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Incidence, Management, and Associated Clinical Outcomes of New-Onset Atrial Fibrillation Following Transcatheter Aortic Valve Replacement

An Analysis From the STS/ACC TVT Registry

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ABSTRACT

OBJECTIVES The aim of this study was to evaluate incidence, care patterns, and clinical outcomes in patients developing new-onset atrial fibrillation (AF) following transcatheter aortic valve replacement (TAVR).

BACKGROUND Pre-procedural AF has been associated with adverse outcomes in patients undergoing TAVR, but the incidence of new-onset AF, associated anticoagulant management, and subsequent clinical outcomes are unclear.

METHODS Using the Society of Thoracic Surgeons/American College of Cardiology TVT (Transcatheter Valve Therapy) Registry linked with Medicare claims, patients undergoing TAVR from 2011 to 2015 who developed post-procedural AF were evaluated. Patients with known AF prior to TAVR were excluded. Outcomes of interest included in-hospital mortality and stroke and all-cause mortality, stroke, and bleeding at 12 months. Multivariate adjustment was then performed to determine differences in 1-year outcomes among those with and without new post-procedural AF, stratified by anticoagulation status.

RESULTS We identified 1,138 of 13,556 patients (8.4%) who developed new onset AF (4.4% of transfemoral [TF]-access patients, 16.5% of non-TF-access patients). Patients developing AF were older, more likely female, had higher Society of Thoracic Surgeons risk scores, and were often treated using non-TF access. Despite having a median CHA_2DS_2-VASc score of 5 (25th and 75th percentile: 5 to 6), only 28.9% of patients with new AF were discharged on oral anticoagulation. In-hospital mortality (7.8% vs. 3.4%; $p < 0.01$) and stroke (4.7% vs. 2.0%; $p < 0.01$) were higher among patients who developed post-procedural AF compared with those who did not. At 1 year, rates of death (adjusted hazard ratio [HR]: 1.37; 95% confidence interval [CI]: 1.19 to 1.59), stroke (adjusted HR: 1.50; 95% CI: 1.14 to 1.98), and bleeding (adjusted HR: 1.24; 95% CI: 1.10 to 1.40) were higher among patients with new-onset AF. One-year mortality rates were highest among patients who developed new-onset AF but were not discharged on anticoagulation.

CONCLUSIONS Post-TAVR AF occurred in 8.4% of patients (4.4% with TF access, 16.5% with non-TF access), with fewer than one-third of patients receiving anticoagulation at discharge, and was associated with increased risk for in-hospital and 1-year mortality and stroke. Given the clinical significance of post-TAVR AF, additional studies are necessary to delineate the optimal management strategy in this high-risk population. (J Am Coll Cardiol Intv 2018;11:1746–56)

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Transcatheter aortic valve replacement (TAVR) has emerged as an important therapeutic option among intermediate- and high-risk patients with symptomatic severe aortic stenosis (1). Heart rhythm disorders frequently complicate TAVR, particularly atrial fibrillation (AF), which can affect >40% patients undergoing the procedure (2,3). The presence of pre-procedural AF has been associated with significantly worse outcomes among patients undergoing TAVR, with up to 37% higher mortality at 1 year in patients with pre-procedural AF compared with those without (4).

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However, data on patients without AF at baseline who develop new-onset AF after TAVR are less well defined. There is wide variation in rates of new-onset AF following TAVR across the initial pivotal randomized trials as well as subsequent observational studies (3,5-10). Additionally, the management of post-procedural AF following TAVR is not well defined. Current American Heart Association, American College of Cardiology (ACC), and Heart Rhythm Society guidelines for the management of AF following cardiac surgery give a Class IIa recommendation for the administration of amiodarone and oral anticoagulant therapy (11). Given the recommendation for at least short-term dual-antiplatelet therapy following TAVR (1), there may be reluctance by treating physicians to consider oral anticoagulation, either with warfarin or a direct oral anticoagulant, in these patients, who may be at high risk for bleeding and stroke.

Therefore, using the National Cardiovascular Data Registry Society of Thoracic Surgeons (STS)/ACC TVT (Transcatheter Valve Therapy) Registry, we sought to evaluate 1) the incidence of new-onset, post-procedural AF among patients undergoing TAVR; 2) factors associated with increased risk for developing new-onset AF; 3) patterns of discharge anticoagulation and antiarrhythmic therapy among patients developing new-onset AF; and 4) in-hospital and 1-year rates of mortality, ischemic, and bleeding outcomes comparing patients who developed new-onset AF with those who did not.

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

CI = confidence interval

CMS = Centers for Medicare and Medicaid Services

DAPT = dual-antiplatelet therapy

HR = hazard ratio

MI = myocardial infarction

OR = odds ratio

STS = Society of Thoracic Surgeons

TAVR = transcatheter aortic valve replacement

METHODS

DATA SOURCES. The National Cardiovascular Data Registry STS/ACC TVT Registry is the largest quality improvement registry for TAVR in the world. Because of the national coverage decision by the Centers for Medicare and Medicaid Services (CMS), participation in the STS/ACC TVT Registry is a requirement for commercial implantation of transcatheter aortic valves in the United States. The Duke Clinical Research Institute is the analytic center for the registry and is responsible for data management and analysis. Details of the design and conduct of this registry have been previously described (12), and the registry is regularly and rigorously audited for data completeness and accuracy (13). Registry establishment and maintenance were approved by a central Institutional Review Board, and the Duke Institutional Review Board has provided a waiver of informed consent and authorization of this registry.

One-year follow-up data were ascertained using Medicare claims data from CMS. Clinical records for procedures captured in the STS/ACC TVT Registry were linked by CMS to Medicare administrative claims data using direct patient identifiers (name and Social Security number) using previously described methodology (14).

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STUDY COHORT. Between November 1, 2011, and September 30, 2015, we identified 47,698 eligible patients undergoing TAVR at 394 sites participating in the STS/ACC TVT Registry in the United States. Given that the focus of our analysis was to evaluate incidence and outcomes in patients with new-onset AF, we excluded patients with a prior history of AF (n = 19,538). We excluded patients already on anticoagulant therapy (n = 5,419) and those with incomplete information with which to calculate a CHA_2DS_2-VASc score (n = 769). We also excluded patients who were unable to be linked with CMS claims data because they were younger than 65 years of age (n = 1,147), did not have Medicare insurance (n = 1,911), were not eligible to link to Medicare, were unable to be linked to Medicare (n = 4,089), or were not eligible for fee-for-service Medicare (n = 1,257), yielding a final study population of 13,556 patients at 381 sites nationwide.

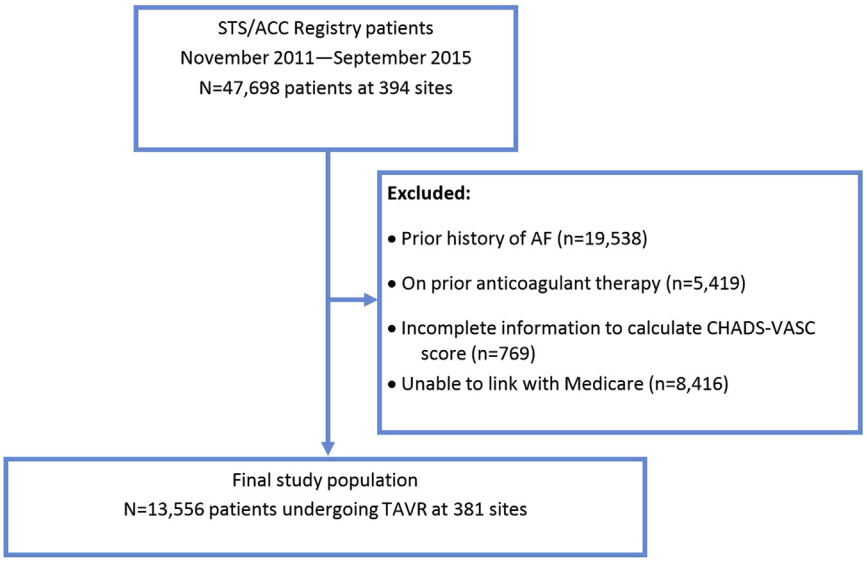
OUTCOMES AND DEFINITIONS. The presence of AF prior to TAVR (prevalent AF) as well as the development of new-onset AF following the procedure (incident AF) was denoted on the STS/ACC TVT Registry data collection form. We calculated the CHA_2DS_2-VASc score using the data elements from the data collection form; for this analysis, the presence of vascular disease was defined as having a history of myocardial infarction (MI), peripheral artery disease, prior percutaneous coronary intervention, or prior coronary artery bypass grafting. To classify patients according to bleeding risk, we calculated the ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation) score, which assigned points for anemia (hemoglobin <13 g/dl for men and <12 g/dl for women, 3 points), severe renal disease (glomerular filtration rate <30 ml/min or dialysis, 3 points), age ≥75 years (2 points), and hypertension (1 point) (15). The ATRIA score assigns 1 point to history of prior bleeding, which was not captured in this registry; as such, we used CMS claims data to assess for a hospitalization for bleeding in the 6 months prior to TAVR using the same International Classification of Diseases-Ninth Revision codes that we used to capture the bleeding endpoint described below. An ATRIA score ≥4 is considered to indicate high risk for bleeding. The HAS-BLED score was not used, as not all of the components in that risk score are captured by the TVT Registry.

In-hospital complications and outcomes were captured on the data collection form. We evaluated 6 long-term outcomes: 1) a composite endpoint including all-cause mortality and rehospitalization for MI or stroke; 2) all-cause mortality; 3) readmission for stroke; 4) readmission for MI; 5) rehospitalization for heart failure; and 6) readmission for bleeding. Readmission for MI, stroke, bleeding, and heart failure was defined using the primary International Classification of Diseases-Ninth Revision-Clinical Modification diagnosis code and procedure codes for subsequent hospitalizations after the index hospitalization. All-cause mortality was ascertained from the Medicare denominator file. Administrative claims codes for each of these endpoints are given in the Online Appendix.

STATISTICAL ANALYSIS. We compared baseline demographic, clinical history, echocardiographic, and procedural characteristics between patients developing new-onset AF following TAVR and those not developing AF during the index procedure. Continuous variables are expressed as median (interquartile range), and categorical values are presented as percentages. Pearson chi-square tests were used to compare categorical variables, and Wilcoxon rank sum tests were used to compare continuous variables between 2 groups. In-hospital events and discharge medications were compared using similar methods.

In examining the association between clinical factors and post-procedural AF, a multivariate logistic regression was used to calculate the odds ratios (ORs) while adjusting for known and important clinical covariates. The generalized estimating equation method with exchangeable working correlation structure was used to account for within-hospital clustering, because patients at the same hospital are more likely to have similar responses relative to patients in other hospitals (i.e., within-center correlation for response). The method produces estimates similar to those from ordinary logistic regression, but the variances of the estimates are adjusted for the correlation of outcomes within each hospital. The clinical variables considered include those in the TVT mortality model (16): age, sex, left ventricular ejection fraction, hemoglobin, platelet count, estimated glomerular filtration rate, race (non-Hispanic white vs. other), current dialysis, left main stenosis ≥50%, proximal left anterior descending coronary artery stenosis ≥70%, prior MI, endocarditis, prior stroke or transient ischemic attack, carotid stenosis, prior peripheral arterial disease, current or recent smoker, diabetes, New York Heart Association class IV, severe chronic lung disease, use of home oxygen, hostile chest, porcelain aorta, access site (femoral vs. other), pacemaker, previous implantable cardioverter-defibrillator, prior percutaneous coronary intervention, prior coronary artery bypass grafting, prior cardiac operators (≥2 vs. 1 vs. 0), prior aortic valve

FIGURE 1 Study Population Characteristics



This figure displays the study population characteristics, including exclusions. ACC = American College of Cardiology; AF = atrial fibrillation; STS = Society of Thoracic Surgeons; TAVR = transcatheter aortic valve replacement.

procedure, prior non-aortic valve procedure, aortic etiology (degenerative vs. other), valve morphology ([moderate/severe vs. other], mitral insufficiency [moderate/severe vs. other], tricuspid insufficiency [moderate/severe vs. other]), acuity (elective vs. urgent vs. shock or inotropes or assist device vs. emergency or salvage or cardiac arrest), and discharge medications (angiotensin-converting enzyme inhibitors, warfarin, aspirin, dabigatran, beta-blockers, antiarrhythmic agents, $P2Y_{12}$ inhibitors, and factor Xa inhibitors). The adjusted in-hospital events did not take into account in-hospital clustering, because of the paucity of events.

We then examined the unadjusted cumulative incidence of each outcome studied from the index procedure date through 1 year, using the long-rank test and Kaplan-Meier methods for death and using Gray's method to account for mortality as a competing risk for nonfatal outcomes (17). We then used multivariate Cox proportional-hazards models to compare risk-adjusted outcomes between patients who developed AF and those that did not. Outcomes were adjusted for the variables noted earlier.

Statistical significance was defined as $p < 0.05$. All analyses were performed by the National Cardiovascular Data Registry data analysis center at the Duke Clinical Research Institute using SAS versions 9.3 and 9.4 (SAS Institute, Cary, North Carolina).

RESULTS

BASELINE CHARACTERISTICS. After exclusions, we identified 13,356 patients undergoing TAVR at 381 sites nationwide (Figure 1). Overall, 1,138 patients (8.4%) developed new-onset, post-procedural AF. Patients developing new-onset AF were older, more likely to be female, and more likely to have severe chronic obstructive pulmonary disease ($p < 0.01$ for all). The incidence of AF was 4.4% among transfemoral-access patients and 16.5% among transapical-access patients. Rates of hypertension, New York Heart Association class III or IV heart failure, and known coronary artery disease were similar between the groups. Patients developing new-onset AF were more likely to have higher median STS Predicted Risk of Mortality scores (6.5 vs. 6.0; $p < 0.01$), and a greater proportion were at either extreme risk or high risk for surgery compared with those who did not develop new-onset AF. The median CHA_2DS_2-VASC score was 5 and the median ATRIA score was 6 in both groups (Table 1). Other potential markers of frailty, including 5-m walk distance >6 m, albumin, platelet count, and hemoglobin, were not significantly different between the 2 groups. The median length of stay among patients developing AF was 9 days (interquartile range: 6 to 15 days) and 5 days (interquartile range: 3 to 8 days) among those not developing AF ($p < 0.01$).

TABLE 1 Patient Characteristics According to the Development of New-Onset Atrial Fibrillation

	Developed New-Onset AF (n = 1,138)	Did Not Develop New-Onset AF (n = 12,418)	p Value
Demographics			
Age, years	85 (78-88)	84 (78-88)	<0.01
Female	61.4	50.8	<0.01
BMI, kg/m^2	26.3 (23.3-30.4)	26.8 (23.5-31.0)	<0.01
Race			0.19
White	95.8	94.4	
Black	2.4	3.6	
Asian	0.8	1.2	
Other	1.1	0.9	
Hispanic ethnicity	2.3	3.2	0.08
Clinical characteristics			
Coronary artery disease	61.1	63.0	0.20
NYHA functional class III/IV heart failure	78.3	79.8	0.25
Prior PCI	34.3	34.8	0.73
Prior CABG	20.1	29.8	<0.01
Prior stroke	10.5	10.6	0.96
Peripheral arterial disease	38.9	29.5	<0.01
Diabetes	30.2	35.8	<0.01
Hypertension	91.1	89.5	0.08
Smoker	6.9	5.2	0.01
COPD, severe	15.2	11.8	<0.01
Oxygen-dependent lung disease	14.2	11.4	<0.01
Dialysis dependent	2.9	4.0	0.35
Hostile chest	6.0	7.6	0.05
Porcelain aorta	9.1	5.8	<0.01
Permanent pacemaker or ICD	6.2	12.6	<0.01
LVEF <30%	4.0	6.6	<0.01
STS-PROM score	6.5 (4.4-10)	6.0 (4.0-9.1)	<0.01
CHA_2DS_2-VASc score	5 (5-6)	5 (5-6)	<0.01
ATRIA score	6 (3-6)	6 (3-6)	0.93
Procedure characteristics			
Access site			<0.01
Transfemoral	36.3	71.5	
Transapical	43.1	20.0	
Other	20.7	8.5	
Discharge medications			
Aspirin	81.1	89.0	<0.01
$P2Y_{12}$ receptor inhibitor	54.2	74.3	<0.01
Warfarin	24.0	6.1	<0.01
Factor Xa inhibitor	4.4	1.2	<0.01
Dabigatran	0.5	0.6	0.76
DAPT (ASA + $P2Y_{12}$ inhibitor)	46.6	67.9	<0.01
OAC alone	28.0	7.8	<0.01
Triple antithrombotic therapy	4.7	1.5	<0.01
Antiarrhythmic agent	49.4	8.2	<0.01
Beta-blocker	72.6	69.7	0.05

Values are median (interquartile range) or %.

AF = atrial fibrillation; ASA = aspirin; ATRIA = Anticoagulation and Risk Factors in Atrial Fibrillation; BMI = body mass index; CABG = coronary artery bypass graft surgery; COPD = chronic obstructive pulmonary disease; DAPT = dual-antiplatelet therapy; ICD = implantable cardioverter-defibrillator; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; OAC = oral anticoagulation; PCI = percutaneous coronary intervention; STS-PROM = Society of Thoracic Surgeons Predicted Risk of Mortality.

FACTORS ASSOCIATED WITH NEW-ONSET AF. Factors that were significantly associated with new-onset AF were age (OR: 1.02 per year; 95% confidence interval [CI]: 1.01 to 1.03; p < 0.01), left ventricular ejection fraction (OR: 1.07 per 5% decrease; 95% CI: 1.03 to 1.11; p < 0.01), chronic lung disease (severe vs. none; OR: 1.44; 95% CI: 1.14 to 1.80; p < 0.01), and nontransfemoral access (OR: 3.09; 95% CI: 2.60 to 3.68; p < 0.01) (Figure 2).

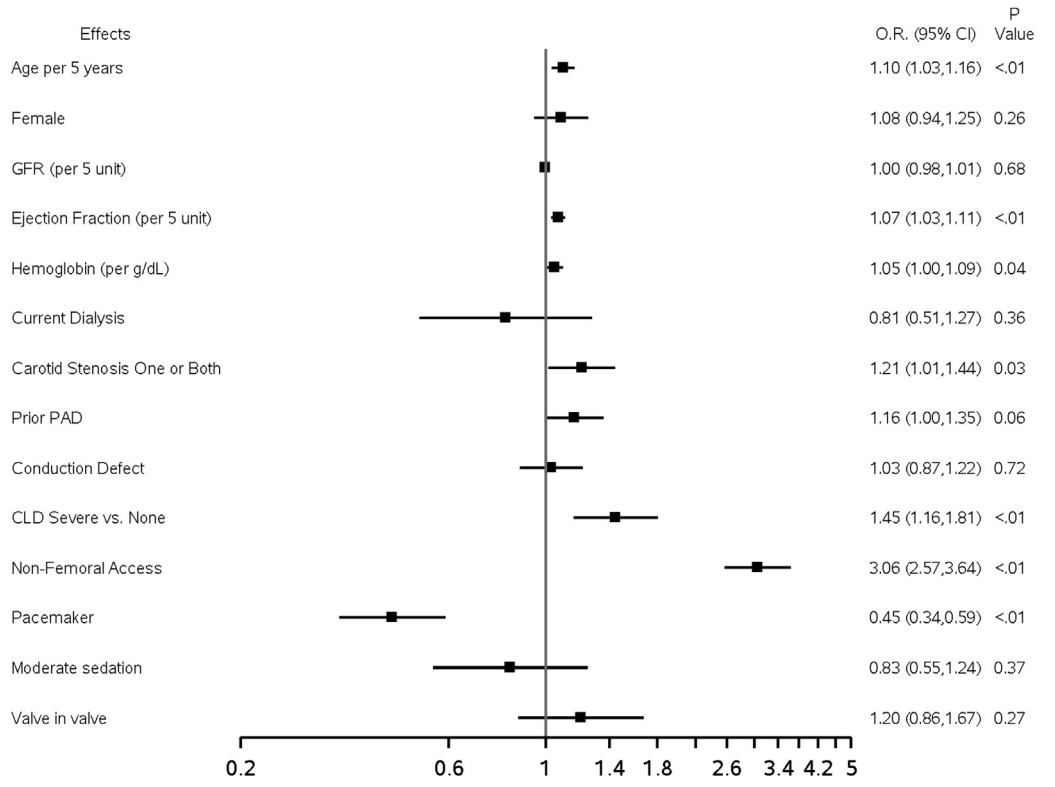
ANTITHROMBOTIC AND RHYTHM CONTROL MANAGEMENT. At discharge, patients who developed new-onset AF were less likely to be discharged on aspirin (81.1% vs. 89.0%; p < 0.01) or $P2Y_{12}$ inhibitors (54.2% vs. 74.3%; p < 0.01) than those who did not. Among patients with new-onset AF, <30% were discharged on any oral anticoagulant therapy despite a median CHA_2DS_2-VASc score of 5; 4.7% of patients were discharged on triple-antithrombotic therapy. Among patients who developed AF post-procedure, the median ATRIA score was not statistically different between those discharged on oral anticoagulation versus those not (5 vs. 6; p = 0.17, respectively). Among patients with AF, the median CHA_2DS_2-VASc score for patients discharged on aspirin monotherapy was 5 (25th and 75th percentile: 5 to 6). Rates of beta-blocker therapy were modestly higher among patients with new-onset AF, whereas almost half of patients with new-onset AF were discharged on antiarrhythmic therapy (Table 1).

CLINICAL OUTCOMES. Rates of in-hospital death (7.8% vs. 3.4%), stroke (4.7% vs. 2.0%), MI (1.4% vs. 0.5%), cardiac arrest (9.3% vs. 3.6%), and Valve Academic Research Consortium major bleeding events (10.6% vs 6.1%) were higher among patients developing new-onset AF compared with those who maintained sinus rhythm (p < 0.01 for all) (Online Table 1). After multivariate adjustment, new-onset AF remained associated with higher in-hospital event rates.

At 1 year, the unadjusted cumulative incidence of all-cause mortality was 30.1% for patients with new-onset AF versus 16.1% for patients who did not develop AF, which persisted after multivariate adjustment (adjusted hazard ratio [HR]: 1.37; 95% CI: 1.19 to 1.59) (Figure 3). The rate for stroke at 1 year was higher among patients with new-onset AF (7.2% vs. 3.8%; adjusted HR: 1.50; 95% CI: 1.14 to 1.98), as was the rate of bleeding requiring rehospitalization (31.7% vs. 23.0%; adjusted HR: 1.24; 95% CI: 1.10 to 1.40). Although patients developing AF were at higher risk for rehospitalization for heart failure at 1 year (14.8% vs. 10.5%), this difference did not persist after multivariate adjustment (adjusted HR: 1.12; 95% CI: 0.93 to 1.35) (Table 2).

After stratifying patients with new-onset AF by discharge anticoagulation, rates of the composite endpoint (39.7% vs. 28.4%; p < 0.01), mortality (33.8% vs. 20.7%; p < 0.01), and rehospitalization for stroke (7.5% vs. 6.3%; p < 0.01) were higher among

FIGURE 2 Factors Associated With New-Onset Atrial Fibrillation Post-Transcatheter Aortic Valve Replacement Procedure



This figure shows factors associated with new-onset atrial fibrillation (AF) following the transcatheter aortic valve replacement (TAVR) procedure. CI = confidence interval; CLD = chronic lung disease; GFR = glomerular filtration rate; O.R. = odds ratio; PAD = peripheral artery disease.

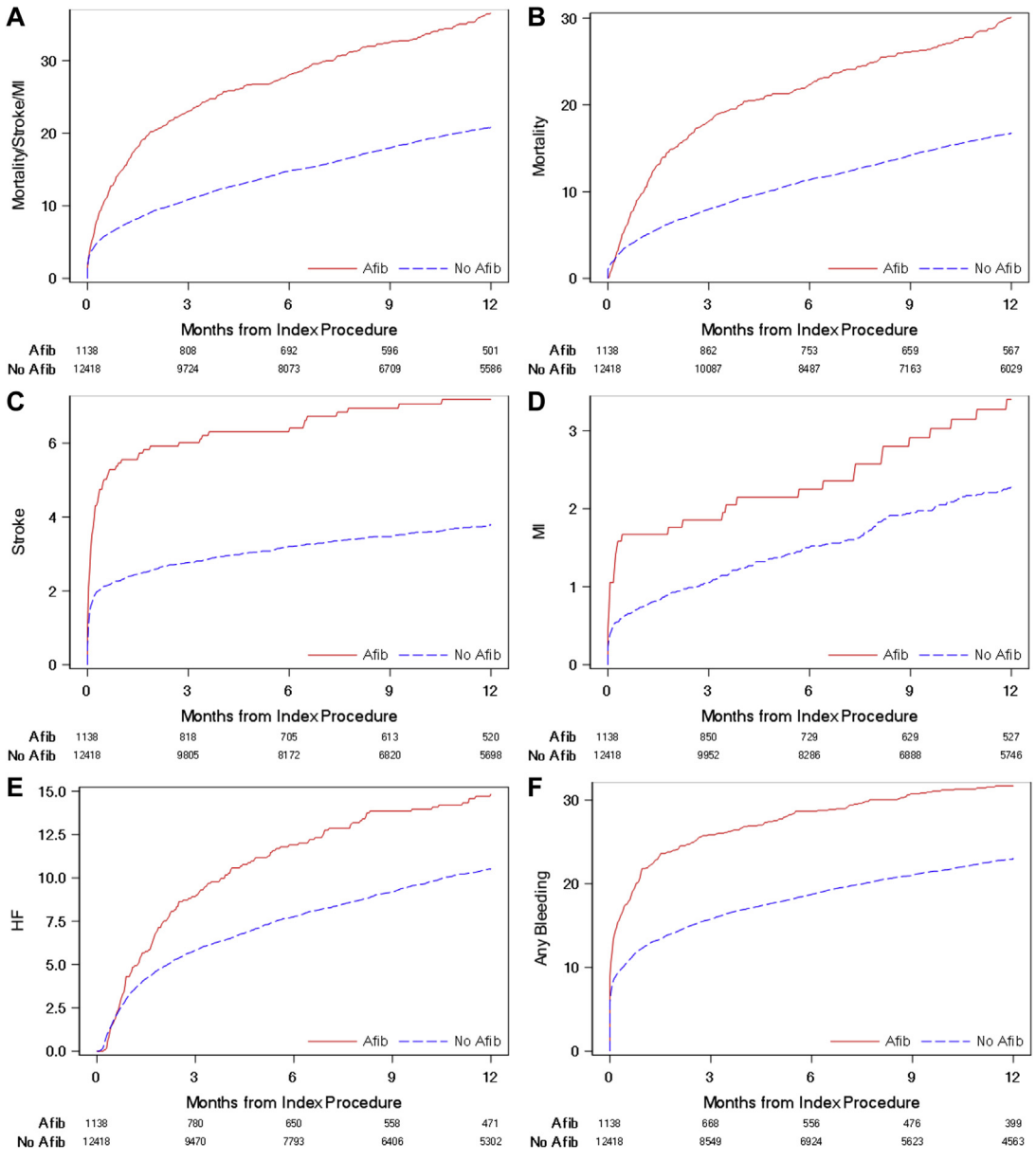
patients who were not discharged on anticoagulation, with lower rates of rehospitalization for heart failure (13.0% vs. 19.6%; $p < 0.01$) and rehospitalization for major bleeding (30.1% vs. 35.7%; $p < 0.01$). Although the difference in rehospitalization for stroke was attenuated, the remaining differences persisted after multivariate adjustment (**Table 3**). Survival curves are presented in the Online Figure 1.

NEW-ONSET AF AMONG TRANSFEMORAL PATIENTS. We performed a sensitivity analysis restricting the patient population to those undergoing TAVR via transfemoral access. Patients developing new-onset AF were older, more likely to be female, more likely to have severe chronic obstructive pulmonary disease, and more likely to have New York Heart Association class III or IV heart failure. The median CHA_2DS_2-VASC score was 5 and the median modified ATRIA score was 6 among patients with new-onset AF and those with non-new-onset AF. Antithrombotic and antiarrhythmic management were also similar to the overall analysis, with 26.4% of patients with new-onset AF discharged on oral anticoagulation (compared with 7.0% among patients not developing AF). Both in-hospital and 1-year outcomes were higher among transfemoral patients who developed AF (Online Tables 2 to 4).

DISCUSSION

Our study represents the first nationwide examination of the incidence of post-procedural AF among patients without pre-existing AF undergoing TAVR. We report that 8.4% of patients developed new-onset AF following TAVR, with the strongest factor associated with new-onset AF being nontransfemoral access. Only about 30% of patients who developed new-onset TAVR were prescribed oral anticoagulant therapy at discharge. Finally, patients who developed new-onset AF had significantly worse outcomes during the hospitalization and at 1 year, even after extensive multivariate adjustment. The patients at highest risk for adverse events were those who

FIGURE 3 One-Year Outcomes Following Transcatheter Aortic Valve Replacement



This figure demonstrates survival curves for patients at 1 year, stratified by the development of atrial fibrillation (Afib) **(red)** versus no atrial fibrillation **(blue)**. **(A)** Composite outcome of mortality/stroke and myocardial infarction. **(B)** Mortality. **(C)** Readmission for stroke. **(D)** Readmission for myocardial infarction (MI). **(E)** Readmission for heart failure (HF). **(F)** Readmission for bleeding. Note that the scales are different for each outcome.

developed new-onset AF and were not discharged on anticoagulation.

Data from the pivotal randomized trials suggest that rates of post-TAVR AF range between 8.6% and 11.7% in the first 30 days (5-8). An analysis from the SOURCE XT study, an international, multicenter registry of patient treated with the Edwards SAPIEN XT valve, demonstrated 7.2% incidence of new-onset AF following TAVR and noted an association with worse outcomes compared with patients who maintained sinus rhythm (10). However, this was a small analysis that focused exclusively on 1 device. From

TABLE 2 One-Year Outcomes

	Unadjusted Cumulative Incidence (%)				
	Developed New-Onset AF (n = 1,138)	Did Not Develop New-Onset AF (n = 12,418)	p Value	Adjusted HR (95% CI)	p Value
Composite endpoint (mortality/stroke/MI)	36.5	20.9	<0.01	1.41 (1.25–1.59)	<0.01
Mortality	30.1	16.8	<0.01	1.37 (1.19–1.58)	<0.01
Rehospitalization for stroke	7.2	3.8	<0.01	1.50 (1.14–1.98)	<0.01
Rehospitalization for MI	3.4	2.3	0.42	1.22 (0.83–1.78)	0.32
Rehospitalization for heart failure	14.8	10.5	<0.01	1.12 (0.93–1.35)	0.23
Rehospitalization for major bleeding	31.7	23.0	<0.01	1.24 (1.10–1.40)	<0.01

Values are % unless otherwise indicated.
AF = atrial fibrillation; CI = confidence interval; HR = hazard ratio; MI = myocardial infarction.

the initial 1-year outcomes analysis for the TVT Registry, 42% of patients undergoing TAVR had histories of AF, and the presence of AF was associated with 37% higher mortality than those without AF (4). In this analysis, we demonstrate than an additional 8.4% of patients developed new-onset AF following TAVR, and patients who developed AF appeared to have a 2-fold higher observed mortality rate. After multivariate adjustment, new-onset AF was associated with 37% higher risk for mortality, essentially identical to the previous report of patients in the registry with pre-procedural AF. This also suggests that more than half of all patients undergoing TAVR must contend with concomitant AF either before or after their procedure.

In our analysis, significant predictors of new-onset AF among patients with no history of AF included older age, lower left ventricular function, chronic lung disease, and nontransfemoral access, with the latter being the strongest predictor. This finding mirrors prior analyses evaluating predictors of new-onset AF. In 1 analysis of surgical procedures, only procedures without pericardiotomy were associated with a lower incidence of AF (adjusted OR: 0.18; 95% CI: 0.05 to 0.59), although higher STS score, history of chronic obstructive pulmonary disease, and moderate to severe left atrial enlargement showed a trend toward increased incidence of post-operative AF (3). Patients undergoing TAVR with a nontransfemoral route have more comorbidities than those for whom femoral access is used, though it is also possible that there may be a direct, pathogenic mechanism for new-onset AF, especially in patients in whom transapical access is used (9), thought to be related to a local and systemic inflammatory response to pericardiotomy (3,18,19). Although the incidence of new-onset AF is lower among patients undergoing transfemoral access, antithrombotic management and rates of short- and long-term adverse outcomes remain similar to that of the overall population. Interestingly, the presence of pacemaker prior to the TAVR procedure was associated with lower rates of new-onset AF. We speculate that this may be due to the role of physiological pacing (i.e., maintaining atrioventricular synchrony) in preventing right and left atrial remodeling or the suppression of ectopic atrial beats that may lead to the initiation of AF (20–23).

Additionally, our study demonstrates broad variability in the management of new-onset, post-procedural AF following TAVR. Currently, there are no

TABLE 3 One-Year Outcomes for Patients With Atrial Fibrillation Treated Without Versus With Oral Anticoagulation

	Unadjusted Cumulative Incidence (%)				
	AF Without OAC (n = 319)	AF With OAC (n = 819)	p Value	Adjusted HR (95% CI)	p Value
Composite endpoint (mortality/stroke/MI)	39.7	28.4	<0.01	1.72 (1.35–2.22)	<0.01
Mortality	33.8	20.7	<0.01	2.08 (1.56–2.78)	<0.01
Rehospitalization for stroke	7.5	6.3	<0.01	1.12 (0.67–1.89)	0.66
Rehospitalization for MI	3.5	3.1	0.82	1.14 (0.49–2.63)	0.77
Rehospitalization for heart failure	13.0	19.6	<0.01	0.60 (0.41–0.88)	0.01
Rehospitalization for major bleeding	30.1	35.7	<0.01	0.77 (0.61–0.98)	0.03

Values are % unless otherwise indicated.
OAC = oral anticoagulation; other abbreviations as in Table 2.

TAVR-specific guidelines regarding the management of post-procedural AF. For patients who develop AF following cardiac surgery, current American Heart Association, ACC, and Heart Rhythm Society guidelines offer a Class IIa recommendation for the administration of amiodarone and oral anticoagulant therapy (11). In our analysis, we found that 49% of patients developing AF were discharged on antiarrhythmic therapy. Although no studies have directly evaluated the utility of rate versus rhythm control in patients undergoing TAVR, a recent analysis demonstrated no benefit of either strategy over the other among patients developing new-onset post-operative AF undergoing cardiac surgery (24).

There was notable evidence of significant variation in post-procedural antithrombotic therapy. Traditionally, dual-antiplatelet therapy (DAPT) has been used to avoid thrombotic events post-TAVR. In patients with AF, however, the addition of anticoagulant therapy to DAPT (so-called triple therapy) significantly increases the risk for bleeding. In our analysis, most patients with new-onset AF were discharged on aspirin despite a median CHA_2DS_2-VASc score of 5, but only half of patients with AF were discharged on $P2Y_{12}$ inhibitors. Additionally, <30% were discharged on anticoagulant therapy. There were no differences in some markers of frailty status, such as hemoglobin, 5-m walk distance >6 m, or albumin, between patients who were anticoagulated and those not. In our study, patients with new-onset AF had a higher risk for stroke as well as a higher risk for in-hospital bleeding and bleeding requiring rehospitalization than those without new AF despite no significant differences in objective bleeding risk as calculated by the ATRIA score. This suggests that a more granular approach may be necessary to classify bleeding risk in patients who may be likely to derive ischemic benefit from anticoagulation. A recent small study comparing DAPT versus aspirin alone demonstrated similar rates of ischemic events and higher rates of major bleeding in the DAPT arm (25), which calls into question the need for DAPT in these patients, underscoring the need for a more tailored strategy to minimize the risk for stroke while also mitigating the risk for bleeding in these patients.

Because stroke is among the most feared complications following TAVR as well as the primary risk in patients with AF, the cornerstone of the mitigation of stroke risk has been anticoagulant therapy (11). Importantly, our study is unable to infer causality between the development of new-onset AF and stroke, especially in the first 72 h, as stroke risk during this time period may be more related to procedural factors. However, our study demonstrates the challenge with this approach in patients at high risk for bleeding, as demonstrated by high ATRIA scores in this cohort. Our study did not demonstrate significant stroke reduction in patients with AF when stratified by oral anticoagulation status despite numerically lower rates of stroke. This may be due to a low event rate overall or the fact that we did not have a large enough sample size to detect a meaningful difference in the absolute rate of stroke. Additionally, early divergence of the event curve with respect to stroke may suggest stroke incidence post-procedure but prior to initiation of anticoagulation.

Nevertheless, the optimal antithrombotic strategy in patients following TAVR remains an important clinical question and is currently the focus of a number of ongoing studies, though none are focusing exclusively on patients with AF. More broadly, however, stroke prevention in high-risk TAVR patients is likely the combination of a number of factors. It is likely that pre-existing AF is underdetected among patients undergoing TAVR. A prior study by Urena et al. (26) demonstrated that among patients who developed post-procedural AF, more than 30% were newly diagnosed with AF via electrocardiographic monitoring 24 h prior to the TAVR procedure. The development of new-onset AF has been associated with a higher risk for acute stroke (<24 h) (27). Additionally, almost one-third of patients with AF have demonstrated left atrial appendage thrombus on cardiac computed tomography, and patients with appendage thrombus were at higher risk for stroke than those without (28). Because approximately half of strokes occur within the first 72 h following TAVR, periprocedural modifications, such as using transcatheter embolic protection devices and determining the optimal procedural anticoagulation strategy, may limit periprocedural strokes. Among patients with AF, Kapadia et al. (28) outlined a number of potential risk mitigation strategies. These may include more aggressive detection of paroxysmal AF prior to the procedure, dedicated imaging to detect left atrial appendage thrombus, consideration of a left atrial appendage occlusion devices in patients without thrombus but at prohibitive risk for bleeding on long-term oral anticoagulation, and tailored antithrombotic strategies to mitigate stroke risk while minimizing bleeding risk. Although many studies evaluating antithrombotic therapy strategy (GALILEO [29], ARTE [25]) do not include patients with AF, the POPULAR-TAVI trial (cohort B) (30), AVATAR (NCT02735902), and ATLANTIS (NCT02664649) include patients with AF and will offer insight into the optimal strategy for these patients.

STUDY LIMITATIONS. First, we cannot definitively exclude the possibility that some patients classified as developing new-onset AF had paroxysmal, undetected AF prior to the procedure, as systematic cardiac monitoring was not performed routinely prior to TAVR.

Second, we were unable to characterize whether patients had paroxysmal versus persistent forms of post-procedure AF.

Third, 1-year outcomes data are derived from CMS claims and are not individually adjudicated, though prior analyses using similar methodology have demonstrated consistent results (31).

Fourth, it is possible the incidence of new-onset AF may be different in the future if the overall risk profile of patients undergoing the procedure changes to include lower risk patients or if the distribution of transfemoral versus nontransfemoral access varies.

Fifth, our study excluded patients on prior anticoagulation and those unable to be linked via Medicare claims data, and our results may not be generalizable to those patients.

Finally, as this is an observational study, it is subject to measured and unmeasured confounding, and we are unable to infer causality. These unmeasured confounders may include markers of disability or frailty, which may affect the decision for anticoagulation and/or specific outcomes.

CONCLUSIONS

The development of new-onset AF following TAVR is common, occurring in 8.4% of patients with no histories of AF, though with wide variation by access site (4.4% with transfemoral access, 16.5% with nontransfemoral access). Patterns of care for patients with AF are variable, with low rates of discharge on oral anticoagulant therapy. New-onset AF was associated with higher rates of mortality, stroke, and bleeding requiring rehospitalization. Further studies are needed to determine the optimal management strategy in these high-risk patients.

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PERSPECTIVES

WHAT IS KNOWN? Although the presence of pre-procedure AF is associated with worse outcomes following TAVR, the incidence of new-onset AF and its associated management strategies and outcomes are unclear.

WHAT IS NEW? New-onset AF is common and occurs in about 10% of patients following TAVR who do not have histories of prior AF. Care patterns for these patients with respect to discharge on oral anticoagulant therapy are variable, and it is associated with worse outcomes, including higher rates of mortality, stroke, and bleeding requiring hospitalization.

WHAT IS NEXT? Additional studies are warranted to fully understand the impact of new-onset AF in order to develop strategies to mitigate stroke and mortality risk in these high-risk patients.

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KEY WORDS atrial fibrillation, TAVR

APPENDIX For a list of administrative claims codes for outcomes of interest as well as supplemental tables and a figure, please see the online version of this paper.