increased risk of stroke and major bleeding, and for whom alternative strategies for prevention of late neurologic complications should be adopted. (J Thorac Cardiovasc Surg 2019;157:896-904)



Incidence rate of stroke/TIA per 100 patient years according to CHA_2DS_2-VASc scores.

Central Message

CHA_2DS_2-VASc is a valuable tool to identify patients for whom alternative strategies for prevention of late neurologic complications such as left atrial appendage occlusion should be considered.

Perspective

There is an unmet clinical need to identify patients at high risk for stroke and clinically significant bleeds occurring late after SAVR. These high-risk patients may benefit from approaches aimed at reducing the risk of stroke such as long-term oral anticoagulation therapy or surgical occlusion of the left atrial appendage. Therefore, measures to assess these risks would be useful.

See Commentary on page 905.

Stroke and transient ischemic attack (TIA) are common complications after surgical aortic valve replacement (SAVR) with a bioprosthesis both in the short and long term.[1-4] Because of increased mortality and disability as well as incremental treatment costs related to strokes, there is an unmet clinical need to identify patients at high risk for such neurologic complications after SAVR. Indeed, these high-risk patients may benefit from

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Abbreviations and Acronyms

AF = atrial fibrillation
BARC = Bleeding Academic Research Criteria
CHA_2DS_2-VASc = Congestive heart failure; Hypertension; Age ≥75 (doubled); Diabetes mellitus; prior Stroke, transient ischemic attack or thromboembolism (doubled); Vascular disease; Age 65 to 74; Sex category (female)
SAVR = surgical aortic valve replacement
TIA = transient ischemic attack
TOAST = Trial of Org 10172 in Acute Stroke Treatment

Scanning this QR code will take you to a supplemental video for this article.

approaches aimed at reducing the risk of stroke such as long-term oral anticoagulation therapy.[5] Nevertheless, oral anticoagulation therapy is itself associated with an increased risk of severe bleeding events, and thus, some patients might be candidates for closure of the left atrial appendage. Therefore, measures to assess the risk and benefit of currently available treatment options would be useful.

The Congestive heart failure; Hypertension; Age ≥ 75 (doubled); Diabetes mellitus; prior Stroke, transient ischemic attack or thromboembolism (doubled); Vascular disease; Age 65 to 74; Sex category (female) (CHA_2DS_2-VASc) score is a well validated and widely used stroke risk stratification score in patients with atrial fibrillation (AF).[5,6] Patients with scores < 2 are considered low-stroke-risk patients, whereas those with scores ≥ 2 are at high risk.[6] The predictive performance of CHA_2DS_2-VASc score in patients undergoing SAVR so far has not been assessed. In this observational, multicenter study we sought to evaluate the performance of CHA_2DS_2-VASc score in predicting stroke, TIA, and major bleeds in patients undergoing SAVR with a bioprosthesis.

MATERIAL AND METHODS

Data Collection

The Consortium of studies in the field of AF, Stroke, and Bleeding in Patients Undergoing Aortic Valve Replacement is a Finnish multicenter retrospective study (ClinicalTrials.gov identifier: NCT02626871) assessing the incidence and risks of AF, thromboembolic complications, and bleeding events in patients undergoing isolated bioprosthetic SAVR. The data were collected as a part of a broader ongoing consortium in Finland to evaluate the risk of thromboembolic and bleeding complications of AF in patients undergoing different cardiac procedures.[4,7,8]

Patient data were retrieved from cardiac surgery units at 4 Finnish university hospitals (in Helsinki, Turku, Oulu, and Kuopio) over the period from 2002 to 2014 (in Helsinki 2006-2014). Hospital records were reviewed for patients who underwent isolated surgical bioprosthetic SAVR. Patients undergoing any concomitant surgery such as coronary artery bypass grafting, maze procedure with or without left atrial appendage occlusion, cryoablation, or any procedure on the ascending aorta or other heart valves were excluded from the study. Implanted valves included St Jude Medical (St Paul, Minn) Epic, Epic Supra, Biocor, and Trifecta; Medtronic (Minneapolis, Minn) Hancock II, Mosaic, and Mosaic Ultra; Carpentier Edwards (Edwards Lifesciences, Irvine, Calif) Perimount, Magna, and Magna Ease; as well as Sorin Biomedica Spa (Saluggio, Italy) Mitroflow, Soprano, Freedom solo, and Perceval. To obtain accurate follow-up data, only patients from the hospitals' catchment areas were included in this registry. All major adverse events such as cerebrovascular and bleeding events and myocardial infarctions were treated at the same hospitals, and therefore, patient follow-up for adverse events can be considered complete and reliable. Patient records were individually reviewed with a standardized structured data collection protocol for pre- and perioperative data, discharge data, and long-term follow-up events, including postoperative AF, stroke, TIA, bleeding events, and mortality.

The end points included the first occurrence of stroke or TIA or major bleeding event. Fatal strokes and bleeds were identified from Statistics Finland. This governmental office monitors the time and causes of death in Finland.

An ischemic stroke was defined as a permanent focal neurologic deficit adjudicated by a neurologist and confirmed with computed tomography or magnetic resonance imaging. TIA was defined as a transient (<24 hours) focal neurologic deficit. If a stroke or TIA was clinically diagnosed during the index hospitalization by the treating physician and confirmed by computed tomography or magnetic resonance imaging, a separate adjudication by a neurologist was not required. Only ischemic strokes and TIAs considered definite by the treating neurologist or physician were included. Subtypes of ischemic strokes were categorized by the treating physicians using the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification system.[9] Lacunar stroke was defined as an infarct < 20 mm in diameter. Bleeding events were defined according to the Bleeding Academic Research Criteria (BARC).[10] BARC 3a, 3b, 3c, and 5 bleeds were considered as major bleeding events, whilst bleeding occurring immediately after the index SAVR at the hospital (BARC 4) were not considered for this analysis.

The patients were divided into 3 risk groups according to the CHA_2DS_2-VASc score that were calculated before index surgery: low (scores, 0-1), high (scores, 2-4), and very high (scores, 5-9).[5] Use of very high risk score category was based on the annual > 5% rate of thromboembolisms in the validation study.[6] Diabetes, dyslipidemia, and hypertension were defined as a disease requiring drug therapy and chronic lung disease as a pulmonary disease requiring a long-term use of bronchodilators or steroids. Peripheral arterial disease was defined as 1 or more of the following: claudication, carotid artery disease > 50% diameter, and previous or planned intervention of the abdominal aorta, limb arteries, or carotids. Heavy alcohol consumption was defined as > 14 doses a week for women and > 21 doses a week for men. Poor mobility was defined as severe impairment of mobility secondary to musculoskeletal or neurologic dysfunction. Urgent operation was defined as an operation scheduled during the same in-hospital stay, emergency operation as an operation before the next working day, and salvage procedure as an operation where patients require cardiopulmonary

resuscitation en route to the operating theatre or before the induction of anesthesia.

During the study period, the routine anticoagulation practice was 40 mg enoxaparin given subcutaneously once daily starting in the evening of the day of the surgery and continuing until vitamin K antagonist treatment (started on the first postoperative day) reached the therapeutic level (international normalized ratio $\geq$ 2.0). All patients were on vitamin K antagonist treatment a minimum duration of 3 months after index surgery. Continuation of oral anticoagulation beyond 3 months was at the treating physician's discretion.

An independent, certified third-party data monitor controlled the integrity of the data at each study site.

The study protocol was approved by the Medical Ethics Committee of the Hospital District of Southwest Finland and the ethics committee of the National Institute for Health and Welfare (Finland). Because of the retrospective, observational nature of the study, an informed consent was not required. The study conforms to the Declaration of Helsinki.

Statistical Analysis

Statistical analyses were conducted with SPSS version 24.0 (IBM-SPSS Inc, Armonk, NY) and competing risks analysis with Stata version 14.2 (StataCorp, College Station, Tex) statistical software. Continuous variables were reported as mean with standard deviation if normally distributed, and as median with interquartile range if skewed. Data were tested for normal distribution using Kolmogorov-Smirnov and Shapiro-Wilk tests. Categorical variables were described as counts and percentages. Pearson χ^2, Fisher exact test, and 1-way analysis of variance with Bonferroni correction were used for univariable analysis. Incidences of stroke/TIA and major bleeds are presented as crude cumulative Kaplan-Meier estimates. Incidence rate were calculated as number of events divided by the sum of person time at risk (events/100 patient years). Competing risk analysis was performed to account for death as a competing risk for stroke or TIA. Competing risk analysis was used to estimate the impact of CHA_2DS_2-VASc score on neurologic events. A competing risk is present when patients are at risk of more than one mutually exclusive event. This means that patient may die any time after surgery and this event competes with neurologic events because death prevents stroke/TIA from occurring. Herein, competing risk analysis allowed us to estimate the risk of neurologic event adjusted for the occurrence of death. Competing risk analysis was based on Fine and Gray's proportional subhazards model.[11]

RESULTS

A total of 721 patients underwent isolated bioprosthetic SAVR at the 4 participating hospitals during the study period. The median follow-up time was 4.9 (3.0-7.0) years. The final study population consisted of 714 patients as summarized in the CONSORT flow chart (Figure 1 and Online Data Supplement).

The mean preoperative CHA_2DS_2-VASc scores were 4.1 $\pm$ 1.6. Low (score, 0-1), high (score, 2-4), and very high (score, 5-9) scores were detected in 39 (5.5%), 400 (56.0%), and 275 (38.5%) patients, respectively. Baseline characteristics are presented in Table 1 and rhythm status and medication in Table 2. Patients with high scores had significantly more traditional risk factors for stroke such as advanced age, prior stroke, congestive heart failure, treatment for hypertension, diabetes, and larger left atrium diameter. These patients also had a higher AF burden preoperatively, at discharge, and at 3 to 12 months postoperatively.

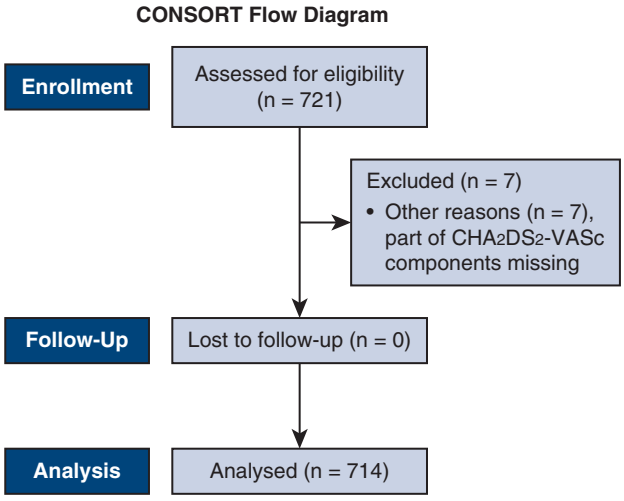


FIGURE 1. Flow chart of the study. *CHA_2DS_2-VASc*, Congestive heart failure; Hypertension; Age $\geq$75 (doubled); Diabetes mellitus; prior Stroke, transient ischemic attack or thromboembolism (doubled); Vascular disease; Age 65 to 74; Sex category (female).

Strokes and TIAs

The Kaplan-Meier cumulative incidences of any stroke or TIA at 1 year were 2.6%, 4.8%, and 10.7%; at 5 years incidences were 5.2%, 14.0%, and 21.9%; and at 10 years incidences were 5.2%, 20.7%, and 37.9% for patients in low, high, and very high scores, respectively. Altogether 6 out of 38 patients (15.8%) with a TIA experienced a stroke later in life. The Kaplan-Meier cumulative incidences of cardioembolic strokes at 1 year were 0%, 1.5%, and 2.6%; at 5 years incidences were 0%, 4.0%, and 7.8%; and at 10 years incidences were 5.3%, 7.4%, and 13.9% in patients with low, high, and very high scores, respectively. Table 3 summarizes rates of stroke, TIA, stroke/TIA, and mortality per 100 patient years according to CHA_2DS_2-VASc scores.

Competing risk analysis showed that patients with very high risk (CHA_2DS_2-VASc scores, 5-9) had significantly increased risk of stroke or TIA (hazard ratio, 4.41 95% confidence interval, 1.10-17.6; $P = .036$) compared with the low-risk group, whereas patients with high risk (CHA_2DS_2-VASc scores, 2-4) had nonsignificantly increased risk of stroke or TIA (hazard ratio, 2.49; 95% confidence interval, 0.62-9.98; $P = .198$). The predictive performance of CHA_2DS_2-VASc in competing risk analysis remained significant for CHA_2DS_2-VASc scores between 5 and 9 when adjusted for preoperative AF and new-onset in-hospital AF (Table 4). Figure 2 depicts competing risk incidence rates of first stroke or TIA according to CHA_2DS_2-VASc scores classes derived from competing risks analysis. Results remained similar in a sensitivity analysis excluding patients who died in-hospital (data not shown).

At 12-month follow-up, 14.3% versus 44.3% versus 61.7% of patients were receiving oral anticoagulation

TABLE 1. Baseline characteristics and operative data of patients and Congestive heart failure; Hypertension; Age ≥75 (doubled); Diabetes mellitus; prior Stroke, transient ischemic attack or thromboembolism (doubled); Vascular disease; Age 65 to 74; Sex category (female) (CHA_2DS_2-VASc) score

Characteristic	CHA_2DS_2-VASc score			*P* value
	0-1 (n = 39)	2-4 (n = 400)	5-9 (n = 275)	
Age (y)				<.001
Mean ± standard deviation	62.7 ± 10.3	74.7 ± 6.0	78.2 ± 4.6	
Median (range)	63.4 (33.0-74.7)	74.4 (53.6-90.9)	78.4 (59.3-90.6)	
Logistic European system for cardiac operative risk evaluation II score	1.8 ± 3.9	2.1 ± 1.8	3.0 ± 3.4	<.001
CHA_2DS_2-VASc score*				<.001
Mean ± standard deviation	0.9 ± 0.3	3.3 ± 0.7	5.7 ± 0.8	
Median (range)	1.0 (0-1)	3.0 (2-4)	5.0 (5-9)	
Females	5 (12.8)	202 (50.5)	195 (70.9)	<.001
Body mass index	25.3 ± 3.8	27.0 ± 4.4	28.9 ± 13.3	.28
Preoperative estimated glomerular filtration rate† (mL/min)	91.2 ± 23.0	75.7 ± 20.6	70.0 ± 20.4	<.001
Treatment for diabetes	2 (5.1)	46 (11.5)	93 (33.8)	<.001
Treatment for dyslipidemia	12 (30.8)	218 (54.6)	174 (63.3)	<.001
Treatment for hypertension	9 (23.1)	262 (65.5)	258 (93.8)	<.001
Congestive heart failure	1 (2.6)	108 (27.0)	203 (73.8)	<.001
Concomitant coronary artery disease	0	68 (17.0)	120 (43.6)	<.001
History of permanent atrial fibrillation	1 (2.6)	39 (9.8)	47 (17.1)	.003
History of paroxysmal atrial fibrillation	7 (17.9)	46 (11.5)	40 (14.5)	.33
Prior myocardial infarction	1 (2.6)	24 (6.0)	25 (9.1)	.17
Prior percutaneous coronary intervention	0	19 (4.8)	34 (12.4)	.001
Prior coronary bypass surgery	0	15 (3.8)	12 (4.4)	.41
Prior aortic valve operation	4 (10.3)	8 (2.0)	4 (1.5)	.002
Prior stroke	0	10 (2.6)	52 (19.5)	<.001
Prior transient ischemic attack	0	12 (3.2)	43 (16.1)	<.001
Prior pulmonary embolism	1 (2.6)	7 (1.8)	3 (1.1)	.69
Prior venous thromboembolism	2 (5.1)	8 (2.0)	7 (2.6)	.46
Extracardiac arteriopathy	3 (7.7)	15 (3.8)	24 (8.8)	.02
Recent acute myocardial infarction	1 (2.6)	5 (1.3)	3 (1.1)	.74
Pulmonary artery hypertension	7 (20.6)	96 (27.1)	86 (37.7)	.011
Chronic lung disease	7 (17.9)	69 (17.3)	54 (19.7)	.74
Self-reported alcohol consumption				<.001
Abstinent	6 (31.6)	129 (77.2)	96 (88.1)	
Moderate	6 (31.6)	27 (16.2)	6 (5.5)	
Heavy	7 (36.8)	11 (6.6)	7 (6.4)	
Hepatic cirrhosis	2 (5.1)	5 (1.3)	3 (1.1)	.13
Active smoker	5 (13.9)	31 (8.4)	14 (6.0)	.22
Exsmoker	12 (35.3)	80 (23.6)	47 (21.2)	.19
Previous intracranial bleed	1 (2.6)	3 (0.8)	2 (0.7)	.48
Previous gastrointestinal tract bleed	4 (10.3)	25 (6.3)	19 (6.9)	.63
Previous genitourinary tract bleed	0	7 (1.8)	1 (0.4)	.19

(Continued)

TABLE 1. Continued

Characteristic	CHA_2DS_2-VASc score 0-1 (n = 39)	2-4 (n = 400)	5-9 (n = 275)	*P* value
Preoperative echocardiography				
Left ventricular ejection fraction (%)	58.8 ± 12.6	59.5 ± 12.0	59.8 ± 13.1	.89
Left atrial diameter (mm)	40.4 ± 9.2	42.8 ± 7.0	44.2 ± 8.1	.016
Aortic valve max gradient (mm Hg)	75.1 ± 23.9	81.5 ± 22.3	81.6 ± 22.6	.27
Aortic valve mean gradient, (mm Hg)	52.6 ± 15.3	48.1 ± 13.9	48.7 ± 14.8	.29
Severe aortic regurgitation grade > 2/4	5 (12.8)	29 (7.3)	20 (7.3)	.05
In-hospital stay (d)				.33
Mean ± standard deviation	9.0 ± 3.3	10.9 ± 7.7	10.8 ± 7.6	
Median (range)	8.0 (6-20)	9 (4-78)	8 (3-57)	

Categorical variables are presented as n (%) or mean ± standard deviation unless stated otherwise. *CHA_2DS_2-VASc*, Congestive heart failure; Hypertension; Age ≥75 (doubled); Diabetes mellitus; prior Stroke, transient ischemic attack or thromboembolism (doubled); Vascular disease; Age 65 to 74; Sex category (female). *Congestive heart failure, hypertension, age ≥ 65 y, diabetes, vascular disease, and female sex receive 1 point each, whereas age ≥ 75 y and prior stroke receive 2 points each. †Estimated glomerular filtration rate determined using the Chronic Kidney Disease Epidemiology Collaboration formula: moderate consumption ≤ 21 (males)/< 14 (females) doses/wk; heavy consumption ≥ 21 (males)/≥ 14 (females) doses/wk.

therapy in the low, high, and very high score classes, respectively. In contrast at the time of stroke or TIA, 50.0%, 45.7%, and 46.4% of patients were receiving oral anticoagulation therapy in the low, high, and very high score classes, respectively. No differences were observed in international normalized ratio levels at the time of stroke/TIA in patients receiving warfarin therapy: 2.1 ± 0.7 versus 2.5 ± 1.4 versus 2.2 ± 0.8, for low, high, and very high scores, respectively.

Major Bleeds

The Kaplan-Meier cumulative incidences of major bleeds at 1 year were 0%, 1.9%, and 2.4%; at 5 years incidences were 0%, 5.4%, and 8.5%; and at 10 years incidences were 0%, 9.1%, and 27.1% in patients in low, high, and very high scores, respectively.

Because there were no major bleeds in the low risk group during the follow-up, the competing risk analysis included only patients with very high versus high risk

TABLE 2. Rhythm status and medication preoperative and at discharge, by Congestive heart failure; Hypertension; Age ≥75 (doubled); Diabetes mellitus; prior Stroke, transient ischemic attack or thromboembolism (doubled); Vascular disease; Age 65 to 74; Sex category (female) (CHA_2DS_2-VASc) score

Medication	CHA_2DS_2-VASc score 0-1 (n = 39)	2-4 (n = 400)	5-9 (n = 275)	*P* value
Antithrombotic medication preoperatively				
Warfarin	2 (5.1)	65 (16.3)	69 (25.1)	.001
Low-molecular-weight heparin	2 (5.1)	24 (6.1)	18 (6.6)	.93
Nonvitamin K antagonist	0	0	0	1.00
Aspirin	15 (38.5)	193 (48.7)	158 (57.7)	.018
Antithrombotic medication at discharge				
Warfarin	35 (92.1)	377 (96.9)	260 (97.0)	.27
Low-molecular-weight heparin	17 (43.6)	131 (34.0)	70 (26.7)	.04
Nonvitamin K antagonist	0	1 (0.3)	0	.68
Aspirin	7 (18.4)	52 (13.6)	45 (17.2)	.40
Antithrombotic medication after 3 mo*				
Warfarin	2 (11.8)	99 (42.5)	99 (55.6)	<.001
Aspirin	9 (52.9)	91 (39.2)	71 (39.7)	.72
Atrial fibrillation rhythm at discharge	6 (15.4)	100 (25.0)	98 (35.6)	.006
Atrial fibrillation rhythm at 3-mo follow-up	2 (5.4)	75 (20.4)	67 (27.1)	.01
Atrial fibrillation rhythm at 12-mo follow-up†	2 (6.9)	44 (16.5)	47 (27.0)	.02

Categorical variables are reported as n (%). *CHA_2DS_2-VASc*, Congestive heart failure; Hypertension; Age ≥75 (doubled); Diabetes mellitus; prior Stroke, transient ischemic attack or thromboembolism (doubled); Vascular disease; Age 65 to 74; Sex category (female). *Data available for 60.8% of patients. †Data available for 66.2% of patients.

TABLE 3. Incidence rates of strokes, transient ischemic attacks (TIAs), and stroke/TIA mortality per 100 patient years according to Congestive heart failure; Hypertension; Age ≥75 (doubled); Diabetes mellitus; prior Stroke, transient ischemic attack or thromboembolism (doubled); Vascular disease; Age 65 to 74; Sex category (female) (CHA_2DS_2-VASc) score

CHA_2DS_2-VASc score	n	Strokes	Cardioembolic strokes	TIAs	Strokes or TIAs	Major bleeds	Mortality
0	4	0	0	0	0	0	0
1	35	0	0	1.14	1.14	0	2.17
2	73	2.17	1.03	0.30	2.47	1.05	3.89
3	148	1.35	0.68	1.16	2.51	1.24	3.40
4	179	2.65	0.80	0.54	3.19	0.94	6.29
5	151	3.01	1.33	1.75	4.76	2.10	5.66
6	80	4.73	2.42	1.05	5.78	1.59	6.99
7-9*	44	4.93	1.66	3.62	8.55	3.29	11.7

TIAs, Transient ischemic attacks. *CHA_2DS_2-VASc scores 7, 8, and 9 were combined due to low sample size.

(CHA_2DS_2-VASc scores 5-9). Competing risk analysis showed that very high CHA_2DS_2-VASc score (ie, 5-9) compared with high score was associated with increased the risk of major bleeds (HR, 1.92; 95% CI, 1.06-3.4; $P = .032$).

At the time of major bleeding event, 61.7% of patients were receiving warfarin therapy, 2.3% were receiving a nonvitamin K antagonist, 14.0% were receiving low-molecular-weight heparin, 23.3% were taking aspirin, and 2.4% were taking P2Y12 receptor blocker medication.

DISCUSSION

CHA_2DS_2-VASc appears to be a simple tool to identify patients at high risk of stroke or TIA after isolated SAVR with a bioprosthesis. More than one-third of all patients undergoing SAVR were classified to be at very high estimated stroke risk (CHA_2DS_2-VASC score ≥ 5) and every fifth of these high-risk patients experienced a stroke or TIA within 5 years from index surgery indicating heavy burden of cerebrovascular events.

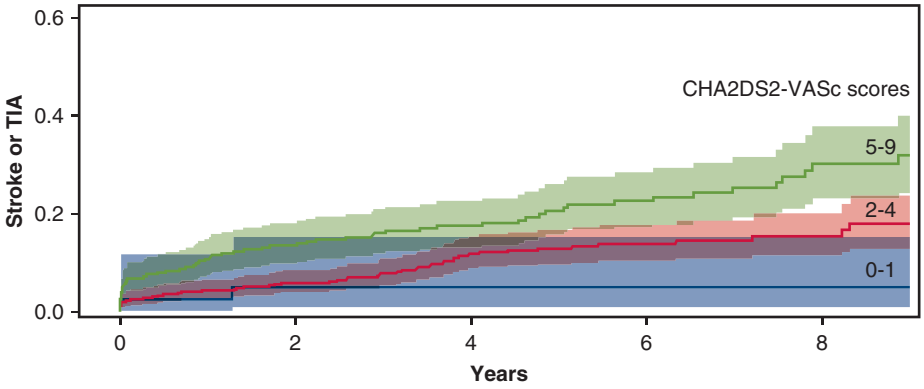
TABLE 4. Competing risk analysis

Risk variable	Hazard ratio (95% Confidence interval)	*P* value
Univariate model		
CHA_2DS_2-VASc score		
2-4 vs 0-1	2.57 (0.62-10.7)	.20
> 4 vs 0-1	4.83 (1.16-20.1)	.03
Multivariate model		
CHA_2DS_2-VASc score		
2-4 vs 0-1	2.55 (0.60-10.9)	.20
> 4 vs 0-1	4.75 (1.09-20.6)	.04
Atrial fibrillation		
Preoperative atrial fibrillation vs no	1.13 (0.62-2.07)	.69
New-onset atrial fibrillation vs no	0.98 (0.66-1.47)	.92

CHA_2DS_2-VASc, Congestive heart failure; Hypertension; Age ≥75 (doubled); Diabetes mellitus; prior Stroke, transient ischemic attack or thromboembolism (doubled); Vascular disease; Age 65 to 74; Sex category (female).

The present study showed that the risk of late stroke or TIA in these patients is significant and there is a need of measures for valid stratification of the risk of stroke in these patients. In patients with prior cardiac surgery, the etiology of strokes is cardioembolic in almost half of patients when assessed using TOAST criteria.[4] In fact, in our study the proportion of cardioembolic etiology of all strokes was much higher than reported in the general stroke population.[12] The rate of cardioembolic strokes also increased with increasing CHA_2DS_2-VASc scores. In patients with very-high-risk (CHA_2DS_2-VASc score ≥ 5) cardiogenic embolism occurred almost twice as often as in high-risk patients (CHA_2DS_2-VASc score 2-4) and the difference was evident already within the first year after the surgery.

The herein observed high incidence of strokes suggests that some patients with bioprosthetic SAVR may need permanent anticoagulation therapy to prevent AF-related strokes as well as emboli arising from the leaflets of the bioprosthesis.[13] Preventive strategies should be targeted in patients at high and very high risk for stroke. Obviously, cardioembolism may originate from the left atrial appendage in case of AF, from the left atrium, heart valves, left ventricle, or ascending aorta. Preventive measures include use of anticoagulant or antiplatelet medications, and occlusion of the left atrial appendage. Currently, European Society of Cardiology management guidelines for patients with AF recommend use of anticoagulation in AF patients with CHA_2DS_2-VASc scores ≥ 2 for males and ≥ 3 for females.[5] In addition, with CHA_2DS_2-VASc scores of 1 for males and 2 for females, the use of anticoagulant therapy should be considered.[5] In contrast, the use of anticoagulants without AF is far less straightforward. The European Association for Cardio-Thoracic Surgery guidelines suggest that vitamin K antagonist treatment may be considered for 3 months after SAVR with a bioprosthesis (IIb indication, level of evidence C), but no large-scale trials have addressed this issue.[14]



Patients at risk				
CHA2DS2-VASc 0-1:				
39	37	28	12	3
CHA2DS2-VASc 2-4:				
399	342	230	131	52
CHA2DS2-VASc 5-9:				
275	192	132	77	35

FIGURE 2. Competing risk cumulative incidence of stroke or transient ischemic attack according to low (0-1), high (2-4), and very high (5-9) Congestive heart failure; Hypertension; Age ≥75 (doubled); Diabetes mellitus; prior Stroke, transient ischemic attack or thromboembolism (doubled); Vascular disease; Age 65 to 74; Sex category (female) (*CHA_2DS_2-VASc*) score. *TIA*, Transient ischemic attack.

Anticoagulation therapy may be able to reduce the rate of leaflet thrombosis as indicated in a recent report from Portico Resheathable Transcatheter Aortic Valve System US IDE (Portico-IDE) Trial as well as Subclinical Aortic Valve Bioprosthesis Thrombosis Assessed With 4D CT (SAVORY) and Assessment of Transcatheter and Surgical Aortic Bioprosthetic Valve Thrombosis and Its Treatment With Anticoagulation (RESOLVE) registries.[13] Nevertheless, in an observational study, the use of anticoagulation was not associated with decreased risk of strokes.[15]

Preoperative permanent AF or new-onset in-hospital AF were not associated with a higher risk of stroke or TIA. This is likely explained by the more frequent use of anticoagulation therapy after surgery in patients with AF. Overall, fewer than half of patients were receiving anticoagulation therapy at the time of event. Among patients not receiving oral anticoagulation, silent AF may account for a great share of the events.[16] Among those receiving oral anticoagulation, poor anticoagulation control or stroke of atherosclerotic origin may partly account for such events.

Concomitant surgical closure of the left atrial appendage during the index surgery is also an option to be tested in randomized clinical trials. The efficacy of the left atrial appendage closure in these patients is currently under investigation in the Left Atrial Appendage Closure for the Prevention of Thromboembolisms in Patients Undergoing Aortic Bioprosthesis Surgery (LAA-CLOSURE) trial (ClinicalTrials.gov ID: NCT02321137) testing whether prophylactic surgical closure of the left atrial appendage decreases strokes and cardiovascular mortality in patients undergoing bioprosthetic SAVR. Indeed, the present study confirmed that major bleeding events are not infrequent complications occurring late after bioprosthetic SAVR and are mostly related to the use of antithrombotic medication. In addition, the risk of bleeding was high among patients with CHA_2DS_2-VASc score $\geq$ 2. Therefore, we speculate that patients at high risk of late stroke might benefit from the closure of the left atrial appendage at the time of primary surgery, avoiding the risk of stroke and TIA as well as the potential risks associated with prolonged anticoagulation.

These results should be interpreted in the light of some limitations. First, the retrospective nature is the main limitation of this study. Nevertheless, data were derived from electronic patient records and data on baseline, operative, and outcomes are routinely recorded in details at each of the participating hospitals. A validated, structured case report form was used at all study sites. As a quality control, a professional third party monitored the data. The patient population was from regional catchment areas where cerebrovascular events were treated exclusively at the participating centers. Second, the diagnosis of neurologic events was made by the treating physicians, which might have affected the sensitivity of registered end points. Nonetheless, as a result of the retrospective nature and physicians' diagnoses, there is a risk with false-negative cerebrovascular events rather than false positives. The decision regarding the use of imaging methods in the etiologic assessment of stroke or TIA was at discretion of the treating neurologist. However, especially in the case of cardioembolic stroke, the categorization is always an educated guess made by the treating

VIDEO 1. Principal Investigator Tuomas Kiviniemi explains the key message of the article. Video available at: https://www.jtcvs.org/article/S0022-5223(18)32030-0/fulltext.

physician instead of an absolute medical finding. In practice, this means that the treating neurologists used the imaging methods needed (eg, computed tomography, carotid ultrasound imaging, and echocardiogram) to exclude large artery atherosclerosis, small vessel occlusion, and other determined etiologies of stroke and to evaluate the probability of cardioembolic etiology. Based on these findings, the treating neurologists classified the neurologic events as being of cardioembolic or other etiologies. Neurologic events were defined as unknown TOAST when not otherwise categorized by the treating neurologists. Finally, the small sample size of this study is another limitation of this analysis, and therefore these findings should be viewed as hypothesis-generating.

CONCLUSIONS

More than one-third of patients undergoing SAVR are at very high of stroke or TIA as defined by CHA_2DS_2-VASc score ≥ 5 (Video 1). CHA_2DS_2-VASc is a valuable tool to identify patients with increased risk of stroke and major bleeding, and for whom alternative strategies for prevention of late neurologic complications should be considered.

Conflict of Interest Statement

Dr Kiviniemi lectures for Bayer, Boehringer Ingelheim, AstraZeneca, St Jude Medical, Bristol-Myers Squibb-Pfizer, and MSD; has received research grants from The Finnish Medical Foundation, Helsinki, Finland, the Finnish Foundation for Cardiovascular Research, Clinical Research Fund of Turku University Hospital, Turku, Finland, Finnish Cardiac Society, the Emil Aaltonen Foundation, the Maud Kuistila Foundation, and received an unrestricted grant from Bristol-Myers Squibb-Pfizer. He is also a member of the advisory board for Boehringer Ingelheim and MSD. Dr Lehto has received research grants from Orion Research Foundation and the Finnish Foundation for Cardiovascular Research. Dr Nieminen lectures for AstraZeneca, Boehringer Ingelheim, FCG Koulutus, GE Healthcare, Medtronic, Orion, Sanofi, and has received research grants from Abbvie, Medtronic, Research Fund of Helsinki, and Uusimaa Hospital District. Dr Hartikainen has received research grants from EU 2020 Horizon and the Finnish Foundation for Cardiovascular Research, Clinical Research Fund of Kuopio University Hospital, Kuopio, Finland, and lectures for Cardiome AG, MSD, and AstraZeneca. He is also a member of the advisory boards for Amgen, Pfizer, MSD, AstraZeneca, Bayer, and BMS. Dr Malmberg has received research grant from Clinical Research Fund of Turku University Hospital, Turku, Finland. Dr Airaksinen has received research grants from the Finnish Foundation for Cardiovascular Research, Clinical Research Fund of Turku University Hospital, Turku, Finland; lectures for Bayer, Cardiome AG, and Boehringer Ingelheim; and is a member of the advisory boards for Bayer, Astra Zeneca, Bristol-Myers Squibb-Pfizer, and Boston Scientific.

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References

1. Brennan JM, Edwards FH, Zhao Y, O'Brien S, Booth ME, Dokholyan RS, et al. Long-term safety and effectiveness of mechanical versus biologic aortic valve prostheses in older patients: results from the society of thoracic surgeons adult cardiac surgery national database. *Circulation*. 2013;127:1647-55.
2. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, et al. Heart disease and stroke statistics—2016 update a report from the American Heart Association. *Circulation*. 2016;133:338-60.
3. Miller DC, Blackstone EH, Mack MJ, Svensson LG, Kodali SK, Kapadia S, et al. Transcatheter (TAVR) versus surgical (AVR) aortic valve replacement: occurrence, hazard, risk factors, and consequences of neurologic events in the PARTNER trial. *J Thorac Cardiovasc Surg*. 2012;143:832-43.
4. Lehto J, Malmberg M, Biancari F, Hartikainen J, Ihlberg L, Yannopoulos F, et al. Occurrence and classification of cerebrovascular events after isolated bioprosthetic surgical aortic valve replacement: a competing risk analysis of the CAREAVR study. *Structural Heart*. 2018;2:157-63.
5. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J*. 2016;37:2893-962.
6. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the Euro heart survey on atrial fibrillation. *Chest*. 2010;137:263-72.
7. Palomäki A, Kiviniemi T, Mustonen P, Odei C, Hartikainen JEK, Nuotio I, et al. Mortality after stroke in patients with paroxysmal and chronic atrial fibrillation—the FibStroke study. *Int J Cardiol*. 2017;227:869-74.
8. Lautamäki A, Gunn JM, Airaksinen KEJ, Biancari F, Kajander OA, Anttila V, et al. Permanent work disability in patients ≤50 years old after percutaneous coronary intervention and coronary artery bypass grafting (the CRAGS study). *Eur Heart J Qual Care Clin Outcomes*. 2017;3:101-6.
9. Adams H, Bendixen B, Kappelle L, Biller J, Love BB, Gordon DL, et al. Classification of subtype of acute ischemic stroke. *Stroke*. 1993;24:35-41.
10. Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the bleeding academic research consortium. *Circulation*. 2011;123:2736-47.
11. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc*. 1999;94:496-509.
12. Kolomensky-Rabas PL, Weber M, Gefeller O, Neundorfer B, Heuschmann PU. Epidemiology of ischemic stroke subtypes according to TOAST criteria. *Stroke*. 2001;32:2735-40.

13. Makkar RR, Fontana G, Jilaihawi H, Chakravarty T, Kofoed KF, De Backer O, et al. Possible subclinical leaflet thrombosis in bioprosthetic aortic valves. *N Engl J Med*. 2015;373:2015-24.
14. Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, et al. 2017 ESC/EACTS guidelines for the management of valvular heart disease. *Eur Heart J*. 2017;38:2739-91.
15. Owais T, Rouman M, Breuer M, Hüter L, Fuchs J, Lauer B, et al. Anticoagulation after biological aortic valve replacement: is there an optimal regimen? *J Heart Valve Dis*. 2016;25:139-44.
16. Jaakkola J, Mustonen P, Kiviniemi T, Hartikainen JE, Palomäki A, Hartikainen, et al. Stroke as the first manifestation of atrial fibrillation. *PLoS One*. 2016;11:e0168010.

Key Words: aortic valve replacement, cardiovascular surgery, ischemic stroke, transient ischemic attack