

## Valvular Heart Disease And “Nonvalvular Atrial Fibrillation” Coumadin or a Novel Oral Anticoagulant Variables to Consider

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### Abstract

*Clinicians treating atrial fibrillation must initially identify and ultimately verify whether this rhythm fits within the definition of “non-valvular” atrial fibrillation (NVAF). The spectrum of structural heart disease can render this process a challenge as what is meant by NVAF is continually evolving. Phenotypic variants in valvular heart disease including repaired valvular injury have undergone definitional updates pertaining to NVAF. This has produced inconsistencies in each subsequent authoritative guideline often further confusing practitioners. At issue is whether a vitamin K dependent antagonist (VKA) exemplified by warfarin, or one of the new novel oral anticoagulants (NOACs) is appropriate to treat NVAF in a patient with a form of valvular heart disease. The present effort is a practical review of the current clinical landscape wherein practitioners struggle to advise and treat patients with optimal anticoagulation therapy with NVAF as currently defined. It is also a review of why certain valvular conditions may actually still fit within the definition of NVAF allowing NOAC use.*

### Introduction

A common problem encountered is whether atrial fibrillation fits within the definition of “non-valvular atrial fibrillation” (NVAF). The subtle continuum of structural heart disease can challenge clinicians attempting to categorize a patient’s rhythm as NVAF, in part because its definition has continually evolved [1-4]. Further, phenotypic variants in valvular heart disease including repaired valvular injury have undergone definitional updates pertaining to NVAF within each subsequent authoritative guideline [1-6]. This has resulted in inconsistencies in the definition of NVAF further confusing practitioners. Ultimately, the management strategy often begins by first deciding on whether anticoagulation should be initiated for NVAF. Caregivers using either the CHADS or CHA2DS2-VASC clinical predictors assess stroke potential associated with NVAF but then face several choices in anticoagulants [7]. Choosing the appropriate anticoagulant is most often a decision between a vitamin K dependent antagonist (VKA) exemplified by warfarin, or one of the new novel oral anticoagulants (NOACs) (alternatively called direct oral anticoagulants-DOACs). But a pivotal variable in the choice of anticoagulants is determining whether the patient actually has NVAF as currently defined by different authoritative sources [1, 3, 5, 6]. The present effort is a practical review of the ongoing challenges that clinical practitioners face in advising and treating patients with optimal anticoagulation therapy with NVAF as it is currently defined. It is also a review of why certain valvular conditions may actually still fit within the definition of NVAF allowing NOAC use.

### Historical Perspective: Use of Vitamin K Dependent Agents

Clinicians have used warfarin or one of its derivatives as a VKA-

based therapy to reduce the incidence and frequency of embolic stroke believed to originate in cardiac structures [8]. Several pivotal trials in the 1990’s demonstrated warfarin provided a significant protective effect in the setting of NVAF [8-11]. The endorsement of this strategy was made even more poignant after studies demonstrated that atrial fibrillation is implicated in approximately 15% of all strokes in the United States [12]. Both the human cost expressed in reduced quality of life and necessary rehabilitation coupled with actual economic impact from lost productivity speak to the imperative of reducing stroke rates [13]. Thus, the rapid assimilation of VKA to treat NVAF occurred, but so did concern about VKA-associated expense and its inherent potential for harm [5].

Warfarin and other VKA derivatives require monitoring with repetitive sampling of the level of anticoagulation [5]. While this fact is a nuisance for some, it may be a life-saving requirement for others in whom levels of anticoagulation may fluctuate dramatically with VKAs. This has been problematic in some groups, such as the elderly, where diet and other drug therapies impacting VKA were observed to be more common [14]. Pharmacological alternatives reducing VKA-associated hemorrhage potential along with the burden of expense and inconvenience became a priority.

### Introduction of Novel Oral Anticoagulants and Consequences

NOACs in America were first introduced in 2010 with dabigatran, a direct thrombin inhibitor being the initial agent followed by Xa inhibitors rivaroxaban in 2011 and apixaban in 2012 [15-17]. Collectively, these demonstrate a rapid onset of action and a more predictable pharmacologic profile with less dietary and other drug-drug interactions [6]. However, very soon after introduction of

dabigatran, evidence from the RE-ALIGN trial and from case reports supported an increased stroke and thrombosis rate in patients when dabigatran was used with mechanical prosthetic valves [(18,19)]. While the RE-ALIGN trial outcomes may differ from the clinical settings in early isolated case reports, several mechanistic observations attempted to illuminate the observed outcomes. This effort was important since RE-ALIGN led to a general class prohibition in the use of NOACs involving mechanical prosthetic valves [20-22].

Explanations focused on the initial trigger for thrombosis on MHVs. It was felt to be activation of the contact system with triggered clotting via the intrinsic pathway. The intrinsic pathway is initiated by contact activation of fXII, propagated by fXIIa-mediated activation of fXI and leading ultimately to thrombin generation [15]. Evidence supports that MHVs trigger clotting more often, but not exclusively, at their Dacron and Teflon sewing ring segments compared with their leaflet structures [23]. The apparent disparity between dabigatrin and warfarin in preventing propagation of the clot is that thrombotic growth occurs involving IIa (thrombin) at a concentration that exceeds dabigatrin's protective 1:1 stoichiometric inhibition [14]. There is simply too much IIa proportional to dabigatrin at the levels found in the microenvironment of the newly implanted valve. In fact, peak levels of dabigatrin given 150 mg twice daily were protective at the micro-concentration achieved, but trough levels fell below the requisite threshold [24].

So why did warfarin work? It has the well-documented effect of collectively reducing the functional levels of fIX, fX and fII [14]. This more generalized impact of warfarin has long been considered disadvantageous as it plays a role in the significant dietary and drug-drug interactions found with warfarin. But here, its more "global" impact on clotting factors resulted in the attenuation of fXa and thrombin generation via both intrinsic and common pathways respectively [14]. There was proportionally less IIa made due to this multifactor inhibition by warfarin, whereas the selective inhibition of IIa by dabigatrin simply was unable to match the proliferation of IIa in the setting of a newly implanted valve [14]. Thus, warfarin likely prevented thrombus formation associated with the Dacron and Teflon sewing rings because it reduced the total IIa concentration through its aggregate impact on its precursors. Thus, while the prohibition of dabigatrin was expanded to the general class of NOACs, no current clinical data regarding the fXa inhibitors has been published. In fact there is early evidence that rivaroxaban is more effective than enoxaparin at preventing porcine thrombosis [25]. Yet this must be considered preliminary and it is not known at this point in time whether either rivaroxaban or apixaban is protective and different from dabigatrin.

With this uncertainty as to NOAC efficacy in the setting of MHV compared to warfarin, clinicians appropriately questioned other settings of valvular pathology with and without prosthetic surgical intervention. These included previously implanted stable bioprosthetic valves, prior surgical valvular repair or valvular annuloplasty (using annular rings). The fundamental concern remains as to whether these settings should also be included in this more general NOAC prohibition. Again, the data is absent. Ultimately, an even more basic question arose regarding the definitional precision of NVAF since the label "NVAF" appears to be inconsistent and imprecise. Since expert and guideline publications continue to evolve commensurate with coordinated investigative efforts, it is reasonable

to expect that what is meant by NVAF will continue to change.

### What Constitutes Non-Valvular Atrial Fibrillation?

The definition of NVAF has continued to change with each update in guidelines and expert opinion panels [(1-3,6)]. Early guidelines defined NVAF as a rhythm disturbance occurring in the absence of rheumatic mitral valve disease or a prosthetic heart valve [26]. Subsequent updates revised the definition of NVAF to include the absence of mitral valve repair [1]. By 2014 NVAF was defined by the absence of rheumatic mitral stenosis, a mechanical or bioprosthetic heart valve or mitral valve repair [2]. There continued to be subtle but important differences in what European and American experts considered NVAF in addition to disparities between expert societies such as the American College of Chest Physicians [12].

A more recent consensus has defined NVAF as AF in the absence of prosthetic mechanical heart valves or hemodynamically significant valve disease [3]. The latter label of "hemodynamically significant", being a valve abnormality warranting surgical or percutaneous intervention, or one that would adversely effect survival or well-being [3]. But historic debates regarding timing and criteria influencing "survival" or "well being" in valvular heart disease support concern over definitional ambiguity. Thus, clinicians must account for the evolving expert recommendations and the inherent NVAF definitional discrepancies that are both understandable but challenging in the care of patients.

In part, this continuing ambiguity is a legacy of the inclusion or exclusion criteria found in the major trials establishing the efficacy of the NOACs [27, 28]. For example, ARISTOTLE (apixaban) and ROCKET-AF (rivaroxaban) trials each had different exclusion criteria (See Table 1) regarding specific cardiac valvular conditions [27-30]. Thus, drawing definitive clinical conclusions for NOAC use in specific cardiac valvular conditions was problematic. It required caregivers to in effect potentially use a single set of inclusion data from one of several trials, each of which were not originally designed to address this specific concern. It is thus reasonable to conclude that ambiguity remains as to safety in the use of specific NOACs for patients with specific valvular conditions. It is also fair to conclude that imprecision remains in the definition of NVAF.

**Table 1: Valvular heart disease subanalyses of direct oral anticoagulant atrial fibrillation trials**

Original Trial	N	Drug Tested against warfarin	Valvular Heart Disease Exclusion Criteria	Patients with VHD, N (%)
ARISTOTLE (2011)	18201	Apixaban	Valvular Disease requiring surgery, prosthetic mechanical heart valve, moderate or severe MS.	4808 (26)
RE-LY (2009)	18113	Dabigatran	History of heart valve disorder	3950 (22)
ROCKET AF (2011)	14264	Rivaroxaban	Hemodynamically significant MS or prosthetic heart valve	2003 (14)

**Abbreviations:** ARISTOTLE for Reduction in Stroke and Other Thrombotic Events in Atrial Fibrillation; RE-LY, Randomized Evaluation of Long-Term Anticoagulant 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

## Case and NOAC Considerations

So where does this leave the clinician caring for a 78 year old female with atrial fibrillation and a mitral valve repair with an annuloplasty ring and a bovine bioprosthetic aortic valve. As the above analysis suggests there are as of yet no authoritative trials addressing the use of NOACs in patients with valvular heart disease. We must instead depend upon expert consensus and subanalyses of the pivotal NOAC trials. Remembering that these were designed for a different purpose than to derive safety of NOACs versus warfarin in patients with valvular heart disease; the following can be concluded.

### NOAC Use with Bioprosthetic versus Mechanical Valve

ARISTOTLE had 4,808 patients with VHD at baseline [27]. A total of 251 had prior valve surgery but again there is no report as to the specific surgery performed. Thus, the distinction between bioprosthetic implants or valve repair was not made but those with VHD were older and had a mean higher CHADS2 score [12, 23]. There was no statistical difference in this small group between warfarin and apixaban in bleeding complications, stroke rate and all-cause mortality [6]. Is it safe to use in patients with valvular surgery such as valvuloplasty or mitral valve repair? There is no conclusive data. Clinicians are aware of the potentially flawed inferences possible from the subanalysis of a very small group of the total, but in addition this subanalysis did not list the specific types of surgery further clouding attempts at assisting clinicians in making rationally based decisions.

Of some interest a small group of 106 patients in the ROCKET-AF trial had prior cardiac valvular procedures evenly distributed between the warfarin and the rivaroxaban groups [28]. The procedures were defined as including valvuloplasty or other procedures. Embolic events were not different between the two groups but major bleeding was higher in the rivaroxaban group ( $p=0.01$ ) [6]. These are very small groups to address this question and must be viewed with the appropriate degree of caution. A more general summation is that in the ARISTOTLE, RE-LY, and ROCKET-AF trials, patients with VHD, although separately and at times ambiguously defined, were older with more co-morbidities than those without VHD [27,28,31].

Stroke rates were similar in RE-LY, and ROCKET-AF trials with and without VHD once baseline criteria were adjusted, but in ARISTOTLE, the embolic rate was higher in patients with VHD [6, 27, 28]. Major bleeding rates in those with VHD were higher in all three trials comparing those with and without VHD, again suggesting the role of co-morbidities and age-dependency [6]. However, the embolic risk was lower in all three trials for the NOACs in comparison to warfarin for those with and without VHD [6]. This enhanced protective benefit of NOACs may in fact be secondary to the variability found in warfarin's therapeutic efficacy. Published reports note that the "time in therapeutic range" for warfarin may range between 56-75% underscoring a disadvantage in its efficacy and thus clinical outcomes compared with the NOACs [32].

Where does this leave us with the 78 year old female with atrial fibrillation and a mitral valve repair with an annuloplasty ring and a bovine bioprosthetic aortic valve? Of course, a VKA may be used but can we transfer the outcomes data from the pivotal NOAC trials to this patient inferring that she would derive benefit from them, with less hemorrhage potential and greater efficacy in the prevention of cardio embolic events? Presently this is an unknown. Importantly, bioprosthetic valves are less thrombogenic

than MHVs. It also appears that bovine bioprosthetic valves have less thrombosis than porcine valves [33]. But guidelines recommend warfarin anticoagulation for bioprosthetic valves, especially in the mitral position, for the first 3 months to counter increased thromboembolism associated with new implants [5].

Although there are no current published data, oral inhibitors of fXa are hypothesized to more significantly reduce thrombus production from the Dacron and Teflon sewing rings of a bioprosthetic valve than dabigatran [6]. Since each molecule of fXa generates 1,000 molecules of thrombin, oral inhibitors of fXa may thus attenuate thrombin production by acting to block upstream amplification in a manner that direct thrombin inhibition from dabigatran could not [6]. Beyond the first three months, anticoagulation is often optional for a biological valves but comorbidities require careful individualization. A bovine aortic bioprosthesis would arguably not require any anticoagulation and thus using either apixaban or rivaroxaban is defensible. Further, data is scant but a recent series of 105 patients showed that catheter ablation of AF with uninterrupted NOAC use in patients with biological heart valves is feasible and safe [6].

As to the concern over mitral valve repair with a valvuloplasty ring, updated guidelines by 2006 through 2014 excluded mitral valve repair as within the definition of NVAF. But clinicians appropriately have questioned whether the critical variable in repair is evidence of "hemodynamically significant" valve disease rather than the mere history of repair. In part this concern reflects the consensus definition for NVAF from the European Heart Rhythm Association and its affiliates that does specify exclusion of mitral valve repair [3]. Thus, definitional inconsistencies for NVAF and variability of inclusion/exclusion criteria in pivotal trials of NOAC efficacy contribute to remaining ambiguity in clinical practice.

## Conclusion

Clinicians face a challenging environment when contemplating use of NOACs in the setting of AF with coexistent VHD. The seminal trials all vary in their inclusion criteria and the term NVAF is a term both imprecise and continuing to evolve depending on the expert group or authored guidelines. We are left with select careful use of apixaban and rivaroxaban predicated upon position of the valvular abnormality, the type of prosthesis employed and the comprehensive assessment of clinical co-morbidities. Ongoing research will continue to illuminate the answers to many of these challenges but prudent decisions will always be requisite.

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