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Baseline Characteristics and Prognostic Implications of Pre-Existing and New-Onset Atrial Fibrillation After Transcatheter Aortic Valve Implantation

Results From the FRANCE-2 Registry

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ABSTRACT

OBJECTIVES The aim of this study was to determine baseline characteristics and clinical outcomes of patients with pre-existing atrial fibrillation (AF) and of patients who presented with new-onset AF after transcatheter aortic valve implantation (TAVI).

BACKGROUND Little is known regarding the impact of AF after TAVI.

METHODS The FRANCE-2 registry included all patients undergoing TAVI (N = 3,933) in France in 2010 and 2011. New-onset AF was defined as the occurrence of AF post-procedure in a patient with no documented history of AF.

RESULTS AF was documented before TAVI in 25.8% of patients. New-onset AF was observed in 174 patients after TAVI among patients without a history of pre-existing AF (6.0%). At 1 year, the rates of all-cause death (26.5 vs. 16.6%, respectively; $p < 0.001$) and cardiovascular death (11.5 vs. 7.8%, respectively; $p < 0.001$) were significantly higher in patients with pre-existing AF compared with those without AF. Rehospitalization for worsening heart failure and New York Heart Association functional class was also higher in patients with pre-existing AF versus those without, resulting in a higher rate of combined efficacy endpoint in this group ($p < 0.001$). A history of stroke, surgical (nontransfemoral) approach, cardiological, and hemorrhagic procedure-related events were all independently related to the occurrence of new-onset post-procedural AF. New-onset AF in patients without pre-existing AF was associated with a higher rate of combined safety endpoint at 30 days ($p < 0.001$) and a higher rate of both all-cause death and combined efficacy endpoint at 1 year ($p = 0.003$ and $p = 0.02$, respectively).

CONCLUSIONS Pre-existing and new-onset AF are both associated with higher mortality and morbidity after TAVI. (J Am Coll Cardiol Intv 2015;8:1346-55) © 2015 by the American College of Cardiology Foundation.

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Atrial fibrillation (AF) is the most common cardiac arrhythmia, and its prevalence increases progressively with age to reach >10% in patients aged 80 years of age and older (1,2). In elderly patients with severe degenerative aortic stenosis (AS), coexisting AF is even more frequent (25% to 35%) (3–6) due to chronic left ventricular and left atrial pressure overload (7), with important implications for prognosis. In fact, among patients with AS undergoing conventional surgical aortic valve replacement (SAVR), pre-existing AF is an independent predictor of perioperative and long-term adverse events, including mortality, congestive heart failure, and stroke (5,6,8). Moreover, the occurrence of new-onset AF after cardiac surgery is associated with increased early and late morbidity and mortality (9–11).

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Transcatheter aortic valve implantation (TAVI) has emerged as a viable alternative to SAVR for patients with severe symptomatic AS who are considered to be ineligible or at very high risk for conventional SAVR (12,13). Little is known regarding the impact of pre-existing or new-onset AF after TAVI, with few specific studies that had small sample sizes and presented conflicting results (14–16).

The aims of the present study were therefore 1) to compare baseline characteristics and long-term clinical outcomes after TAVI between patients with and without pre-existing AF and 2) to analyze baseline characteristics, predictive factors, and prognostic value of new-onset AF after TAVI among patients who had no history of AF before the procedure, using data from FRANCE-2, the French national TAVI registry.

METHODS

The FRANCE-2 registry is a multicenter, prospective registry including 33 centers in France and 1 in Monaco. Details of the registry have previously been described (3). Briefly, patients included in the registry were symptomatic adults with severe AS who were not candidates for SAVR because of coexisting illness. Severe AS was defined as an aortic valve area of <0.8 cm^2, a mean aortic valve gradient of ≥40 mm Hg, or a peak aortic jet velocity of ≥4.0 m/s. All patients had New York Heart Association (NYHA) functional class II, III, or IV symptoms. All patients who underwent TAVI based on these criteria in France and Monaco from January 2010 to December 2011 were prospectively included in the registry, without exclusion criteria. Patients provided written informed consent before undergoing the procedure. The registry was approved by the Institutional Review Board of the French Ministry of Health.

STUDY POPULATIONS. In total, 3,933 patients undergoing TAVI were enrolled in the FRANCE-2 registry from January 2010 to December 2011. Information regarding a history of AF was available for 3,875 (98.5%), and these patients comprise the study population for the comparison of pre-existing versus no pre-existing AF. After TAVI, 2,622 of the 2,873 patients (91.3%) without a history of AF before the procedure were still alive at the first in-hospital follow-up. These patients constitute the study sample for the second analysis regarding the impact of new-onset AF after TAVI (Online Figure 1). In-hospital follow-up was performed 6 ± 4 days (minimum of 2 days) after the procedure and included a systematic review of all electrocardiographic events after TAVI identified by serial review of post-procedural 12-lead electrocardiograms (ECGs). AF was defined as the presence of an irregular rhythm with fibrillatory waves and no P waves on the ECG. Because atrial flutter is another supaventricular rhythm that may coexist or precede AF, we assigned patients with atrial flutter to the new-onset AF group (17).

Risk factors for surgery were evaluated prospectively using the Society of Thoracic Surgeons (STS) (18) and the logistic European System for Cardiac Operative Risk Evaluation (EuroSCORE) (19). Two TAVI devices, commercially available at the onset of the registry, were used: the self-expandable Medtronic CoreValve (Medtronic, Inc., Minneapolis,

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation
AR = aortic regurgitation
AS = aortic stenosis
ECG = electrocardiogram
EuroSCORE = European System for Cardiac Operative Risk Evaluation
LVEF = left ventricular ejection fraction
NYHA = New York Heart Association
SAVR = surgical aortic valve replacement
STS = Society of Thoracic Surgeons
TAVI = transcatheter aortic valve implantation
VARC2 = Valve Academic Research Consortium classification 2

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Minnesota) and the balloon-expandable Edwards SAPIEN valve (Edwards Lifesciences, Irvine, California). AF was managed according to current guidelines (17). After the procedure, in patients with no indication for long-term anticoagulation, acetylsalicylic acid was prescribed indefinitely in combination with clopidogrel for 6 months. In patients with an indication for oral anticoagulation, a vitamin K antagonist was prescribed in combination with either acetylsalicylic acid or clopidogrel, at the discretion of the investigator.

CLINICAL FOLLOW-UP. Clinical follow-up was obtained for all patients at a median of 310 days (Q1-Q3 = 190 to 400). Mortality and all adverse events during the procedure, at 30 days, and at 1 year were assessed according to the Valve Academic Research Consortium classification 2 (VARC2) (20) and adjudicated by an independent clinical events committee. The combined safety endpoint was defined at 30 days and included all-cause mortality, stroke (disabling and nondisabling), life-threatening bleeding, acute kidney injury stage 2 or 3 (including renal replacement therapy), coronary artery obstruction requiring intervention, major vascular complication, or valve-related dysfunction requiring repeat intervention (i.e., TAVI, SAVR, balloon aortic valvuloplasty). The combined efficacy endpoint was evaluated at 1 year and defined as all-cause mortality, stroke (disabling and nondisabling), need for hospitalization for valve-related symptoms or worsening congestive heart failure, NYHA functional class III or IV, valve-related dysfunction (mean aortic valve gradient >20 mm Hg, effective orifice area <0.9 to 1.1 cm^2, and/or Doppler velocity index <0.35 m/s, and/or moderate or severe prosthetic valve regurgitation.

Procedure-related events were defined as those occurring during or as a direct result within 24 h after TAVI and were classified as cardiological (myocardial infarction, ventricular or supraventricular arrhythmia, complete atrioventricular block, need for pacemaker implantation, heart failure, tamponade), vascular (hemorrhage, arterial thrombosis/dissection/rupture, aortic dissection), hemorrhagic (life-threatening or not, tamponade), neurological (minor or major stroke), valvular (valve migration, aortic annulus rupture, aortic valve insufficiency), and conversion to surgery (20).

STATISTICAL ANALYSIS. Continuous variables are expressed as mean ± SD when normally distributed or median ± interquartile range if not normally distributed and compared using the Student *t* test or Wilcoxon rank sum test as appropriate. Categorical variables are described as number (percentage) and compared using the chi-square or Fisher exact test. We compared 30-day and 1-year VARC2-defined clinical outcomes: 1) between patients with pre-existing AF versus those without; and 2) between patients with persistent sinus rhythm versus patients with new-onset AF after TAVI. Outcome analyses were adjusted for baseline and procedural characteristics using multivariate logistic regression analysis or a Cox model (after verification of the underlying assumption of proportionality of hazard) that included variables with a p value <0.10 by univariate analysis. Results are reported as the odds ratio or hazard ratio with associated 95% confidence interval, as appropriate, and p value. The Kaplan-Meier method was used to create survival curves at 1 year. Interactions between pre-existing AF and sex, age, logistic EuroSCORE, STS score, chronic obstructive pulmonary disease, chronic kidney disease, peripheral artery disease, low left ventricular ejection fraction (LVEF) (≤35%), pulmonary hypertension, and type of device implanted were tested by the Breslow-Day test. Independent predictors of the occurrence of new-onset AF after TAVI were analyzed by multivariate logistic regression, including all baseline and procedural characteristics with a p value <0.10 by univariate analysis. All p values are 2-sided. A p value <0.05 was considered statistically significant. Statistical analyses were performed with SAS version 9.3 (SAS Institute Inc., Cary, North Carolina).

RESULTS

PRE-EXISTING VERSUS NON-PRE-EXISTING AF. Baseline and procedural characteristics in the overall population. Overall, AF was documented before TAVI (pre-existing AF) in 1,002 patients (25.8%). Tables 1 and 2 display the baseline and procedural characteristics of patients with and without pre-existing AF. Patients in the pre-existing AF group were more frequently male, were older and presented with higher rates of several major comorbidities (i.e., previous stroke, pulmonary hypertension, permanent pacemaker) and worse NYHA functional class. Device success and procedure-related events were similar between patients with and without pre-existing AF, except for the rate of VARC2-defined cardiological events, which was lower in the pre-existing AF group. The rate of significant post-procedural aortic regurgitation (AR) (grade 2 or higher) did not differ significantly between groups. Echocardiographic data at baseline are shown in Table 3. We observed a lower LVEF, a higher pulmonary pressure, and a higher rate of significant mitral regurgitation in the group of patients with pre-existing AF.

TABLE 1 Baseline Clinical Characteristics in the Overall Population (N = 3,875) and in the Population of Patients Without a History of Atrial Fibrillation (n = 2,622)

	Pre-Existing AF			New-Onset AF		
	No (n = 2,873)	Yes (n = 1,002)	p Value	No (n = 2,448)	Yes (n = 174)	p Value
Age, yrs	82.6 ± 7.4	83.5 ± 6.0	0.001	82.4 ± 7.5	83.7 ± 6.7	0.03
Women	1,475 (51.3)	439 (43.8)	<0.001	1,257 (51.3)	80 (46.0)	0.18
BMI, kg/m^2	25.9 ± 5.1	26.1 ± 4.7	0.55	26.0 ± 5.7	25.9 ± 5.4	0.74
STS score	13.6 ± 11.4	15.4 ± 11.6	<0.001	13.3 ± 11.3	14.1 ± 12.3	0.41
Logistic EuroSCORE	20.8 ± 13.6	24.5 ± 15.1	<0.001	20.5 ± 13.4	22.1 ± 12.5	0.11
NYHA functional class III or IV	2,108 (73.3)	803 (80.1)	<0.001	1,793 (73.2)	118 (67.8)	0.13
Clinical history						
Diabetes	710 (24.7)	276 (27.5)	0.08	600 (24.6)	44 (25.3)	0.85
Hypertension	2,011 (70.0)	656 (65.5)	0.004	1,710 (70.3)	129 (74.1)	0.30
CAD	1,394 (48.5)	450 (44.9)	0.03	1,178 (48.4)	90 (51.7)	0.43
Previous CABG	515 (17.9)	171 (17.1)	0.51	442 (18.1)	30 (17.2)	0.83
PAD	793 (27.6)	283 (28.2)	0.69	660 (27.0)	59 (34.1)	0.052
Previous stroke	263 (9.1)	119 (11.9)	0.01	210 (8.6)	24 (13.8)	0.02
CKD	236 (8.2)	96 (9.6)	0.18	183 (7.5)	19 (11.0)	0.10
COPD	650 (22.6)	225 (22.4)	0.91	545 (22.3)	43 (24.9)	0.45
Permanent pacemaker	340 (11.8)	202 (20.1)	<0.001	290 (11.8)	21 (12.1)	0.90
Left bundle-branch block	335 (11.6)	122 (12.1)	0.56	285 (11.7)	20 (11.5)	1.0
LVEF <30%	197 (6.8)	84 (8.4)	0.10	175 (7.1)	5 (2.9)	0.01
Pulmonary hypertension	639 (22.2)	354 (35.3)	<0.001	529 (21.7)	47 (27.2)	0.10

Values are mean ± SD or n (%).

AF = atrial fibrillation; BMI = body mass index; CABG = coronary artery bypass graft surgery; CAD = coronary artery disease; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; EuroSCORE = European System for Cardiac Operative Risk Evaluation; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; PAD = peripheral artery disease; STS = Society of Thoracic Surgeons.

Clinical outcomes in the overall population. VARC2-defined clinical outcomes in the overall population through 30 days and 1 year are summarized in Table 4. During the first 30 days, we observed similar rates of death and overall procedure-related complications, including the combined safety endpoint, between those with and without pre-existing AF. At 1 year, all-cause death and cardiovascular death were significantly higher among patients with pre-existing AF ($p < 0.001$ and $p < 0.001$, respectively). Figure 1A illustrates the survival probability curves after TAVI for patients with and without pre-existing AF. The rate of rehospitalization for worsening heart failure or valve dysfunction was higher, and NYHA functional class was worse in case of pre-existing AF, resulting in a higher rate of the combined efficacy endpoint in this group ($p < 0.001$). The rates of stroke and major bleeding at 1 year were similar between groups.

Cox analysis showed that pre-existing AF was the second most powerful predictor of mortality after TAVI, after post-procedural AR (Figure 2A). By stratified analysis, the increased 1-year mortality risk among patients with pre-existing AF was consistent across major subgroups, including sex, age, logistic EuroSCORE, STS score, chronic obstructive pulmonary disease, chronic kidney disease, peripheral artery disease, low LVEF (≤35%), pulmonary hypertension, and type of device implanted (Figure 3). On echocardiographic follow-up, we observed that LVEF remained lower, whereas pulmonary pressure and the rate of significant mitral regurgitation were significantly higher in the pre-existing AF group (Table 3).

NEW-ONSET AF. Baseline and procedural characteristics in the population without a history of AF. Among the 2,873 patients without a history of AF, post-procedural ECG review could not be performed due to in-hospital death of 251 patients. A comparison of the baseline characteristics of these 251 patients and of those in whom post-procedural ECG review was performed and is presented in Online Table 1. No significant difference was observed between the 2 populations.

New-onset AF was observed in 174 patients (6.0%) after TAVI among patients without a history of pre-existing AF. Patients in whom new-onset AF developed were older and presented with a higher rate of previous stroke compared with those who remained in sinus rhythm (Table 1). Regarding procedural characteristics, device success and post-procedural AR were similar between groups.

TABLE 2 Procedural Characteristics, Procedural Success, and Related Events in the Overall Population (N = 3,875) and in the Population of Patients Without a History of Atrial Fibrillation (n = 2,622)

	Pre-Existing AF			New-Onset AF		
	No (N = 2,873)	Yes (n = 1,002)	p Value	No (n = 2,448)	Yes (n = 174)	p Value
Procedural characteristics						
General anesthesia	1,993 (69.4)	673 (67.1)	0.20	779 (31.8)	35 (20.2)	0.001
Access route						
Transapical	539 (18.7)	151 (15.1)	0.008	421 (17.2)	56 (32.2)	<0.001
Transfemoral	2,068 (72.0)	759 (75.7)	0.02	1,817 (74.2)	99 (56.9)	<0.001
Subclavian	154 (5.3)	68 (6.8)	0.09	123 (5.0)	7 (4.0)	0.71
Transaortic	95 (3.3)	20 (2.0)	0.04	73 (3.0)	12 (6.9)	0.005
Type of valve			0.007			0.17
Edwards SAPIEN valve (Edwards Lifesciences, Irvine, California)	1,943 (67.6)	633 (63.2)		1,657 (67.7)	127 (72.9)	
Medtronic CoreValve (Medtronic Inc., Minneapolis, Minnesota)	930 (32.4)	369 (36.8)		791 (32.3)	47 (27.1)	
Procedural success	2,702 (94.0)	947 (94.5)	0.64	2,383 (97.3)	169 (97.1)	0.80
Procedure-related event						
Conversion	21 (0.73)	8 (0.8)	0.83	13 (0.5)	0 (0)	1.0
Cardiological	425 (14.8)	118 (11.8)	0.01	323 (13.2)	36 (20.7)	0.008
Hemorrhagic	287 (10.0)	85 (8.5)	0.17	219 (8.9)	27 (15.5)	0.006
Vascular	176 (6.1)	65 (6.5)	0.70	149 (6.1)	9 (5.2)	0.74
Neurological	58 (2.0)	18 (1.8)	0.79	44 (1.8)	2 (1.1)	0.76
Valvular	53 (1.8)	25 (2.5)	0.23	32 (1.3)	3 (1.7)	0.50
Post-procedural paravalvular AR >2	337 (11.7)	140 (16.9)	0.08	306 (12.5)	23 (13.2)	0.81

Values are n (%).
AF = atrial fibrillation; AR = aortic regurgitation.

Conversely, the rate of use of an approach other than the transfemoral approach (i.e., surgical transapical and transaortic approaches) was significantly higher in the new-onset patient group, as was the rate of VARC2-defined cardiological events and hemorrhagic procedure-related events (Table 2).

A history of stroke, surgical nontransfemoral approach, cardiological and hemorrhagic procedure-related events were all found to be independently related to the occurrence of new-onset post-TAVI AF (Table 5).

Clinical outcomes in the population without a history of AF. Table 4 displays the VARC2-defined outcomes after TAVI in the population without a history of AF. The duration of hospital stay was significantly longer in patients with new-onset AF after TAVI (12.5 ± 11.3 vs. 9.9 ± 9.5, respectively; $p < 0.001$). New-onset AF was associated with a higher rate of the combined safety endpoint at 30 days ($p < 0.001$). At 1 year, both all-cause death and the combined efficacy endpoint were significantly higher in the new-onset AF group ($p = 0.003$ and $p = 0.02$, respectively), whereas the rates of stroke and major bleeding were similar. The survival probability curves for patients with no history of AF and in whom new-onset AF developed after TAVI are displayed in Figure 1B. Multivariate analysis showed that new-onset AF after TAVI was one of the main predictors of mortality, along with renal failure and AR (Figure 2B) in patients with no history of AF. Finally, echocardiographic follow-up did not reveal any differences between groups (Online Table 2).

DISCUSSION

This large prospective study investigating concomitant AF in patients with severe AS undergoing TAVI showed that both pre-existing and new-onset AF were associated with higher mortality and morbidity at 1 year. The higher rate of death observed in pre-existing AF patients seems to be linked to heart failure, whereas the poorer outcome in patients in whom new-onset AF developed after TAVI could be related to the procedure.

Since the PARTNER (Placement of Aortic Transcatheter Valve) trials (12,13), several prognostic factors for TAVI have been identified, such as low LVEF (21), pulmonary hypertension (22), and post-procedural AR grade 2 or higher (23). A recent analysis from the PARTNER I trial showed that body mass index, coagulopathy, chronic kidney disease, liver disease, cognitive status, STS score, and periprocedural

TABLE 3 Echocardiographic Evolution After TAVI in the Overall Population (N = 3,875)

	Pre-Existing AF		
	No (N = 2,873)	Yes (n = 1,002)	p Value
LVEF, %			
Baseline value	53.9 ± 14.2	51.4 ± 14.0	<0.001
First FU	57.4 ± 12.1	54.8 ± 12.2	<0.001
Last FU	58.0 ± 12.1	55.8 ± 12.0	<0.001
Systolic PAP, mm Hg			
Baseline value	43.7 ± 13.9	49.1 ± 13.7	<0.001
First FU	39.1 ± 13.1	45.9 ± 13.3	<0.001
Last FU	38.7 ± 12.8	45.1 ± 15.1	<0.001
Mitral regurgitation 3/4 or 4/4			
Baseline	48 (1.7)	27 (2.7)	0.04
First FU	19 (0.7)	22 (2.2)	0.003
Last FU	19 (0.7)	18 (1.8)	0.006

Values are mean ± SD or n (%). First FU performed at a median of 35 days (Q1-Q3 = 27 to 42); last FU performed at a median of 310 days (Q1-Q3 = 190 to 400). Comparisons of first FU and last FU were adjusted for baseline value.

FU = follow-up; PAP = pulmonary artery pressure; other abbreviations as in Table 1.

complications were related to mortality between 30 days and 1 year after TAVI (24). In the present study, we observed that AF, whether pre-existing or new onset among patients without a history of AF before TAVI, represents a key predictor of late mortality after TAVI, with an impact of the same magnitude as that of AR and chronic kidney disease.

Pre-existing AF. Regarding pre-existing AF, we observed some differences in the clinical characteristics between patients with and without a history of AF, resulting in a significantly higher preoperative logistic EuroSCORE and STS risk scores in the pre-existing AF group. However, all baseline characteristics were included in the multivariate analysis, and, thus, the results were observed independently of these factors.

Our results are in line with and strengthen preliminary reports from 2 previous registries (25,26) and from 2 specific reports (15,16). However, these previous studies included limited sample sizes (fewer than 400 patients in each study), and found a 1.44- to 4.11-fold increased risk of all-cause mortality at 1 year. In light of these results, the inclusion of pre-existing AF in future risk scores specifically dedicated to selection of patients for either TAVI or SAVR should be considered.

The higher rate of death observed among pre-existing AF patients undergoing TAVI is in accordance with outcomes after SAVR in which pre-existing AF is associated with a 1.5-fold increase in

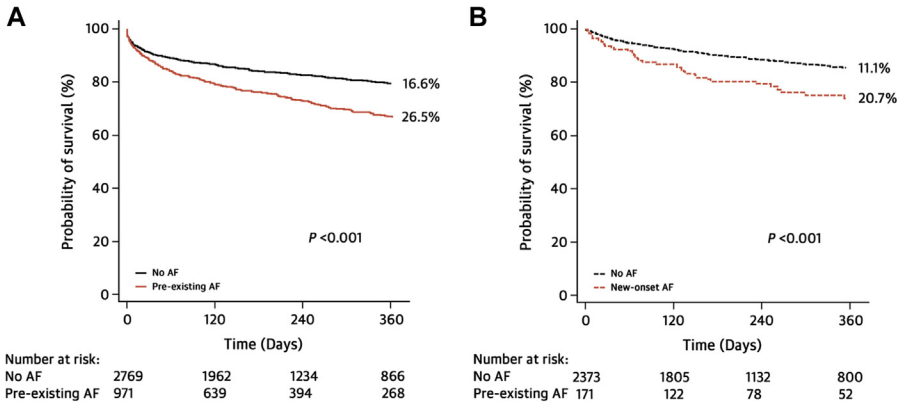
TABLE 4 VARC-Defined Outcomes at 30 Days and 12 Months in the Overall Population (N = 3,875) and in the Population of Patients With No History of Atrial Fibrillation (n = 2,622)

	Pre-Existing AF				New-Onset AF			
	No	Yes	OR/HR (95% CI)	p Value	No	Yes	OR/HR (95% CI)	p Value
Length of hospital stay, days	10.1 ± 10.6	10.7 ± 8.4	1.34 (0.95–1.87)	0.08	9.9 ± 9.5	12.5 ± 11.3	1.77 (1.34–2.33)	<0.001
At 30 days								
All-cause death	246 (8.56)	113 (11.3)	1.15 (0.78–1.71)	0.46	78 (3.2)	11 (6.3)	1.87 (0.85–4.1)	0.11
Cardiovascular death	160 (5.6)	65 (6.5)	1.10 (0.81–1.49)	0.52	42 (1.7)	6 (3.4)	1.80 (0.59–5.51)	0.30
All stroke	97 (3.4)	27 (2.7)	0.81 (0.52–1.25)	0.35	73 (2.9)	9 (5.1)	1.75 (0.86–3.59)	0.12
Acute kidney injury	39 (1.4)	20 (2.0)	1.18 (0.60–2.31)	0.62	25 (1.0)	4 (2.3)	1.91 (0.64–5.70)	0.24
Myocardial infarction	40 (1.4)	8 (0.8)	1.73 (0.80–3.73)	0.15	33 (1.3)	1 (0.6)	3.11 (0.41–23.1)	0.26
Major bleeding	283 (9.8)	82 (8.2)	1.12 (0.86–1.46)	0.36	217 (8.9)	24 (13.8)	0.70 (0.44–1.12)	0.14
Major vascular complication	112 (3.9)	45 (1.1)	1.14 (0.80–1.64)	0.45	91 (9)	9 (5.1)	1.72 (0.84–3.51)	0.13
Valve-related dysfunction	522 (18.2)	167 (16.7)	0.91 (0.75–1.10)	0.36	431 (17.6)	32 (18.4)	1.70 (0.72–1.60)	0.72
Safety endpoint	1,045 (36.4)	364 (36.3)	1.006 (0.86–1.48)	0.77	778 (31.2)	72 (41.4)	1.45 (1.06–1.99)	<0.001
At 1 yr								
All-cause death	477 (16.6)	266 (26.5)	1.72 (1.42–2.1)	<0.001	271 (11.1)	36 (20.7)	1.79 (1.21–2.65)	0.003
Cardiovascular death	225 (7.8)	115 (11.5)	1.96 (1.44–2.67)	<0.001	97 (4.0)	11 (6.3)	1.74 (0.86–3.51)	0.11
All stroke	119 (4.1)	34 (3.4)	0.87 (0.59–1.30)	0.87	89 (3.6)	9 (5.1)	1.05 (0.49–2.19)	0.90
Major bleeding	320 (11.1)	104 (10.4)	0.85 (0.64–1.10)	0.10	396 (10.7)	28 (16.1)	0.84 (0.57–1.23)	0.37
Rehosp.	246 (8.6)	161 (10.1)	2.02 (1.63–2.52)	<0.001	233 (9.1)	136 (16.4)	1.22 (0.62–2.40)	0.55
NYHA functional class III or IV	255 (8.9)	165 (16.5)	1.85 (1.52–2.26)	<0.001	191 (7.8)	18 (10.3)	1.28 (0.79–2.08)	0.31
Valve-related dysfunction	113 (3.9)	45 (4.5)	1.14 (0.79–1.63)	0.46	103 (4.2)	8 (4.6)	1.11 (0.53–2.27)	0.78
Efficacy endpoint	968 (33.7)	470 (46.9)	1.55 (1.36–1.77)	<0.001	713 (29.1)	73 (41.9)	1.44 (1.1–1.87)	0.02

Values are n (%).

CI = confidence interval; HR = hazard ratio; OR = odds ratio; Rehosp. = rehospitalization for worsening heart failure or valve-related dysfunction; other abbreviations as in Table 1.

FIGURE 1 1-Year Follow-Up Survival Curves

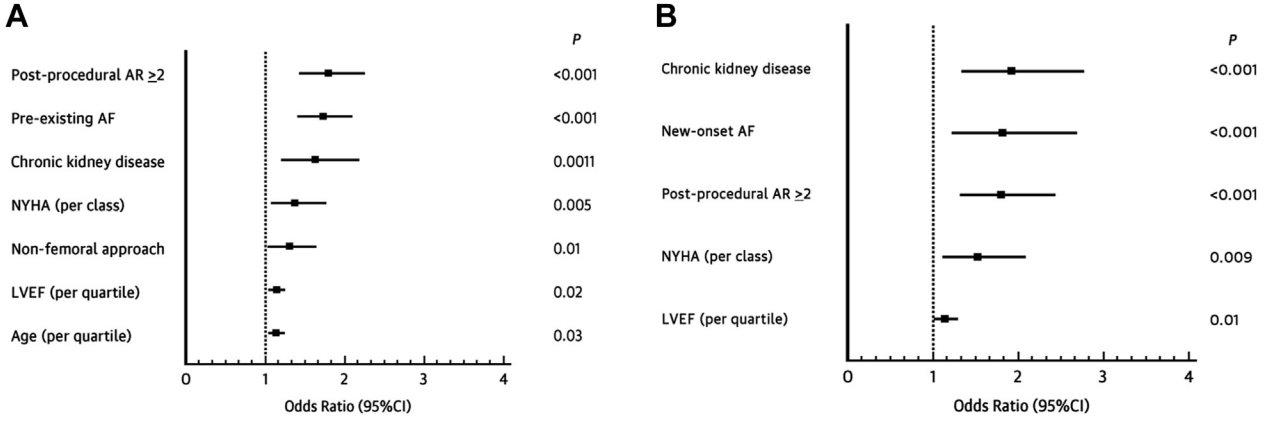


Kaplan-Meier curves of 1-year survival probability in patients with and without pre-existing atrial fibrillation (AF) **(A)** and in patients with and without new-onset AF among the population without a history of AF **(B)**.

the risk of death in an overall population (6) and an 8-fold increase in risk in case of concomitant reduced LVEF (5).

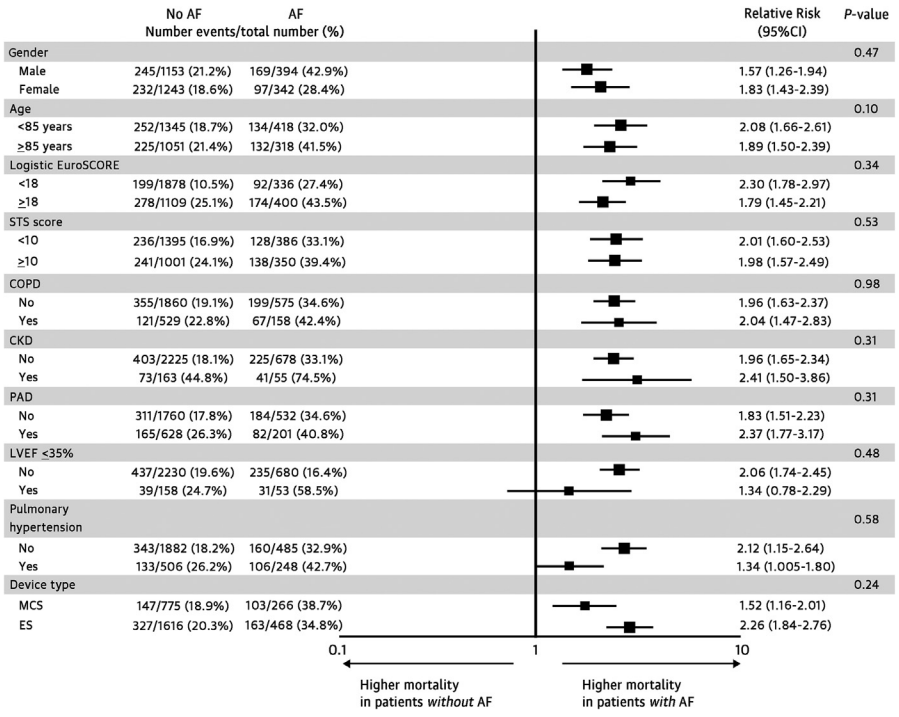
The higher rate of death at 1 year observed in the pre-existing AF group was not related to procedure-related adverse events at 30 days, but rather was associated with heart failure symptoms, including a higher rate of rehospitalization for worsening heart failure and a poorer NYHA functional class. Furthermore, echocardiographic analysis at baseline and during follow-up showed worse cardiac function in the pre-existing AF group. Therefore, the worse outcome after TAVI observed in patients with pre-existing AF could be the expression of advanced heart disease. In this context, structural remodeling and myocardial fibrosis are important synergistic contributors to the AF substrate, which increase mortality by accelerating the process of ventricular and atrial senescence (27). Moreover, the loss of atrioventricular synchrony, leading to impaired ventricular filling, reduced cardiac output, and increased afterload, are hemodynamic factors known to adversely affect clinical outcomes in heart failure patients (28).

FIGURE 2 Predictors of 1-Year Mortality After TAVI



Correlates of pre-existing **(A)** and new-onset atrial fibrillation (AF) **(B)** by multivariate Cox models. AR = aortic regurgitation; NYHA = New York Heart Association; LVEF = left ventricular ejection fraction.

FIGURE 3 Stratified Analysis of All-Cause Mortality in the Overall Population



Stratified analysis for all-cause mortality among subgroups in patients with and without pre-existing atrial fibrillation (AF). CI = confidence interval; COPD = chronic obstructive pulmonary disease; CKD = chronic kidney disease; LVEF = left ventricular ejection fraction; PAD = pulmonary arterial disease.

New-onset AF. In this study, we observed that new-onset AF developed in 6% of patients after TAVI and was directly related to the procedure itself, including the use of a surgical nontransfemoral approach and the occurrence of hemorrhagic and cardiological procedural adverse events. Compared with SAVR, the prevalence of new-onset AF in patients undergoing TAVI was lower (29), but pathophysiological mechanisms could share some common features, especially in the case of a transapical approach. First, it is well known from thoracic surgery that thoracotomy is associated with new-onset AF due to the ventilatory restriction and the hyperadrenergic status generated by postoperative pain (30). Second, bleeding events (31) and myocardial injury such as left ventricular repair or cardiological complications (32) were previously shown to be strongly related to the occurrence of new-onset AF after open-heart surgery.

New-onset AF was associated in our study with poorer outcomes after TAVI compared with patients without a history of AF, a longer hospital stay, a higher rate of combined safety procedure-related endpoint at 30 days, and a higher rate of both all-cause mortality and the combined efficacy endpoint at 1 year. To the best of our knowledge, this is the first study to report such results in a large registry population. Two previous studies that both included pre-existing and new-onset AF found that the mortality rate was not significantly different compared with patients without new-onset AF (15,16). In addition, Amat-Santos et al. (14) showed, in a dedicated study,

TABLE 5 Independent Predictors of the Occurrence of New-Onset Atrial Fibrillation After TAVI

	Univariate Model		Multivariate model	
	HR (95% CI)	p Value	HR (95% CI)	p Value
Previous stroke	1.69 (1.07–2.66)	0.02	1.66 (1.05–2.63)	0.03
PAD	1.39 (1.008–1.93)	0.04	–	
LVEF <30%	0.38 (0.15–0.95)	0.03	–	
Nontransfemoral access	2.18 (1.59–2.98)	<0.001	2.04 (1.47–2.81)	0.001
Cardiological procedure-related event	1.71 (1.16–2.52)	0.006	1.59 (1.08–2.36)	0.01
Hemorrhagic procedure-related event	1.86 (1.21–2.88)	0.004	1.56 (1.004–2.45)	0.04

TAVI = transcatheter aortic valve implantation; other abbreviations as in Tables 1 and 4.

in 138 high-risk patients undergoing TAVI a higher rate of cerebrovascular events, but not death during 30-day follow-up in patients with new-onset AF (n = 44) (14).

Stroke and major bleeding. Population-based studies indicate a 5-fold increase in the risk of stroke and systemic embolism in individuals with AF compared with those with sinus rhythm (33,34), as well as an increased risk of bleeding related to anticoagulant therapy (35). In the present study, contrary to preliminary reports (14,16), we did not observe any difference in the rate of stroke or major bleeding between patients with and without pre-existing or new-onset AF as a potential explanation for differences in mortality and morbidity.

STRENGTH AND LIMITATIONS. This study has several strong points. First, this is the only large-scale TAVI registry to investigate this issue, and we included all consecutive patients treated in a defined geographic territory over a given period, thus limiting the risk of selection bias as much as possible. It is also by far the largest multicenter registry available, including nearly 4 times more patients and analyzing nearly twice as many events than the largest studies available to date, and allowing extensive multivariate adjustment (21).

Conversely, this study also has some limitations that deserve to be emphasized. First, some echocardiographic variables were not recorded at baseline and during follow-up, including left atrial size, myocardial mass, and other specific hemodynamic data. Indeed, an atrial size of ≥27 mm/m^2 was identified as the cutoff point for the detection of new-onset AF after TAVI within 30 days in a previous study (14). Next, the FRANCE-2 registry was not powered to analyze outcomes according to the different type of AF (i.e., paroxysmal, persistent or permanent). Previous studies have shown that patients undergoing TAVI with AF had an increased risk of death irrespective of the type of AF (15). Finally, despite careful and complete assessment of patient data, it is always possible that some episodes of asymptomatic paroxysmal AF may have gone undetected.

CONCLUSIONS

Both pre-existing and new-onset AF represent major predictors of 1-year mortality after TAVI. We did not observe any difference in the rate of stroke and bleeding between patients with and without AF as a potential explanation for differences in mortality. The worse outcome observed in patients with pre-existing AF seems to be the expression of advanced heart disease, as suggested by echocardiographic data and the higher rate of heart failure adverse events observed in this group. The occurrence of new-onset AF after TAVI and the excess mortality that it engenders could be related to the thoracic surgical approach and periprocedural complications, especially VARC2-defined cardiological and hemorrhagic events. The inclusion of pre-existing AF in future risk scores dedicated to the selection of patients for either TAVI or SAVR should be considered, and specific post-procedural management could be envisaged for patients in whom new-onset AF develops after TAVI.

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PERSPECTIVES

WHAT IS KNOWN? In patients with AS undergoing conventional surgical aortic valve replacement, pre-existing AF is an independent predictor of perioperative and long-term adverse events. Similarly, occurrence of new-onset AF after cardiac surgery is associated with increased early and late morbidity and mortality.

WHAT IS NEW? We show that both pre-existing and new-onset AF represent major predictors of 1-year mortality after TAVI, without any difference in the rate of stroke and bleeding. Our data suggest that the worse outcome observed in patients with pre-existing AF may be the expression of advanced heart disease. The occurrence of new-onset AF after TAVI and the excess mortality that it engenders could be related to the thoracic surgical approach and periprocedural complications.

WHAT IS NEXT? The inclusion of pre-existing AF in future risk scores dedicated to selection of patients for either TAVI or SAVR should be considered, and specific post-procedural management could be envisaged for patients in whom new-onset AF develops after TAVI.

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KEY WORDS aortic stenosis, atrial fibrillation, outcomes, transcatheter aortic valve implantation

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