

Incidence, Predictors, Management, and Clinical Significance of New-Onset Atrial Fibrillation After Transcatheter Aortic Valve Implantation



Yong-Hoon Yoon, MD^{a,1}, Jung-Min Ahn, MD^{a,1}, Do-Yoon Kang, MD^a, Euihong Ko, MD^a, Pil Hyung Lee, MD^a, Seung-Whan Lee, MD^a, Ho Jin Kim, MD^b, Joon Bum Kim, MD^b, Suk Jung Choo, MD^b, Duk-Woo Park, MD^{a,*}, and Seung-Jung Park, MD^a

There is limited information on the incidence, management, and prognostic impact of new-onset atrial fibrillation (NOAF) following transcatheter aortic valve implantation (TAVI) for severe aortic valve stenosis. In the prospective ASAN-TAVI registry, we evaluated a total of 347 consecutive patients who underwent TAVI from March 2010 to August 2017. The primary end point was a composite of stroke or systemic embolism at 12 months. The study subjects were categorized into 3 groups; pre-existing AF (50 patients), NOAF (31 patients), and non-AF (266 patients) group. NOAF developed in 10.4% of patients without pre-existing AF after TAVI and most cases were paroxysmal type (93.6%). Pharmacologic and electrical cardioversion were tried in 13 (41.9%) and 6 (19.4%) patients and success rates were 61.5% and 33.3%, respectively. NOAF-associated case rate for primary end point was 22.6%. Transfemoral access and cardiac tamponade were independent predictors of NOAF. Patients with NOAF, as compared with those with pre-existing AF and those without AF, had an increased 1-year rate of primary end point (24.0% vs 9.9% vs 7.2%, respectively; $p < 0.001$). By multivariable analysis, NOAF was an independent predictor of 1-year rate of primary end point (adjusted hazard ratio: 3.31; 95% CI: 1.34 to 8.20; $p = 0.010$). In conclusion, patients with severe aortic valve stenosis who underwent TAVI, NOAF occurred in 10% and 1 of 4 NOAF patients experienced stroke or systemic embolization. The presence of NOAF was associated with a substantially higher risk of stroke or systemic embolization. © 2019 Elsevier Inc. All rights reserved. (Am J Cardiol 2019;123:1127–1133)

Atrial fibrillation (AF) is the most common arrhythmia worldwide and it affects >10% of people aged over 80 years with higher mortality and severe morbidity such as stroke or systemic embolization.^{1,2} Transcatheter aortic valve implantation (TAVI) is an established treatment for patients with aortic valve stenosis (AS) who at high risk for surgery.^{3,4} Because AS is also a degenerative disease usually found in elderly population, a substantial proportion of patients who underwent TAVI are expected to have AF. Previous several studies have reported the prevalence and prognostic impact of AF in patients receiving TAVI.^{5–9} New-onset atrial fibrillation (NOAF) is also a common postprocedural complication of TAVI and was associated with higher morbidity and mortality.^{7,10–12} However, since some studies investigating the prognostic significance of AF, either pre-existing or new-onset, after TAVI showed

conflicting results,^{12–14} it remains unclear whether there is differential clinical impact of NOAF on thromboembolic events compared with pre-existing AF. Thus, the purpose of our study was (1) to determine the incidence, predictors, contemporary therapeutic approach and clinical consequence of NOAF in patients who underwent TAVI and (2) to compare the prognostic impact of NOAF on thromboembolic events of stroke or systemic embolization as compared with pre-existing AF or non-AF patients.

Method

The ASAN-TAVI registry is a prospective, single-center, real-world registry that includes all patients who underwent TAVI at Asan Medical Center (Seoul, Korea). The current study included consecutive patients from March 2010 to February 2017. Clinical, procedural, and outcome data were collected using a dedicated electronic case report form. Clinical follow-up after TAVI was performed through clinical visit and/or telephone interview at 1, 6, 12 months, and then every 6 months thereafter.

At the index hospitalization for TAVI, the presence of pre-existing AF was defined as clinical history of AF of all types (paroxysmal, persistent, or permanent) or any AF documentation on electrocardiogram (ECG) before TAVI procedure. Usual ECG monitoring practice for TAVI procedure was baseline measurement of 12-lead ECG before procedure, continuous ECG recording until 2 days after TAVI,

^aDepartment of Cardiology, University of Ulsan College of Medicine, Asan Medical Center, Seoul, Republic of Korea; and ^bDepartment of Thoracic and Cardiovascular Surgery, University of Ulsan College of Medicine, Asan Medical Center, Seoul, Republic of Korea. Manuscript received September 17, 2018; revised manuscript received and accepted December 20, 2018.

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¹Drs. Y.-H. Yoon and J.-M. Ahn contributed equally to this report.

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*Corresponding author: Tel: +82-2-3010-3995; fax: +82-2-475-6898.

E-mail address: dwpark@amc.seoul.kr (D.-W. Park).

and daily 12-leads ECG before discharge. All telemetry records were reviewed by attending cardiologists before detachment or promptly after when alarm sounded. NOAF following the index TAVI procedure was defined as the occurrence of any episode of AF or flutter (collectively termed AF for this analysis) through hospitalization that lasted at least 30 seconds.¹⁵ Patients were not routinely administered any periprocedural antiarrhythmic agents or prophylactic atrial pacing to prevent the occurrence of NOAF. In case of NOAF, therapeutic approach (electrical or medical cardioversion, initiation of anticoagulation, and rate or rhythm control medications) was determined at the discretion of the physician. Successful pharmacologic or electrical cardioversion were defined as a sustained sinus rhythm for 24 hours after cardioversion trial.

The decision for TAVI and details about procedure (valve type, size, and access route) were determined by discussions with a local multidisciplinary heart team, composed of an interventional cardiologist, a cardiovascular surgeon, an echocardiologist, and an anesthesiologist. After the TAVI procedure, the patients were prescribed dual antiplatelet therapy (DAPT) with aspirin (100 mg once daily) and clopidogrel (75 mg once daily) for at least 6 months.¹⁶ Extended use of DAPT or use of oral anticoagulants was at the discretion of the physician, based on the patient's comorbidities. This study was approved by the institutional review board of Asan Medical Center, and all patients were provided written informed consent.

The primary study outcome was the composite of stroke or systemic embolism at 12 months. Secondary

outcomes included each component of the primary end point, death from any causes, death from cardiovascular causes, and major bleeding. As periprocedural major adverse events, new pacemaker insertion and acute kidney injury at 30 days were evaluated. All study end points were defined according to the criteria of the VARC-2.¹⁵ All stroke events were confirmed by a trained neurologist or stroke specialist. Systemic embolization was diagnosed when an acute vascular occlusion of an extremity or organ was documented in imaging with relevant clinical symptom or sign. All events were independently reviewed and were adjudicated by an independent group of clinicians blinded to the study purpose.

In baseline characteristics of the study population, continuous variables are presented as mean $\pm$ SD and compared using 1-way analysis of variance or Kruskal-Wallis test. Categorical variables are presented as counts or percentages and compared using the chi-square or Fisher's exact test, as appropriate. Predictors of NOAF in patients without pre-existing AF were determined in a logistic regression model with backward elimination including the clinical, anatomic, and procedural variables. The event rates at 30 days and 12 months were estimated using the Kaplan-Meier method and log-rank test. Multivariable Cox proportional hazard model with backward elimination were used to determine whether NOAF was an independent predictor of the primary end point. The following covariates were initially included in the model: NOAF, age, gender, logistic EuroSCORE, STS score, diabetes mellitus, congestive heart failure, previous stroke, renal insufficiency, valve

Table 1

Baseline clinical characteristics in patients without atrial fibrillation, those with pre-existing atrial fibrillation, and those with new-onset atrial fibrillation

	Nonatrial fibrillation (n = 266)	Pre-existing atrial fibrillation (n = 50)	New-onset atrial fibrillation (n = 31)	p
Age (years)	78.4 $\pm$ 5.2	79.6 $\pm$ 5.1	79.4 $\pm$ 5.0	0.21
Men	129 (48.5%)	23 (46%)	16 (52%)	0.89
Body mass index* (kg/m ²)	24.1 $\pm$ 3.2	23.8 $\pm$ 3.7	23.4 $\pm$ 3.0	0.49
Logistic EuroSCORE (%)	16.1 $\pm$ 12.2	20.2 $\pm$ 13.8	20.5 $\pm$ 13.7	0.03
STS score (%)	4.2 $\pm$ 5.0	5.2 $\pm$ 3.2	5.1 $\pm$ 3.3	0.29
Hypertension	230 (86.5%)	45 (90%)	28 (90%)	0.69
Diabetes mellitus	83 (31.2%)	18 (36%)	13 (42%)	0.43
Smoker	34 (12.8%)	7 (14%)	2 (7%)	0.56
Hyperlipidemia	183 (68.8%)	28 (56%)	22 (71%)	0.19
Prior myocardial infarction	15 (5.6%)	3 (6%)	1 (3%)	0.84
Prior percutaneous coronary intervention	79 (29.7%)	13 (26%)	10 (32%)	0.81
Prior coronary artery bypass surgery	16 (6.0%)	4 (8%)	2 (7%)	0.87
Congestive heart failure	52 (19.5%)	18 (36%)	7 (23%)	0.04
Prior stroke	26 (9.8%)	7 (14%)	2 (7%)	0.52
Peripheral vascular disease	16 (6.0%)	4 (8%)	1 (3%)	0.68
Chronic lung disease	39 (14.7%)	13 (26%)	5 (16%)	0.14
Renal insufficiency [†]	72 (27.1%)	22 (44%)	14 (45%)	0.01
Dialysis	9 (3.4%)	4 (8%)	2 (7%)	0.28
CHA ₂ DS ₂ -VASC score [‡]	3.9 $\pm$ 1.2	4.4 $\pm$ 1.2	4.1 $\pm$ 1.4	0.05

Data are mean $\pm$ standard deviation or number (%).

* The body mass index is the weight in kilograms divided by the square of the height in meters.

[†] Renal insufficiency was defined as estimated glomerular filtration rate < 60ml/min/1.73m².

[‡] CHA₂DS₂-VASC is calculated based on congestive heart failure, hypertension, age $\geq$ 75 years, diabetes mellitus, and stroke, transient ischemic attack, or thromboembolism; vascular disease, age 65 to 74 years, and female gender.

type (balloon-expandable vs self-expandable), and approach site (transfemoral vs non-transfemoral). A 2-sided p value <0.05 was considered to be statistically significant for all tests. All statistical analyses were performed with R version 3.3.2 (R Foundation for Statistical Computing, Vienna, Austria).

Result

From March 2010 to August 2017, a total of 347 patients who underwent TAVI procedure were included in the present analysis. Of those, 50 (14.4%) patients had pre-existing AF at baseline. In the 297 patients without pre-existing AF, 31 (10.4%) experienced NOAF during index hospitalization. The median follow-up duration was 364 days (interquartile range, 130 to 945 days). The baseline clinical characteristics of the study population according to AF

status are shown in **Table 1**. The mean age of the study cohort was 79 years, and 48% were men. The mean logistic EuroSCORE and STS score were 17.1 ± 12.5 and 4.4 ± 4.7 , respectively. The majority patients (95.4%) underwent TAVI through transfemoral access. In between-group comparison, logistic EuroSCORE was higher in both pre-existing AF and NOAF groups than non-AF group and the prevalence of congestive heart failure was highest in pre-existing AF group. The mean CHA₂DS₂-VASC score was highest in the pre-existing AF group, intermediate in the NOAF group, and lowest in the non-AF group. There was no significant between-group difference with regard to anatomic and procedural characteristics as shown in **Table 2**.

Onset timing, type, therapeutic approach, and clinical consequence of NOAF are summarized in **Table 3**. Median time to the occurrence of NOAF after TAVI procedure was 2 days (IQR 1 to 7 days) and almost cases were paroxysmal type

Table 2

Imaging data and procedural characteristics in patients without atrial fibrillation, those with pre-existing atrial fibrillation, and those with new-onset atrial fibrillation

	Nonatrial fibrillation (n = 266)	Pre-existing atrial fibrillation (n = 50)	New-onset atrial fibrillation (n = 31)	p
<i>Echocardiography data</i>				
Mean aortic-valve gradient (mmHg)	61.8 $\pm$ 23.5	55.5 $\pm$ 18.3	58.5 $\pm$ 20.6	0.18
Aortic-valve area (cm ²)	0.6 $\pm$ 0.2	0.6 $\pm$ 0.1	0.6 $\pm$ 0.1	0.51
Mitral regurgitation, moderate or severe	27 (10.2%)	8 (16%)	5 (16%)	0.35
Pulmonary hypertension*	60 (22.6%)	17 (34%)	9 (29%)	0.19
Left ventricle ejection fraction (%)	58.9 $\pm$ 11.1	57.7 $\pm$ 9.5	57.1 $\pm$ 11.5	0.59
Left ventricle ejection fraction $\leq$ 30%	10 (3.8%)	0	1 (3.2%)	0.38
Left atrium size (mm)	42.7 $\pm$ 6.5	46.7 $\pm$ 9.3	43.8 $\pm$ 5.3	0.001
Left atrium size $>$ 45mm	91 (34.2%)	26 (52%)	11 (36%)	0.06
<i>Computed tomography data</i>				
Aortic annulus minimal diameter (mm)	26.5 $\pm$ 2.8	26.3 $\pm$ 2.8	26.5 $\pm$ 2.3	0.86
Aortic annulus maximal diameter (mm)	21.0 $\pm$ 2.4	20.5 $\pm$ 2.1	21.1 $\pm$ 1.6	0.24
Aortic annulus area (mm ²)	437.3 $\pm$ 82.0	425.9 $\pm$ 81.1	442.9 $\pm$ 67.2	0.61
Aortic annulus perimeter (mm)	75.5 $\pm$ 7.0	74.5 $\pm$ 7.4	76.2 $\pm$ 5.8	0.57
<i>Procedural data</i>				
Valve system				
Type of deployment				0.92
Balloon-expandable	167 (62.8%)	33 (66%)	19 (61%)	
Self-expandable	99 (37.2%)	17 (34%)	12 (39%)	
Type of valve				0.43
SAPIEN	7 (2.6%)	1 (2%)	0	
SAPIEN XT	86 (32.4%)	15 (30%)	17 (55%)	
SAPIEN 3	74 (27.9%)	17 (34%)	2 (6%)	
CoreValve	63 (23.7%)	11 (22%)	9 (29%)	
Evolut R	32 (12.0%)	5 (10%)	3 (10%)	
Lotus	4 (1.5%)	1 (2%)	0	
Valve size	26.0 $\pm$ 2.3	25.7 $\pm$ 2.5	26.5 $\pm$ 2.1	0.32
Approach route				
Transfemoral	256 (96.2%)	48 (96%)	27 (87%)	0.92
Transapical	8 (3.0%)	2 (4%)	3 (10%)	
Transaortic	2 (0.8%)	0	1 (3%)	
Anesthesia				
Monitored anesthesia care	162 (60.9%)	32 (64%)	22 (71%)	0.49
General anesthesia	104 (39.1%)	18 (36%)	9 (29%)	
Balloon post-dilatation	49 (18.4%)	10 (20%)	6 (19%)	0.96
Concomitant coronary intervention	10 (3.8%)	4 (8%)	1 (3%)	0.38

Data are mean $\pm$ SD or number (%).

* Pulmonary hypertension indicates pulmonary artery systolic pressure $\geq$ 50 mm Hg.

Table 3

Timing, pattern, therapeutic approach, and clinical consequences of new-onset atrial fibrillation

		New-onset atrial fibrillation (n = 31)
<i>Timing</i>		
Median time to atrial fibrillation onset (interquartile range)		2 days (1-7 days)
<i>Pattern</i>		
Sustained type		2/31 (6%)
Paroxysmal type		29/31 (94%)
<i>Therapeutic Approach</i>		
Anticoagulation		11/31 (36%)
Pharmacologic cardioversion trial		13/31 (42%)
Pharmacologic cardioversion success		8/13 (62%)
Electrical cardioversion trial		6/31 (19%)
Electrical cardioversion success		2/6 (33%)
<i>Clinical Consequence*</i>		
Anticoagulation group	2/11 (18%)	Stroke (2)
No anticoagulation group	5/20 (25%) [†]	Stroke (1)
		Bowel infarction (2)
		Splenic infarction (2)
		Renal infarction (1)

* Stroke or systemic embolism events according to anticoagulation status after the development of NOAF.

[†]One patients experienced 2 consecutive embolic events (splenic and renal infarction).

(93.6%). Eleven patients (35.5%) received proper anticoagulation within 2 days after the development of NOAF. Pharmacologic and electrical cardioversion were tried in 13 (41.9%) and 6 (19.4%) patients and success rates were 61.5% and 33.3%, respectively. In NOAF patients who received early anticoagulation, 2 stroke events (18.2%) occurred. In NOAF patients without early anticoagulation, 5 patients (25%) experienced 6 events of stroke or systemic embolization. Thus, a NOAF-associated case rate for stroke or systemic embolization was 22.6%. The status of antithrombotic therapy during

the follow-up according to AF status is summarized in Online Appendix Table 1. Patients with pre-existing AF or NOAF were more frequently discharged with anticoagulant therapy with either warfarin or a novel oral anticoagulant agent, whereas DAPT was more commonly prescribed to patients without AF. After discharge, in NOAF patients, AF was documented in 7 patients (22.6%) after 1 week and 3 patients (11.5%) after 1 month. By multivariable analysis, the independent predictors of NOAF in patients without pre-existing AF were approach site (non-transfemoral vs transfemoral) and cardiac tamponade during the procedure (Table 4).

The primary composite outcome of stroke or systemic embolization at 12 months occurred in 24.0% of the patients in the NOAF group, 9.9% in the pre-existing AF group, and 7.2% in the non-AF group, respectively ($p < 0.001$; Figure 1). In landmark analysis, the risk of stroke or systemic embolization significantly differs within 30 days ($p < 0.001$) and then has been stabilized after the first 30 days ($p = 0.49$). The 7 embolic events occurred within 24 hours after TAVI in non-AF and pre-existing group, and first embolic event in NOAF group occurred 2 days after TAVI procedure. By multivariable analysis, NOAF was an independent predictor of 30-day and 1-year primary composite outcome in the overall population. (Figure 2, Online Appendix Table 2). Conversely, pre-existing AF was not a predictor for a primary outcome of interest. Observed rates of clinical events at 30 days and at 1 year according to AF status are summarized in Online Appendix Table 3. The rate of death and major bleeding was also significantly higher in group of NOAF patients.

Discussion

The major findings from the present analysis, in which the incidence, predictors, therapeutic approach, clinical consequence, and prognostic impact of in-hospital NOAF in patients with severe AS underwent TAVI procedure were examined, are as follows: (1) NOAF occurred in approximately 10% of patients who underwent TAVI; (2)

Table 4

Independent predictors of new-onset atrial fibrillation in patients without pre-existing atrial fibrillation

	Univariate analysis		Multivariate analysis	
	Odds ratio (95% confidence interval)	p	Odds ratio (95% confidence interval)	p
Age (per 10 years)	1.04 (0.97–1.11)	0.50		
Men	1.01 (0.94–1.08)	0.88		
Body mass index (kg/m ²)	0.99 (0.98–1.00)	0.30		
Logistic EuroSCORE (10% unit)	1.03 (1.00–1.06)	0.23	1.02 (1.00–1.05)	0.09
STS score (per unit)	1.00 (1.00–1.01)	0.42		
Diabetes mellitus	1.05 (0.97–1.13)	0.39	1.06 (0.98–1.14)	0.14
Congestive heart failure	1.02 (0.93–1.11)	0.80		
Prior stroke	0.96 (0.86–1.09)	0.37		
Renal insufficiency	1.09 (1.01–1.17)	0.17		
CHA ₂ DS ₂ -VASC score (unit)	1.01 (0.98–1.04)	0.68		
Left ejection fraction (10% unit)	0.99 (0.96–1.02)	0.76		
Left atrium size (mm)	1.00 (1.00–1.01)	0.54		
Balloon-expandable type	0.99 (0.92–1.07)	0.79		
Non-transfemoral approach	1.21 (1.03–1.42)	0.03	1.22 (1.04–1.43)	0.02
Balloon post-dilation	1.01 (0.92–1.10)	0.73		
Cardiac tamponade during the procedure	1.22 (1.01–1.48)	0.02	1.25 (1.03–1.51)	0.02

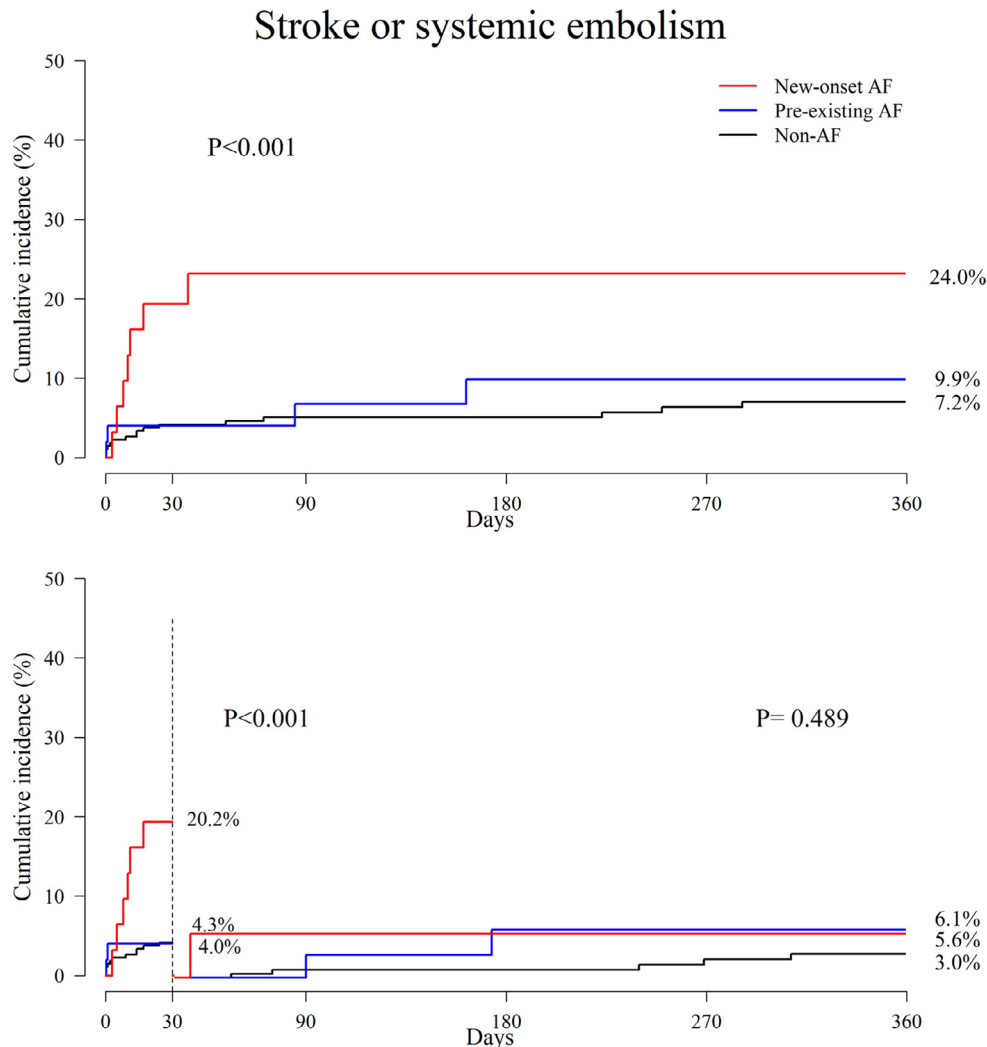


Figure 1. Time-to-event curves for the primary composite outcome of stroke or systemic embolization according to the AF status. In each panel, cumulative incidence curves are shown for the risk of stroke or systemic embolization according to AF status (upper panel) and the landmark analysis at 30 days (lower panel).

Adjusted hazard ratio for stroke or systemic embolization

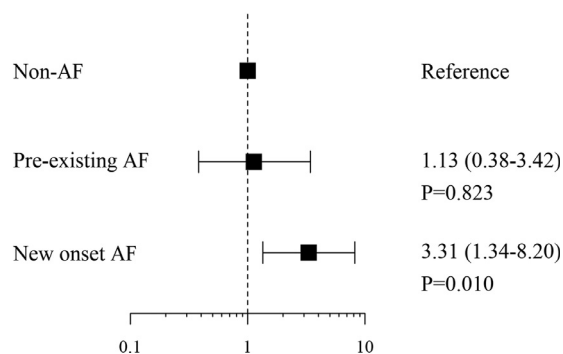


Figure 2. Adjusted hazard ratios for the 1-year primary composite outcome of stroke or systemic embolization according to the AF status. The adjusted risk for stroke or systemic embolization were highest in patients with NOAF and similar in patients with pre-existing AF and in patients without AF. CI = confidence interval; HR = hazard ratio.

NOAF was mostly paroxysmal type, but the NOAF-associated case rate for stroke or systemic embolization was 23%; (3) Non-transfemoral access and cardiac tamponade during the procedure were independent predictors of NOAF; and (4) NOAF was significantly associated with increased 1-year rate of stroke or systemic embolization as compared with non-AF or pre-existing AF.

The 10% rate of NOAF after TAVI for severe AS in the present study is consistent with the rates in previous reports, in which post-TAVI AF developed in 6% to 35% of patients.^{7,9-11} The differences in post-TAVI NOAF rates in studies likely reflects differences in patient population, procedural factors or complications, and variability in the rigor and duration of ECG or cardiac telemetry detection. The pathophysiology of NOAF after TAVI remains largely unknown. However, more is known about underlying mechanisms of postoperative AF, which might be common to post-TAVI AF.¹⁴ Several important predictors of NOAF after TAVI have been reported.^{5-7,9-11} In the present study, non-transfemoral approach and cardiac tamponade

during the procedure were independent predictors of NOAF. Previous studies also showed that NOAF was more common after transaortic approach than transfemoral approach.^{11,17} The pericardial aggression is a well-known predictor of AF development.¹⁸ And the occurrence of cardiac tamponade during the procedure induces hemodynamic instability, which was also a predisposing factor of AF. These factors are suggested as the mechanisms involved in the development of post-TAVI NOAF.¹⁴

Until recently, little was known about the clinical consequences especially regarding the risk of thromboembolic events and optimal management of NOAF after TAVI. Triple therapy with DAPT and anticoagulation is not currently recommended after TAVI.^{14,16} In our study, only 36% of total NOAF patients received anticoagulation within 2 days. The main reasons for low rate of anticoagulation treatment might be due to concern about increasing bleeding risk and AF pattern (mostly paroxysmal). However, surprisingly, NOAF-associated case rate for stroke or systemic embolization was 22.6% and most cases occurred within 1 month after TAVI. Considering a high incidence of stroke or systemic embolization in early period and their relatively lower response to cardioversion therapy, prompt anticoagulation therapy may be required in patients who develop NOAF after TAVI, at least during short-term period. Previous study suggested that prompt anticoagulation therapy resulted in substantial reduction of stroke or systemic embolization in NOAF patients after TAVI.¹⁰ Although no clinical trials are being conducted to identify optimal antithrombotic strategies for NOAF after TAVI, several ongoing trials may provide information on the optimal antithrombotic regimens after TAVI, with or without AF or NOAF.^{19–21} Before these trial results are available, prompt medical attention or clinical practice recommendation should be considered to optimally manage the occurrence and thrombotic risk of NOAF.

Interestingly, in our study, thromboembolic risk was significantly higher in NOAF patients, but not pronounced in pre-existing AF patients, as compared with non-AF patients. These findings were consistent with a recent meta-analysis showing that pre-existing AF was not a predictor of cerebrovascular events, but NOAF is related to the occurrence of cerebrovascular events at short-term follow-up.¹³ This differential clinical impact of NOAF or pre-existing AF on stroke or systemic embolization is not yet fully understood. The negative impact of new-onset AF compared with pre-existing AF on early stroke might be related to the heterogeneous antithrombotic regimen in these patients.¹⁴ In our data, anticoagulation was used only in 35.5% of NOAF patients. Also, several confounding factors should be considered.¹³

Our study had potential limitations. First, our study evaluated nonrandomized, observational data. Study results are possibly affected by unknown confounders and thus overall findings should be considered to be hypothesis-generating. Second, the total number of events was relatively low, and this may have led to overfitting of the multivariate model to assess the independent association of NOAF with thromboembolic events. These results should be confirmed or refuted through larger studies. Third, to determine the incidence of NOAF, although patients with known chronic or

paroxysmal AF were excluded and all patients were in sinus rhythm at baseline, systematic screening for pre-TAVI AF was not done through EKG monitoring studies during long-time; as such, preprocedure episodes of silent AF may cannot be excluded.

In patients with severe AS underwent TAVI, NOAF occurred in 10% of patients and approximately 1 of 4 NOAF patients experienced stroke or systemic embolization. As compared with non-AF or pre-existing AF, NOAF was associated with a substantially higher risk of stroke or systemic embolization. Therefore, prompt medical attention or clinical practice recommendation should be considered to optimally manage the occurrence and thrombotic risk of NOAF. Further studies are needed to identify patients at high risk for NOAF after TAVI to guide preventive measures, to examine the potential impact of rhythm conversion before hospital discharge, and to determine which combination of antithrombotic regimens is optimal for management of in-hospital NOAF in patients who underwent TAVI procedures.

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Disclosures

The investigators have no conflicts of interest to disclose.

Supplementary materials

Supplementary material associated with this article can be found in the online version at <https://doi.org/10.1016/j.amjcard.2018.12.041>.

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