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Stroke Prevention in Atrial Fibrillation and Valvular Heart Disease

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Abstract: There is a clinically staggering burden of disease stemming from cerebrovascular events, of which a majority are ischemic in nature and many are precipitated by atrial fibrillation (AF). AF can occur in isolation or in association with myocardial or structural heart disease. In the latter case, and when considering health at an international level, congenital and acquired valve-related diseases are frequent contributors to the current pandemic of AF and its clinical impact. Guidelines crafted by the American Heart Association, American College of Cardiology, European Society of Cardiology and Heart Rhythm Society underscore the use of vitamin K antagonists (VKAs) among patients with valvular heart disease, particularly in the presence of concomitant AF, to reduce the risk of ischemic stroke of cardioembolic origin; however, the non-VKAs, also referred to as direct, target-specific or new oral anticoagulants (NOACs), have not been actively studied in this particular population. In fact, each of the new agents is approved in patients with AF *not* caused by a valve problem. The aim of our review is to carefully examine the available evidence from pivotal phase 3 clinical trials of NOACs and determine how they might perform in patients with AF and concomitant valvular heart disease.

Keywords: Atrial fibrillation, ischemic stroke, oral anticoagulants, valve-related heart disease.

INTRODUCTION

Approximately 795,000 persons in the United States (US) experience a new or recurrent cerebrovascular event each year [1]. A majority of events are ischemic in nature. It is well known that patients with valvular heart disease are at heightened risk for ischemic stroke, particularly those with mitral stenosis and underlying atrial fibrillation (AF) or atrial flutter [2, 3].

Traditional Perspective of Valvular Heart Disease and AF

Rheumatic heart disease involving the mitral valve causes inflammation and fibrosis with disruption of the atrial architecture. There is increased left atrial pressure that contributes to left atrial dilation and increased wall stress. These acquired local conditions are thought to represent predisposing factors to the development of AF [4, 5].

While non valvular atrial fibrillation (NVAF) is known to increase the risk for ischemic stroke by 5-fold, the risk is even greater among patients with mitral stenosis, increasing up to 17-fold [6]. Approximately two-thirds of patients with valvular atrial fibrillation (VAF) (mitral stenosis) who survive a first ischemic stroke experience a second event in the subsequent decade. Half of the events occur in the first year. A retrospective study by Walker and colleagues reported that patients with rheumatic mitral stenosis in sinus rhythm had an incidence of 8% per year of an embolic event; this increased to 31.5% in patients with concomitant AF. Patients with rheumatic valvular disease characterized predominantly by mitral regurgitation were also at heightened risk for a cardioembolic event, even among those in sinus rhythm who had an incidence of 7.7% per year, increasing to 22% in those with AF [7].

While there have been no large randomized clinical trials to demonstrate the effectiveness of anticoagulation for thrombo-prophylaxis in patients with rheumatic valvular heart disease and atrial fibrillation, observational studies and

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retrospective analyses of patients with mitral stenosis do offer support for treatment. In a study by Fleming and colleagues, patients not anticoagulated had an embolic event incidence of 25% per year; in contrast, patients receiving anticoagulation, primarily a VKA, had 0.8% patient-year incidence of embolic events and a 0% recurrence rate [8]. A review of 254 patients with VAF reported that the incidence of an embolic event was 8 times greater in patients not receiving anticoagulation, *versus* those treated with an oral anticoagulant [9]. In 1977, the Joint Committee for Stroke published a statement that reviewed 11 studies evaluating thrombo-prophylaxis with anticoagulant therapy in patients with rheumatic mitral disease; they recommended anticoagulation in patients with rheumatic heart disease, particularly those with AF and a history of ischemic stroke [10].

Contemporary Perspective of Valvular Heart Disease and AF

AF currently affects over 2 million persons in the US, and this number is projected to increase to 10 million by the year 2050 [11]. The total number may actually be much higher, as nearly 50% of persons with AF do not experience signs or symptoms of the arrhythmia. AF is believed to account for at least 10-12% of all ischemic strokes [12, 13] and the risk increases steadily with age and other common conditions, including systemic hypertension.

The *AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation* has defined AF in the presence of rheumatic heart disease or either mechanical or bioprosthetic valve in the mitral position as VAF [14, 15]. The European Society of Cardiology Guidelines also determined VAF to be present with concomitant rheumatic heart disease (primarily mitral stenosis) or a prosthetic heart valve [16].

Clinical Trials of New Oral Anticoagulants

The development of new oral anticoagulants (NOACs) as an alternative to VKAs in patients with AF focused on those without valvular heart disease (NVAF) (Table **1**). This decision was reflective of a changing landscape in Europe and North America, with a declining incidence and overall prevalence of rheumatic heart disease and rapidly increasing number of persons with AF at risk for ischemic stroke. It also acknowledged the wide phenotypic variability for cardioembolic stroke risk with mild, moderate and severe rheumatic mitral stenosis. Despite the clear decision to perform pivotal trials in patients with NVAF, patients with valvular heart disease were enrolled.

Table 1. Summary of the trials involving the Novel Oral Anticoagulants for treatment of Non Valvular Atrial Fibrillation, with their respective definition of valvular disease and the out comes.

Drug	Trial	Definition of valvular disease	Outcomes
Apixaban	AVERROES [32, 33]	Valvular heart disease requiring surgery, including prosthesis valves	Apixaban reduced the risk of stroke or systemic embolism without significant bleeding risk or intracranial hemorrhage in NVAF.
Apixaban	ARISTOTLE-AF [20, 29]	Prosthetic valve or clinically significant (moderate or severe) mitral stenosis	Apixaban was superior to warfarin in reducing stroke and systemic embolism in NVAF.
Dabigatran	RE-LY [19, 34]	Prosthetic valve or hemo-dynamically relevant valve disease	Dabigatran had lower rates of stroke or systemic embolism but similar rates of hemorrhage as warfarin when dosed at 150mg twice a day in NVAF
Edoxaban	ENGAGE-AF-TIMI 48 [22, 30]	Moderate or severe mitral stenosis, mechanical prosthetic valves	Edoxaban was non inferior to warfarin at both doses for prevention of stroke or systemic embolism in NVAF
Edoxaban	ENSURE-AF (actively enrolling) [35]	Mitral stenosis or rheumatic disease, mechanical prosthetic valve	Currently underway
Rivaroxaban	ROCKET-AF [17, 18]	Hemodynamically significant mitral stenosis or prosthetic valve	Rivaroxaban was non inferior to warfarin for prevention of stroke and systemic embolism in NVAF

In order to better understand the spectrum of valvular heart disease captured in the NOAC registration trials, one must carefully review individual study exclusion criteria. The 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) excluded patients with prosthetic heart valves and those with hemodynamically significant mitral stenosis [17]. In contrast, the Randomized Evaluation of Long-Term Anticoagulation (RE-LY) trial excluded patients with prosthetic heart valves and those with hemodynamically significant native valvular heart disease, but did not distinguish between the aortic and mitral valves [18, 19]. The Apixaban for Reduction in Stoke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial excluded patients with moderate-to-severe mitral stenosis and those with prosthetic heart valve [20]. The Apixaban *versus* Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment (AVERROES) trial excluded patients with valvular heart disease that was severe enough to require surgery. Perhaps the most inclusionary of the phase 3 trials, the Effective

Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48 (ENGAGE AF-TIMI 48) trial, did not exclude patients with either bioprosthetic valves or those who had previously undergone a valve repair [21, 22].

Table 2. Novel Oral Anticoagulant trials with their defined respective safety and efficacy endpoint.

Drug	Trial	Primary safety outcome	Primary efficacy endpoint
Apixaban	AVERROES [32, 33]	Time to major bleeding	Time to stroke or systemic thromboembolus
Apixaban	ARISTOTLE-AF [20, 21]	Time to major bleeding	Time to stroke or systemic thromboembolus
Dabigatran	RE-LY [19, 34]	Major bleeding	Stroke or systemic thromboembolus
Edoxaban	ENGAGE-AF-TIMI 48 [22]	Major bleeding	Time to stroke or systemic thromboembolus
Rivaroxaban	ROCKET-AF [17, 18]	Major and nonmajor clinically relevant bleeding	Stroke or systemic thromboembolus

RE-LY Trial

In the RE-LY trial, a direct thrombin inhibitor, dabigatran etexilate, was compared at two fixed doses with warfarin in a blinded study. The primary outcome was defined as either cerebral or systemic embolism. At 110mg dose, dabigatran was found to be non-inferior to warfarin for the rate of primary outcome. At the higher dose of 150mg, dabigatran was superior to warfarin for primary outcomes risk reduction [23].

In this trial, patients that were excluded had either a history of "severe valvular disorders," defined by prosthetic valve or hemodynamically relevant valve disease [19, 23]. Despite the exclusion criteria, there *were* patients with valvular disease that were included in the trial. In total, 21.8% percent of the patients enrolled in the RE-LY trial had some form of valvular heart disease that did not exclude them from participation; only 1.1% of them had mild mitral stenosis. Additionally, a subgroup analysis compared the overall effects of dabigatran with warfarin in patients with and without symptomatic heart failure (defined as the presence of NYHA class II or higher symptoms in the six months before screening with a prior admission for congestive heart failure) [24]. In this analysis, 26.2% of participants in the symptomatic heart failure group and 20.1% in the group without NYHA class II or greater heart failure, had "valvular heart disease" [24]. The study showed no significant outcome differences with either dabigatran or warfarin in this subset of patients.

While the RE-LY trial illustrates the benefits of dabigatran for thromboembolism protection, the Randomized Phase II Study to Evaluate the Safety and Pharmacokinetics of Oral Dabigatran Etexilate in Patients after Heart Valve Replacement (RE-ALIGN) is perhaps the most direct evaluation of a NOAC *versus* VKA for patients with valvular heart disease - in this particular case, mechanical prosthetic valves [25].

The study compared anticoagulation with dabigatran against warfarin in patients with either mechanical aortic or mitral valve replacement (AVR, MVR) [25]. Patients who had undergone either AVR or MVR within 7 days, or at least 3 months earlier, were then randomly assigned to receive warfarin (dosed to an INR of 2 to 3 or 2.5 to 3.5, on the basis of thromboembolic risk) or dabigatran (dosed to obtain a trough plasma level of at least 50 ng per milliliter). The study was discontinued due to the high thromboembolic and bleeding events among patients in the dabigatran group. The composite of stroke, transient ischemic attack, systemic embolism, myocardial infarction, or death occurred in 15 patients (9%) in the dabigatran group and 4 patients (5%) in the warfarin group (hazard ratio in the dabigatran group, 1.94; 95% confidence interval [CI], 0.64 to 5.86; P=0.24); thromboembolic events were higher in the group started on dabigatran within 7 days of MVR. Additionally, *all* cases of valve thrombosis detected in clinically asymptomatc patients were reported in the dabigatran group (3%) [25].

Based on the available data, dabigatran for patients with mechanical valves cannot not be supported, showing no benefit and an excess risk; however, the RE-ALIGN trial did generate a dialogue and series of questions to better understand the findings that included a lack of uniform aspirin use and reported mean time within the pre-defined target drug range of approximately 50% [26]. The latter suggests changes in dabigatran pharmacokinetics in the setting of cardiac surgery or the dynamics of blood flow and metabolism after heart valve surgery. Whether similar properties should be expected in the setting of trans-aortic valve implantation (TAVR) will require further investigation.

ROCKET AF Trial

In a multicenter randomized double-blinded, double-dummy trial, rivaroxaban was compared against warfarin for risk reduction in NVAF. Patients requiring anticoagulation for any other reason were excluded. The primary end point was stroke and systemic embolism. The hazard ratio was lower in the rivaroxaban group at 0.79 (95% CI 0.66-0.96) [17]. The event rates for disabling stroke and stroke with leading to death were lower in the rivaroxaban group

compared to the warfarin group [27]. Patients were excluded from the clinical trial if they had active endocarditis, atrial myxoma or prosthetic valves. The trial did permit patients with non-critical valvular heart disease, annuloplasty, with or without prosthetic ring, commissurotomy and/or valvuloplasty to be enrolled [17, 18].

A post-hoc analysis showed that 14.1% of the 14,171 patients enrolled in ROCKET AF had significant valvular disease (SVD) and were evaluated by intention- to- treat and in the safety analysis [28]. Rheumatic valve disease was identified in 3.2% of the patients, mitral regurgitation, the most frequent valvular disease present, was present in in 89.6% of the patients. Patients with SVD had more comorbidity, but there was no significant difference in patients on warfarin in terms of their CHADS2 and HASBLED scores. The end points, rate of stroke or systemic embolism, were similar in the rivaroxaban and warfarin groups, consistent with the original trial, HR, 0.89 (95% CI, 0.75-1.07), interaction P value for SVD was 0.76 [17, 18]. Major and non-major clinically relevant bleeding were higher in the SVD patients compared to those without SVD. In patients with SVD, there was a higher incidence of bleeding in the rivaroxaban group (19.8%) compared to those on warfarin (16.8%) with HR 1.25, (95% CI, 1.05-1.49) but there was no significant difference reported in patients without SVD, P value for interaction for SVD and treatment was 0.034. Consistent with the overall findings from ROCKET AF, the rate of ICH was lower in patients randomized to rivaroxaban *versus* those receiving warfarin with or without SVD [28].

ARISTOTLE Trial

Apixaban is a direct Xa inhibitor that was compared to warfarin in NVAF in a double-blinded, double-dummy randomized trial. Apixaban proved to be superior to warfarin in the ARISTOTLE trial for the primary efficacy out come, stroke or systemic embolism. The study also showed the primary safety outcome of major bleeding, morbidity with clinically relevant non-major bleeding and mortality to be significantly lower with apixaban [21, 29].

Patients with concomitant valvular heart disease of moderate or severe mitral stenosis were excluded from this trial, as were patients requiring anticoagulation for indications other than atrial fibrillation, such as a history of prosthetic heart valve [20, 21, 29]. A subanalysis of the ARISTOTLE trial identified 26.4% of the patients enrolled as having some component of significant valvular heart disease other than mechanical heart valve and clinically significant mitral stenosis. This group of patients was comprised of those having prior valve surgery and/or echocardiographic features of moderate valve disease. Mitral stenosis was present in 2.7% of the patients, while moderate mitral regurgitation represented the predominant valvular heart disease at 73.3% [21]. While patients with valvular heart disease were found to have a higher incidence of stroke, systemic embolism or bleeding than their counter-parts without significant valve disease, the interaction p value for the primary endpoint at 0.38, was not significant and paralleled the overall study findings [21, 29].

ENGAGE AF-TIMI 48 Trial

Edoxaban is a direct anti-Xa inhibitor, studied in the ENGAGE AF-TIMI 48 trial, which examined the efficacy and safety of the drug at two separate fixed doses in patients with atrial fibrillation, against warfarin [22]. This was also a randomized double-blinded, double-dummy, multicenter trial. The primary end point of first stroke of systemic embolic event was higher in the warfarin group (1.8%) than in the high dose edoxaban group taking 60mg daily (1.57%). This difference was not significant. At $p < 0.001$, the annual rate of hemorrhagic stroke was significantly lower in both high and low dose edoxaban group compared to warfarin. The trial showed that both regimens of edoxaban were non-inferior to warfarin for prevention of stroke and systemic embolism, with significantly lower rate of bleeding and death from cardiovascular causes. The only exception reported was the subgroup receiving high dose edoxaban, which experienced a higher rate of gastrointestinal bleeding.

The study did allow inclusion of patients with bioprosthetic heart valves and/or valve repair in the trial, but patients with mechanical heart valves and those with moderate to severe mitral stenosis were excluded. Patient with any other indications for anticoagulation besides AF were also excluded from the trial [30]. It is important to study the patient population with prosthetic valves, mild mitral stenosis, mitral regurgitation or aortic valve disease were enrolled in the ENGAGE AF-TIMI 48 trial, to assess outcomes of AF patients with valvular heart disease who were treated with edoxaban.

CONCLUSION

Patients with valvular heart disease, particularly with mitral stenosis and prosthetic valve, have an increased incidence of thromboembolism. Additionally, concomitant AF presents an increased risk in patients with valvular heart

disease. Currently, for patients with valvular AF, including patients with mechanical valve and mitral stenosis, the standard of care remains VKA [15, 31].

As demonstrated by the review of the trials and the post hoc analysis, patients with valvular heart disease were included in the trials. In some of these trials, this included patients with varying degrees of mitral regurgitation, history of mitral repair and bioprosthetic valve, and not all severities of mitral stenosis were a contraindication for these trials. Patients with valvular heart disease, despite an increased risk of embolic event, had similar outcomes to those patients without SVD in these trials for primary end points (Table **2**) [21, 22, 28].

Warfarin, as shown in the RE-ALIGN trial, is better for thromboembolism risk reduction in mechanical valve when compared to dabigatran [25]. This may be due to the fact that the pathogenesis of thrombus formation is different in mechanical valves compared to that in AF. Without a study powered to successfully demonstrate non-inferiority and safety of NOAC compared to warfarin in anticoagulation of patients with prosthetic valves, NOAC should not be used in patients with prosthetic valves, particularly those with mechanical valve.

Given the background of the subanalysis of patients with valvular heart disease included in the trials, the time is right for randomized clinical trials for patients with SVD with AF on target specific oral anticoagulants powered for evaluation of their safety and efficacy in valvular AF patient.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

ABBREVIATIONS

AF	=	Atrial Fibrillation
AVR	=	Aortic Valve Replacement
INR	=	International Normalized Ratio
NOAC	=	New Oral Anticoagulant
NVAF	=	Non-Valvular Atrial Fibrillation
MVR	=	Mitral Valve Replacement
SVD	=	Significant Valvular Disease
TIA	=	Transient Ischemic Attack
VAF	=	Valvular Atrial Fibrillation
VKA	=	Vitamin K Antagonist

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