European Journal of Cardio-Thoracic Surgery 50 (2016) 867–873
doi:10.1093/ejcts/ezw199 Advance Access publication 28 June 2016

ORIGINAL ARTICLE

Cite this article as: Conrotto F, D'Ascenzo F, D'Onofrio A, Agrifoglio M, Chieffo A, Cioni M *et al*. Predictive ability of the $CHADS_2$ and CHA_2DS_2-VASc scores for stroke after transcatheter aortic balloon-expandable valve implantation: an Italian Transcatheter Balloon-Expandable Valve Implantation Registry (ITER) sub-analysis. Eur J Cardiothorac Surg 2016;50:867–73.

Predictive ability of the $CHADS_2$ and CHA_2DS_2-VASc scores for stroke after transcatheter aortic balloon-expandable valve implantation: an Italian Transcatheter Balloon-Expandable Valve Implantation Registry (ITER) sub-analysis

Federico Conrotto[a,*], Fabrizio D'Ascenzo[a], Augusto D'Onofrio[b], Marco Agrifoglio[c], Alaide Chieffo[d], Micaela Cioni[d], Tommaso Regesta[e], Giuseppe Tarantini[b], Davide Gabbieri[f], Francesco Saia[g], Corrado Tamburino[h], Flavio Ribichini[i], Diego Cugola[j], Marco Aiello[k], Francesco Sanna[l], Alessandro Iadanza[m], Esmeralda Pompei[n], Miroslava Stolcova[o], Antioco Cappai[p], Alessandro Minati[q], Mauro Cassese[r], Gian Luca Martinelli[r], Andrea Agostinelli[s], Gino Gerosa[b], Fiorenzo Gaita[a], Mauro Rinaldi[t] and Stefano Salizzoni[t]

[a] Division of Cardiology, Città della Salute e della Scienza Hospital, Torino, Italy
[b] Department of Cardiac, Thoracic and Vascular Sciences, University of Padova, Padova, Italy
[c] Centro Cardiologico Monzino, Department of Clinical Sciences and Community, University of Milano, Milano, Italy
[d] Ospedale San Raffaele, Milano, Italy
[e] Divisione di Cardiochirurgia, IRCCS San Martino-IST, Genova, Italy
[f] Hesperia Hospital, Modena, Italy
[g] AOU Policlinico S. Orsola-Malpighi, Bologna, Italy
[h] Ospedale Ferrarotto, Università di Catania, Catania, Italy
[i] AOU Integrata Verona, Verona, Italy
[j] AO Papa Giovanni XXIII, Bergamo, Italy
[k] IRCCS Policinico S. Matteo, Pavia, Italy
[l] AO Brotzu, Cagliari, Italy
[m] AOU Policlinico Le Scotte, Siena, Italy
[n] AOUD Santa Maria della Misericordia, Udine, Italy
[o] AOU Careggi, Firenze, Italy
[p] Humanitas Research Hospital, Rozzano, Italy
[q] Ospedale Cattinara, Trieste, Italy
[r] Clinica S. Maria, Bari, Italy
[s] Ospedale Maggiore, Parma, Italy
[t] Department of Surgical Sciences, Città della Salute e della Scienza Hospital, Torino, Italy

* Corresponding author. Division of Cardiology, Città della Salute e della Scienza, Corso Bramante 88, 10100 Turin, Italy. Tel: +39-011-6335563; fax: +39-011-6335565; e-mail: federico.conrotto@gmail.com (F. Conrotto).

Received 12 October 2015; received in revised form 22 March 2016; accepted 9 April 2016

Abstract

OBJECTIVES: Stroke incidence after transcatheter aortic valve implantation (TAVI) still represents a concern. This multicentre study aimed at investigating the hypothesis that CHADS2 and CHA2DS2-VASc scores may be used to predict perioperative stroke after TAVI.

METHODS: The Italian Transcatheter Balloon-Expandable Valve Implantation Registry (ITER) is a multicentre, prospective registry of patients undergoing balloon-expandable TAVI using Edwards Sapien and Sapien XT prosthesis between 2007 and 2012. The primary end-point of this study was the 30-day stroke rate. Secondary safety end-points were all the major adverse events based on Valve Academic Research Consortium (VARC-2) criteria.

RESULTS: One thousand nine hundred and four patients were enrolled in the registry. Mean age was 81.6 ± 6.2 years and 1147 (60.2%) patients were female; mean $CHADS_2$ and CHA_2DS_2-VASc scores were 2.2 ± 0.8 and 4.4 ± 1.1, respectively. Fifty-four (2.8%) patients had a stroke within 30 days. At multivariable logistic regression analysis, CHA_2DS_2-VASc (OR: 1.35, 95% CI: 1.03–1.78; $P = 0.031$) and previous cardiac surgery (OR: 1.96, 95% CI: 1.06–3.6; $P = 0.033$) but not $CHADS_2$ (OR: 1.05, 95% CI: 0.76–1.44; $P = 0.77$) were found to be independent predictors of in-hospital stroke. A CHA_2DS_2-VASc score ≥5 was strongly related to the occurrence of in-hospital stroke (OR: 2.51, 95% CI: 1.38–4.57; $P = 0.001$). However, CHA_2DS_2-VASc score showed only poor accuracy for in-hospital stroke with a trend for better accuracy when compared with $CHADS_2$ score (area under the curve: 0.61, 95% CI: 0.59–0.63 vs 0.51; 95% CI: 0.49–0.54, respectively, $P = 0.092$).

CONCLUSIONS: In TAVI patients, CHA_2DS_2-VASc provided a strong correlation for in-hospital stroke but with low accuracy. Dedicated scores to properly tailor procedures and preventive strategies are needed.

Keywords: Aortic stenosis • TAVI • Stroke

INTRODUCTION

Transcatheter aortic valve implantation (TAVI) is a therapeutic option for patients with severe symptomatic aortic stenosis ineligible or at high risk for aortic valve replacement (AVR) [1, 2].

Although in recent years, the TAVI procedure has reached a good safety profile, periprocedural stroke still represents a serious issue, affecting short- and long-term survival [3]. The PARTNER trial showed a higher cerebral vascular event rate at Day 30 for TAVI compared with medical therapy or surgical aortic valve replacement [1, 2]. However, to the best of our knowledge, there is a lack of dedicated scores for stroke prediction after TAVI.

$CHADS_2$ (C: congestive heart failure; H: hypertension; A: age ≥65 years; D: diabetes mellitus; S: prior stroke or TIA or thromboembolism) and CHA_2DS_2-VASc (C: congestive heart failure; H: hypertension; A_2: age ≥75 years; D: diabetes mellitus; S: prior stroke or TIA or thromboembolism; V: vascular disease; A: age 65–74 years; Sc: sex category) scores are validated tools used to estimate overall stroke risk in patients with atrial fibrillation (AF) [4,5]. Recently, it has been shown that these scores may be useful for predicting stroke also in different clinical settings such as in acute coronary syndrome patients [6]. Interestingly, their predictive performances seemed to be irrespective of AF presence [7].

Consequently, the aim of our study was to investigate the hypothesis that $CHADS_2$ and CHA_2DS_2-VASc scores may be used to predict stroke after TAVI.

METHODS

Study population

The ITER (Italian Transcatheter Balloon-Expandable Valve Implantation Registry) is a multicentre registry involving 33 centres in Italy. All consecutive patients undergoing balloon-expandable TAVI at each centre between 2007 and 2012, regardless of the access, were enrolled in this registry. All procedures were performed using Edwards Sapien and Sapien XT prosthesis. Data were collected at each study site and then anonymously sent to the University of Turin for storage and analysis. Ethic committees approved data collection and patient informed consent was always obtained. As this is a real-world all-comers experience, patient selection and procedure strategy were done according to single site policies, experience and protocols.

End-points

The primary end-point of this analysis was the in-hospital stroke. Secondary safety end-points were all the major adverse events based on Valve Academic Research Consortium (VARC-2) criteria [8].

Data analysis and definitions

Data were divided into two groups based on the occurrence of stroke for the analysis of baseline, echocardiographic, procedural characteristics and end-points. The $CHADS_2$ and CHA_2DS_2-VASc scores were calculated for all patients. Incidences of the primary and secondary end-points were also presented according to CHA_2DS_2-VASc classes (low <2, intermediate 2–4 and high ≥5) and to $CHADS_2$ classes (low 0–1, intermediate 2 and high ≥3). Preoperative risk factors were defined according to the EuroSCORE (ES) 2 [9] classification. Postoperative outcomes were defined according to the updated VARC-2 definitions. The echocardiographic measurements were performed according to the current recommendations of the European and American Societies of Echocardiography [10].

Statistical analysis

Continuous data are expressed by mean and standard deviation or median and interquartile range as appropriate. Categorical values were compared by the χ^2 or the Fisher's exact test for expected cell frequencies <5. Continuous variables were compared by the *t*-test. All periprocedural variables significantly associated (with a *P*-value <0.10) for in-hospital stroke were incorporated into multivariable logistic regression analysis. Three models were run separately for $CHADS_2$, CHA_2DS_2-VASc and CHA_2DS_2-VASc ≥5. The three different risk scores entered into the models were forced into the multivariable model as per the study objectives. For each model, discrimination was tested with an area under the curve (AUC) and calibration with Hosmer–Lemeshow test. Missing data were excluded from the multivariable models (case-complete analysis). For the primary end-point, predictive accuracy of $CHADS_2$ and CHA_2DS_2-VASc scores was tested with AUC. AUCs of $CHADS_2$ and CHA_2DS_2-VASc scores were compared according to Hanley and McNeil [11]. Patients were divided into $CHADS_2$ and CHA_2DS_2-VASc risk classes according to the value of $CHADS_2$ and CHA_2DS_2-VASc, which performed the most accurate to predict low, medium or high risk of stroke using receiver operating characteristic (ROC) analysis models. The effects of reclassification using CHA_2DS_2-VASc versus $CHADS_2$ score were then assessed, estimating the net reclassification improvement (NRI). The NRI focuses on reclassification tables and quantifies the correct movement in the right category offered by the new model [12].

A *P*-value <0.05 indicated statistical significance. Sensitivity analysis was performed according to the presence or absence of AF. All statistical analyses were performed with the use of SPSS, version 20 (IBM Corp., Armonk, NY, USA).

RESULTS

One thousand nine hundred and four patients were enrolled in the registry. Mean age was 81.6 ± 6.2 years; 1147 (60.2%) patients were female; mean $CHADS_2$ and CHA_2DS_2-VASc scores were 2.2 ± 0.8 and 4.4 ± 1.1, respectively. Fifty-four (2.8%) patients had a stroke after TAVI within in-hospital stay. Patients who suffered a stroke presented more frequently with peripheral vascular disease and a history of previous cardiac surgery. Patients who had a stroke showed also a significantly higher CHA_2DS_2-VASc score (4.8 vs 4.3%, $P = 0.005$) and a higher proportion of CHA_2DS_2-VASc ≥5 (68.5 vs 43.8%, $P = 0.001$). Baseline clinical, echocardiographic and procedural characteristics are summarized in Table 1.

Table 1: Baseline clinical, procedural and echocardiographic characteristics

	All (*n* = 1904)	No stroke (*n* = 1850)	Stroke (*n* = 54)	*P*-value
Age (years)	81.7 ± 6.2	81.7 ± 6.2	81.2 ± 7	0.58
Female gender	1147 (60.2)	1115 (60.3)	32 (59.3)	0.88
Body mass index (m^2)	25.8 ± 4.5	25.8 ± 4.5	25.6 ± 4.3	0.69
Hypertension	1553 (81.6)	1505 (81.4)	48 (88.9)	0.16
Diabetes mellitus	491 (25.8)	473 (25.6)	18 (33.3)	0.2
Insulin-treated diabetes mellitus[a]	182 (9.6)	173 (9.4)	9 (16.7)	0.072
Peripheral vascular disease[a]	674 (35.4)	647 (35)	27 (50)	0.023
COPD	468 (24.6)	451 (24.4)	17 (31.5)	0.23
Previous stroke	182 (9.6)	175 (9.5)	7 (13)	0.39
Previous cardiac surgery[a]	352 (18.5)	335 (18.1)	17 (31.5)	0.01
Previous myocardial infarction[a]	371 (19.5)	356 (19.2)	15 (27.8)	0.067
New York Heart Association functional class				
I	51 (2.7)	51 (2.8)	0	0.27
II	317 (16.7)	304 (16.4)	13 (24.1)	
III	1294 (68.0)	1261 (68.2)	33 (61.1)	
IV	242 (12.7)	234 (12.6)	8 (14.8)	
LVEF %	53.5 ± 12.3	53.5 ± 12.4	52.6 ± 11.1	0.58
LVEF <30%	80 (4.2)	79 (4.3)	1 (1.9)	0.38
Glomerular filtration rate (ml/min)[a]	44.4 ± 19.8	44.5 8 ± 19.9	39.5 ± 15.5	0.063
Creatinine >2.2 mg/dl or dialysis	152 (8.0)	145 (7.8)	7 (13)	0.17
Haemoglobin (g/dl)	11.8 ± 1.6	11.8 ± 1.5	12 ± 1.7	0.52
Baseline rhythm				
Sinus rhythm	1357 (71.3)	1320 (71.4)	37 (68.5)	0.71
Atrial fibrillation	414 (21.7)	400 (21.6)	14 (25.9)	
Pace maker	133 (7.0)	130 (7)	3 (5.6)	
Porcelain aorta	185 (9.7)	178 (10.3)	7 (13)	0.53
Logistic EuroSCORE 2	7.2 ± 6.7	7.2 ± 6.7	8.6 ± 7.2	0.22
STS mortality score (%)	9.2 ± 7.6	9.2 ± 7.6	9.8 ± 5.7	0.61
$CHADS_2$[a]	2.2 ± 0.8	2.2 ± 0.8	2.3 ± 0.8	0.76
$CHADS_2$>3[a]	625 (32.8)	604 (32.6)	21 (38.9)	0.34
CHA_2DS_2-VASc[a]	4.4 ± 1.1	4.3 ± 1.1	4.8 ± 1	0.005
Systolic pulmonary artery pressure (mmHg)	42.1 ± 13	42.1 ± 12.9	44.2 ± 14	0.25
sPAP ≥60 mmHg	200 (10.5)	191 (10.3)	9 (16.7)	0.13
Mean aortic gradient (mmHg)[a]	50.2 ± 15.0	50.4 ± 15	45.3 ± 14.9	0.015
Aortic valve area (indexed)	0.45 ± 0.14	0.48 ± 0.16	0.46 ± 0.14	0.18
BAV bridge to TAVI	221 (11.6)	216 (11.7)	5 (9.3)	0.59
Kind of valve				
Edwards SAPIEN	601 (31.6)	584 (31.6)	17 (31.5)	0.98
SAPIEN XT	1303 (68.4)	1266 (68.4)	37 (68.5)	

Data are expressed as mean ± SD or *n* (%).
BAV: balloon aortic valvuloplasty; COPD: chronic obstructive pulmonary disease; LVEF: left ventricle ejection fraction; sPAP: systolic pulmonary artery pressure; STS: Society of Thoracic Surgeons; TAVI: transcatheter aortic valve implantation.
[a]Used in the multivariable analysis.

No differences were recorded in procedural complications in patients who did or did not have stroke, except for device embolization that was significantly related to stroke (Table 2).

Patients who suffered an in-hospital stroke had a significantly higher mortality (25.9 vs 6.6%, $P = 0.001$), a significantly higher incidence of bleeding driven by higher incidences of both life threatening and major bleeding (18.5 vs 9.6% and 18.5 vs 10.6%, respectively, $P = 0.024$) and higher incidence of acute kidney injury (7.8 vs 22.2%; $P = 0.001$). Of note, new onset of AF was not related to higher stroke rate. Detailed in-hospital outcomes are reported in Table 3.

Outcomes according to $CHADS_2$ classes

Three hundred and six (16.1%) patients had a low $CHADS_2$ score, 973 (51.1%) intermediate and 625 (32.8%) high. Patients in the three classes had similar rates of in-hospital complications. In particular, no differences in stroke rates were detected (3.3, 2.4 and 3.4%, $P= 0.45$) (Fig. 1).

Outcomes according to CHA_2DS_2-VASc classes

Sixty-eight (3.6%) patients had a low CHA_2DS_2-VASc score, 989 (51.9%) intermediate and 847 (44.5%) high. Patients in the higher CHA_2DS_2-VASc classes had a significantly higher incidence of in-hospital stroke (0, 1.7 and 4.4%, $P = 0.001$) and presented a trend for higher mortality (2.9, 6.9 and 7.9%, $P = 0.26$) (Fig. 2).

Independent predictors of in-hospital stroke

At multivariable logistic regression analysis, CHA_2DS_2-VASc (OR: 1.35, 95% CI: 1.03–1.78; $P = 0.031$) and previous cardiac surgery (OR: 1.96, 95% CI: 1.06–3.6; $P = 0.033$) but not $CHADS_2$ (OR: 1.05,

Table 2: Procedural complications

	All (n = 1904)	No stroke (n = 1850)	Stroke (n = 54)	P-value
Prosthesis embolization	12 (0.6)	10 (0.5)	2 (3.7)	0.04
Need for extracorporeal circulation	32 (1.7)	30 (1.6)	2 (3.7)	0.23
Conversion to sternotomy	32 (1.7)	31 (1.7)	1 (1.9)	0.61
Apex complications	33/629 (1.7)	30 (1.6)	3 (5.6)	0.07
Need for external cardiac massage	63 (3.3)	59 (3.2)	4 (7.4)	0.10
Coronary occlusion	22 (1.2)	22 (1.2)	0	0.99
Aortic dissection	26 (1.4)	25 (1.4)	1 (1.9)	0.53
Bail-out valve-in-valve	10 (0.5)	9 (0.5)	1 (1.9)	0.25
Conversion to AVR	10 (0.5)	9 (0.5)	1 (1.9)	0.25

Table 3: Perioperative outcomes according to the updated Valve Academic Research Consortium (VARC-2) definitions

	All (n = 1904)	No stroke (n = 1850)	Stroke (n = 54)	P-value
Device in success	227 (11.9)	218 (11.8)	9 (16.7)	0.28
VARC mortality	137 (7.2)	123 (6.6)	14 (25.9)	0.001
Acute myocardial infarction	29 (1.6)	28 (1.5)	1 (1.9)	0.99
Bleeding				
Life threatening	186 (9.8)	176 (9.6)	10 (18.5)	0.024
Major	200 (10.5)	190 (10.4)	10 (18.5)	
Minor	110 (5.8)	107 (5.8)	3 (5.6)	
Vascular complication				
Major	177 (9.3)	172 (9.3)	5 (9.3)	0.33
Minor	131 (6.9)	130 (7.0)	1 (1.9)	
Acute kidney injury (AKIN) grade 2–3	156 (8.2)	144 (7.8)	12 (22.2)	0.001
Pace maker implantation (before discharge)	116 (6.1)	111 (6)	5 (9.3)	0.37
New onset atrial fibrillation	170 (9)	163 (8.9)	7 (13)	0.31

95% CI: 0.76–1.44; P = 0.77) were found to be independently related to in-hospital stroke. At sensitivity analysis, the presence or the absence of AF did not alter these results. A CHA_2DS_2-VASc score ≥5 was strongly related to the occurrence of in-hospital stroke (OR: 2.51, 95% CI: 1.38–4.57; P = 0.001) (Table 4).

Predictive accuracy of $CHADS_2$ and CHA_2DS_2-VASc

CHA2DS2-VASc score showed a trend for better accuracy for in-hospital stroke when compared with $CHADS_2$ score (AUC: 0.61, 0.59–0.63 vs 0.51, 0.49–0.54, respectively, P = 0.09) (Fig. 3). The overall NRI calculated for CHA2DS2-VASc score compared with $CHADS_2$ score was of 15.3%, P = 0.001.

DISCUSSION

The present study is the first attempt to evaluate the ability of $CHADS_2$ and CHA_2DS_2-VASc scores to predict cerebral events after TAVI. The most important findings of our analysis are as follows: (i) in our real-world TAVI registry, stroke incidence is low, but it significantly affects in-hospital mortality, (ii) CHA_2DS_2-VASc but not CHADS2 is independently related to the risk of stroke and (iii) both CHA_2DS_2-VASc and $CHADS_2$ presented low accuracy.

Stroke may represent a serious complication occurring during or after TAVI. The most likely causes of periprocedural brain injury include embolization owing to direct manipulation of the atherosclerotic arch and the calcified native valve during positioning and implantation of the valves [13]. In the PARTNER trial, incidence of periprocedural stroke was higher in TAVI patients compared with medical therapy or surgical AVR [1, 2]. However, more recent trials have shown a reduction of cerebral events after TAVI with no difference compared with surgery [14, 15]. Similarly to previous studies, in our registry stroke, incidence was low (2.8%).

$CHADS_2$ is an easy-to-use classification scheme that estimates stroke risk in patients who have non-rheumatic AF [5]. To create $CHADS_2$, 2 points are given for a history of prior cerebral ischaemia and 1 point is given for the presence of other risk factors (recent congestive heart failure, hypertension, age 75 years or older and diabetes). CHA_2DS_2-VASc was developed to be more inclusive of common stroke risk modifiers and to further improve stroke risk stratification. It includes three adjunctive risk factors: female gender, vascular disease and age between 65 and 74 years old. Interestingly, the pre-stroke CHA_2DS_2-VASc score showed better ability than the $CHADS_2$ score in estimating 3-month stroke outcomes in patients with and without AF [16].

Recently, it has been shown that $CHADS_2$ score may also be predictive for MACE (such as myocardial infarction and cardiovascular mortality) [17, 18].

Although stroke significantly worsens short- and mid-term prognosis after TAVI, with an ∼3.5-fold higher mortality [18], only a few studies have been dedicated to evaluate predictors of cerebral events after TAVI [19].

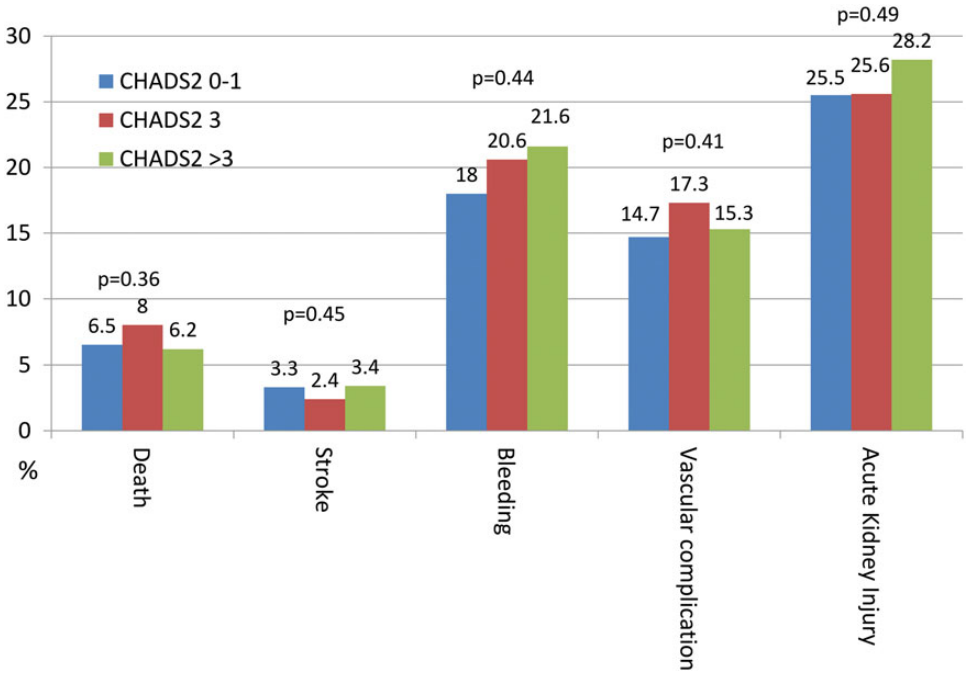

Figure 1: Crude rates of in-hospital outcomes according to $CHADS_2$ score classes.

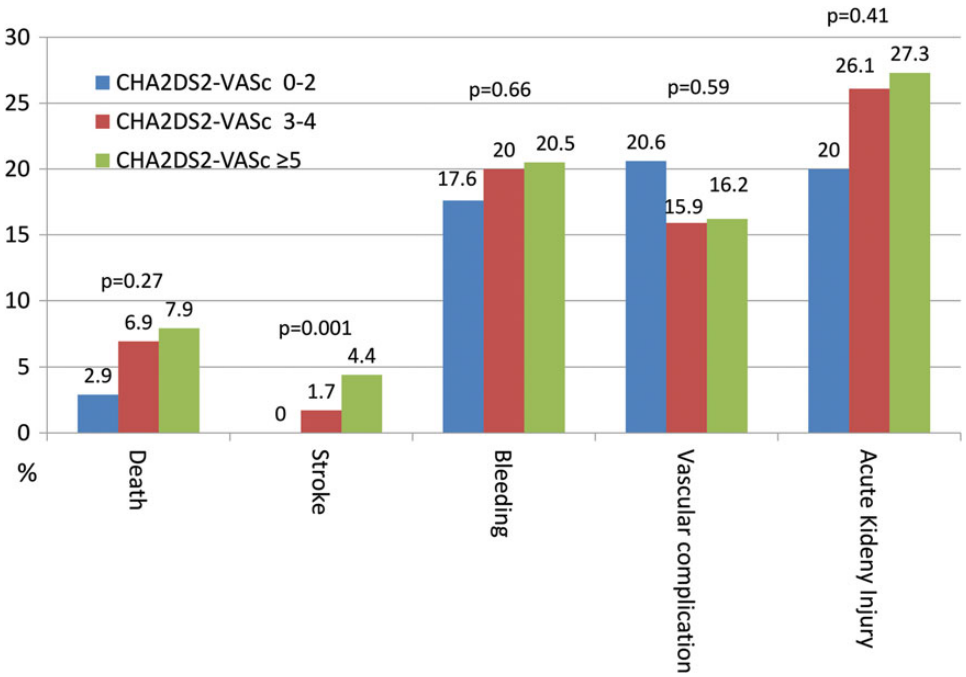

Figure 2: Crude rates of in-hospital outcomes according to CHA_2DS_2-VASc score classes.

Similarly to previous findings [20], in our registry, patients who suffered a stroke had a significantly higher mortality (25.9 vs 6.6%, $P = 0.001$). Identifying patients at high risk of stroke during TAVI procedure may, therefore, be helpful in patient selection and trigger the adoption of stronger preventive strategies as less-traumatic devices, avoidance of extensive manipulations and active cerebral protection [21]. Fairbairn *et al.* [22] demonstrated that age, severity of aortic arch atheroma and catheterization time were stroke risk factors, whereas the report of Miller *et al.* [23] showed the independent power of smaller aortic valve area index which is usually associated with a higher degree of valve calcification. Interestingly, in the latter study as in our registry, AF was not identified to be a risk factor for neurological events after TAVI underlying the stronger link existing between stroke and implantation at least in the early phase.

These factors (mainly age and atherosclerotic burden) are part of both $CHADS_2$ and CHA_2DS_2-VASc. In addition, CHA_2DS_2-VASc score also presents female gender and peripheral artery disease as

Table 4: Predictors of in-hospital stroke

Covariates	OR	95% CI	*P*-value
Model 1			
Previous myocardial infarction	1.02	0.71–1.47	0.91
Insulin-treated diabetes	1.36	0.62–2.97	0.15
Glomerular filtration rate (ml/min)	0.99	0.97–1.01	0.069
Previous cardiac surgery	1.97	1.06–3.67	0.031
$CHADS_2$	1.05	0.76–1.44	0.77
Model 2			
Previous myocardial infarction	0.98	0.68–1.41	0.91
Insulin-treated diabetes	1.36	0.62–2.96	0.45
Glomerular filtration rate (ml/min)	0.99	0.97–1.01	0.12
Previous cardiac surgery	1.96	1.06–3.60	0.033
$CHADS_2$-$VASc_2$[a]	1.35	1.03–1.78	0.031
Model 3			
Previous myocardial infarction	0.98	0.68–1.40	0.89
Insulin-treated diabetes	1.32	0.61–2.83	0.47
Glomerular filtration rate (ml/min)	0.99	0.97–1.01	0.12
Previous cardiac surgery	1.96	1.06–3.60	0.033
$CHADS_2$-$VASc_2$>5[a]	2.51	1.38–4.57	0.001

At Hosmer–Lemeshow test *P*= 0.35 for Model 1, *P*= 0.62 for Model 2 and *P*= 0.09 for Model 3.
[a]Three models were run separately for these variables. Area under the curve test resulted, respectively, 0.62 for Model 1, 0.65 for Model 2 and 0.67 for Model 3.

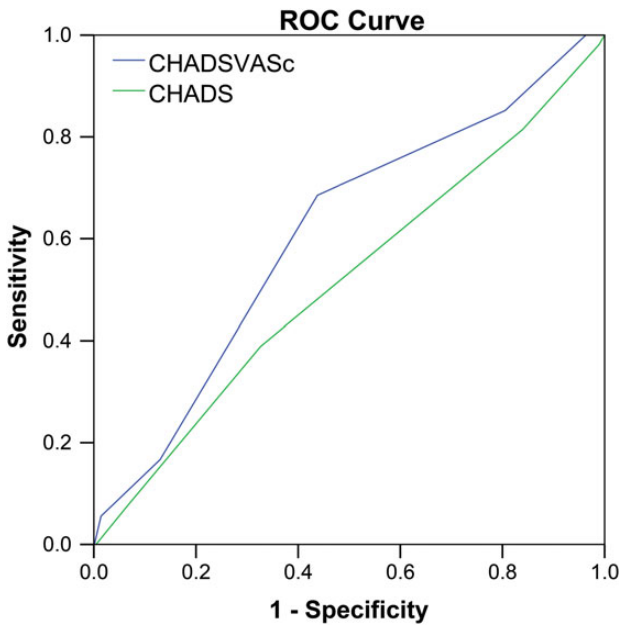

Figure 3: Receiver operating characteristic (ROC) curves for in-hospital stroke of CHA_2DS_2-VASc score (AUC: 0.61, 95% CI: 0.59–0.63) and $CHADS_2$ score (AUC: 0.51, 95% CI: 0.49–0.54).

risk factors: both these factors have been previously related to a less-successful outcome after TAVI [24, 25]. Consequently, it could easily explain the strong correlation we found between CHA_2DS_2-VASc score TAVI-related cerebrovascular injury. In fact, we found the risk of stroke to be 2.5 times higher in TAVI patients with CHA_2DS_2-VASc score ≥5 than in patients with low CHA_2DS_2-VASc score.

As already demonstrated in different clinical settings [6], the CHA_2DS_2-VASc score seems to be related to mortality also in TAVI patients, showing a trend of higher mortality in higher CHA_2DS_2-VASc classes.

However, ROC curve analysis showed that accuracy of CHA_2DS_2-VASc score, although better than accuracy of $CHADS_2$ score, remains poor. Probably, the clinical features represented in CHA_2DS_2-VASc scores are good stroke predictors in TAVI patients but are weighted on a different setting (non-rheumatic AF), consequently explaining the low accuracy of the score.

In conclusion, in TAVI patients, CHA_2DS_2-VASc provided a strong correlation for in-hospital stroke but with poor accuracy. Dedicated scores to properly tailor procedures and preventive strategies are needed.

Limitations

The present study has several limitations. The main limit is the observational design because differences in baseline characteristics or in selection criteria, which might not have been recorded, could affect the present results. Data were self-adjudicated and there was no external adjudication of events. The number of patients enrolled at each centre was heterogeneous. The limited number of events may represent another limit for calibration of the multivariable model. Missing data were <2% for all the baseline variables and outcomes data. In particular, missing data for the variables included in the regression models were 1.1% (21/1904).

ACKNOWLEDGEMENTS

We thank Michele La Torre, Maurizio D'Amico, Claudio Moretti, Sebastiano Marra, Mario Lupo, Antonio Bartorelli, Ottavio Alfieri, Chiara Tessari, Valeria Gasparetto, Laura Besola, Antonio Colombo, Filippo Rapetto, Massimo Vischi, Valentina Boasi, Bindo Missiroli, Alberto Benassi, Carlo Savini, Antonio Marzocchi, Roberto Di Bartolomeo, Massimo Napodano, Sebastiano Immè, Carmelo Sgroi, Antonio Salvatore Rubino, Giuseppe Faggian, Francesco Onorati, Alessandro Terzi, Orazio Valsecchi, Maurizio Ferrario, Emilio Maria Cirio, Giovanni Lixi, Alberto Boi, Bruno Loi, Carlo Pierli, Giuseppe Sincropi, Flavio D'Ascenzi, Ugolini Livi, Enzo Mazzaro, Alessandro Proclemer, Leonardo Spedicato, Guglielmo Bernardi, Pierluigi Stefàno, Gennaro Santoro, Diego Ornaghi, Alessandro Salvi, Aniello Pappalardo, Diego Ardissino, Tiziano Gherli, Roberto Violini, Claudia Boschetti, Andrea Audo, Corrado Cavozza, Maurizio Reale, Giorgio Ballestrero, Rosario Fiorilli, Francesco Casilli, Luigi Inglese, Carlo De Vincentis, Andrea Garatti, Francesco Bedogni, Nedy Brambilla, Paolo Panisi, Rosalba Mozzillo, Antonio Rapacciuolo, Anna Sonia Petronio, Cristina Giannini, Andrea Pieroni, Giovanni Scioti, Roberto Bonmassari, Michel Dallago, Angelo Graffigna, Carlo Briguori, Giudeppe De Maio, Luigi Marino, Armando Liso, Roberto Gregorini, Fabio Miraldi, Gennaro Sardella, Giuseppe Bruschi, Luigi Martinelli, Federico De Marco, Silvio Klugman, Claudia Fiorina, Federica Ettori, Claudia Filippini and Orazio Valsecchi who contributed to the present study.

Conflict of interest: Augusto D'Onofrio, Marco Aiello and Davide Gabbieri report consulting fees from Edwards Lifesciences. Mauro Cassese reports consulting fees from Edwards Lifesciences and Medtronic, as well as lecture fees from Medtronic. Mauro Rinaldi reports consulting fees from Edwards Lifesciences and lecture fees

from Edwards Lifesciences, Medtronic and Novartis. Gino Gerosa reports consulting fees from AstraZeneca, lecture fees from HeartWare and St. Jude Medical and grant support from Edwards. Gian Luca Martinelli reports speaker honorarium from Edwards. Corrado Tamburino reports speaker honorarium from Abbott, Medtronic and St. Jude Medical. All other authors none declared.

REFERENCES

[1] Leon MB, Smith CR, Mack M, Miller DC, Moses JW, Svensson LG *et al*. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. N Engl J Med 2010;363:1597–607.

[2] Smith CR, Leon MB, Mack MJ, Miller DC, Moses JW, Svensson LG *et al*. Transcatheter versus surgical aortic-valve replacement in high-risk patients. N Engl J Med 2011;364:2187–98.

[3] Bax JJ, Delgado V, Bapat V, Baumgartner H, Collet JP, Erbel R *et al*. Open issues in transcatheter aortic valve implantation. Part 2: procedural issues and outcomes after transcatheter aortic valve implantation. Eur Heart J 2014;35:2639–54.

[4] Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. JAMA 2001;285:2864–70.

[5] 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.

[6] Poçi D, Hartford M, Karlsson T, Herlitz J, Edvardsson N, Caidahl K. Role of the CHADS2 score in acute coronary syndromes: risk of subsequent death or stroke in patients with and without atrial fibrillation. Chest 2012;141:1431–40.

[7] Barra S, Almeida I, Caetano F, Providência R, Paiva L, Dinis P *et al*. Stroke prediction with an adjusted R-CHA_2DS_2VASc score in a cohort of patients with a myocardial infarction. Thromb Res 2013;132:293–9.

[8] Kappetein AP, Head SJ, Généreux P, Piazza N, van Mieghem NM, Blackstone EH *et al*. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document (VARC-2). Eur J Cardiothorac Surg 2012;42:S45–60.

[9] Nashef SAM, Roques F, Sharples LD, Nilsson J, Smith C, Goldstone AR *et al*. EuroSCORE II. Eur J Cardiothorac Surg 2012;41:1–12.

[10] Zoghbi WA, Enriquez-Sarano M, Foster E, Grayburn PA, Kraft CD, Levine RA *et al*. American Society of Echocardiography. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. J Am Soc Echocardiogr 2003;16:777–802.

[11] Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. Radiology 1982;143:29e36.

[12] Pencina MJ, D'Agostino RB Sr, D'Agostino RB Jr, Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. Stat Med 2008;27:157e172.

[13] Kahlert P, Al-Rashid F, Döttger P, Mori K, Plicht B, Wendt D *et al*. Cerebral embolization during transcatheter aortic valve implantation: a transcranial Doppler study. Circulation 2012;126:1245–55.

[14] Panchal HB, Ladia V, Desai S, Shah T, Ramu V. A meta-analysis of mortality and major adverse cardiovascular and cerebrovascular events following transcatheter aortic valve implantation versus surgical aortic valve replacement for severe aortic stenosis. Am J Cardiol 2013;112:850–60.

[15] Cao C, Ang SC, Indraratna P, Manganas C, Bannon P, Black D *et al*. Systematic review and meta-analysis of transcatheter aortic valve implantation versus surgical aortic valve replacement for severe aortic stenosis. Ann Cardiothorac Surg 2013;2:10–23.

[16] Tu HT, Campbell BC, Meretoja A, Churilov L, Lees KR, Donnan GA *et al*. Pre-stroke $CHADS_2$ and CHA_2DS_2-VASc scores are useful in stratifying three-month outcomes in patients with and without atrial fibrillation. Cerebrovasc Dis 2013;36:273–80.

[17] Crandall MA, Horne BD, Day JD, Anderson JL, Muhlestein JB, Crandall BG *et al*. Atrial fibrillation significantly increases total mortality and stroke risk beyond that conveyed by the CHADS2 risk factors. Pacing Clin Electrophysiol 2009;32:981–6.

[18] Kim YD, Cha MJ, Kim J, Lee DH, Lee HS, Nam CM *et al*. Ischaemic cardiovascular mortality in patients with non-valvular atrial fibrillation according to $CHADS_2$ score. Thromb Haemost 2011;105:712–20.

[19] Leber AW, Kasel M, Ischinger T, Ebersberger UH, Antoni D, Schmidt M *et al*. Aortic valve calcium score as a predictor for outcome after TAVI using the CoreValve revalving system. Int J Cardiol 2013;166:652–7.

[20] Eggebrecht H, Schmermund A, Voigtländer T, Kahlert P, Erbel R, Mehta RH. Risk of stroke after transcatheter aortic valve implantation (TAVI): a meta-analysis of 10,037 published patients. EuroIntervention 2012;8:129–38.

[21] Nietlispach F, Wijesinghe N, Gurvitch R, Tay E, Carpenter JP, Burns C *et al*. An embolic deflection device for aortic valve interventions. JACC Cardiovasc Interv 2010;3:1133–8.

[22] Fairbairn TA, Mather AN, Bijsterveld P, Worthy G, Currie S, Goddard AJ *et al*. Diffusion-weighted MRI determined cerebral embolic infarction following transcatheter aortic valve implantation: assessment of predictive risk factors and the relationship to subsequent health status. Heart 2012;98:18–23.

[23] 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.

[24] Giordana F, D'Ascenzo F, Nijhoff F, Moretti C, D'Amico M, Biondi Zoccai G *et al*. Meta-analysis of predictors of all-cause mortality after transcatheter aortic valve implantation. Am J Cardiol 2014;114:1447–55.

[25] Conrotto F, D'Ascenzo F, Salizzoni S, Presbitero P, Agostoni P, Tamburino C *et al*. A gender based analysis of predictors of all cause death after transcatheter aortic valve implantation. Am J Cardiol 2014;114:1269–74.