Journal of the American Heart Association

ORIGINAL RESEARCH

Use of Direct Oral Anticoagulant and Outcomes in Patients With Atrial Fibrillation after Transcatheter Aortic Valve Replacement: Insights From the STS/ACC TVT Registry

Tanyanan Tanawuttiwat, MD, MPH; Amanda Stebbins, MS; Guillaume Marquis-Gravel, MD, MSc; Sreekanth Vemulapalli, MD; Andrzej S. Kosinski, PhD; Alan Cheng, MD

BACKGROUND: Clinical evidence on the safety and effectiveness of using direct oral anticoagulants (DOACs) in patients with atrial fibrillation after transcatheter aortic valve replacement (TAVR) remains limited. The aim of this study was to investigate the trends and outcomes of using DOACs in patients with TAVR and atrial fibrillation.

METHODS AND RESULTS: Data from the STS/ACC TVT (Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy) Registry was used to identify patients who underwent successful TAVR with preexisting or incident atrial fibrillation who were discharged on oral anticoagulation between January 2013 and May 2018. Patients with a mechanical valve, valve-in-valve procedure, or prior stroke within a year were excluded. The adjusted primary outcome was 1-year stroke events. The adjusted secondary outcomes included bleeding, intracranial hemorrhage, and death. A total of 21 131 patients were included in the study (13 004 TAVR patients were discharged on a vitamin K antagonist and 8127 were discharged on DOACs.) The use of DOACs increased 5.5-fold from 2013 to 2018. The 1-year incidence of stroke was comparable between DOAC-treated patients and vitamin K antagonist-treated patients (2.51% versus 2.37%; hazard ratio [HR], 1.00; 95% CI, 0.81–1.23) whereas DOAC-treated patients had lower 1-year incidence of any bleeding (11.9% versus 15.0%; HR, 0.81; 95% CI, 0.75–0.89), intracranial hemorrhage (0.33% versus 0.59%; HR, 0.54; 95% CI, 0.33–0.87), and death (15.8% versus 18.2%; HR, 0.92; 95% CI, 0.85–1.00).

CONCLUSIONS: In patients with TAVR and atrial fibrillation, DOAC use, when compared with vitamin K antagonists, was associated with comparable stroke risk and significantly lower risks of bleeding, intracranial hemorrhage, and death at 1 year.

Key Words: atrial fibrillation ■ direct oral anticoagulants ■ oral anticoagulation ■ transcatheter aortic valve replacement ■ vitamin K antagonist

Atrial fibrillation (AF) occurs in more than 40% of patients with transcatheter aortic valve replacement (TAVR)[1] and has been associated with an increased risk of both subacute and late stroke development.[2,3] Over the last decade, direct oral anticoagulants (DOACs) have been introduced and shown to be a better alternative in patients with nonvalvular AF.[4] Given its benefits and convenience in use, DOACs are being used with increasing frequency among patients in need of oral anticoagulation (OAC) undergoing TAVR.[5] Although the current clinical practice guidelines on the management of patients with AF include the

Correspondence to: Tanyanan Tanawuttiwat, MD, MPH, Krannert Institute of Cardiology, Indiana University, 1800 N Capitol Ave. Room 300B, Indianapolis, IN 46202. E-mail: ttanawu@iu.edu

Supplementary Material for this article is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.121.023561

For Sources of Funding and Disclosures, see page 9.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- Based on a large, observational, clinical data registry of US patients with transcatheter aortic valve replacement and atrial fibrillation, using direct oral anticoagulants in this population is associated with lower risks of bleeding and intracranial hemorrhage, without an increased risk of stroke, when compared with vitamin K antagonists.

What Are the Clinical Implications?

- Direct oral anticoagulants could be considered as an alternative to warfarin in patients with atrial fibrillation after transcatheter aortic valve replacement.
- Because the number of transcatheter aortic valve replacement is expanding and atrial fibrillation is highly prevalent in this population and the inherit limitation of observational data in this study, additional research is needed for long-term evaluation of efficacy and safety of different anticoagulation agents.

Nonstandard Abbreviations and Acronyms

BHV	bioprosthetic heart valve
CMS	Centers for Medicare & Medicaid Services
DOAC	direct oral anticoagulant
OAC	oral anticoagulation
TAVR	transcatheter aortic valve replacement
VKA	vitamin K antagonist

use of DOACs for those with bioprosthetic heart valves (BHV),[4] no specific recommendations are available for patients undergoing TAVR. With the differences in structure and procedural factors of surgical and transcatheter BHV, it remains unclear whether the recommendations can be applied to patients with TAVR interchangeably and whether the effectiveness profiles of vitamin K antagonists (VKAs) and DOACs are similar in TAVR populations.

Using the NCDR (National Cardiovascular Data Registry) STS/ACC TVT (Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy) Registry, we sought to evaluate (1) characteristics of patients with AF who were discharged on VKAs versus DOACs; (2) trends of VKA versus DOAC use for stroke prevention in patients with TAVR and AF; and (3) the 1-year rate of stroke, bleeding, and mortality outcomes comparing between patients discharged with VKA versus DOACs.

METHODS

The authors declare that all supporting data are available within the article and its online supplementary files.

Data Sources

The NCDR STS/ACC TVT Registry was established as a data repository to track patient safety and real-world outcomes related to TAVR procedures performed in the United States. The registry data collection process and details of the design have been previously described.[6,7] The clinical records of the TVT Registry were linked to Centers for Medicare & Medicaid Services (CMS) administrative claims data using direct patient identifiers, and this linked data set was used to determine 1-year outcomes.[8] The Duke Clinical Research Institute is the analytic center for the registry and is responsible for data management and analysis. Activities of this registry have been approved by a central institutional board review (Chesapeake Research Review, Inc) and waiver of informed consent has been granted by the Duke University School of Medicine institutional review board.

Study Cohort

Between January 2013 and May 2018, we identified 21 131 patients who had undergone successful TAVR implantation in the STS/ACC TVT Registry with data linked to CMS claims. Patients with a diagnosis of AF before the procedure and a new diagnosis of AF during hospitalization, who had a successful implant, were discharged on an OAC, and were linked to CMS were included in the study. For evaluation of the outcomes and use of OAC in patients with TAVR and AF, we excluded all patients with a prior mechanical valve, prior stroke within 1 year, in-hospital endocarditis within 1 year, valve-in-valve procedure, TAVR procedure converted to open-heart surgery, in-hospital death, and no OAC or more than 1 OAC recorded on discharge medications (Figure 1).

Definitions

The types of OAC at the time of discharge were denoted on the STS/ACC TVT Registry data collection form as VKA, dabigatran, and Factor Xa inhibitors. For the purpose of analysis, we classified patients who were discharged with an OAC into 2 groups: (1) VKAs and (2) DOACs (eg, dabigatran and Factor Xa inhibitors). CHA_2DS_2-VASc scores were calculated using the data elements from the data collection form.[9] Because not all the components in the HAS-BLED risk score are captured by the TVT Registry, the Anticoagulation and Risk Factors in Atrial Fibrillation bleeding score was used.[10] Because the registry does not capture the data on the previous bleeding, we used CMS claims data for bleeding in the year before TAVR implantation using the

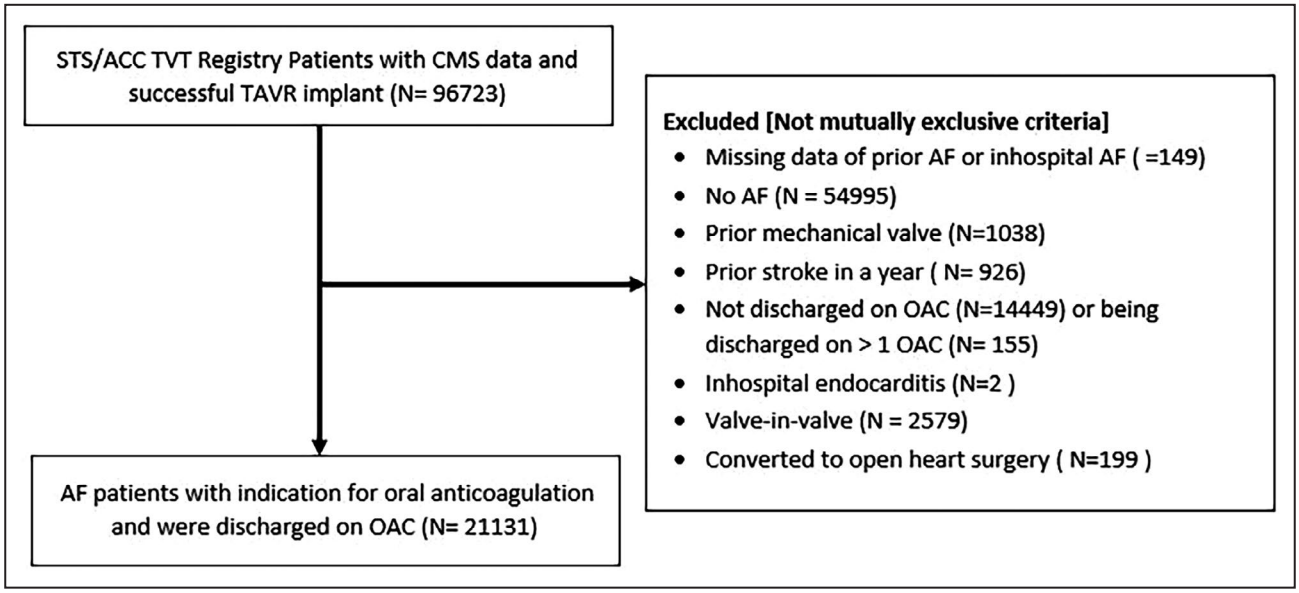

Figure 1. Participant flow in the present study.
ACC indicates American College of Cardiology; AF, atrial fibrillation; CMS, Centers for Medicare & Medicaid Services; OAC, oral anticoagulation; STS, Society of Thoracic Surgery; TAVR, transcatheter aortic valve replacement; and TVT, transcatheter valve therapy.

International Classification of Diseases, Ninth Revision (*ICD-9*) and *Tenth Revision* (*ICD-10*) codes for the bleeding component of the Anticoagulation and Risk Factors in Atrial Fibrillation score. Administrative claims codes for each of these end points are given in Data S1.

Outcome Measures

We evaluated the safety and efficacy outcomes of DOACs compared with VKAs. The primary outcome was 1-year stroke events. The secondary outcomes included both short- and long-term outcomes. The long-term secondary outcomes were 1-year bleeding events, intracranial bleeding, and mortality. The short-term secondary outcomes are the 30-day incidence of device thrombosis, myocardial infarction, valve-related readmission, nonvalve-related readmission, and death. Thirty-day outcomes were captured on the data collection form of the TVT Registry and the 1-year outcomes were evaluated using CMS claims data. The 30-day outcomes were reported to the TVT Registry using standardized definitions consistent with Valve Academic Research Consortium guidelines.[11] The 1-year outcomes were defined using the primary *ICD-9/ICD-10* codes and procedure codes after the index hospitalization (Data S1).

Statistical Analysis

Demographics, clinical characteristics, procedural details, discharge measures, and medications are reported for patients discharged on VKA or DOAC in Table 1. Categorical factors are reported as counts and frequencies. Continuous measures are reported as the median, the 25th and 75th percentile. *P* values were generated using a chi-square for categorical factors and Wilcoxon test for group means. A flow chart explaining which patients were eligible for the analysis is reported in Figure 1 and anticoagulant at the time of discharge is reported in Figure 2.

The unadjusted cumulative incidence of outcomes from discharge date through 30 days and 1 year were examined using the log-rank test and Kaplan-Meier methods for death and using Fine and Gray's method to account for mortality as a competing risk for nonfatal outcomes. Unadjusted and adjusted Cox proportional hazards models are reported to assess the impact of discharge medication on prespecified end points. The clinical variables proven in the literature to be related to the outcomes and $P<0.1$ were considered in the adjusted model for primary and secondary outcomes and were listed in Table 2. Covariates, outcomes, and model structures for the adjusted analyses were prespecified and agreed upon a priori in the statistical analysis plan before generating any data. Significance was tested at a 2-sided alpha level of 0.05. All statistical analyses were performed by the Duke Clinical Research Institute using SAS 9.4 (SAS Institute Inc, Cary, NC).

RESULTS

Baseline Characteristic

A total of 96 723 patients with linked CMS data underwent successful TAVR and were enrolled in the TVT Registry from January 2013 to March 2018. Overall, 39 078 (40.40%) had a prior diagnosis of AF and 2501

Table 1. Baseline Characteristics of Patients Who Underwent Transcatheter Aortic Valve Replacement, Had Diagnosis of Atrial Fibrillation, and Were Discharged on Anticoagulation, Stratified by Types of Oral Anticoagulation

	Discharged on VKA (N=13 004)	Discharged on DOAC (N=8127)	*P* value
Demographics			
Age, y	84.0 (78.0–87.0)	83.0 (78.0–87.0)	0.168
Female sex	5649 (43.4)	3500 (43.1)	0.593
Race			0.003
White	12 658 (97.8)	7851 (97.2)	
Black	198 (1.5)	142 (1.7)	
Asian	49 (0.4)	62 (0.8)	
Other*	35 (0.3)	19 (0.2)	
Hispanic ethnicity	221 (1.7)	198 (2.5)	<.001
Weight, kg	79.00 (67.0–93.0)	79.65 (67.3–93.8)	0.034
Body mass index, kg/m^2	27.47 (24.1–31.8)	27.55 (24.1–32.1)	0.182
Insurance payer: Medicare	4413 (34.0)	2763 (34.0)	0.926
Clinical characteristics			
New York Heart Association Class IV	2072 (15.9)	1212 (14.9)	0.046
Prior percutaneous coronary intervention	4173 (32.1)	2607 (32.1)	0.986
Prior coronary artery bypass graft	3167 (24.3)	1771 (21.8)	<0.001
Prior myocardial infarction	2957 (22.7)	1811 (22.3)	0.441
Porcelain aorta	578 (4.4)	256 (3.2)	<0.001
Pacemaker	3362 (25.9)	1742 (21.4)	<0.001
Implantable cardioverter-defibrillator	818 (6.3)	393 (4.8)	<0.001
Prior stroke	1377 (10.6)	793 (9.8)	0.053
Transient ischemic attack	1235 (9.5)	756 (9.3)	0.649
Prior atrial fibrillation/atrial flutter	12 555 (96.6)	7819 (96.2)	0.200
Peripheral arterial disease	3818 (29.4)	2228 (27.4)	0.002
Current/recent smoker	481 (3.7)	311 (3.8)	0.634
Hypertension	11 876 (91.4)	7492 (92.2)	0.027
Diabetes	4897 (37.7)	2891 (35.6)	0.002
Dialysis dependent	552 (4.3)	131 (1.6)	<0.001
Chronic lung disease: severe	1622 (12.5)	939 (11.6)	0.046
Hostile chest	777 (6.0)	472 (5.8)	0.616
Society of Thoracic Surgeons score	6.74 (4.6–10.3)	6.26 (4.18–9.5)	<0.001
CHA2DS2-VASc score	3.00 (2.0–4.0)	3.00 (2.0–4.0)	0.015
CHA2DS2-VASc score			0.048
Score 0	55 (0.4)	27 (0.3)	
Score 1	676 (5.2)	429 (5.3)	
Score 2	2816 (21.7)	1826 (22.5)	
Score 3–4	7097 (54.6)	4493 (55.3)	
Score ≥5	2360 (18.2)	1352 (16.6)	
Anticoagulation and Risk Factors in Atrial Fibrillation score	6.00 (3.0–6.0)	5.00 (3.0–6.0)	<0.001
Creatinine, mg/dL	1.10 (0.9–1.4)	1.10 (0.9–1.4)	<0.001
Glomerular filtration rate, mL/min per 1.73 m^2	59.28 (44.4–75.1)	61.01 (46.9–75.5)	<0.001
Hemoglobin, g/dL	12.10 (10.8–13.3)	12.20 (10.9–13.4)	<0.001
Platelet count, *10^3/μL	189 (152–233)	194 (158–239)	<0.001
Procedure characteristics			
Left ventricular ejection fraction, %	56.00 (45.0–63.0)	57.00 (45.0–63.0)	0.109
Aortic valve area, cm^2	0.69 (0.6–0.8)	0.70 (0.6–0.8)	<0.001

(*Continued*)

Table 1. Continued

	Discharged on VKA (N=13 004)	Discharged on DOAC (N=8127)	*P* value
Annular calcification	10 317 (80.6)	6469 (80.9)	0.544
Mitral valve stenosis	1501 (13.4)	816 (11.8)	0.002
Mitral valve insufficiency			0.002
None or trace	1596 (14.1)	1020 (14.5)	
Mild (1+)–Moderate (2+)	8913 (78.6)	5504 (78.4)	
≥Moderate-Severe (3+)	834 (7.4)	494 (7.0)	
Anticoagulants (24 h before the procedure)	3585 (29.1)	1967 (24.5)	<0.001
Access site			<0.001
Transfemoral	11 188 (86.1)	7532 (92.7)	
Transapical	950 (7.3)	196 (2.4)	
Transaortic	451 (3.5)	120 (1.5)	
Subclavian	231 (1.8)	161 (2.0)	
Axillary	88 (0.7)	58 (0.771)	
Transiliac	23 (0.2)	7 (0.1)	
Transeptal	1 (0.0)	0 (0.0)	
Transcarotid	32 (0.3)	34 (0.4)	
Other	32 (0.3)	18 (0.2)	
Discharge and discharge medications			
Length of stay	4.00 (2.0–7.0)	3.00 (2.0–6.0)	<0.001
Aspirin	9274 (71.3)	5276 (64.2)	<0.001
$P2Y_{12}$ receptor inhibitor	4434 (34.1)	2456 (30.2)	<0.001
Triple therapy (dual antiplatelet therapy plus anticoagulant)	2123 (16.3)	820 (10.1)	<0.001
VKA	13 004 (100.0)	0 (0.0)	<0.001
Factor Xa inhibitor	0 (0.0)	7413 (91.2)	<0.001
Dabigatran	0 (0.0)	714 (8.8)	<0.001

Values are median (interquartile range), or number (%).
DOAC indicates direct oral anticoagulation; and VKA, vitamin K antagonist.
*American Indian or Alaskan Native, Native Hawaiian or Pacific Islander.

(2.59%) developed new-onset, postprocedural AF. A total of 14 449 patients were discharged on neither VKAs nor DOACs, accounting for 34.75% of the patients with a diagnosis of AF. After exclusions, 21 131 patients were included in the study; 13 004 (61.53%) were discharged with VKA and 8127 (38.46%) were discharged with DOACs (Figure 1). The median age of the study population was 83 (78–87) years, and 11 982 (56.70%) were male. Among the patients with DOACs, 714 (8.79%) were discharged with dabigatran and 7413 (91.21%) were discharged with Factor Xa inhibitors (eg, rivaroxaban, apixaban, edoxaban). Demographic and baseline characteristics are presented in Table 1. The warfarin group appeared to be sicker and had higher risks of bleeding than the DOAC group because more patients in the warfarin group had New York Heart Association class IV, prior coronary artery bypass graft, porcelain aorta, pacemaker, implantable cardioverter-defibrillator, prior stroke, diabetes, dialysis dependent, chronic lung disease, higher STS score, higher Anticoagulation and Risk Factors in Atrial Fibrillation score, and mitral valve stenosis. The presence of a prior stroke or transient ischemic attack and prior AF were similar between the 2 groups. The median CHA_2DS_2-VASC score was 3 in both groups, and the median Anticoagulation and Risk Factors in Atrial Fibrillation score was 6 and 5 in the VKA and DOAC groups, respectively ($P<0.001$). The length of stay was shorter among patients who were discharged with DOAC compared with those who were discharged on VKA (3 versus 4 days, $P<0.001$). At discharge, patients in the DOACs group were less likely to be discharged on aspirin, $P2Y_{12}$ receptor inhibitor, or triple therapy than those in the VKA group ($P<0.001$).

Trends in Oral Anticoagulation Therapy Use in Patients With TAVR and AF

Figure 2 demonstrates time trends in the use of oral anticoagulation therapy between 2013 and 2018 in patients with TAVR and AF. The use of DOAC incrementally increased over time from 10% in 2013 to more

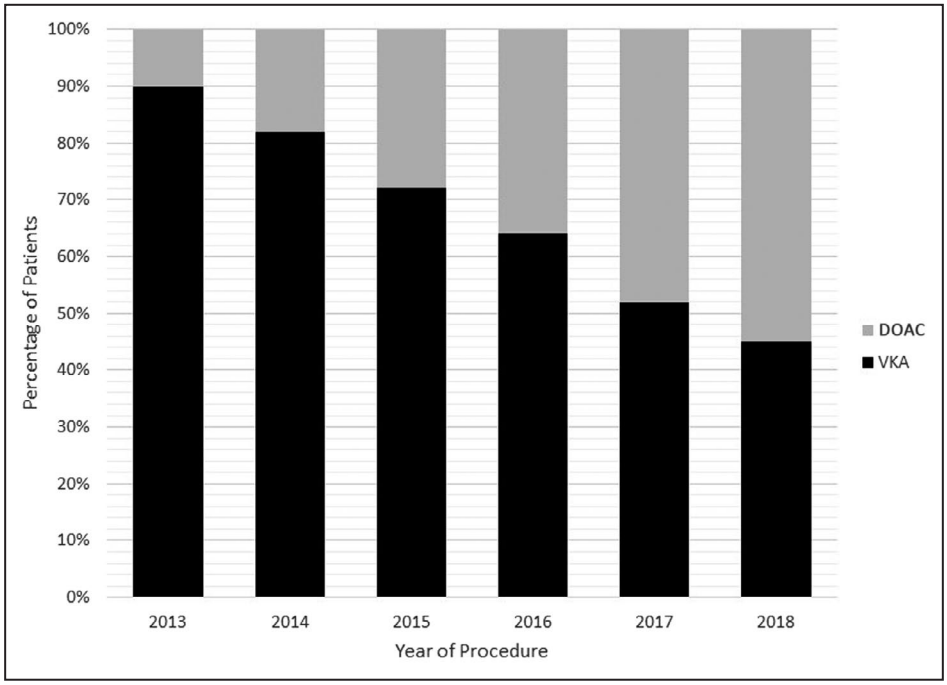

Figure 2. Time trends in the use of oral anticoagulation therapy between 2013 and 2018 in patients with transcatheter aortic valve replacement and atrial fibrillation.
DOAC indicates direct oral anticoagulation; and VKA, vitamin K antagonist.

than 55% in 2018. From 2013 to 2018, there was a 5.5-fold increase in the use of DOACs.

Primary and Secondary Outcomes

Figure 3 demonstrates the cumulative incidences of long-term primary and secondary outcomes. For the primary outcomes, a total of 446 patients developed stroke events at 1 year; 278 patients were treated with VKA and 168 patients were treated with DOAC. The cumulative incidence rate of stroke was not different between the 2 groups (2.51% versus 2.37%, *P*=0.485), which persisted after multivariate adjustment (adjusted

Table 2. 1-Year Unadjusted and Adjusted Outcomes for Patients With Atrial Fibrillation Treated With VKA Versus With DOACs (Reference Group: VKA)

	Unadjusted cumulative incidence (%)			Unadjusted		Adjusted	
	VKA group	DOAC group	*P* value	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
1-year outcomes							
Stroke*	2.37	2.51	0.485	0.97 (0.79–1.19)	0.762	1.00 (0.81–1.23)	0.980
Any bleeding†	15	11.9	<0.001	0.73 (0.67–0.80)	<0.001	0.81 (0.75–0.89)	<0.001
Intracranial hemorrhage†	0.59	0.33	0.014	0.50 (0.31–0.81)	0.005	0.54 (0.33–0.87)	0.011
All-cause mortality‡	18.2	15.8	<0.001	0.85 (0.79–0.91)	<0.001	0.92 (0.85–1.00)	0.043

DOAC indicates direct oral anticoagulation; and VKA, vitamin K antagonist.

*Adjusted variables for stroke at 1 year: age, female sex, weight, prior peripheral artery disease (PAD), prior stroke/transient ischemic attack (TIA), current smoker, prior atrial fibrillation/atrial flutter (AF/AFL), left ventricular ejection fraction (LVEF), diabetes, hypertension, Dialysis dependent, Society of Thoracic Surgeons-Patient-Reported Outcome Measures (STS-PROM) score, CHA2DS2-VASc score, estimated glomerular filtration rate (eGFR), New York Heart Association (NYHA) Class IV, platelet, annular calcification, aortic valve area (AVA), carotid stenosis, nonfemoral access, discharged on aspirin, P2Y12, antiarrhythmics.

†Adjusted variables for bleeding/intracranial hemorrhage: age, female sex, weight, prior PAD, prior stroke/TIA, current smoker, prior AF/AFL, LVEF, diabetes, hypertension, dialysis, STS-PROM score, Anticoagulation and Risk Factors in Atrial Fibrillation score, eGFR, NYHA Class IV, hemoglobin, platelet, anticoagulants (within 24 hour before the procedure), nonfemoral access, discharged on aspirin, P2Y12, antiarrhythmics.

‡Adjusted variables for mortality: age, female sex, weight, prior PAD, prior stroke/TIA, current smoker, prior AF/AFL, LVEF, diabetes, hypertension, dialysis dependent, pacemaker, implantable cardioverter-defibrillator, prior myocardial infarction, severe chronic lung disease, NYHA Class IV, STS-PROM score, CHA2DS2-VASc score, eGFR, hemoglobin, AVA, nonfemoral access, discharged on aspirin, P2Y12, antiarrhythmics, betablocker, angiotensin-converting enzyme inhibitor, mitral regurgitation, and mitral stenosis.

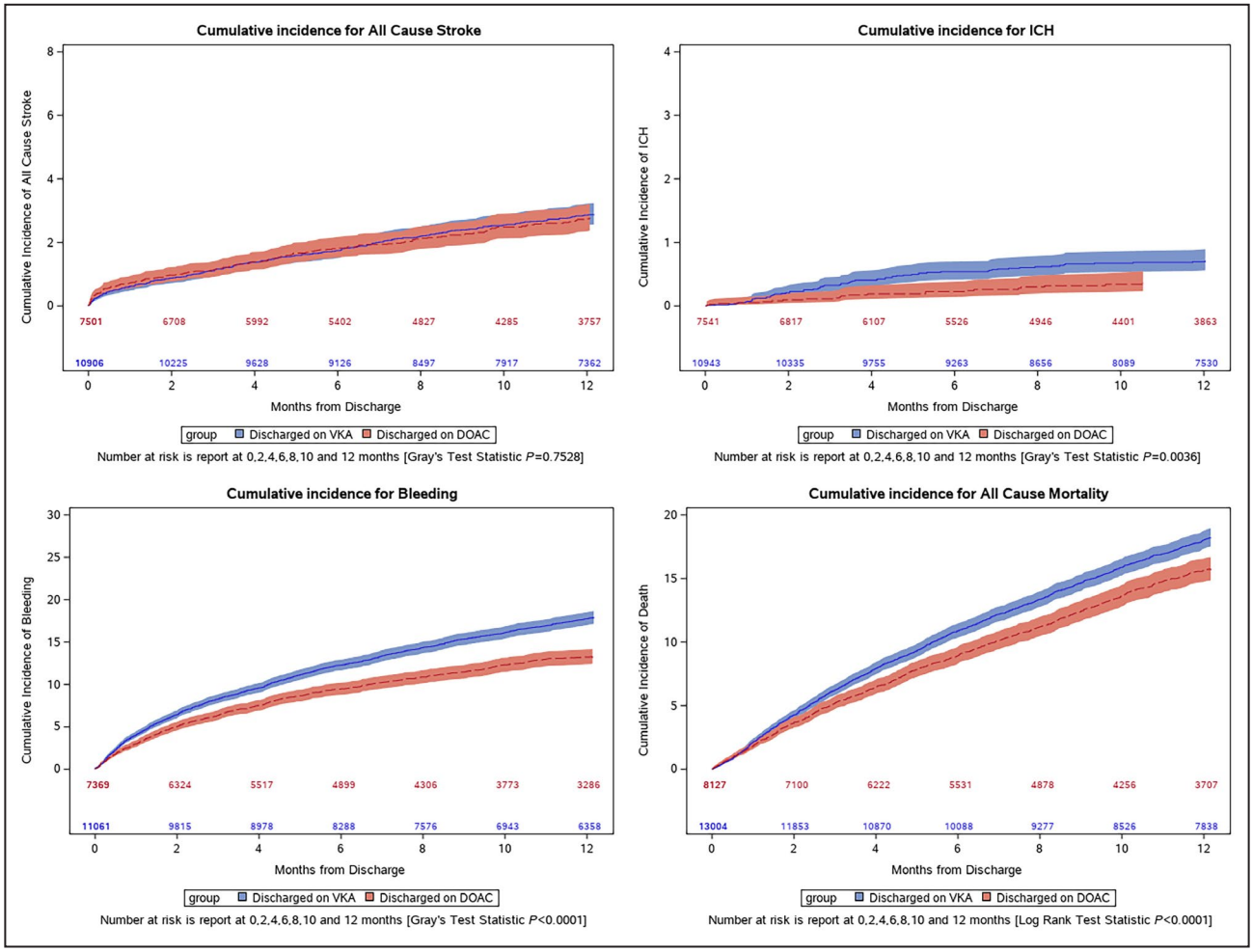

Figure 3. One-year outcomes following transcatheter aortic valve replacement.
DOAC indicates direct oral anticoagulation; ICH, intracranial hemorrhage; and VKA, vitamin K antagonist.

hazard ratio [HR], 1.00; 95% CI, 0.81–1.23; *P*=0.980) (Table 2).

For the long-term secondary outcomes (Tables 2), bleeding occurred in 2582 patients (1775 in VKA group and 807 in DOAC group). The rate of bleeding at 1 year was lower among patients treated with DOAC (11.9% versus 15%, *P*<0.001; adjusted HR, 0.81; 95% CI, 0.33–0.87; *P*<0.001). Intracranial hemorrhage was rare (92 patients) and occurred less frequently in patients treated with DOAC (0.33% versus 0.59%, *P*=0.014; adjusted HR, 0.54; 95% CI, 0.33–0.87; *P*=0.011). The unadjusted cumulative incidence of all-cause mortality was 15.8% for patients treated with DOAC versus 18.2% for patients treated with VKA. This difference persisted after multivariate adjustment (adjusted HR, 0.92; 95% CI, 0.85–1.00; *P*=0.043).

For the short-term secondary outcomes at 30 days, the unadjusted cumulative incidence of all-cause mortality (1.45% versus 1.41%, *P*=0.853), myocardial infarction (0.15% versus 0.19%, *P*=0.483), device thrombosis (0.01% versus 0.01%, *P*=0.725), and valve-related admission (1.19% versus 1.08%, *P*=0.472) were similar between the VKA and DOAC groups. The nonvalve-related readmission was slightly higher in the VKA group (12.1% versus 11.1%, *P*=0.046).

DISCUSSION

This is the largest observational study comparing outcomes between the use of DOACs and VKA for oral anticoagulation in patients with TAVR and preexisting or incident AF. Between 2013 and 2018, approximately 60% of patients were discharged with VKA whereas 40% of patients were discharged with DOACs. The use of DOACs increased 5.5-fold from 2013 to 2018. When compared with VKA, DOAC was associated with comparable stroke outcomes and significantly lower bleeding, intracranial hemorrhage, and mortality risks at 1 year, even after multivariate adjustment.

DOACs have been approved for the prevention of stroke in patients with nonvalvular AF since 2010 and the adoption of DOACs for the prevention and treatment

of thromboembolism by cardiologists has been rapid.[12] Similarly, this study demonstrated the rapid adoption in patients with TAVR, 5.5-fold in 5 years, despite inconclusive guideline recommendations.[4,13–15] Despite the rapid adoption, DOACs appear to be used only in a selected population. The patients in the DOAC group had lower prevalence of known bleeding risk factors, lower nonfemoral approach, were less likely to have triple therapy and were less sick when compared with the warfarin group. Direct aortic access and transapical access are known to be associated with increased mortality and adverse events. We hypothesized that limited access to antidote, limited evidence of using DOAC in patients with dialysis/advanced chronic kidney disease, lack of studies for triple therapy uses, lack of guidelines/clinical trials support, and lower experience with DOACs during the study period could affect clinician decisions in prescribing DOACs in TAVR with AF and prescribed DOACs only in the patients with lower risks. Although these risk factors were statistically adjusted for the outcomes, this clinical selective could affect the results of this study.

The current US guidelines for managing valvular diseases do not specifically address the use of VKA versus DOAC for patients with TAVR with an indication for OAC.[4,14,15] Some clinicians apply the recommendations for the use of DOAC in patients with surgical BHV to patients with TAVR.[5] However, the structure and hemodynamic impact of surgical and transcatheter BHV are different.[16] The metal stent, a frame offering mechanical support for the oversewn xenograft tissue, is covered by fabric in surgical BHVs but is left exposed in TAVR devices.[16] The different locations of where the valves are implanted may also have implications for their thrombogenicity because the endothelization of the protruding struts in the ascending aorta lumen is less than the part with direct endocardial contact. Also, there is a region of relative fluid stagnation between the Valsalva sinus and the native valve leaflets in TAVR.[16] These factors may result in possibly different thrombogenic and endothelization profiles between TAVR devices and surgical BHV. Until more definitive data are available, OAC recommendations for patients with surgical BHV should be applied to patients with TAVR with caution.

Thromboembolic and bleeding complications after TAVR have been the major concerns.[5] The risk factors of stroke in TAVR vary based on the timing of stroke occurrence.[5] Strokes that occur periprocedurally result from embolization of thrombus, calcification, and valve tissue/arterial wall-derived debris,[16,17] and the risk is potentially modifiable by the use of cerebral embolic protection devices.[5,18] In subacute and late stroke, AF and systemic atherosclerosis are well-known risk factors.[5,16] However, the association of AF and late stroke is not consistent in some studies, raising the concern of leaflet thrombosis causing stroke in patients with TAVR.[5] Although neither antiplatelet therapy nor OAC therapy was associated with the risk of 30-day neurologic events in the recent study,[19] the lack of OAC was associated with late ischemic stroke/transient ischemic attack (>30 days postprocedure).[20] Optimal antithrombotic management in patients undergoing TAVR with or without AF is still debated. The clinical trials in patients with TAVR with an indication for OAC are limited. The only clinical trial to assess the use of VKA versus DOAC (edoxaban) in patients with an indication for OAC after TAVR is ENVISAGE TAVI AF (Edoxaban Compared to Standard Care After Heart Valve Replacement Using a Catheter in Patients With Atrial Fibrillation).[21] The study demonstrated that the outcomes of edoxaban use were comparable with warfarin use in all-cause mortality, ischemic stroke, and intracranial hemorrhage. However, the incidence of major bleeding was higher with edoxaban than with warfarin, mainly owing to more gastrointestinal bleeding. Several factors could possibly explain the difference in bleeding outcomes between ENVISAGE TAVI AF and our study. Endoxaban is the least commonly dispensed DOACs in the United States and apixaban is the most commonly dispensed DOACs.[22] The different bleeding profiles in each DOAC, different antiplatelet protocol in ENVISAGE-TAVI (dual antiplatelet for 3 months or single antiplatelet indefinitely), and the selected population for DOACs in our observational study could contribute to the different findings.[23]

The other evidence supporting the clinical use of DOAC in patients with TAVR and AF is limited to small observational studies from Europe. Geis et al conducted a retrospective observational study evaluating 6-month outcomes between patients with TAVR and VKA (N=172) and DOAC (N=154) monotherapy.[24] No significant differences in mortality, stroke, embolism, and severe bleeding were found.[24] Similarly, Seeger et al compared the outcomes between apixaban (n=141) and VKA (n=131) at 1 year after TAVR by using a single-center observational study. There were no significant differences in all-cause mortality, bleeding, and stroke between the 2 groups.[25] Jochheim et al used the database from the 4-European-center, observational registry for evaluation of 1-year composite of death, myocardial infarction and cerebrovascular event outcomes between VKA and DOAC (326 patients using DOACs versus 636 patients using VKAs). Despite the findings of statistically comparable in bleeding, ischemic stroke, and mortality between groups, the investigators noted a higher stroke rate in DOAC groups (4.2% [13 patients] versus 2.8% [17 patients]).[26] However, these 3 studies were limited to small populations and numbers of events, and the study by Seeger et al

was limited to apixaban. Using a large, US practice-based registry, we demonstrate no difference in the 1-year stroke risk between DOAC and VKA (2.51% versus 2.37%; adjusted HR, 1.00; 95% CI, 0.81–1.23; *P*=0.980). The rate of stroke was comparable with the aforementioned studies, approximately 1% to 3%.[24–26] This finding suggests the comparable efficacy of DOAC in stroke prevention in patients with TAVR requiring OAC for AF.

Unlike previous studies,[24–26] our results suggest a significantly lower bleeding risk (11.9% versus 15%; adjusted HR, 0.81; 95% CI, 0.75–0.89; *P*<0.001), intracranial hemorrhage (0.33% versus 0.59%; adjusted HR, 0.54; 95% CI, 0.33–0.87; *P*=0.011) and mortality risk (15.8% versus 18.2%; adjusted HR, 0.92; 95% CI, 0.85–1.00; *P*=0.043) with DOACs. The findings mirror a favorable safety profile, with reductions in intracranial hemorrhage and mortality of DOAC when compared with VKA in the general population with AF.[27] However, this finding should be applied to patients with TAVR and AF with caution. The benefits on bleeding in our study could be limited by the different baseline characteristics between the warfarin group and DOAC group as mentioned previously.

Study Limitations

First, inherent limitations in using retrospective, observational data from the registry, including unmeasurable confounders, should be noted. The 1-year outcomes data and data on prior bleeding are derived from CMS claims and are not adjudicated. Second, the analysis was based on the type of OAC at the time of discharge. Approximately 34.75% of patients with TAVR and AF were discharged on no OAC. It is possible that some of these patients started on OAC after discharge. Data on medication compliance, time in the therapeutic international normalized ratio range in the VKA group, the use of low-molecular weight heparin as bridging therapy, and change or discontinuation of medication during follow-up and crossover are not available. However, this limitation does not affect the scope of our findings as intention to treat analysis based on OAC treatment strategy at discharge was used in this study. Third, the patients with incident AF were less than 5% of the studied population and our results may not be generalizable for this patient subgroup. Fourth, despite including antiplatelet treatment in multivariate adjustment, the duration of antiplatelet treatment along with OAC is unknown. Fifth, the study included the patients from 2013 to 2018, before the current 2019 AF guidelines were published. Therefore, use of oral anticoagulation in the data set may not reflect current clinical practice. Finally, device thrombosis is one of the thromboembolic complications after TAVR. The median time from TAVR procedure to the diagnosis of device thrombosis is 181 days[5] but only data on device thrombosis at 30 days were available for analysis. The 1-year echocardiographic data evaluating the valvular function for the detection of subclinical device thrombosis were not available. However, symptomatic obstructive leaflet thrombosis after TAVR is rare and whether subclinical leaflet thrombosis is related to stroke or the progression to clinical leaflet thrombosis remains unknown.

CONCLUSIONS

In an analysis from a large clinical data registry of US patients with AF undergoing TAVR, we found that the 1-year risk of stroke was similar between VKAs and DOACs whereas DOACs use was associated with a reduction in risks of bleeding, intracranial hemorrhage, and all-cause mortality when compared with VKA. Because of the limitations of observational study, further randomized controlled trials and long-term studies are warranted to evaluate whether DOACs should be recommended over VKA in patients with TAVR requiring anticoagulation for AF.

ARTICLE INFORMATION

Received August 10, 2021; accepted December 6, 2021.

Affiliations

Krannert Institute of Cardiology, Indiana University, Indianapolis, IN (T.T.); ; Duke Clinical Research Institute, Durham, NC (A.S., G.M.-G, S.V., A.S.K.); and Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD (A.C.).

Acknowledgments

The authors are grateful to Leo Brothers for his irreplaceable work on the Society of Thoracic Surgeons Data Warehousing and Analytic project at the Duke Clinical Research Institute.

Sources of Funding

This research was supported by the National Cardiovascular Data Registry (NCDR) STS/ACC TVT Registry.

Disclosures

Dr Marquis-Gravel received honoraria from Servier and Novartis. Dr Vemulapalli reports grants from American College of Cardiology, Society of Thoracic Surgeons, National Institutes of Health, Patient Centered Outcomes Research Institute, Food and Drug Administration (National Evaluation System for Health Technology), Abbott Vascular, and Boston Scientific. Dr Vemulapalli also serves on the advisory board for Janssen, Boston Scientific, and Heart Flow. Dr Cheng serves as an employee of Medtronic but this work preceded his time at Medtronic. Dr Kosinski received grants from American College of Cardiology, Society of Thoracic Surgeons, National Institutes of Health, and Patient Centered Outcomes Research Institute. The remaining authors have no disclosures to report.

Supplemental Material

Data S1

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SUPPLEMENTAL MATERIAL

Data S1. Administrative claims codes for outcomes of interest

- **Stroke:** [ICD-9] 434.x1, 436, 433.x1, 997.02, 437.1, 437.9, 430, 431, 432.x (Diagnosis Codes), [ICD-10] G9731, G9732, I60.x, I61.x, I62.x, I63.x, I6781, I6782, I6789, I679, I97810, I97811, I97820, I97821 (Diagnosis Codes)
- **Intracranial hemorrhage**: [ICD-9] 430, 431, 4320, 4321, 4329 (Diagnosis Codes), [ICD-10] I60.x, I61.x, I62.x (Diagnosis Codes)
- **Any bleeding includes the following:**
    - GI Bleed: [ICD-9] 455.2, 455.5, 455.8, 456.0, 456.20, 530.21, 530.7, 530.82, 531.0x, 531.2x, 531.4x, 531.6x, 532.0x, 532.2x, 532.4x, 532.6x, 533.0x, 533.2x, 533.4x, 533.6x, 534.0x, 534.2x, 534.4x, 534.6x, 535.x1, 537.83, 562.12, 562.13, 562.02, 562.03, 569.3, 569.86, 578.0, 578.1, 578.9 (Diagnosis Codes) [ICD-10] I8501, I8511, K2211, K226, K250, K252, K254, K256, K260, K262, K264, K266, K270, K272, K274, K276, K280, K282, K284, K286, K2901, K2921, K2931, K2941, K2951, K2961, K2971, K2981, K2991, K31811, K5281, K5701, K5711, K5713, K5721, K5731, K5733, K5741, K5751, K5753, K5781, K5791, K5793, K625, K6381, K920, K921, K922 (Diagnosis Codes)
    - GU Bleed: [ICD-9] 596.7, 599.7, 623.8, 626.2, 626.6, 626.8 (Diagnosis Codes) [ICD-10] N897, N920, N921, N925, N938 (Diagnosis Codes)
    - ICH: [ICD-9] 430, 431, 432.0, 432.1, 432.9 (Diagnosis Codes) [ICD-10] 160x, 161x, 162x (Diagnosis Codes)
    - Other bleeding: [ICD-9] 56881, 36281, 7847, 7848, 2851, 4590, V582, 56985, 430, 431, 4320, 4321, 4329, 4230, 78559, 51189, [ICD-10 DX] K661, D62, H356*, I312, I60*, I61*, I62*, J942, K5521, R040, R041, R571, R578, R58, R042, R0489, R049, J949, R570, R579 (Diagnosis Codes); [ICD-9] 9902, 9903, 9904, 9905, 9906, 9907, 9908 (Procedure codes), [ICD-10] 30230H0, 30230H1, 30230K0, 30230K1, 30230L0, 30230L1, 30230M0, 30230M1, 30230N0, 30230N1, 30230P0, 30230P1, 30230R0, 30230R1, 30230T0, 30230T1, 30230V0, 30230V1, 30230W0, 30230W1, 30233H0, 30233H1, 30233K0, 30233K1, 30233L0, 30233L1, 30233M0, 30233M1, 30233N0, 30233N1, 30233P0, 30233P1, 30233R0, 30233R1, 30233T0, 30233T1, 30233V0, 30233V1, 30233W0, 30233W1, 30240H0, 30240H1, 30240K0, 30240K1, 30240L0, 30240L1, 30240M0, 30240M1, 30240N0, 30240N1, 30240P0, 30240P1, 30240R0, 30240R1, 30240T0, 30240T1, 30240V0, 30240V1, 30240W0, 30240W1, 30243H0, 30243H1, 30243K0, 30243K1, 30243L0, 30243L1, 30243M0, 30243M1, 30243N0, 30243N1, 30243P0, 30243P1, 30243R0, 30243R1, 30243T0, 30243T1, 30243V0, 30243V1, 30243W0, 30243W1, 30250H0, 30250H1, 30250K0, 30250K1, 30250L0, 30250L1, 30250M0, 30250M1, 30250N0, 30250N1, 30250P0, 30250P1, 30250R0, 30250R1, 30250T0, 30250T1, 30250V0, 30250V1, 30250W0,

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