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ORIGINAL RESEARCH

Direct Oral Anticoagulants Versus Vitamin K Antagonists After Mitral Valve Transcatheter Edge-to-Edge Repair in Patients With Atrial Fibrillation: A Single-Center Observational Study

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BACKGROUND: Mitral valve transcatheter edge-to-edge repair (M-TEER) has emerged as a viable therapy option in patients with severe mitral regurgitation and high surgical risk. Although atrial fibrillation is common among patients undergoing M-TEER, the optimal anticoagulatory treatment after the intervention is unknown.

METHODS: A single-center retrospective observational analysis was conducted using data from the M-TEER registry at the University Hospital Cologne collected from 2019 untill 2021 including patients undergoing M-TEER between November 2012 and April 2019. Patients with atrial fibrillation receiving consistent anticoagulation following M-TEER were categorized into a direct oral anticoagulant or a vitamin K antagonist (VKA) group. The primary end point was a composite of ischemic cerebrovascular and bleeding events. Additionally, overall survival was assessed.

RESULTS: Among 613 patients undergoing M-TEER, 206 met the inclusion criteria, with 61 receiving direct oral anticoagulants and 145 receiving VKAs. After a median follow-up of 833 (interquartile range, 355–1271) days, the incidence of the composite primary end point did not differ between direct oral anticoagulant and VKA groups (hazard ratio [HR], 0.51 [95% CI, 0.23–1.12]; *P*=0.07). Similarly, rates of ischemic cerebrovascular events and bleeding events were similar between groups. However, the overall mortality rate was higher in the VKA group (HR, 2.56 [95% CI, 1.54–4.26]; *P*=0.002). In the multivariable analysis, oral anticoagulation with a VKA was an independent predictor for death (adjusted HR, 2.23 [95% CI, 1.08–5.06]; *P*=0.03).

CONCLUSIONS: Our findings suggest that direct oral anticoagulants may offer comparable efficacy and safety to VKAs in preventing thromboembolic events following M-TEER in patients with atrial fibrillation. Further randomized trials are needed to confirm these results and establish optimal anticoagulation strategies in this patient population.

Key Words: bleeding events ■ direct oral anticoagulants ■ mitral regurgitation ■ mitral valve transcatheter edge-to-edge repair ■ thromboembolic events ■ vitamin K antagonists

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CLINICAL PERSPECTIVE

What Is New?

- This study provides long-term data comparing direct oral anticoagulants (DOACs) to vitamin K antagonists in patients with atrial fibrillation after mitral valve transcatheter edge-to-edge repair.
- It shows no significant difference in thromboembolic and bleeding events between DOAC and vitamin K antagonist groups.
- Overall survival was higher in the DOAC group, highlighting potential advantages over vitamin K antagonists.

What Are the Clinical Implications?

- DOACs may be a safe and effective alternative to vitamin K antagonists in patients undergoing mitral valve transcatheter edge-to-edge repair with atrial fibrillation.
- There is a need for randomized trials to confirm the noninferiority of DOACs in this setting.
- Clinicians should consider renal function and other comorbidities when choosing an anticoagulation strategy following mitral valve transcatheter edge-to-edge repair.

Nonstandard Abbreviations and Acronyms

AF	atrial fibrillation
APT	antiplatelet therapy
ARISTOTLE	Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation
COAPT	Clinical Outcomes Assessment of the MitraClip Percutaneous Therapy for Extremely High Surgical Risk Patients
DOAC	direct oral anticoagulant
ENGAGE TIMI-48 AF	Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48
INVICTUS	Investigation of Rheumatic AF Treatment Using Vitamin K Antagonists, Rivaroxaban or Aspirin Studies
MR	mitral regurgitation
M-TEER	mitral valve transcatheter edge-to-edge repair
MV	mitral valve
RE-LY	Randomized Evaluation of Long-Term Anticoagulation Therapy
RIVER	Rivaroxaban for Valvular Heart Disease and Atrial Fibrillation
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
TPG	transmitral pressure gradient
VHD	valvular heart disease
VKA	vitamin K antagonist

Severe symptomatic mitral regurgitation (MR) is a prevalent valvular heart disease (VHD) linked with an adverse prognosis if left untreated.[1] In this context, mitral valve (MV) transcatheter edge-to-edge repair (M-TEER) has emerged as a pivotal therapeutic strategy for the treatment of MR to mitigate symptoms and improve outcomes, especially in patients with high surgical risk or ineligible for conventional surgery.[2–6] Since MR begets atrial fibrillation (AF) and vice versa,[7–9] patients scheduled for M-TEER often present with AF,[10] further complicating their clinical course and increasing the chances of heart failure and cardiac death.[11] Due to the heightened risk of ischemic strokes and systemic embolism linked to AF, effective oral anticoagulation (OAC) remains crucial to prevent thromboembolic events,[12] particularly in this frequently older and frail patient population.[13]

Over the past 2 decades, direct oral anticoagulants (DOACs) progressively replaced vitamin K antagonists (VKAs) in managing nonvalvular AF due to their established efficacy, reduced risk of major bleeding, and predictable dosing.[14–18] However, concerns persist regarding the role of DOACs in patients undergoing M-TEER, particularly considering potential occurrence of a mitral stenosis after edge-to-edge therapy, which affects ≈25% of patients undergoing M-TEER.[19] Since

thrombus formation in the presence of mitral stenosis is triggered by different factors than in patients with nonvalvular AF, the use of DOACs in this scenario is debatable.[20,21] Despite the emerge of M-TEER and the high incidence of AF in this cohort, randomized data comparing DOACs to VKAs in this distinct scenario are lacking. So far, current guidelines do not provide specific recommendations for the anticoagulant treatment following M-TEER,[4,5] resulting in varied practices across centers.[22] Consequently, many centers still favor VKAs,[3,23] emphasizing the paucity of data regarding the efficacy and safety of DOACs after M-TEER.

Therefore, this study aims to investigate the efficacy and safety profiles of DOACs in direct comparison to VKAs among patients who underwent M-TEER in a single-center retrospective observational analysis.

METHODS

Study Design

This single-center, retrospective observational study was based on data from the M-TEER registry from the University Hospital Cologne in Germany collected from 2019 to 2021. Patients undergoing M-TEER between November 2012 and April 2019 were identified. Before the procedure, all patients were discussed interdisciplinarily by a heart team consisting of an interventional cardiologist, a cardiothoracic surgeon, and an anesthesiologist. The date of the M-TEER procedure was defined as the index date for each patient. M-TEER was performed as previously described under transesophageal echocardiographic and fluoroscopic guidance[24] with either a MitraClip (Abbott Vascular, Abbott Park, IL) or PASCAL (Edwards Lifesciences, Irvine, CA) device. The choice of the implanted device was at the discretion of the operator.

This study primarily tracked the anticoagulation regimens in patients requiring OAC following the procedure due to AF, that was diagnosed before the procedure or during M-TEER hospitalization. Patients adhering to a consistent anticoagulatory treatment throughout the follow-up period were identified and categorized into 2 groups for analysis: 1 receiving DOACs (apixaban, edoxaban, rivaroxaban, dabigatran) and the other receiving VKAs (phenprocoumon). Consistent OAC was defined as maintaining the same type of OAC therapy (either DOAC or VKA) from discharge through each documented follow-up in our outpatient clinic or during any subsequent hospitalizations. Patients in the DOAC group were permitted to switch between different DOACs.

Patients requiring OAC due to indications other than AF (eg, mechanical prosthesis, pulmonary embolism, deep vein thrombosis) were excluded. Patients receiving simultaneous antiplatelet therapy (APT) were excluded, as APT could influence stroke and bleeding risks, potentially acting as a confounder in the analysis.

The study was approved by the local Ethics Committee of the University of Cologne (14–116). Patient consent was waived due to the retrospective character of the study. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Follow-Up

Follow-up appointments were routinely scheduled at 1 month and 12 months after the M-TEER procedure, involving both clinical and echocardiographic assessment. Retrospective screening of patients' digital records at the University Hospital Cologne was conducted to identify additional patient visits. Supplementary telephone inquiries were used to ensure comprehensive follow-up data for patients who had not recently attended the outpatient clinic. Data regarding occurrences of study end points and the type of anticoagulatory treatment at each instance were documented.

End Points

The study end point was a composite of ischemic cerebrovascular (ischemic stroke, transient ischemic attack) and bleeding events (cranial and gastrointestinal). Moreover, all-cause death was assessed.

Statistical Analysis

Data analysis entailed presenting continuous variables as means±SDs, while categorical variables were summarized using counts and percentages. The D'Agostino–Pearson test assessed the normality of the data. Student's *t* tests were applied for normally distributed continuous variables, with Mann–Whitney *U* tests used otherwise. Fisher's exact test was used for dichotomous variables. Kaplan–Meier estimators, along with the Mantel–Cox test for *P* value and log-rank test for hazard ratio (HR), were used for the outcome analysis. A univariable Cox proportional hazards analysis was conducted to assess the association between death and individual covariates. Variables with *P* values <0.1 in the univariable analysis were then incorporated into the multivariable model. Data processing and statistical analyses were conducted using Microsoft Excel version 16.80 for Mac (Microsoft Corporation, Redmond, WA) and Prism version 9.1.0 for Mac (GraphPad Software, San Diego, CA). A *P* value of <0.05 was considered statistically significant.

RESULTS

Study Cohort

Between November 2012 and April 2019, 613 patients underwent M-TEER for symptomatic MR in the

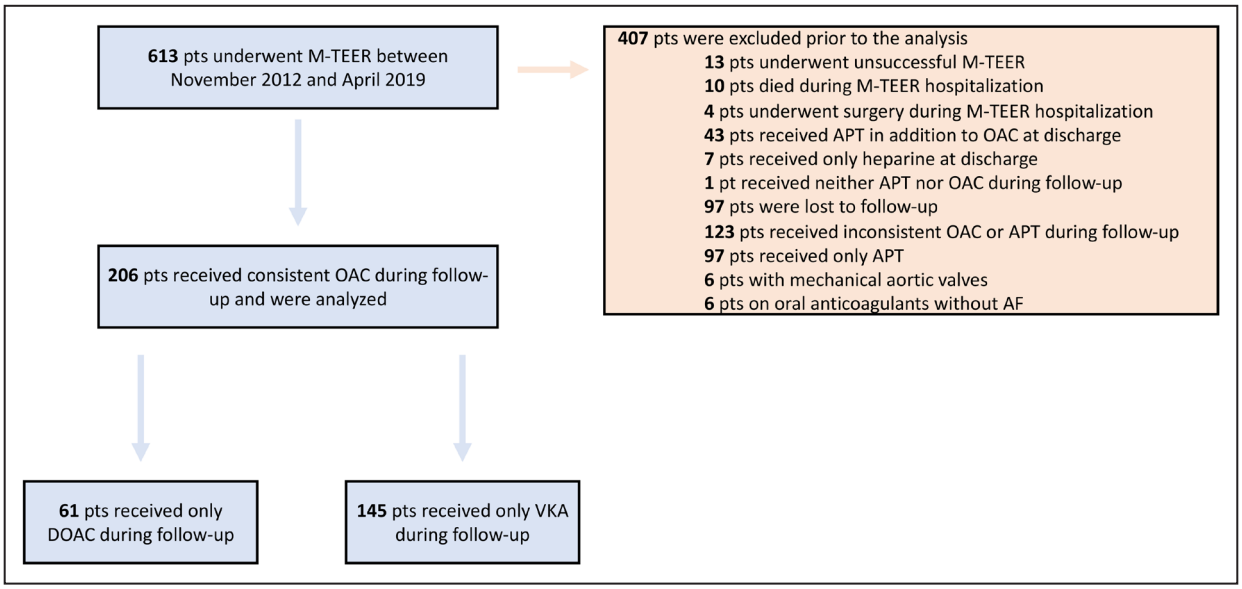

Figure 1. Patient allocation and analysis.
APT indicates antiplatelet therapy; DOAC, direct oral anticoagulant; M-TEER, mitral valve edge-to-edge repair; OAC, oral anticoagulation; Pts, patients.; and VKA, vitamin K antagonist.

University Hospital Cologne. Figure 1 shows the flowchart of the study cohort.

Of those 613 treated patients, 206 (34%) patients received consistent anticoagulatory treatment regime due to AF throughout the follow-up and were therefore included in the final analysis: Sixty-one of 206 (30%) patients were treated with a DOAC, and 145 of 206 (70%) patients were treated with a VKA.

Of note, 407 of 613 (66%) patients were excluded before the analysis. A total of 123 of 613 (20%) patients were excluded because of inconsistent OAC or APT during the follow-up period. In this group, 45 of 613 (7%) patients were excluded since a crossover between OAC regimens during follow-up occurred (Figure 2). There was a switch from VKA to DOAC in 36 of 613 (6%) patients, and 9 of 613 (1%) patients switched from DOAC to VKA.

Ninety-seven of 613 (16%) patients were lost to follow-up since the regular scheduled follow-up was not noticed or patients refused to report follow-up data. Furthermore, 97 of 613 (16%) patients received APT (without any switch to OAC) after M-TEER presenting without any indication or with contraindications for OAC and were therefore excluded from the final analysis. Additionally, 43 of 613 (7%) patients were not included because they received a combination of OAC and APT.

Despite maintaining consistent OAC with a VKA, 6 of 613 (1%) patients were excluded due to the presence of a mechanical aortic valve, indicating an inherently increased risk of thromboembolic events. Of note, 6 of

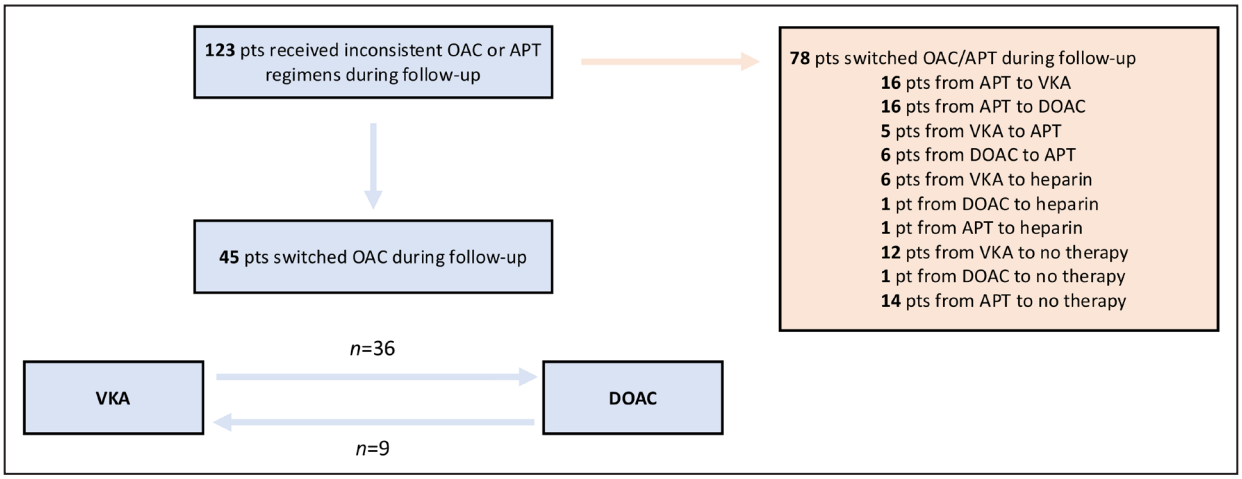

Figure 2. Crossover between OAC regimens.
APT indicates antiplatelet therapy; DOAC, direct oral anticoagulant; OAC, oral anticoagulation; and VKA, vitamin K antagonist.

Table 1. Baseline Characteristics

	VKA (n=145)	DOAC (n=61)	*P* value
Age, y	78.6±7.9	78.4±7.4	0.74
Female sex	65 (45)	30 (49)	0.65
Hypertension	100 (69)	45 (74)	0.62
Type 2 diabetes	37 (26)	13 (21)	0.60
Coronary artery disease	74 (51)	29 (48)	0.76
Prior heart surgery	34 (23)	12 (20)	0.59
Chronic lung disease	20 (14)	6 (10)	0.50
Chronic kidney disease	99 (68)	28 (46)	0.003
Atrial fibrillation	142 (98)	57 (93)	0.20
Peripheral vascular disease	11 (8)	5 (8)	1.0
Prior ischemic cerebrovascular event			
Stroke	22 (15)	13 (21)	0.31
Transient ischemic attack	3 (2)	1 (2)	1.0
Prior bleeding			
Cerebral	0	1 (2)	0.30
Gastrointestinal	6 (4)	1 (2)	0.68
Other	1 (1)	1 (2)	0.51
CHA_2DS_2-VASc score	4.6±1.5	4.6±1.5	0.84
HAS-BLED score	2.6±0.9	2.6±1.1	0.79
NYHA functional class			
II	8 (6)	6 (10)	0.36
III	120 (83)	49 (80)	0.69
IV	17 (12)	6 (10)	0.81
LVEF, % (n=169)	45.7±15.4	49.0±14.3	0.25
MR pathogenesis (n=166)			
Degenerative	56/121 (46)	25/45 (56)	0.23
Functional	53/121 (44)	18/45 (40)	0.30
Mixed	12/121 (10)	2/45 (5)	0.36

Values are presented as mean±SD. Categorical data are given as n (%). Chronic kidney disease was defined as a glomerular filtration rate<60 mL/min. DOAC indicates direct oral anticoagulant; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; NYHA, New York Heart Association; and VKA, vitamin K antagonist.

613 (1%) patients were not included in the final analysis as they were prescribed OAC for other indications than AF. Further reasons for exclusion in 35 of 613 (6%) patients are described in Figure 1.

Baseline Characteristics

Baseline characteristics are summarized in Table 1. Overall mean age was 78.6±7.7 years (DOAC group, 78.4±7.4 years; VKA group, 78.6±7.9 years; *P*=0.74). The CHA_2DS_2-VASc (DOAC group, 4.6±1.5; VKA group, 4.6±1.5; *P*=0.84) and HAS-BLED score (DOAC group, 2.6±1.1; VKA group, 2.6±0.9; *P*=0.79) was equal in both groups. There was no difference regarding left ventricular ejection fraction between the study groups (DOAC group, 49.0±14.3%; VKA group, 45.7±15.4%; *P*=0.25). Chronic kidney disease (defined as glomerular filtration rate <60 mL/min) was more common in the VKA group (DOAC group, 28/61 [46%] patients; VKA group, 99/145 [68%] patients; *P*=0.003). There were 4 patients in the DOAC group and 3 patients in the VKA group initially diagnosed with AF during the M-TEER hospitalization.

Postprocedural Echocardiographic Parameters

After M-TEER, there were no differences between both groups regarding echocardiographic parameters including the transmitral pressure gradient (TPG; DOAC group, 3.7±1.6 mm Hg; VKA group, 4.2±1.8 mm Hg; *P*=0.07). Furthermore, the same number of patients suffered from an elevated TPG >5 mm Hg in both groups (DOAC group, 8/61 [13%] patients; VKA group, 31/144 [23%] patients; *P*=0.18). Postprocedural echocardiographic parameters are shown in Table 2.

Outcomes

After a median follow-up of 833 days (interquartile range, 355–1271 days), the composite study end point of an ischemic stroke, transient ischemic attack, or cranial or gastrointestinal bleeding event occurred in 14 of 61 (23%) patients in the DOAC group and in 13 of 145 (9%) in the VKA group. The Kaplan–Meier analysis is shown in Figure 3 and revealed no difference between both anticoagulants regarding the composite study end point (HR, 0.51 [95% CI, 0.23–1.12]; *P*=0.07). An ischemic cerebrovascular event occurred in 7 of 61 (11%) patients receiving a DOAC and in 5 of 145 (3%) patients receiving a VKA. Of note, there was no difference regarding the Kaplan–Meier estimators (HR, 0.35 [95% CI, 0.10–1.16]; *P*=0.06).

Cranial or gastrointestinal bleeding was seen in 9 of 61 (15%) patients in the DOAC group and in 9 of 145 (6%) patients in the VKA group resulting in equal outcomes in the Kaplan–Meier estimators (HR, 0.61 [95% CI, 0.24–1.59]; *P*=0.29).

Table 2. Echocardiographic Parameters at Discharge

	VKA (n=145)	DOAC (n=61)	*P* value
LVEF, % (n=171)	45.2±16.0	46.8±16.6	0.55
TPG, mm Hg (n=205)	4.2±1.8	3.7±1.6	0.07
TPG >5 mm Hg (n=205)	31/144 (23)	8/61 (13)	0.18
Residual MR severity			
I	72 (50)	28 (46)	0.65
II	56 (38)	31 (51)	0.12
III	17 (12)	2 (3)	0.07

Values are presented as mean±SD. Categorical data are given as n (%). DOAC indicates direct oral anticoagulant; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; TPG, transmitral pressure gradient; and VKA, vitamin K antagonist.

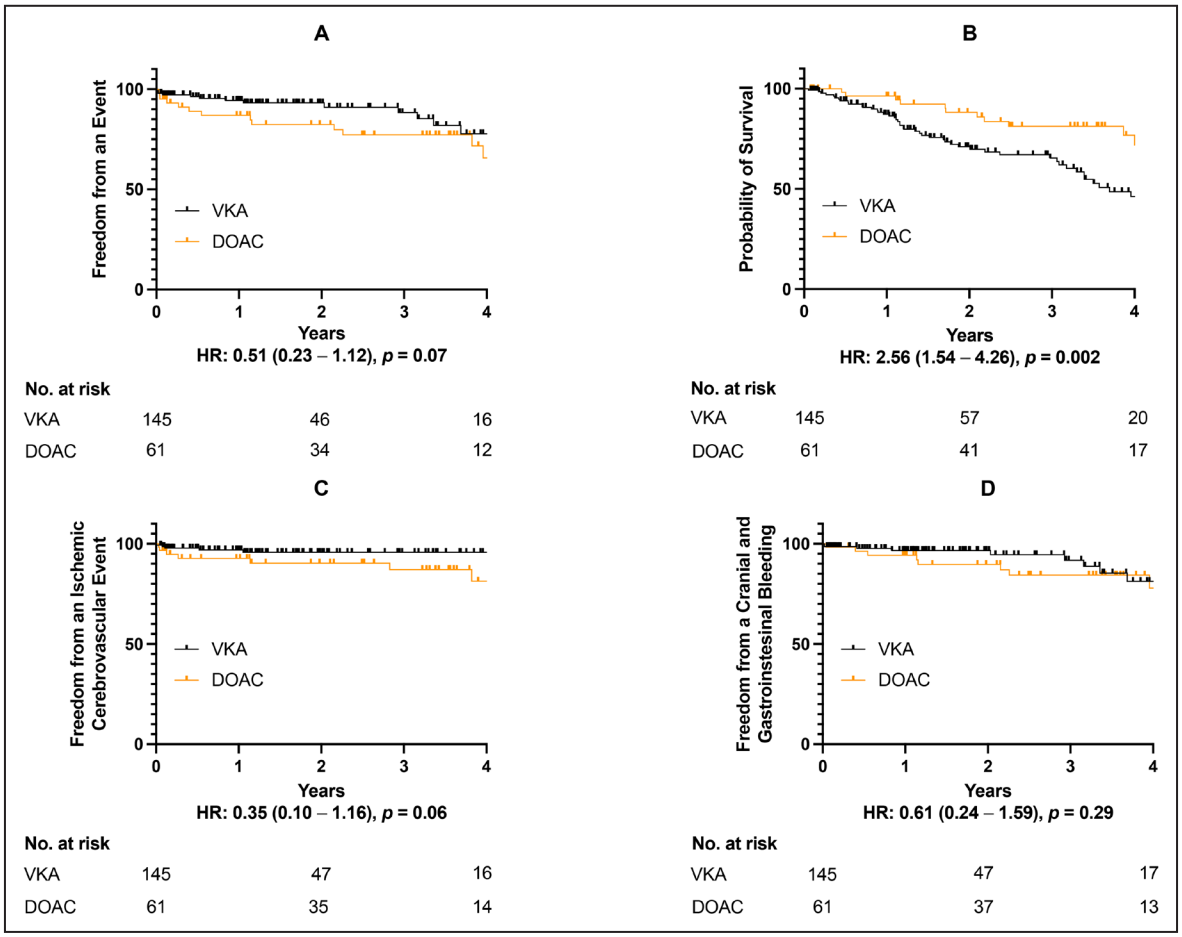

Figure 3. The graphs show Kaplan–Meier estimators for freedom from (A) an event (ischemic stroke, transient ischemic attack, cranial and gastrointestinal bleeding), (B) death, (C) an ischemic cerebrovascular event, and (D) cranial and gastrointestinal bleeding.
DOAC indicates direct oral anticoagulant; HR, hazard ratio; and VKA, vitamin K antagonist.

However, overall survival was worse in patients receiving a VKA (DOAC group, 12/61 [20%] patients died; VKA group, 51/145 [35%] patients died; HR, 2.56 [95% CI, 1.54–4.26]; *P*=0.002). Clinical outcomes are shown in Table 3.

In univariable analysis (Table 4), VKA therapy, type 2 diabetes, coronary artery disease, and elevated TPG were associated with an increased risk of death. In multivariable analysis (Table 4), the strongest predictors of death were coronary artery disease (adjusted HR, 1.89 [95% CI, 1.34–4.74]; *P*=0.005), postprocedural TPG (adjusted HR, 1.24 [95% CI, 1.10–1.44]; *P*=0.005), and VKA therapy (adjusted HR, 2.23 [95% CI, 1.08–5.06]; *P*=0.03).

Outcomes in Patients With Elevated Transmitral Pressure Gradients After M-TEER

Thirty-nine patients had an elevated TPG (>5 mm Hg) after M-TEER in our cohort. In this subgroup, the composite study end point occurred in 1 of 8 (13%) patients in the DOAC group and in 4 of 31 (13%) patients in the VKA group. Clinical outcomes of this subgroup are summarized in Table 5.

Table 3. Primary and Secondary Outcomes

	VKA (n=145)	DOAC (n=61)	Hazard ratio	*P* value
Composite primary end point: ischemic stroke, transient ischemic attack, cranial or gastrointestinal bleeding	13 (9)	14 (23)	0.51	0.07
Secondary end points				
Ischemic cerebrovascular event	5 (3)	7 (11)	0.35	0.06
Ischemic stroke	5 (3)	3 (5)		
Transient ischemic attack	0	4 (7)		
Bleeding event	9 (6)	9 (15)	0.61	0.29
Cranial bleeding	3 (2)	1 (2)		
Gastrointestinal bleeding	6 (4)	8 (13)		

Categorical data are given as n (%). DOAC indicates direct oral anticoagulant; and VKA, vitamin K antagonist.

Table 4. Cox Proportional Hazard Models for Death

	Univariable analysis			Multivariable analysis		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Age, y	1.00	0.97–1.04	0.96			
Female sex	0.60	0.35–1.00	0.06	0.73	0.37–1.39	0.34
Vitamin K antagonist	2.59	1.42–5.10	0.003	2.23	1.08–5.06	0.03
Hypertension	1.06	0.62–1.91	0.83			
Type 2 diabetes	2.00	1.18–3.30	0.008	1.47	0.80–2.65	0.21
Coronary artery disease	2.3	1.38–3.94	0.002	1.89	1.34–4.74	0.005
Prior heart surgery	1.17	0.63–2.03	0.60			
Chronic lung disease	1.63	0.75–3.16	0.18			
Chronic kidney disease	1.68	1.00–2.90	0.05	1.89	1.01–3.69	0.05
Peripheral vascular disease	1.77	0.73–3.64	0.16			
Postprocedural LVEF, % (n=176)	0.98	0.97–1.00	0.07	0.98	0.96–1.00	0.12
Postprocedural TPG, mm Hg (n=204)	1.17	1.03–1.32	0.017	1.24	1.10–1.44	0.005

Variables with a *P* value of <0.1 in the univariable analysis were included in the multivariable analysis. HR indicates hazard ratio; LVEF, left ventricular ejection fraction; and TPG, transmitral pressure gradient.

DISCUSSION

Despite M-TEER becoming a widely accepted treatment for both degenerative and functional MR, especially in patients with high surgical risk, the optimal OAC strategy for preventing thromboembolic and bleeding events remains a topic of controversial debate. Our study contributes to this discussion by being 1 of the first to offer long-term data comparing the effectiveness and safety of DOACs and VKAs. The main findings of our study are as follows:

- Despite missing recommendations in the current guidelines and certain persisting concerns, many patients received DOACs after M-TEER.
- Patients treated with DOACs and VKAs have comparable rates of thromboembolic and bleeding events after M-TEER.
- Overall survival was worse in the VKA group.

Table 5. Primary and Secondary Outcomes in Patients With Elevated Transmitral Pressure Gradients After M-TEER

	VKA (n=31)	DOAC (n=8)
Composite primary end point: ischemic stroke, transient ischemic attack, cranial or gastrointestinal bleeding	4 (13)	1 (13)
Secondary end points		
Ischemic cerebrovascular event	3 (10)	0
Ischemic stroke	3 (10)	0
Transient ischemic attack	0	0
Bleeding event	1 (3)	1 (13)
Cranial bleeding	0	0
Gastrointestinal bleeding	1 (3)	1 (13)

Categorical data are given as n (%). DOAC indicates direct oral anticoagulant; and VKA, vitamin K antagonist.

High Number of Patients Treated With DOACs

There is still a lack of evidence regarding which anticoagulatory treatment after M-TEER should be preferred in patients with AF. Therefore, the guidelines of the European Society of Cardiology and the American Heart Association do not provide any specific recommendation whether DOACs or VKAs should be used in this patient subset. In our study, 30% of the patients receiving consistent OAC throughout the follow-up were treated with DOACs. This finding is in line with findings from the COAPT (Clinical Outcomes Assessment of the MitraClip Percutaneous Therapy for Extremely High Surgical Risk Patients) trial, in which 42 of 120 (35%) patients on OAC therapy received DOACs 1 year after the MitraClip procedure.[3] Of note, in another trial by Mentias and colleagues comparing the efficacy and safety of DOACs and VKAs in patients with surgical or transcatheter MV repair and AF, 491 of 1178 (42%) patients were treated with DOACs.[25]

Comparable Thromboembolic and Bleeding Events in the DOAC and VKA Groups

Because of their favorable safety profile, proven efficacy and substantial impact on patients' quality of life, DOACs have replaced VKAs as the standard anticoagulatory

therapy in nonvalvular AF. In the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial led by Granger and colleagues, which included over 18 000 patients, apixaban demonstrated superiority over the VKA warfarin in preventing stroke or systemic embolism, while also resulting in fewer bleeding events and improved overall survival among patients receiving apixaban.[16]

However, data on the efficacy of DOACs after M-TEER in patients with an indication for OAC is scarce. Our study is the first to deliver data on the performance DOAC in this context. The occurrence of the composite primary end point of ischemic stroke, transient ischemic attack, and cerebral and gastrointestinal bleeding events in the DOAC group was comparable to the VKA group (HR, 0.51 [95% CI, 0.23–1.12]; *P*=0.07). Although we could not detect a superiority of DOACs as shown in the ARISTOTLE trial, our retrospective observation supports the hypothesis that DOACs might be noninferior to VKAs after M-TEER in patients with an indication for OAC due to AF. Our analysis showed a numerically higher occurrence of the primary end point in the DOAC group. However, given the sample size of our study, these results should be considered hypothesis generating only, and our findings need validation in larger randomized controlled trials. Since our analysis excluded patients receiving OAC for indications other than AF, no conclusions can be drawn regarding the efficacy and safety of DOACs and VKAs for this subset of patients after M-TEER.

Valvular and Nonvalvular AF

There are still ongoing discussions whether VHD increases the thromboembolic risk in patients with AF and whether this patient subset should therefore be treated with VKAs. As there was heterogeneity regarding the inclusion of patients with VHD in the phase 3 studies ARISTOTLE (apixaban), ENGAGE TIMI-48 AF (Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48; edoxaban), 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; rivaroxaban), and RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy; pradaxa), data are limited on the performance of DOACs in this patient subset.[15–18] For example, patients with relevant VHD were excluded in the RE-LY trial.[15] Notably, ARISTOTLE and ENGAGE AF-TIMI 48 were unique, including patients with bioprosthetic valves.[16,17] In a subanalysis of the ENGAGE TIMI-48 AF trial comparing the DOAC edoxaban with warfarin in patients with VHD, edoxaban was as effective as warfarin in preventing strokes, but led to fewer bleedings.[26] In the recently published randomized RIVER (Rivaroxaban for Valvular Heart Disease and Atrial Fibrillation) trial by Guimarães and colleagues investigating the effects of rivaroxaban in patients with bioprosthetic MVs and AF, rivaroxaban was noninferior to VKAs regarding the primary outcome of death, cardiovascular events and major bleedings.[27]

While these conclusions may have limited applicability to patients undergoing M-TEER, both trials highlight that the category of valvular AF, for which DOACs are not recommended due to their suboptimal efficacy compared with VKAs, should be narrowed down to patients with significant mitral stenosis or mechanical heart valves.[28] These conditions are associated with distinct mechanisms of thrombus formation.[20,21] So far, there is no evidence that bioprosthetic valves or valve repairs increase the thromboembolic risk compared with the risk triggered by AF alone and, additionally, that the performance of DOACs is different from those of VKAs in this context.[21] Therefore, patients undergoing M-TEER should be classified as having nonvalvular AF, which is underlined by our findings, if no elevated TPG after M-TEER occurs.

Transmitral Pressure Gradient

A significant concern after M-TEER is the potential increase in TPG, as MV stenosis is known to elevate the risk of thrombus formation in the left atrium, particularly when accompanied by AF. Current guidelines from the European Society of Cardiology and the American Heart Association advocate for the use of VKAs in cases of relevant mitral stenosis due to this risk, and therefore, DOACs are not approved in this patient subset. The randomized INVICTUS (Investigation of Rheumatic AF Treatment Using Vitamin K Antagonists, Rivaroxaban or Aspirin Studies) trial led by Connolly and colleagues comparing the efficacy and safety of DOACs to VKAs in patients with rheumatic mitral stenosis with an MV orifice area of <2 cm^2, VKAs led to a lower rate of cardiovascular events and improved survival.[29] However, data are lacking regarding whether DOACs can be as effective as VKAs in the context of elevated TPG after M-TEER.

In our study, only a minority of 39 patients experienced a significant rise in TPG. Among those treated with DOACs to prevent thromboembolic events, there were 8 patients with a TPG >5 mm Hg. However, no incidents of stroke or transient ischemic attack were reported. Furthermore, the occurrence of the composite primary end point was comparable to the VKA group. However, due to this small subgroup analysis, further randomized trials are warranted.

Reduced Survival Among Patients Treated With VKAs

Our study observed that patients treated with VKAs had lower overall survival rates compared with those receiving DOACs after M-TEER (HR, 2.56 [95% CI,

1.54–4.26]; *P*=0.002) contradicting findings from the aforementioned published study by Mentias and colleagues.[25] They assessed the efficacy and safety of DOACs compared with VKAs in a heterogeneous study cohort with previous MV repair or bioprosthetic valves.[25] In the MV repair group including patients after surgical MV repair and M-TEER, there were no differences after propensity score matching regarding overall survival between DOACs and VKAs.[25]

In the multivariable analysis, VKA therapy was independently associated with an increased mortality rate (adjusted HR, 2.23 [95% CI, 1.08–5.06]; *P*=0.03).

First, the difficulty in maintaining a stable therapeutic range with VKAs may increase risks related to both subtherapeutic (thromboembolic) and supratherapeutic (bleeding) international normalized ratio levels, potentially leading to complications that indirectly impact overall survival without affecting stroke or bleeding rates specifically.

Additionally, VKAs are associated with accelerated vascular calcification,[30] which could explain the observed association between VKA therapy and death. This vascular calcification risk may be especially relevant in patients already at high cardiovascular risk, such as those undergoing M-TEER.

In our multivariable analysis, postprocedural TPG was an independent predictor of death (adjusted HR, 1.24 [95% CI, 1.10–1.44]; *P*=0.005) and, additionally, trended to be higher in the VKA group without reaching statistical significance (TPG: DOAC group. 3.7±1.6 mm Hg; VKA group, 4.2±1.8 mm Hg; *P*=0.07). Patients with elevated TPG may be at increased risk for progressive mitral stenosis and left atrial pressure overload, leading to adverse outcomes[31] not directly related to stroke or bleeding events.

Together, these factors may contribute to the higher mortality rate observed among VKA-treated patients, suggesting that the choice of anticoagulant may carry implications beyond direct thromboembolic or bleeding risks.

Limitations

This study has several limitations. Despite achieving well-balanced baseline characteristics, this was a nonrandomized retrospective study with all its inherent shortcomings. Due to a certain number of patients lost to follow-up, some thromboembolic and bleeding events might have been undetected. Of note, we included patients in the DOAC group switching from one DOAC to another; hence, drawing definitive conclusions regarding the thromboembolic and bleeding risk associated with specific DOACs would be premature.

CONCLUSIONS

Our study addresses the critical question of optimal OAC following M-TEER. Despite the absence of specific guidelines, a substantial proportion of patients received DOACs following M-TEER. Our findings demonstrate comparable rates of thromboembolic and bleeding events between patients treated with DOACs and VKAs, suggesting noninferiority of DOACs in this context. Notably, overall survival was superior in patients receiving DOACs. VKA therapy was independently associated with worse overall survival. Despite these insights, our study has inherent limitations as a retrospective, hypothesis-generating analysis, warranting further randomized trials to establish optimal OAC strategies in patients undergoing M-TEER.

ARTICLE INFORMATION

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REFERENCES

1. Goel SS, Bajaj N, Aggarwal B, Gupta S, Poddar KL, Ige M, Bdair H, Anabtawi A, Rahim S, Whitlow PL, et al. Prevalence and outcomes of unoperated patients with severe symptomatic mitral regurgitation and heart failure: comprehensive analysis to determine the potential role of MitraClip for this unmet need. *J Am Coll Cardiol*. 2014;63:185–186. doi: 10.1016/j.jacc.2013.08.723
2. Feldman T, Foster E, Glower DD, Kar S, Rinaldi MJ, Fail PS, Smalling RW, Siegel R, Rose GA, Engeron E, et al. Percutaneous repair or surgery for mitral regurgitation. *N Engl J Med*. 2011;364:1395–1406. doi: 10.1056/NEJMoa1009355
3. Stone GW, Lindenfeld J, Abraham WT, Kar S, Lim DS, Mishell JM, Whisenant B, Grayburn PA, Rinaldi M, Kapadia SR, et al. Transcatheter mitral-valve repair in patients with heart failure. *N Engl J Med*. 2018;379:2307–2318. doi: 10.1056/NEJMoa1806640

4. Otto CM, Nishimura RA, Bonow RO, Carabello BA, Erwin JP, Gentile F, Jneid H, Krieger EV, Mack M, McLeod C, et al. 2020 ACC/AHA guideline for the Management of Patients with Valvular Heart Disease: a report of the American College of Cardiology/American Heart Association joint committee on clinical practice guidelines. *Circulation*. 2021;143:e72–e227. doi: 10.1161/CIR.0000000000000960
5. Vahanian A, Beyersdorf F, Praz F, Milojevic M, Baldus S, Bauersachs J, Capodanno D, Conradi L, De Bonis M, De Paulis R, et al. 2021 ESC/EACTS guidelines for the management of valvular heart disease: developed by the task force for the management of valvular heart disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J*. 2022;43:561–632. doi: 10.1093/eurheartj/ehab395
6. Hausleiter J, Stocker TJ, Adamo M, Karam N, Swaans Martin J, Praz F. Mitral valve transcatheter edge-to-edge repair. *EuroIntervention*. 2023;18:957–976. doi: 10.4244/EIJ-D-22-00725
7. Kim D-H, Heo R, Handschumacher MD, Lee S, Choi Y-S, Kim K-R, Shin Y, Park H-K, Bischoff J, Aikawa E, et al. Mitral valve adaptation to isolated annular dilation. *JACC Cardiovasc Imaging*. 2019;12:665–677. doi: 10.1016/j.jcmg.2017.09.013
8. Deferm S, Bertrand PB, Verbrugge FH, Verhaert D, Rega F, Thomas JD, Vandervoort PM. Atrial Functional Mitral Regurgitation. *J Am Coll Cardiol*. 2019;73:2465–2476. doi: 10.1016/j.jacc.2019.02.061
9. Darby AE, DiMarco JP. Management of atrial fibrillation in patients with structural heart disease. *Circulation*. 2012;125:945–957. doi: 10.1161/CIRCULATIONAHA.111.019935
10. Arora S, Vemulapalli S, Stebbins A, Ramm CJ, Kosinski AS, Sorajja P, Piccini JP, Cavender MA, Vavalle JP. The prevalence and impact of atrial fibrillation on 1-year outcomes in patients undergoing transcatheter mitral valve repair. *JACC Cardiovasc Interv*. 2019;12:569–578. doi: 10.1016/j.jcin.2018.12.012
11. Grigioni F, Avierinos J-F, Ling LH, Scott CG, Bailey KR, Tajik AJ, Frye RL, Enriquez-Sarano M. Atrial fibrillation complicating the course of degenerative mitral regurgitation: determinants and long-term outcome. *J Am Coll Cardiol*. 2002;40:84–92. doi: 10.1016/s0735-1097(02)01922-8
12. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, Boriani G, Castella M, Dan G-A, Dilaveris PE, et al. 2020 ESC guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): the task force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) developed with the special contribution of the European heart rhythm association (EHRA) of the ESC. *Eur Heart J*. 2021;42:373–498. doi: 10.1093/eurheartj/ehaa612
13. Kundi H, Popma JJ, Reynolds MR, Strom JB, Pinto DS, Valsdottir LR, Shen C, Choi E, Yeh RW. Frailty and related outcomes in patients undergoing transcatheter valve therapies in a nationwide cohort. *Eur Heart J*. 2019;40:2231–2239. doi: 10.1093/eurheartj/ehz187
14. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, Camm AJ, Weitz JI, Lewis BS, Parkhomenko A, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet*. 2014;383:955–962. doi: 10.1016/S0140-6736(13)62343-0
15. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2009;361:1139–1151. doi: 10.1056/NEJMoa0905561
16. Granger CB, Alexander JH, McMurray JJV, Lopes RD, Hylek EM, Hanna M, Al-Khalidi HR, Ansell J, Atar D, Avezum A, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2011;365:981–992. doi: 10.1056/NEJMoa1107039
17. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, Waldo AL, Ezekowitz MD, Weitz JI, Špinar J, et al. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2013;369:2093–2104. doi: 10.1056/NEJMoa1310907
18. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med*. 2011;365:883–891. doi: 10.1056/NEJMoa1009638
19. Neuss M, Schau T, Isotani A, Pilz M, Schöpp M, Butter C. Elevated mitral valve pressure gradient after MitraClip implantation deteriorates long-term outcome in patients with severe mitral regurgitation and severe heart failure. *JACC Cardiovasc Interv*. 2017;10:931–939. doi: 10.1016/j.jcin.2016.12.280
20. Lip GYH, Collet JP, De Caterina R, Fauchier L, Lane DA, Larsen TB, Marin F, Morais J, Narasimhan C, Olshansky B, et al. Antithrombotic therapy in atrial fibrillation associated with valvular heart disease. *Europace*. 2017;19:1757–1758. doi: 10.1093/europace/eux240
21. De Caterina R, Camm AJ. What is 'valvular' atrial fibrillation? A reappraisal. *Eur Heart J*. 2014;35:3328–3335. doi: 10.1093/europace/eux240
22. Hohmann C, Ludwig M, Walker J, Iliadis C, Schipper J-H, Baldus S, Pfister R. Real-world anticoagulatory treatment after percutaneous mitral valve repair using MitraClip: a retrospective, observational study on 1300 patients. *Clin Res Cardiol*. 2022;111:889–899. doi: 10.1007/s00392-022-01988-2
23. Waechter C, Ausbuettel F, Chatzis G, Cheko J, Fischer D, Nef H, Barth S, Halbfass P, Deneke T, Mueller J, et al. Antithrombotic treatment and its association with outcome in a multicenter cohort of transcatheter edge-to-edge mitral valve repair patients. *J Cardiovasc Develop Dis*. 2022;9:366. doi: 10.3390/jcdd9110366
24. Maisano F, La Canna G, Colombo A, Alfieri O. The evolution from surgery to percutaneous mitral valve interventions: the role of the edge-to-edge technique. *J Am Coll Cardiol*. 2011;58:2174–2182. doi: 10.1016/j.jacc.2011.07.046
25. Mentias A, Saad M, Michael M, Nakhla S, Menon V, Harb S, Chaudhury P, Johnston D, Saliba W, Wazni O, et al. Direct Oral anticoagulants versus warfarin in patients with atrial fibrillation and valve replacement or repair. *J Am Heart Assoc*. 2022;11:e026666. doi: 10.1161/JAHA.122.026666
26. De Caterina R, Renda G, Carnicelli AP, Nordio F, Trevisan M, Mercuri MF, Ruff CT, Antman EM, Braunwald E, Giugliano RP. Valvular heart disease patients on edoxaban or warfarin in the ENGAGE AF-TIMI 48 trial. *J Am Coll Cardiol*. 2017;69:1372–1382. doi: 10.1016/j.jacc.2019.01.002
27. Guimarães HP, Lopes RD, De Barros e Silva PG, Liporace IL, Sampaio RO, Tarasoutchi F, Hoffmann-Filho CR, De Lemos Soares Patriota R, Leiria TL, Lamprea D, et al. Rivaroxaban in patients with atrial fibrillation and a bioprosthetic mitral valve. *N Engl J Med* 2020;383:2117–2126. doi: 10.1056/NEJMoa2029603
28. Eikelboom JW, Connolly SJ, Brueckmann M, Granger CB, Kappetein AP, Mack MJ, Blatchford J, Devenny K, Friedman J, Guiver K, et al. Dabigatran versus warfarin in patients with mechanical heart valves. *N Engl J Med*. 2013;369:1206–1214. doi: 10.1056/NEJMoa1300615
29. Connolly SJ, Karthikeyan G, Ntsekhe M, Haileamlak A, El Sayed A, El Ghamrawy A, Damasceno A, Avezum A, Dans AM, Gitura B, et al. Rivaroxaban in rheumatic heart disease–associated atrial fibrillation. *N Engl J Med*. 2022;387:978–988. doi: 10.1056/NEJMoa2209051
30. Roumeliotis S, Dounousi E, Salmas M, Eleftheriadis T, Liakopoulos V. Vascular calcification in chronic kidney disease: the role of vitamin K-dependent matrix Gla protein. *Front Med*. 2020;7:154. doi: 10.3389/fmed.2020.00154
31. Bartkowiak J, Kassar M, Brülisauer SJ, Bubulyte L, Samim D, Ruberti A, Madhkour R, Büllesfeld L, Windecker S, Pilgrim T, et al. Findings from transoesophageal echocardiographic follow-up after mitral transcatheter edge-to-edge repair. *EuroIntervention*. 2024;20:e1298–e1308. doi: 10.4244/EIJ-D-24-00297