JACC: CARDIOVASCULAR INTERVENTIONS
VOL. 12, NO. 16, 2019

PUBLISHED BY ELSEVIER

Oral Anticoagulant Type and Outcomes After Transcatheter Aortic Valve Replacement

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ABSTRACT

OBJECTIVES The purpose of the study was to investigate the impact of oral anticoagulation (OAC) type on clinical outcomes 1 year after transcatheter aortic valve replacement (TAVR).

BACKGROUND Non-vitamin K oral anticoagulants (NOACs) are superior to vitamin K antagonists (VKAs) in nonvalvular atrial fibrillation (AF), while their comparative performance among patients in need of OAC undergoing TAVR is underinvestigated.

METHODS The study enrolled 962 consecutive patients who underwent TAVR in 4 tertiary European centers and were discharged on either NOACs (n = 326) or VKAs (n = 636). By using propensity scores for inverse probability of treatment weighting (IPTW), the comparison of treatment groups was adjusted to correct for potential confounding.

RESULTS Mean age and Society of Thoracic Surgeons score of the population were 81.3 ± 6.3 years and 4.5% (interquartile range: 3.0% to 7.3%); 52.5% were women and a balloon-expandable valve was used in 62.7% of cases. The primary outcome of interest, combined incidence of all-cause mortality, myocardial infarction, and any cerebrovascular event at 1-year after TAVR, was 21.2% with NOACs versus 15.0% with VKAs (hazard ratio [HR]: 1.44; 95% confidence interval [CI]: 1.00 to 2.07; p = 0.050, IPTW-adjusted). The 1-year incidence of any Bleeding Academic Research Consortium bleeds and all-cause mortality were comparable between the NOAC and VKA groups, 33.9% versus 34.1% (HR: 0.97; 95% CI: 0.74 to 1.26; p = 0.838, IPTW-adjusted) and 16.5% versus 12.2% (HR: 1.36; 95% CI: 0.90 to 2.06; p = 0.136, IPTW-adjusted), respectively.

CONCLUSIONS Chronic use of both NOACs and VKAs among patients in need of OAC after TAVR are comparable regarding 1-year bleeding risk. The higher ischemic event rate observed with NOACs needs to be evaluated in large randomized trials. (J Am Coll Cardiol Intv 2019;12:1566–76) © 2019 by the American College of Cardiology Foundation.

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Manuscript received October 29, 2018; revised manuscript received March 5, 2019, accepted March 6, 2019.

ISSN 1936-8798/$36.00
https://doi.org/10.1016/j.jcin.2019.03.003

About 15% to 50% of patients with symptomatic aortic valve stenosis (AS) undergoing transcatheter aortic valve replacement (TAVR) are in need of chronic oral anticoagulation (OAC) mostly due to concomitant atrial fibrillation (AF) (1). Due to their advanced age, these patients are at particularly high risk for both thromboembolic and bleeding events (2).

Vitamin K antagonists (VKAs) have proven to be highly effective in preventing thromboembolic events in patients with both valvular and nonvalvular AF (3) and are still routinely used in daily clinical practice. Need for high patient compliance, narrow therapeutic window, and multiple food and drug interactions hamper the use of VKAs, particularly among multimorbid and elderly patients (4,5). These limitations can be overcome by use of non-vitamin K oral anticoagulants (NOACs), proven superior to VKAs regarding the risk of bleeding in the long term (6,7). Furthermore, NOACs seem to reduce the risk of myocardial infarction and 1-year mortality among patients with acute coronary syndrome and nonvalvular AF (8).

Although limited by lack of evidence, NOACs are frequently being used in routine settings for patients in need of OAC undergoing TAVR and are being recommended by the current European guidelines as an acceptable option for these patients (9). On the other hand, there are reports about occurrence of clinical and subclinical TAVR prosthesis thrombosis under NOACs (10). Moreover, attenuation of bleeding risk under NOACs compared with VKAs is less pronounced among elderly patients with concomitant valvular heart disease, who are usually excluded from the randomized approval trials (6).

Thus, the purpose of this multicenter study is to evaluate the impact of oral anticoagulant type on short-term and midterm clinical outcomes among patients undergoing TAVR in need of OAC therapy at discharge.

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METHODS

STUDY POPULATION. This is an investigator-initiated multicenter observational registry study conducted in 4 European centers. Only patients in need of oral anticoagulation who underwent TAVR procedure and survived the hospital stay between June 2007 and February 2017 were considered. Demographics, clinical and procedural data, and hospital and 1-year clinical outcomes were collected prospectively as part of national quality control requirements and were documented in the institutional databases. Thereafter, the datasets were merged for statistical analysis.

PERIPROCEDURAL AND MAINTENANCE ANTITHROMBOTIC THERAPY. Before TAVR, for patients admitted on VKA therapy, a pre-procedural international normalized ratio of ≤2 was required. For patients on NOACs, OAC treatment was stopped 24 h before the TAVR procedure. During TAVR, unfractionated heparin (as bolus of 50 to 70 IU/kg of body weight) or bivalirudin was given. OAC therapy with either VKAs or NOACs was reinitiated when the patient was stabilized and no additional invasive procedures during the in-hospital stay were planned or expected. No heparin as bridge therapy was given routinely before and after TAVR. Patients in need of dialysis therapy were receiving VKAs when indicated. In case of previous percutaneous coronary intervention or known coronary artery disease, concomitant antiplatelet therapy was prescribed at the discretion of the responsible physician. If indicated, triple maintenance therapy was only given for a maximum time period of 3 months. Dose adjustments of antithrombotic drugs were done in accordance to the instructions of use.

OUTCOMES AND DEFINITIONS. The primary outcome of interest was the cumulative incidence of ischemic events defined as a nonhierarchical combined endpoint of all-cause mortality, myocardial infarction, and any cerebrovascular event (CVE) at 1-year follow-up. Net adverse clinical event was defined as the combined incidence of all-cause death, myocardial infarction, CVE, or major or life-threatening bleeding complications. Major adverse cardiovascular and cerebrovascular events were defined as the composite of cardiovascular or cerebrovascular death, myocardial infarction, or stroke. Procedural and clinical events were defined in accordance to the Valve Academic Research Consortium Criteria-2 (11). Bleeding complications were defined according to Bleeding Academic Research Consortium criteria (12). Cardiovascular and cerebrovascular death was defined as sudden death or death due to cardiovascular reasons or death due to any CVE. Clinically relevant valve thrombosis was either diagnosed by multidetector computed tomography or transesophageal echocardiography.

STATISTICAL ANALYSIS. The distribution of data is presented using descriptive statistics such as mean ± SD or median (interquartile range) for continuous

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation
AS = aortic valve stenosis
BVT = bioprosthetic valve thrombosis
CI = confidence interval
CVE = cerebrovascular event
HR = hazard ratio
IPTW = inverse probability of treatment weighting
NOAC = non-vitamin K oral anticoagulant
OAC = oral anticoagulation
TAVR = transcatheter aortic valve replacement
VKA = vitamin K antagonist

JACC: CARDIOVASCULAR INTERVENTIONS VOL. 12, NO. 16, 2019
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TABLE 1 Baseline Demographics, Procedural Data, and Antithrombotic Therapy at Discharge of the Entire Study Population and According to Type of Oral Anticoagulation Therapy at Discharge

	All (N = 962)	NOAC (n = 326)	VKA (n = 636)	p Value
Baseline demographics				
Age, yrs	81.3 ± 6.3	81.6 ± 6.7	81.1 ± 6.1	0.25
Women	505 (52.5)	170 (52.1)	335 (52.7)	0.89
Body mass index, kg/m^2	26.4 ± 4.8	26.3 ± 5.2	26.6 ± 4.9	0.32
STS-PROM score, %	4.5 (3.0–7.3)	4.5 (3.0–7.4)	4.5 (3.0–7.3)	0.97
CHA_2DS_2-VASc score ≥2	916 (95.2)	305 (93.6)	611 (96.1)	0.12
Indication for oral anticoagulation therapy				<0.001
Permanent atrial fibrillation	680 (70.7)	202 (62.0)	478 (75.2)	
Paroxysmal atrial fibrillation	275 (28.6)	121 (37.1)	152 (23.9)	
Others	7 (0.7)	3 (0.9)	6 (0.9)	
Hypertension	862 (89.6)	293 (89.9)	569 (89.5)	0.91
Diabetes mellitus	311 (32.3)	94 (28.8)	217 (34.1)	0.11
Peripheral artery disease	86 (8.9)	13 (4.0)	73 (11.5)	<0.001
Chronic obstructive lung disease	206 (21.4)	67 (20.6)	139 (21.9)	0.68
History of any cerebrovascular event	165 (17.2)	60 (18.4)	105 (16.5)	0.47
History of myocardial infarction	139 (14.9)	45 (14.1)	94 (15.4)	0.63
History of aortocoronary bypass graft surgery	106 (11.0)	29 (8.9)	77 (12.1)	0.16
History of percutaneous coronary intervention	296 (30.8)	106 (32.5)	190 (29.9)	0.42
Chronic kidney disease	456 (47.4)	174 (53.3)	282 (44.3)	0.009
NYHA functional class >II	753 (78.3)	279 (85.6)	474 (74.5)	<0.001
Malignancy	135 (16.0)	52 (16.9)	83 (15.4)	0.63
Hemoglobin at admission, mg/dl	12.2 ± 1.9	12.2 ± 1.8	12.3 ± 1.9	0.98
Multivessel coronary artery disease	457 (55.9)	178 (56.9)	279 (55.4)	0.72
Left ventricular ejection fraction <50%	380 (39.5)	130 (39.9)	250 (39.3)	0.91
Aortic valve area, cm^2	0.7 ± 0.2	0.7 ± 0.2	0.7 ± 0.2	0.42

Continued on the next page

variables and absolute and relative frequencies for categorical variables. Patients were divided into 2 groups according to their OAC therapy (NOAC or VKA) after procedure. These groups were compared by Fisher exact test, Student's *t* test, and Mann-Whitney *U* tests, as appropriate.

Overall survival was estimated by the Kaplan-Meier method. The risks of other time-to-event endpoints were estimated by cumulative incidence functions as death of a patient induces a competing risk problem in this setting. The Cox proportional hazards regression model was used to estimate cause-specific hazard ratios (HRs) and conduct corresponding hypothesis testing. Following recent advances in statistical methodology on the estimation of causal treatment effects in observational studies, inverse probability of treatment weighting (IPTW) (13) by propensity scores was used in the aforementioned analyses to prevent potential bias in the comparison of patient groups induced by confounders. The latter were considered to be center and year of TAVR procedure, patient age at TAVR, sex, incidence of prior CVE, diagnosis of chronic kidney disease, Society of Thoracic Surgeons Predicted Risk of Mortality score, left ventricular function, and prosthesis type. The stabilized weights used in IPTW were computed from propensity scores that were assessed through a random forest prediction model, which is capable of modeling the possibly complex relations among confounders more accurately than logistic regression (14).

Hypothesis testing was performed on 2-sided 5% significance levels. Statistical analyses were implemented in R version 3.5.0 (R Foundation for Statistical Computing, Vienna, Austria) with the use of the packages "partykit" and "rms" to build a random forest model and to conduct the time-to-event analyses, respectively.

RESULTS

Baseline, procedural and medical treatment data are displayed in **Table 1**. Of the total 962 patients, 326 (33.9%) were discharged with NOAC therapy, while 636 (66.1%) received VKA therapy. The mean age of overall population was 81.3 ± 6.3 years, 52.5% of them were women, and the median Society of Thoracic Surgeons Predicted Risk of Mortality score of 4.5%

TABLE 1 Continued

	All (N = 962)	NOAC (n = 326)	VKA (n = 636)	p Value
Procedural data and periprocedural events				
TAVR in bioprosthesis	55 (5.7)	11 (3.4)	44 (6.9)	0.027
Implanted prosthesis type				<0.001
SAPIEN S3	450 (46.8)	225 (69.0)	225 (5.4)	
SAPIEN XT	153 (15.9)	27 (8.3)	126 (9.8)	
CoreValve	167 (17.4)	15 (4.6)	152 (3.9)	
CoreValve Evolut R	67 (6.9)	13 (3.9)	54 (8.5)	
Lotus	76 (7.9)	40 (12.3)	36 (5.7)	
Direct Flow	27 (2.8)	2 (0.6)	25 (3.9)	
Accurate Neo	15 (1.6)	2 (0.6)	13 (2.0)	
Portico	5 (0.5)	2 (0.6)	3 (0.5)	
Centera	2 (0.2)	0 (0)	2 (0.3)	
Implanted prosthesis size				0.004
≤23 mm	255 (26.5)	108 (33.1)	147 (3.1)	
25–27 mm	413 (42.9)	127 (39.0)	286 (5.0)	
≥29 mm	294 (30.6)	91 (27.9)	203 (31.9)	
Pre-dilation performed	794 (82.5)	279 (85.6)	515 (81.0)	0.088
Post-dilation performed	116 (12.1)	23 (7.1)	93 (14.6)	<0.001
Any prosthesis regurgitation	428 (44.5)	108 (33.1)	320 (50.3)	<0.001
Regurgitation ≥2	45 (4.7)	8 (2.5)	37 (5.8)	
Prosthesis dislocation	13 (1.4)	0 (0)	13 (2.0)	0.006
Major VARC-2 vascular complications	73 (7.6)	15 (4.6)	58 (9.1)	0.014
Acute kidney injury stage II or III	39 (4.1)	7 (2.1)	32 (5.0)	0.041
Antithrombotic therapy				
Periprocedural anticoagulation				<0.001
Unfractionated heparin	884 (91.9)	315 (96.6)	569 (9.5)	
Bivalirudin	78 (8.1)	11 (3.4)	67 (10.5)	
At discharge				
Aspirin	510 (53.0)	171 (52.5)	339 (53.3)	0.85
ADP receptor inhibitors alone	84 (8.7)	21 (6.4)	63 (9.9)	0.09
Triple therapy	204 (21.1)	75 (23.0)	129 (20.3)	0.37

Values are mean ± SD, n (%), or median (interquartile range).

ADP = adenosine diphosphate; CHA_2DS_2-VASc = congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism, vascular disease, age 65–74 years, sex category; NOAC = non–vitamin K oral anticoagulant; NYHA = New York Heart Association; STS-PROM = Society of Thoracic Surgeons Predicted Risk of Mortality; VARC = Valve Academic Research Consortium; VKA = vitamin K antagonist.

(interquartile range: 3.0% to 7.3%) was similar in both groups. There were important differences among both groups regarding baseline and procedural data, as shown in **Table 1**.

TYPE OF NOAC. Of the 326 patients discharged with NOAC therapy, 175 (53.7%) received rivaroxaban and 128 (39.2%) received apixaban, and only 23 (7.1%) were on dabigatran therapy.

OUTCOMES AT 30 DAYS. Overall, 14 (2.2% NOAC, 1.1% VKA) (HR: 1.94; 95% confidence interval [CI]: 0.68 to 5.55; p = 0.213) patients died within 30 days. Incidence of any bleeding complications and major or life-threatening bleeding events were comparable between the groups: for NOACs versus VKAs, 29.8% versus 33.0% (HR: 0.86; 95% CI: 0.67 to 1.09; p = 0.222) and 18.1% versus 21.4% (HR: 0.82; 95% CI: 0.60 to 1.11; p = 0.206), respectively. Patients treated with NOACs showed higher 30-day nondisabling stroke rates as compared with those treated with VKAs (1.2% vs. 0%; p < 0.001). No difference regarding the composite endpoint within 30 days was observed. After adjustment by IPTW, only minor differences were observed in any of the events (**Table 2**).

OUTCOMES AT 1 YEAR. Follow-up was at a median of 593.5 (interquartile range: 401.5 to 1,121.5) days. The primary outcome of interest (composite of all-cause mortality, myocardial infarction, or any CVE) was higher by use of NOACs compared with VKAs (20.9% vs. 14.4%; HR: 1.47; 95% CI: 1.06 to 2.04; p = 0.018). This effect remained after IPTW adjustment (21.2%

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TABLE 2 Unadjusted and IPTW-Adjusted Clinical Outcomes at 30-Day and 1-Year Follow-Up According to Oral Anticoagulation Therapy at Discharge

	Unadjusted				Adjusted			
	NOAC (n = 326)	VKA (n = 636)	Hazard Ratio (95% CI)	p Value	NOAC (n = 326)	VKA (n = 636)	Hazard Ratio (95% CI)	p Value
At 30-day follow-up								
Combined endpoint*	15 (4.6)	19 (3.0)	1.54 (0.78–3.03)	0.210	5.1	3.2	1.59 (0.76–3.30)	0.214
All-cause mortality	7 (2.2)	7 (1.1)	1.94 (0.68–5.55)	0.213	2.6	1.2	2.19 (0.72–6.64)	0.164
Cardio-cerebrovascular mortality	3 (0.9)	4 (0.6)	1.46 (0.32–6.54)	0.618	1.6	0.7	2.42 (0.56–10.29)	0.232
Any BARC bleeding	97 (29.8)	210 (33.0)	0.86 (0.67–1.09)	0.222	31.7	32.0	0.96 (0.73–1.27)	0.815
Minor	36 (11.1)	73 (11.5)	0.95 (0.63–1.41)	0.800	12.6	11.2	1.12 (0.72–1.73)	0.612
Major or life-threatening	59 (18.1)	136 (21.4)	0.82 (0.60–1.11)	0.206	18.6	20.6	0.88 (0.62–1.25)	0.481
Fatal	1 (0.6)	2 (0.2)	3.90 (0.35–43.06)	0.266	0.5	0.1	3.88 (0.23–64.10)	0.343
Cerebrovascular events	7 (2.2)	10 (1.6)	1.36 (0.51–3.58)	0.530	2.3	1.8	1.28 (0.44–3.70)	0.644
TIA	2 (0.6)	4 (0.6)	0.97 (0.17–5.29)	0.972	1.1	0.8	1.36 (0.28–6.46)	0.695
Nondisabling	4 (1.2)	0	N/A	<0.001	0.9	0	N/A	<0.001
Disabling	1 (0.3)	6 (0.9)	0.32 (0.03–2.68)	0.296	0.3	1.0	0.26 (0.01–3.92)	0.334
Myocardial infarction	1 (0.3)	3 (0.5)	0.65 (0.06–6.24)	0.709	0.3	0.4	0.69 (0.04–10.60)	0.796
MACCE†	11 (3.4)	17 (2.7)	1.26 (0.59–2.69)	0.546	4.1	2.8	1.45 (0.65–3.25)	0.357
NACE‡	72 (22.1)	148 (23.3)	0.92 (0.69–1.22)	0.572	22.7	22.6	0.98 (0.71–1.35)	0.908
At 1-yr follow-up								
Combined endpoint*	63 (20.9)	87 (14.4)	1.47 (1.06–2.04)	0.018	21.2	15.0	1.44 (1.00–2.07)	0.050
All-cause mortality	47 (15.7)	70 (11.7)	1.36 (0.94–1.96)	0.103	16.5	12.2	1.36 (0.90–2.06)	0.136
Cardio-cerebrovascular mortality	14 (4.6)	24 (4.0)	1.17 (0.60–2.27)	0.631	5.2	4.2	1.29 (0.63–2.65)	0.473
Any BARC bleeding	105 (32.4)	219 (34.5)	0.89 (0.70–1.12)	0.349	33.9	34.1	0.97 (0.74–1.26)	0.838
Minor	36 (11.1)	73 (11.5)	0.95 (0.63–1.41)	0.800	12.6	11.2	1.12 (0.72–1.73)	0.612
Major or life-threatening	67 (20.7)	144 (22.7)	0.88 (0.66–1.17)	0.397	20.7	22.5	0.90 (0.64–1.26)	0.548
Fatal	2 (0.6)	2 (0.3)	1.95 (0.27–13.8)	0.502	0.5	0.3	1.57 (0.16–15.0)	0.694
Cerebrovascular events	13 (4.2)	17 (2.8)	1.52 (0.74–3.14)	0.250	4.1	2.9	1.38 (0.61–3.13)	0.437
TIA	3 (1.0)	4 (0.6)	1.46 (0.32–6.55)	0.616	1.3	0.8	1.62 (0.37–7.07)	0.520
Nondisabling	5 (1.6)	2 (0.3)	5.00 (0.97–25.81)	0.054	1.3	0.3	4.78 (0.68–33.50)	0.115
Disabling	5 (1.7)	11 (1.8)	0.90 (0.31–2.61)	0.907	1.5	1.9	0.76 (0.21–2.75)	0.687
Valve thrombosis	1 (0.3)	3 (0.5)	0.65 (0.06–6.33)	0.718	0.3	0.7	0.36 (0.02–6.13)	0.487
Myocardial infarction	4 (1.3)	4 (0.6)	1.99 (0.49–7.96)	0.330	1.1	0.6	1.86 (0.35–9.85)	0.463
MACCE†	30 (9.7)	42 (6.9)	1.44 (0.90–2.30)	0.126	10.0	7.1	1.43 (0.85–2.43)	0.173
NACE‡	115 (36.5)	211 (33.8)	1.04 (0.83–1.31)	0.692	37.5	34.2	1.07 (0.82–1.38)	0.596

Values are n (%) or %, unless otherwise indicated. *Composite of all-cause mortality, myocardial infarction, and any clinically relevant cerebrovascular event. †Composite of cardiovascular or cerebrovascular death, myocardial infarction, or stroke. ‡Composite of all-cause mortality, major or life-threatening bleeding, myocardial infarction, and any clinically relevant cerebrovascular event.

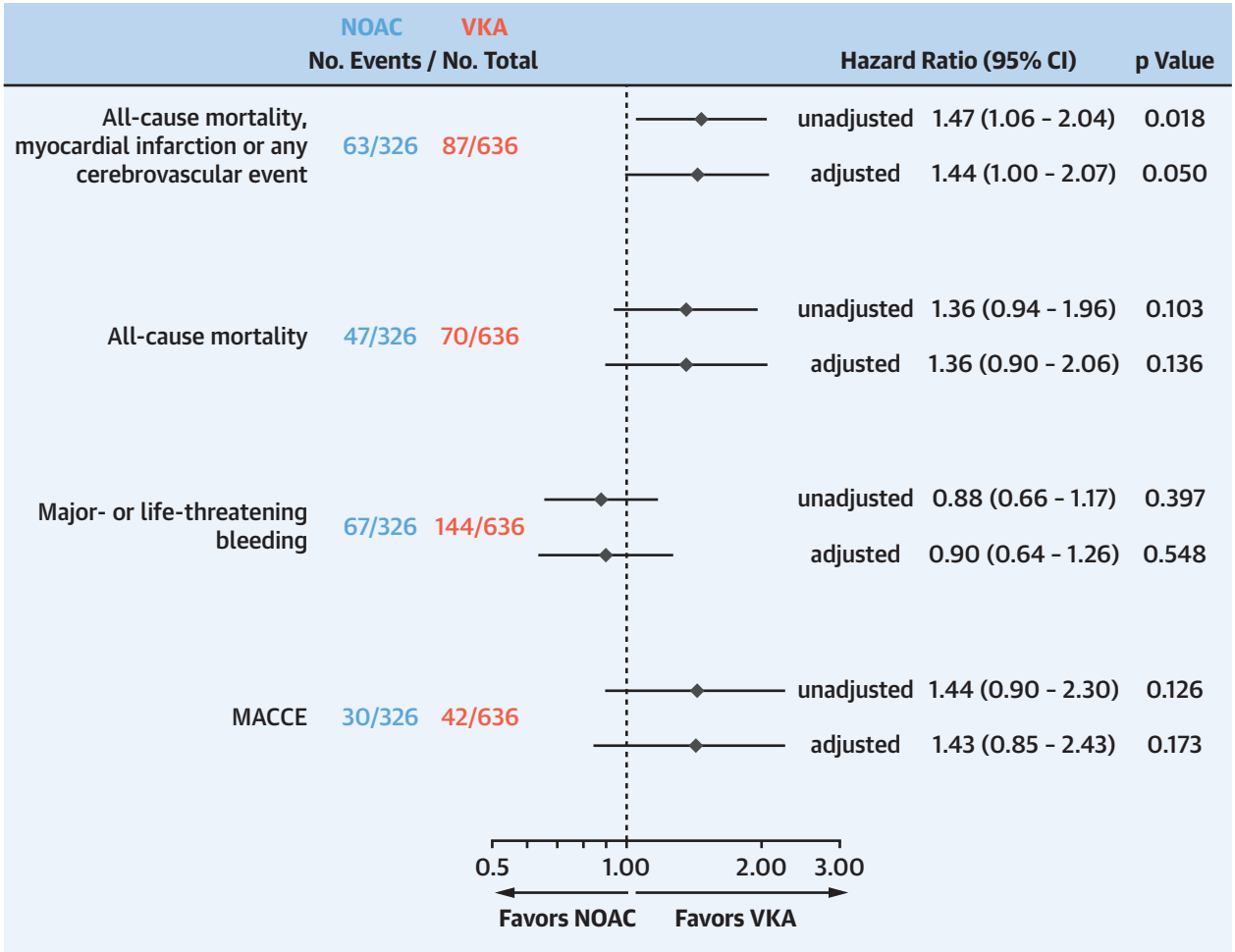
BARC = Bleeding Academic Research Consortium; CI = confidence interval; IPTW = inverse probability of treatment weighting; MACCE = major adverse cardiovascular and cerebrovascular events; N/A = not applicable; NACE = net adverse clinical event; TIA = transient ischemic attack; other abbreviations as in Table 1.

vs. 15.0%; HR: 1.44; 95% CI: 1.00 to 2.07; p = 0.050) (Central Illustration). One-year all-cause mortality of the entire cohort was 12.2% (n = 117), without significant differences among unadjusted groups (NOACs vs. VKAs: 15.7% vs. 11.7%; HR: 1.36; 95% CI: 0.94 to 1.96; p = 0.103) (Table 2). Any bleeding rates were comparable after IPTW adjustment (NOACs vs. VKAs: 33.9% vs. 34.1%; HR: 0.97; 95% CI: 0.74 to 1.26; p = 0.838). Patients in the NOAC group showed higher nondisabling stroke events compared with those treated with VKAs (1.6% vs. 0.3%; HR: 5.00; 95% CI: 0.97 to 25.81; p = 0.054). This effect was attenuated after IPTW adjustment (1.3% vs. 0.3%; HR: 4.78; 95% CI: 0.68 to 33.50; p = 0.115). Landmark analyses between 30-day and 1-year follow-up for all-cause mortality, major or life-threatening bleeding, ischemic events, and net adverse clinical events are shown in Figures 1 to 4. In addition, we performed the outcome analysis for the subgroup of patients undergoing implantation of SAPIEN S3 prosthesis (Edwards Lifesciences, Irvine, California). Although the observed absolute difference in event rates remains the same as in the overall population, the statistical power was decreased due to the small number of SAPIEN S3 patients (Online Table 1).

DISCUSSION

In our multicenter registry—the largest one comparing NOACs versus VKAs in patients in need of

CENTRAL ILLUSTRATION Unadjusted and Adjusted Relative Risk of 1-Year Outcomes After Transcatheter Aortic Valve Replacement According to Oral Anticoagulation Regimen



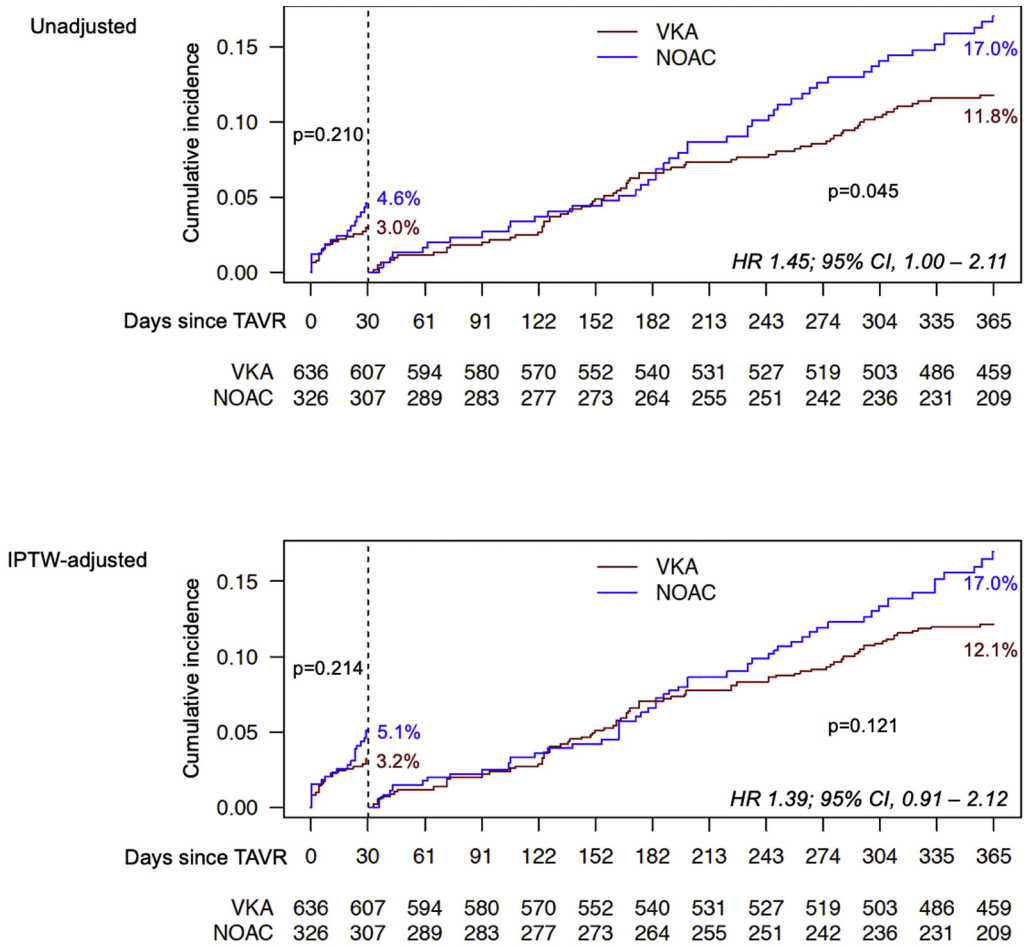
Jochheim, D. et al. J Am Coll Cardiol Intv. 2019;12(16):1566–76.

CI = confidence interval; MACCE = major adverse cardiovascular and cerebrovascular events; NOAC = non-vitamin K oral anticoagulant; VKA = vitamin K antagonist.

OAC after TAVR—we observed a trend toward higher risk of ischemic events 1 year after TAVR with NOACs compared with VKAs. On the other hand, among these multimorbid and elderly patients, the risk of bleeding up to 1 year was comparable with both treatment regimens.

OAC TYPE AND ISCHEMIC EVENTS. Selection of the optimal antithrombotic regimen in patients undergoing TAVR and concomitant indication for OAC therapy remains challenging. This clinical conundrum is reflected by conflicting guideline recommendations. European guideline recommendations favors VKAs for patients who undergo bioprosthetic valve implantation and require longer-term OAC therapy. NOACs use can be considered, but only after an initial 3 months of post-procedural VKA treatment to ensure endothelialization of the prosthesis (Class IIa, Level of Evidence: C) (9). In contrast, American guidelines discourage NOAC use after bioprosthetic valve replacement (15). These recommendations mostly arise from the RE-ALIGN (Randomized, Phase II Study to Evaluate the Safety and Pharmacokinetics of Oral Dabigatran Etexilate in Patients after Heart Valve Replacement) trial including patients undergoing mechanical valve replacement showing considerable higher ischemic event rates with use of NOACs compared with VKAs during the early post-

FIGURE 1 Landmark Analysis of the Combined Endpoint of All-Cause Mortality, Myocardial Infarction, or Any Cerebrovascular Event Within 30 Days and 1 Year After TAVR

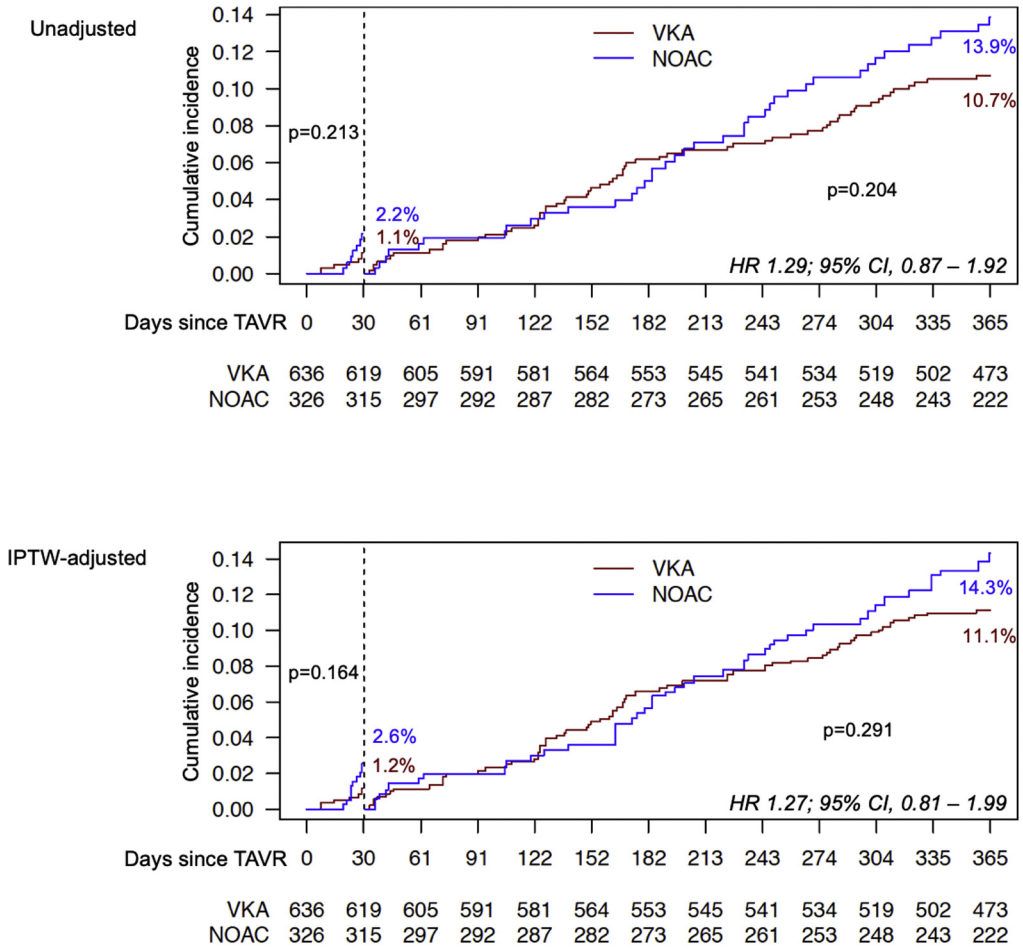


CI = confidence interval; HR= hazard ratio; IPTW = inverse probability of treatment weighting; NOAC = non-vitamin K oral anticoagulant; TAVR = transcatheter aortic valve replacement; VKA = vitamin K antagonist.

operative time period (16). In our registry, the 1-year cumulative incidence of all-cause mortality, myocardial infarction, and CVE with NOACs was 20.9% (adjusted 21.2%), whereas with VKAs it was 14.4% (adjusted 15.0%). These findings are comparable with the observations from Seeger et al. (2), who analyzed 272 AF patients undergoing TAVR and reported a 1-year incidence of all-cause death and all stroke of 24.7% with NOACs versus 14.0% with VKAs. Mechanistic explanation for these observations might be the VKAs' broader interference with the coagulation cascade compared with NOACs (5).

On the other hand, meta-analyses of the pivotal trials comparing OAC regimens in the setting of AF have demonstrated significant reduction of ischemic events among patients ≥75 years of age with NOACs compared with VKAs (7). However, contradictory results regarding the anti-ischemic performance of NOACs and VKAs have been reported in post hoc subgroup analyses of AF patients with previous valve surgery in the setting of ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial (n = 251) and the ENGAGE AF-TIMI 48 (Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis In Myocardial Infarction 48) trial (n = 191) (17,18). The modest sample size of these subgroups reduces the power of analysis to investigate

FIGURE 2 Landmark Analysis of All-Cause Mortality Within 30 Days and 1 Year After TAVR According to Oral Anticoagulation Treatment at Discharge



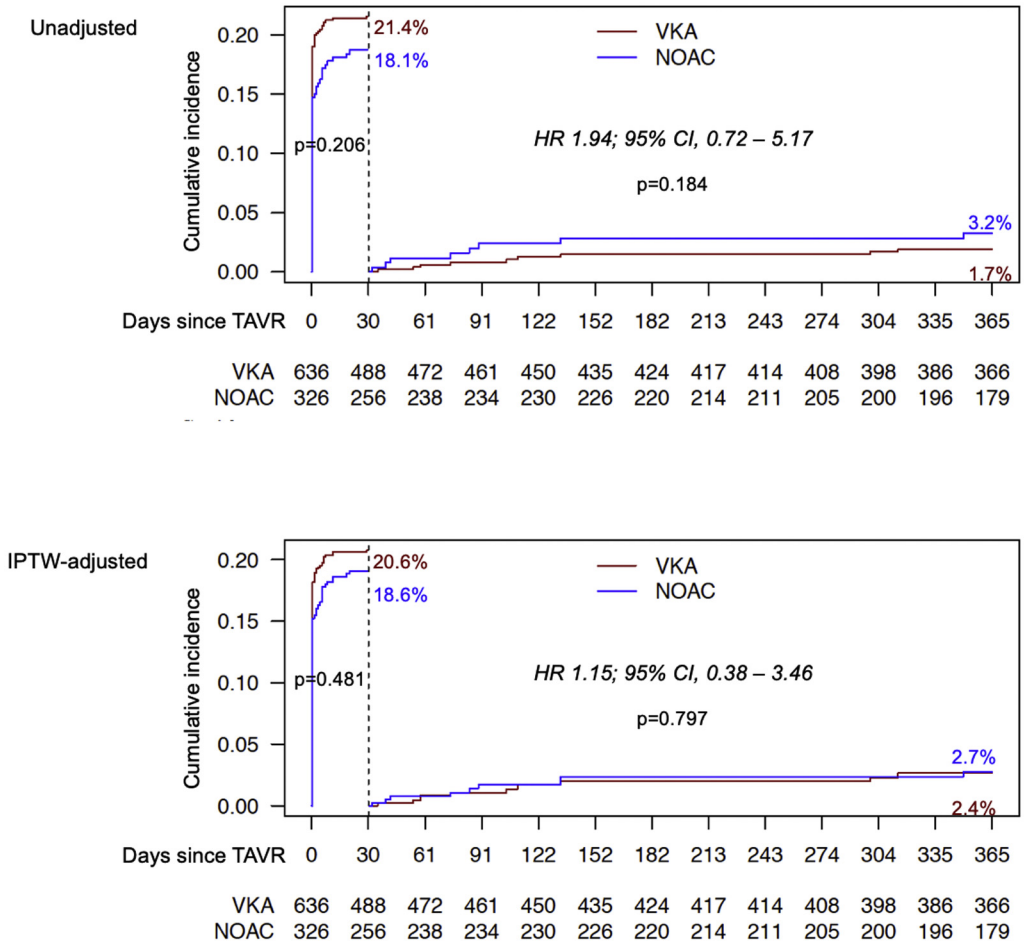
Abbreviations as in Table 1.

this question. Furthermore, it highlights the multifactorial origin of ischemic events in the valvular heart disease population.

Among TAVR patients, age is one of the most important independent predictors of long-term risk for CVE (19). In addition to age, clinical und subclinical bioprosthetic valve thrombosis (BVT) have been reported to be associated with an increased CVE incidence after aortic valve repair (20). Recently published data focusing on pure TAVR populations question these findings (21). In our study, the rate of clinically relevant BVT was below 0.5% (1 NOAC and 3 VKA patients). Although comparable to previously published data, between 0.6% and 2.8% (22,23), different from the others, our population is a select one, considering only TAVR patients on OAC.

OAC TYPE AND BLEEDING COMPLICATIONS. A major limitation of OAC treatment is the considerably higher bleeding risk particularly among the elderly patients. The reported rates of major or life-threatening bleeding in anticoagulated patients 1 year after TAVR typically reach 17%, which increases to 25% in patients receiving antiplatelet drugs in addition to OAC (24). Unlike the expectations based on pivotal randomized trials enrolling AF patients, in our study, no difference in bleeding rates was observed among treatment regimens, with overall 1-year major or life-threatening bleeding rate of 21.9%. Post-TAVR bleeds are mostly mechanically induced rather than spontaneous, which might explain this important observation. Another explanation is attributable to age: among AF patients

FIGURE 3 Landmark Analysis of Major or Life-Threatening Bleeding Within 30 Days and 1 Year After TAVR According to Oral Anticoagulation Treatment at Discharge



Abbreviations as in Table 1.

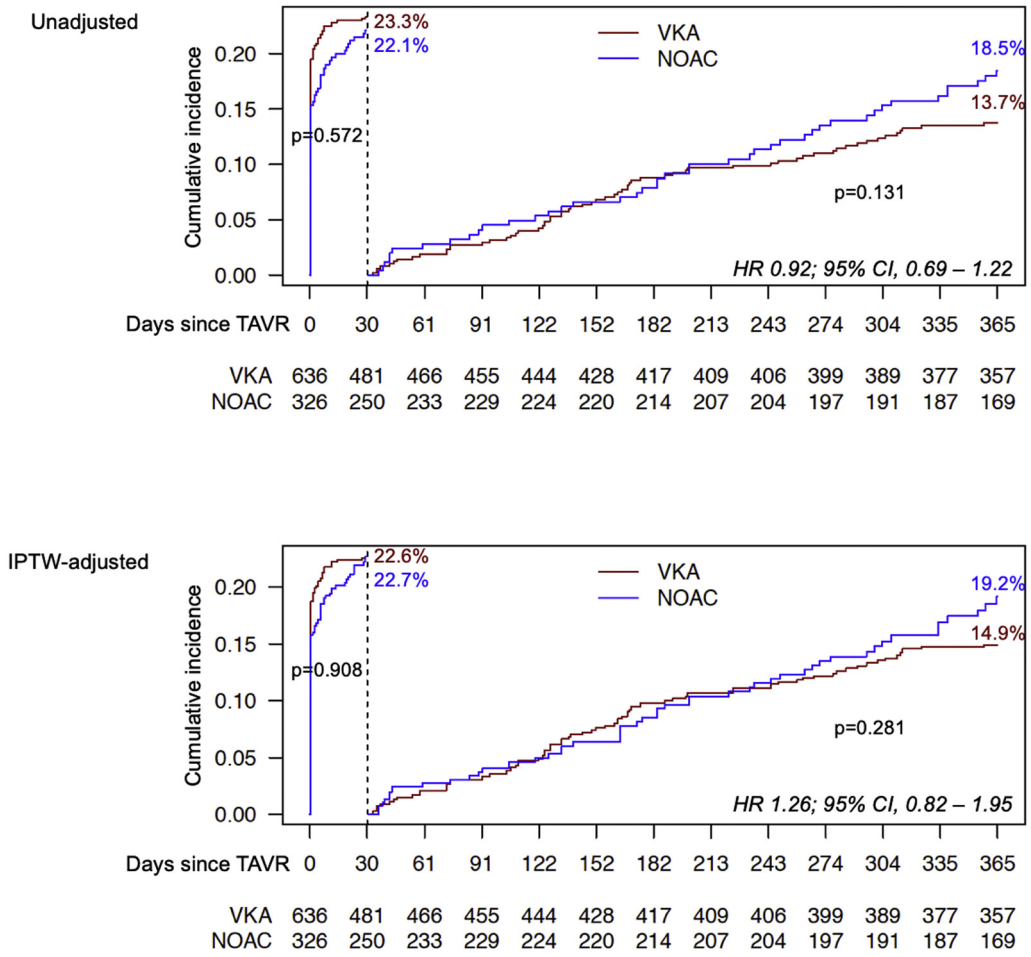
younger than 75 years of age, Ruff et al. (7) reported a 21% significant reduction of major bleeds with NOACs compared with VKAs, while vulnerable patients ≥75 years of age only experienced a moderate, nonsignificant bleeding reduction. In the post hoc analysis of the ROCKET AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) trial, valvular heart disease patients treated with factor Xa inhibitors (mean 75 years of age) more frequently experienced major bleeding compared with VKA-treated patients (25).

STUDY LIMITATIONS. The limitations of this study are: 1) the status as a nonconfirmatory, hypothesis-generating study in a nonrandomized setting with its known limitations; 2) the lack of central event adjudication; 3) that drug usage compliance and dosage was not assessed; 4) that timing of initiation and type of OAC treatment was done according to the local regularities; 5) the lack of systematic computer tomography at follow-up, which limits our ability to investigate the rate of subclinical BVT; and 6) the lack of information about mitral valve disease.

CONCLUSIONS

Both NOACs and VKAs, used as maintenance therapy among patients in need of OAC after TAVR, are comparable regarding the bleeding risk at 1-year

FIGURE 4 Landmark Analysis of Net Adverse Clinical Events Within 30 Days and 1 Year After TAVR According to Oral Anticoagulation Treatment at Discharge



Abbreviations as in Table 1.

follow-up. Despite adjustment, a higher ischemic risk was observed with NOACs compared with VKAs, a finding that should critically challenge the routine use of NOACs after TAVR. Results of the ongoing dedicated large randomized trials—ATLANTIS (Anti-Thrombotic Strategy After Trans-Aortic Valve Implantation for Aortic Stenosis) trial (26) and ENVISAGE-TAVI AF (Effective aNticoaGulation with factor Xa next GEneration in Atrial Fibrillation) trial (27)—will fill this gap in knowledge.

ACKNOWLEDGMENTS The authors thank Fátima Maimer Rodrigues da Cunha and Martina Schulz for data acquisition and data management.

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JACC: CARDIOVASCULAR INTERVENTIONS VOL. 12, NO. 16, 2019
AUGUST 26, 2019:1566–76

PERSPECTIVES

WHAT IS KNOWN? Patients undergoing TAVR with indication for OAC treatment at the time of discharge are well known exposed to a higher ischemic and bleeding risk at 1-year follow-up. However, selection of the optimal antithrombotic treatment in these patients remains challenging and data are still lacking.

WHAT IS NEW? We were able to demonstrate that both NOACs and VKAs, as chronic OAC maintenance therapy after TAVR, are associated with a comparable risk profile regarding 1-year bleeding events, while a higher risk of the composite of all-cause mortality, myocardial infarction, and any CVE was observed in patients treated with NOACs.

WHAT IS NEXT? These findings should be validated in large randomized trials to further improve outcomes in patients in need of chronic OAC treatment after TAVR procedure.

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KEY WORDS bleeding risk, ischemic events, oral anticoagulation, TAVR

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