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Atrial Fibrillation and Aortic Stenosis

Impact on Clinical Outcomes Among Patients Undergoing Transcatheter Aortic Valve Implantation

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Background—Atrial fibrillation (AF) is an important risk factor for stroke and is common among elderly patients undergoing transcatheter aortic valve implantation. The aim of this study was to assess the impact of AF on clinical outcomes among patients undergoing transcatheter aortic valve implantation.

Methods and Results—Between August 2007 and October 2011, a total of 389 high-risk patients undergoing transcatheter aortic valve implantation were included into a prospective registry. AF was recorded in 131 patients (33.7%) with a mean CHA_2DS_2–VASC score of 4.5±1.2 and was paroxysmal in 26 (25.0%), persistent in 8 (7.7%), and permanent in 70 patients (67.3%). Patients with and without AF had similar baseline characteristics except for fewer revascularization procedures (coronary artery bypass grafting: 12% versus 22%; *P*=0.03) among AF patients. At 1 year, all-cause mortality was higher among patients with AF (30.9%) compared with those without AF (13.9%; hazard ratio [HR], 2.36; 95% confidence interval [CI], 1.43–3.90; *P*=0.0008). This was observed irrespective of the type of AF (permanent, HR, 2.47; 95% CI, 1.40–4.38; persistent, HR, 3.60; 95% CI, 1.10–11.78; paroxysmal, HR, 2.88; 95% CI, 1.37–6.05). Mortality gradually increased with higher CHA_2DS_2–VASC scores (score 1–3: HR, 2.20; 95% CI, 0.92–5.27; score 6–8: HR, 4.12; 95% CI, 2.07–8.20). The risks of stroke (3.9% versus 5.1%; HR, 0.76; 95% CI, 0.23–1.96; *P*=0.47) and life-threatening bleeding (19.8% versus 14.7%; HR, 1.37; 95% CI, 0.86–2.19; *P*=0.19) were similar among patients with and without AF.

Conclusions—AF is common among high-risk patients with severe aortic stenosis undergoing transcatheter aortic valve implantation and is associated with a >2-fold increased risk of all-cause and cardiovascular mortality, irrespective of the type of AF. The gradient of risk directly correlates with the CHA_2DS_2–VASC score. **(*Circ Cardiovasc Interv*. 2013;6:77-84.)**

Key Words: aortic stenosis ■ atrial fibrillation ■ outcomes ■ transcatheter aortic valve implantation

Atrial fibrillation (AF) is the most common arrhythmia in the general population characterized by uncoordinated electric activation of the atria.[1] Its prevalence increases with age ranging from 0.1% among patients <55 years to >9.0% in patients aged ≥80 years.[2] Because of the high prevalence of this rhythm disorder in the elderly population as well as similar risk factors for AF and severe degenerative aortic stenosis, both conditions may coexist in ≤50% of patients.[3,4] AF importantly affects cardiovascular physiology attributable to loss of atrioventricular synchrony and irregularity of ventricular contraction resulting in reduced cardiac output and increased filling pressures,[5] which may be further accentuated in the presence of severe aortic stenosis and myocardial hypertrophy. Conversely, left ventricular outflow obstruction attributable to aortic stenosis results in left ventricular hypertrophy and diastolic dysfunction, which itself may precipitate AF attributable to increased left atrial pressures.

AF has an important impact on cardiovascular morbidity and mortality. Population-based studies indicate an increased risk of stroke and systemic embolism as well as impaired long-term survival of individuals with AF compared with those with normal sinus rhythm.[6,7] Among patients with severe aortic stenosis and reduced left ventricular function undergoing surgical aortic valve replacement (SAVR), AF has been associated with an increased risk of perioperative and long-term adverse events.[8] Moreover, AF is an independent predictor for late adverse cardiac and cerebrovascular events, including congestive heart failure, stroke, and mortality after

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WHAT IS KNOWN

- Atrial fibrillation is the most frequent arrhythmia and its prevalence increases with age.
- Because of similar risk factors, atrial fibrillation and degenerative aortic stenosis may coexist in ≤50% of patients.
- Atrial fibrillation has an important impact on cardiovascular morbidity and mortality and is an independent predictor for adverse cardiac and cerebrovascular events after surgical aortic valve replacement.

WHAT THE STUDY ADDS

- Atrial fibrillation is observed in up to one third of high-risk patients with symptomatic, severe aortic stenosis undergoing transcatheter aortic valve implantation.
- Atrial fibrillation is associated with a 2-fold increased risk of all-cause and cardiovascular mortality among patients undergoing transcatheter aortic valve implantation at 1-year follow-up.
- Among patients with atrial fibrillation and severe aortic stenosis undergoing transcatheter aortic valve implantation, the CHA_2DS_2–VASC score directly correlates with the risk of all-cause mortality.

SAVR.[9] Transcatheter aortic valve implantation (TAVI) has become the treatment of choice among inoperable patients with severe, symptomatic aortic stenosis and is a treatment alternative to SAVR among high-risk elderly patients. However, little is known regarding the impact of preexisting and new-onset AF among those patients undergoing TAVI for treatment of severe aortic stenosis. We, therefore, compared the long-term clinical outcomes between patients with and without AF undergoing TAVI enrolled in a single center prospective registry and followed through 1 year.

Methods

Patient Population

Between August 2007 and October 2011, a total of 389 high-risk elderly patients with symptomatic severe aortic stenosis were included in a prospective single center registry (Bern TAVI Registry). Patients underwent TAVI with the self-expandable Medtronic CoreValve (Medtronic, Minneapolis, MN) and the balloon-expandable Edwards Sapien transcatheter heart valve (Edwards LifeSciences, Irvine, CA) via the transfemoral, the transapical, and the subclavian access routes, as previously described.[10] After the procedure, patients were either admitted to the intensive care or coronary care unit and monitored during the first 48 hours after the intervention for rhythm disturbances and other adverse events. After this, patients were transferred to the general ward, and rhythm disturbances were recorded with continuous monitoring using telemetric ECG surveillance. All patients were treated with acetylsalicylic acid 100 mg per day indefinitely and clopidogrel 75 mg per day for 6 months. Among patients with an indication for oral anticoagulation, a vitamin K antagonist was combined with either acetylsalicylic acid or clopidogrel alone.

The study complied with the Declaration of Helsinki, and the registry was approved by the local ethics committee. All patients provided written informed consent to participate in the registry with prospective follow-up assessment.

Data Collection

All patients were evaluated for the presence and absence of AF, including a systematic review of all electrocardiograms at the time of admission, during the hospitalization and at discharge. Moreover, any new episode of AF, irrespective of the requirement of a therapeutic intervention or early spontaneous conversion into normal sinus rhythm, during the hospitalization was recorded. Because atrial flutter is another supraventricular rhythm that may coexist or precede AF, we assigned patients with atrial flutter to the AF study group.

Adverse events were assessed in hospital, and regular clinical follow-up was performed for 30 days and 12 months by means of a clinical in-hospital visit or a standardized telephone interview. All suspected events were adjudicated by an unblinded clinical event committee consisting of interventional cardiologists and cardiac surgeons.

Definitions

For the purpose of this study, patients were categorized into 2 groups: (1) patients with AF specified according to the American College of Cardiology Foundation/American Heart Association/Heart Rhythm Society classification[11]—paroxysmal (recurrent episodes of AF that terminate spontaneously within 7 days), persistent (recurrent episodes with a duration of >7 days), and permanent AF (ongoing long-term episode) or new-onset AF after the TAVI intervention; and (2) patients without AF. $CHADS_2$ scores and CHA_2DS_2–VASC scores were calculated for patients with AF.

Clinical adverse events were adjudicated according to the Valve Academic Research Consortium (VARC) end point definitions, described in detail elsewhere.[12] The prespecified primary end point of the study was all-cause mortality.

Statistical Analysis

Baseline clinical and procedural characteristics, as well as follow-up data, were entered into a dedicated database, held at an academic clinical trials unit (Cardiobase, CTU Bern, Bern University Hospital) responsible for central data audits and maintenance of the database. Statistical analyses were performed by a statistician of an academic clinical trials unit (D.H., P.J.) using Stata 12 (StataCorp LP, College Station, TX). Continuous variables are presented as mean±SD and are compared by means of unpaired *t* tests. Categorical data are expressed as frequencies and percentages and are compared using χ^2 and Fisher exact tests. Survival estimates were reconstructed using the Kaplan–Meier method at 12-month follow-up. Outcomes in the AF group (raw counts [%]) were compared using Cox regression analysis censoring at last follow-up or death, respectively (crude). The corresponding hazard ratios (HR, 95% confidence interval [CI]) with probability values are also given. The proportional hazards assumption was tested using Schoenfeld residuals. Endpoints with zero events were presented with continuity corrected risk ratios (and 95% CI), but no attempt was made to estimate risk ratio comparing 1 event versus 0 event. The adjusted Cox regression analyses (inverse probability of treatment weight [IPTW]) of end points at 12 months were performed by weighing each patient's effect with the IPTW, where the treatment is AF (coded yes=1 and no AF=0). The propensity score was calculated by including all baseline characteristics affecting AF with a *P* value of <0.2 or affecting overall death at 12 months with a *P* value of <0.2. Bleeding events up to 12-month follow-up comparing AF groups were analyzed using Poisson regression with robust error variances and reported as counts (%) with risk ratio (95% CI). We prespecified crude analyses comparing the different types of AF versus no AF. We prespecified stratified outcome IPTW analyses, comparing the group of patients with AF with those without AF according to age (cutoff point 80 years of age), sex, diabetes mellitus, renal failure (cutoff point glomerular filtration rate <60 mL/min per 1.73 m^2), and ejection fraction (cutoff point left ventricular ejection fraction, 40%). In this stratified analysis, we tested for the difference between patients with AF and without AF in each subgroup separately (eg, EF <40 and >40), and we tested whether the interaction between the subgroup and the AF group was significant

in the model containing both subgroups (eg, EF group × AF group interaction). All *P* values and CIs are 2-sided. A *P* value <0.05 was considered statistically significant. The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the article as written.

Results

Patient Population

Among 389 consecutive patients undergoing TAVI for treatment of degenerative aortic valve stenosis, AF was recorded in 131 patients (33.7%). The mean CHA_2DS_2–VASC score amounted to 4.5±1.2 with 96% of patients with AF having a score >3. AF was documented before the procedure (preexisting) in 104 patients (26.7%) and was classified as paroxysmal in 26 (25.0%), persistent in 8 (7.7%), and permanent in 70 (67.3%) patients. New-onset AF was observed in 27 patients (6.9%) within 11±6 days after TAVI. Baseline clinical characteristics of patients undergoing TAVI are summarized in Table 1. Previous revascularization procedures were less common among TAVI patients with AF compared with patients without AF (coronary artery bypass grafting: 12% versus 22%; *P*=0.03; percutaneous coronary intervention: 18% versus 28%; *P*=0.03). Antithrombotic treatment more frequently included oral anticoagulation with a vitamin K antagonist among TAVI patients with (52%) than without AF (15%; *P*<0.001).

Procedural Results

Procedural characteristics and results are shown in Table 2**.** The preferred treatment strategy was the transfemoral access route (79%), and patients were treated either with the Medtronic CoreValve (58%) or the Edwards Sapien (42%) transcatheter heart valve prosthesis. There was no significant difference for any of the procedural characteristics, including procedure time, type of anesthesia, access route, and revascularization strategy among TAVI patients with and without AF.

Clinical Outcomes

Clinical outcomes through 1 year are summarized in Table 3**.** All-cause mortality was higher among patients with AF (30.9%) compared with those without AF (13.9%; HR, 2.36; 95% CI, 1.43–3.90; *P*=0.0008), which was mainly attributable to a higher cardiac mortality (23.4% versus 9.7%; HR, 2.37; 95% CI, 1.32–4.26; *P*=0.004). The composite of all-cause death, major stroke, or myocardial infarction was more common among patients with AF (32.2%) than without AF (18.6%; HR, 1.80; 95% CI, 1.14–2.85; *P*=0.01), whereas there were no differences with respect to myocardial infarction (1.5% versus 1.5%; HR, 1.53; 95% CI, 0.26–9.19; *P*=0.64), major stroke (3.9% versus 5.1%; HR, 0.67; 95% CI, 0.23–1.96; *P*=0.47), or transient ischemic attack (0% versus 0.6%).

The increased risk of death among patients with AF as compared with those without AF was more pronounced for preexisting (HR, 2.50; 95% CI, 1.48–4.23; *P*=0.00061) than for new-onset AF (HR, 1.91; 95% CI, 0.78–4.68; *P*=0.16) at 1 year (Table I in the online-only Data Supplement) (Figure 1). All-cause mortality was increased for any type of AF including permanent (HR, 2.47; 95% CI, 1.40–4.38; *P*=0.002), persistent (HR, 3.60; 95% CI, 1.10–11.78; *P*=0.034), and paroxysmal AF (HR, 2.88; 95% CI, 1.37–6.05; *P*=0.005) (Figure 2). In stratified analyses, the increased mortality risk among patients with AF as compared with those without AF was consistent across major subgroups, including age, diabetes mellitus, renal function, coronary artery disease, and left ventricular ejection fraction (Figure 3). Among patients with AF, the risk of death at 1 year correlated with the CHA_2DS_2–VASC score and was highest in the group of patients with a CHA_2DS_2–VASC score of >6 (HR, 4.12; 95% CI, 2.07–8.20; *P*=0.00039) (Figure 4).

Table 1. Baseline Clinical Characteristics

	All Patients	No AF	AF	*P* Value
	N=389	N=258	N=131	
Age, y	82.5±5.8	82.4±6.1	82.6±5.3	0.86
Female sex, n (%)	224 (58)	148 (57)	76 (58)	0.91
Body mass index, kg/m^2	26.1±5.1	26.1±5.1	26.4±5.0	0.58
Cardiovascular risk factors				
Hypertension, n (%)	303 (78)	195 (76)	108 (82)	0.16
Diabetes mellitus, n (%)	105 (27)	70 (27)	35 (27)	1.00
Past medical history				
Previous myocardial infarction, n (%)	64 (16)	47 (18)	17 (13)	0.20
Previous CABG, n (%)	72 (19)	56 (22)	16 (12)	0.03
Previous PCI, n (%)	94 (24)	71 (28)	23 (18)	0.03
Previous cerebrovascular event, n (%)	30 (8)	19 (7)	11 (8)	0.69
Symptoms				
NYHA functional class				0.46
NYHA I, n (%)	22 (6)	17 (7)	5 (4)	
NYHA II, n (%)	109 (28)	76 (30)	33 (25)	
NYHA III, n (%)	206 (53)	133 (52)	73 (56)	
NYHA IV, n (%)	49 (13)	30 (12)	19 (15)	
Risk assessment				
Logistic EuroSCORE, %	24.3±14.2	23.7±14.2	25.4±14.1	0.26
STS score, %	6.8±5.3	6.8±5.6	6.9±4.5	0.85
Clinical features				
Renal failure (GFR<60 mL/min per 1.73 m^2)	268 (69)	172 (67)	96 (73)	0.20
Coronary artery disease, n (%)	238 (61)	165 (64)	73 (56)	0.12
Left ventricular ejection fraction, %	51.9±14.8	52.7±15.1	50.2±14.1	0.12
Aortic valve area, cm^2	0.6±0.2	0.6±0.2	0.5±0.2	0.23
Mean transaortic gradient, mm Hg	44.2±16.8	45.1±17.0	42.4±16.2	0.14
Antithrombotic therapy				
Aspirin, n (%)	237 (62)	184 (72)	53 (41)	<0.001
Clopidogrel, n (%)	69 (18)	53 (21)	16 (12)	0.0490
Oral anticoagulation, n (%)	106 (28)	38 (15)	68 (52)	<0.001

AF indicates atrial fibrillation; CABG, coronary artery bypass surgery; EuroSCORE, European System for Cardiac Operative Risk Evaluation; GFR, glomerular filtration rate; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; and STS, Society of Thoracic Surgeons.

Table 2. Procedural Characteristics

	All Patients	No AF	AF	*P* Value
	N=389	N=258	N=131	
Procedure time, min	82.7±35.4	82.3±34.5	83.4±37.1	0.85
Amount of contrast, mL	252.2±96.7	255.8±96.5	245.3±96.9	0.18
General anesthesia, n (%)	164 (42)	106 (41)	58 (44)	0.43
Access route				0.46
Femoral, n (%)	308 (79)	211 (82)	97 (74)	
Apical, n (%)	76 (20)	45 (17)	31 (24)	
Subclavian, n (%)	5 (1)	2 (1)	3 (2)	
Valve type				0.62
Edwards Sapien valve, n (%)	165 (42)	104 (40)	61 (47)	
Medtronic CoreValve, n (%)	224 (58)	154 (60)	70 (53)	
Revascularization				
Concomitant PCI, n (%)	63 (16)	39 (15)	24 (18)	0.27
Staged PCI, n (%)	35 (9)	24 (9)	11 (8)	1.00

AF indicates atrial fibrillation; and PCI, percutaneous coronary intervention.

Antithrombotic regimen after TAVI was different in patients with AF compared with those without AF (Table II in the online-only Data Supplement). The majority of patients without AF received dual antiplatelet therapy with aspirin and clopidogrel (84%) at the time of hospital discharge, whereas few patients received an individualized treatment approach with either vitamin K antagonist monotherapy (2%), combination of either aspirin and vitamin K antagonist (5%), or clopidogrel and vitamin K antagonist (4%). Patients with AF received dual antiplatelet therapy in 31%, a combination of clopidogrel and vitamin K antagonist in 19%, aspirin and vitamin K antagonist in 20%, or vitamin K antagonist monotherapy in 14% of cases at the time of hospital discharge. The differences in antithrombotic treatment between patients with AF and without AF were sustained at 30 days and 1 year of follow-up ($P<0.001$).

Discussion

The present study investigating clinical outcomes of patients with symptomatic severe aortic stenosis and concomitant AF undergoing TAVI has the following main findings:

- AF is common among high-risk elderly patients with symptomatic severe aortic stenosis undergoing TAVI.
- AF is associated with a >2-fold increased risk of all-cause and cardiovascular mortality at 1 year in this patient population.
- AF confers an increased risk of mortality irrespective of type of AF among TAVI patients.
- The CHA_2DS_2–VASC score among patients with AF and severe aortic stenosis undergoing TAVI directly correlates with the risk of death.

The prevalence of AF in patients with symptomatic severe aortic stenosis is high and amounted to 34% in this elderly patient population. AF may be the direct result of heart failure precipitated by aortic stenosis attributable to increased atrial pressures and atrial dilatation leading to atrial fibrosis and regional conduction abnormalities which beget AF. Conversely, AF may impair symptoms of heart failure among patients with severe aortic stenosis attributable to loss of atrioventricular synchrony, the fast and irregular ventricular response, and sympathetic activation leading to therapeutic intervention. In the PARTNER (Placement of Aortic Transcatheter Valve) cohort B comparing TAVI with medical treatment among inoperable patients, the prevalence of AF was as high as 48.8% (TAVI group 32.9%, medical group 48.8%),[13] whereas in the PARTNER A cohort comparing TAVI with SAVR among high-risk surgical patients, AF was present in up to 42.7% of patients (TAVI group 40.8%, SAVR group 42.7%).[14] Compared with SAVR, the prevalence of new-onset AF in patients undergoing TAVI is lower (PARTNER A: TAVI 8.6% versus SAVR 16%; $P=0.006$), the duration shorter and limited,[15] and the pathophysiological mechanisms different. Although inflammatory components are responsible for the occurrence of new-onset AF after cardiac surgery,[16] the mechanisms leading to the arrhythmia after minimal-invasive

Table 3. Clinical Outcomes at 12 Months

	12 mo			HR or RR (95% CI) AF vs No AF		*P* Value	
	Overall (n=389)	No AF (n=258)	AF (n=131)	Crude	IPTW	Crude	IPTW
All-cause death, n (%)	66 (19.6)	31 (13.9)	35 (30.9)	2.45 (1.51–3.98)	2.36 (1.43–3.90)	0.0003	0.0008
Cardiac events							
Cardiac death, n (%)	48 (14.2)	22 (9.7)	26 (23.4)	2.53 (1.44–4.47)	2.37 (1.32–4.26)	0.001	0.004
Myocardial infarction, n (%)	5 (1.6)	3 (1.5)	2 (1.5)	1.42 (0.24–8.52)	1.53 (0.26–9.19)	0.70	0.64
Neurological events							
Stroke, n (%)	17 (4.8)	12 (5.1)	5 (3.9)	0.85 (0.30–2.40)	0.67 (0.23–1.96)	0.75	0.47
Transient ischemic attack, n (%)	1 (0.4)	1 (0.6)	0 (0.0)	na	na	na	na
Bleeding events							
Life-threatening bleeding, n (%)	64 (16.5)	38 (14.7)	26 (19.8)	1.35 (0.86–2.12)	1.37 (0.86–2.19)	0.20	0.19
Major bleeding, n (%)	125 (32.1)	85 (32.9)	40 (30.5)	0.93 (0.68–1.27)	1.02 (0.74–1.40)	0.63	0.92
Composite outcomes							
All-cause death or stroke, n (%)	77 (22.6)	40 (17.7)	37 (32.6)	1.98 (1.27–3.10)	1.89 (1.19–3.00)	0.003	0.01

AF indicates atrial fibrillation; CI, confidence interval; HR, hazard ratio; IPTW, inverse probability of treatment weight; na, not available; and RR, risk ratio. HR from Cox regression for crude and adjusted analyses: for all-cause death, cardiac death, myocardial infarction, major stroke, and composites. RR from Poisson regression with robust error variances for crude and adjusted analyses: for bleeding events. IPTW adjusted, where the treatment is AF.

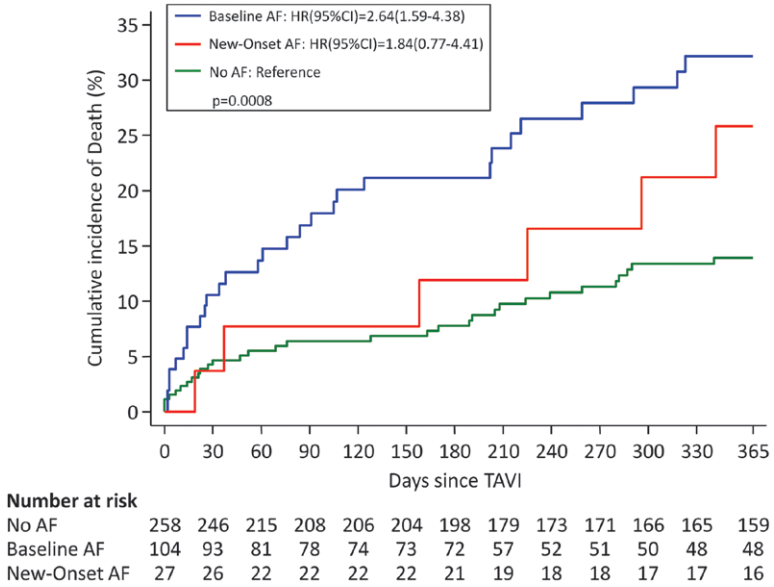


Figure 1. Cumulative incidence of all-cause mortality among patients with preexisting, new-onset atrial fibrillation (AF), and patients without AF during the follow-up period of 12 months. CI indicates confidence interval; HR, hazard ratio; and TAVI, transcatheter aortic valve implantation.

catheter-based aortic valve implantation are less well understood. Amat-Santos et al[17] investigated the impact of new-onset AF among 138 high-risk patients without a history of previous AF undergoing TAVI and, therefore, excluded a priori patients with preexisting AF. In this study, new-onset AF was observed in up to one third of patients as compared with 7% in the present study and was associated with a higher rate of cerebrovascular events, but not death, during the follow-up period.

In the general population, AF is estimated to increase the risk of death 1.5-fold among men and 1.9-fold among women.[6,18] Among patients with heart failure and reduced left ventricular function, new-onset AF has been identified as an independent predictor of mortality and long-term follow-up of the Framingham cohort, suggesting that patients with AF have a deleterious outcome.[19] In the present study of elderly patients undergoing TAVI, patients with AF experienced worse clinical outcome with respect to all-cause death and cardiovascular mortality compared with patients without AF. These findings are supported by a recent multicenter study evaluating prognostic factors and long-term outcomes after TAVI. In this study, chronic AF emerged as 1 of the predictors of late mortality with a 1.4-fold increased risk for all-cause mortality.[20] This observation among patients undergoing TAVI is in accordance with outcomes after SAVR in patients with preexisting AF and reduced left ventricular function, where AF is associated with an ≈8-fold increased risk of mortality[8] compared with patients without AF during short- and long-term follow-up.[9] Multiple reasons might be responsible for this. In most cases, the development of AF is an expression of advanced heart disease with structural remodeling and myocardial fibrosis,[21] which by accelerating the process of cardiac senescence may increase cardiovascular mortality. Moreover, the loss of atrioventricular synchrony and the variation in ventricular cycle length lead to impaired ventricular filling, reduced cardiac output, and increased afterload, which are hemodynamic factors known to adversely affect clinical outcomes among heart failure patients. Of note, we did not observe differences in rates of stroke or systemic embolism between patients with and without AF in the present study as potential explanation for differences in mortality. Although we cannot exclude the

All-cause Mortality at 12 Months According to Atrial Fibrillation Classification

	n	events (%)	HR (95% CI)	p - value
No Atrial Fibrillation (Pre and Post)	258	31 (12.0%)	reference	
Permanent Atrial Fibrillation	70	19 (27.1%)	2.47 (1.40-4.38)	0.002
Persistent Atrial Fibrillation	8	3 (37.5%)	3.60 (1.10-11.78)	0.034
Permanent / Persistent Atrial Fibrillation	78	22 (28.2%)	2.59 (1.50-4.47)	0.001
Paroxysmal Atrial Fibrillation / Atrial Flutter	31	9 (29.0%)	2.88 (1.37-6.05)	0.005
Any Atrial Fibrillation (Pre or Post)	131	35 (26.7%)	2.45 (1.51-3.98)	<0.0001

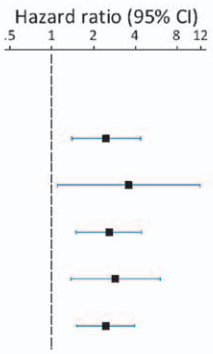
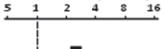


Figure 2. Stratified analysis according to type of atrial fibrillation (AF) for all-cause mortality at 12 months. CI indicates confidence interval.

Stratified IPTW Adjusted Analyses of All-Cause Mortality Across Major Subgroups

	No AF N = 258	AF N = 131	Hazard ratio (95% CI)	p value	p value interaction
Age					0.870
≤80 years	5/66	7/31	2.53 (0.78-8.22)	0.124	
>80 years	26/192	28/100	2.29 (1.32-3.98)	0.003	
Gender					0.469
Male	13/110	17/55	2.86 (1.35-6.03)	0.006	
Female	18/148	18/76	1.97 (1.01-3.84)	0.047	
Diabetes mellitus					0.462
No	22/188	22/96	2.05 (1.12-3.78)	0.020	
Yes	9/70	13/35	3.22 (1.36-7.62)	0.008	
Renal Function					0.691
GFR < 60ml/min/1.73m^2	8/86	6/35	1.93 (0.65-5.72)	0.233	
GFR ≥ 60ml/min/1.73m^2	23/172	29/96	2.48 (1.41-4.37)	0.002	
Coronary Artery Disease					0.366
No	11/93	11/58	1.70 (0.73-3.97)	0.222	
Yes	20/165	24/73	2.81 (1.52-5.19)	0.001	
Left ventricular ejection fraction					0.610
>40%	21/195	23/92	2.55 (1.39-4.68)	0.003	
≤40%	10/62	12/39	1.98 (0.83-4.69)	0.122	



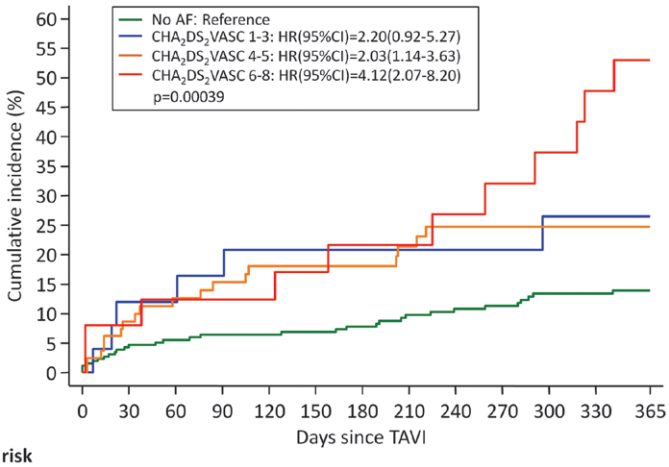
IPTW: Inverse Probability of Treatment Weight adjusted, where the "treatment" is AF.

Figure 3. Stratified analysis for all-cause mortality among major subgroups. CI indicates confidence interval; GFR, glomerular filtration rate; and IPTW, inverse probability of treatment weight.

benefit of appropriately chosen antithrombotic therapy, it is more likely that the majority of strokes occurred during the peri-interventional period and, therefore, represented adverse events related to the procedure potentially camouflaging the risk of stroke inherent to AF.[22]

Patients with AF experienced an increased risk of death irrespective of the type of AF, including permanent (HR, 2.47; 95% CI, 1.40–4.38; *P*=0.002), persistent (HR, 3.60; 95% CI, 1.10–11.78; *P*=0.034), and paroxysmal AF (HR, 2.88; 95% CI, 1.37–6.05; *P*=0.005) in the present study. The European Heart Survey on AF observed the highest rate of death among patients with permanent AF, although mortality remained substantial among patients with first onset of AF.[23] In the French Etude en Activité Libérale de la Fibrillation Auriculaire (ALFA) study, the type of AF was not predictive of mortality and risk of systemic embolism. Similarly, the risk of stroke has been shown as high for paroxysmal as for persistent and permanent AF in previous cohort studies.[24]

AF constitutes a major risk factor for cardioembolic ischemic events that are associated with significant disability, partial or total loss of independence in everyday life activities, and a high rate of mortality.[22] The recommended antithrombotic therapy is able to reduce these events, while increasing the risk for bleeding especially in this elderly patient population.[25] The $CHADS_2$- and more recently the CHA_2DS_2–VASC score provide a reliable risk stratification



Number at risk

No AF	258	246	215	208	206	204	198	179	173	171	166	165	159
CHA_2DS_2VASC 1-3	25	22	20	19	18	18	18	14	14	14	13	13	13
CHA_2DS_2VASC 4-5	81	74	64	62	59	59	59	47	42	42	42	42	42
CHA_2DS_2VASC 6-8	25	23	19	19	19	18	16	15	14	13	12	10	9

Figure 4. Cumulative incidence of all-cause mortality among patients with atrial fibrillation (AF) compared with patients without AF according to the CHA_2DS_2–VASC risk stratification. CI indicates confidence interval; HR, hazard ratio; and TAVI, transcatheter aortic valve implantation.

for cerebrovascular events in patients with AF.[26] The CHA_2DS_2–VASC score was a marker of impaired prognosis in the present study with a gradual increase in the risk of death with increasing CHA_2DS_2–VASC scores (Figure 4). The predictive ability of the CHA_2DS_2–VASC score in terms of death in patients with AF has been recently confirmed in a large patient population from the Prospective Danish Diet, Cancer and Health cohort study.[27]

Limitations

Several limitations need to be acknowledged, when interpreting the results of this study. First, the study population is based on the experience of a single, tertiary care center, and the results may not be applicable to other centers with different procedural experience, as well as device and patient selection. Second, the assessment of AF was based on preprocedural ECG evaluation and the review of patient charts, including past medical history as well as previous reports from referring cardiologists and general practitioners. Despite careful and complete assessment of patient data, only symptomatic and apparent episodes of AF have been detected, leaving a small proportion of patients with asymptomatic, paroxysmal AF which may have been undetected. Finally, because of the preprocedural evaluation algorithm at our institution to perform transesophageal echocardiography rather than transthoracic echocardiography, we are unable to include reliable data on left atrial size, myocardial mass, or other specific hemodynamic data in our analysis.

Conclusion

AF is common among high-risk patients with severe aortic stenosis undergoing TAVI and is associated with a >2-fold increased risk of all-cause and cardiovascular mortality, irrespective of the type of AF. The gradient of risk directly correlates with the CHA_2DS_2–VASC score.

Disclosures

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Supplemental Table 1 **Clinical Outcomes at 12 Months**

	12 Months			Baseline AF vs No AF		New-Onset AF vs No AF		Overall p-value	
	No AF n=258	Baseline AF n=104	New-Onset AF n=27	Crude	IPTW	Crude	IPTW	Crude	IPTW
All Cause Death, n(%)	31(13.9%)	29(32.2%)	6(25.8%)	2.64(1.59-4.38)	2.50(1.48-4.23)	1.84(0.77-4.41)	1.91(0.78-4.68)	0.0009	0.0025
Cardiac Events									
Cardiac Death, n(%)	22(9.7%)	23(26.0%)	3(13.3%)	2.89(1.61-5.20)	2.72(1.49-4.97)	1.30(0.39-4.34)	1.22(0.36-4.14)	0.0016	0.0045
Myocardial Infarction, n(%)	3(1.5%)	1(1.0%)	1(3.7%)	0.91(0.09-8.78)	1.26(0.14-11.54)	3.21(0.33-30.87)	2.49(0.25-24.37)	0.57	0.74
Neurologic Events									
Stroke, n(%)	12(5.1%)	5(4.9%)	0(0.0%)	1.08(0.38-3.07)	0.87(0.30-2.51)	0.003(0->99)*	na	0.78*	na
Transient Ischemic Attack, n(%)	1(0.6%)	0(0.0%)	0(0.0%)	na	na	na	na	na	na
Bleeding Events									
Life Threatening Bleeding, n(%)	38(14.7%)	17(16.3%)	9(33.3%)	1.11(0.66-1.88)	1.16(0.68-2.00)	2.26(1.23-4.16)	2.13(1.11-4.07)	0.0301	0.0728
Major Bleeding, n(%)	85(32.9%)	30(28.8%)	10(37.0%)	0.88(0.62-1.24)	0.99(0.70-1.41)	1.12(0.67-1.90)	1.11(0.63-1.94)	0.64	0.93
Composite Outcomes									
All Cause Death or Stroke, n(%)	40(17.7%)	31(34.2%)	6(25.8%)	2.16(1.35-3.46)	2.02(1.24-3.30)	1.39(0.59-3.28)	1.45(0.61-3.48)	0.0056	0.0182

Hazard ratios HR from Cox's regression: for all-cause death, cardiac death, MI, major stroke and composites
Relative risk ratios RR from Poisson regression with robust error variances: for bleeding events
Index: RR with continuity correction (adding 1/n of opposite treatment group), p-value from Fisher's exact test

Supplemental Table 2 **Antithrombotic Regimen According to Atrial Fibrillation**

	No AF	AF	p-value
	N = 258	N = 131	
Discharge			<0.001
Aspirin Single Therapy, n (%)	5 (2%)	5 (4%)	
Clopidogrel Single Therapy, n (%)	4 (2%)	4 (3%)	
Warfarin Single Therapy, n (%)	6 (2%)	17 (14%)	
Aspirin + Clopidogrel, n (%)	209 (84%)	37 (31%)	
Aspirin + Warfarin, n (%)	13 (5%)	24 (20%)	
Clopidogrel + Warfarin, n (%)	9 (4%)	23 (19%)	
Aspirin + Clopidogrel + Warfarin, n (%)	2 (1%)	9 (8%)	
30 Days Follow Up			<0.001
Aspirin Single Therapy, n (%)	23 (10%)	11 (10%)	
Clopidogrel Single Therapy, n (%)	10 (4%)	4 (4%)	
Warfarin Single Therapy, n (%)	7 (3%)	22 (20%)	
Aspirin + Clopidogrel, n (%)	173 (73%)	38 (34%)	
Aspirin + Warfarin, n (%)	14 (6%)	15 (14%)	
Clopidogrel + Warfarin, n (%)	4 (2%)	17 (15%)	
Aspirin + Clopidogrel + Warfarin, n (%)	7 (3%)	4 (4%)	
12 Months Follow Up			<0.001
Aspirin Single Therapy, n (%)	78 (49%)	12 (21%)	
Clopidogrel Single Therapy, n (%)	6 (4%)	6 (11%)	
Warfarin Single Therapy, n (%)	15 (9%)	23 (40%)	
Aspirin + Clopidogrel, n (%)	47 (29%)	7 (12%)	
Aspirin + Warfarin, n (%)	12 (8%)	6 (11%)	
Clopidogrel + Warfarin, n (%)	2 (1%)	3 (5%)	
Aspirin + Clopidogrel + Warfarin, n (%)	0 (0%)	0 (0%)	