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Can Direct Oral Anticoagulants Be Used for Stroke Prevention Among Patients with Valvular Atrial Fibrillation?

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Abstract

Purpose of Review To review the clinical evidence underlying the efficacy and safety of the use of direct oral anticoagulants (DOACs) for the treatment of patients with valvular atrial fibrillation (AF).

Recent Findings The recent focused update to the 2014 AHA/ACC/HRS Atrial Fibrillation Guidelines defines valvular AF as AF in the setting of moderate-to-severe mitral stenosis (MS) and/or in the presence of a mechanical heart valve. Landmark clinical trials of DOACs in patients with AF systematically excluded these patient populations. However, there are trial data in both animals and humans regarding the use of DOACs in patients with MS and in those with mechanical heart valves.

Summary Based on sub-analyses and meta-analyses of clinical trial data in patients with AF, the use of DOACs in valvular AF is not recommended. Patients with moderate-to-severe MS or a mechanical heart valve and AF should be anticoagulated with dose-adjusted warfarin. DOACs are reasonable alternatives to warfarin in patients with AF and other types of valvular disease, including mild MS and bioprosthetic valves.

Keywords Direct oral anticoagulant · Valvular atrial fibrillation · Atrial fibrillation · Anticoagulation

Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia in clinical practice, affecting 2.7 to 6.1 million Americans and is expected to rise to 12.1 million by 2030 [1]. The incidence of AF increases with increasing age; the risk of developing AF after the age of 40 is approximately 25% [2]. In addition to age, hypertension (HTN) and coronary heart disease (CHD) are other common risk factors for the development of AF [3]. Patients who develop AF are at an increased risk of heart failure, hospitalization, cardioembolic stroke, and death [4–6].

The main method for mitigating cardioembolic stroke risk in patients with AF is with oral anticoagulation. Clinical trials have demonstrated that in patients with AF at moderate to high risk of cardioembolic stroke (CHA_2DS_2-VASc score of ≥ 2 in males and ≥ 3 in females), use of an oral anticoagulant significantly decreases the incidence of stroke with a small, but acceptable, increase in the risk of bleeding [7••]. Of the available anticoagulants, direct oral anticoagulants (DOACs)—apixaban, dabigatran, edoxaban, and rivaroxaban—are preferred alternatives to warfarin in patients with non-valvular AF (NVAF) [7••]. However, controversy remains as to whether DOAC use is safe and effective in patients with valvular AF.

The 2019 focused update to the 2014 AHA/ACC/HRS Atrial Fibrillation Guidelines specifically defines valvular AF as AF in the setting of moderate-to-severe mitral stenosis (MS) and/or in the presence of a mechanical heart valve [7••]. Nonvalvular AF, therefore, is AF in the absence of either moderate-to-severe MS or a mechanical heart valve but may include certain other types of valvular heart disease (VHD). Patients with AF and VHD are not synonymous with patients with valvular AF. In fact, it has been proposed that a means to distinguish NVAF from valvular AF is to re-term the latter "mitral and rheumatic mitral valvular AF" (abbreviated MARM-AF) [8]. The 2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients with Valvular Heart Disease continues to recommend dose-adjusted warfarin therapy for patients with

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concurrent rheumatic MS and AF as well as those with mechanical heart valves [9••]. This review aims to describe the safety and efficacy of data related to the use of DOACs in patients with valvular AF in order to elucidate the rationale behind the recent guideline recommendations.

Patients with AF and VHD

Each of the four DOACs—apixaban, dabigatran, edoxaban, and rivaroxaban—has data to support their Food and Drug Administration (FDA)-approved use in patients with NVAF [10–13]. However, each trial included a variety of patients with valvular heart disease (VHD) and sub-analyses of these patient groups in each of the landmark clinical trials has been performed [14–19]. In each case, the various types of VHD included were slightly different, but patients with moderate to severe MS and/or mechanical heart valves were excluded (Table 1).

Three meta-analyses exploring the safety and efficacy of DOAC use in patients with VHD have been performed [20–22]. It should be noted that the meta-analyses did not sub-analyze any specific form of VHD. Both Renda et al. and Patel et al. performed trial-based analyses of the 4 phase III clinical trials comparing the safety and efficacy of each of the 4 FDA-approved DOACs versus warfarin for stroke prevention in patients with AF and patients with AF and VHD [20, 21]. The meta-analysis by Caldeira et al. included the same 4 phase III clinical trials as well as the phase II clinical trial of dabigatran versus warfarin after bioprosthetic valve replacement for the management of atrial fibrillation postoperatively (DAWA Pilot Study) [22, 23]. These meta-analyses specifically reviewed the outcomes of stroke or systemic embolism, major bleeding, intracranial hemorrhage, and all-cause death. Where there were different DOAC doses studied (e.g., dabigatran 150 mg PO twice daily vs. 110 mg PO twice daily and edoxaban 60 mg PO daily vs. 30 mg PO daily), the higher dose was used for analysis. These meta-analyses concluded that patients with AF and VHD were at higher risk, had higher rates of bleeding, and had higher rates of all-cause death compared to patients with AF and no VHD. However, the efficacy and safety of DOAC use between those patients with AF with and without VHD were similar. The meta-analysis by Caldeira et al. added that while the data were limited, there was similar efficacy and safety data in patients with AF and bioprosthetic valves [22]. The authors of each meta-analysis concluded that presence of VHD did not affect the overall efficacy or safety of the use of DOACs in patients with AF [20–22]. Each meta-analysis independently concluded that in patients with AF and native valve disease or VHD, DOACs are a viable alternative to dose-adjusted warfarin [20–22].

DOAC Use in AF and MS

As discussed previously, the use of DOACs in patients with AF and moderate or severe MS has not been evaluated in landmark clinical trials evaluating patients with AF and VHD [10–13].

Table 1 VHD inclusion and exclusion criteria in DOAC Phase III Clinical Trials [10–14, 16–18]

Trial (year) *N* without VHD *N* with VHD	Intervention	VHD included	VHD excluded
RE-LY (2009) *N* = 14,162 *N* = 3950	Dabigatran 110 mg PO BID Dabigatran 150 mg PO BID Warfarin (target INR 2.5)	AR AS MR Mild MS TR	History of heart valve disorder (e.g., prosthetic valve or hemodynamically relevant valve disease)
ROCKET-AF (2011) *N* = 12,179 *N* = 1992	Rivaroxaban 20 mg PO daily Rivaroxaban 15 mg PO daily (if CrCl 30–49 ml/min) Warfarin (target INR 2.5)	AR AS MR	Hemodynamically significant MS Prosthetic heart valve
ARISTOTLE (2011) *N* = 13,389 *N* = 4808	Apixaban 5 mg PO BID Apixaban 2.5 mg PO BID (if ≥ 2 of the following: age > 80, SCr > 2.5, weight < 60 kg) Warfarin (target INR 2.5)	AR AS MR Mild MS TR Valve surgery	Moderate or severe MS Prosthetic heart valve
ENGAGE AF-TIMI 48 (2013) *N* = 18,222 *N* = 2824	Edoxaban 60 mg PO daily Edoxaban 30 mg PO daily Warfarin (target INR 2.5)	AR AS MR Valve surgery	Moderate or severe MS Unresected atrial myxoma Mechanical heart valve

AR, aortic regurgitation; *AS*, aortic stenosis; *BID*, twice daily; *CrCl*, creatinine clearance; *DOAC*, direct oral anticoagulants; *INR*, International Normalized Ratio; *kg*, kilogram; *MR*, mitral regurgitation; *MS*, mitral stenosis; *MS*, mitral stenosis; *PO*, per os; *SCr*, serum creatinine; *TR*, tricuspid regurgitation; *VHD*, valvular heart disease

However, 3 of these 4 landmark DOAC studies in the AF population included patients with mild MS as seen in Table 1 [10, 12–13].

The Randomized Evaluation of Long-Term Anticoagulant Therapy (RE-LY) trial enrolled patients with AF and assigned them to receive dabigatran or dose-adjusted warfarin (target International Normalized Ratio [INR] 2.5) [10]. Secondary analysis of the RE-LY trial found that 3950 patients enrolled (21.8%) had VHD, MR comprised a majority of those with VHD (79.4%), and only 4.9% of the VHD patients had mild MS. No difference in rates of mortality was seen in patients with and without VHD regardless of treatment arm (adjusted HR 1.09; 95% CI 0.96–1.23; $p = 0.18$) [16]. No difference in risk of stroke and systemic embolism was noted between patients with and without VHD (HR, 1.09; 95% CI, 0.88–133; $p = 0.43$). Similar to the overall RE-LY study results, patients with VHD who received dabigatran 150 mg PO twice daily had a significantly lower risk of stroke or systemic embolism compared to those who received warfarin (HR 0.59; 95% CI 0.37–0.93; $p = 0.021$). Patients with VHD had a higher risk of major bleeding regardless of treatment assignment (propensity score-adjusted HR 1.32; 95% CI 1.16–1.50; $p < 0.001$). In the sub-analysis of RE-LY, those with VHD (of which a majority had MR) had no difference noted related to efficacy or safety with the use of dabigatran vs. warfarin [16].

The Apixaban for Reduction in Stroke and Other Thrombotic Events in Atrial Fibrillation (ARISTOTLE) trial enrolled patients with AF and at least one risk factor for stroke to receive apixaban or dose-adjusted warfarin (target INR 2.5). The ARISTOTLE trial excluded patients with moderate or severe MS. Of the 4808 VHD patients enrolled, the vast majority (73.3% [3526 patients]) had MR and only 2.7% (131 patients) had mild MS. [14] As with previous studies, ARISTOTLE also demonstrated that patients with VHD had higher rates of stroke, systemic embolism, and mortality. Despite these higher event rates, there was no statistical difference in stroke reduction or reduction in systemic embolism in VHD patients receiving apixaban versus warfarin compared to patients without VHD (HR 0.70; 95% CI 0.51–0.97 vs. HR 0.84; 95% CI 0.67–1.04; $p = 0.38$) [14]. In addition, no statistically different rate of bleeding was seen in patients with or without VHD relative to apixaban or warfarin exposure (HR 0.79; 95% CI 0.61–1.04 vs. HR 0.65; 95% CI 0.55–0.77; $p = 0.23$) [14]. One limitation of applying these findings to the population with MS is that fewer than 3% of the study patients had mild MS. However, the authors concluded safety and efficacy data across the VHD population was consistent to those without VHD.

The Effective Anticoagulation with factor Xa Next Generation in Atrial Fibrillation-Thrombolysis In Myocardial Infarction 48 (ENGAGE AF-TIMI 48) trial enrolled patients with moderate-to-high risk AF to receive edoxaban or dose-adjusted warfarin (target INR 2.5) [12]. Patients were excluded if they had moderate or severe MS. Of the 2824 VHD patients enrolled, a majority (79.7% [2550 patients]) had MR, mild MS was not reported [17]. Consistent with previous studies, patients with VHD had a higher rate of death, major cardiovascular (CV) events, and major bleeding than the patients without VHD. Patients with VHD who received the edoxaban 60 mg dose had similar rates of stroke or systemic embolism compared to those without VHD (HR 0.69; 95% CI 0.44–1.07 vs. HR 0.91; 95% CI 0.53–1.02; interaction p value = 0.26). In addition, no statistically different rate of major bleeding was seen in patients with or without VHD relative to edoxaban or warfarin exposure (HR 0.74; 95% CI 0.53–1.02 vs. HR 0.82; 95% CI 0.71–0.94; interaction p value = 0.57) [17]. The authors concluded that despite the higher rates of death, CV events, and major bleeding in the population with VHD, there were similar efficacy and safety outcomes when comparing edoxaban to warfarin with or without VHD.

A recent retrospective observational study by Kim et al. evaluated the efficacy of DOACs in 2230 patients with AF and any severity of MS. [24] The study population was enrolled from the Health Insurance Review and Assessment Service (HIRA) database in the Republic of Korea. Patients receiving DOACs experienced thromboembolic event rates of 2.2% per year compared to 4.2% per year in the warfarin arm (adjusted HR 0.28; 95% CI 0.18–0.45) [24]. There was a trend towards a lower rate of intracranial hemorrhage (ICH) with DOACs compared with warfarin (0.5% vs 0.9%; adjusted HR 0.53; 95% CI, 0.22–1.26) which proved not statistically significant [24]. The authors acknowledged that a limitation of their study is that patients who underwent mitral valve surgery were excluded, which excluded patients with severe MS. The authors concluded these are promising findings for the use of DOACs in patients with AF and MS, but results should be further evaluated in a randomized trial.

Based on the sub-analyses of clinical trials which included AF patients with mild MS and the recent retrospective evaluation of Korean patients with AF and any severity of MS, there is moderate quantity of evidence to support the role of DOACs as an anticoagulation option in patients with mild MS. However, there is not enough information to support use of DOACs in patients with moderate or severe MS. Table 2 summarizes the quantity of evidence across various forms of VHD including MS.

DOAC Use in AF and Mechanical Heart Valves

Patients with mechanical heart valves were excluded from all phase III clinical trials of apixaban, dabigatran, edoxaban, and rivaroxaban for AF (see Table 1). There have been pre-clinical swine model studies with both apixaban and dabigatran evaluating their use following implantation with the bileaflet mechanical aortic valve which showed lower rates of bleeding compared to warfarin and thus drove the development of

Table 2 Quantity of evidence available for the use of DOACs in AF and VHD

Medication category	VHD						
	AR	AS	MR	Mild MS	Moderate or severe MS	Prosthetic heart valve	TR
DOAC	++	++	++	++	+	+	++
VKA	+++	+++	+++	+++	+++	+++	+++

[+] Limited quantity of evidence

[++] Moderate quantity of evidence

[+++] Large quantity of evidence

AF, atrial fibrillation; *AR*, aortic regurgitation; *AS*, aortic stenosis; *DOAC*, direct oral anticoagulant; *MR*, mitral regurgitation; *MS*, mitral stenosis; *TR*, tricuspid regurgitation; *VHD*, valvular heart disease; *VKA*, vitamin K antagonist

human studies in this population [25–26]. The Randomized, Phase II Study to Evaluate the Safety and Pharmacokinetics of Oral Dabigatran Etexilate in Patients after Heart Valve Replacement (RE-ALIGN) study enrolled patients with a mechanical bileaflet mitral or aortic valve to receive dabigatran or dose-adjusted warfarin (target INR 2.5 or 3.0 based on risk factors) [27•]. Based on an interim safety analysis, this study was stopped early as there was an increased risk with dabigatran without benefit seen. Stroke occurred in 9 dabigatran-treated patients (5%) compared to no strokes in the warfarin group. Increased bleeding risk occurred in 45 dabigatran-treated patients (27%) compared to 10 patients (12%) in the warfarin group (HR 2.45; 95% CI 1.23–4.86; $p = 0.01$) [27•].

Following the halted study, there was another dabigatran study performed to evaluate an AF patient population with bioprosthetic valve replacement. The Dabigatran Versus Warfarin After Bioprosthesis Valve Replacement for the Management of Atrial Fibrillation Postoperatively (DAWA) study was designed to evaluate the safety and efficacy of dabigatran in patients with AF and a bioprosthetic mitral and/or aortic valve replacement [23]. Patients were randomized to dabigatran or dose-adjusted warfarin (target INR 2.5). The primary endpoint was evidence of a new intracardiac thrombus at 3 months. Based on low study enrollment, it was stopped early. These small numbers enrolled in the study created limits to the conclusions that can be drawn from this study. The outcomes reported out at 3 months included 2 patients in the warfarin group developing an event (1 intracardiac thrombus and 1 ischemic stroke) and 1 patient in the dabigatran group developing an event (1 reversible ischemic neurological deficit) [23]. Overall, the DAWA study investigators concluded this was hypothesis-generating and warranted further evaluation in larger studies.

A subgroup analysis of ARISTOLE was performed on 156 patients enrolled in the study who had prior valve surgery [28]. Of the 156 patients with full data available, 104 patients had bioprosthetic valve replacement and 52 had a history of valve repair. No patients were reported as having a mechanical heart valve. Among the patients with a bioprosthetic valve replacement, 55 received apixaban and 49 received warfarin [28]. Based on the small number of patients in the sub-analysis, the event rates were low and no significant differences were seen between apixaban and warfarin relative to efficacy and safety outcomes. The authors concluded the results seen in this subgroup of bioprosthetic valve replacement and history of valve repair were consistent with the results of the overall ARISTOLE trial.

A recent meta-analysis by An et al. evaluated the role of antiplatelet therapy versus anticoagulation after surgical bioprosthetic aortic valve replacement (BAVR) [29]. This analysis identified 2 randomized controlled trials ($n = 397$) and 5 observational studies ($n = 2012$) in patients who underwent BAVR and received either warfarin or a DOAC for at least 3 months post-BAVR compared to antiplatelet therapy with aspirin and/or P2Y12 inhibitors for a least 3 months post-BAVR. No difference in stroke, thromboembolism, or mortality was seen between antiplatelet therapy and anticoagulation therapy. However, antiplatelet therapy demonstrated a trend towards fewer major bleeding events compared to anticoagulation (relative risk [RR] 0.34; 95% CI 0.11–1.04; $p = 0.06$) [29]. Additionally, a recent systemic review identified 6 clinical trials and 13 cohort studies evaluating anticoagulation strategies following surgical or transcatheter BAVR [30]. This analysis found moderate evidence to support that mortality, thromboembolic events, and bleeding rates were similar between aspirin and warfarin after surgical BAVR. There is a trend towards a small decrease in thromboembolism and morality with the combination of aspirin and warfarin, but with an increase is bleeding. Unfortunately, DOACs were not included in analysis when comparing antiplatelet therapy versus anticoagulation therapy. Overall, these analyses highlight that some patients may benefit from only receiving antiplatelet therapy versus anticoagulation (warfarin or DOAC) post-BAVR as it relates to safety and efficacy.

Implications for Practice

The definition of NVAF has evolved to include patients with certain types of VHD. It is important to evaluate the

quantity of evidence available for use of DOACs in patients with AF and VHD compared to warfarin in the same population, which is summarized in Table 2. Patients with valvular AF, defined as moderate-to-severe MS and/or mechanical heart valves, have been deliberately excluded from DOAC clinical trials, yet they represent a group of patients at high risk for cardioembolic stroke [31]. Sub-analyses of patients with AF and other types of VHD have strengthened recommendations for the use of DOAC in patients with mild MS and bioprosthetic valves. However, this evidence should not be extrapolated to patients with moderate to severe MS or those with mechanical heart valves. Dabigatran is the only DOAC to be studied in patients with mechanical heart valves and this study was terminated early due to excess thromboembolic and bleeding risks in patients receiving dabigatran compared with patients received dose-adjusted warfarin [27•]. Based on the safety concerns resulting in early trial termination, it is unlikely that similar trials will be pursued with other DOACs. While the data from the retrospective study of Korean patients with AF and MS are promising, the trial excluded patients with severe MS and is limited by its retrospective nature. Positive outcome data with DOAC use in patients with AF and mild MS should not be extrapolated to patients with more severe MS. [24] Healthcare providers should continue to refrain from using DOACs in patients with moderate-to-severe MS or mechanical heart valves until randomized, controlled clinical trial data demonstrate efficacy and safety in these populations.

Conclusion

Apixaban, dabigatran, edoxaban, and rivaroxaban are FDA-approved DOACs for patients with NVAF, defined by the 2019 update to the 2014 AHA/ACC/HRS Atrial Fibrillation Guidelines as AF in the absence of moderate-to-severe MS or mechanical heart valves. This recommendation is predominately supported by the exclusion of these high-risk populations in DOAC clinical trial data, as well as in sub-analyses and meta-analyses of these trials. Based on the lack of data to support safety and efficacy of DOAC use in patients with valvular AF, dose-adjusted warfarin should remain the cornerstone of anticoagulation for these patients.

Compliance with Ethical Standards

Conflict of Interest Sarah L. Anderson and Joel C. Marrs declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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