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Comparison of Direct Oral Anticoagulants vs Vitamin K Antagonists After Transcatheter Mitral Valve Replacement

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ABSTRACT

BACKGROUND There is currently no established recommendation for antithrombotic treatment following transcatheter mitral valve replacement (TMVR). However, based on the analogy with surgical mitral bioprosthesis, vitamin K antagonists (VKAs) are predominantly used.

OBJECTIVES The purpose of this study was to compare bleeding and thrombotic events associated with direct oral anticoagulants (DOACs) or VKAs in a prospective cohort of TMVR patients.

METHODS We enrolled consecutive patients who underwent transseptal TMVR using a SAPIEN family prosthesis at our center between 2011 and 2023. The primary outcome was the occurrence of bleeding. VKAs were administered to patients until October 2019, after which DOACs were prescribed. The median follow-up was 4.7 months (Q1-Q3: 2.6-6.7 months).

RESULTS A total of 156 patients were included. The mean age was 65 ± 18.5 years, and 103 patients (66%) were women. The median EuroSCORE II was 7.48% (Q1-Q3: 3.80%-12.97%). Of the participants, 20.5% received DOACs and 79.5% were treated with VKAs. The primary outcome was observed in 50 (40%) patients in the VKA group and 3 (9%) patients in the DOAC group (adjusted HR: 0.21; 95% CI: 0.06-0.74; $P = 0.02$). Treatment with DOAC was associated with a shorter length of hospital stay. No significant differences were found in terms of thrombotic events, major vascular complications, stroke, or death.

CONCLUSIONS The use of DOACs after TMVR, compared with VKAs, appears to reduce the risk of bleeding complications and decrease the length of hospital stay for patients, without a significant increase in the risk of thrombotic events. (J Am Coll Cardiol 2024;83:334-346) © 2024 by the American College of Cardiology Foundation.

Severe mitral valve disease is a global cause of morbidity and mortality. Despite clear indications for surgery, nearly one-half of the patients do not undergo surgical intervention.[1] Transcatheter valve therapies have emerged as an alternative to surgery for those patients, although with differences between repair and replacement therapies. While transcatheter mitral valve repair therapies are now commonly performed, transcatheter mitral valve replacement (TMVR) is primarily limited to patients with bioprosthesis or annuloplasty ring failure[2,3] or those with severe mitral annulus calcification (MAC).[4,5] The latest guidelines recommend the use of TMVR for patients with bioprosthesis failure at high risk for surgical reintervention.[4,5]

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Although it is widely acknowledged that antithrombotic therapy is essential after TMVR, the optimal antithrombotic regime remains to be determined. In clinical practice, anticoagulation therapy is typically indicated based on analogy with surgical mitral bioprosthesis. However, the ideal duration of anticoagulation therapy in patients without indication for lifelong anticoagulation and the most appropriate agent (vitamin K antagonists [VKAs] or direct oral anticoagulants [DOACs]) remain unknown.

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In patients with atrial fibrillation, DOACs are preferred to VKAs because of their ease of use, lack of need for regular biological monitoring, and reduced risk of thrombosis and bleeding.[6-9] However, DOACs are contraindicated in patients with mechanical valves or mitral stenosis, and their use in postoperative care is controversial.[4,5] After mitral bioprosthesis implantation, VKAs are generally favored because of the possibility of reversal. Nonetheless, several trials have demonstrated that DOACs can be used after mitral bioprosthesis[10] even in the early postoperative period.[11] Regarding TMVR, published studies do not directly address this specific topic, and most studies do not clearly report the antithrombotic therapy used after TMVR.[2,3,12]

The objective of our study is to compare bleeding and thrombotic events according to the type of anticoagulant treatment (DOAC or VKA) in a prospective cohort of patients who underwent transseptal TMVR with a SAPIEN prosthesis.

METHODS

PATIENT POPULATION. Among 186 patients who underwent TMVR at our center between March 2011 and March 2023, a total of 156 patients were included. Patients were included if TMVR was performed using the transseptal approach, they were alive at discharge, and they received either DOAC or VKA at discharge (**Figure 1**, Supplemental Table 1). The indications for TMVR included severe symptomatic mitral valve disease resulting from bioprosthesis or ring failure, severe MAC in high-risk or inoperable patients, or young women with current pregnancy or a desire for pregnancy in whom TMVR was favored by the heart team to avoid a surgical reintervention with a bioprosthesis.[2] Data collection was prospectively performed in local electronic case report forms. The study was approved by the local Institutional Review Board (Paris Nord), and all patients signed consent forms before the procedures. The study adheres to the principled outlined in the Declaration of Helsinki and was carried out in accordance with applicable local legislation.

TRANSCATHETER PROCEDURE. Transcatheter mitral valve replacement work-up was as previously reported.[13] Briefly, in addition to the standard preoperative examination, transesophageal echocardiography (TEE) and contrast computed tomography (CT) were performed to identify concomitant diseases contraindicating the procedure, evaluate the risk of left ventricular outflow tract obstruction, and determine the size of the transcatheter heart valve. All procedures were carried out by a team of interventional cardiologists, under general anesthesia, with TEE and fluoroscopy guidance. The SAPIEN XT or SAPIEN 3 transcatheter heart valves (Edwards Lifesciences) were used. Transseptal procedures were performed as previously described.[13] After the transcatheter heart valve was implanted, a TEE evaluation was performed.

ANTITHROMBOTIC THERAPY. During the TMVR procedures, patients received intravenous heparin at a dose of 70 IU/kg. Following the procedure, patients were anticoagulated for a minimum of 3 months. Until October 2019, patients were prescribed VKAs, except for rare cases of therapeutic nonadherence in whom DOACs were indicated. Since October 2019, a change in practice was implemented and DOACs became the preferred choice unless contraindicated or unless the patient or responsible physician preferred to continue VKAs when anticoagulation was indicated before TMVR. The specific type of DOAC and the addition of aspirin were left to the operator's discretion. Anticoagulation therapy was initiated 3 to 6 hours after the procedure, provided there were no complications. For patients receiving VKA therapy, initial anticoagulation was achieved using either unfractionated heparin or low-molecular-weight heparin. The target international normalized ratio ranged between 2 and 3, and patients were discharged once their international normalized ratio was >2. In the case of patients receiving DOACs, the therapy was initiated directly 6 hours after the procedure without administration of heparin or later, if deemed necessary by the operator, after heparin bridging.

In patients without an indication for lifelong anticoagulation, anticoagulants were discontinued after 3 to 6 months if imaging tests (transesophageal echocardiography and/or computed

ABBREVIATIONS AND ACRONYMS

CT = computed tomography

DOAC = direct oral anticoagulant

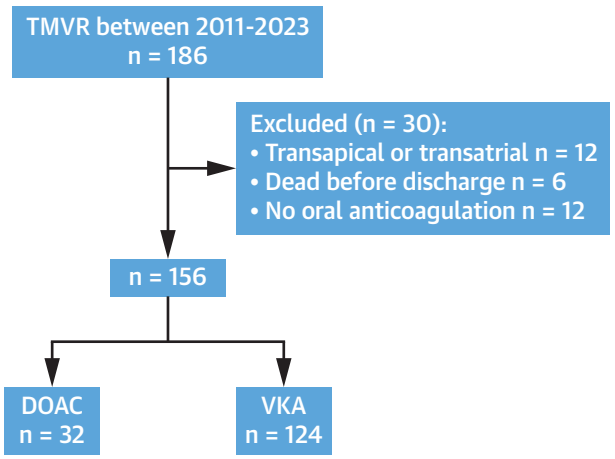
MAC = mitral annulus calcification

TEE = transesophageal echocardiography

TMVR = transcatheter mitral valve replacement

VKA = vitamin-K antagonist

FIGURE 1 Flow Chart



Flow chart showing the inclusion and exclusion criteria of patients and the study period. Of a total of 186 patients undergoing transcatheter mitral valve replacement (TMVR) between 2011 and 2013 in our institution, 156 were finally included. DOAC = direct oral anticoagulant; VKA = vitamin K antagonist.

tomography) confirmed the absence of valve thrombosis. These patients were prescribed lifelong aspirin therapy.

OUTCOMES. Outcomes were defined according to the Mitral Valve Academic Research Consortium.[14] The primary outcome was the occurrence of any bleeding, including both major or minor bleeding[14] events during the study period. The starting point for event monitoring was immediately after the procedure. Complications arising during the procedure were not considered as part of the outcome measures.

The secondary outcomes were thrombotic complications (valve thrombosis or stroke), death, major vascular complications, and the length of stay. Valve thrombosis was defined as the presence of at least 1 thickened leaflet with restricted motion or a mobile mass suggestive of thrombus confirmed by TEE and/or contrast CT. Hemodynamically significant valve thrombosis was defined as valve thrombosis and a mean transmitral gradient of ≥10 mm Hg. Clinical valve thrombosis was defined as hemodynamically significant valve thrombosis and heart failure symptoms.

FOLLOW-UP. Patients were followed up after the procedure at 1 month, 3 to 6 months, 1 year, and yearly thereafter through inpatient or outpatient clinic visits. In our study, patients were censored at the 3 to 6 months visit. The median follow-up was 4.7 months (Q1-Q3: 2.6-6.7 months).

Transthoracic echocardiography and TEE were performed by expert echocardiographers at each visit. All patients underwent transthoracic echocardiography at each follow-up visit. In addition, a contrast CT and TEE were planned for each visit to detect transcatheter heart valve thrombosis, unless contraindicated. Additionally, 90% had at least 1 cardiac CT scan, and 79% had at least 1 TEE during follow-up.

STATISTICAL ANALYSIS. Categorical variables are presented as percentage and continuous variables as mean ± SD or median (Q1-Q3) according to variable distribution. Chi-square or Fisher exact tests were used to compare qualitative variables as appropriate. Comparisons of continuous variables were performed using Student's *t*-tests or Mann-Whitney Wilcoxon rank tests as appropriate. Censored variables were evaluated using Kaplan-Meier estimates, and survival curves were compared using log-rank tests. Univariate and multivariable Cox regression models were utilized to assess the association between covariates and censored outcomes. The assumptions of hazard proportional were confirmed using complementary log-log survival plots and proportional hazards tests based on Schoenfeld residuals.[15]

In the univariate analysis, variables with a P value <0.10 were considered for inclusion in the multivariable analyses. Collinear variables, determined by the calculation of variance-inflation factors and generalized variance-inflation factors, were not included.

Age, sex and aspirin therapy were also forced into the model because they are known potential confounders. The variables finally included in the model for bleeding were age, sex, previous diabetes, type of procedure, and aspirin therapy. The variables finally included in the model for thrombotic events were age, sex, and aspirin therapy. The variables finally included in the model for length of stay were age, sex, and aspirin therapy. A landmark analysis was conducted at day 30. Additionally, a sensitivity analysis was conducted by excluding patients with severe chronic renal failure (eGFR <30 mL/min), because these patients typically have a clinical indication for VKA rather than DOAC. We also performed a sensitivity analysis on the subgroup of valve-in-valve patients, because they constitute the majority of the DOAC cohort, to ascertain the robustness of our findings within this specific patient population. To evaluate the length of stay, we used a negative

binomial regression model, motivated by observed over dispersion in a Poisson model. To control for the temporal trend and given the fact that DOAC patients were included later than VKA patients, we incorporated specific periods into our multivariable model for length of stay: 2011-2015, 2016-2017, 2018-2019, 2020-2021, and 2022-2023. Effects are presented as ORs or HRs associated with their 95% CIs.

A P value <0.05 was considered statistically significant, and all tests were 2-sided. All statistical analyses were conducted using R version 4.2.2 (R Foundation for Statistical Computing).[16]

RESULTS

PATIENT AND PROCEDURAL CHARACTERISTICS. Baseline, procedural characteristics, and hemodynamic results of the study population are displayed in Table 1. The mean age of the patients was 65 ± 18.5 years, and 103 patients (66%) were women. The majority of patients were deemed high risk for surgery, with a median EuroSCORE II of 7.48% (Q1-Q3: 3.80%-12.97%). The indications for TMVR were bioprosthesis failure in 97 (62.6%) patients, ring annuloplasty failure in 36 (23.2%) patients, and severe MAC in 22 (14.2%) patients. The mean transmitral gradient was 10.7 ± 4.8 mm Hg, and mitral regurgitation ≥2/4 was observed in 88 (56.4%) patients. A minority of patients were on dual antiplatelet therapy before the procedure (n = 5 [3.2%]), and 37 (23.7%) had an aspirin prescription. At the time of hospital discharge, 32 patients received DOAC and 124 patients received VKA. Among patients receiving DOAC, apixaban was prescribed in 81% (26 of 32) of patients, rivaroxaban in 13% (4 of 32) of patients, and dabigatran in 6% (2 of 32) of patients. There were no significant differences between the 2 groups regarding the age, sex, and EuroSCORE II. However, a lower proportion of patients in the DOAC group had renal failure compared with the VKA group (29% vs 62.9%; $P < 0.001$), with no significant difference in severe renal failure (16% vs 19%; $P = 0.96$). Patients in the DOAC group also had a lower frequency of mitral regurgitation ≥2/4 (34.4% vs 62.1%; $P < 0.01$) and had a higher transmitral gradient (13.4 ± 5.2 mm Hg vs 10 ± 4.5 mm Hg; $P < 0.001$). In addition, the type of procedure differed between groups, with 93.8% of patients in the DOAC group undergoing a valve-in-valve, 3.1% valve in ring, and 3.1% valve in MAC, whereas in the VKA group, 54.5% underwent valve-in-valve, 28.5% valve in ring, and 17.1% valve in MAC ($P < 0.001$). As for antiplatelet treatment at discharge, aspirin was prescribed in 3.1% of patients receiving DOACs compared with 68% of patients receiving VKAs ($P < 0.001$). Patients undergoing TMVR after 2019 less frequently had chronic kidney disease (44.8% vs 62.9%; $P = 0.04$) and had a higher mean transmitral gradient (12.0 ± 4.9 mm Hg vs 10.0 ± 4.7 mm Hg; $P = 0.02$). Regarding the type of intervention, after 2019, most procedures were valve-in-valve (88.1% vs 47.4%), and the SAPIEN 3 valve was mainly used (98.3% vs 71.1%). No significant differences were observed regarding the urgency of the procedure, the need of a second valve, or procedural success (Supplemental Table 2).

OUTCOMES. The 30-day outcomes are displayed in Table 2. No deaths occurred between discharge and 30 days. Bleeding events were more frequent in the VKA group compared with the DOAC group (35% vs 9%; $P = 0.02$). This difference was also statistically significant for major bleedings (14% vs 0%; $P = 0.01$). Although not statistically significant, there was a trend suggesting a higher occurrence of minor bleeding in the VKA group compared with the DOAC group (23% vs 9%; $P = 0.09$). The length of hospital stay was shorter in the DOAC group (4.50 days [Q1-Q3: 2.75-6.00 days] vs 8.00 days [Q1-Q3: 6.00-13.25 days]; $P < 0.001$). This difference remained significant after adjustment ($P = 0.002$). No significant differences were observed in vascular complications and stroke.

Table 3 presents the cumulative outcomes. Any bleeding complication occurred in 50 (40%) patients in the VKA group and 3 (9%) patients in the DOAC group (unadjusted HR: 0.21; 95% CI: 0.07-0.69; $P = 0.01$). After adjustment, DOAC treatment remained associated with a reduced risk of bleeding (adjusted HR: 0.21; 95% CI: 0.06-0.74; $P = 0.02$). Kaplan-Meier curves (unadjusted and adjusted) for bleeding are shown in Figure 2. The landmark analysis (Figure 3) revealed an association between anticoagulant treatment and bleeding before day 30 (unadjusted HR for DOAC vs VKA: 0.20; 95% CI: 0.06-0.63; $P < 0.01$), which remained significant after adjustment (adjusted HR: 0.20; 95% CI: 0.06-0.71; $P = 0.01$). However, there was no significant association between anticoagulation therapy and bleeding after day 30 ($P = 0.20$).

Patient characteristics according to the occurrence of bleeding are presented in Table 4. VKA treatment (HR: 4.83; 95% CI: 1.35-17.29; $P = 0.02$) and diabetes (HR: 2.48; 95% CI: 1.32-4.68; $P < 0.01$) were the only independent predictors of bleeding (Supplemental Table 3). In the sensitivity analysis conducted excluding patients with severe chronic renal failure

TABLE 1 Baseline Characteristics, Procedural Findings, and Hemodynamic Outcomes at Hospital Discharge According to Study Groups

	Overall (N = 156)	DOAC (n = 32)	VKA (n = 124)	*P* Value
Clinical characteristics at baseline				
Age, y	65 ± 18.5	60 ± 20.6	66 ± 17.9	0.13
Female	103 (66.0)	18 (56.2)	85 (68.5)	0.27
Body mass index, kg/m^2	25.5 ± 5.7	25.7 ± 5.5	25.5 ± 5.8	0.89
COPD	25 (16.0)	4 (12.5)	21 (16.9)	0.73
Diabetes mellitus	28 (17.9)	4 (12.5)	24 (19.4)	0.52
High blood pressure	64 (41.0)	10 (31.2)	54 (43.5)	0.29
eGFR <60 mL/min	87 (56.1)	9 (29)	78 (62.9)	<0.01
Atrial fibrillation	102 (65.4)	19 (59.4)	83 (66.9)	0.55
Coronary artery disease	40 (25.6)	6 (18.8)	34 (27.4)	0.44
Previous cardiac surgery	146 (93.6)	30 (93.8)	116 (93.5)	1.00
EuroSCORE II	7.48 (3.80-12.97)	5.44 (3.14-11.65)	8.69 (4.27-12.96)	0.11
Echocardiographic findings at baseline				
LVEF, %	57.1 ± 10.5	53.7 ± 10.5	58 ± 10.4	0.04
Mean mitral gradient, mm Hg	10.7 ± 4.8	13.4 ± 5.2	10 ± 4.5	<0.01
Mitral regurgitation ≥2/4	88 (56.4)	11 (34.4)	77 (62.1)	<0.01
Left atrium area, cm^2	41 ± 45	31.9 ± 8.6	42.5 ± 47.8	0.60
PASP, mm Hg	55.9 ± 16	51.9 ± 17.7	56.9 ± 15.5	0.13
Tricuspid regurgitation ≥3/4	50 (32.1)	9 (28.1)	41 (33.1)	0.75
Procedural characteristics				
Type of procedure				<0.01
Valve-in-valve	97 (62.6)	30 (93.8)	67 (54.5)	
Valve-in-ring	36 (23.2)	1 (3.1)	35 (28.5)	
Valve-in-MAC	22 (14.2)	1 (3.1)	21 (17.1)	
Sapien 3 prosthesis	127 (81.4)	31 (96.9)	96 (77.4)	0.61
Prosthesis size, mm				0.45
23	9 (5.8)	2 (6.2)	7 (5.6)	
26	64 (41.0)	10 (31.2)	54 (43.5)	
29	83 (53.2)	20 (62.5)	63 (50.8)	
Urgency				0.93
Elective	130 (83.3)	26 (81.2)	104 (83.9)	
Urgent	22 (14.1)	5 (15.6)	17 (13.7)	
Emergency	4 (2.6)	1 (3.1)	3 (2.4)	
Postdilatation	37 (24.2)	12 (38.7)	25 (20.5)	0.06
Need for second valve	14 (9.1)	2 (6.5)	12 (9.8)	0.82
Technical success (MVARC)	139 (91.4)	28 (93.3)	111 (91.0)	0.96
Conversion to surgery	0 (0.0)	—	—	—
Tamponade	0 (0.0)	—	—	—
New-onset atrial fibrillation	6 (4.0)	2 (6.9)	4 (3.3)	0.72
Echocardiographic findings at discharge				
LVEF, %	56.7 ± 10.4	55.5 ± 10.7	56.6 ± 10.3	0.61
Mean mitral gradient, mm Hg	5.9 ± 2.3	6.2 ± 2.8	5.9 ± 2.2	0.50
Mitral regurgitation ≥2/4	29 (18.6)	2 (6.2)	27 (21.8)	0.08
Antithrombotic treatment after the procedure				
Aspirin	37 (23.7)	7 (21.9)	30 (24.2)	0.967
Clopidogrel	6 (3.9)	2 (6.2)	4 (3.3)	0.795
Prasugrel or Ticagrelor	0 (0)	0 (0)	0 (0)	—
Dual antiplatelet therapy	5 (3.2)	2 (6.2)	3 (2.4)	0.593
Antiplatelet therapy at discharge				
Aspirin	85 (54.8)	1 (3.1)	84 (68.3)	<0.01

Values are mean ± SD, n (%), or median (Q1-Q3).

COPD = chronic obstructive pulmonary disease; CT = computed tomography; DOAC = direct oral anticoagulant; eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction; MAC = mitral annulus calcification; PASP = pulmonary artery systolic pressure; TEE = transesophageal echocardiography; VKA = vitamin K antagonist.

(n = 127), DOAC treatment remained associated with a reduced risk of bleeding (adjusted HR: 0.17; 95% CI: 0.04-0.83; $P = 0.03$) (Supplemental Table 4). DOAC treatment also remained associated with a reduced risk of bleeding in the valve-in-valve population (adjusted HR: 0.18; 95% CI: 0.04-0.75; $P = 0.02$).

A thrombotic event occurred in 16 (13%) patients in the VKA group and 6 (19%) patients in the DOAC group (unadjusted HR: 2.05; 95% CI: 0.80-5.27; $P = 0.14$, adjusted HR: 1.23; 95% CI: 0.42-3.65; $P = 0.70$). The Kaplan-Meier curves (univariate and adjusted) for thrombotic events are shown in Figure 4. Valve thrombosis was observed in 14 patients (11%) in the VKA group and 6 patients (19%) in the DOAC group (unadjusted HR: 2.44; 95% CI: 0.93-6.38; $P = 0.07$, adjusted HR: 1.38; 95% CI: 0.45-4.19; $P = 0.57$). A stroke was observed in 2 patients (2%) in the VKA group and in none of the DOAC group ($P = 0.50$).

Hemodynamically significant valve thrombosis occurred in 10 patients (8%) in the VKA group and in 4 patients (13%) in the DOAC group ($P = 0.09$). Clinically significant valve thrombosis was observed in 2 (2%) patients in the VKA group and in none of the DOAC group ($P = 0.50$). Of note, there were no significant differences between the 2 groups regarding the number of patients who had TEE (76% in the DOAC group vs 80% in the VKA group; $P = 0.9$) and CT scan (93% in the DOAC group vs 89% in the VKA group; $P = 0.8$) during follow-up.

No significant interaction was observed between a mean transmitral gradient >5 mm Hg after the procedure and type of anticoagulant treatment with respect to the risk of bleeding (P for interaction = 0.99) or thrombotic events (P for interaction = 0.95), suggesting the lack of influence of residual gradients on DOAC effects.

TABLE 2 30-Day Outcomes According to Study Groups

	Overall (N = 156)	DOAC (n = 32)	VKA (n = 124)	*P* Value
Length of stay, d	7.00 (6.00-13.00)	4.50 (2.75-6.00)	8.00 (6.00-13.25)	<0.001
All bleeding	46 (29)	3 (9)	43 (35)	0.02
Major bleeding	18 (12)	0 (0)	18 (14)	0.01
Minor bleeding	31 (20)	3 (9)	28 (23)	0.09
Thrombotic events	11 (7)	4 (13)	7 (6)	0.24
Valve thrombosis	10 (6)	4 (13)	6 (5)	0.12
Stroke	1 (0)	0 (0)	1 (0)	1.00
Major vascular complications	9 (6)	0 (0)	9 (7)	0.21
Death	0 (0)	0 (0)	0 (0)	–

Values are median (Q1-Q3) or n (%).
Abbreviations as in Table 1.

DISCUSSION

The main results of this study are as follows: 1) in patients undergoing TMVR, the use of DOACs is associated with a lower incidence of bleeding complications than treatment with VKAs, particularly early bleeding events; 2) there were no significant differences in the risk of thrombotic events, including valve thrombosis, between patients receiving DOACs and VKAs; and 3) the use of DOACs was associated with a shorter length of hospital stay compared with VKAs (Central Illustration).

The findings of this study have significant implications for clinical practice. Although the specific impact of bleeding after TMVR has not yet been fully understood, it is well-known that bleeding events are associated with increased mortality after percutaneous interventions, including transcatheter aortic valve replacement (TAVR) and percutaneous coronary interventions.[17,18] Given the association between bleeding and adverse events, all efforts should

TABLE 3 1-Year Cumulative Outcomes According to Study Groups

	DOAC (n = 32)	VKA (n = 124)	Univariable HR (95% CI)	*P* Value	Multivariable HR (95% CI)	*P* Value
All bleeding	3 (9)	50 (40)	0.21 (0.07-0.69)	0.01	0.21 (0.06-0.74)	0.02
Major bleeding	0 (0)	23 (19)	–	0.02	–	–
Minor bleeding	3 (9)	31 (25)	0.39 (0.12-1.26)	0.11		
Thrombotic events	6 (19)	16 (13)	2.05 (0.80-5.27)	0.14	1.23 (0.42-3.65)	0.70
Valve thrombosis	6 (19)	14 (11)	2.44 (0.93-6.38)	0.07	1.38 (0.45-4.19)	0.57
Hemodynamically significant	4 (13)	10 (8)	2.87 (0.86-9.57)	0.09		
Clinically significant	0 (0)	2 (2)	–	0.50		
Major vascular complications	0 (0)	10 (8)	–	0.10		
Stroke	0 (0)	2 (2)	–	0.50		
Death	2 (6)	11 (9)	0.95 (0.21-4.31)	0.95		

Values are n (%) unless otherwise indicated. Reference for HR is the VKA group.
Abbreviations as in Table 1.

TABLE 4 Patient Characteristics According to the Occurrence of Bleeding

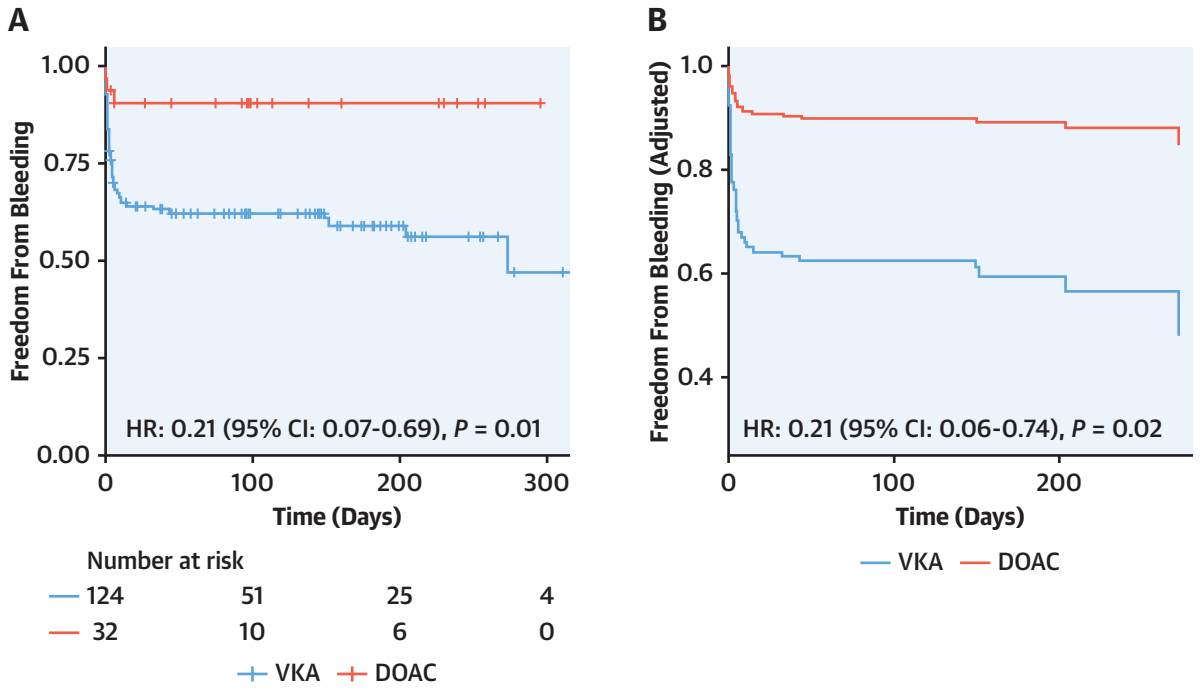
	Bleeding (n = 53)	No Bleeding (n = 103)	*P* Value
Clinical characteristics at baseline			
Age, y	66.32 ± 16.24	64.25 ± 19.64	0.68
Female	32 (60.4)	71 (68.9)	0.22
Body mass index, kg/m^2	24.98 ± 4.29	25.81 ± 6.35	0.34
COPD	8 (15.1)	17 (16.5)	0.64
Diabetes mellitus	17 (32.1)	11 (10.7)	<0.01
High blood pressure	22 (41.5)	42 (40.8)	0.60
eGFR <60 mL/min	36 (67.9)	51 (50.0)	0.06
eGFR <30 mL/min	15 (28.3)	13 (12.7)	0.03
Atrial fibrillation	35 (66.0)	67 (65.0)	0.99
Coronary artery disease	17 (32.1)	23 (22.3)	0.17
Previous cardiac surgery	50 (94.3)	96 (93.2)	1.00
EuroSCORE II	10.06 (3.84-13.56)	6.96 (3.80-12.26)	0.26
Echocardiographic findings at baseline			
LVEF, %	57.70 ± 11.05	56.80 ± 10.28	0.51
Mean mitral gradient, mm Hg	10.85 ± 5.64	10.68 ± 4.39	0.58
Mitral regurgitation ≥2/4	32 (60.4)	56 (54.4)	0.50
Left atrium area, cm^2	33.77 ± 13.03	46.59 ± 57.92	0.49
PASP, mm Hg	59.18 ± 14.96	54.21 ± 16.38	0.07
Tricuspid regurgitation ≥3/4	22 (41.5)	28 (27.2)	0.03
Procedural characteristics			
Type of procedure			0.02
Valve-in-valve	25 (47.2)	73 (70.9)	
Valve-in-ring	17 (32.1)	19 (18.4)	
Valve-in-MAC	11 (20.8)	11 (10.7)	
Sapien 3 prosthesis	44 (89.8)	94 (95.9)	0.48
Prosthesis size, mm			0.40
23	2 (3.8)	7 (6.8)	
26	23 (43.4)	41 (39.8)	
29	28 (52.8)	55 (53.4)	
Urgency			0.90
Elective	44 (83.0)	86 (83.5)	
Urgent	8 (15.1)	14 (13.6)	
Emergency	1 (1.9)	3 (2.9)	
Postdilatation	14 (26.9)	23 (22.8)	0.43
Need for second valve	3 (5.7)	11 (10.9)	0.43
Technical success (MVARC)	49 (94.2)	90 (90.0)	0.35
Conversion to surgery	0 (0.0)	0 (0.0)	—
Tamponade	0 (0.0)	0 (0.0)	—
New atrial fibrillation	3 (5.7)	3 (2.9)	0.34
Echocardiographic findings at discharge			
LVEF, %	55.60 ± 10.21	56.76 ± 10.50	0.65
Mean mitral gradient, mm Hg	6.24 ± 2.25	5.74 ± 2.31	0.13
Mitral regurgitation ≥2/4	12 (22.6)	17 (16.5)	0.47
Antithrombotic therapy at discharge			
Aspirin	34 (65.4)	51 (49.5)	0.20
VKA	50 (94.3)	74 (71.8)	0.01

Values are mean ± SD, n (%), or median (Q1-Q3).
Abbreviations as in Table 1.

be made to minimize the risk of bleeding events in these patients.

To the best of our knowledge, this study is the first to compare outcomes following TMVR based on anticoagulant treatment with DOAC or VKA. However, similar comparisons have been conducted in other populations, such as those with atrial fibrillation, TAVR, mechanical valve prosthesis, and

FIGURE 2 Kaplan-Meier Curves for Bleeding Events



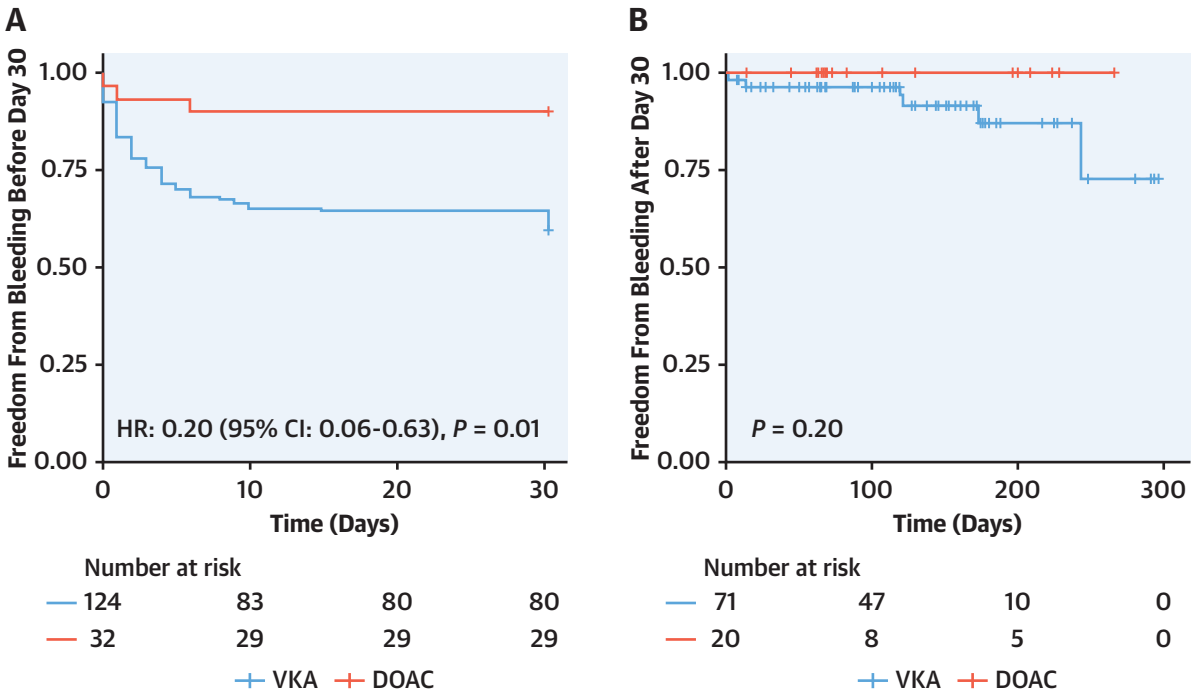
Kaplan-Meier curves displaying the survival without bleeding events over time. (A) Unadjusted Kaplan-Meier curve for bleeding events. (B) Adjusted Kaplan-Meier curve for bleeding Events. The multivariate Cox model confirmed a lower risk for bleeding events in patients receiving DOACs compared with those on VKAs. Abbreviations as in Figure 1.

biological valve prosthesis, yielding heterogeneous results.

In patients with atrial fibrillation without significant valve disease, previous studies have reported a decrease in bleeding events without a significant increase in thrombotic events[6-9] in patients receiving DOAC, similar to that observed in this study. It is worth noting that in these studies, there was a trend toward fewer thrombotic events with DOACs.

Although for patients undergoing TAVR, the current recommended regimen is single antiplatelet therapy,[5] 2 recent randomized trials have compared DOACs with VKAs in patients with other indications for anticoagulant therapy, the majority of them caused by the presence of atrial fibrillation. The ENVISAGE-TAVR AF (Edoxaban Compared to Standard Care After Heart Valve Replacement Using a Catheter in Patients With Atrial Fibrillation) trial,[19] which compared edoxaban with VKAs, found no significant difference between the 2 treatments, except for an increased risk of bleeding, particularly major bleeding of digestive origin, in patients treated with edoxaban. In the ATLANTIS (Anti-Thrombotic Strategy After Trans-Aortic Valve Implantation for Aortic Stenosis) trial,[20] which compared apixaban with VKAs, no significant differences were observed in bleeding or thrombotic events. We observed a significant difference in bleeding events between VKAs and DOACs in contrast to trials in TAVR populations. The potential causes that could explain the significant difference in bleeding complications in this study are as follows. First, patients in the VKA group systematically received bridging with heparin to reduce the risk of early valve thrombosis, whereas most patients with DOAC did not. Bridging therapy with heparin might have played a major role on the risk of bleeding in these patients. Importantly, no differences were observed regarding the risk of bleeding after 30 days between groups. This might be explained by a reduced risk of bleeding after day 30. Although the rate of heparin bridging was not reported in TAVR trials, in clinical practice, heparin bridging is only indicated in patients who are at high risk of ischemic events. Second, the patients

FIGURE 3 Landmark Kaplan-Meier Curves for Bleeding Events



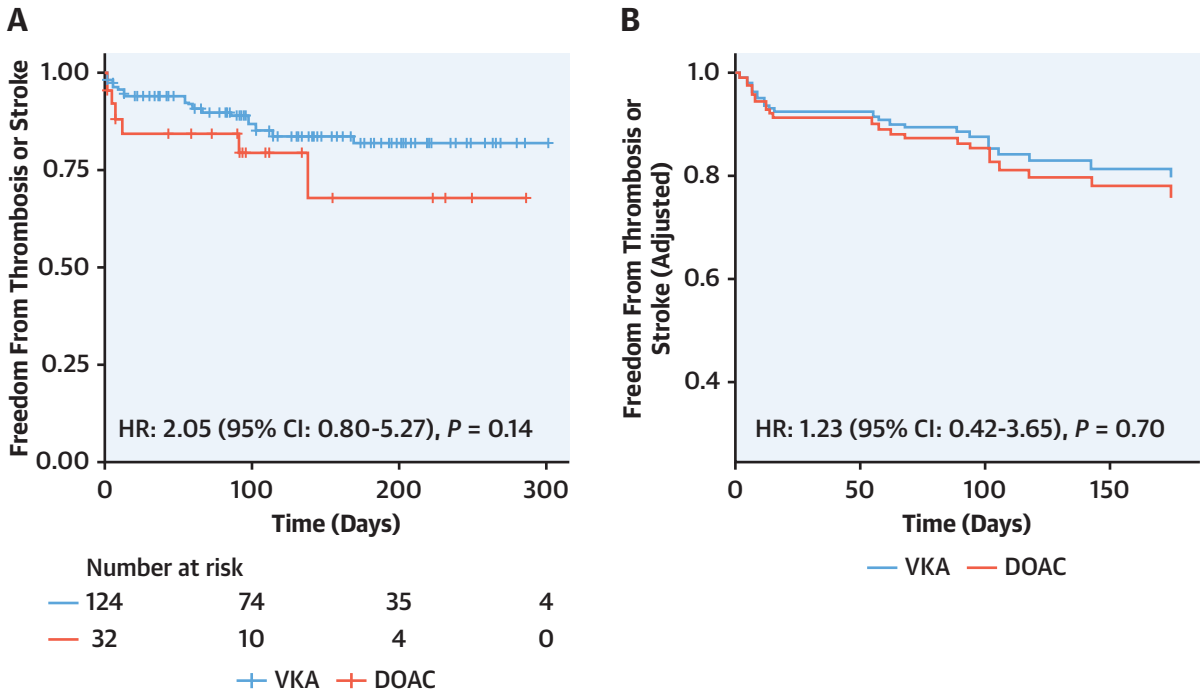
Kaplan-Meier curves for bleeding events before day 30 (A) and after 30 days (B). Kaplan-Meier curves demonstrate a lower bleeding risk in the DOAC group within the initial 30 days. However, after 30 days, the risk profiles between the 2 treatments become statistically nonsignificant. Abbreviations as in Figure 1.

included in this study were frail and comorbid, with a high risk of bleeding. Whereas the mean EuroSCORE II was 10% in our study, the mean risk scores (EuroSCORE II and STS) were 5% in both TAVR trials. Furthermore, patients considered to be at high risk of bleeding were excluded from the TAVR trials. Third, anticoagulation was initiated 3 to 6 hours after the procedure in this study, whereas in ENVISAGE TAVR AF and ATLANTIS trials, patients were randomized up to 7 days after TAVR and no patients with ongoing complications received anticoagulation therapy. Thus, these studies did not capture most periprocedural bleeding complications. Last, all bleeding events, both minor and major, were included in this study. This thorough approach distinguishes our study, because much of the existing TMVR literature predominantly focuses on major bleeding. Nevertheless, the bleeding rates observed in this study are consistent with those reported in the literature on TMVR.

A notable observation was the predominance of bleeding events during the early postprocedural period. Heparin bridging, universally acknowledged for its bleeding risk, might be even more pronounced in our cohort because of the specificities of the TMVR procedure and its inherent complications. Indeed, the heightened bleeding risk observed during the initial postoperative phase potentially underscores the perilous nature of the heparin bridging period. Although the overarching treatment protocol with VKAs necessitates heparin bridging, it is crucial to juxtapose this with DOACs, which do not mandate such a phase, thereby potentially showcasing a safer profile, at least in the immediate post procedural timeframe. The landmark analysis beyond 30 days did not reveal any substantial difference between DOACs and VKAs, which further emphasizes the critical period immediately following the procedure as especially risk-prone because of heparin bridging.[2,3,21,22]

After surgery, rivaroxaban was noninferior to warfarin in terms of bleeding and thrombotic events for patients with mitral bioprosthesis and atrial fibrillation in the late postoperative period in RIVER (RIvaroxaban for Valvular Heart diseasE and atRial

FIGURE 4 Kaplan-Meier Curves for Thrombotic Events

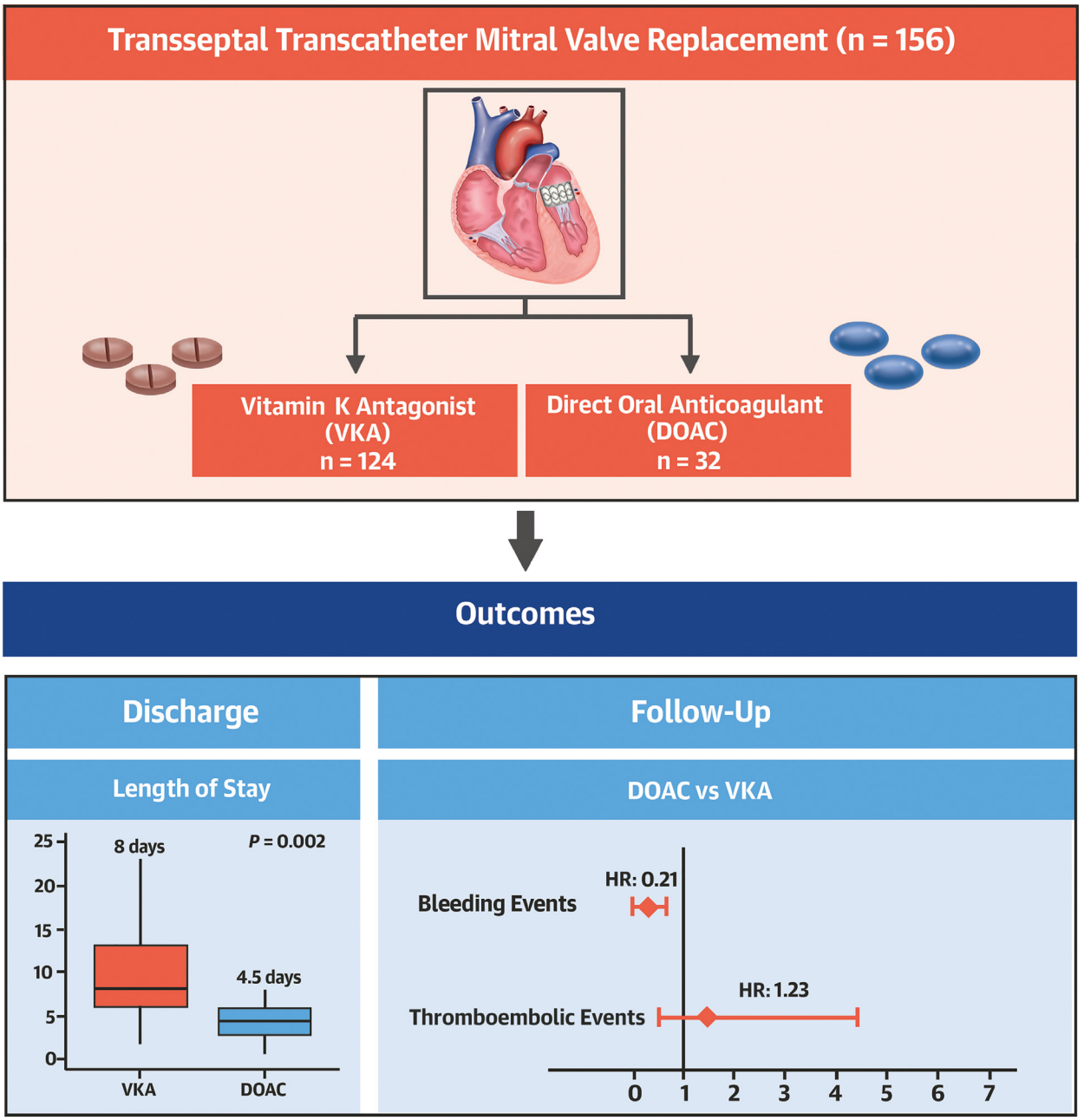


Unadjusted (A) and adjusted (B) Kaplan-Meier curves for thrombotic events. No statistically significant differences in thrombotic events were observed between the DOAC and VKA groups throughout the observation period. Abbreviations as in Figure 1.

Fibrillation Trial).[10] In addition, in the ENAVLE (Explore the Efficacy and Safety of Edoxaban in Patients after Heart Valve Repair or Bioprosthetic Valve Replacement) trial, edoxaban was noninferior to warfarin in the prevention of thrombotic events and major bleeding within the first 3 months after aortic or mitral bioprosthesis.[11] Nonetheless, it is important to note than in the ENAVLE study,[11] DOACs were introduced at a median of 8 days of heparin bridge therapy, whereas in the present study, DOACs were initiated within 24 hours after the procedure.

The incidence of valve thrombosis after TMVR varies significantly across studies, ranging from 0.5% to 14.4%.[2,3,23] This variability can be attributed to the differences in diagnostic modalities used to detect valve thrombosis. Studies that use systematic TEE and CT report higher incidence rates compared with studies relying solely on clinical and transthoracic echocardiography follow-up. Thrombi on prosthetic valves may form and dissolve intermittently, which could occasionally elude detection.[24] In the present study, under our standardized follow-up protocol, the rate of TEE and CT scans was similar for patients on both DOACs and VKAs. Although the incidence of early valve thrombosis was slightly higher in the DOAC group in the univariate analysis, this difference did not reach statistical significance after adjustment by potential confounding factors. Importantly, no increased risk of valve thrombosis has been reported in patients receiving DOACs, whether in the context of atrial fibrillation, TAVR, or surgical mitral bioprosthesis. However, in patients with mechanical valves and rheumatic valve disease, DOACs have been associated with reduced efficacy in preventing thrombotic events compared with VKAs. The recently published INVICTUS-VKA (INVestIgation of rheumatiC AF Treatment Using Vitamin K Antagonists, Rivaroxaban or Aspirin Studies, Non-Inferiority) study showed that VKAs were more effective in reducing the risk of thrombotic events and death in patients with rheumatic mitral stenosis and atrial fibrillation.[25] Interestingly, in the present study, no interaction was found between residual transmitral gradients and anticoagulant treatment in relation to outcomes, suggesting that the impact of anticoagulation therapy on thrombotic events was not significantly influenced by the severity of residual transmitral gradients.

CENTRAL ILLUSTRATION **Outcomes Regarding Anticoagulant Treatment After Transcatheter Mitral Valve Replacement**



El Bèze N, et al. J Am Coll Cardiol. 2024;83(2):334-346.

Study design, baseline characteristics, and key results of 156 transseptal transcatheter mitral valve replacements (TMVRs), of which 124 were treated with vitamin K antagonists (VKAs) and 32 with direct oral anticoagulants (DOACs). Key results highlight a reduction in bleeding risk and length of hospital stay for the DOAC group, with no significant differences in thrombotic events between the 2 groups.

STUDY LIMITATIONS. First, this is a single-center observational study, and thus, these results might not be generalized. Second, there was a difference in aspirin therapy and in procedure type between groups. However, the use of aspirin was not associated with an increased risk of thrombosis or bleeding, and the higher bleeding risk and longer length of stay persisted after adjustment for the type of procedure. Third, in this study, patients were censored at the 6-month visit. Outcomes may vary with extended follow-up. Nonetheless, at the 3 to 6 months visit, anticoagulation therapy was discontinued in patients without an indication for lifelong anticoagulation, and in those with indication for long-term anticoagulation, the therapy might be changed according to the responsible physician's preferences. Fourth, an effect-time bias cannot be excluded. Nonetheless, two-thirds of patients underwent TMVR after the implementation of main technical improvements in our institution. Moreover, the time-dependent treatment allocation helps to minimize the risk of unmeasured confounding factors related to treatment indication.

CONCLUSIONS

Patients receiving DOACs after TMVR had a lower risk of bleeding and shorter length of hospital stay compared with those receiving VKAs, without a significant increase in the risk of thrombotic events. Nonetheless, these findings should be considered as hypothesis generating and should be confirmed in randomized trials.

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Dr Himbert is a proctor for Edwards Lifesciences and Abbott. Dr Brochet is a proctor for Abbott. Prof Urena has received speaker fees from Edwards Lifesciences and Medtronic. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Treatment with a target-specific DOAC after TMVR is associated with a lower risk of bleeding than anticoagulation with a VKA without a significant increase in the risk of thrombotic events.

TRANSLATIONAL OUTLOOK: Large randomized trials are needed to confirm these findings and guide selection of the optimum antithrombotic treatment strategy for patients undergoing TMVR.

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KEY WORDS anticoagulation, direct oral anticoagulant, TMVR, vitamin K antagonist

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