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FOCUS ON TRANSCATHETER AORTIC VALVE REPLACEMENT

Direct Oral Anticoagulants Versus Vitamin K Antagonists in Patients With Atrial Fibrillation After TAVR

Hideyuki Kawashima, MD,[a,b,c] Yusuke Watanabe, MD, PhD,[a] Hirofumi Hioki, MD,[a] Ken Kozuma, MD, PhD,[a] Akihisa Kataoka, MD, PhD,[a] Makoto Nakashima, MD,[a] Fukuko Nagura, MD,[a] Yugo Nara, MD, PhD,[a] Fumiaki Yashima, MD,[d,e] Norio Tada, MD,[f] Toru Naganuma, MD,[g] Masahiro Yamawaki, MD, PhD,[h] Futoshi Yamanaka, MD,[i] Shinichi Shirai, MD,[j] Kazuki Mizutani, MD, PhD,[k] Minoru Tabata, MD, PhD, MPH,[l] Hiroshi Ueno, MD,[m] Kensuke Takagi, MD,[n] Masanori Yamamoto, MD, PhD,[o,p] Kentaro Hayashida, MD, PhD,[e] on behalf of the OCEAN-TAVI Investigator

ABSTRACT

OBJECTIVES The aim of this study was to compare long-term all-cause mortality between direct oral anticoagulants (DOACs) and vitamin K antagonists (VKAs) in patients with atrial fibrillation (AF) after transcatheter aortic valve replacement (TAVR).

BACKGROUND The optimal anticoagulant agent for patients with AF after TAVR has not been clarified.

METHODS OCEAN (Optimized Transcatheter Valvular Intervention) is a prospective, multicenter, observational cohort registry comprising 2,588 patients who underwent TAVR between October 2013 and May 2017. Of these, 403 patients (15.6%) with AF on anticoagulant therapy were identified, of whom 227 (56.3%) were prescribed DOACs and 176 (43.7%) were prescribed VKAs. Patients who successfully discharged after TAVR were stratified into DOAC and VKA groups on the basis of the prescription of anticoagulant agents, and the analyses started from discharge.

RESULTS In total, 33.3% of patients were men. The mean age was 84.4 ± 4.7 years, and the average CHA_2DS_2-VASc score was 5.1 ± 1.1. The median follow-up duration was 568 days. A multivariate Cox regression model and inverse probability of treatment weighting based on the propensity score demonstrated that the DOAC group was significantly associated with a lower incidence of all-cause mortality compared with the VKA group (10.3% vs. 23.3%; Cox-adjusted hazard ratio: 0.391; 95% confidence interval: 0.204 to 0.749; $p = 0.005$; and 10.2% vs. 20.6%; inverse probability of treatment weighting-adjusted hazard ratio: 0.531; 95% confidence interval: 0.294 to 0.961; $p = 0.036$, respectively).

CONCLUSIONS Compared with VKAs, DOACs might be associated with lower long-term all-cause mortality in patients with concomitant AF who are successfully discharged after TAVR. This finding warrants investigation in ongoing prospective randomized trials. (J Am Coll Cardiol Intv 2020;13:2587–97) © 2020 by the American College of Cardiology Foundation.

From the [a]Department of Cardiology, Teikyo University School of Medicine, Tokyo, Japan; [b]Amsterdam UMC, University of Amsterdam, Heart Center; Department of Clinical and Experimental Cardiology, Amsterdam Cardiovascular Sciences, Amsterdam, the Netherlands; [c]Department of Cardiology, National University of Ireland, Galway (NUIG), Galway, Ireland; [d]Department of Cardiology, Saiseikai Utsunomiya Hospital, Tochigi, Japan; [e]Department of Cardiology, Keio University School of Medicine, Tokyo, Japan; [f]Department of Cardiology, Sendai Kosei Hospital, Sendai, Japan; [g]Department of Cardiology, New Tokyo Hospital, Chiba, Japan; [h]Department of Cardiology, Saiseikai Yokohama City Eastern Hospital, Yokohama, Japan; [i]Department of Cardiology, Shonan Kamakura General Hospital, Kanagawa, Japan; [j]Department of Cardiology, Kokura Memorial Hospital, Kokura, Japan; [k]Department of Cardiovascular Medicine, Osaka City University Graduate School of Medicine, Osaka, Japan; [l]Department of Cardiovascular Surgery, Tokyo Bay Urayasu-Ichikawa Medical Center, Chiba, Japan; [m]Department of Cardiology, Toyama University Hospital, Toyama, Japan; [n]Department of Cardiology, Ogaki Municipal Hospital, Gifu, Japan; [o]Department of Cardiology, Toyohashi Heart Center, Toyohashi, Japan; and the [p]Department of Cardiology, Nagoya Heart Center, Nagoya, Japan.

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ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

CI = confidence interval

CKD = chronic kidney disease

CrCl = creatinine clearance

DAPT = dual-antiplatelet therapy

DOAC = direct oral anticoagulants

HR = hazard ratio

IPTW = inverse probability of treatment weighting

IQR = interquartile range

SAPT = single-antiplatelet therapy

TAVR = transcatheter aortic valve replacement

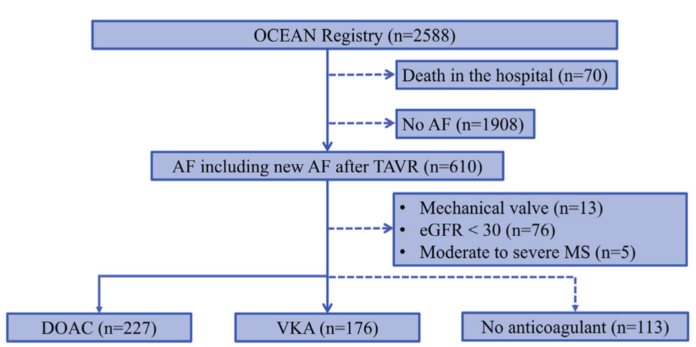
VKA = vitamin K antagonist

The approved use of transcatheter aortic valve replacement (TAVR) for low-risk patients has paved way for even more rapid expansion on the basis of the results of the randomized PARTNER (Placement of Aortic Transcatheter Valve) 3 and Evolut Low Risk trials (1,2). Atrial fibrillation (AF) was associated with a significantly higher rate of all-cause mortality at 1 year in patients undergoing TAVR compared with those in sinus rhythm (3). The reported prevalence of pre-existing AF in patients undergoing TAVR ranges from 16% to 51% (4).

The European guidelines recommend lifelong oral anticoagulation with vitamin K antagonists (VKAs) for patients with known AF undergoing TAVR (5). However, the requirements for high patient compliance, narrow therapeutic window, and multiple food and drug interactions hamper the use of VKAs, particularly among multimorbid and elderly patients (6). Direct oral anticoagulants (DOACs) are frequently used in routine settings for patients in need of oral anticoagulation undergoing TAVR and are recommended in the current European and American guidelines as an acceptable option for these patients (5,7). Recently, Butt et al. (8) demonstrated, on the basis of the registry data in patients with AF undergoing TAVR, that there was no significant difference in the rate of bleeding or all-cause death between DOACs and VKAs during approximately 1-year follow-up. However, the long-term efficacy and safety of DOACs in patients with AF after TAVR have not yet been clarified. The aim of this study was to compare the risks for long-term all-cause mortality, bleeding, and ischemic events between DOACs and VKAs in patients with AF after TAVR from a multicenter cohort.

SEE PAGE 2598

FIGURE 1 **Study Population of the Present Study**



AF = atrial fibrillation; DOAC = direct oral anticoagulants; eGFR = estimated glomerular filtration rate; MS = mitral stenosis; OCEAN = Optimized Transcatheter Valvular Intervention; TAVR = transcatheter aortic valve replacement; VKA= vitamin K antagonist.

METHODS

PATIENT POPULATION AND ANTITHROMBOTIC REGIMEN. OCEAN (Optimized Transcatheter Valvular Intervention) is a Japanese multicenter prospective registry comprising 14 institutions (Teikyo University School of Medicine, Keio University School of Medicine, Kokura Memorial Hospital, Sendai Kosei Hospital, Yokohama City Eastern Hospital, New Tokyo Hospital, Shonan Kamakura General Hospital, Toyama University Hospital, Tokyo Bay Urayasu Ichikawa Medical Center, Osaka City University Graduate School of Medicine, Kishiwada Tokushukai Hospital, Ogaki Municipal Hospital, Toyohashi Heart Center, and Nagoya Heart Center) (9).

Between October 2013 and May 2017, 2,588 patients with severe aortic valve stenosis underwent TAVR and were included in the registry. Of these, 70 patients died during hospitalization for TAVR, and we excluded 1,908 patients who did not have AF, 13 with mechanical valves, 76 with estimated glomerular filtration rates <30 ml/min/1.73 m^2, 5 with moderate to severe mitral valve stenosis (because of the contraindication to DOACs), and 113 who had not received anticoagulant therapy at discharge. The final analysis included 403 patients (15.6%) with AF who had received anticoagulant therapy after TAVR. Among those, 227 patients (56.3%) with AF were prescribed DOACs, and 176 (43.7%) were prescribed VKAs (**Figure 1**). Both patient groups included those receiving no antiplatelet therapy, single-antiplatelet therapy (SAPT), or dual-antiplatelet therapy (DAPT). Hospital discharge was defined as departure from the institution at which TAVR was performed, including a

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: Cardiovascular Interventions* author instructions page.

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TABLE 1 Baseline Clinical and Procedural Variables

	Overall (N = 403)	DOAC (n = 227)	VKA (n = 176)	p Value
Clinical variables				
Male	134 (33.3)	69 (30.4)	65 (36.9)	0.167
Age, yrs	84.4 ± 4.7	84.4 ± 4.7	84.3 ± 4.9	0.741
Body surface area, m^2	1.44 ± 0.18	1.44 ± 0.17	1.44 ± 0.18	0.923
Body mass index, kg/m^2	22.2 ± 3.8	22.6 ± 3.8	21.7 ± 3.7	0.027
Clinical frailty scale	4.0 ± 1.3	4.0 ± 1.3	4.1 ± 1.3	0.299
CHA_2DS_2-VASc score*	5.1 ± 1.1	5.1 ± 1.0	5.2 ± 1.1	0.285
HAS-BLED score†	2.7 ± 0.8	2.6 ± 0.8	2.9 ± 0.9	<0.001
STS score, %	8.5 ± 7.4	7.7 ± 5.1	9.5 ± 9.5	0.020
NYHA functional class III or IV	229 (56.8)	117 (51.5)	112 (63.6)	0.015
Hyperlipidemia	151 (37.5)	85 (37.4)	66 (37.5)	0.991
DM	98 (24.3)	55 (24.2)	43 (24.4)	0.962
Insulin-dependent DM	19 (4.3)	12 (5.3)	7 (4.0)	
Non-insulin-dependent DM	79 (19.6)	43 (18.9)	36 (20.5)	
Hypertension	307 (76.2)	172 (75.8)	135 (76.7)	0.827
Previous myocardial infarction	24 (6.0)	14 (6.2)	10 (5.7)	0.838
Previous pacemaker implantation	37 (9.2)	19 (8.4)	18 (10.2)	0.522
Previous balloon aortic valvuloplasty	20 (5.8)	11 (5.6)	9 (6.0)	0.869
Previous CABG	23 (5.7)	10 (4.4)	13 (7.4)	0.201
Peripheral artery disease	67 (16.6)	34 (15.0)	33 (18.8)	0.313
Previous stroke	58 (14.4)	24 (10.6)	34 (19.3)	0.013
COPD	64 (15.9)	30 (13.2)	34 (19.3)	0.096
Previous coronary artery disease	121 (30.0)	59 (26.0)	62 (35.2)	0.045
CKD‡	306 (75.9)	169 (74.4)	137 (77.8)	0.430
Left ventricular ejection fraction, %	57.2 ± 13.3	57.4 ± 12.5	56.8 ± 14.4	0.688
AF				0.919
Chronic AF	166 (41.2)	94 (41.4)	72 (40.9)	
Paroxysmal AF	237 (58.8)	133 (58.6)	104 (59.1)	0.919
Year of TAVR procedure				<0.001
October 2013 to December 2014	63 (15.6)	17 (7.5)	46 (26.1)	
January 2015 to December 2015	82 (20.3)	48 (21.1)	34 (19.3)	
January 2016 to December 2016	168 (41.7)	104 (45.8)	64 (36.4)	
January 2017 to May 2017	90 (22.3)	58 (25.6)	32 (18.2)	
Procedural variables				
Access site				<0.001
Transfemoral	341 (84.6)	206 (90.7)	135 (76.7)	
Alternative approach	62 (15.4)	21 (9.3)	41 (23.3)	
Valve type				0.001
SAPIEN 3	134 (33.3)	89 (39.4)	45 (25.6)	
Evolut R	26 (6.5)	17 (7.5)	9 (5.1)	
SAPIEN XT	206 (51.2)	96 (42.5)	110 (62.5)	
CoreValve	36 (9.0)	24 (10.6)	12 (6.8)	
Valve size, mm	24.8 ± 2.3	24.8 ± 2.3	24.8 ± 2.3	0.838
Contrast, ml	108.6 ± 53.7	107.8 ± 53.4	109.6 ± 54.2	0.750
Fluoroscopy time, min	19.9 ± 8.4	20.3 ± 7.7	19.5 ± 9.3	0.357
Anesthesia				0.329
Local anesthesia	87 (21.6)	53 (23.3)	34 (19.3)	
General anesthesia	316 (78.4)	174 (76.7)	142 (80.7)	
Device success	379 (94.0)	212 (93.4)	167 (94.9)	0.530

Values are mean ± SD or n (%). *The CHA_2DS_2-VASc score was derived from congestive heart failure, hypertension, age ≥75 years (2 points), diabetes, history of stroke (2 points), vascular disease, age 65 to 74 years, and female sex (22,23). †The HAS-BLED score was calculated by adding 1 point for each of the following parameters: hypertension, abnormal renal/liver dysfunction, history of stroke, history of bleeding or predisposition to bleeding, labile international normalized ratio, age >65 years, and drug consumption of antiplatelet agents, nonsteroidal anti-inflammatory drugs, or alcohol abuse (16,24). ‡Defined as an estimated glomerular filtration rate of creatinine clearance of <60 ml/min/1.73 m^2 on the basis of the MDRD (Modification of Diet in Renal Disease) formula.

AF = atrial fibrillation; CABG = coronary artery bypass grafting; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; DM = diabetes mellitus; DOAC = direct oral anticoagulants; NYHA = New York Heart Association; STS = Society of Thoracic Surgeons; TAVR = transcatheter aortic valve replacement; VKA = vitamin K antagonist.

JACC: CARDIOVASCULAR INTERVENTIONS VOL. 13, NO. 22, 2020
NOVEMBER 23, 2020:2587–97

TABLE 2 Medical Therapy at Hospital Discharge

	Overall (N = 403)	DOAC (n = 227)	VKA (n = 176)	p Value
Antiplatelet regimen				0.017
No antiplatelet therapy	126 (31.3)	82 (36.1)	44 (25.0)	
SAPT	255 (63.3)	137 (60.4)	118 (67.0)	
DAPT	22 (5.5)	8 (3.5)	14 (8.0)	
Other medications				
ACE inhibitor/ARB	195 (48.4)	106 (46.7)	89 (50.6)	0.440
Beta-blocker	179 (44.4)	94 (41.4)	85 (48.3)	0.168
Calcium blocker	179 (44.4)	99 (43.6)	80 (45.5)	0.712
Digitalis	28 (6.9)	16 (7.0)	12 (6.8)	0.928
Statin	139 (34.5)	76 (33.5)	63 (35.8)	
Steroid	16 (4.0)	9 (4.0)	7 (4.0)	0.995

Values are n (%).

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; DAPT = dual-antiplatelet therapy; SAPT = single-antiplatelet therapy; other abbreviations as Table 1.

move to another hospital. In all patients, doses of DOACs were determined according to prescribing information. Among European countries, the United States, and Japan, the customary doses of DOACs are the same except for rivaroxaban. In Japan, the indication for rivaroxaban in patients with creatinine clearance (CrCl) ≥50 ml/min is 15 mg once daily, and that with CrCl 30 to 49 ml/min is 10 mg, whereas in European countries and the United States, that with CrCl ≥50 ml/min is 20 mg, and that with CrCl 30 to 49 ml/min is 15 mg. Doses of VKAs were titrated to achieve a prothrombin time-international normalized ratio of 2.0 to 3.0 according to current recommendations (7,10). At all institutions, the choice of antithrombotic regimen was determined at the discretion of each center after the heart team considered the risk for bleeding and thrombotic complications. This trial is registered with the University Hospital Medical Information Network (UMIN000020423). The study protocol was developed in accordance with the Declaration of Helsinki and was approved by the ethics committee of each participating hospital.

PROCEDURAL DETAILS. Valve type and size were determined on the basis of pre-procedural echocardiographic and multidetector computed tomographic findings. The devices were delivered via the transfemoral, transapical, transiliac, transsubclavian, or direct aortic approach. The selection of approach was determined on the basis of the iliofemoral or subclavian artery diameters, calcifications, and tortuosity. The transcatheter heart valves used included the SAPIEN 3 (20, 23, 26, and 29 mm; Edwards Lifesciences, Irvine, California), Evolut R (23, 26, and 29 mm; Medtronic, Dublin, Ireland), SAPIEN XT (20, 23, 26, and 29 mm; Edwards Lifesciences), and CoreValve (26 and 29 mm; Medtronic). Procedural success and complications during the TAVR procedure were defined according to the Valve Academic Research Consortium-2 criteria (11).

CLINICAL OBJECTIVES. The primary objective of the present study was all-cause mortality in patients with concomitant AF who successfully discharged after TAVR. Similarly, the secondary objectives were bleeding and ischemic events after the discharge. These events were determined on the basis of the definitions in the Valve Academic Research Consortium-2 criteria (11).

FOLLOW-UP AND CAUSE OF DEATH. Follow-up was performed by telephone interview, soliciting information from relatives or local doctors, or direct consultation. At each center in our registry, follow-up was performed primarily by direct consultation. Cause of death was identified by telephone interview of an acquaintance of the patient or through medical records.

BLEEDING AND DEFINITIONS. Definitions of bleeding were also framed in accordance with Valve Academic Research Consortium-2 criteria (11). Life-threatening bleeding was defined as that causing hypovolemic shock or severe hypotension requiring vasopressors or surgery, an overt source of bleeding with a decrease in hemoglobin level >5 g/dl or requiring a red blood cell transfusion of >4 U. Major bleeding was defined as a decrease in hemoglobin level >3 g/dl or requiring a transfusion of 2 or 3 U of whole blood. Minor bleeding was defined as any bleeding worthy of clinical mention that did not qualify as life threatening or major.

STATISTICAL ANALYSIS. Quantitative variables are expressed as mean ± SD or as median (interquartile range [IQR]). Qualitative variables are expressed as number (percentage). A comparison of quantitative variables was performed using the unpaired Student's *t*-test or the Mann-Whitney *U* test depending on variable distribution. The chi-square test or Fisher exact test was used to compare qualitative variables. Baseline, procedural, and medical therapy at discharge were compared between the DOAC and VKA groups. The cumulative incidence of all-cause mortality between the DOAC and VKA groups at hospital discharge after TAVR was calculated using the Kaplan-Meier method, and data were compared using the log-rank test. Hazard ratios (HRs) with 95% confidence intervals (CIs) were derived from a Cox regression model. In the present study, patients who were successfully discharged after TAVR were stratified into DOAC and VKA groups on the basis of the prescription of anticoagulant agents, and the analysis started at discharge. The multivariate Cox regression model included the following variables: male sex, age, New York Heart Association functional class III or IV, diabetes mellitus, peripheral artery disease, previous stroke and coronary artery disease, chronic kidney disease (CKD), left ventricular ejection fraction, year of TAVR procedure, alternative approach, no antiplatelet therapy or DAPT at discharge, anticoagulant choice per center, and DOAC at discharge. To reduce confounding effects due to the diversity of the patients' background in a comparison with the DOAC and VKA groups, the propensity score method was used. The propensity score was defined as the probability of treatment assignment subjective to observed baseline characteristics, and the inverse probability of treatment weighting (IPTW) method on the basis of the propensity score was used to adjust for confounding factors in the time-to-event analysis (12,13). For estimation of the propensity score, we used a logistic regression model of assigned anticoagulant agent (DOAC or VKA) at discharge on the following variables: body mass index, HAS-BLED score, Society of Thoracic Surgeons score, New York Heart Association functional class III or IV symptoms, history of stroke and coronary artery disease, year of TAVR procedure, access site, implanted transcatheter aortic valve type, antiplatelet regimen at discharge, and anticoagulant choice per center, which were significantly different in baseline and procedural variables between the DOAC and VKA groups. A p value <0.05 was considered to indicate statistical significance. All data were processed using SPSS version 26.0 (IBM, Armonk, New York) and R version 3.6.0 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

PATIENT CHARACTERISTICS, PROCEDURAL VARIABLES, AND MEDICAL THERAPY AT DISCHARGE. Baseline patient characteristics and procedural variables are presented in Table 1. In total, 33.3% of patients were men. The mean age was 84.4 ± 4.7 years, and the average CHA_2DS_2-VASc score was 5.1 ± 1.1. HAS-BLED and Society of Thoracic Surgeons scores were lower in the DOAC group than in the VKA group (2.6 ± 0.8 vs. 2.9 ± 0.9 [$p < 0.001$] and 7.7 ± 5.1 vs 9.5 ± 9.5 [$p = 0.020$], respectively). In the DOAC group, the frequency of New York Heart Association functional class III or IV symptoms (51.5% vs. 63.6%; $p = 0.015$), history of stroke (10.6% vs. 19.3%; $p = 0.013$), and coronary artery disease (26.0% vs 35.2%; $p = 0.045$) were significantly lower compared with the VKA group. Transfemoral procedures were more frequently observed in the DOAC group than in the VKA group (90.7% vs. 76.7%; $p < 0.001$), and implantation of the prosthesis valve type was significantly different between the 2 groups (DOAC vs. VKA: SAPIEN 3, 39.4% vs. 25.6%; Evolut R, 7.5% vs. 5.1%; SAPIEN XT, 42.5% vs. 62.5%; CoreValve, 10.6% vs. 6.8%; $p = 0.001$).

Table 2 shows medical therapy at hospital discharge. Concomitant antiplatelet regimens (no antiplatelet therapy, SAPT, or DAPT) at discharge were significantly different between the 2 groups (DOAC vs VKA: 36.1% vs. 25.0%, 60.4% vs. 67.0%, and 3.5% vs. 8.0%, respectively; $p = 0.017$).

TABLE 3 Breakdown of Treatment Choice of Anticoagulant Agent

	DOAC (n = 227)	VKA (n = 176)	p Value
Institution			<0.001
1	32 (14.0)	22 (12.5)	
2	38 (16.7)	31 (17.6)	
3	19 (8.3)	26 (14.7)	
4	45 (19.8)	12 (6.8)	
5	15 (6.6)	3 (1.7)	
6	13 (5.7)	15 (8.5)	
7	8 (3.5)	22 (12.5)	
8	16 (7.0)	3 (1.7)	
9	1 (0.4)	21 (11.9)	
10	9 (3.9)	8 (4.5)	
11	7 (3.0)	4 (2.2)	
12	9 (3.9)	0 (0)	
13	5 (2.2)	5 (2.8)	
14	10 (4.4)	4 (2.2)	

Values are n (%).
Abbreviations as in Table 1.

BREAKDOWN OF TREATMENT CHOICE OF ANTICOAGULANT PER SITE. Table 3 demonstrates the breakdown of treatment choice of anticoagulant at the 14 centers, and there was a significant difference between the DOAC and VKA groups ($p < 0.001$). Supplemental Table 1 presents the type of oral anticoagulant agent per site and the number of patients.

CLINICAL OUTCOMES. The median duration of hospitalization was 10 days (IQR: 7 to 16 days). The median follow-up duration was 568 days (IQR: 367 to 819 days).

The multivariate Cox regression model demonstrated that the prescription of DOACs at discharge was significantly associated with reduced all-cause mortality (10.3% vs. 23.3%; Cox-adjusted HR: 0.391; 95% CI: 0.204 to 0.749; $p = 0.005$) and that the presence of diabetes mellitus was an independent predictor of all-cause mortality (Table 4).

TABLE 4 Predictors of All-Cause Mortality

	Unadjusted HR (95% CI)	p Value	Adjusted HR (95% CI)	p Value
Male	2.179 (1.284–3.697)	0.004		
Age (per 1-yr increase)	0.988 (0.934 (1.045)	0.668		
NYHA functional class III or IV	1.926 (1.030–3.235)	0.039		
DM	2.380 (1.393–4.069)	0.002	2.226 (1.231–4.024)	0.008
Peripheral artery disease	1.864 (1.016–3.419)	0.044		
Previous stroke	1.360 (0.685–2.699)	0.379		
Previous coronary artery disease	1.231 (0.706–2.146)	0.465		
CKD*	1.952 (0.922–4.131)	0.080		
Left ventricular ejection fraction (per 1% increase)	0.999 (0.979–1.020)	0.957		
Year of TAVR procedure		0.787		
October 2013 to December 2014	Reference			
January 2015 to December 2015	1.232 (0.559–2.715)			
January 2016 to December 2016	0.877 (0.409–1.883)			
January 2017 to May 2017	0.928 (0.369–2.335)			
Alternative approach	1.199 (0.604–2.380)	0.604		
No antiplatelet therapy or DAPT at discharge	1.481 (0.868–2.529)	0.150		
Anticoagulant choice per center		0.394		
DOAC at discharge	0.448 (0.259–0.776)	0.004	0.391 (0.204–0.749)	0.005

*Defined as an estimated glomerular filtration rate of creatinine clearance of <60 ml/min/1.73 m^2 on the basis of the MDRD (Modification of Diet in Renal Disease) formula.
CI = confidence interval; HR = hazard ratio; other abbreviations as in Table 1.

The IPTW-adjusted Kaplan-Meier curve showed that all-cause mortality was lower in the DOAC group than in the VKA group (10.2% vs. 20.6%; IPTW-adjusted HR: 0.531; 95% CI: 0.249 to 0.961; p = 0.036) (**Central Illustration**).

The relationship between anticoagulant therapy and bleeding or ischemic events in patients who successfully discharged after TAVR is shown in **Figure 2**. The rates of all bleeding, life-threatening or major bleeding, minor bleeding, gastrointestinal bleeding, hemorrhagic stroke, and ischemic stroke were comparable between the 2 groups.

LANDMARK ANALYSES. The Kaplan-Meier curves of the post-discharge events at day 0 to day 30 and after day 31 in a separate analysis are shown in Supplemental Figures 1 and 2.

The landmark analysis between 31 days and 2 years post-discharge after TAVR demonstrated significantly lower all-cause mortality in the DOAC group compared with the VKA group (8.7% vs. 20.0%; IPTW-adjusted HR: 0.465; 95% CI: 0.249 to 0.866; p = 0.016) (Supplemental Figure 1). All other event rates were comparable between the 2 groups (Supplemental Figure 2).

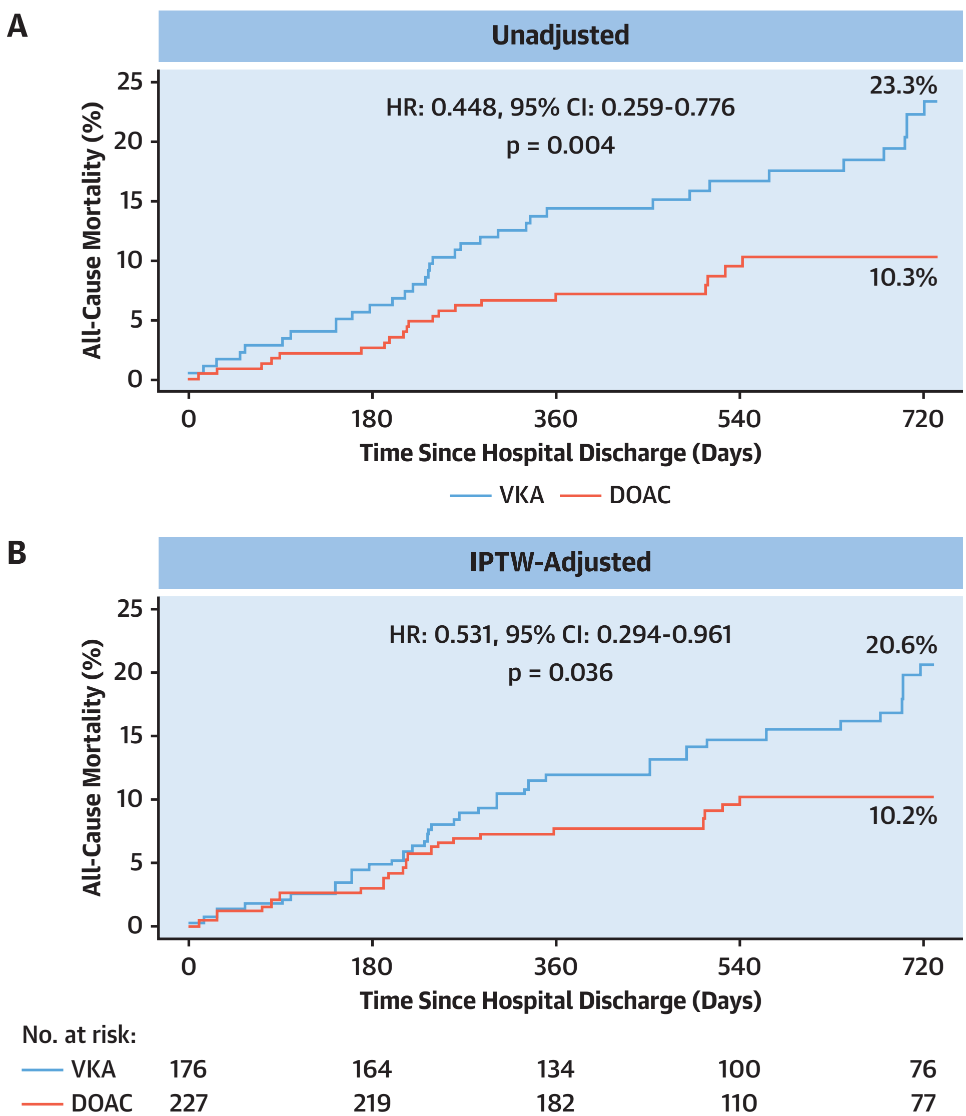
COMBINATION OF ANTIPLATELET AND ANTICOAGULANT THERAPY. The Kaplan-Meier curves demonstrated that among patients with SAPT plus DOACs, DOACs only, DAPT plus DOACs, SAPT plus VKAs, VKAs only, and DAPT plus VKAs, there were significant differences in all-cause mortality (log-rank p = 0.004) (**Figure 3**) and ischemic stroke (log-rank p = 0.025) (Supplemental Figure 3).

DISCUSSION

We compared and evaluated long-term clinical outcomes in patients with AF who were successfully discharged after TAVR receiving either DOACs or VKAs. The main findings of the present study can be summarized as follows: 1) In accordance with the results of the multivariate Cox analysis and IPTW, DOAC therapy at discharge after TAVR was associated with reduced long-term all-cause mortality compared with VKA therapy; and 2) the rates of long-term bleeding and ischemic events after discharge were comparable between the DOAC and VKA groups.

Because of the absence of convincing evidence, the optimal oral anticoagulant agent in patients with AF undergoing TAVR has not yet been established. Mechanical valves warranted routine VKA rather than DOAC therapy (14). However, bioprosthetic valves are used in TAVR procedures, so we speculated that the use of DOACs would confer clinical efficacy and safety

CENTRAL ILLUSTRATION Relationship Between Anticoagulant Therapy and All-Cause Mortality in Patients Who Were Successfully Discharged After Transcatheter Aortic Valve Replacement



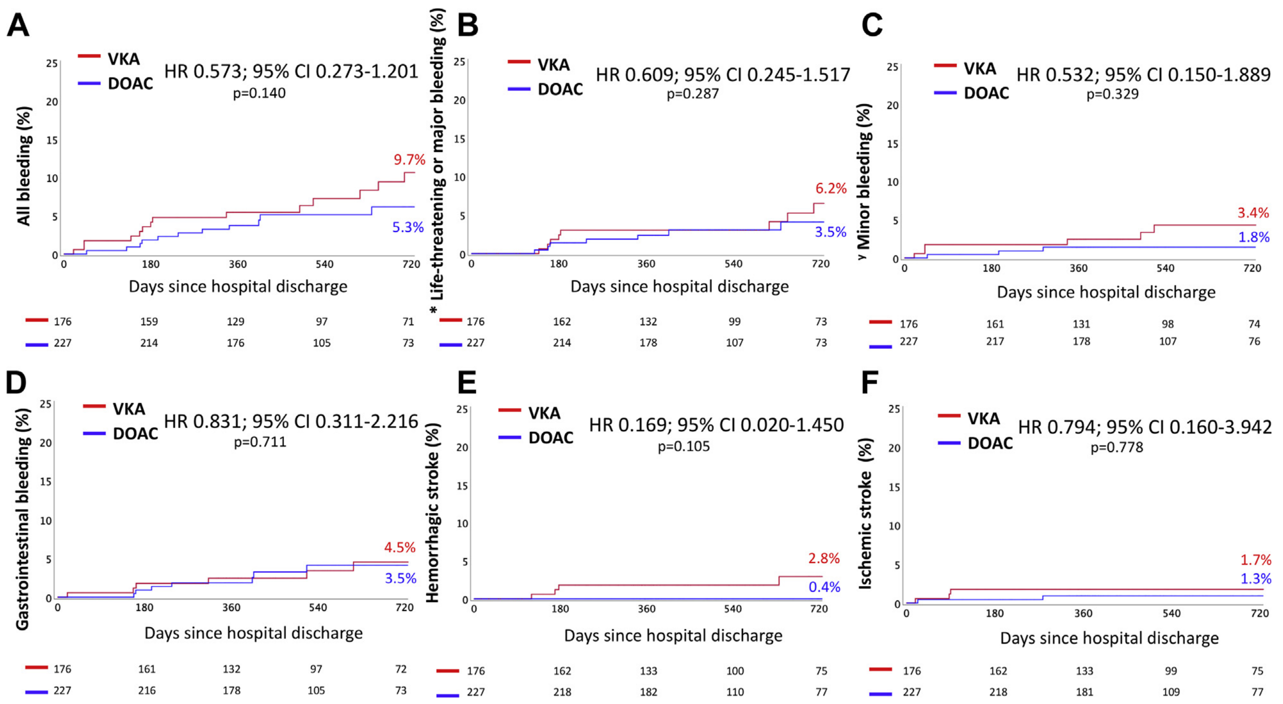
Kawashima, H. et al. J Am Coll Cardiol Intv. 2020;13(22):2587-97.

Kaplan-Meier curves show the incidence rate of all-cause mortality: **(A)** unadjusted and **(B)** inverse probability of treatment weighting (IPTW) adjusted. CI = confidence interval; DOAC = direct oral anticoagulants; HR = hazard ratio; VKA = vitamin K antagonist

on this population of patients with AF undergoing TAVR. To our knowledge, our study is the first to demonstrate the long-term efficacy of DOAC therapy compared with VKAs in a large nationwide, unselected cohort of patients with AF who were successfully discharged after TAVR. After adjusting for comorbidity and concomitant platelet therapy, we found that treatment with DOACs was associated with a lower risk for long-term all-cause mortality compared with VKA. This finding might support the uniform use of DOACs in patients with AF undergoing TAVR who are indicated for anticoagulation therapy.

A plausible explanation for a lower rate of long-term all-cause mortality in the DOAC group compared with the VKA group is the treatment preference for VKAs over DOACs in advanced stages of CKD, which is a contraindication to DOACs. Although in a previous publication, the prevalence of advanced

FIGURE 2 Relationship Between Anticoagulant Therapy and Bleeding/Ischemic Events in Patients Who Were Successfully Discharged After Transcatheter Aortic Valve Replacement



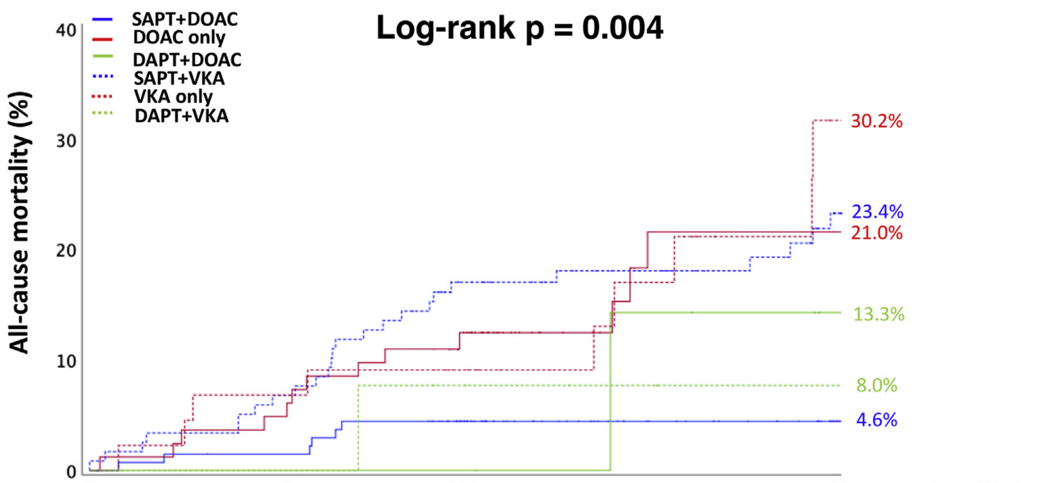
Kaplan-Meier curves show incidence rates of **(A)** all bleeding, **(B)** life-threatening or major bleeding, **(C)** minor bleeding, **(D)** gastrointestinal bleeding, **(E)** hemorrhagic stroke, and **(F)** ischemic stroke. *Definitions of bleeding were also framed in accordance with the Valve Academic Research Consortium (VARC)-2 criteria (11). Life-threatening bleeding was defined as that causing hypovolemic shock or severe hypotension requiring vasopressors or surgery, an overt source of bleeding with a decrease in hemoglobin level >5 g/dl or requiring a red blood cell transfusion of >4 U. Major bleeding was defined as a decrease in hemoglobin level >3 g/dl or requiring a transfusion of 2 or 3 U of whole blood. ᵞDefinitions of bleeding were also framed in accordance with the VARC-2 criteria (11). Minor bleeding was defined as any bleeding worthy of clinical mention that did not qualify as life-threatening or major. CI = confidence interval; HR = hazard ratio; other abbreviations as in Figure 1.

stages of CKD was associated with increased risk for all-cause mortality after TAVR (15), in the present study, the prevalence of CKD at baseline was not significantly different between patients with DOACs and those with VKAs. In addition, patients with estimated glomerular filtration rates <30 ml/min/1.73 m^2 who were not eligible for DOACs were excluded in our analysis. However, the statistical differences of the HAS-BLED score and Society of Thoracic Surgeons score between the 2 groups, in which renal dysfunction was included as one of the variables, might be confounding factors for the prediction of long-term all-cause mortality. In our registry, Honda et al. (16) demonstrated that the HAS-BLED score could predict the risk for life-threatening and major bleeding and all-cause mortality in patients who underwent transfemoral TAVR.

Another potential explanation is that the combination of anticoagulant and antiplatelet agents influenced long-term all-cause mortality. In the present study, antiplatelet regimen (no antiplatelet therapy, SAPT, or DAPT) at discharge was statistically different between the DOAC and VKA groups. The frequency of no antiplatelet therapy at discharge after TAVR was higher in the DOAC group than in the VKA group, and conversely, DAPT was more frequent in the VKA group. The Kaplan-Meier curves demonstrated that there were significant differences in all-cause mortality and ischemic stroke among patients with SAPT plus DOACs, DOACs only, DAPT plus DOACs, SAPT plus VKAs, VKAs only, and DAPT plus VKAs. Importantly, these are the results by the observational analyses in comparison with the 6 arms. To verify these differences, multivariate analyses are required. However, the number of events is not enough for analysis, and therefore further studies would be needed.

Recently, the POPular-TAVI (Antiplatelet Therapy for Patients Undergoing Transcatheter Aortic Valve Implantation) trial demonstrated that in patients

FIGURE 3 Relationship Between the Combination of Antiplatelet and Anticoagulant Therapy and All-Cause Mortality After Discharge



	0	180	360	540	720
SAPT+DOAC	137	133	115	79	60
DOAC only	82	78	59	25	15
DAPT+DOAC	8	8	8	6	2
SAPT+VKA	118	110	89	71	56
VKA only	44	41	34	20	12
DAPT+VKA	14	13	11	9	8

Kaplan-Meier curves of single-antiplatelet therapy (SAPT) plus DOAC versus DOAC only versus dual-antiplatelet therapy (DAPT) plus DOAC versus SAPT plus VKA versus VKA only plus VKA versus DAPT + VKA in all-cause mortality. Abbreviations as in Figure 1.

undergoing TAVR and receiving oral anticoagulant agents, the incidence of serious bleeding over a period of 1 month or 1 year was lower with oral anticoagulant agents alone than with oral anticoagulant agents plus SAPT (17). In a meta-analysis, Zhu et al. (18) found that the application of DAPT plus anticoagulant agents was ranked worst among all treatment modalities and should be avoided because of increased risk for bleeding. In these regards, IPTW on the basis of the propensity score was performed, taking into account these considerable confounding factors, and resulted in maintained reduced all-cause mortality in patients receiving DOACs at discharge compared with those receiving VKAs. Although multivariate regression methods attempt to adjust for measured confounders, the risk for bias due to unmeasured confounders remains (19). The aim of the ongoing randomized ATLANTIS (Anti-Thrombotic Strategy After Trans-Aortic Valve Implantation for Aortic Stenosis) trial (NCT02664649) is to compare apixaban with the current standard of care (either VKA or antiplatelet therapy, as appropriate) after TAVR, and the trial includes patients with AF (20). The aim of the ongoing randomized ENVISAGE-TAVI AF (Edoxaban Compared to Standard Care After Heart Valve Replacement Using a Catheter in Patients With Atrial Fibrillation) trial (NCT02943785) is to establish the safety and efficacy of an oral antithrombotic regimen with apixaban for patients with AF after TAVR compared with a VKA (21). Optimal antithrombotic regimens in patients with AF after TAVR will be prospectively clarified in these ongoing randomized control trials.

STUDY LIMITATIONS. This study was conducted using a prospective multicenter TAVR cohort with a nonrandomized design. The inclusion of 14 different institutions might have resulted in some biases due to differences in clinical treatments. However, the treatment choice of anticoagulant per study site at discharge was included in the multivariate Cox regression and IPTW models. Furthermore, as our study was based on observational registry data, we believe that this represents a real-world unselected population of patients with severe aortic valve stenosis undergoing TAVR. Selection bias should be considered with this nonrandomized study even after IPTW on the basis of the propensity score. All events were self-reported by the individual centers. In particular, the number of minor bleeding events was relatively small compared with life-threatening or major bleeding rates after discharge. Although

JACC: CARDIOVASCULAR INTERVENTIONS VOL. 13, NO. 22, 2020
NOVEMBER 23, 2020:2587–97

bleeding events with readmission were accurately gathered, possible underreporting of minor bleeding events was noted. Data on valve thrombosis were not available for this study. Furthermore, the lack of data on international normalized ratios during follow-up precludes assessment of the quality of anticoagulation and time in therapeutic range in the VKA group and may potentially influence outcomes. In addition, we excluded patients with AF who were not prescribed anticoagulant agents at discharge. These patients were not evaluated in the present study, which may potentially influence outcomes. However, the current European and American guidelines recommend that the use of DOACs is an "acceptable" option in patients with AF undergoing TAVR (5,7), and long-term efficacy and safety have not yet been elucidated. Therefore, in the present study, we focused on the comparison between patients prescribed DOACs and VKAs at discharge, not those without anticoagulant agents. Moreover, the antithrombotic regimens will have been altered over time during the follow-up period. Information regarding detailed antithrombotic treatments and whether the regimen was changed could not be traced during this study. This point is obviously beyond the scope of this study, and a further randomized study focusing on antithrombotic therapy after TAVR is required.

CONCLUSIONS

Compared with VKAs, DOACs might be associated with lower long-term all-cause mortality in patients with concomitant AF who are successfully discharged after TAVR. This finding warrants investigation in ongoing prospective randomized trials.

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AUTHOR RELATIONSHIP WITH INDUSTRY

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ADDRESS FOR CORRESPONDENCE: Dr. Yusuke Watanabe, Department of Cardiology, Teikyo University School of Medicine, 2-11-1 Kaga, Itabashi-ku, Tokyo, Japan. E-mail: yusuke0831@gmail.com.

PERSPECTIVES

WHAT IS KNOWN? Patients with concomitant AF need anticoagulation after TAVR. Although DOACs have been proved to be superior or noninferior in nonvalvular AF, little is known about their long-term safety and efficacy after TAVR.

WHAT IS NEW? This study is the first to demonstrate that DOACs provide better long-term all-cause mortality compared with VKAs.

WHAT IS NEXT? Optimal antithrombotic regimens in patients with AF after TAVR will be prospectively clarified in ongoing randomized trials.

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KEY WORDS oral anticoagulant, survival, transcatheter aortic valve replacement, vitamin K antagonist

APPENDIX For a supplemental table and figures, please see the online version of this paper.