Type of Atrial Fibrillation and Clinical Outcomes in Patients Undergoing Transcatheter Aortic Valve Replacement

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Background: There are limited data available regarding the relationship between atrial fibrillation (AF) clinical type, oral anticoagulation (OAC) treatment, and clinical outcome after transcatheter aortic valve replacement (TAVR). The study was designed to evaluate this relationship.

Methods: We analyzed data from the Rabin Medical Center TAVR registry, including 319 consecutive patients who underwent TAVR from 2008 to 2014. Patients were divided into three groups based on their history of AF: sinus rhythm (SR), paroxysmal AF (PAF), or nonparoxysmal AF (NPAF).

Results: There were 211 (66%), 56 (18%), and 52 (16%) patients in the SR, PAF, and NPAF groups, respectively. The cumulative risk for stroke or death at 2 years was highest among patients with NPAF (38%), but similarly low in PAF (15%) and SR patients (16%, $P < 0.001$). By multivariate analysis, patients with NPAF demonstrated a significantly higher risk of stroke or death (HR = 2.76, 95% CI 1.63–4.66, $P < 0.001$), as compared with SR. In contrast, patients with PAF had a similar risk of stroke or death compared with SR (HR = 0.80, $P = 0.508$). Patients with NPAF not treated with OAC demonstrated an 8.3-fold ($P < 0.001$) increased risk of stroke or death, whereas patients with PAF not treated with OAC had a similar risk of stroke or death compared with the SR group (HR = 1.25, $P = 0.569$).

Conclusion: History of NPAF, but not PAF, is associated with a significant increased risk of stroke or death compared with sinus rhythm in patients undergoing TAVR.

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Transcatheter aortic valve replacement (TAVR) has become an established treatment option for patients with severe aortic stenosis who cannot undergo surgical aortic valve replacement or are at high surgical risk. Currently, the vast majority of patients who undergo TAVR are elderly with multiple comorbidities.¹ Atrial fibrillation (AF) is the most common sustained arrhythmia encountered in clinical practice; its prevalence increases with advancing age,² and it is associated with increased

risk for stroke, heart failure, and death. Although much is known about the outcome of patients with AF postsurgical aortic valve replacement,^{3–5} there are only limited and conflicting data available regarding the relationship between AF clinical type (i.e., paroxysmal vs nonparoxysmal AF) and clinical outcome after TAVR. While some studies found that AF has no effect on prognosis after TAVR,^{6–8} irrespective of the clinical type of AF, other studies found that AF is associated with

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increased risk of stroke and all-cause mortality.^{9–12} In addition, there are accumulating data, that the duration and clinical type of AF may be important determinants of clinical outcome among patients with AF in the general population.^{8,13–20} Thus, we sought to investigate the relation between AF clinical types, oral anticoagulation (OAC) therapy and long-term (up to 5 years) clinical outcomes among patients with severe aortic stenosis who underwent TAVR at our center.

METHODS

We included 319 consecutive patients who underwent TAVR at our center and were followed up prospectively between August 2008 and November 2014. The design and management of the Rabin Medical Center TAVR registry has been reported previously.^{21–23} In brief, all patients with severe and symptomatic aortic stenosis were referred to a dedicated consultation “heart team” forum at our hospital. All patients considered for valve replacement were assessed by coronary and peripheral angiography. Patients selected for TAVR underwent transesophageal echocardiography and multislice computed tomography angiography, as required. Both the logistic European System for Cardiac Operative Risk Evaluation score (log EuroSCORE) and Society of Thoracic Surgeons (STS) score were calculated and determined before the TAVR procedure. Patients with a log EuroSCORE >15% and an STS score >8% were evaluated individually and often referred for TAVR. Patients were assessed by a neurologist and a psychogeriatrician before the procedures and patients’ baseline neurological status were documented. During the study period, we used the following transcatheter aortic valve devices: The SAPIEN or SAPIEN XT prosthesis (Edwards Lifesciences, Irvine, CA, USA) and the CoreValve prosthesis (Medtronic, Minneapolis, MN, USA).

The standard antithrombotic treatment after TAVR was a combination of lifelong aspirin and 6 months clopidogrel. For patients already treated with OAC (the vast majority was warfarin), 6 months clopidogrel was added to OAC. Demographic, clinical, and laboratory data were collected before TAVR, during hospitalization, and postoperatively at 30 days, 6, 12 months, and yearly after. All patients were examined in a dedicated TAVR clinic following the procedure.

All collected data were registered in an electronic database.

Data on history of AF were collected by revision of medical records, including hospitalizations and outpatient clinics visits that contained ECG descriptions. Patients were divided into three groups based on their history of AF and AF type: sinus rhythm (SR), paroxysmal AF (PAF), or nonparoxysmal AF (NPAF). PAF was defined as an episode of AF that terminates spontaneously or with intervention in less than 7 days.²⁴ NPAF was defined as any other type of AF, i.e., persistent AF, long-standing persistent, and permanent AF. Data regarding OAC treatment were obtained by revision of medical records. OAC status (on off) was determined relative to the date of TAVR and was used in the analyses as a time-dependent variable. For patients that were off OAC treatment before TAVR, but treated after TAVR, we calculated the time elapsed from TAVR to initiation of OAC. Risk factors not captured by traditional risk scores, like porcelain aorta, were defined according to the Valve Academic Research Consortium-2 (VARC-2) consensus document.²⁵

The primary endpoint was a composite of stroke and all-cause death throughout 5 years follow-up after TAVR. The separate endpoints of death or stroke were used as secondary endpoints. Stroke was defined according to the VARC-2 consensus document.²⁵ All stroke events were diagnosed by an independent neurologist who was called whenever a neurologic event was suspected based on new neurologic symptoms and neuroimaging findings occurring after TAVR or during follow-up.

Continuous variables were expressed as mean $\pm$ standard deviation or median (interquartile range) as appropriate. Categorical data were summarized as frequencies and percentages. Characteristics of study patients were compared by the ANOVA or Kruskal-Wallis test for continuous variables, and chi-square (or Fisher’s exact) test for dichotomous variables, as appropriate.

The probability of death or stroke by history of AF type was graphically displayed according to the method of Kaplan and Meier, with comparison of cumulative events by the log-rank test. The association between the type of AF and clinical outcome was investigated using the Cox proportional hazard regression models. The best subsets regression procedure was used to identify significant variables to be included in the multivariate regression model. The

variables that were included are age, frailty, left ventricular ejection fraction (LVEF), hospitalization 6 months prior to TAVR, creatinine, EuroSCORE, CHA₂DS₂-VASc score, and AF type. In the model investigating the association between history of AF and stroke alone, the prespecified variables that were included are CHA₂DS₂-VASc score and AF type. The association between type of AF, OAC status and clinical outcome was assessed using OAC as a time-dependent variable. Analyses were conducted with SAS software (version 9.4, SAS institute, Cary, NC, USA). A 2-sided P value <0.05 was used for declaring statistical significance.

RESULTS

This study comprised 319 consecutive patients that have undergone TAVR, of whom 211 (66.1%) did not have a history of AF (SR group) and 108 (33.9%) had a history of AF. Fifty-six patients (17.6%) had a history of PAF (PAF group) and 52 (16.3%) had a history of persistent or permanent AF (NPAF group).

The baseline characteristics of study patients by history of SR and AF type are shown in Table 1. The distribution of demographic and clinical characteristics including age, gender, comorbidities, New York Heart Association functional class, CHA₂DS₂-VASc score, STS score, aortic valve area, LVEF, and the type of valve implanted was similar among the three groups. However, there was a gradual increase in the proportion of patients who underwent prior valvular surgery or a pacemaker implantation among the SR, PAF, and NPAF groups, respectively. Patients in the NPAF and PAF groups were less likely to receive aspirin compared with the SR group, whereas there was a gradual increase in the proportion of patients treated with anticoagulation among the SR, PAF, and NPAF groups, respectively. Patients with PAF were more likely to receive antiarrhythmic medications compared with SR or NPAF patients.

During a median follow-up of 2 years (interquartile range 0.7–3.0 years), 81 patients (25.4%) experienced the primary endpoint of stroke or death, 67 patients (21.0%) died (10 of them had stroke before death), and 24 patients (7.5%) experienced a stroke event (including 23 ischemic stroke events, and 1 hemorrhagic stroke). Patients with NPAF exhibited significantly higher rates of stroke or death compared with the PAF and SR groups during study follow-up. Thus, at 1 year of

follow-up, the cumulative risk for stroke or death was 32% in the NPAF group, but was similarly low among patients in the PAF group (12%) and SR group (12%, $P < 0.001$; Fig. 1). At 2 years of follow-up, the cumulative risk for stroke or death was 38% in the NPAF group, 15% in the PAF group, and 16% in the SR group.

Consistent with this finding, multivariate analysis demonstrated (Table 2) that patients with NPAF had a significantly higher risk of stroke (Hazard ratio [HR] = 2.58, $P = 0.042$), death (HR = 2.54, $P = 0.002$), and stroke or death (HR = 2.76, $P < 0.001$), as compared with SR. By contrast, patients with PAF compared with SR had a similar risk of stroke (HR = 0.81, $P = 0.745$), death (HR = 0.85, $P = 0.657$), and stroke or death (HR = 0.80, $P = 0.508$).

Among the 56 patients with PAF and 52 patients with NPAF, 28 (50%) and 42 (81%) were treated with OAC before TAVR, respectively. The rest of the patients were not treated with OAC; the decision not to prescribe OAC before TAVR was made at the discretion of the primary care physician. One patient had to stop OAC treatment after TAVR due to bleeding. Seventeen patients that were not treated with OAC before TAVR started new OAC treatment during hospitalization, as the cardiologist assessed that their stroke risk is higher than their bleeding risk. By multivariate analysis, patients with NPAF not treated with OAC demonstrated an 8.3-fold increased risk of stroke or death ($P < 0.001$), whereas patients with PAF not treated with OAC had a similar risk of stroke or death (HR = 1.25, $P = 0.569$) compared with the SR group (Table 3). Patients with NPAF that were treated with OAC demonstrated increased risk, albeit milder, of stroke or death (HR = 2.16, $P = 0.011$), whereas no statistically significant difference in the risk of stroke or death was observed in patients with PAF treated with OAC compared with the SR group (HR = 0.44, $P = 0.167$).

Of note, in a separate analysis, evaluating the effect of AF clinical type among patients treated with OAC, we found that NPAF was associated with almost a five-fold increased risk of stroke or death (HR = 4.95, $P = 0.013$) compared with PAF.

DISCUSSION

The results of this study among patients undergoing TAVR, demonstrate that history of

Table 1. Patient Characteristics

Variables	SR (n = 211)	PAF (n = 56)	NPAF (n = 52)
Age (years)	82.0 ± 6.4	81.2 ± 7.1	82.8 ± 6.2
Male	38%	52%	46%
Diabetes mellitus	33%	30%	31%
Hypertension	91%	93%	92%
Peripheral vascular disease	19%	18%	12%
Chronic obstructive pulmonary disease	23%	23%	21%
Myocardial infarction	10%	11%	2%
History of stroke	18%	29%	19%
Porcelain aorta	7%	5%	4%
Percutaneous coronary intervention	31%	23%	15%
Coronary artery bypass graft	23%	24%	19%
History of valvular surgery	7%	7%	19%*
History of pacemaker implantation	6%	11%	19%*
Recent (6 months) hospitalization	51%	61%	62%
Creatinine (mg/dL)	1.0 (0.8–1.3)	1.0 (0.84–1.32)	1.0 (0.9–1.5)
Estimated glomerular filtration rate (mL/min per 1.73m ²)	67.2 ± 27.0	64.1 ± 24.6	60.6 ± 26.1
CHA ₂ DS ₂ -VASc score	5 (5–6)	5 (5–7)	5 (5–6)
EuroSCORE	16.6 (11.4–25.5)	15.3 (12.2–26.0)	18.2 (12.5–29.9)
STS score	6.1 (4.3–9.1)	7.4 (4.7–11.2)	6.6 (5.1–10.1)
Baseline echocardiography			
Aortic valve area (cm ²)	0.6 ± 0.2	0.7 ± 0.2	0.6 ± 0.2
Left ventricular ejection fraction (%)	51.0 ± 8.2	49.0 ± 8.9	51.1 ± 8.0
TAVR features			
CoreValve (vs SAPIEN)	71%	80%	69%
Transfemoral approach	84%	84%	81%
Medications			
Aspirin	80%	54%	42%*
Oral anticoagulation	1%	41%	83%*
Angiotensin converting enzyme inhibitors or angiotensin receptor blockers	67%	74%	75%
Beta-blockers	54%	66%	67%
Antiarrhythmic medications	0%	32%	4%*

*P < 0.05 for comparison among the three groups.

Data are presented as percentage, mean ± standard deviation, or median (interquartile range).

NPAF = nonparoxysmal atrial fibrillation; PAF = paroxysmal atrial fibrillation; SR = sinus rhythm; STS = Society of Thoracic Surgeons.

Table 2. Risk of Stroke or Death by Atrial Fibrillation Type

Stroke or death	HR ^a	95% CI	P Value
PAF	0.80	0.41–1.56	0.508
NPAF	2.76	1.63–4.66	<0.001
Stroke			
PAF	0.81	0.23–2.83	0.745
NPAF	2.58	1.04–6.43	0.042
Death			
PAF	0.85	0.40–1.77	0.657
NPAF	2.54	1.42–4.54	0.002

^aCompared with SR.Multivariate analysis for stroke or death and for death alone included: CHA₂DS₂-VASc score, creatinine, EuroSCORE, hospitalization 6 months prior to TAVR, left ventricular ejection fraction, and gender.Multivariate analysis for stroke included CHA₂DS₂-VASc score.

PAF = paroxysmal atrial fibrillation; NPAF = nonparoxysmal atrial fibrillation; SR = sinus rhythm.

Figure 1. Kaplan-Meier estimates of probability of death or stroke events by atrial fibrillation type.

Table 3. Risk of Stroke or Death by Atrial Fibrillation Type and Oral Antioagulation Treatment Status before TAVR

	HR ^a	95% CI	P Value
PAF, no OAC	1.25	0.58–2.72	0.569
PAF, OAC	0.44	0.13–1.42	0.167
NPAF, no OAC	8.25	3.32–20.51	<0.001
NPAF, OAC	2.16	1.20–3.90	0.011

^aCompared with SR.

Multivariate analysis included: CHA₂DS₂-VASc score, creatinine, EuroSCORE, hospitalization 6 months prior to TAVR, left ventricular ejection fraction, and male gender.

PAF = paroxysmal atrial fibrillation; NPAF = nonparoxysmal atrial fibrillation; SR = sinus rhythm.

NPAF is associated with a significant increased risk of stroke or death, compared with SR, whereas PAF is not associated with an increased risk of stroke or death during a long-term follow-up after TAVR. Results were consistent irrespective of OAC status, showing that patients with NPAF had poor outcomes compared with PAF even among patients who were treated with OAC in addition to clopidogrel for 6 months.

History of AF is common among patients referred for TAVR. The prevalence of AF among patients who underwent TAVR in the PARTNER A²⁶ and PARTNER B²⁷ studies was 33% and 41%. There is controversy regarding the effect of AF and clinical outcome among patients after TAVR. Stortecky et al.¹² following 389 TAVR patients up to 1 year found that AF is associated with more than two-fold increased risk of all-cause mortality. The investigators found no effect of AF on the risk of stroke during the 1-year follow-up. Barbash et al.⁹ showed that preexisting AF was associated with

increased risk of 1-year, but not 30-day, mortality. Nuis et al.⁶ found that preexisting AF was not associated with increased in-hospital stroke. It is possible that these inconsistent findings may be related to different proportions of paroxysmal, persistent and permanent AF in these studies.

There are accumulating data from studies conducted in the general population suggesting that the risk for stroke or death is related to the duration and clinical type of AF. A registry-based cohort study of 9816 patients with AF showed that patients with permanent AF had higher stroke rates, compared with persistent AF or PAF.¹⁵ Another study from a cohort of 619 AF patients with stroke found that persistent AF was associated with more severe neurologic deficits after stroke, compared with PAF.¹⁶ Consistently, subanalyses of several major trials demonstrated that NPAF compared to PAF was associated with more than 50% increased risk for stroke^{13,19} and higher risk of stroke or death.²⁰ Thus, there is a growing body

of evidence suggesting a different risk in these two groups of patients.

There are only limited and conflicting data regarding the effect of AF clinical type and clinical outcomes after TAVR. Two studies investigating predictors of stroke or death after TAVR found that permanent AF was a predictor of late (>30 days) stroke¹⁰ and late (>30 days) mortality.¹¹ Conversely, in a larger cohort study of 3191 patients from the French Aortic Nation CoreValve and Edwards-2 (FRANCE-2) registry, permanent AF was not associated with increased 6-months stroke rates.⁸ In our study, we found that NPAF, but not PAF, was associated with increased risk of stroke, death and the composite endpoint of stroke or death, compared with SR during a mean follow-up time of 2 years.

In this study, patients with PAF not treated with OAC had a similar risk of stroke and death as patients with SR. There are some potential explanations to this finding. First, it is possible that the benefit conferred by the standard antithrombotic treatment given after TAVR for all patients, aspirin and clopidogrel for 6 months and aspirin-only given thereafter, is not significantly different compared with the treatment regimen of warfarin and clopidogrel for 6 months and warfarin-only given thereafter in elderly patients with severe aortic stenosis. These results are somewhat inconsistent with the results of the Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events (ACTIVE W)²⁸ study which demonstrated that warfarin is superior to aspirin and clopidogrel in AF patients. However, in the ACTIVE W trial, the vast majority of patients (82 %) had non-PAF. Second, patients undergoing TAVR according to current guidelines consist of high-risk elderly patients with multiple comorbidities who commonly experience short episodes of AF (few minutes per day/week); these short episodes of AF, relative to the other major comorbidities, may have only minor effect on the overall clinical outcome. Third, TAVR may lead to a decrease in left ventricular hypertrophy and left atrial pressure and therefore may improve outcomes in PAF patients by decreasing the incidence of AF episodes or their associated thromboembolic risk. Finally, it should be noted that in both the PAF and the SR subgroups the cumulative risk of stroke or death at 2 years was still as high as 15% and 16%, respectively. Thus, it is possible that patients with SR who undergo

TAVR and have a high CHA₂DS₂-VASc score are at a high risk for stroke or death similar to those with PAF. We found that the risk for stroke or death among patients with PAF who were treated with OAC was somewhat lower compared to patients with SR (HR = 0.44, P = 0.17). Thus, it is possible that all patients (both SR and PAF) should be prescribed OAC to reduce the long-term risk of stroke in patients with a high CHA₂DS₂-VASc score.

Our study has several limitations that require attention. This study is subjected to the limitations of post hoc retrospective analyses, including unknown confounders that may have affected results. It is a single-center study, reflecting local treatment and procedure expertise, and therefore caution is warranted when extrapolating the results to the general population. This study was statistically underpowered to determine what antithrombotic strategy (OAC and aspirin vs clopidogrel and aspirin) is preferable in terms of risk-benefit ratio among patients with PAF and SR; nevertheless, it provides important insight into the differences in risk of stroke or death among the AF subgroups. Finally, we did not collect data on left atrial size; thus, we could not investigate the direct relationship between left atrial volumes and stroke. However, it is conceivable that patients with NPAF had a greater left atrial volume compared to patients with PAF and that the higher risk of stroke among NPAF patients could be partially explained by the increased left atrial volume and other possible left atrial remodeling processes.

In conclusion, history of NPAF, but not PAF, is associated with a significant increased risk of stroke or death compared with sinus rhythm in patients undergoing TAVR. Should our findings be confirmed in a larger cohort, these results may be helpful in risk stratification of patients undergoing TAVR who have a history of AF. These results may also provide data to estimate the risk-benefit of anticoagulation therapy in patients undergoing TAVR.

It is clear that careful attention should be addressed to TAVR patients with NPAF not treated with OAC because they are at the highest risk for stroke or death. The observation that patients with PAF who were treated with the combination of aspirin and clopidogrel, but not with OAC and patients with SR had a similar risk of stroke or death should be interpreted with caution. Further research is needed to explore the relation between

AF duration, AF clinical type, OAC treatment and risk of stroke after TAVR, and to explore the risk-benefit ratio of OAC treatment in the different subgroups.

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