Defining nonvalvular atrial fibrillation: A quest for clarification

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Defining Non-Valvular Atrial Fibrillation: a Quest for Clarification

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Abstract

Non-vitamin K oral anticoagulants (NOACs) are currently recommended for patients with non-valvular atrial fibrillation (NVAF) since the publication of the four major pivotal trials evaluating the efficacy and safety of factor IIa and factor Xa inhibitors. The definition of NVAF is unclear, varying from one trial to another, and even between North-American and European guidelines, which is a source of uncertainties in clinical practice. However, many patients with atrial fibrillation (AF) present signs of valvular involvement, and clarification of this term is needed in order to not deny NOACs to patients based on the wrong perception that they may have valvular AF.

The currently unique contraindications to NOACs are patients with mechanical heart valves and those with moderate-to-severe mitral stenosis, as stated by the recent 2015 position paper of the European Heart Rhythm Association. Patients with native heart valve involvement, regardless of their severity are suitable for NOAC therapy. Patients with bioprosthetic heart valves and mitral valve repair may be suitable for NOACs except for the first 3 and the first 3-6 months post-operatively, respectively. Patients with transaortic valve implantation (TAVI) or percutaneous transluminal aortic valvuloplasty are also considered as being eligible for NOACs, although the bleeding risk has to be carefully considered in this population often requiring a combination with antiplatelet therapy.

Future studies are warranted to increase the level of evidence of use of NOACs, particularly in patients with TAVI and valvular surgery, and to determine whether they could be used in the future in the only two remaining contraindications.

Introduction

Atrial fibrillation (AF) is the most common arrhythmia in clinical practice, with currently in Europe approximately 10 million patients with AF and 100,000–200,000 with new-onset AF.[1] This arrhythmia has a high morbidity and mortality risk, mainly due to the elevated risk of ischemic stroke. The CHA_2DS_2VASc score is a validate tool to estimate the annual risk of stroke or systemic embolism, ranging from less than 1% to approximately 20% in the absence of oral anticoagulants.[2]

Historically, vitamin-K antagonists (VKA) were the gold-standard treatment for the prevention of systemic embolism. However, this therapy has many downsides, like the interactions with food and other drugs, a narrow therapeutic window, the need for frequent coagulation monitoring and dosage adjustment, or its' particular pharmacokinetics (delayed onset and offset of anticoagulant effect) somehow complicating the management of patients. Recently, non-VKA Oral Anticoagulants (NOAC) have been introduced. This therapeutic class facilitates the management of oral anticoagulation since the four currently available molecules do not have most of the downsides described above. Though, its use is contraindicated in patients with severe renal impairment and with so-called "valvular AF". The definition of valvular and non-valvular AF (NVAF) are unclear, varying from one to the other NOAC study, [3-6] and even between North-American and European guidelines,[7, 8] which is a source of ambiguity in clinicians' minds. A clarification of the term NVAF is needed in order to not deny NOACs to patients based on the wrong perception that they may have NVAF.

In the present comprehensive review, we aimed at clarifying this point, by analyzing results of the main randomized trials in the area and recommendations in current guidelines and by describing the safety and efficacy of NOACs in patients with valvular abnormalities, based on the results of published studies.

The magnitude of the problem

A large proportion of the patients with AF have signs of valvular involvement. Among those included in the EURObservational Research Programme Atrial Fibrillation, a prospective survey in european countries, 63.5% had a valvular disease.[9] The presence of such anomalies increase the risk of AF by 1.8 and 3.4 in men and women, respectively.[10] On the other hand, animal studies have shown that AF, through atrial dilatation, results in a progressive mitral regurgitation, already present at the transition stage between paroxysmal and persistent AF, which becomes significant after one year of long-standing persistent AF.[11] Thus, the

relationship between both anomalies is frequent and often unclear, particularly in the presence of atrial dilatation.

From NOAC trials to current guidelines

Factor IIa (dabigatran) and factor Xa (rivaroxaban, apixaban, and edoxaban) inhibitors have demonstrated their non-inferiority or superiority compared to VKA to reduce the risk of stroke and systemic thrombo-embolism.[3-6] In the meta-analysis published in 2014 by Ruff et al[12] compelling the 4 major trials on stroke prevention for AF published so far, a significant reduction of 19% of this endpoint was observed. Importantly, major bleedings were significantly reduced by 14%. In these seminal trials, patients with contra-indications to NOACs were excluded, including those with chronic kidney disease or in case of treatment interactions. One of the major exclusion criteria was the presence of a "valvular" AF, but the definition varied widely between the pivotal trials. As shown in Table 1, the inclusion criteria of the RE-LY,[4] the ROCKET-AF,[6] the ARISTOTLE,[3] and the ENGAGE-AF TIMI 48[5] trials were substantially dissimilar. The most restrictive study was the RE-LY trial,[4] since a "history of heart valve disorder (i.e., prosthetic heart valve or hemodynamically relevant valve disease)" was an exclusion criterion. The definition of the "hemodynamically" relevance of a valvular involvement is unclear, since it may suggest the presence of clinical and/or echocardiographic parameters of intolerance. Conversely, the ARISTOTLE[3] and the ENGAGE-AF TMI 48[5] trials had more lenient inclusion criteria, allowing the inclusion of patients with bioprosthesis or mitral valve repair. To note, the term NVAF only appears in the ROCKET-AF trial,[6] the other trials having avoided to overuse it.

The current ESC guidelines for the management of AF published in 2012 rightly state that there is "no satisfactory or uniform definition" of NVAF, and authors defined NVAF as AF related to "rheumatic valvular disease (predominantly mitral stenosis) or prosthetic heart valves".[7] These two conditions are the only one contraindicating the use of NOACs in patients with AF in European guidelines. In the more recent 2014 AHA/ACC/HRS guidelines for the management of AF, AF is defined as "valvular" when associated with "rheumatic mitral stenosis, a mechanical or bioprosthetic heart valve, or a mitral valve repair".[8] Thus, one can appreciate the discrepancy between European and North-American guidelines, since patients with mitral valve repair are eligible for NOACs in one side of the Atlantic but not in the other. Such divergences, in conjunction with physicians' fear about ischemic embolism and its potential forensic consequences, complicate the therapeutic decision of prescribing or not NOACs in some patients. The term NVAF by itself is confusing since it may imply in many

physicians' minds the absence of any given valvular involvement to allow the prescription of NOACs. A recent study assessed the different aspects of the definition of NVAF by conducting a web-based survey filled by a total of 513 Italian cardiologists and internists.[13] To the question "Do you think that the existing definitions of NVAF are sufficiently clear?", 57.1 and 67.9% of them answered "yes", respectively. Surprisingly, the answers of the following questions were not in accordance with this initial result. Indeed, for 28.2% of the cardiologists, the presence of a mitral regurgitation alone was sufficient to define AF as valvular AF, and 26.7% defined patients with biological aortic valve prosthesis as having NVAF. A clarification of the term NVAF is then urgently needed in order to homogenize current clinical practice and remove uncertainties regarding this common issue.

Valvular heart diseases, AF and thrombo-embolic risk

Mitral stenosis

Mitral stenosis has historically been considered a distinct disease in the area of AF. Indeed, it results in a low atrial flow, significantly increasing the risk of atrial thrombi, which, besides, are often located in various regions of the atria but the left atrial appendage (91% in NVAF and 57% in AF associated with mitral stenosis).[14] Since the thrombo-embolic risk is increased, and the efficacy of new anticoagulants uncertain, such patients were excluded from randomized controlled trials about NOACs, and to date, there are no data regarding the efficacy and safety of these molecules in patients with mitral stenosis. Whether pathophysiology of thrombi genesis in these patients is substantially different to contraindicate NOAC prescription is unknown and would probably require further studies.

Other valvular diseases

The other valvular diseases (mitral or tricuspid regurgitations, aortic stenosis) were not considered to increase per-se the risk of thrombo-embolic event. However, Philippart et al recently demonstrated that patients with left-sided valvular disease had a 1.39-fold increase risk of stroke/thrombo-embolic events, probably explained by a higher CHA_2DS_2-VASc score and significantly more comorbidities in these patients, compared to those with no valvular diseases.[15] Indeed, older age and higher CHA_2DS_2-VASc scores were the only independent predictors of ischemic events, but not the presence of a valvular disease.

Many studies have shown that mitral regurgitation might reduce the risk of stroke since atrial flow is increased and atrium and left atrial appendage are "washed" by the regurgitant flow.

This phenomenon has been described especially in case of severe regurgitation, and not demonstrated for mild or moderate regurgitations.[16, 17] Regarding aortic stenosis, one have to keep in mind that calcic microemboli may occur, and that stroke in the presence of AF may have a different pathophysiologic origin.

Data regarding the use of rivaroxaban and apixaban in patients with valvular involvement have recently been published. Among the 14 171 patients included in the ROCKET-AF trial, 2003 (14.1%) had a valvular disease, mainly mitral or aortic regurgitations (respectively 89.6% and 24.8% of the patients) or aortic stenosis (11.0%), half of them from degenerative origin. The severity of those valvular diseases was not reported.[18] To note, 5.3% had prior cardiac valvular surgeries. Baseline characteristics of patients with or without valvular involvement significantly differed, since the former were older and had more comorbidities like congestive heart failure, prior myocardial infarction, chronic obstructive pulmonary disease or smoking. Although rivaroxaban had a similar efficacy in patients with or without valvular disease, a significant lower bleeding rate was observed in the latter group, probably explained by the differences in terms of baseline characteristics. The interaction of valvular disease in patients randomized to rivaroxaban and warfarin was not significant in intention-to-treat in terms of efficacy outcomes. However, a significant higher bleeding rate was observed in patients with valvular involvement randomized to rivaroxaban compared to warfarin.

A similar analysis was performed among patients included in the ARISTOTLE trial comparing efficacy and safety outcomes in patients randomized to apixaban or warfarin.[19] Among the 18 201 patients included, 4808 had valvular heart diseases (26.4%), including mitral, tricuspid and aortic regurgitations, or aortic stenosis, with various grades of severity (from mild to severe). To note, a total of 465 patients with mild mitral stenosis were included, as were 251 patients with prior valve surgeries (see below for details). As previously described in the subanalysis of the ROCKET-AF trial, patients with valvular heart diseases were older and had more comorbidities; CHADS2 score was also significantly higher in this group. Patients with valvular heart disease had higher rates of stroke or systemic embolism (3.2% versus 2.4%; HR, 1.34; 95% CI, 1.10–1.62; p=0.003) and bleeding (4.6% versus 4.3%; HR, 1.11; 95% CI, 0.95–1.29; p=0.21) compared to patients without valvular heart diseases. However, no differential effect of apixaban over warfarin in patients with and without valvular diseases in reducing stroke and systemic embolism was observed. Similarly, bleeding and mortality were similar among patients randomized to apixaban or warfarin, whether valvular involvement was present or not.

As previously stated, the NOAC trial with the most restrictive inclusion criteria was the RE-LY trial. Results about the outcomes of patients with valvular heart diseases included in this trial (21.0% of the population) have not been published yet but presented as preliminary form.[20] Similarly to the results of the subanalysis of the ROCKET-AF and the ARISTOTLE trials, the benefit of dabigatran in reducing stroke and systemic embolism, major bleeding and life-threatening or intracranial bleeds, were similar in patients with valvular diseases compared to those without. Similar data for patients included in the ENGAGE-AF TIMI 48 trial and receiving edoxaban have not been published or presented so far. In summary, patients with valvular diseases are not at higher risk of stroke per-se, but are often older, with several comorbidities, and consequently have a higher thrombo-embolic (CHA_2DS_2-VASc) score, putting them at risk for stroke and embolic complications of AF independently of the type of anticoagulant. NOACs appear to have similar efficacy and safety profiles irrespective to the presence of a valvular disease. In parallel to the CHA_2DS_2-VASc score, hemorrhagic scores (HAS-BLED or HEMORRAGE scores) are also often increased, and one have to keep in mind that a careful attention is required when NOACs are prescribed in such patients.

Mechanical valves

Patients with mechanical valves are at a high risk of thrombo-embolic complications and require permanent anticoagulation after valve implantation. Warfarin has been shown to decrease this risk to an annual rate of 0.7-1%.[21, 22] Thrombi may form directly in the surface of the valve or in the left atrial appendage as a consequence of the low-flow induced by the presence of the valve. During the post-operative time or later during follow-up, AF may appear, further increasing thrombo-embolic risk. The phase-2 RE-ALIGN study was designed to test the safety and efficacy profile of dabigatran in patients with aortic and/or mitral mechanical prosthesis.[23] Drug doses varied from 150 mg x 2 to 300 mg x 2 depending on kidney function and blood concentrations of the molecule. Two populations of patients were studied, i.e. those with early (< 7 days) or late (> 3 months) initiation of dabigatran after the surgery. The trial was terminated prematurely since the use of dabigatran in patients with mechanical prosthesis was associated with an increased risk of thromboembolic and major bleeding complications (5% vs. 0%, and 4% vs 2%, respectively) compared to warfarin. Most thrombo-embolic events occurred in patients from the early-initiation group, while bleeding events occurred similarly in both groups. However, major bleeding occurred only in patients for whom dabigatran was initiated early after the valve implantation, all being pericardial bleeding. Thus, authors conclude that dabigatran is not a safe alternative for patients requiring

anticoagulation after the implantation of a mechanical heart valve, and VKAs remain the gold-standard treatment in such patients.

Bioprosthesis

The antithrombic strategy after bioprosthesis valve implantation is currently controversial, but most of the times, aspirin may be a safe option in such patients in sinus rhythm.[24-27] Whenever AF occurs, an oral anticoagulation has to be prescribed.[26] As recently demonstrated, the presence of a bioprosthesis is associated with a non-significant increase in stroke/thromboembolic events but is not independently associated with their occurrence.[28]

Whether pathophysiology of thrombi formation is sufficiently different in these patients to contraindicate NOAC prescription is unknown.

The only dedicated trial was the DAWA study (Dabigatran versus warfarin after mitral and/or aortic bioprosthesis replacement and atrial fibrillation postoperatively) was designed to compare dabigatran (at a dose of 110 mg x 2) with warfarin in patients with bioprostheses,[29] but results cannot be interpreted due to the very limited number of patients enrolled.[30]

To date, the only data available on the efficacy and safety profiles of NOACs in patients with bioprosthesis come from subgroup analyses. The ARISTOTLE trial brings us some insights about this specific group of patients, with data recently presented at the 2015 AHA meeting.[31] As stated above, 251 patients (1.7%) included in the ARISTOTLE trial had a history of valve surgery. Details on the valve surgery were not collected at the time of the trial but gathered retrospectively after the completion of the study, and were completely available for 165 patients. Baseline clinical characteristics of patients with bioprothetic aortic and/or mitral valves receiving apixaban (N=56) or warfarin (N=52) were similar. Efficacy (stroke and systemic embolism) and safety outcomes (major bleeding, intracranial hemorrhage, cardiovascular and all-cause death) were similar among both groups. Data about patients with bioprosthetic heart valves included in the ENGAGE-AF TIMI 48 trial (the only trial having clearly stated this inclusion criterion) have not been presented so far.

Trans-aortic valve implantation

Trans-aortic valve implantation (TAVI) has emerged as an alternative to surgical aortic valve replacement for patients with aortic stenosis. Antithrombic management after implantation remains empiric, often based on a dual antiplatelet therapy, associating aspirin and clopidogrel for 3 to 6 months, followed by long-term aspirin or a thienopyridine alone.[25-27]

The optimal management of TAVI recipients experiencing AF is currently unknown. The

ESC and the European Association for CardioThoracic Surgery recommend a combination of VKA and aspirin or thienopyridine, weighed against increased risk of bleeding.[26] Similarly to what was stated for bioprosthetic valves, whether pathophysiology of thrombi formation is sufficiently different in TAVI patients to contraindicate them to NOACs would require further studies, and to the best of our knowledge, there are no data published so far in the literature in this topic.

Moving towards new recommendations?

In 2015, the European Heart Rhythm Association (EHRA) published a practical guide on the use of NOACs in patients with AF.[32] In this position paper, authors state that NVAF refers to "AF that occurs in the absence of mechanical prosthetic heart valves and in the absence of moderate-to-severe mitral stenosis", and add that patients with biological valves or valve repair are in a "grey area" and may be suitable for NOAC prescription. Indeed, it is stated that patients with bioprosthetic heart valves and mitral valve repair are suitable for NOAC therapy except for the first 3 and the first 3-6 months post-operatively, respectively. Patients with TAVI or percutaneous transluminal aortic valvuloplasty are also considered as being eligible for NOACs, although the bleeding risk has to be carefully considered in this population often requiring a combination with antiplatelet therapy. The only remaining contraindications of NOAC remain mechanical prosthetic valves and moderate-to-severe mitral stenosis, while patients with other native valvular diseases are not considered as having valvular AF, regardless of severity. A flow chart to guide decision making is depicted in the Figure.

Future perspectives

Elderly patients are at risk of AF and may at some point present with a degenerative calcific aortic stenosis, requiring surgery or percutaneous therapy. To date and as stated above, there is a clear lack of evidence of NOAC suitability in such patients. Thus, studies analyzing the safety and efficacy profile of NOACs in patients with bioprosthetic heart valves and TAVI are urgently warranted.

Lifelong oral anticoagulation with VKAs is mandatory for patients with mechanical heart valves to prevent thromboembolic complications although lability of INRs is a major drawback in this situation, requiring strict coagulation monitoring and drug-adjustments. Initial promising results of in-vitro and animal studies showing the efficacy of dabigatran in preventing valve thrombosis raised hope about use of NOACs in patients with mechanical prosthetic heart valves,[33, 34] unfortunately deceived by the results of the RE-ALIGN trial.[23] In-

vitro coagulation studies later demonstrated that mechanical heart valves induce a local generation of thrombin via the intrinsic pathway in concentrations that overwhelm the inhibitory effect of dabigatran at clinical doses,[35] probably explaining the negative results of the trial. Whether a similar effect occurs with factor Xa inhibitors would require further studies. Preliminary in-vitro[36] and animal[37] studies demonstrated that high-dosed rivaroxaban might be effective in preventing thromboembolic events after mechanical heart valve replacement. However, in the light of the results of the RE-ALIGN trial,[23] further studies would be needed to provide additional data to support clinical trials evaluating factor Xa inhibitors as an alternative to warfarin in patients with prosthetic heart valves.

Patients with moderate-to-severe mitral stenosis (usually of rheumatic origin) have not been included in NOAC trials on the basis of a potential higher risk and different pathophysiologic mechanism of thrombi formation. The prevalence of rheumatic heart disease, the most common cause of mitral stenosis, is widely variable, remaining a major problem in developing areas of the world. Irrespective to atrial rhythm, thrombo-embolic strokes are frequent, estimated to reach around 4 million events per year. Oral anticoagulation using VKAs is recommended in patients with mitral stenosis and AF, and may be proposed to patients with mitral stenosis in the absence of AF.[24-27] However, times in therapeutic range, already suboptimal in developed countries, are even worst in developing parts of the world with high incidence of rheumatic fever.[38] Alternative therapeutic strategies, such as aspirin, are sometimes offered to such patients, despite the well-known inferiority to VKAs.[2] Based on these assumptions, De Caterina and Camm recently wrote "the concept for a trial" comparing NOACs to the standards of care for thromboembolic prophylaxis (antiplatelet agents or VKA) in patients with mitral stenosis.[39] They claim that a randomized, open-label, superiority trial should be conducted in specific countries with a high prevalence of mitral stenosis using a NOAC available for once daily use (rivaroxaban or edoxaban) to facilitate patients' compliance, at the same dosage used in pivotal trials in AF. The overall sample size would vary depending on the expected stroke rate, the study duration and the expected hazard ratio of stroke reduction, from around 600 to 7000. Such study appears to be feasible, at least by academic centers, if not by pharmaceutical companies, and is warranted to improve the suboptimal current standard antithrombotic treatment of patients with mitral stenosis.

Lastly, it may be now time to stop using the confusing term "non-valvular" to define a type of AF. As stated by De Caterina and Camm, a novel terminology should be used in order to clarify this confusion situation.[40] Authors proposed the term "MARM-AF", acronym standing for "Mechanical And Rheumatic Mitral-AF", since it clearly describes the currently real

contraindications to NOACs. The future will tell us whether this term will be life-standing and used by futures researchers.

Conclusion

The term "NVAF" and the inclusion and exclusion criteria in NOACs pivotal trials have created some confusion in physicians' minds about patients who are eligible or not to this therapy. Evidences are progressively coming and showing that NOACs can be safely used in patients with native valvular diseases, regardless of their severity, and probably in bioprosthetic heart valve recipients. The only contraindications remain the presence of a mechanical heart valve and moderate-to-severe mitral stenosis. Future studies are warranted to increase the level of evidence of the safety and efficacy of NOACs in specific populations, particularly in patients with TAVI and bioprosthetic valve, and to determine whether they could be used in the future in the two remaining contraindications.

Disclosures

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Figure legend

Flow chart to guide decision making in patients with atrial fibrillation.

Tables

Trial	Molecule	Exclusion criteria
RE-LY	Dabigatran	History of heart valve disorder (i.e., prosthetic valve or hemodynamically relevant valve disease)
ROCKET-AF	Rivaroxaban	Hemodynamically significant mitral valve stenosis, prosthetic heart valves (annuloplasty with or without prosthetic ring, commisurotomy and/or valvuloplasty are permitted)
ARISTOTLE	Apixaban	Conditions other than AF that require anticoagulation (i.e. prosthetic heart valves)
ENGAGE AF	Edoxaban	Moderate-to-severe mitral stenosis, other indication for anticoagulation (subjects with bioprosthetic heart valves and/or valve repair could be included)

Table 1.Inclusion criteria in NOACs pivotal trials.

AF = Atrial fibrillation.

Group	Year	Moderate to severe mitral stenosis	Mechanichal heart valve	Bioprosthetic heart valve	TAVI	Mitral valve repair	Native valvular disease
ESC	2012	X	X	X	X	√	√
HRS/ACC/AHA	2014	X	X	X	X	X	√
EHRA	2015	X	X	√ Except for the first 3 months post-operatively	√ May require combination with antiplatelet therapy	√ Except for the first 3-6 months post-operatively	√

Table 2. Guidelines about NOACs use in patients with valvular diseases.

X = Contraindicated; √ = Eligible; ACC = American College of Cardiology; AHA = American Heart Association; EHRA = European Heart Rhythm Association; ESC = European Society of Cardiology; HRS = Heart Rhythm Society; TAVI = trans-aortic valve implantation.

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Fig. 1