

Defining nonvalvular atrial fibrillation: A quest for clarification



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Non-vitamin K oral anticoagulants (NOACs) are currently recommended for patients with nonvalvular atrial fibrillation since the publication of the 4 major pivotal trials evaluating the efficacy and safety of factor IIa and factor Xa inhibitors. The definition of *nonvalvular atrial fibrillation* 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 present signs of valvular involvement, and clarification of this term is needed to not deny NOACs to patients based on the wrong perception that they may have valvular atrial fibrillation.

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 postoperatively, respectively. Patients with transaortic valve implantation 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 transaortic valve implantation and valvular surgery, and to determine whether they could be used in the future in the only 2 remaining contraindications. [Am Heart J 2016;178:161-7.]

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 because of the elevated risk of ischemic stroke. The Cardiac failure or dysfunction, Hypertension, Age \geq 75 [Doubled], Diabetes, Stroke [Doubled]-Vascular disease, Age 65-74, and Sex category [Female] (CHA₂DS₂-VASc) score is a validated tool to estimate the annual risk of stroke or systemic embolism,

ranging from <1% to approximately 20% in the absence of oral anticoagulants.²

Historically, vitamin K antagonists (VKAs) 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 (NOACs) have been introduced. This therapeutic class facilitates the management of oral anticoagulation because the 4 currently available molecules do not have most of the downsides described above. However, its use is contraindicated in patients with severe renal impairment and with so-called valvular AF. The definition of valvular and nonvalvular AF (NVAF) is unclear, varying from one to the other NOAC study³⁻⁶ 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 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 the results of the main randomized trials in the area and recommendations in

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Conflicts of interests: C.L.: consulting fees/speaker honoraria for Daiichi Sankyo, Boehringer, Pfizer, Bristol Myers Squibb, and Bayer; P.M.: consulting fees from Daiichi; speaker honoraria from Boehringer, Pfizer, and Bristol Myers Squibb; consulting fees/speaker honoraria from Bayer; R.P.M.: speaker honoraria from Daiichi Sankyo, Pfizer, and Bristol Myers Squibb.

Submitted March 1, 2016; accepted May 25, 2016.

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0002-8703

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<http://dx.doi.org/10.1016/j.ahj.2016.05.014>

Table I. Inclusion criteria in NOACs pivotal trials

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

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 increases 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 1 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 noninferiority or superiority compared with VKA to reduce the risk of stroke and systemic thromboembolism.^{3,6} In the meta-analysis published in 2014 by Ruff et al¹² compelling the 4 major trials on stroke prevention for AF published so far, a significant reduction of 19% of this end point was observed. Importantly, major bleedings were significantly reduced by 14%. In these seminal trials, patients with contraindications 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 I, the inclusion criteria of the RE-LY,⁴ the ROCKET-AF,⁶ the ARISTOTLE,³ and the ENGAGEAF TIMI 48⁵ trials were substantially dissimilar. The most restrictive study was the RE-LY trial⁴ because a “history of heart valve disorder (ie, prosthetic heart valve or hemodynamically relevant valve disease)” was an exclusion criterion. The definition of the *hemodynamic* relevance of a valvular involvement is unclear because it may suggest the presence of clinical and/or echocardiographic parameters of intolerance. Conversely, the ARISTOTLE³ and the ENGAGEAF TMI 48⁵ 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 European Society of Cardiology (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 2 conditions are the only ones contraindicating the use of NOACs in patients with AF in European guidelines. In the more recent 2014 American Heart Association (AHA)/American College of Cardiology/Heart Rhythm Society 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 because 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 because 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 to homogenize current clinical practice and remove uncertainties regarding this common issue.

Valvular heart diseases, AF, and thromboembolic 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% of thrombi located in the left atrial appendage in NVAF patients and only 57% in AF associated with mitral stenosis).¹⁴ Because the thromboembolic risk is increased and the efficacy of new anticoagulants is 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 thromboembolic event. However, Philippart et al¹⁵ recently demonstrated that patients with left-sided valvular disease had a 1.39-fold increased risk of stroke/thromboembolic events, probably explained by a higher CHA₂DS₂-VASc score and significantly more comorbidities in these patients, compared with those with no valvular diseases. Indeed, older age and higher CHA₂DS₂-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 because 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 has to keep in mind that calcic microemboli may occur and that stroke in the presence of AF may have a different pathophysiological 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, 2,003 (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 because 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 significantly 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 significantly higher bleeding rate was observed in patients with valvular involvement randomized to rivaroxaban compared with 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, 4,808 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% vs 2.4%; hazard ratio, 1.34; 95% CI, 1.10-1.62; *P* = .003) and bleeding (4.6% vs 4.3%; hazard ratio, 1.11; 95% CI, 0.95-1.29; *P* = .21) compared with 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 benefits of dabigatran in reducing stroke and systemic embolism, major bleeding, and life-threatening or intracranial bleeds were similar in patients with valvular diseases compared with 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 thromboembolic (CHA₂DS₂-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 of the presence of a valvular disease. Parallel to the CHA₂DS₂-VASc score, hemorrhagic scores (HAS-BLED [Hypertension, Abnormal renal and liver function, Stroke, Bleeding, Labile INRs, Elderly > 5 years, Drugs or alcohol] or HEMORRAGE [hepatic or renal disease, ethanol abuse, malignancy, age > 75, reduced platelet count or function, rebleeding risk (doubled), hypertension, anemia, genetic factors, excessive fall risk and stroke] scores) are also often increased, and one has to keep in mind that careful attention is required when NOACs are prescribed in such patients.

Mechanical valves

Patients with mechanical valves are at a high risk of thromboembolic 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 postoperative time or later during follow-up, AF may appear, further increasing thromboembolic risk. The phase 2 REALIGN 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 \times 2 to 300 mg \times 2 depending on kidney function and blood concentrations of the molecule. Two populations of patients were studied: those with early (<7 days) or late (>3 months) initiation of dabigatran after the surgery. The trial was terminated prematurely because 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 with warfarin. Most thromboembolic events occurred in patients from the early-initiation group, whereas 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, the 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 criterion-standard treatment in such patients.

Bioprosthesis

The antithrombotic strategy after bioprosthesis valve implantation is currently controversial, but most of the time, 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 nonsignificant 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) designed to compare dabigatran (at a dose of 110 mg \times 2) with warfarin in patients with bioprostheses,²⁹ but results cannot be interpreted because of 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.

Transaortic valve implantation

Transaortic valve implantation (TAVI) has emerged as an alternative to surgical aortic valve replacement for patients with aortic stenosis. Antithrombotic 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 toward new recommendations?

In 2015, the European Heart Rhythm Association published a practical guide on the use of NOACs in patients with AF.³² In this position paper, the 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 (Table II). 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 postoperatively, 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, whereas patients with other native valvular diseases are not considered as having valvular AF, regardless of severity. A flowchart 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,

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

Group	Year	Moderate to severe mitral stenosis	Mechanical 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 m postoperatively	May require combination with antiplatelet therapy	Except for the first 3-6 m postoperatively	

X = Contraindicated; √ = Eligible. HRS, Heart Rhythm Society; ACC, American College of Cardiology; EHRA, European Heart Rhythm Association.

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 international normalized ratios 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 vitro³⁶ and animal³⁷ studies demonstrated that high-dose 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 potentially 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, thromboembolic 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

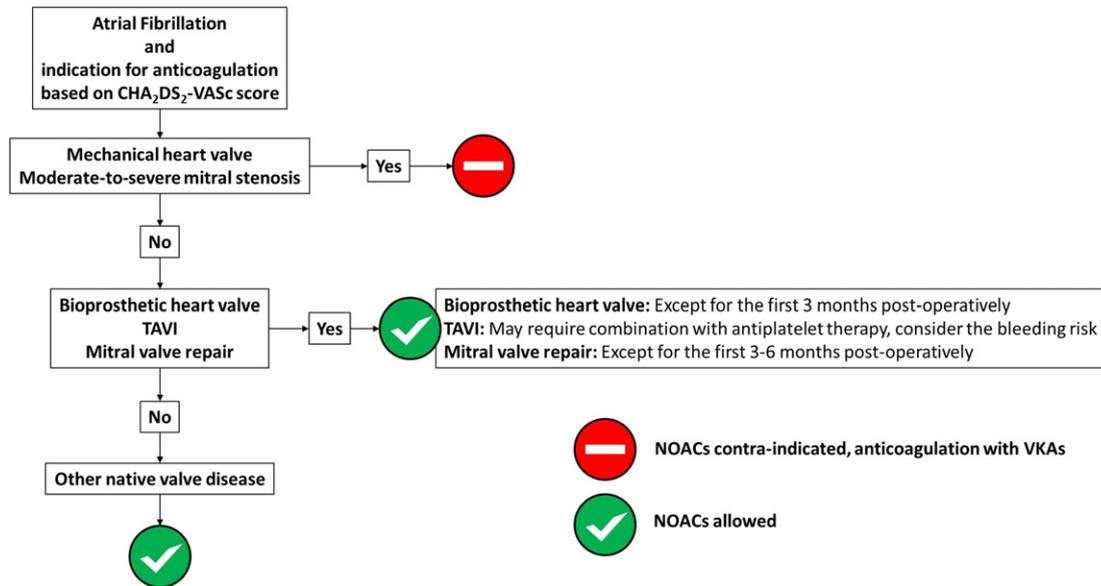
the world with high incidence of rheumatic fever.³⁸ Alternative therapeutic strategies, such as aspirin, are sometimes offered to such patients, despite the well-known inferiority to VKAs.² Based on these assumptions, De Caterina and Camm³⁹ recently wrote “the concept for a trial” comparing NOACs with the standards of care for thromboembolic prophylaxis (antiplatelet agents or VKA) in patients with mitral stenosis. 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 7,000. 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 *nonvalvular* to define a type of AF. As stated by De Caterina and Camm,⁴⁰ a novel terminology should be used to clarify this confusing situation. The authors proposed the term *MARM-AF*, acronym for “Mechanical And Rheumatic Mitral-AF,” because it clearly describes the currently real contraindications to NOACs. The future will tell us whether this term will be life-standing and used by future 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 for 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

Figure



Flowchart to guide decision making in patients with AF.

valve, and to determine whether they could be used in the future in the 2 remaining contraindications.

Disclosures

No extramural funding was used to support this work. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper, and its final contents.

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