

REVIEWS

Direct oral anticoagulant use in nonvalvular atrial fibrillation with valvular heart disease: a systematic review

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Direct oral anticoagulants (DOACs) are indicated for stroke prevention in patients with nonvalvular atrial fibrillation (NVAF), which, according to the American College of Cardiology/American Heart Association/Heart Rhythm Society atrial fibrillation (AF) guidelines, excludes patients with rheumatic mitral stenosis, a mechanical or bioprosthetic heart valve, or mitral valve repair. However, the data regarding use of DOACs in AF patients with other types of valvular heart disease (VHD) are unclear. We aimed to summarize and evaluate the literature regarding the safety and efficacy of DOAC use in NVAF patients with other types of VHD. After an extensive literature search, a total of 1 prospective controlled trial, 4 subanalyses, and 1 abstract were identified. Efficacy of the DOAC agents in NVAF patients with VHD mirrored the overall trial results. Bleeding risk was significantly increased in VHD patients treated with rivaroxaban, but not for dabigatran or apixaban. Of the bioprosthetic valve patients enrolled in the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial, no safety or efficacy concerns were identified. In conclusion, subanalyses of DOAC landmark AF trials revealed that dabigatran, rivaroxaban, and apixaban may be safely used in AF patients with certain types of VHD: aortic stenosis, aortic regurgitation, and mitral regurgitation. More evidence is needed before routinely recommending these agents for patients with bioprosthetic valves or mild mitral stenosis. Patients with moderate to severe mitral stenosis or mechanical valves should continue to receive warfarin, as these patients were excluded from all landmark AF trials.

KEYWORDS

Arrhythmia/all, management, Clinical trials, Stroke prevention, Valvular heart disease

1 | INTRODUCTION

Atrial fibrillation (AF) is the most common arrhythmia and confers a substantial stroke risk, ranging from <1% to >20% in the absence of anticoagulation.¹ Stroke prevention is a pivotal part of the management of AF patients, with anticoagulation recommended for patients with a CHA₂DS₂-VASc score ≥ 2 .² Warfarin has been an anticoagulation therapy standard for decades, but now the use of direct oral anticoagulants (DOACs) has become increasingly popular due to enhanced patient convenience secondary to lack of routine therapeutic monitoring and dietary restrictions, rapid onset of action, and predictable pharmacodynamics and pharmacokinetics. Overall, the DOAC agents have been found to reduce the rates of hemorrhagic stroke compared with warfarin, with differences among each agent

regarding other measures of efficacy. The major endpoints of the landmark clinical trials are summarized in Table 1.³⁻⁶

AF associated with valvular heart disease (VHD) is associated with an even higher thromboembolic risk than AF alone.^{1,7} Compared with patients in normal sinus rhythm, AF increases the risk of stroke 5 \times , whereas AF coupled with mitral stenosis increases the risk 20 \times .² AF associated with rheumatic mitral stenosis or a mechanical heart valve carries the highest thromboembolic risk secondary to possible alternative mechanisms of thrombogenesis than those seen with nonvalvular atrial fibrillation (NVAF).^{1,7,8} Given the differences in thromboembolic risk profiles, it is essential to differentiate NVAF from valvular AF when determining anticoagulation strategies. NVAF is defined by the American College of Cardiology/American Heart Association/Heart Rhythm Society AF guidelines as AF in the

TABLE 1 Summary of clinical trials data: DOAC vs dose-adjusted warfarin in AF

Trial	RE-LY, N = 18 113, Dabigatran	ROCKET-AF, N = 14 264, Rivaroxaban	ARISTOTLE, N = 18 201, Apixaban	ENGAGE AF-TIMI 48, N = 21 505, Edoxaban
Dose	110 mg BID, 150 mg BID	20 mg daily (15 mg daily if CrCl <30–49 mL/min)	5 mg BID (2.5 mg BID if ≥2 of the following: age ≥80 years, weight ≤60 kg, SCr ≥1.5 mg/dL)	30 mg daily, 60 mg daily (doses reduced by 50% if CrCl 30–50 mL/min, weight <60 kg, or DI) ¹
Mean CHADS ₂ score	2.1	3.5	2.1	2.8
Mean time in INR therapeutic range	64%	55%	62.2%	64.9%
Primary endpoint: stroke or systemic embolism (vs warfarin)	110 mg: 1.53% vs 1.69%, P < 0.001 (NI); 150 mg: 1.11% vs 1.69%, P < 0.001	2.1% vs 2.4%, P < 0.001 (NI)	1.27% vs 1.6%, P = 0.01	30 mg: 2.01% vs 1.5%, P = 0.10; 60 mg: 1.18% vs 1.5%, P = 0.08
Primary safety (vs warfarin)	Major bleeding: 110 mg: 2.71% vs 3.36%, P = 0.003; 150 mg: 3.11% vs 3.36%, P = 0.31	Major and NMCR bleeding: 20.7% vs 20.3%, P = 0.44	Major bleeding: 2.13% vs 3.09%, P < 0.001	Major bleeding: 30 mg: 1.61% vs 3.43%, P < 0.001; 60 mg: 2.75% vs 3.43%, P < 0.001
Comments	Both doses of dabigatran significantly reduced the rate of hemorrhagic stroke and intracranial bleeding. Only 150-mg dose reduced rates of ischemic stroke. GI bleeding higher with 150-mg dose.	Rivaroxaban significantly reduced the rate of hemorrhagic stroke and intracranial bleeding. Increased risk of GI bleeding.	Apixaban significantly reduced the rate of hemorrhagic stroke and intracranial bleeding. No difference in rate of GI bleeding.	Both doses of edoxaban significantly reduced the rate of hemorrhagic stroke and intracranial bleeding. Increased risk of ischemic stroke with 30-mg dose. Increased risk of GI bleeding with 60-mg dose.

Abbreviations: AF, atrial fibrillation; ARISTOTLE, Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; BID, twice daily; CHADS₂, congestive HF, HTN, age ≥75 y, DM, prior stroke/TIA/TE; Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction Study 48, Global Study to Assess the Safety and Effectiveness of Edoxaban (DU-176b) vs Standard Practice of Dosing With Warfarin in Patients With Atrial Fibrillation; CrCl, creatinine clearance; DI, drug interaction; DM, diabetes mellitus; GI, gastrointestinal; HF, heart failure; HTN, hypertension; INR, international normalized ratio; NI, noninferiority; NMCR, nonmajor clinically relevant; RE-LY, Randomized Evaluation of Long-Term Anticoagulation Therapy; 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; SCr, serum creatinine; TE, thromboembolism; TIA, transient ischemic attack.

¹ Drug interactions: dronedarone, quinidine, verapamil.

absence of rheumatic mitral stenosis, a mechanical or bioprosthetic heart valve, or mitral valve repair.² However, definitions of NVAF vary based upon the guideline consulted, yielding a source of confusion for practicing clinicians.^{2,9,10}

Although warfarin is approved for treatment of both NVAF and valvular AF, the DOACs are approved only for patients with NVAF.^{11–15} However, each of the DOAC landmark AF trials varied slightly in their inclusion and exclusion criteria, allowing patients with certain other types of VHD to be enrolled. Growing use of DOACs in clinical practice and confusion over NVAF criteria may cause some practitioners to incorrectly avoid DOACs in AF patients with concurrent VHD. The purpose of this review is to summarize and evaluate the safety and efficacy of DOAC use in NVAF patients with other types of VHD.

2 | METHODS

Searches of MEDLINE (from 2010 to September 2016), the Cochrane Database (from 2010 to September 2016), and Google Scholar were conducted using the search terms “atrial fibrillation,” “valve disease,” “dabigatran,” “rivaroxaban,” “apixaban,” and “edoxaban.” Limits were set for articles written in English with human subjects. Additional data were identified through bibliographic reviews. A total of 1 prospective controlled trial and 1 subanalysis evaluating dabigatran, 2 subanalyses

evaluating rivaroxaban, and 1 subanalysis and 1 abstract evaluating apixaban were identified in the search. The landmark clinical trials Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY; dabigatran vs warfarin), Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF; rivaroxaban vs warfarin), Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE; apixaban vs warfarin), and Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction Study 48 (ENGAGE-AF TIMI 48; edoxaban vs warfarin) all enrolled AF patients with certain other types of VHD, although the ENGAGE AF-TIMI 48 subanalysis results are currently unpublished. One ongoing clinical trial evaluating rivaroxaban was also identified using the registry <http://www.clinicaltrials.org> from the US National Institutes of Health.

The exclusion criteria specific to the VHD population are summarized in Table 2.^{16–18} One consistency noted is that all trials excluded patients with moderate to severe mitral stenosis and mechanical heart valves. However, patients with aortic stenosis, aortic regurgitation, mild mitral stenosis, and mitral regurgitation were enrolled as long as all other inclusion criteria were met. Uniquely, the ARISTOTLE and ENGAGE AF-TIMI 48 trials enrolled patients with bioprosthetic valves. Each subanalyses tested for differences in outcomes based upon overall VHD status (VHD vs no VHD) and each

TABLE 2 Description of VHD population in landmark clinical trials

Trial	RE-LY, Dabigatran	ROCKET AF, Rivaroxaban	ARISTOTLE, Apixaban
Excluded population	Prosthetic heart valves; hemodynamically significant mitral stenosis; valve disease likely to require intervention before study end	Artificial valve prosthesis; hemodynamically significant mitral stenosis	Clinically significant (moderate or severe) mitral stenosis; mechanical valve prosthesis
VHD patient population included	N = 3950 (21.8%), mitral regurgitation (78.5%), tricuspid regurgitation (29.8%), aortic regurgitation (20.7%), aortic stenosis (11.9%), mild mitral stenosis (4.9%)	N = 2003 (14.0%), mitral regurgitation (89.6%), aortic regurgitation (24.8%), aortic stenosis (11%), other (0.6%)	N = 4808 (26.4%), mitral regurgitation (73.3%), tricuspid regurgitation (44.2%), aortic regurgitation (18.4%), aortic stenosis (8%), previous valve surgery (5.2%), mild mitral stenosis (2.7%) ¹

Abbreviations: ARISTOTLE, Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; RE-LY, Randomized Evaluation of Long-Term Anticoagulation Therapy; 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; VHD, valvular heart disease.

¹ Patient could be in ≥ 1 category.

individual DOAC agent compared with warfarin for both the VHD and no-VHD population. The major endpoints of the subanalyses are summarized in Table 3.¹⁶⁻¹⁸

3 | RESULTS

3.1 | Dabigatran

RE-LY was a multicenter, prospective, randomized trial evaluating dabigatran vs warfarin in 18 113 AF patients with a mean CHADS₂ score of 2.1.³ Patients were randomized to receive dabigatran 110 mg BID, dabigatran 150 mg BID, or dose-adjusted warfarin to maintain a goal international normalized ratio (INR) of 2.0 to 3.0. Overall, the authors concluded that dabigatran 150 mg was superior to warfarin regarding rates of stroke or systemic embolism (SE) and noninferior regarding rates of major bleeding, whereas dabigatran 110 mg was noninferior for stroke or SE and superior in rates of major bleeding.

Further examining the NVAF population in RE-LY, investigators excluded patients with prosthetic heart valves, hemodynamically significant mitral stenosis, and those with valve disease likely to lead to an intervention before the end of the study period. For subanalysis comparison, 3950 (21.8%) of the total population were deemed to have VHD by investigators, the majority of which were mitral regurgitation.¹⁶ Patients with VHD were older (74 vs 72 years; $P = 0.01$), more likely to have congestive heart failure (CHF; 39.7% vs 29.8%; $P = 0.01$) and coronary artery disease (32.5% vs 26.5%; $P = 0.01$), and had higher mean CHADS₂ scores (2.3 vs 2.1; $P < 0.001$).

Dabigatran 150-mg event rates appeared significantly lower regarding the risk of stroke or SE compared with warfarin for both patients with VHD (1.12% dabigatran vs 1.9% warfarin; hazard ratio [HR]: 0.59, 95% confidence interval [CI]: 0.37-0.93) and without VHD (1.11% dabigatran vs 1.66% warfarin; HR: 0.67, 95% CI: 0.52-0.86). Major bleeding rates with the 150-mg dose were similar among patients with VHD (4.21% dabigatran vs 5.12% warfarin; HR: 0.82, 95% CI: 0.64-1.06) compared with those without VHD (3.06%

TABLE 3 Summary of outcomes by VHD status in landmark clinical trials

Trial	RE-LY, Dabigatran	ROCKET AF, Rivaroxaban	ARISTOTLE, Apixaban
Stroke and systemic embolism ¹	VHD ² : dabigatran 150 mg 1.12%, warfarin 1.90% (HR: 0.59, 95% CI: 0.37-0.93); no VHD ² : dabigatran 150 mg 1.11%, warfarin 1.66% (HR: 0.67, 95% CI: 0.52-0.86)	VHD: rivaroxaban 2.01%, warfarin 2.43% (HR: 0.83, 95% CI: 0.55-1.27); no VHD: rivaroxaban 1.96%, warfarin 2.22% (HR: 0.89, 95% CI: 0.75-1.07)	VHD: apixaban 1.46%, warfarin 2.08% (HR: 0.70, 95% CI: 0.51-0.97); no VHD: apixaban 1.20%, warfarin 1.43% (HR: 0.84, 95% CI: 0.67-1.04)
Bleeding ¹	Major bleeding-VHD ² : dabigatran 150 mg 4.2%, warfarin 5.12% (HR: 0.82, 95% CI: 0.64-1.06); no VHD ² : dabigatran 150 mg 3.06%, warfarin 3.14% (HR: 0.98, 95% CI: 0.83-1.15)	Major or NMCR bleeding-VHD: rivaroxaban 19.8%, warfarin 16.8% (HR: 1.25, 95% CI: 1.05-1.49); no VHD: rivaroxaban 14.2%, warfarin 14.1% (HR: 0.98, 95% CI: 0.94-1.10)	Major Bleeding-VHD: Apixaban 2.49%, warfarin 3.14% (HR: 0.79, 95% CI: 0.61-1.04); no VHD: apixaban 2.01%, warfarin 3.07% (HR: 0.65, 95% CI: 0.55-0.77)
Comments	Major bleeding significantly increased in the total VHD population vs no VHD.	Major and NMCR bleeding significantly increased in the total VHD population vs no VHD.	Significantly higher rates of stroke or systemic embolism in the VHD population compared with those without VHD.

Abbreviations: ARISTOTLE, Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; CI, confidence interval; FDA, US Food and Drug Administration; HR, hazard ratio; NMCR, nonmajor clinically relevant; RE-LY, Randomized Evaluation of Long-Term Anticoagulation Therapy; 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; VHD, valvular heart disease.

¹ Outcomes reported in percentage of event rates per year.

² Trial included 110-mg dosing as well, but it was not reported here because this dose is not FDA approved for use in the NVAF population.

dabigatran vs 3.14% warfarin; HR: 0.98, 95% CI: 0.83-1.15). Dabigatran 110 mg exhibited similar rates of stroke or SE compared with warfarin regardless of VHD status. However, rates of major bleeding were significantly lower with dabigatran 110 mg both in patients with VHD and without VHD. The authors also compared patients with exclusive right-sided valve lesions and patients with rheumatic mitral stenosis and found that outcomes were similar to those without VHD. Overall, VHD patients had comparable rates of stroke or SE but a significantly higher risk of major bleeding than those without VHD (HR: 1.32, 95% CI: 1.16-1.50).

Durães and colleagues most recently observed the effects of dabigatran compared with warfarin after bioprosthetic valve replacement, a population not originally included in the RE-LY trial.¹⁹ The primary endpoint was intracardiac thrombus at 90 days by transesophageal echocardiography. Of the 27 patients randomized, 1 patient (8.3%) in the warfarin group compared with none in the dabigatran group developed a new intracardiac thrombus at 30 days. Although no incidences of valve thrombosis or hemorrhagic stroke were observed, 1 (8.3%) patient in the warfarin group did experience an ischemic stroke. Despite positive preliminary results, the trial was terminated prematurely due to low enrollment.

3.2 | Rivaroxaban

The ROCKET AF trial was a multicenter, randomized, double-blind trial examining rivaroxaban vs warfarin in 14 264 AF patients with a mean CHADS₂ score of 3.2.⁴ Patients were randomized to receive either rivaroxaban 20 mg daily (renally adjusted to 15 mg daily) or dose-adjusted warfarin to maintain a goal INR of 2.0 to 3.0. Overall, the authors concluded that rivaroxaban was noninferior to warfarin regarding stroke or SE and similar to warfarin for rates of major and nonmajor clinically relevant (NMCR) bleeding.

In defining their NVAf population, ROCKET AF investigators excluded patients with hemodynamically significant mitral stenosis and prosthetic heart valves. For subanalysis comparison, 2003 (14%) patients were identified as having significant valve disease, the majority being mitral regurgitation.¹⁷ Data from 1992 VHD patients were used for efficacy analysis and data from 1999 patients were used for safety analysis. VHD patients were older (75 vs 72 years; $P < 0.0001$), more likely to have CHF (70.4% vs 61.2%; $P < 0.0001$), and less likely to have previous stroke, embolism, or transient ischemic attack (48.2% vs 55.9%; $P < 0.0001$). VHD patients exhibited similar stroke and bleeding risks to those without VHD, as the mean CHADS₂ score was 3.5 and the mean HAS-BLED score was 2.8 in both groups.

Rivaroxaban efficacy was similar regarding rates of stroke or SE among patients with VHD (2.01% rivaroxaban vs 2.43% warfarin; HR: 0.83, 95% CI: 0.55-1.27) compared with those without VHD (1.96% rivaroxaban vs 2.22% warfarin; HR: 0.89, 95% CI: 0.75-1.07, $P = 0.76$). However, rates of major and NMCR bleeding were significantly higher with rivaroxaban in patients with VHD (19.8% rivaroxaban vs 16.8% warfarin; HR: 1.25, 95% CI: 1.05-1.49) compared with patients without VHD (14.2% rivaroxaban vs 14.1% warfarin; HR: 1.01, 95% CI: 0.94-1.10). Overall, patients with VHD had higher rates of SE (0.32% VHD vs 0.14% no VHD; $P = 0.049$) and higher rates of major or NMCR bleeding (18.24% VHD vs 14.16% no VHD; $P = 0.011$).

A separate subanalysis of ROCKET AF was conducted examining outcomes for patients based upon valve disease location, specifically comparing aortic stenosis to mitral regurgitation or aortic regurgitation.²⁰ Stroke or SE occurred twice as often in the aortic stenosis group (4.21 events/100 patient-years) compared with the mitral regurgitation or aortic regurgitation group (2.01 events/100 patient-years; $P < 0.05$) and no-VHD group (2.09 events/100 patient-years; $P < 0.05$). Major and NMCR bleeding occurred more often in mitral regurgitation or aortic regurgitation group (17.66 events/100 patient-years) than those with no VHD (14.16 events/100 patient-years; $P < 0.05$). Although major and NMCR bleeding was highest with aortic stenosis (24.36 events/100 patient-years), this did not reach significance when compared with the other groups. Evaluating treatment effects, rivaroxaban efficacy was consistent among those with and without VHD, although patients with mitral regurgitation or aortic regurgitation had an increased risk of major bleeding (HR: 1.32) and major or NMCR bleeding (HR: 1.63). This significant increased risk of bleeding was not found in the aortic stenosis patients treated with rivaroxaban.

Rivaroxaban is also being actively investigated in VHD patients in the Rivaroxaban for Valvular Heart Disease and Atrial Fibrillation (RIVER) trial, a phase 2 study examining rivaroxaban vs warfarin in AF patients with a bioprosthetic mitral valve.²¹

3.3 | Apixaban

The ARISTOTLE trial was a multicenter, randomized, double-blind trial examining apixaban vs warfarin in 18 201 AF patients with a mean CHADS₂ score of 2.1.⁵ Patients were randomized to receive either apixaban 5 mg twice daily or dose-adjusted warfarin to maintain a goal INR of 2.0 to 3.0. Apixaban was reduced to 2.5 mg twice daily in patients with ≥ 2 of the following: age ≥ 80 years, weight ≤ 60 kg, and serum creatinine ≥ 1.5 mg/dL. Overall, the authors concluded that apixaban was superior in prevention of stroke or SE and superior in reduction of rates of major bleeding.

The ARISTOTLE investigators excluded patients with moderate or severe mitral stenosis and patients with other indications for anticoagulation, therefore excluding those with mechanical prosthetic heart valves. For subanalysis comparison, 4808 (26.4%) patients had a history of moderate or severe VHD, the majority being mitral regurgitation.¹⁸ VHD patients were older (71 vs 69 years; $P < 0.0001$), more likely to have CHF (48.6% vs 30.7%; $P < 0.0001$), and less likely to have hypertension (85.3% vs 88.2%; $P < 0.0001$) and diabetes mellitus (22.6% vs 25.8%; $P < 0.0001$). The mean CHADS₂ score was also higher in patients with VHD (2.2 vs 2.1; $P < 0.0001$).

Apixaban efficacy was similar in prevention of stroke or SE in those with VHD (1.46% apixaban vs 2.08% warfarin; HR: 0.70, 95% CI: 0.51-0.97) compared with those without VHD (apixaban 1.20% vs 1.43% warfarin; HR: 0.84, 95% CI: 0.67-1.04). Rates of major bleeding were also similar in patients with VHD (2.49% apixaban vs 3.14% warfarin; HR: 0.79, 95% CI: 0.61-1.04) and those without VHD (2.01% apixaban vs 3.07% warfarin; HR: 0.65, 95% CI: 0.55-0.77). Outcomes by valve location (mitral vs aortic) were also assessed, and no significant treatment effects were found. A sensitivity analysis was performed that included patients with mild VHD by baseline

echocardiography and found that 59.4% of the total ARISTOTLE population had at least mild VHD at baseline. When analyzing this cohort of patients, outcomes were similar to the main analysis for both the primary efficacy (interaction $P = 0.90$) and safety outcome (interaction $P = 0.67$). Overall, patients with VHD experienced higher rates of stroke or SE (3.2% VHD vs 2.4% no VHD; HR: 1.34, 95% CI: 1.10-1.62) and death (9.1% VHD vs 6.2% no VHD; HR: 1.48, 95% CI: 1.32-1.67).

A separate subanalysis was published evaluating the outcomes of the 82 patients with a bioprosthetic valve included in the ARISTOTLE trial, 41 patients in each arm.²² There were no statistical differences between groups other than a higher incidence of hypertension in the warfarin group (98% vs 81%; $P = 0.03$). No differences were seen regarding the incidence of stroke or SE with the only 2 events occurring in the apixaban group. Rates of major bleeding were also similar (7.9 apixaban vs 5.2 warfarin/100 patient-years; $P = 0.61$).

3.4 | Edoxaban

The ENGAGE AF-TIMI 48 trial was a multicenter, randomized, double-blind trial examining edoxaban vs warfarin in 21 105 AF patients with a mean CHADS₂ score of 2.8.⁶ Patients were randomized to receive either edoxaban 60 mg, edoxaban 30 mg, or dose-adjusted warfarin to maintain a goal INR of 2.0 to 3.0. Edoxaban doses were halved if patients had a creatinine clearance of 30 to 50 mL/min or were receiving concurrent potent P-glycoprotein inhibitors (verapamil or quinidine). Overall, the authors concluded that both doses of edoxaban were noninferior to warfarin for preventing stroke or SE but exhibited significantly lower rates of major bleeding.

ENGAGE AF-TIMI 48 investigators excluded moderate to severe mitral stenosis and prosthetic heart valves by excluding patients with other indications for anticoagulation, similar to the ARISTOTLE NVAF population. A description or analysis of the VHD population included in ENGAGE AF-TIMI 48 has yet to be published in full at this time. Of note, ENGAGE AF-TIMI 48 did include patients with preexisting bioprosthetic valves or previous valve surgery, enrolling the largest population of these specific VHD patients in a DOAC trial to date.

4 | DISCUSSION

Although RE-LY, ROCKET AF, ARISTOTLE, and ENGAGE AF-TIMI 48 were designed to assess efficacy in the NVAF population, a number of patients with other types of VHD were included in these trials. All the trials excluded patients with moderate to severe mitral stenosis and mechanical heart valves but included patients with aortic stenosis, aortic regurgitation, mild mitral stenosis, and mitral regurgitation. In these patients with other types of VHD, subanalyses revealed that DOAC efficacy remains similar to those patients without VHD. Regarding safety, bleeding risk was similar with dabigatran and apixaban, whereas rivaroxaban was associated with a higher bleeding risk in the VHD population. Although the authors did note that the heightened bleeding risk with rivaroxaban may be a chance finding given the post hoc nature of the analysis, use should still be cautioned given the high baseline bleed risk associated with VHD.¹⁷

Although these trials demonstrate promising results, the findings should be interpreted with caution, as these were not prespecified subgroup analyses. It should also be noted that the findings cannot be generalized to all VHD patients, as no patients with moderate to severe mitral stenosis or mechanical heart valves were included in any of the trials. Results from the ROCKET AF subanalysis highlighted that varying types of VHD should not be considered equal, as thromboembolic and/or bleeding risks differed by type of concurrent VHD.²⁰ Larger studies of VHD patients comparing outcomes based on specific valve location are needed before tailoring anticoagulation therapy to specific VHD etiology. However, it is prudent to examine the VHD etiology and/or location of patients included in each of the clinical trials to avoid use in a patient with a subset of VHD not studied.

Utilization of DOACs in the setting of bioprosthetic valves should be determined on a patient-specific basis based on the limited patient populations studied currently. Although preliminary results with dabigatran are promising, other studies are needed to validate these findings due to the premature termination.¹⁹ In the ARISTOTLE study, outcomes of apixaban with bioprosthetic valves should be viewed as hypothesis generating, given the small number of bioprosthetic valve patients included in the original trial.²² Results of the ongoing RIVER trial and ENGAGE AF-TIMI 48 VHD subanalysis may also help provide insights regarding DOAC use in AF patients with concurrent bioprosthetic valves for rivaroxaban and edoxaban, respectively.^{6,21}

Based upon the current evidence available, NVAF patients with concurrent mitral regurgitation, aortic stenosis, or aortic regurgitation should not be excluded from DOAC therapy based solely upon the presence of VHD. Although mild mitral stenosis patients were included in some clinical trials, concern for increased thrombosis risk with VHD progression may warrant avoidance of DOACs with mild mitral stenosis until further evidence is available. As with all NVAF patients, those with concurrent VHD should still be examined on an individual basis, assessing both thromboembolic and bleed risk, to determine appropriate candidates for DOAC therapy.

4.1 | Review limitations

Limitations of this systematic review include the low number of trials identified examining the use of DOACs in patients with certain other types of VHD and the lack of information published regarding edoxaban. Despite the low number of trials, the subanalyses of the DOAC landmark clinical trials all provided data on a large percentage of patients, approximately 15% to 20% of the total population. Given these large populations, conclusions may be adequately drawn from these subanalyses while awaiting larger, randomized trials of DOAC use in patients with other types of VHD specifically.

5 | CONCLUSION

DOACs are currently indicated for stroke prevention in patients with NVAF defined as AF in the absence of rheumatic mitral stenosis, a mechanical or bioprosthetic heart valve, or mitral valve repair by the ACC/AHA/HRS AF guidelines. Clinical trials have shown that

they are efficacious in NVAF patients with concurrent aortic stenosis, aortic regurgitation, and mitral regurgitation. Dabigatran and apixaban also proved efficacious in a small subset of NVAF patients with mild mitral stenosis. Aside from the increased bleed risk in NVAF patients with other types of VHD treated with rivaroxaban compared with warfarin in post hoc analysis, the safety and efficacy profiles of dabigatran, rivaroxaban, and apixaban all appear to be similar. Prospective randomized controlled trials comparing DOACs to each other and warfarin are needed in NVAF patients with VHD to determine the true comparative safety and efficacy profiles.

Conflict of interests

The authors declare no potential conflict of interests.

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