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Prevalence and Impact of Atrial Fibrillation in Patients With Severe Aortic Stenosis Undergoing Transcatheter Aortic Valve Replacement

An Analysis From the SOURCE XT Prospective Multicenter Registry

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CME Objective for This Article: 1) Appraise the prevalence of pre-existing atrial fibrillation and new onset atrial fibrillation in patients undergoing transcatheter aortic valve replacement. 2) Compare the rates of new onset atrial fibrillation in transfemoral versus non transfemoral access routes after transcatheter aortic valve replacements. 3) Compare major adverse cardiovascular event rates in patients with new onset atrial fibrillation versus patients with pre-existing atrial fibrillation.

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ABSTRACT

OBJECTIVES The aims of this study were to assess the epidemiology of atrial fibrillation (AF) in patients treated with transcatheter aortic valve replacement (TAVR) and included in the large prospective SOURCE XT (SAPIEN XT Aortic Bioprosthesis Multi-Region Outcome Registry) study and to evaluate their outcomes according to the presence of pre-existing or new-onset AF (NOAF) (defined as AF occurring within 30 days after TAVR).

BACKGROUND Data on the epidemiology and clinical impact of AF in patients undergoing TAVR are scant and limited to small retrospective studies.

METHODS The SOURCE XT study is a multicenter, prospective registry of consecutive patients treated with the SAPIEN XT valve at 99 sites in 17 countries. Follow-up was scheduled at discharge, 1 month, 1 year, and yearly thereafter. Patients (n = 2,706) were categorized according to the presence of pre-existing or NOAF.

RESULTS The prevalence of pre-existing AF was 35.6%, whereas NOAF occurred in 7.2% of patients. Both pre-existing AF and NOAF correlated with worse clinical outcomes compared with patients in sinus rhythm, including all-cause death, cardiac death, and bleeding events. NOAF was associated with higher rates of stroke at 2 years compared with sinus rhythm. Independent predictors of NOAF were age (hazard ratio: 1.1), New York Heart Association class III or IV (hazard ratio: 1.9), nontransfemoral access route (hazard ratio: 3), and balloon post-dilation (odds ratio: 1.6). No interaction was observed between any degree of post-implantation paravalvular leak and NOAF.

CONCLUSIONS In the large dataset of the SOURCE XT registry, the presence of either pre-existing or NOAF increased all-cause and cardiac mortality and bleeding events. NOAF was associated with increased stroke rates at long-term follow-up. (J Am Coll Cardiol Intv 2016;9:937–46)

Transcatheter aortic valve replacement (TAVR) is an established treatment for patients with aortic valve stenosis who are inoperable or at high risk for surgery (1,2). A substantial proportion of patients who are scheduled for TAVR are diagnosed with paroxysmal or permanent atrial fibrillation (AF) at the time of the screening for eligibility for TAVR (3). Moreover, new-onset AF (NOAF) is a frequent finding in the post-operative period after TAVR procedures (4). AF is a well-established predictor of adverse outcomes in patients with aortic stenosis, and several previous studies demonstrated increased risk for mortality related to AF in patients undergoing open-chest valve surgery (5–7). However, data on the prevalence and impact of pre-existing AF or NOAF in the setting of TAVR are scant and limited to small retrospective studies that have specifically focused on this issue (8–11). In the present study, we sought to evaluate the epidemiology, predictors, and prognostic implications of AF, either pre-existing or new onset, in TAVR patients using the large dataset of the SOURCE XT (SAPIEN XT Aortic Bioprosthesis Multi-Region Outcome Registry) prospective registry (12).

SEE PAGE 947

METHODS

REGISTRY. The SOURCE XT study (NCT01238497) is a multination, multicenter, prospective, observational registry of consecutively enrolled patients. Data on all patients consecutively treated with the commercially available SAPIEN XT valve (Edwards Lifesciences, Irvine, California) at 99 sites in 17 countries were used for this analysis. Patients treated with other valves were not included. One site, which enrolled 6 patients, was excluded for noncompliance with

regulatory requirements. Additionally, 9 patients from other participating sites were excluded for not providing informed consent forms. From a total of 2,706 consented patients enrolled between July 2010 and November 2011, no procedure was attempted in 18 patients. Therefore, 2,688 patients remained in the final cohort and were included in this analysis. Patient data were collected at discharge, 30 days, 12 months, and 24 months post-implantation. This study complied with the Declaration of Helsinki, and the local regulatory authorities approved the research protocol at each site. Informed consent was obtained from all subjects (or their guardians).

DEVICES AND PROCEDURE. The SAPIEN XT valve is composed of a nickel-cobalt chromium stent frame, a trileaflet bovine pericardial tissue valve, and a polyethylene-terephthalate fabric skirt. The valve was available in 23- and 26-mm sizes for all delivery approaches. The 29-mm valve size was available for the transapical approach only. The NovaFlex delivery system, which includes an integrated distal tip and has a low-crossing profile, was used for the transfemoral approach with 18-F (23-mm valve) or 19-F (26-mm valve) introducer sheaths. The Ascendra delivery system was used for transapical access.

PATIENT SELECTION. High-surgical-risk patients with severe symptomatic aortic stenosis were deemed eligible for the procedure. Logistic European System for Cardiac Operative Risk Evaluation score was used as a general tool for surgical risk assessment. However, the local heart team, considering all underlying conditions, made the final decision. Examinations were based on standards of care for TAVR at each participating site. Annular diameter was measured by computed tomography and/or transthoracic and/or transesophageal echocardiography; however, only transthoracic echocardiographic data were required.

DATA COLLECTION. All data were entered in the electronic data capturing system and monitored. An independent clinical events committee adjudicated all adverse events, according to the Valve Academic Research Consortium criteria (13).

STUDY DEFINITIONS. NOAF was defined as any episode of AF occurring within 30 days after TAVR in a patient with no previous known AF, lasting long enough to be recorded on a 12-lead electrocardiogram or at least 30 s on a rhythm strip (8,14,15). All study endpoints were defined according to Valve Academic Research Consortium definitions (13). The main outcome measures in the SOURCE XT registry were all-cause death, cardiac death, and stroke. Secondary measures included major vascular complications, major and life-threatening bleeding episodes, acute kidney injury, permanent pacemaker insertion, procedural and device-related complications, functional status, and echocardiographic assessment of valve and heart function. No echocardiography core laboratory was used. Therefore, all echocardiographic data were site reported. Procedural success was defined as 1 valve implanted at the intended site in 1 attempted procedure without procedure-related death within 48 h of implantation. Device success was defined further as a successfully delivered valve with a final gradient ≤20 mm Hg and no moderate or severe aortic regurgitation at discharge.

STATISTICAL ANALYSES. Continuous variables are presented as mean ± SD, and comparisons were made with 2-sample Student *t* tests. Categorical data are presented as percentages, and comparisons between groups were done using Fisher exact tests or chi-square tests. Paired Student *t* tests and McNemar tests were used to perform paired comparisons of continuous and categorical variables. The log-rank test was used to compare survival curves for time-to-event variables, which were constructed with the use of Kaplan-Meier estimates. An analysis was made to consider a site effect in the all-cause mortality analysis by use of the Wei-Lin-Weissfeld model. Predictors of adverse outcomes and of AF were determined using univariate Cox proportional hazards regression with baseline variables and NOAF as covariates. A multivariate model with a stepwise procedure was then used to test all independent predictors with p values <0.10. The Cox proportional hazards assumption of the final mortality model was tested using the Wei-Lin-Yang method. Analyses were performed with SAS version 9.3 (SAS Institute, Cary, North Carolina).

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

HR = hazard ratio

NOAF = new-onset atrial fibrillation

TAVR = transcatheter aortic valve replacement

RESULTS

Among 2,706 consecutive patients with aortic stenosis enrolled in the SOURCE XT registry (**Figure 1**), 2,688 patients underwent TAVR via transfemoral (n = 1,685 [62.7%]), transapical (n = 894 [33.3%]), direct transaortic (n = 101 [3.8%]), or trans-subclavian (n = 8 [0.3%]) access routes. Follow-up was complete in 99% of patients at 1 year and in 86% at 2 years. Among 1,925 patients with complete heart rhythm data at baseline and follow-up, the observed prevalence of pre-existing AF (either paroxysmal or permanent) was 35.6%. A significantly higher prevalence of pre-existing AF was observed in patients treated using the transapical approach compared with those treated using the transfemoral approach (41.8% and 32.7%, respectively; p < 0.01). NOAF was observed in

7.2% of patients following TAVR. For subsequent analyses, 3 study groups were considered: patients in sinus rhythm up to 30 days after TAVR and without any history of AF (n = 1,102), patients with pre-existing AF (n = 685), and patients with NOAF (n = 138). The baseline characteristics and procedural data of these groups are shown in **Tables 1 and 2**. Notably, patients with pre-existing AF had the highest surgical risk compared with the other groups. Related to procedural characteristics, the NOAF group had higher rates of transapical access, use of the largest prosthetic valve size (29 mm, available for the transapical access only), general anesthesia, balloon pre- or post-dilation, technical success, and device success compared with both other study groups.

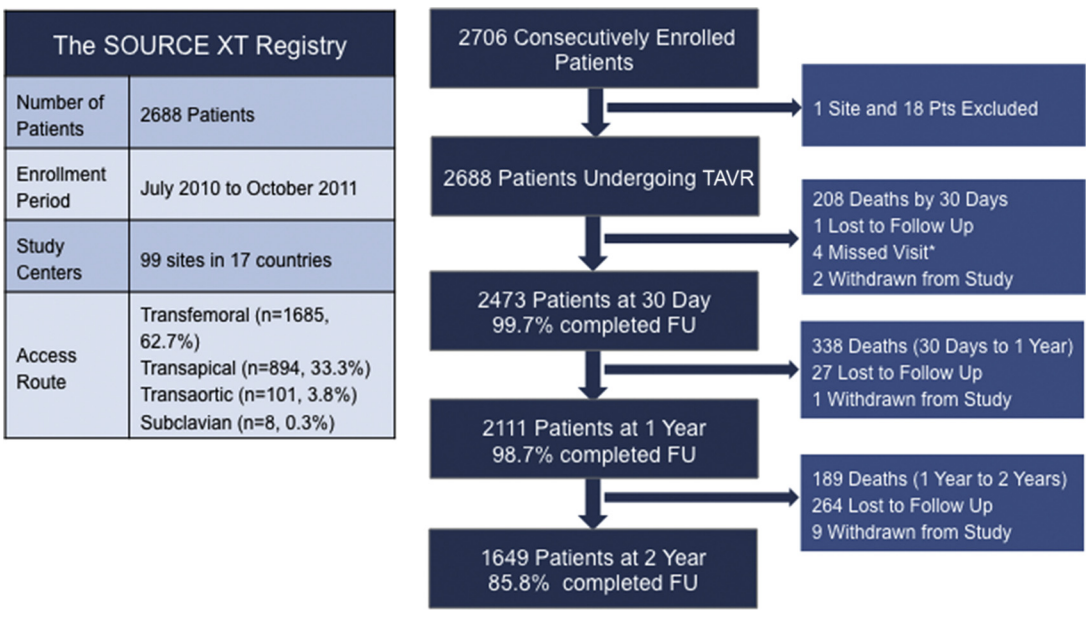
The event-free survival curves at 1 year of patients treated by TAVR according to the presence of AF are shown in **Figure 2**. Overall, patients with AF (either pre-existing or new onset) had worse outcomes compared with those in sinus rhythm in terms of all-cause mortality and of the combination of all-cause mortality and stroke. These results were not affected by site variability. Among patients with AF, NOAF trended toward an association with increased all-cause mortality and combined all-cause mortality and stroke compared with the pre-existing AF group.

Table 3 reports combined and single adverse event rates at 1 year for each study group. Higher rates of both all-cause mortality and cardiac death were observed in patients with AF compared with the sinus rhythm group. Also, a numerically higher rate of all-cause and cardiac mortality was observed in the NOAF group compared with the pre-existing AF group.

Overall, patients with AF showed also higher rates of bleeding, renal impairment, and rehospitalization compared with those in sinus rhythm. Patients with NOAF had a higher incidence of bleeding and renal impairment compared with the pre-existing AF group. Cerebrovascular event rates did not differ among groups. Among 194 adjudicated strokes, 51.0% (n = 99) occurred more than 30 days after TAVR. The time course of stroke events after the index procedure is shown in the Online Appendix.

Consistent with 1-year results, at 2-year follow-up, patients with AF had worse outcomes compared with the sinus rhythm group in terms of all-cause and cardiac mortality, bleeding (both major and minor), and rehospitalization. Outcomes and event-free survival curves at 2-year follow-up are detailed in the Online Appendix. At 2 years, only the NOAF group showed a significantly higher stroke rate compared with the sinus rhythm group (6.6% vs. 11.8%,

FIGURE 1 Flow of Patients in the SAPIEN XT Aortic Bioprosthesis Multi-Region Outcome Registry



Among 2,706 patients (Pts) enrolled between July 2010 and October 2011, 62.7% underwent transfemoral transcatheter aortic valve replacement (TAVR) and 33.3% underwent transapical TAVR. Of the total cohort, 98.7% of patients had study follow-up (FU) available at 1 year and 85.8% at 2 years. *4 patients who missed the 30-day visit were assessed at the 1-year follow-up.

p = 0.02). A detailed description of all cerebrovascular events at all follow-up intervals is provided in the Online Appendix. Of note, 90.6% of surviving patients in the NOAF group (n = 125) were found to have AF at 30-day follow-up, while this rate increased to 100% both at 1-year and 2-year follow-up visits.

PREDICTORS OF ADVERSE OUTCOMES. By multivariate analysis, both NOAF (hazard ratio [HR]: 1.96) and pre-existing AF (HR: 1.55) were independent predictors of increased mortality at 1 year. All significant predictors for 1-year mortality are reported in Table 4. Independent predictors of stroke at 1 year were a history of stroke (HR: 2.08) and the presence of coronary artery disease. AF was not an independent predictor of stroke, either at 30 days or 1 year, or of death and stroke at 1 year (see the Online Appendix). No significant interaction was observed between TAVR access site (transapical or transfemoral) and pre-existing AF or NOAF in terms of all-cause death, cardiac death, stroke, or the combination of all-cause death and stroke.

PREDICTORS OF AF. Predictors of pre-existing AF and NOAF were different. Independent predictors of NOAF were age (HR: 1.07; p = 0.0001), New York Heart Association class III or IV (HR: 1.9; p = 0.02), nontransfemoral access route (HR: 2.9; p < 0.0001), and balloon post-dilation of the prosthetic valve (HR: 1.6; p = 0.03). No interaction was observed between the degree of post-implantation paravalvular leak and NOAF. Predictors of pre-existing AF were the presence of moderate to severe mitral regurgitation (HR: 1.42; 95% confidence interval: 1.1 to 1.9; p = 0.01), moderate to severe tricuspid regurgitation (HR: 2.33; 95% confidence interval: 1.7 to 3.1; p < 0.0001), and pulmonary hypertension (HR: 1.58; 95% confidence interval: 1.23 to 2.2; p = 0.0001).

TABLE 1 Baseline Characteristics According to the Presence of Pre-Existing or New-Onset Atrial Fibrillation

	Pre-Existing AF (n = 685)	NOAF (n = 138)	Sinus Rhythm (n = 1,102)	p Value
Age (yrs)	81.6 ± 5.8	82.8 ± 6.0	81.0 ± 6.5	0.002
Women	387 (56.5%)	79 (57.2%)	664 (60.3%)	0.27
BMI (kg/m^2)	26.7 ± 5.0	27.0 ± 5.2	26.7 ± 4.8	0.78
Logistic EuroSCORE (%)	22.4 ± 13.4	21.6 ± 12.4	18.9 ± 11.3	<0.0001
STS score	8.5 ± 6.7	7.6 ± 5.1	7.3 ± 6.0	0.001
NYHA functional class		0.16		
I/II	134 (19.6%)	23 (16.9%)	259 (23.6%)	
III/IV	550 (80.4%)	113 (83.1%)	838 (76.4%)	
History of syncope	83 (12.1%)	18 (13.0%)	161 (14.6%)	0.31
History of angina (CCS 1-4)	316 (46.7%)	55 (40.1%)	475 (43.5%)	0.34
Congestive heart failure	480 (70.1%)	83 (60.1%)	631 (57.3%)	<0.0001
Myocardial infarction	104 (15.2%)	23 (16.7%)	152 (13.8%)	0.54
Hyperlipidemia/hypercholesterolemia	334 (48.8%)	77 (55.8%)	653 (59.3%)	<0.0001
Hypertension	550 (80.3%)	121 (87.7%)	904 (82.0%)	0.12
Smoker (current or previous)	168 (24.6%)	36 (26.1%)	259 (23.5%)	0.74
Previous pacemaker/ICD	102 (14.9%)	24 (17.4%)	50 (4.5%)	<0.0001
Peripheral vascular disease	151 (22.1%)	29 (21.0%)	224 (20.3%)	0.67
Porcelain aorta	38 (5.6%)	4 (2.9%)	75 (6.8%)	0.16
Endocarditis	11 (1.6%)	1 (0.7%)	11 (1.0%)	0.45
Diabetes	219 (32.0%)	37 (26.8%)	289 (26.2%)	0.02
Stroke	71 (10.4%)	12 (8.7%)	83 (7.5%)	0.11
TIA	29 (4.2%)	9 (6.5%)	46 (4.2%)	0.44
Previous PCI	198 (28.9%)	45 (32.6%)	332 (30.1%)	0.65
Previous CABG	106 (15.5%)	18 (13.0%)	164 (14.9%)	0.76
Previous peripheral vascular intervention	17 (2.5%)	3 (2.2%)	19 (1.7%)	0.53
Previous thoracic aorta surgery	5 (0.7%)	0 (0.0%)	2 (0.2%)	0.24
Aortic regurgitation (moderate/severe)	111 (17.3%)	27 (20.3%)	160 (15.4%)	0.27
Mitral regurgitation (moderate/severe)	184 (27.3%)	30 (21.9%)	188 (17.4%)	<0.0001
Pulmonary hypertension	230 (33.6%)	33 (23.9%)	218 (19.8%)	<0.0001
COPD	156 (22.8%)	28 (20.3%)	221 (20.1%)	0.37
CNS disorder	14 (2.0%)	4 (2.9%)	45 (4.1%)	0.07
Dementia	10 (1.5%)	6 (4.3%)	20 (1.8%)	0.08
Severe renal impairment (eGFR <30 ml/min) or dialysis	214 (31.3%)	47 (34.1%)	257 (23.3%)	0.0002
Severe liver disease	18 (2.6%)	1 (0.7%)	37 (3.4%)	0.23
Chest deformities	4 (0.6%)	1 (0.7%)	12 (1.1%)	0.54
Malignancy	109 (15.9%)	25 (18.1%)	193 (17.5%)	0.63
AV block (any)	24 (3.5%)	23 (16.8%)	150 (13.6%)	<0.0001
Left bundle branch block (complete)	46/685 (6.7%)	9/138 (6.5%)	102 (9.3%)	0.12
Right bundle branch block (complete)	58/685 (8.5%)	8/138 (5.8%)	58 (5.3%)	0.02

Values are mean ± SD, n (%), or n/N (%).

AF = atrial fibrillation; AV = atrioventricular; BMI = body mass index; CABG = coronary artery bypass grafting; CCS = Canadian Cardiovascular Society; CNS = central nervous system; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; EuroSCORE = European System for Cardiac Operative Risk Evaluation; ICD = implantable cardioverter-defibrillator; NOAF = new-onset atrial fibrillation; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; STS = Society of Thoracic Surgeons; TIA = transient ischemic attack.

DISCUSSION

The main findings of the present analysis in real-world TAVR patients treated with balloon-expandable prosthetic valves and enrolled in the SOURCE XT registry are as follows. First, AF was a frequent finding, present in more than 40% of patients. The prevalence rates of pre-existing AF and NOAF were 35.6% and 7.2%, respectively. Second, both pre-existing AF and NOAF correlated with worse clinical outcomes compared with sinus rhythm, including all-cause death, cardiac death, and bleeding events. Third, only patients with NOAF had a higher rate of stroke at long-term (2-year) follow-up compared with the sinus rhythm group. Last, predictors of NOAF were different from those of pre-existing AF and included procedural variables such as nontransfemoral access route and balloon post-dilation. Specifically, patients treated using nontransfemoral approaches had a 3-fold greater risk for NOAF compared with the transfemoral group.

AF is the most common sustained arrhythmia in the general population and is characterized by an increased prevalence and incidence worldwide (16).

TABLE 2 Procedural Characteristics According to the Presence of Pre-Existing or New-Onset Atrial Fibrillation

	Baseline AF (n = 685)	NOAF (n = 138)	Sinus Rhythm (n = 1,102)	p Value
Implantation access route				<0.0001
Transapical	271 (39.6%)	77 (55.8%)	300 (27.2%)	
Transfemoral	395 (57.7%)	54 (39.1%)	760 (69.0%)	
Subclavian	1 (0.1%)	0 (0.0%)	6 (0.5%)	
Transaortic	18 (2.6%)	7 (5.1%)	36 (3.3%)	
Bioprosthetic valve size (mm)				
23	267 (39.3%)	52 (37.7%)	522 (47.5%)	<0.0001
26	339 (49.9%)	59 (42.8%)	502 (45.7%)	
29	74 (10.9%)	27 (19.6%)	75 (6.8%)	
Percentage valve oversizing*	13.9 ± 8.3	13.3 ± 9.3	13.2 ± 8.5	0.28
Type of anesthesia				
General	492 (76.3%)	107 (84.9%)	712 (70.1%)	0.0003
Conscious sedation	153 (23.7%)	19 (15.1%)	303 (29.9%)	
Total procedure time (min)	89.2 ± 55.2	80.6 ± 49.9	80.4 ± 51.1	0.002
Volume of contrast used (ml)	129.3 ± 96.1	125.3 ± 92.0	124.1 ± 100.2	0.55
Fluoroscopy time (min)	12.5 ± 17.8	9.1 ± 8.4	12.5 ± 24.4	0.2
Pre-implantation BAV	654 (95.5%)	136 (99.3%)	1,070 (97.2%)	0.045
BAV balloon size (mm)				
18	4 (0.7%)	0 (0.0%)	7 (0.7%)	0.75
20	353 (58.5%)	81 (62.8%)	604 (60.3%)	
23	225 (37.3%)	41 (31.8%)	355 (35.4%)	
25	21 (3.5%)	7 (5.4%)	36 (3.6%)	
Number of balloon inflations for BAV				
1	559 (88.6%)	124 (91.9%)	890 (85.7%)	0.18
≥2	67 (10.6%)	11 (8.1%)	138 (13.3%)	
Balloon dilations after valve deployment				
None	512 (75.5%)	99 (71.7%)	903 (82.3%)	0.001
1	154 (22.7%)	36 (26.1%)	174 (15.9%)	
2	12 (1.8%)	3 (2.2%)	20 (1.8%)	
Technical success†	648 (94.6%)	136 (98.6%)	1,074 (97.5%)	0.003
Device success‡	449 (82.7%)	97 (89.8%)	830 (87.7%)	0.01
Valve position				
Correct at intended site	660 (96.5%)	136 (98.6%)	1,075 (97.5%)	0.26
Too high	9 (1.3%)	2 (1.4%)	10 (0.9%)	0.66
Too low	7 (1.0%)	0 (0.0%)	14 (1.3%)	0.89
Tilted	1 (0.1%)	0 (0.0%)	2 (0.2%)	0.98
Not implanted	8 (1.2%)	0 (0.0%)	3 (0.3%)	0.09
Procedure aborted				
Before any device introduced	3 (0.4%)	0 (0.0%)	1 (0.1%)	0.39
Before BAV	0 (0.0%)	0 (0.0%)	1 (0.1%)	0.99
Conversion to conventional surgery	4 (0.6%)	0 (0.0%)	1 (0.1%)	0.24
Valve embolization	8 (1.2%)	0 (0.0%)	3 (0.3%)	0.09
Valve in valve (any)	13 (1.9%)	2 (1.4%)	20 (1.8%)	0.93
Planned	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.9
Due to complication	7 (1.0%)	2 (1.4%)	12 (1.1%)	NA
Valve in other bioprosthesis	6 (0.9%)	0 (0.0%)	8 (0.7%)	0.94
Any complication during the procedure	105 (15.3%)	21 (15.3%)	127 (11.5%)	0.051
AV block	32 (4.7%)	9 (6.5%)	36 (3.3%)	0.1
Requiring temporary pacing	22 (3.2%)	4 (2.9%)	20 (1.8%)	0.16
Requiring permanent pacemaker	13 (1.9%)	4 (2.9%)	11 (1.0%)	0.11
Device malfunction	4 (0.6%)	0 (0.0%)	2 (0.2%)	1

Values are n (%) or mean ± SD. *Percentage valve oversizing is defined as: [(nominal valve diameter − annular diameter)/annular diameter] × 100. †An implantation procedure is considered technical success if the valve is delivered to the intended site by 1 attempted procedure without procedure-related death within 48 h from implantation. ‡An implantation procedure is considered device success if technical success is achieved and the subject is free of moderate or severe aortic regurgitation and the subject has a mean gradient less than 20 mm Hg at discharge.

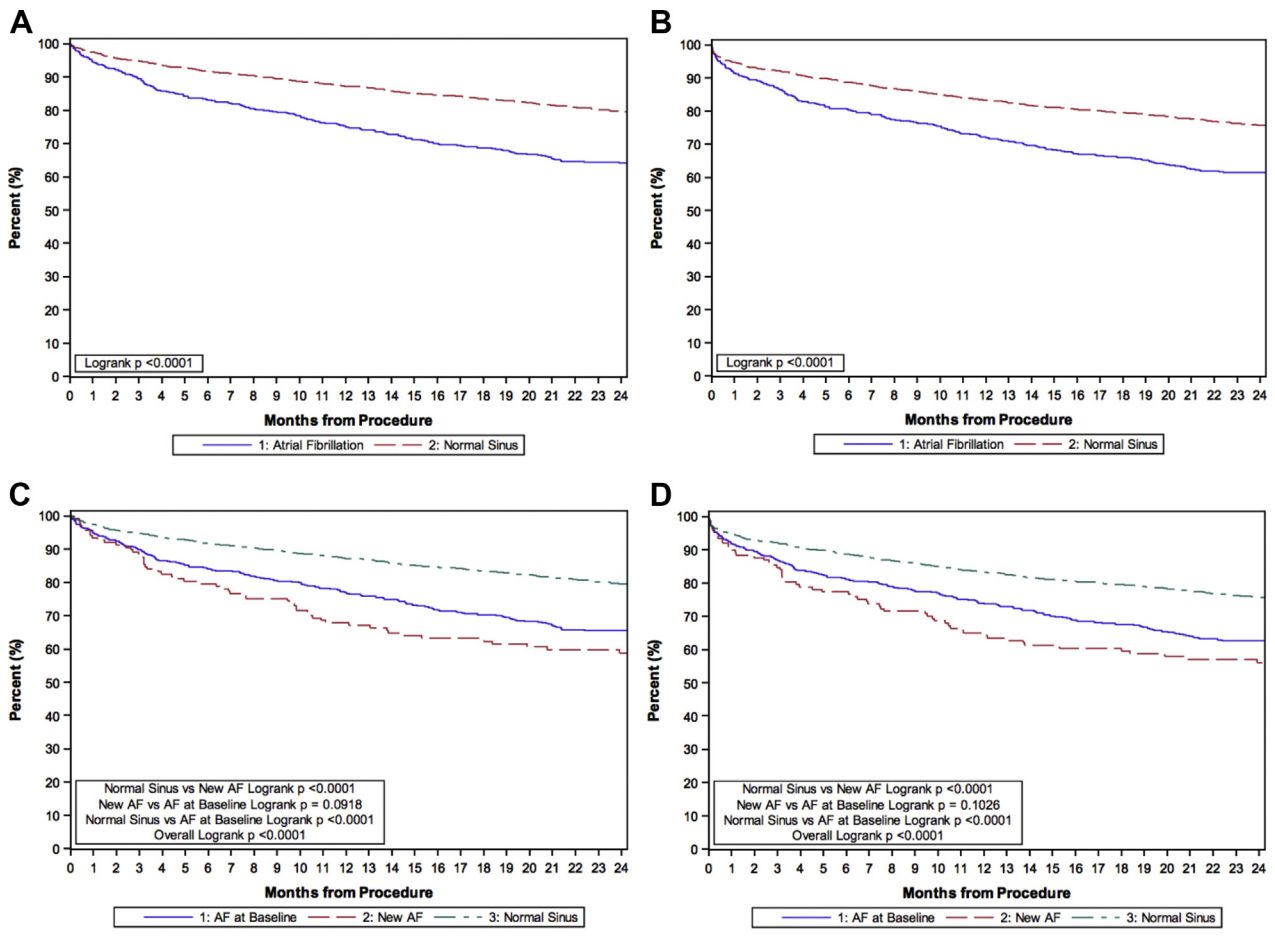
BAV = balloon aortic valvuloplasty; other abbreviations as in Table 1.

Aortic valve stenosis and AF share multiple common risk factors, such as age and hypertension, and aortic valve stenosis by itself is associated with a higher rate of AF (5). Although AF has been shown to be a major predictor of death, stroke, and congestive heart failure in patients treated or not by cardiac surgery, only very few and small studies have assessed the epidemiology and clinical impact of AF in TAVR-treated patients (5–7,17). On the basis of previous reports, the prevalence of pre-existing AF ranges from 22% up to 41%, whereas the reported rate of NOAF after TAVR varies widely from <1% to 32%, with higher rates observed in the transapical TAVR series (6% to 38%) compared with transfemoral ones (0% to 16%) (3–5,18,19). The large differences among studies might be explained by their heterogeneity in terms of definitions and methods for AF detection, as well as in terms of patient selection and TAVR approach (5). In the pivotal PARTNER (Placement of Aortic Transcatheter Valves) trial, the rate of NOAF in cohort A was 7.5% in patients treated with transfemoral access and 11.5% in those treated with transapical access, whereas in cohort B, the NOAF rate was as low as 0.7% (1,2). Similar inconsistencies can be observed also in terms of the prognostic impact of AF in TAVR patients. In 2 small series of patients undergoing TAVR, Nuis et al. (10) and Amat-Santos et al. (8) observed a significant direct correlation between NOAF and stroke only. Conversely, Yankelson et al. (11) and Barbash et al. (9) found that pre-existing AF, but not NOAF, increased the rate of mortality and stroke at 1 year. Finally, Stortecky et al. (18) and Nombela-Franco et al. (3) found that both NOAF and pre-existing AF increased the risk for ischemic cardiac and cerebrovascular events at follow-up.

Our study confirms and extends these observations to both total and cardiovascular mortality as well as to bleeding events. Moreover, in our study patients with AF had also a higher rate of rehospitalization for recurrent congestive heart failure compared with sinus rhythm.

Related to stroke, similarly to previous reports, we found that the event rate was equally distributed between early (<30 days) and late (>30 days) follow-up, and trended higher in patients with NOAF at long-term follow-up (8,20,21). Pre-existing AF and NOAF were related to a numerically higher rate of stroke but were not independent predictors of stroke in this cohort. A significantly higher stroke rate was observed at 2-year follow-up only in the NOAF group compared with the sinus rhythm group. This results replicate those observed in the recent FRANCE-2 (French Transcatheter Aortic Valve Intervention Registry) study for this specific endpoint (22). This

FIGURE 2 Event-Free Survival Curves of Study Groups (Sinus Rhythm, Pre-Existing Atrial Fibrillation, and New-Onset Atrial Fibrillation)



(A) Event-free survival curves for all-cause mortality according to the presence of any atrial fibrillation (AF) (either pre-existing or new onset). **(B)** Event-free survival curves for the combination of all-cause mortality and stroke according to the presence of any AF (either pre-existing or new onset). **(C)** Event-free survival curves for all-cause mortality according to the presence of pre-existing AF or new-onset AF. **(D)** Event-free survival curves for the combination of all-cause mortality and stroke according to the presence of pre-existing AF or new-onset AF.

might be related to the mixed pre-existing antithrombotic regimen of patients treated with TAVR as well as to a heterogeneous etiology of cerebral ischemic events and their overall low rate. In contrast, the prominent impact of AF on cardiovascular mortality without a comparable impact on stroke appears to be more related to hemodynamic impairment (i.e., recurrence of congestive heart failure) and bleedings rather than to cerebrovascular events. In this regard, patients with AF also had significantly higher rates of rehospitalization compared with the sinus rhythm group. Granted, alternative treatment strategies (e.g., left atrial appendage occlusion, non-vitamin K-dependent anticoagulant agents) may play a role in optimizing the risk/benefit ratio in patients not suitable for standard anticoagulation. The ongoing GALILEO (Global Study Comparing a Rivaroxaban-Based Antithrombotic Strategy to an Antiplatelet-Based Strategy After Transcatheter Aortic Valve Replacement to Optimize Clinical Outcomes) randomized trial comparing 2 antithrombotic strategies following TAVR (aspirin plus rivaroxaban vs. aspirin plus clopidogrel) will provide more data. Of note, patients with pre-existing AF are excluded from this study (23).

Related to bleeding events, the interaction between AF and bleedings in TAVR patients has been mostly overlooked in the published research. In our series, we found a significant increase in bleeding events in patients with AF compared with the sinus rhythm group. Accordingly, a recent pooled analysis from the PARTNER-1 trial and continued access

TABLE 3 1-Year Outcome Summary According to the Presence of Pre-Existing AF or NOAF

Outcome	Pre-Existing AF (n = 685)	NOAF (n = 138)	p Value, Pre-Existing AF vs. NOAF	Sinus Rhythm (n = 1,102)	p Value, Pre-Existing AF vs. Sinus Rhythm	p Value, NOAF vs. Sinus Rhythm
All-cause death	178 (26.1%)	44 (32.1%)	0.22	92 (8.4%)	<0.0001	<0.0001
Cardiac death	88 (13.8%)	21 (16.4%)	0.48	40 (3.8%)	<0.0001	<0.0001
Stroke	42 (6.9%)	11 (8.6%)	0.42	56 (5.2%)	0.16	0.09
All vascular complications	120 (18.0%)	23 (17.0%)	0.78	172 (15.7%)	0.21	0.69
Major vascular complications	52 (7.7%)	8 (5.8%)	0.45	59 (5.4%)	0.04	0.76
Minor vascular complications	62 (9.2%)	14 (10.4%)	0.72	116 (10.6%)	0.36	0.91
Non-access-related vascular complication	8 (1.4%)	1 (0.7%)	0.64	3 (0.3%)	<0.01	0.33
All bleeding events	163 (25.0%)	46 (34.2%)	0.02	212 (19.3%)	0.01	<0.0001
Major/life-threatening bleeding events	120 (18.2%)	28 (20.5%)	0.48	157 (14.3%)	0.03	0.051
Life-threatening bleeding events	46 (7.0%)	9, 10 (6.8%)	0.90	53 (4.8%)	0.05	0.35
Major bleeding events	86 (13.1%)	22 (16.1%)	0.30	117 (10.7%)	0.12	0.04
Minor bleeding events	59 (9.5%)	20 (15.7%)	0.03	70 (6.4%)	0.04	0.0003
Myocardial infarction	14 (2.5%)	2 (1.5%)	0.66	23 (2.2%)	0.77	0.73
Renal failure	157 (24.1%)	44 (32.5%)	0.03	155 (14.2%)	<0.0001	<0.0001
Rehospitalization	225 (37.4%)	53 (44.0%)	0.16	254 (23.4%)	<0.0001	<0.0001
Endocarditis	5 (0.9%)	2 (1.7%)	0.41	10 (1.0%)	0.9	0.41
New permanent pacemaker	85 (13.0%)	13 (9.7%)	0.30	66 (6.1%)	<0.0001	0.08

Abbreviations as in Table 1.

registries populations by Généreux et al. (24) showed that AF both at baseline and at 30 days nearly doubled the risk for late major bleeding events after TAVR (≥30 days) (24). Furthermore, AF increased 1-year mortality in the same population, irrespective of the occurrence major bleedings. These results from North American pivotal studies are almost superimposable on our observations in a European real-world cohort. Also, in our series, TAVR patients with NOAF had more bleeding events compared with those with pre-existing AF. Because AF is not known to increase bleeding events by itself, we might hypothesize that this association of AF with bleeding events reported in both studies is influenced by the antithrombotic regimens used in these patients (25,26). To note, evidence on the most appropriate post-procedural antithrombotic regimen in terms of safety and efficacy in the setting of TAVR, especially when AF is present, is currently lacking (25). According to the SOURCE XT protocol, antithrombotic treatment of patients was not recorded in the registry dataset. Therefore, in this analysis it was not possible to evaluate the relationship between antithrombotic regimens and subsequent ischemic and bleeding events, either globally or in the subset of patients with AF. At the moment, antithrombotic treatment of these patients is not supported by evidence coming from any randomized study and is thus largely translated in the TAVR setting from current pharmacological standards in patients undergoing percutaneous coronary interventions (25).

TABLE 4 Predictors of Mortality at 1-Year Follow-Up by Multivariate Logistic Regression

Significant Predictor	Hazard Ratio	95% Confidence Interval	p Value
NOAF	1.96	(1.39–2.76)	0.0001
Baseline AF	1.55	(1.26–1.91)	<0.0001
Renal failure	1.53	(1.25–1.86)	<0.0001
Tricuspid regurgitation (moderate to severe)	1.37	(1.09–1.73)	0.008
Coronary artery disease	1.29	(1.07–1.57)	0.008
NYHA functional class III/IV	1.28	(1.002–1.63)	0.01
COPD	1.28	(1.03–1.62)	0.03
BMI	0.96	(0.94–0.98)	<0.0001
Logistic EuroSCORE	1.01	(1.004–1.01)	0.0012

Abbreviations as in Table 1.

The association between nontransfemoral access and NOAF has been already reported and has been previously attributed to epicardial and pericardial injury, similar to that occurring in cardiac surgery (26). This finding, along with nonrandomized outcome data of transfemoral versus nontransfemoral access, represents additional evidence in favor of the transfemoral route whenever feasible (5,27). The gradual size reduction of new delivery systems and transcatheter heart valves are allowing a progressive shifting of TAVR procedures in this direction.

Balloon post-dilation was another independent procedural predictor of NOAF observed in this study. On the contrary, the final presence of a paravalvular

leak was not associated with NOAF. This observation might be explained by improvement of paravalvular leak severity after balloon post-dilation, but the association between post-deployment paravalvular leak and NOAF deserves further investigation.

STUDY LIMITATIONS. We cannot exclude an underestimation of AF rate or some overlap between the NOAF and pre-existing AF groups because of the limited sensitivity of the methods used in clinical practice to assess AF. Systematic 72-h continuous post-TAVR electrocardiographic monitoring was not routinely performed in this cohort. Additionally, no information was available on the overall cohort to differentiate paroxysmal from permanent AF at baseline. Pre- and post-TAVR echocardiographic evaluations were site reported and not reviewed by an independent core laboratory. Finally, this study was conducted in a population treated with TAVR by means of balloon-expandable prosthetic valves only. Generalizations of our results to patients treated with other prosthesis types might be not appropriate.

CONCLUSIONS

Presence of AF before and after TAVR was associated with markedly increased risk for adverse events in patients with aortic valve stenosis treated with TAVR. We cannot exclude that our results were influenced by the higher baseline risk of AF subgroups compared with those in sinus rhythm. Notwithstanding, these results appear consistent with those of the multicenter FRANCE-2 and PARTNER studies, showing that AF had an independent detrimental effect on outcomes including cardiac death, bleeding, renal failure, and rehospitalization (22,24). More data are needed to define the role of AF prevention and treatment on outcomes in these patients. Finally, the implementation of more comprehensive TAVR risk scores, taking into account AF, remains a relevant clinical need (28).

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PERSPECTIVES

WHAT IS KNOWN? Patients undergoing TAVR who have histories of AF or who develop AF in the post-procedural period have an increased risk for adverse events.

WHAT IS NEW? Procedural factors, such as the procedure access route, may influence the chance to develop AF after TAVR. The optimal antithrombotic regimen in TAVR patients, particularly for those with AF (either pre-existing or new onset), is unclear.

WHAT IS NEXT? Studies comparing different antithrombotic therapies in such subsets of patients are needed. Also, more data are needed to define the role of AF prevention and treatment in TAVR patients.

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KEY WORDS atrial fibrillation, new-onset atrial fibrillation, pre-existing atrial fibrillation, stroke, TAVR

APPENDIX For supplemental material, please see the online version of this article.

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