Journal of the American College of Cardiology
© 2012 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 59, No. 2, 2012
ISSN 0735-1097/$36.00
doi:10.1016/j.jacc.2011.09.061

EXPEDITED PUBLICATIONS

Incidence, Predictive Factors, and Prognostic Value of New-Onset Atrial Fibrillation Following Transcatheter Aortic Valve Implantation

Ignacio J. Amat-Santos, MD, Josep Rodés-Cabau, MD, Marina Urena, MD, Robert DeLarochellière, MD, Daniel Doyle, MD, Rodrigo Bagur, MD, Jacques Villeneuve, MD, Mélanie Côté, MSc, Luis Nombela-Franco, MD, François Philippon, MD, Philippe Pibarot, DVM, PhD, Eric Dumont, MD

Quebec City, Quebec, Canada

Objectives This study sought to evaluate the incidence, predictive factors, and prognostic value of new-onset atrial fibrillation (NOAF) following transcatheter aortic valve implantation (TAVI).

Background Very few data exist on the occurrence of NOAF following TAVI.

Methods A total of 138 consecutive patients with no prior history of atrial fibrillation (AF) underwent TAVI with a balloon-expandable valve. Patients were on continuous electrocardiogram monitoring until hospital discharge, and NOAF was defined as any episode of AF lasting >30 s. All clinical, echocardiographic, procedural, and follow-up data were prospectively collected.

Results NOAF occurred in 44 patients (31.9%) at a median time of 48 h (interquartile range: 0 to 72 h) following TAVI. The predictive factors of NOAF were left atrial (LA) size (odds ratio [OR]: 1.21 for each increase in 1 mm/m^2, 95% confidence interval [CI]: 1.09 to 1.34, $p < 0.0001$) and transapical approach (OR: 4.08, 95% CI: 1.35 to 12.31, $p = 0.019$). At 30-day follow-up, NOAF was associated with a higher rate of stroke/systemic embolism (13.6% vs. 3.2%, $p = 0.021$, $p = 0.047$ after adjustment for baseline differences between groups), with no differences in mortality rate between groups (NOAF: 9.1%, no-NOAF: 6.4%, $p = 0.57$). At a median follow-up of 12 months (interquartile range: 5 to 20 months), a total of 27 patients (19.6%) had died, with no differences between the NOAF (15.9%) and no-NOAF (21.3%) groups, $p = 0.58$. The cumulative rate of stroke and stroke/systemic embolism at follow-up were 13.6% and 15.9%, respectively, in the NOAF group versus 3.2% in the no-NOAF group ($p = 0.039$, adjusted $p = 0.037$ for stroke; $p = 0.020$, adjusted $p = 0.023$ for stroke/systemic embolism).

Conclusions NOAF occurred in about one-third of the patients with no prior history of AF undergoing TAVI and its incidence was increased in patients with larger LA size and those undergoing transapical TAVI. NOAF was associated with a higher rate of stroke/systemic embolism, but not a higher mortality, at 30 days and at 1-year follow-up. (J Am Coll Cardiol 2012;59:178–88) © 2012 by the American College of Cardiology Foundation

Transcatheter aortic valve implantation (TAVI) has become an alternative treatment for patients with severe symptomatic aortic stenosis considered to be at very high or prohibitive operative risk (1–10). New-onset atrial fibrillation (NOAF) is a well-known complication of cardiovascular interventions, and its occurrence has been associated with a higher rate of periprocedural cerebrovascular events and cardiac mortality (11,12). However, very few data exist on the occurrence of NOAF following TAVI, and no studies to date have evaluated the predictive factors of this complication during transcatheter valve procedures. The potential role of NOAF in the occurrence of cardioembolic events following TAVI is also unknown. The occurrence of cerebrovascular events is probably the most worrisome complication associated with TAVI, with an incidence of about 4% (1–10), one of the highest ever reported in the field of interven-

See page 189

From the Quebec Heart & Lung Institute, Laval University, Quebec City, Quebec, Canada. Dr. Amat-Santos received support from the Institute of Heart Sciences (ICICOR, Clinical Hospital of Valladolid, Spain). Dr. Rodés-Cabau is a consultant for Edwards Lifesciences Inc. and St. Jude Medical. Dr. DeLarochellière is a consultant for St. Jude Medical. Drs. Doyle and Dumont are consultants for Edwards Lifesciences Inc. The other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received July 25, 2010; revised manuscript received August 24, 2011, accepted September 20, 2011.

tional cardiology. Although about one-third of cerebrovascular events occur during the TAVI procedure, >50% of them occur several days after TAVI (1), suggesting that mechanisms other than those directly related to the procedure may be involved. The objectives of this study were therefore to determine the incidence and predictive factors of NOAF in patients with no history of chronic/paroxysmal atrial fibrillation (AF) undergoing TAVI, and to evaluate the prognostic value of NOAF as a complication of TAVI, with special attention to cardioembolic events.

Methods

Study population and TAVI procedures. Between May 2007 and May 2011, a total of 195 consecutive patients with severe symptomatic aortic stenosis underwent TAVI with a balloon-expandable valve (Edwards SAPIEN, SAPIEN XT, Edwards Lifesciences, Irvine, California) at our institution. Of these, 57 patients with prior chronic or paroxysmal AF were excluded, leading to a final study population of 138 patients. Details about the TAVI procedure (transfemoral and transapical) have been extensively explained in previous studies (3). Selection of transapical approach was based on the following criteria: small diameter of the iliofemoral arteries (<8, <7, <6.5, and <6 mm for the 24-, 22-, 19-, and 18-F sheaths, respectively), significant peripheral vascular disease, severe calcification or tortuosity of both iliofemoral arteries, severely calcified or porcelain aorta, and horizontal ascending aorta. Patients received full-dose heparin (100 U/kg, adjusted for an activated clothing time >250 s) during the procedure, and aspirin (80 mg/day) + clopidogrel (75 mg/day) were administered following the procedure. All procedures were performed under a compassionate clinical program approved by Health Canada (Ottawa, Ontario, Canada), and all patients provided signed informed consent for the procedures. Clinical, echocardiographic, and procedural data were entered prospectively into a dedicated database. Left atrial size was defined as the anteroposterior diameter measured during systole in the parasternal long-axis view by M-mode echocardiography using the leading edge of the posterior aortic wall to the leading edge of the posterior atrial wall. All periprocedural complications were recorded and defined on the basis of the Valve Aortic Research Consortium criteria (13). Cerebrovascular events were classified as transient ischemic attack (TIA) or stroke, which in turn was also categorized in accordance to the Modified Rankin Scale (MRS) as major stroke if MRS ≥2 at 30 days, or minor stroke if MRS <2 at 30 days (13). All cerebrovascular events were evaluated by a neurologist and confirmed through neuroimaging techniques. Strokes were further classified as early/procedure, if a new neurological deficit was immediately apparent upon recovery from anesthesia or within 24 h of the procedure, and late/post-procedure, defined as those occurring >24 h after the intervention. Systemic embolism was defined as an abrupt vascular insufficiency associated with clinical or radiological evidence of arterial occlusion in the absence of other likely mechanisms (e.g., trauma, atherosclerosis, or instrumentation).

Abbreviations and Acronyms

AF = atrial fibrillation
CI = confidence interval
HR = hazard ratio
IQR = interquartile range
MRS = Modified Rankin Score
NOAF = new-onset atrial fibrillation
OR = odds ratio
ROC = receiver-operating characteristic
TAVI = transcatheter aortic valve implantation
TIA = transient ischemic attack

NOAF definition. Patients were on continuous electrocardiogram monitoring until hospital discharge, and NOAF was defined as any episode of AF lasting longer than 30 s (14,15). The timing and duration of the NOAF episode and the need for electrical or pharmacological cardioversion were recorded. The duration of the NOAF episode was classified as follows: <1 min, 1 min to 1 h, 1 to 12 h, 12 to 24 h, 24 to 48 h, or >48 h. NOAF was managed following the criteria of the latest reviewed guidelines of the American College of Cardiology/American Heart Association (15). Anticoagulation was started, unless contraindicated, immediately after the diagnosis of NOAF and continued for at least 1 month. In case of short episodes (<12 h) of AF, the potential risks/benefits of anticoagulation were evaluated in each patient, and the decision was finally made by the physician responsible for the patient. In patients with an epidural catheter for pain relief after transapical TAVI, anticoagulation was delayed 24 h after the removal of the catheter following the criteria of the American Association of Regional Anesthesia and Pain Medicine (16). Warfarin was used as anticoagulant therapy in all cases, with the objective of an international normalized ratio between 2 and 3. Intravenous heparin was administered until therapeutic anticoagulation levels were achieved.

Follow-up. The clinical follow-up was carried out through clinical visits or telephone contact and was available in 100% of the study population. Cardiovascular events were defined following the Valve Aortic Research Consortium criteria (13). The occurrence and timing of new episodes of AF was also recorded. Death at any time during the follow-up period was recorded and further classified as of cardiac or noncardiac origin.

Statistical analysis. Continuous variables are expressed as mean ± SD or median (25th to 75th interquartile range [IQR]), depending on variable distribution. Group comparisons were analyzed using Student *t* test or Wilcoxon rank sum test for continuous variables, and chi-square test or Fisher exact test for categorical variables. The variables associated with NOAF were determined by univariate analysis, and those variables with a p value <0.05 were entered in a logistic regression analysis to determine the independent predictors of NOAF. The univariate normality assumptions were verified with the Shapiro-Wilk test. The multivariate normality assumptions were verified with the Shapiro-Wilk test after a Cholesky factorization. Receiver-operating characteristic (ROC) curve analysis was per-

JACC Vol. 59, No. 2, 2012
January 10, 2012:178–88

Table 1 Baseline Characteristics of the Study Population (N = 138)

Baseline variables	
Age, yrs	79 ± 8
Male	54 (39.1)
BMI, kg/m^2	27 ± 5
Diabetes	52 (37.7)
Dyslipidemia	114 (82.6)
Hypertension	126 (91.3)
NYHA functional class	
I–II	23 (16.7)
III–IV	115 (83.3)
Coronary artery disease	90 (65.2)
Previous myocardial infarction	48 (34.8)
Previous PCI	55 (39.9)
Prior coronary artery bypass grafting	52 (37.7)
Cerebrovascular disease	31 (22.5)
Peripheral vascular disease	53 (38.4)
COPD	39 (28.3)
Creatinine, mg/dl	1.18 (0.88–1.61)
eGFR <60 ml/min	89 (64.5)
Logistic EuroSCORE	21.7 ± 15.7
STS-PROM score, %	7.4 ± 4.8
CHADS2 score	3 (3–4)
Severely calcified or porcelain aorta	42 (30.4)
Frailty	24 (17.4)
Severe pulmonary hypertension	13 (9.4)
Echocardiographic variables	
Mean aortic gradient, mm Hg	43 ± 17
Aortic valve area, cm^2	0.6 (0.5–0.7)
LVEF, %	55 ± 14
LVEF <40	23 (16.7)
Severe mitral regurgitation	4 (2.9)
Left ventricular mass, g/m^2	125.5 ± 36.4
LVEDD, mm	46.9 ± 7.9
Left atrial size, mm	44.7 ± 8.0
Left atrial size, indexed, mm/m^2	26.4 ± 5.4
Systolic pulmonary pressure, mm Hg	43.5 ± 11.9
Baseline treatment	
Aspirin	120 (86.9)
Clopidogrel	11 (7.9)
Warfarin	1 (0.7)
ACE inhibitors/ARA2	80 (57.9)
Diuretics	102 (73.9)
Beta-blockers	70 (50.7)
Statins	116 (84.1)
Amiodarone	0
Procedural variables and 30-day outcomes	
Approach	
Transfemoral	38 (27.5)
Transapical	100 (72.5)
Procedural success	129 (93.5)
Valve embolization	1 (0.7)
Need for a second valve	5 (3.6)
Need for hemodynamic support	4 (2.9)
Major vascular complications	13 (9.4)
Myocardial infarction	0
Cerebrovascular event	
Transient ischemic attack	0
Stroke	8 (5.8)
Minor	3 (2.2)
Major	5 (3.6)
Fatal	0
Death	10 (7.3)

Values are mean ± SD, n (%), or median (interquartile range).

ACE = angiotensin-converting enzyme; ARA2 = angiotensin II receptor antagonist; BMI = body mass index; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; STS-PROM = Society of Thoracic Surgeons predicted risk of mortality.

formed to discriminate power of the atrial size for the occurrence of NOAF. The maximum sum of sensitivity and specificity was used as the criterion to identify an optimal cutoff point in the ROC analysis. The association between NOAF and clinical outcomes (i.e., cardioembolic events and death) was analyzed with the use of univariate and multivariate logistic regression (30-day outcomes) or Cox proportional hazards (late outcomes) analyses. The multivariate models were adjusted for the baseline differences ($p < 0.05$ in the univariate analysis) between the NOAF and no-NOAF groups. The variables included in the models were prior coronary bypass grafting, severely calcified or porcelain aorta, left atrial size, and transapical approach. Late outcomes were also assessed by Kaplan-Meier estimates and compared using the log-rank test. The results were considered significant with p values <0.05. All analyses were conducted using the statistical package SAS version 9.2 (SAS Institute, Cary, North Carolina).

Results

The clinical, echocardiographic, and procedural characteristics of the study population are shown in Table 1. Procedural success and 30-day mortality rates were 93.5% and 7.3%, respectively. Eight patients (5.8%) had a stroke following the procedure, all of which were ischemic in etiology as evidenced by neuroimaging techniques. One more patient without prior significant peripheral artery disease who underwent transapical TAVI suffered acute left lower limb ischemia 2 days after the procedure secondary to an infrapopliteal arterial obstruction as diagnosed by Doppler ultrasonography. The initial management with anticoagulation therapy resolved the arterial occlusion, and no further intervention was required, which corroborated its thrombotic nature.

NOAF occurred in a total of 44 patients (31.9%) within 30 days following TAVI. The timing and duration of the episodes of NOAF are shown in Figures 1 and 2, respectively. NOAF occurred at a median time of 48 h (IQR: 0 to 72 h) following TAVI. Up to 40% of the NOAF episodes occurred either during (n = 16, 36.3%) or within the 24 h following the procedure (n = 2, 4.6%). A total of 10 arrhythmic episodes (22.7%) resolved spontaneously, lasting <12 h in all cases, and 34 episodes (77.3%) required

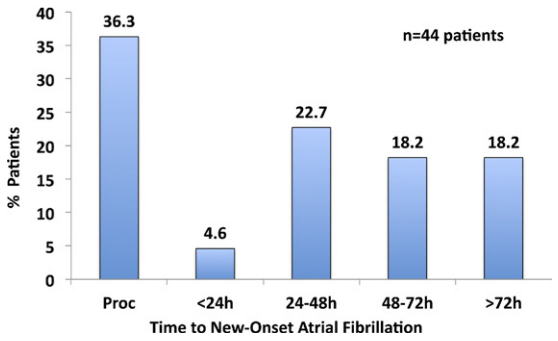

Figure 1 **Timing of NOAF Following TAVI**

Temporal distribution of the first episodes of atrial fibrillation with respect to the transcatheter aortic valve implantation (TAVI) procedure in the 44 patients with new-onset atrial fibrillation (NOAF).

pharmacological (intravenous amiodarone; n = 19, 43.2%) or electrical (n = 15, 34.1%) cardioversion. The cardioversion was effective in all but 1 patient, who remained in AF at hospital discharge. Anticoagulation (with intravenous heparin and warfarin) was initiated immediately after the diagnosis of NOAF in 34 of the 44 patients (77.3%) with NOAF. Anticoagulation treatment was delayed 24 h in 3 patients with epidural catheters to allow the safe removal of the catheter. In the other 7 patients, a decision to maintain antithrombotic treatment with aspirin and clopidogrel without anticoagulation was made due to the very short duration of the NOAF episode (<12 h in all of them) and an estimated high risk of bleeding with the addition of anticoagulation therapy. The length of hospital stay for the patients who experienced NOAF was 9 days (IQR: 7 to 14 days), which was significantly longer than that of the rest of the study population (6 days, IQR: 5 to 9 days, p =0.0004). At hospital discharge, the antithrombotic treatment for the 44 patients who presented with NOAF was as follows: aspirin alone (n = 2, 4.5%), aspirin + clopidogrel (n = 6, 13.6%), warfarin alone (n = 1, 2.3%), warfarin + aspirin (n = 24, 54.5%), and warfarin + aspirin + clopidogrel (11 patients, 25.0%). A total of 14 patients (31.8%) and 20 patients (45.5%) were on amiodarone or beta-blockers, respectively, at hospital discharge. Mean international normalized ratio level at hospital discharge was 2.6 ± 0.5 for the 36 patients under warfarin therapy, with 3 and 6 patients exhibiting international normalized ratio levels below 2 and above 3, respectively.

Predictive factors of NOAF. Baseline and procedural characteristics of the patients grouped according to the occurrence of NOAF are shown in Table 2. In the multivariate analysis, a larger atrial size (odds ratio [OR]: 1.21 for each increase in 1 mm/m^2, 95% confidence interval [CI]: 1.09 to 1.34, p < 0.0001) and transapical approach (OR: 4.08, 95% CI: 1.35 to 12.31, p = 0.019) were the 2 independent predictors of NOAF following the procedure. An atrial size ≥27 mm/m^2 as measured by echocardiography was identified as the cutoff point with the best sensitivity (67%) and specificity (61%) for the prediction of NOAF following TAVI within 30 days, with an area under the ROC curve of 0.71 (95% CI: 0.62 to 0.80, p = 0.0001) (Fig. 3). The incidence of NOAF in patients with an atrial size ≥27 mm/m^2 undergoing TAVI by transapical approach was 51% compared with 12% in patients with an atrial size <27 mm/m^2 undergoing TAVI by transfemoral approach.

Follow-up. The median follow-up for the study population was 12 months (IQR: 5 to 20 months). During the follow-up period, a total of 7 patients with NOAF (15.9%) had at least 1 more episode of AF compared with 2 patients (2.1%) in the group with no-NOAF at 30 days (p = 0.005). The Kaplan-Meier curves at 1-year follow-up showing freedom from new episodes of AF during the follow-up period are shown in Figure 4. A total of 17 patients (12.3%) died during the follow-up period: 4 (2.9%) from cardiac causes and 13 (9.4%) from noncardiac causes.

Cerebrovascular events, systemic embolism, and NOAF. The incidence of cerebrovascular events, systemic embolism, and death following TAVI grouped according to the occurrence of NOAF are shown in Table 3. The incidence of stroke at 30 days tended to be higher in the NOAF group (11.4%) compared with the no-NOAF group (3.2%, OR: 3.89, 95% CI: 0.89 to 17.08, p = 0.056, p = 0.068 after adjusting for baseline differences between groups), and the incidence of the combined endpoint of stroke and systemic embolism was higher in the NOAF group compared with the no-NOAF group (13.6% vs. 3.2%, OR: 4.79, 95% CI: 1.14 to 20.15, p = 0.021, p = 0.047 after adjusting for baseline differences between groups). During the follow-up period, 1 patient in the NOAF group had a stroke, and 1 patient in the no-NOAF group presented with a TIA, 22 and 4 months after the procedure, respectively. The cumulative incidence of stroke at follow-up was higher in the NOAF group compared with the no-NOAF group (13.6% vs. 3.2%, hazard ratio [HR]: 4.32, 95% CI: 1.08 to 17.28, p = 0.039, p = 0.037 after adjusting for baseline differences

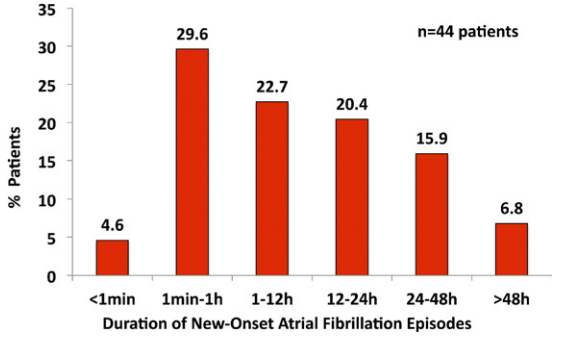

Figure 2 **Duration of NOAF Episodes**

Duration of the episodes of atrial fibrillation following TAVI.
NOAF = new-onset atrial fibrillation.

JACC Vol. 59, No. 2, 2012
January 10, 2012:178–88

Table 2 Clinical and Procedural Characteristics of the Patients According to the Occurrence of NOAF

Variables	NOAF		p Value
	Yes (n = 44)	No (n = 94)	
Baseline variables			
Age, yrs	79 ± 9	79 ± 8	0.81
Male	14 (31.8)	40 (42.6)	0.26
BMI, kg/m^2	26 ± 4	27 ± 5	0.20
Diabetes	15 (34.1)	37 (39.4)	0.58
Dyslipidemia	37 (84.1)	77 (81.9)	0.63
Hypertension	41 (93.2)	85 (90.4)	0.75
Coronary artery disease	25 (56.8)	65 (69.1)	0.18
Previous myocardial infarction	14 (31.8)	34 (36.2)	0.70
Previous PCI	14 (31.8)	41 (43.6)	0.20
Prior coronary artery bypass grafting	11 (25.0)	41 (43.6)	0.039
Cerebrovascular disease	8 (18.2)	23 (24.5)	0.51
Peripheral vascular disease	16 (36.4)	37 (39.4)	0.85
COPD	11 (25.0)	28 (29.8)	0.69
Creatinine, mg/dl	1.18 (0.96–1.58)	1.18 (0.86–1.65)	0.61
eGFR <60 ml/min	31 (70.5)	58 (61.7)	0.35
Logistic EuroSCORE	20.3 ± 19.5	22.3 ± 13.6	0.06
STS score, %	6.8 ± 5.0	7.6 ± 4.6	0.12
CHADS2 score	3 (3–4)	3 (3–4)	0.40
Severely calcified or porcelain aorta	19 (43.2)	23 (24.4)	0.03
Frailty	7 (15.9)	17 (18.1)	0.81
Severe pulmonary hypertension	5 (11.4)	8 (8.5)	0.75
Echocardiographic variables			
Mean aortic gradient, mm Hg	44.9 ± 17.5	42.3 ± 16.4	0.40
Aortic valve area, cm^2	0.60 (0.50–0.70)	0.64 (0.50–0.76)	0.26
LVEF, %	57 ± 13	53 ± 16	0.21
LVEF <40	4 (9.1)	19 (20.2)	0.14
Severe mitral regurgitation	2 (4.5)	2 (2.1)	0.59
Left ventricular mass, g/m^2	56.8 ± 12.2	53.8 ± 15.2	0.96
LVEDD, mm	45.7 ± 7.0	47.4 ± 8.2	0.25
Left atrial size, mm	49.7 ± 9.5	42.5 ± 6.0	<0.0001
Left atrial size, indexed, mm/m^2	29.3 ± 6.5	25.0 ± 4.3	0.0002
Systolic pulmonary pressure, mm Hg	42.4 ± 15.2	43.9 ± 10.3	0.58
Baseline treatment			
Aspirin	37 (84.1)	83 (88.3)	0.59
Clopidogrel	2 (4.5)	9 (9.6)	0.70
Warfarin	0	1 (1.1)	1.00
ACE inhibitors/ARA2	24 (54.5)	56 (59.6)	0.59
Diuretics	31 (70.5)	71 (75.5)	0.54
Beta-blockers	22 (50.0)	48 (51.1)	1.00
Statins	37 (84.1)	79 (84.0)	1.00
Amiodarone	0	0	—
Procedural variables			
Approach			
Transfemoral	6 (13.6)	32 (34.0)	0.014
Transapical	38 (86.4)	62 (65.9)	
Procedural success	42 (95.5)	87 (92.5)	0.72
Valve embolization	0	1 (1.1)	1.00
Need for a second valve	2 (4.5)	3 (3.2)	0.65
Need for hemodynamic support	2 (4.5)	2 (2.1)	0.59
Major vascular complications	2 (4.5)	11 (11.7)	0.23

Values are mean ± SD, n (%), or median (interquartile range).
NOAF = new-onset atrial fibrillation; other abbreviations as in Table 1.

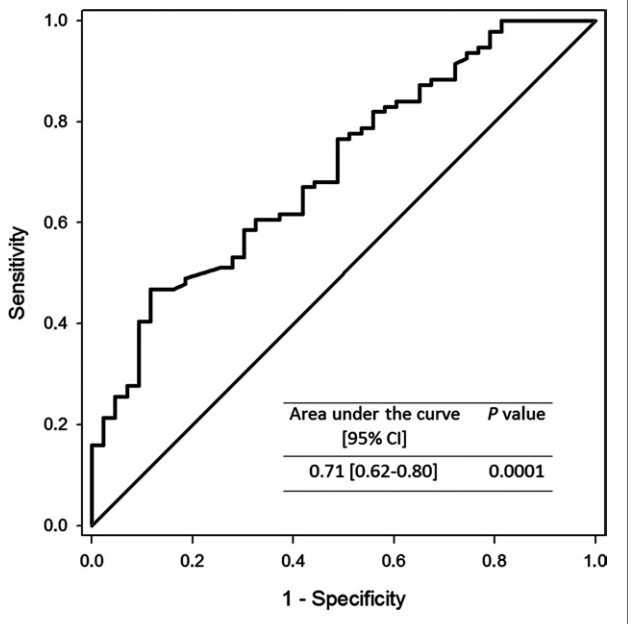

Figure 3 ROC Curve Analysis for Atrial Size

Receiver-operating characteristic (ROC) curve showing the sensitivity and specificity of atrial size ≥27 mm/m^2 for determining the occurrence of new-onset atrial fibrillation following transcatheter aortic valve implantation.

between groups). The cumulative incidence of the composite of stroke or systemic embolism was also higher in the NOAF group (15.9% vs. 3.2%; HR: 5.0, 95% CI: 1.29 to 19.35; p = 0.020, p = 0.023 after adjusting for baseline differences between groups). The main individual characteristics and the timing of the event in the 9 patients who had a stroke and the patient who developed a systemic embolism following the procedure are shown in Table 4. A total of 4 strokes occurred early (≤24 h post-TAVI) and 5 late (>24 h post-TAVI). One of the 4 early strokes (25%) occurred in a patient with NOAF, whereas all 5 late strokes occurred in patients with NOAF (100%, p = 0.048 compared with early strokes). Among the patients with NOAF, the stroke/systemic embolism rate at 30 days in those patients for whom anticoagulant therapy was not initiated immediately after the diagnosis of NOAF was 40% compared with 2.9% in those who received anticoagulant treatment immediately after the diagnosis of NOAF (p = 0.008). Figure 5 shows the distribution of NOAF patients according to the duration of the NOAF episode, anticoagulant treatment upon the diagnosis of NOAF, and cardioembolic events. There were no differences between the NOAF and no-NOAF groups regarding follow-up mortality (NOAF: 15.9%, no-NOAF: 21.3%, HR: 0.79, 95% CI: 0.33 to 1.86, p = 0.58, p = 0.56 after adjusting for baseline differences) and the combined endpoint of death and stroke (NOAF: 27.3%, no-NOAF: 24.5%, HR: 1.16, 95% CI: 0.58 to 2.35, p = 0.67, p = 0.76 after adjusting for baseline differences). The Kaplan-Meier curves at 1-year follow-up for freedom of death, stroke, cerebrovascular event (stroke and TIA), and the combined endpoint of death and stroke are shown in Figure 6.

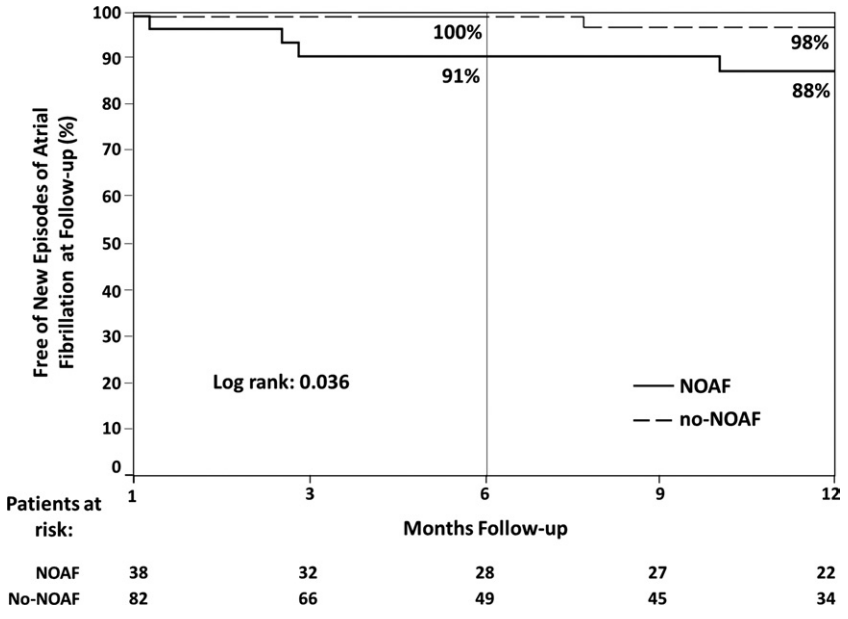

Figure 4 New Episodes of AF During the Follow-Up Period

Kaplan-Meier survival curves at 1-year follow-up showing the percent of patients free of new episodes of atrial fibrillation (AF) during the follow-up period (>30 days after the transcatheter aortic valve implantation procedure), according to the occurrence of new-onset atrial fibrillation (NOAF) within 30 days.

JACC Vol. 59, No. 2, 2012
January 10, 2012:178–88

Table 3 30-Day and Late Cardioembolic Events and Death According to the Occurrence of NOAF

Variables	NOAF Yes (n = 44)	NOAF No (n = 94)	OR/HR (95% CI)*	p Value
30-day outcomes				
Cerebrovascular event	5 (11.4)	3 (3.2)	3.89 (0.89–17.08)	0.056
TIA	0	0	—	—
Stroke	5 (11.4)	3 (3.2)	3.89 (0.89–17.08)	0.056
Minor	2 (4.5)	1 (1.1)	4.54 (0.40–51.49)	0.18
Major	3 (6.8)	2 (2.1)	3.45 (0.55–21.45)	0.16
Fatal	0	0	—	—
Systemic embolism	1 (2.3)	0	—	—
Stroke or systemic embolism	6 (13.6)	3 (3.2)	4.79 (1.14–20.15)	0.021
Death	4 (9.1)	6 (6.4)	1.47 (0.39–5.49)	0.57
Death or stroke	9 (20.5)	9 (9.6)	2.43 (0.89–6.63)	0.077
Follow-up (>30-day) outcomes				
Months follow-up	12 (12–24)	12 (5–23)	—	0.17
Cerebrovascular event	1 (2.3)	1 (1.1)	—	—
TIA	0	1 (1.1)	—	—
Stroke	1 (2.3)	0	—	—
Minor	1 (2.3)	0	—	—
Major	0	0	—	—
Fatal	0	0	—	—
Systemic embolism	0	0	—	—
Stroke or systemic embolism	1 (2.3)	0	—	—
Death	3 (6.8)	14 (14.9)	0.48 (0.14–1.67)	0.25
Cardiac	1 (2.3)	3 (3.2)	0.82 (0.08–7.97)	0.86
Noncardiac	2 (4.5)	11 (11.7)	0.39 (0.09–1.79)	0.23
Death or stroke	3 (6.8)	14 (14.9)	0.48 (0.14–1.67)	0.25
Cumulative outcomes				
Cerebrovascular event	6 (13.6)	4 (4.3)	4.27 (1.07–17.09)	0.040
TIA	0	1 (1.1)	—	—
Stroke	6 (13.6)	3 (3.2)	4.32 (1.08–17.28)	0.039
Minor	3 (6.8)	1 (1.1)	6.39 (0.66–61.42)	0.11
Major	3 (6.8)	2 (2.1)	3.21 (0.54–19.23)	0.20
Fatal	0	0	—	—
Systemic embolism	1 (2.3)	0	—	—
Stroke or systemic embolism	7 (15.9)	3 (3.2)	5.00 (1.29–19.35)	0.020
Death	7 (15.9)	20 (21.3)	0.79 (0.33–1.86)	0.58
Cardiac	5 (11.4)	9 (9.6)	1.28 (0.43–3.82)	0.66
Noncardiac	2 (4.5)	11 (11.7)	0.39 (0.086–1.79)	0.23
Death or stroke	12 (27.3)	23 (24.5)	1.16 (0.58–2.35)	0.67

Values are n (%) or median (25th to 75th interquartile range). *Values are expressed as odds ratios (OR) for 30-day outcomes and hazard ratios (HR) for follow-up (>30-day) outcomes and cumulative outcomes. †p Value refers to the significance of the logistic regression analysis (OR) or Cox proportional hazards regression (HR).

CI = confidence interval; NOAF = new-onset atrial fibrillation; TIA = transient ischemic attack.

Discussion

NOAF occurred in up to 31% of the patients with no prior chronic/paroxysmal AF undergoing TAVI with a balloon-expandable valve by transfemoral or transapical approach. A larger atrial size and transapical approach were the predictive factors of NOAF following TAVI. NOAF was associated with a higher rate of stroke or systemic embolism acutely and at midterm follow-up, but there were no differences in global and cardiac mortality between patients with and without NOAF.

Very few data exist on the occurrence of NOAF following TAVI. In fact, NOAF has not been included as a potential complication of TAVI in any of the recent large multicenter TAVI registries (3–10). The PARTNER (Placement of Aortic Transcatheter Valve) trial (high-risk cohort) included 347 patients who underwent TAVI with a balloon-expandable valve either by transfemoral or transapical approach (2). The incidence of NOAF within 30 days was 15% among the patients with no prior AF, which is about one-half the incidence reported in the present study. Unlike our study, most (two-thirds) of the patients included in the

Table 4 Individual Characteristics of the Patients With Stroke or Systemic Embolism Ordered According to the Time to Cardioembolic Event

Age (yrs)	Logistic EuroSCORE (%)	CHADS2 Score	Approach	NOAF (Yes/No)	NOAF: Time From TAVI	Duration of NOAF	Cardioversion (Pharmacological or Electrical)	Anticoagulation Initiated Upon Diagnosis of NOAF	Type of Cardioembolic Event	Stroke Severity: MRS (30 Day)	Cardioembolic Event: Time From TAVI
83	9.5	2	TA	No	—	—	—	—	Stroke	1	Procedure
78	12.87	5	TF	No	—	—	—	—	Stroke	2	Procedure
83	7.03	4	TF	No	—	—	—	—	Stroke	3	Procedure
79	7.54	4	TA	Yes	48 h	>24h	Yes (pharmacological)	Yes	Stroke	2	Procedure
78	35.05	3	TA	Yes	Procedure	<1h	Yes (electrical)	No	Stroke	4	36 h
74	5.46	2	TA	Yes	20 days	>24h	Yes (pharmacological)	Yes	Stroke	1	36 h
78	19.23	6	TA	Yes	36 h	<12h	Yes (pharmacological)	No	Stroke	5	48 h
71	28.19	4	TA	Yes	Procedure	<1h	Yes (electrical)	No	Systemic embolism	—	48 h
87	29.11	6	TA	Yes	48 h	<12h	Yes (electrical)	No	Stroke	1	25 days
85	46.59	3	TA	Yes	5 days	<24h	Yes (electrical)	Yes	Stroke	1	645 days*

*International normalized ratio of 2.2 at hospital admission for stroke.
MRS = Modified Rankin Score (degree of disability); NOAF = new-onset atrial fibrillation; TA = transapical; TAVI = transcatheter aortic valve implantation; TF = transfemoral.

PARTNER trial underwent the procedure by transfemoral approach, and the rate of NOAF was close to the rate of 16% observed in our cohort of transfemoral approach patients. Our patients also were continuously monitored until hospital discharge, and NOAF was defined as any episode of AF lasting >30 s (including those episodes during the TAVI procedure), with up to 5% of the AF episodes lasting <1 min and about one-third of them lasting <1 h. It is unclear whether prior studies were reporting such very short episodes of atrial arrhythmias, and this might explain the higher NOAF rate observed in our study. However, the 31% rate of NOAF observed in our study population would have decreased to 21% if patients with prior AF had not been excluded, and this incidence is still lower than the 33% to 49% rate reported following valvular cardiac surgery or the 36% to 63% rate reported following combined valvular and coronary artery bypass surgery (11). To the best of our knowledge, this is the first study evaluating the timing and duration of NOAF following TAVI. Interestingly, about one-third of the AF episodes occurred during the TAVI procedure, and up to 45% of them occurred within the 24 h following TAVI. Also, and in accordance with previous cardiac surgery studies (11), the occurrence of NOAF was associated with a prolongation of hospital stay (mean of 3 days), which in turn would be associated with a significant increase in hospital costs for the TAVI procedure.

Predictive factors of NOAF following TAVI. Previous studies have shown an association between severe aortic stenosis and atrial enlargement (17,18), but no prior data were available for the subset of patients considered at very high or prohibitive surgical risk. The mean atrial size in our study population was larger than that observed in other studies in the general population and in patients with systemic hypertension (19,20). Aortic stenosis is associated with diastolic dysfunction, which in turn might lead to a dilation of the left atrium (17,18,21). This atrial enlargement has been recognized as a predictive factor of NOAF following cardiac surgery as well as of AF recurrence in patients with paroxysmal AF (22,23). Atrial dilation is associated with fibrotic changes of the atrial wall and slow atrial conduction, which might increase the vulnerability for AF (24). The present study has shown that atrial enlargement is an independent predictor of NOAF in patients undergoing TAVI, with an indexed atrial size of 27 mm/m^2 exhibiting the best sensitivity and specificity for predicting the occurrence of NOAF. The transapical approach was also an independent predictor of NOAF following TAVI. Unlike the transfemoral approach, the transapical approach requires a left mini-thoracotomy and a direct puncture of the left ventricular apex. It is well known from thoracic surgery studies (excluding cardiac interventions) that thoracotomy is associated with NOAF in 10% to 20% of patients (25,26). The ventilatory restriction and the hyperadrenergic status generated by post-operative pain have been identified as factors associated with NOAF following noncardiac thoracic interventions (25,26). Particularly in the transapical

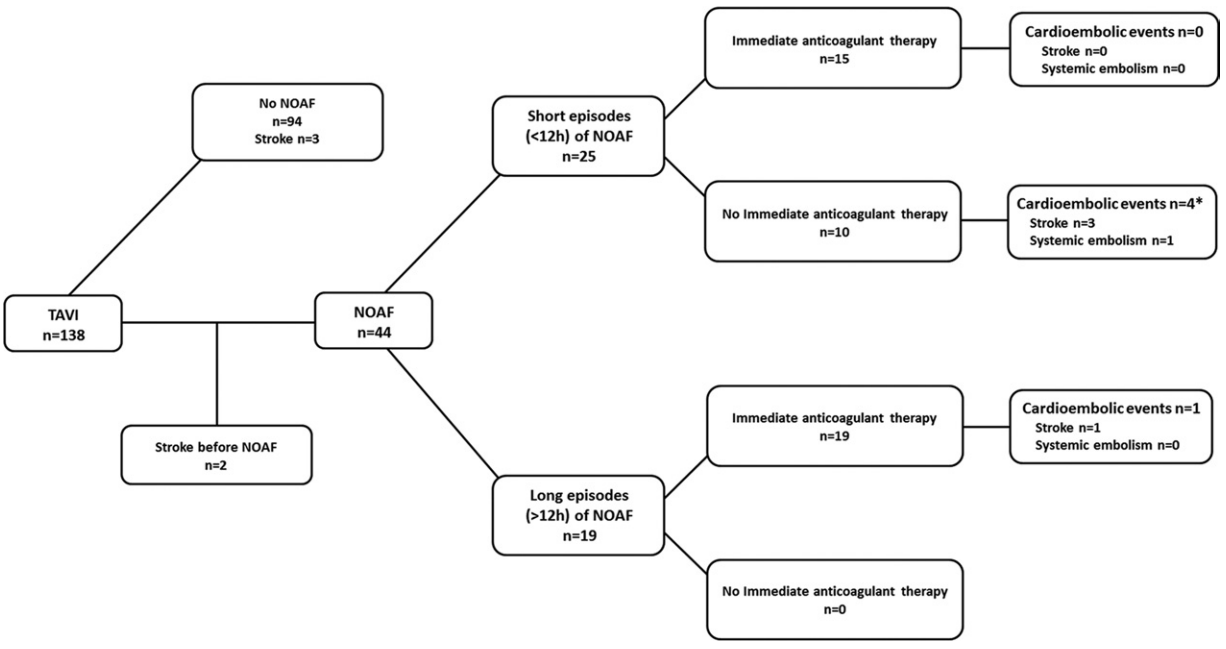

Figure 5 **Duration of NOAF, Anticoagulation Treatment, and Cardioembolic Events**

Patients with new-onset atrial fibrillation (NOAF) grouped according to the duration of the atrial fibrillation episode, anticoagulant treatment upon the diagnosis of NOAF, and cardioembolic events. TAVI = transcatheter aortic valve implantation. *p = 0.017 for differences between short episodes of NOAF groups (immediate [cardioembolic rate 0%] vs. no immediate [cardioembolic rate 40%] anticoagulation therapy).

approach, direct myocardial injury secondary to the apex puncture and surgical repair may also play a role in the occurrence of NOAF (27). Several preventive strategies such us amiodarone, beta-blockers, or angiotensin-converting enzyme inhibitors/angiotensin II receptor antagonists have shown their efficacy in preventing NOAF in systemic hypertension following cardiac surgery procedures (21,28). Knowing the predictive factors of NOAF following TAVI should allow us to select the patients at higher risk for NOAF preventive studies in the setting of TAVI.

NOAF and cardioembolic events following TAVI. The occurrence of cerebrovascular events has become the most worrisome complication associated with TAVI. The stroke rate of 5.8% at 30 days observed in the present study is consistent with the ~4% (0.6% to 5%) rate reported in recent multicenter registries (3–10) as well as with the 6.7% and 4.7% rates reported in the nonoperable and high-risk cohorts of the PARTNER trial, respectively (1,2). Transcranial Doppler studies have shown that cerebral emboli can occur any time during the TAVI procedure but seem to occur most frequently during valve prosthesis positioning and implantation, suggesting that the embolization of calcific particles from the native valve might be 1 of the main mechanisms for cerebrovascular events during TAVI procedures (29). Consistent with the results of the present study, however, it has been shown that only about one-half of the neurological events are directly related to the TAVI procedure, whereas the other half are late (≥24 h) events (1). Our results suggest that NOAF may be an important mechanism for the late neurological events after TAVI. All patients with a late (>24 h) stroke following TAVI had at least 1 episode of AF, compared with only 25% of the patients who complicated with a procedural stroke. Indeed, a plausible temporal relationship between NOAF and stroke was found in 4 of the 5 patients with late stroke and also in the patient who suffered a systemic embolism. Importantly, anticoagulation treatment was not optimal in 3 of the 5 patients with late stroke, either because the episode of AF was considered too short to start anticoagulant therapy (2 patients) or for safety reasons due to the presence of an epidural catheter for pain relief after a transapical procedure (1 patient). The risk of a cardioembolic event was as high as 40% in those patients who had NOAF and did not receive anticoagulant therapy, even if AF episodes were of short (<12 h) duration. These results strongly suggest that anticoagulation therapy should have been started immediately after diagnosis of the AF episode and continued for several months. No clear guidelines exist on anticoagulation therapy following short episodes of postoperative AF (15,30). However, patients undergoing TAVI nowadays are at high risk for thromboembolism in case of atrial arrhythmia (median CHADS2 score of the study population of 3), and a more aggressive antithrombotic treatment should probably be implemented in these cases. Also, although the guidelines recommend a 24-h delay for initiating anticoagulation in the presence of an epidural catheter (16), some

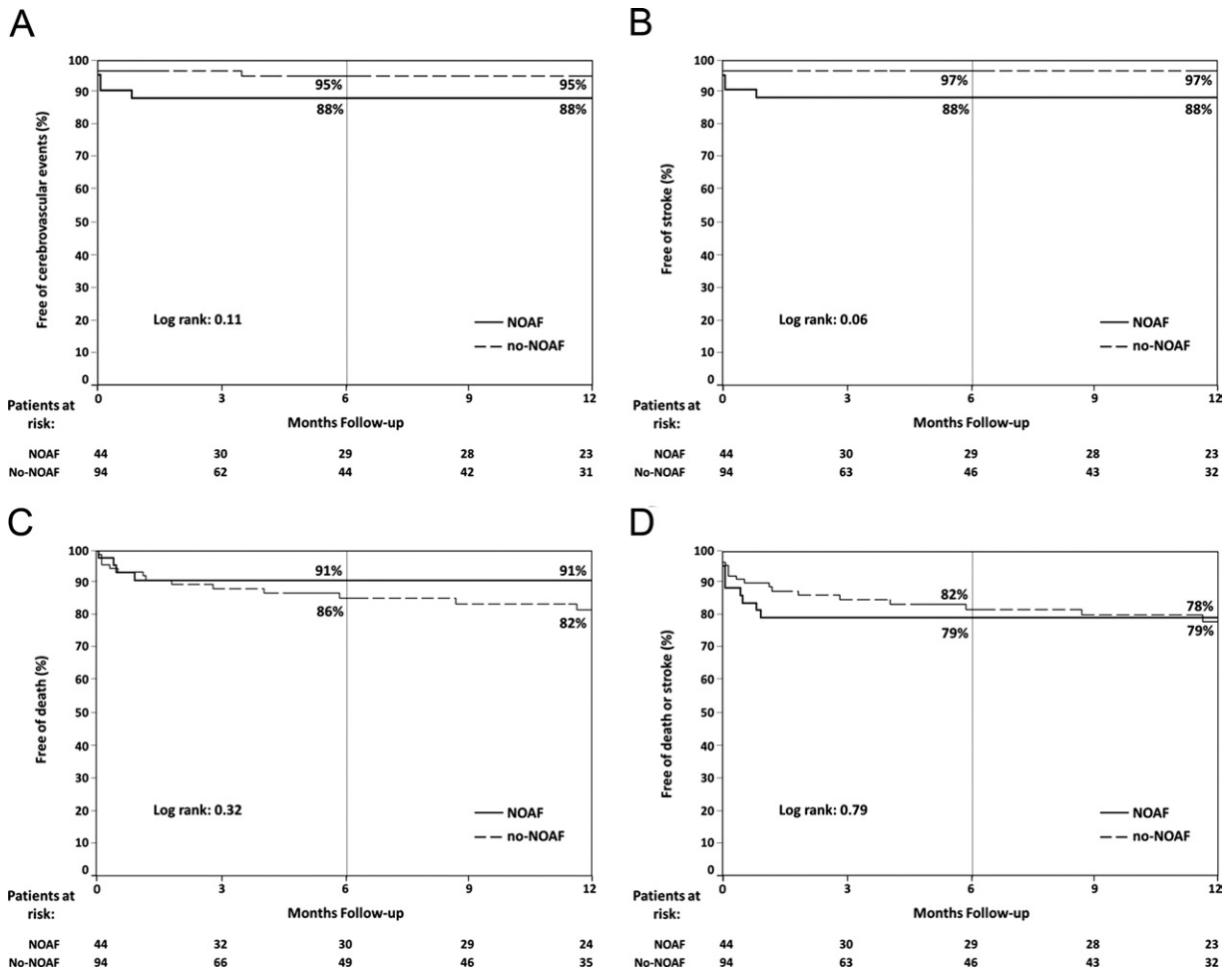

Figure 6 **Survival Curves at 1-Year Follow-Up**

Kaplan-Meier survival curves showing the percent of patients free of cerebrovascular event (transient ischemic attack or stroke) **(A)**, stroke **(B)**, death **(C)**, and death or stroke **(D)** at 1-year follow-up, according to the occurrence of new-onset atrial fibrillation (NOAF) following transcatheter aortic valve implantation.

recent studies have shown the safety of anticoagulant therapy in the presence of or when removing an epidural catheter (31,32). Finally, although double antiplatelet therapy with aspirin and clopidogrel has been empirically recommended following TAVI, future randomized studies will have to evaluate the more appropriate antithrombotic treatment following these procedures and the potential role for systematic anticoagulant therapy either with warfarin or direct thrombin inhibitors in this setting.

Study limitations. Although patients with known chronic or paroxysmal AF were excluded from this study, and all patients were in sinus rhythm at baseline, no electrocardiogram monitoring studies were performed before the TAVI procedures to evaluate the presence of silent episodes of AF. Although the occurrence of NOAF remained associated with a higher rate of cardioembolic events after adjustment for baseline differences between groups (NOAF vs. no-NOAF), the total number of events was relatively low, and this may have led to overfitting of the multivariate model. These results must, therefore, be confirmed by larger studies.

Conclusions

NOAF is a frequent complication associated with TAVI, with about half of the AF episodes occurring within 24 h and >80% within the first 3 days after the procedure. Larger atrial size and transapical approach were independent predictors of NOAF following TAVI. The mortality rates at 30 days and at follow-up were similar between patients with and without NOAF. However, NOAF was associated with a higher rate of cardioembolic events (stroke, systemic embolism) following the procedure, especially late (>24 h) events, and this provides important new insight into the mechanisms of cerebrovascular events following TAVI. Indeed, some cardioembolic events seemed to be related to the no initiation of anticoagulant therapy upon documentation of the AF episode, which further

emphasizes the clinical relevance of optimizing antithrombotic treatment in this high-risk subset of patients. It is also important to note that these results were obtained in a TAVI cohort made up predominantly of patients treated by transapical approach. Finally, future studies will have to determine the potential usefulness of implementing preventive strategies to reduce the occurrence of NOAF and its potentially devastating consequences in the setting of TAVI.

Acknowledgments

The authors want to thank Jacinthe Aubé, RN, and Nathalie Boudreau, research assistant, for their outstanding work on patients' follow-up.

Reprint requests and correspondence: Dr. Josep Rodés-Cabau, Quebec Heart & Lung Institute, Laval University, 2725 chemin Ste-Foy, G1V 4G5 Quebec City, Quebec, Canada. E-mail: josep.rodes@criucpq.ulaval.ca.

REFERENCES

1. Leon MB, Smith CR, Mack M, 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, et al. Transcatheter versus surgical aortic valve replacement in high-risk patients. N Engl J Med 2011; 364:2187–98.
3. Rodés-Cabau J, Webb JG, Cheung A, et al. Transcatheter aortic valve implantation for the treatment of severe symptomatic aortic stenosis in patients at very high or prohibitive surgical risk. Acute and late outcomes of the multicenter Canadian experience. J Am Coll Cardiol 2010;55:1080–90.
4. Thomas M, Schymik G, Walther T, et al. Thirty-day results of the SAPIEN aortic bioprosthesis European outcome (SOURCE) registry: a European registry of transcatheter aortic valve implantation using the Edwards SAPIEN valve. Circulation 2010;122:62–9.
5. Piazza N, Grube E, Gerckens U, et al. Procedural and 30-day outcomes following transcatheter aortic valve implantation using the third generation (18 Fr) CoreValve ReValving System: results from the multicentre, expanded evaluation registry 1-year following CE mark approval. EuroIntervention 2008;4:242–9.
6. Tamburino C, Capodanno D, Ramondo A, et al. Incidence and predictors of early and late mortality after transcatheter aortic valve implantation in 663 patients with severe aortic stenosis. Circulation 2011;123:229–308.
7. Zahn R, Gerckens U, Grube E, et al. Transcatheter aortic valve implantation: first results from a multi-centre real-world registry. Eur Heart J 2011;32:198–204.
8. Walther T, Kasimir MT, Doss M, et al. One-year follow-up results of the TRAVERCE trial: the initial feasibility study for trans-apical aortic-valve implantation. Eur J Cardiothorac Surg 2011;39:532–7.
9. Eltchaninoff H, Prat A, Gilard M, et al. Transcatheter aortic valve implantation: early results of the FRANCE (FRench Aortic National CoreValve and Edwards) registry. Eur Heart J 2011;32:191–7.
10. Bosmans JM, Kefer J, De Bruyne B, et al. Procedural, 30-day and one year outcome following CoreValve or Edwards transcatheter aortic valve implantation: results of the Belgian national registry. Interact Cardiovasc Thorac Surg 2011;12:762–7.
11. Kaireviciute D, Aidietiset A, Lip GY. Atrial fibrillation following cardiac surgery: clinical features and preventive strategies. Eur Heart J 2009;30: 410–25.
12. Almassi GH, Schowalter T, Nicolosi AC, et al. Atrial fibrillation after cardiac surgery: a major morbid event? Ann Surg 1997;226:501–11.
13. Leon MB, Piazza N, Nikolsky E, et al. Standardized endpoint definitions for transcatheter aortic valve implantation clinical trial. A consensus report from the Valve Academic Research Consortium. J Am Coll Cardiol 2011;57:253–69.
14. Murdock DK, Rengel LR, Schlund A, et al. Stroke and atrial fibrillation following cardiac surgery. WMJ 2003;102:26–30.
15. Wann LS, Curtis AB, Ellenbogen KA, et al. 2011 ACCF/AHA/HRS focused update on the management of patients with atrial fibrillation (updating the 2006 guideline): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2011;57:223–42.
16. Horlocker TT, Wedel DJ, Rowlingson JC, et al. Regional anesthesia in the patient receiving antithrombotic or thrombolytic therapy: American Society of Regional Anesthesia and Pain Medicine evidence-based guidelines. Reg Anesth Pain Med 2010;35:64–101.
17. Dahl JS, Videbaek L, Poulsen MK, et al. Noninvasive assessment of filling pressure and left atrial pressure overload in severe aortic valve stenosis: relation to ventricular remodeling and clinical outcome after aortic valve replacement. J Thorac Cardiovasc Surg 2011;142:e77–83.
18. Casaclang-Verzosa G, Malouf JF, Scott CG, Juracan EM, Nishimura RA, Pellikka PA. Does left atrial size predict mortality in asymptomatic patients with severe aortic stenosis? Echocardiography 2010;27:105–9.
19. Abhayaratna WP, Seward JB, Appleton CP, et al. Left atrial size: physiologic determinants and clinical applications. J Am Coll Cardiol 2006;47:2357–63.
20. Kizer JR, Bella JN, Palmieri V, et al. Left atrial diameter as an independent predictor of first clinical cardiovascular events in middle-aged and elderly adults: the Strong Heart Study (SHS). Am Heart J 2006;151:412–8.
21. Wachtell K, Gerdts E, Aurigemma GP, et al. In-treatment reduced left atrial diameter during antihypertensive treatment is associated with reduced new-onset atrial fibrillation in hypertensive patients with left ventricular hypertrophy. Blood Press 2010;19:169–75.
22. Osranek M, Fatema K, Qaddoura F, et al. Left atrial volume predicts the risk of atrial fibrillation after cardiac surgery: a prospective study. J Am Coll Cardiol 2006;48:779–86.
23. Zacà V, Galderisi M, Mondillo S, Focardi M, Ballo P, Guerrini F. Left atrial enlargement as a predictor of recurrences in lone parxysmal atrial fibrillation. Can J Cardiol 2007;23:869–72.
24. Ravelli F, Masè M, del Greco M, Marini M, Disertoni M. Acute atrial dilatation slows conduction and increases AF vulnerability in the human atrium. J Cardiovasc Electrophysiol 2011;22:394–401.
25. Onaitis M, D'Amico T, Zhao Y, O'Brien S, Harpole D. Risk factors for atrial fibrillation after lung cancer surgery: analysis of the society of Thoracic Surgeons General Thoracic Surgery Database. Ann Thorac Surg 2010;90:368–74.
26. Tisdale JE, Wroblewski HA, Kesler KA, et al. Prophylaxis of atrial fibrillation after noncardiac thoracic surgery. Semin Thorac Cardiovasc Surg 2010;22:310–20.
27. Rodés-Cabau J, Gutiérrez M, Bagur R, et al. Incidence, predictive factors, and prognostic value of myocardial injury following uncomplicated transcatheter aortic valve implantation. J Am Coll Cardiol 2011;57:1988–99.
28. Halonen J, Loponen P, Järvinen O, et al. Metoprolol versus amiodarone in the prevention of atrial fibrillation after cardiac surgery: a randomized trial. Ann Intern Med 2010;153:703–9.
29. Kahlert P, Doettger P, Mori K, et al. Cerebral embolization during transcatheter aortic valve implantation (TAVI): a transcranial Doppler study [abstr]. Circulation 2010;122:e525–5.
30. Mitchell LB, CCS Atrial Fibrillation Guidelines Committee. Canadian Cardiovascular Society atrial fibrillation guidelines 2010: prevention and treatment of atrial fibrillation following cardiac surgery. Can J Cardiol 2011;27:91–7.
31. Green L, Machin SJ. Managing anticoagulated patients during neuraxial anaesthesia. Br J Haematol 2010;149:195–208.
32. Liu SS, Buvanendran A, Viscusi ER, et al. Uncomplicated removal of epidural catheters in 4365 patients with international normalized ratio greater than 1.4 during initiation of warfarin therapy. Reg Anesth Pain Med 2011;36:231–5.

Key Words: atrial fibrillation ■ stroke ■ transapical ■ transcatheter aortic valve implantation ■ transcatheter aortic valve replacement ■ transfemoral.