REVIEW

How to define valvular atrial fibrillation?

Comment définir la fibrillation atriale valvulaire?

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Summary Atrial fibrillation (AF) confers a substantial risk of stroke. Recent trials comparing vitamin K antagonists (VKAs) with non-vitamin K antagonist oral anticoagulants (NOACs) in AF were performed among patients with so-called ''non-valvular'' AF. The distinction between ''valvular'' and ''non-valvular'' AF remains a matter of debate. Currently, ''valvular AF'' refers to patients with mitral stenosis or artificial heart valves (and valve repair in North American guidelines only), and should be treated with VKAs. Valvular heart diseases, such as mitral regurgitation, aortic stenosis (AS) and aortic insufficiency, do not result in conditions of low flow in the left atrium, and do not apparently increase the risk of thromboembolism brought by AF. Post-hoc analyses suggest that these conditions probably do not make the thromboembolic risk less responsive to NOACs compared with most forms of ''non-valvular'' AF. The pathogenesis of thrombosis is probably different for blood coming into contact with a mechanical prosthetic valve compared with what occurs in most other forms of AF. This may explain the results of the only trial performed with a NOAC in patients with a mechanical prosthetic valve (only a few of whom had AF), where warfarin was more effective and safer than dabigatran. By contrast, AF in the presence of a bioprosthetic heart valve or after valve repair appears to have a risk of thromboembolism that is not markedly different from other forms of ''non-valvular'' AF. Obviously, we should no longer consider the classification of AF as ''valvular'' (or not) for the purpose of defining the aetiology of the arrhythmia, but for the determination of a different risk of thromboembolic events and the need for a specific antithrombotic strategy. As long as

there is no better new term or widely accepted definition, ''valvular AF'' refers to patients with mitral stenosis or artificial heart valves. Patients with ''non-valvular AF'' may have other types of valvular heart disease. One should emphasize that ''non-valvular AF'' does not exclude patients with some types of valvular heart disease from therapy with NOACs.

Résumé La fibrillation atriale (FA) est associée à un risque d'accident vasculaire cérébral. Les essais récents comparant antivitamines K (AVK) et anticoagulants oraux directs non-AVK (NACO) dans la FA ont été réalisés chez des patients avec FA, dite « non valvulaire ». La différence entre FA « valvulaire » et « non valvulaire » reste néanmoins sujet à controverses. Actuellement, la FA « valvulaire » fait référence aux patients avec rétrécissement mitral ou prothèse valvulaire cardiaque (ainsi qu'aux plasties mitrales dans les recommandations nord américaine) et nécessite un traitement par AVK. Les valvulopathies, telles que l'insuffisance mitrale, le rétrécissement aortique ou l'insuffisance aortique ne sont pas associées à un bas débit dans l'oreillette gauche et semblent ne pas augmenter le risque thromboembolique lié à la FA. Des analyses post-hoc suggèrent que le bénéfice des NACO dans ces pathologies n'est pas différent de celui constaté pour les autres patients avec FA « non valvulaire ». Le processus de thrombogénicité est probablement différent des autres formes de FA lorsque le sang entre en contact avec du matériel de prothèse valvulaire mécanique. Ceci pourrait expliquer les résultats négatifs du seul essai réalisé à ce jour avec un NACO chez des patients avec prothèses mécaniques (dont seulement une minorité avaient de la FA) et où la warfarine à été plus efficace et plus sûre que le dabigatran. En revanche, la FA chez des patients avec une bioprothèse ou une plastie valvulaire semble associée à un risque thromboembolique assez similaire à celui attendu pour une FA « non valvulaire ». Manifestement, il ne faut plus envisager la classification d'une FA comme « valvulaire » (ou « non valvulaire ») pour définir l'étiologie de l'arythmie, mais dans le but de déterminer un risque différent d'évènements thromboemboliques et pour établir un traitement antithrombotique spécifique. Tant qu'il n'y aura pas de meilleur terme ou de nouvelle définition largement acceptée, la FA « valvulaire » fait référence aux patients avec rétrécissement mitral ou avec prothèse valvulaire (mécanique ou biologique). Les patients avec FA « non valvulaire » peuvent avoir d'autres types de valvulopathies. Il faut donc insister sur le fait que la définition de FA « non valvulaire » n'exclut pas certains patients avec valvulopathies des possibilités de traitement par NACO.

Background

Atrial fibrillation (AF) is the most common arrhythmia, and confers a substantial risk of stroke. In the absence of anticoagulation, thromboembolic risk ranges from < 1% per year — similar to the background risk of the age-matched population — to > 20% per year. The risk of stroke and systemic embolism in AF may be assessed by simple clinical risk factors and scoring systems [1]. This has led to the wide use of oral anticoagulation as a preventive strategy for most patients with AF, unless clearly at very low risk [1,2]. The recent availability of non-vitamin K antagonist oral anticoagulants (NOACs) is likely to increase the number of AF patients efficiently treated for stroke prevention. Recent trials comparing vitamin K antagonists (VKAs) with NOACs in AF were performed among patients with so-called ''non-valvular'' AF, and excluded patients at high risk of thromboembolism, such as those with AF accompanying mitral stenosis or with mechanical prosthetic valves. Beyond the higher risk of stroke and ethical issues in the clinical development of NOACs, a reason for excluding these patients in trials testing NOACs was the possibility that the pathogenesis of thromboembolism may be substantially different from that in other AF patients. The distinction between ''valvular'' AF and ''non-valvular'' AF still remains a matter of debate, however, with different designations adopted in the literature.

We discuss the definitions of the terms ''valvular'' and ''non-valvular'' AF in different trials with NOACs and in current guidelines. We also review the thromboembolic risk associated with AF in the presence of the various valve diseases, and the qualitative type of possible thrombus in such conditions. All of these factors may have implications for clinical practice and future investigations.

Differing definitions of ''valvular atrial fibrillation''

Trials of thromboprophylaxis in atrial fibrillation

The issue of ''valvular AF'' definition is relevant because most of these patients were excluded from recent trials testing NOACs in patients with AF [3—19]. Consequently, NOACs have been registered and are currently indicated only for patients with so-called ''non-valvular AF''. The reasons for excluding patients with ''valvular AF'' included uncertainties about whether the mechanism of thrombogenesis in such patients is similar to that occurring in the more common forms of ''non-valvular'' AF and, consequently, whether a similar anticoagulation strategy is appropriate. The criteria for excluding such patients were, however, variable (Table 1). In the RE-LY trial testing dabigatran versus warfarin, ''history of heart valve disorders'' was an exclusion criterion, and the disorders were defined as prosthetic valve or haemodynamically relevant valve disease, resulting in the exclusion of patients with AF and severe mitral or aortic insufficiency or severe AS [6].

The ROCKET-AF trial, evaluating rivaroxaban against warfarin, excluded only haemodynamically significant mitral valve stenosis and prosthetic heart valves, but permitted the inclusion of patients with other diseases in native valves, as well as patients treated with annuloplasty, commisurotomy or valvuloplasty [17].

In ARISTOTLE, evaluating apixaban versus warfarin, patients with ''clinically significant (moderate or severe) mitral stenosis'', as well as ''onditions other than AF that require chronic anticoagulation (e.g. prosthetic mechanical heart valve)'' were excluded, therefore allowing the inclusion of patients with native valvular heart disease other than mitral stenosis and bioprosthetic heart valves [11].

In the AVERROES trial, evaluating apixaban versus aspirin in patients considered ''unsuitable'' for VKAs, ''valvular disease requiring surgery'' was among the exclusion criteria and ''unsuitability'' for VKAs thus excluded patients with mechanical prosthetic valves [5].

In the last trial, the ENGAGE-AF study, which tested two strategies of edoxaban versus warfarin, patients with ''moderate or severe mitral stenosis or a mechanical heart valve'' were excluded, while the inclusion of patients with bioprosthetic heart valves and/or valve repair was permitted [10].

After the publication of the main trial results, some subanalyses are now addressing the outcomes of patients included with some sort of valvular heart disease, but only a few specific subgroup analyses of patients with ''valvular heart disease'' have been reported.

In a subgroup analysis of RE-LY in patients with symptomatic heart failure, 1283 (26%) of the patients with heart failure and 2661 (20%) of the patients without heart failure had some sort of ''valvular heart disease'', but no information on outcomes is currently available for these patients [20].

The most detailed information comes from a secondary analysis of ROCKET-AF, which included 14,171 AF patients, 14% of whom had ''significant'' valvular disease, some with combined lesions [21]. Mitral regurgitation was by far the most frequent valve disease, seen in 90% of the patients, while only 11% had AS. The authors raised the point that many patients with ''non-valvular AF'' have significant valve lesions, and this is likely to be even more common in patients seen outside the context of a randomized trial. The risk of stroke in those with ''significant'' valvular disease was found to be similar to that in patients without significant valve disease after controlling for stroke risk factors. Combined efficacy endpoints in patients with and without valvular disease were similar in patients treated with warfarin or rivaroxaban. Bleeding outcomes were similar in those without valvular disease, but were more frequent with rivaroxaban than warfarin in valvular disease patients. Intracranial bleeding was significantly reduced by rivaroxaban in patients with no valvular disease, and was also reduced, albeit not significantly, in valvular disease patients (non-significant interaction). Whether this effect is real or simply the result of multiple post-hoc analyses of the data is debatable. Anyway, the authors concluded that AF patients with and without valve disease experience the same stroke preventive benefit from oral anticoagulants.

In a subanalysis of ARISTOTLE, which has only been reported in preliminary form, 4808 (26%) of the enrolled patients had ''at least moderate'' heart valve disease [22]. The results of this subanalysis were consistent with those of the overall ARISTOTLE trial, with no significant interaction according to the presence or absence of valvular heart disease for both stroke and systemic embolism and major bleeding.

In summary, exclusion criteria for concomitant valve disease varied slightly in pivotal trials with NOACs for stroke prevention in AF, with exclusion of most valvular disease patients implemented in some studies, while others included some patients with non-rheumatic valvular disease, valve repair or bioprostheses. However, a general term of ''non-valvular AF'' was used for the labelling of NOACs, because a clinician cannot refer to the specific inclusion criteria of each trial before prescribing an NOAC, which were not widely available at the same time in all countries. In recent years, this has led the scientific societies to redefine more precisely which patients with AF may be considered to have ''valvular'' and ''non-valvular'' AF.

Guidelines

In addition to the lack of absolute consistency reported above, the definitions of ''valvular'' and ''non-valvular'' AF also differ slightly in the various guidelines. In 2008, the American College of Chest Physicians guidelines proposed recommendations for patients with valvular heart disease and AF, including mitral stenosis and prosthetic heart valves [23]; no specific change to the definition was made in the latest edition of these guidelines, published in 2012 [24]. The 2012 focused update of the European Society of Cardiology (ESC) guidelines on AF indicated that it is ''conventional'' to divide AF into cases that are described as ''valvular'' or ''non-valvular''. Although stating that no satisfactory or uniform definition of these terms exists, the term ''valvular AF'' used in this guideline implied that AF was ''related to rheumatic valvular disease (predominantly mitral stenosis) or prosthetic heart valves'' [1]. The 2011 American Heart

Table 1 Exclusion criteria related to valve disease in phase II and III trials with the new anticoagulants in atrial fibrillation.

Study drug	Study acronym/name	Year of publication	Atrial fibrillation exclusion criteria related to valve disease
Apixaban	AVERROES [5,7]	2011	Valvular disease requiring surgery, prosthetic mechanical heart valve
Apixaban	ARISTOTLE [11,14]	2011	Clinically significant (moderate or severe) mitral stenosis, prosthetic mechanical heart valve
Apixaban	ARISTOTLE-J [15]	2011	Valvular heart disease
Betrixaban	EXPLORE-Xa [4]	2013	Prosthetic mechanical heart valve
Dabigatran	PETRO [9]	2007	Mitral stenosis, prosthetic valves
Dabigatran	RE-LY [6,8]	2009	History of heart valve disorder (including haemodynamically relevant valve disease and prosthetic valve)
Edoxaban	Edoxaban phase II study [19]	2012	Comorbid rheumatic valvular disease, history of valvular surgery, infective endocarditis
Edoxaban	ENGAGE-AF-TIMI 48 [10,18]	2013	Moderate or severe mitral stenosis, unresected atrial myxoma, mechanical heart valve
Rivaroxaban	ROCKET-AF [17]	2011	Haemodynamically significant mitral valve stenosis, prosthetic heart valve
Rivaroxaban	J-ROCKET-AF [13]	2012	Haemodynamically significant mitral valve stenosis, prosthetic heart valve
Ximelagatran	SPORTIF III [12,16]	2003	Mitral stenosis, previous valvular heart surgery, active infective endocarditis
Ximelagatran	SPORTIF V [3,12]	2005	Mitral stenosis, previous valvular heart surgery, active infective endocarditis

Association/American College of Cardiology/Heart Rhythm Society AF guidelines said that: ''the historical term 'non-valvular AF' is restricted to cases in which the rhythm disturbance occurs in the absence of rheumatic mitral valve disease, a prosthetic heart valve or mitral valve repair'' [25]. This was confirmed in the 2014 update, where non-valvular AF was defined as AF in the absence of rheumatic mitral stenosis, a mechanical or bioprosthetic heart valve or mitral valve repair [26].

Overall, the main scientific societies agree that patients with mitral rheumatic valve disease or a prosthetic valve (whether mechanical or biological) have ''valvular AF'', but there are disagreements, mainly regarding patients with valve repair and possibly those with AF and rheumatic valve disease not located at the mitral valve.

Valve diseases, atrial fibrillation and the risk of stroke

The discrepancies mentioned above raise the question of whether the mechanisms of thrombogenesis and thromboembolic risks might vary in AF patients with various valve conditions. Valvular heart disease, independent of the underlying cardiac rhythm, may be associated with an increased risk of thromboembolic events. On the other hand, some types of AF, such as those accompanying rheumatic mitral stenosis and mechanical prosthetic valves, have long been known to have a high risk of thromboembolism, and

have been excluded from recent AF trials with NOACs. There is wide uncertainty, however, about the possible different risks of thromboembolism in other forms of valvular disease. A precise reappraisal of what is currently known for each of these conditions may be needed for a better understanding of the different issues, including the risk of thromboembolic events, and the benefits and risks associated with antithrombotic therapy in each setting; this will help us to understand the remaining questions surrounding the current definitions of ''valvular AF''.

Native valve disease

Mitral stenosis

Up to 80% of patients with mitral stenosis and systemic embolism have AF. Mitral stenosis was estimated to be responsible for 25% of all deaths from systemic embolism when surgery and anticoagulation were not available [27]. While the stroke rate in patients with AF is, on average, approximately six times the stroke risk in people without AF, the relative risk is about 15 in patients who have AF and mitral stenosis [28]. It is controversial whether patients with mitral stenosis, but without AF, are at a higher risk of embolic events, and there is only a low-grade recommendation for oral anticoagulants in recent guidelines [29]. By contrast, patients with mitral stenosis and AF who have experienced an embolic event have recurrences at a rate that is the highest reported for AF patients. This may be

related to the low flow occurring in the left atrium in case of AF with mitral stenosis. There have been no specific randomized trials evaluating the benefit of anticoagulation for stroke prevention in patients with mitral stenosis, and current recommendations are based on retrospective analysis showing a 4-fold to 15-fold decrease in the incidence of embolic events with anticoagulation in these patients [30]. Such patients have not yet been randomized between alternative treatments, but there are no clear reasons to suggest a differential response to various anticoagulants.

Mitral regurgitation

The multiple mechanisms of mitral regurgitation with very different patient profiles may explain the various findings when studying the prevalence of thromboembolism in these patients. While some degree of mitral regurgitation may be associated with rheumatic mitral stenosis, which itself substantially increases the risk of thromboembolism in AF, this may be different in AF with mitral regurgitation of non-rheumatic aetiology. There are now some data on the effect of mild mitral regurgitation on the occurrence of thromboembolic events.

Many studies have suggested that the presence of mitral regurgitation with AF may have a protective role in the occurrence of thromboembolic events [31,32]. In a retrospective study of 313 AF patients, the incidence of thromboembolism was significantly higher in the group with no mitral regurgitation [33]. Mild and moderate mitral regurgitation might increase the thromboembolic risk [34], in contrast to severe mitral regurgitation, which might have a protective effect [35,36]. The proposed mechanism would be an increase in atrial washing and emptying, and reduced intra-atrial stasis, but these suggestions remain controversial. A recent analysis by our group does not allow firm conclusions to be drawn on this point, although 917 (61%) of the AF patients with valve disease had mitral regurgitation, which makes it one of the largest reports on outcomes for such patients. Neither mitral regurgitation nor severity of valve disease was associated with a higher risk of stroke/thromboembolic events in multivariable analysis [37].

The idea that the occurrence of mitral regurgitation per se does not result in an increased risk of stroke in AF has also been supported by studies of spontaneous echo contrast on transoesophageal echocardiography, considered to be a manifestation of a hypercoagulable state. Spontaneous echo contrast in the left atrium (LA) is more common in patients with atrial arrhythmias, mitral stenosis, mitral valve prosthesis and enlarged LA — all conditions associated with LA stasis — while, interestingly, patients with severe mitral regurgitation may have less frequent LA spontaneous echo contrast [35,38]. Similarly, plasma D-dimer levels, which partly correlate with embolic risk in both mitral valve disease and non-valvular AF, have been found to be highest in patients with mitral stenosis with AF and non-valvular AF. D-dimer levels were lower and similar to control levels in a small series of patients with mitral stenosis and/or AF with severe mitral regurgitation [39,40]. Overall, one cannot firmly state that mitral regurgitation is protective against left atrial thrombus and systemic thromboembolism, but it at least seems that mitral regurgitation does not increase

the risk of stroke beyond the other risk factors commonly found in patients with such valve disease.

Mitral valve prolapse is a relatively common form of valve disease occurring in 1—2.5% of the general population, and early case series suggested an association with stroke [41]. More recent and relatively large reports did not replicate this finding [42,43]. Mitral valve prolapse may be complicated by AF, as a consequence of mitral regurgitation with possible LA dilatation and left ventricular enlargement, but it is uncertain if the combination of mitral valve prolapse and AF increases the risk of stroke per se beyond the risk brought by AF and the usual possibly associated risk factors in these patients [41].

Other valve disease

AS has now became the most common valvulopathy in Western countries, and frequently co-exists with AF, but there are only a few reports in the literature referring to the risk of thromboembolism for AF accompanying AS and comparing it with that for AF with no AS. Thromboembolic events related to aortic valve disease are less common than those associated with a mitral disease. The precise physiopathology of stroke in a patient with calcified AS is sometimes difficult to establish. In our registry, AS was present in 32% of AF patients with valve disease (18% with non-severe AS and 14% with severe AS) [37]. These latter patients had a higher risk of stroke, but patients with AS were older and more frequently had co-morbidities, and therefore had a higher CHA_2DS_2-VASc risk score; this probably contributed to the increased risk of stroke/thromboembolic events for patients in the group with valve disease. In current guidelines, anticoagulation is not indicated when there is no AF [29]. However, silent AF might be responsible for some thromboembolic events in addition to atherosclerosis or calcic microemboli in patients with valve diseases [44].

To our knowledge, there is no established relationship between aortic regurgitation and the risk of thromboembolic events in patients with AF. In our study mentioned above, this condition did not seem to be predictive of stroke/thromboembolic events [37]. Finally, there is no evidence in the literature for a specific role for tricuspid regurgitation in increasing the incidence of thromboembolism once AF has occurred.

The recent report from our registry of the Loire Valley Atrial Fibrillation Project adds to our general knowledge of patients with valve disease who, nevertheless, meet the criteria of non-valvular AF [37]. Among 8962 patients seen in a cardiology department, there were 10% with ''valvular AF'' as currently defined in the ESC guidelines, whereas the remaining patients had ''non-valvular AF''. These patients were categorized into those without any valve disease (85%) and those with valve disease, but with neither rheumatic mitral stenosis nor valve prosthesis (15%).

Patients with valve disease were older, had a higher CHA_2DS_2-VASc score and had a higher risk of thromboembolic events than patients without valve disease. The main finding was that the predictive value of the CHA_2DS_2-VASc score was similar in both groups. As a valve disease in non-valvular AF was not independently associated with an increased risk of embolic events, the higher CHA_2DS_2-VASc score was likely to explain the increased risk observed in these patients,

and should remain the principal determining factor when deciding whether oral anticoagulation is needed for stroke prevention. In this subgroup, 23% were considered to have a severe valve disease based on echocardiography and, to date, very little information is available on the incidence of stroke in these patients. Importantly, the severity of valve disease in our registry was not independently associated with a higher risk of stroke or systemic embolism.

Therefore, with the remarkable exception of mitral stenosis, all forms of native valvular heart disease accompanying AF do not appear to increase the risk of thromboembolism beyond the level expected with AF stratified with the CHA_2DS_2-VASc score alone, and do not actually act as independent additional risk factors.

Valve surgery

Mechanical prostheses

Patients with a mechanical heart valve are at risk of thromboembolism and require chronic anticoagulation. A VKA is required even for patients with sinus rhythm, but AF still enhances the risk of thromboembolism [45]. Without anticoagulation, the thromboembolic risk may reach 23% per year with the oldest valves, but is lower with new-generation valves [46,47]. The risk of thromboembolism is estimated to be 4.0%/year with no anticoagulation in patients with mechanical valves, and, among them, those with mitral valve prostheses are at approximately twice the risk compared with those with aortic valve prostheses [46]. Systemic embolization and cerebrovascular events are reduced to a rate of 0.7—1.0% per patient-year in patients with mechanical valves treated with warfarin [48,49]. There are several mechanisms for thrombosis and thromboembolism in patients with a mechanical prosthetic valve and AF. Thrombus may occur on the prosthesis and its different elements, consisting of an initial layer of platelets and a fibrin network, and in the left atrium, most often in the left atrial appendage, related to flow disturbances caused by the prosthesis, and mainly consisting of a fibrin network trapping blood components. It is likely that these two mechanisms vary in their responsiveness to current antithrombotic drugs [50].

Patients with AF and a mechanical heart valve were systematically excluded from all the recent major trials with NOACs, based on the hypothesis that a specific anticoagulation intensity may be needed in such patients, and because of the lack of experience. There were, however, hopes that NOACs could be a valuable substitute for VKAs in this setting. A phase II dose-validation study with dabigatran was performed in such patients. This is the only intervention trial performed so far with an NOAC in patients with a mechanical prosthetic valve (only 23% of whom had AF), and included patients with implantation within the past 7 days of a mechanical bileaflet valve in the aortic and/or mitral position or patients who had undergone implantation of a mechanical bileaflet mitral valve more than 3 months before randomization [50]. The initial dabigatran dose (150, 220 or 300 mg twice daily) was adjusted to obtain a trough plasma concentration of at least 50 ng/mL. The primary endpoint was the trough plasma concentration of dabigatran. The trial was terminated prematurely after the enrolment of 252

patients because of an excess of thromboembolic events (5% vs. 0%) and major bleeding events (4% vs. 2%) among patients in the dabigatran group, showing no benefit and an excess risk compared with warfarin [50].

Differences in the mechanisms of action of dabigatran and warfarin may explain at least some of the findings. In patients with a mechanical heart valve, coagulation activation and thrombin generation induced by the release of tissue factor during surgery may explain the higher risk of early thromboembolic complications. Thrombin generation can also be triggered by exposure of the blood to the artificial surface of the valve leaflets and sewing ring, which induces activation of the contact pathway of coagulation before endothelialization has occurred. Whereas dabigatran exclusively inhibits thrombin, VKAs are likely to be more effective in this early postoperative period because they inhibit the activation of both tissue factor-induced coagulation (by inhibiting the synthesis of coagulation factor VII) and contact pathway-induced coagulation (by inhibiting the synthesis of factor IX), as well as inhibiting the synthesis of factor X and thrombin in the common pathway [51]. The negative experience with dabigatran has temporarily stopped the development of NOACs for such patients. Therefore, at the present time, patients with AF and a mechanical heart valve should only be treated with a VKA.

Bioprostheses

Bioprostheses are considered to be less thrombogenic than mechanical valves, although the incidence of valve thrombosis in porcine valves without anticoagulation may be close to that of mechanical valves with anticoagulation. Pericardial valves were introduced in the 1970s to improve haemodynamics and decrease the rate of structural failure, and they appear less at risk of valve thrombosis than porcine valves [52]. Stentless bioprosthesis was introduced in 1992 with the aim of improving haemodynamic function and increasing durability compared with stented tissue valves [53].

After biological valve replacement, thromboembolic risk is estimated to be between 0.6% and 3.3% per year without anticoagulation, after the third month [45]. Many guidelines recommend anticoagulation with VKAs during the first 3 postoperative months. This period allows the endothelialization of bioprosthetic material [54]. This recommendation is well established for mitral bioprosthesis because of the higher risk of postoperative AF. Anticoagulation during the first 3 months is more debatable for aortic bioprostheses, given the absence of high-level evidence [55,56]. The risk of bioprostheses thrombosis is increased by low cardiac output and by valve deterioration with calcified surface [57,58]. The risk of embolization is more important in patients who also have AF, coagulation disorders, atrial dilatation and a history of systemic embolism [54].

It is accepted that anticoagulation can be avoided in the long-term in patients with bioprostheses, sinus rhythm and no additional risk factors, but controversy remains about antithrombotic management in the first 3 months after surgery [59]. Previous studies indicated that the thromboembolic risk associated with a prosthesis was significant in the first 3 months after the surgical operation, the risk being almost eliminated in anticoagulated patients with an aortic bioprosthesis, but remaining higher in patients with

a mitral bioprosthesis [60,61]. These embolisms have been linked to deposits of fibrin and platelet aggregation on foreign surfaces, such as Dacron sutures, as well as to a lack of endothelialization [55]. Conversely, some more recent studies suggested that there was no benefit associated with anticoagulant treatment during the 90 days following an aortic valve replacement with a bioprosthesis and no AF [26,62,63]. This might be explained by a different mechanism, with release of calcium microemboli during the peri- and early postoperative periods [64], which, however, are often asymptomatic. In addition, these calcium microemboli do not appear to be limited by anticoagulant treatment.

Despite a lack of firm evidence and long-term studies, current American College of Cardiology/American Heart Association guidelines recommend aspirin use for patients with both aortic and mitral bioprostheses and no AF or other risk factors [65]. American and European societies consider that the specific risk caused by the bioprosthesis added to the thromboembolic risk of AF is enough to facilitate a decision about effective anticoagulation [1,26]. These patients with AF (whether permanent or non-permanent, and whatever the CHA$_2$DS$_2$-VASc score) should always receive long-term anticoagulation, currently with a VKA, and targeting an international normalized ratio of 2 to 3 [29,66].

Transcatheter aortic valve implantation (TAVI) is actually the insertion of a bioprosthesis within an expandable stented structure, and has been used increasingly in recent years as an alternative to surgical aortic valve replacement for patients with AS. A combination of low-dose aspirin and a thienopyridine is usually prescribed early after TAVI, followed by aspirin or a thienopyridine alone [29]. If AF is also present, one should consider that the patient after TAVI has ''valvular AF'' if one refers to the most recent ESC guidelines. The optimal antithrombotic treatment in this setting is still unknown. Among TAVI patients with AF but without coronary artery disease, oral anticoagulation is recommended in accordance with the recommendations for AF alone [67]. The experience with patients receiving biological aortic valve replacement suggests that oral anticoagulation alone with VKAs may be sufficient to prevent thrombotic events. Whether the addition of antiplatelet therapy to oral anticoagulation is required in the context of TAVI with AF remains to be determined. In AF patients undergoing TAVI, a combination of a VKA and/or aspirin and/or or a thienopyridine may be used on an individual basis, particularly when coronary stenting is needed, but should be weighed against the increased risk of bleeding [29]. There are no data for patients with TAVI from trials with the NOACs.

Overall, whether thromboembolic risk related to bioprosthetic valve implantation differs from other forms of AF has not been established with certainty. Thromboembolism in patients with bioprosthetic valves and AF may presumably relate to both the bioprosthetic valve and the AF [24]. The incidence of thromboembolism in these patients was reported to be in the range of 5—6%/year [68,69], which is not very different from that found in an average age-matched AF population with risk factors. This may still allow options for therapy with NOACs in AF patients with bioprosthesis, particularly after the third month of surgery for those with only an aortic bioprosthesis [70].

Valve repair

Patients undergoing mitral valve repair have a small risk of thromboembolic events [71], with the highest risk of thromboembolism occurring during the first year after surgery. Guidelines therefore recommend oral anticoagulation during months 3—6 post-surgery [72]. However, only limited data are available on the efficacy of warfarin therapy early after valve surgery, and the use of short-term warfarin in patients with mitral valve annuloplasty is also controversial. It is therefore not clear whether patients with AF in addition to valve repair are markedly different from the patients with so-called ''non-valvular'' AF, and require a specific treatment or the avoidance of NOACs. The North American and European guidelines have different positions on this issue: the former publication considers AF to be valvular while the latter does not.

Suggestions for alternative definitions and conclusions

Obviously, we should no longer consider the classification of AF as ''valvular'' (or not) for the purpose of defining the aetiology of the arrhythmia, but for the determination of a different risk of thromboembolic events and the need for a specific antithrombotic strategy. The term ''valvular AF'' and its opposite ''non-valvular AF'' may actually cause confusion, because they should each determine homogeneous groups of patients with a similar pathogenesis of thromboembolism, similar thromboembolic risk and similar treatment needs, which is not the case. In a recent survey among physicians involved in the prescription of anticoagulants to AF patients, only 57% of the cardiologists and 68% of the internists agreed that the current definitions of non-valvular AF (e.g. from guidelines) were sufficiently clear [73]. As none of the objectives mentioned above are fulfilled by the current definitions, such terms should be either systematically defined (or reinforced) or changed to a more specific terminology.

There is a general agreement that the risk of thromboembolism is particularly high in AF accompanying moderate-to-severe mitral stenosis and mechanical prosthetic valves. As mitral stenosis, with or without other associated valvular disease, is virtually always rheumatic, the terms ''rheumatic AF'' and ''valvular AF'' may be used interchangeably in Western countries. It is not clear, however, whether the pathogenesis of thrombosis in AF accompanying rheumatic valve diseases (particularly when there is no significant mitral stenosis, which may be seen in non-Western countries) is qualitatively different from that of most common forms of ''non-valvular'' AF. Thus, some authors recently suggested that properly conducted trials of NOACs in patients with mitral stenosis may be justified [51].

Valvular heart diseases, such as mitral regurgitation, AS or aortic insufficiency, do not result in conditions of low flow in the left atrium, and do not, apparently, increase the risk of thromboembolism brought by AF per se. Post-hoc analyses suggest that these conditions, when they present in a moderate form, probably do not make the thromboembolic risk less responsive to NOACs compared with most forms of ''non-valvular'' AF.

The pathogenesis of thrombosis is most likely to be different for blood coming into contact with the artificial surface of a mechanical prosthetic valve compared with what occurs in most other forms of AF without concomitant valvular disease. This may explain the results of the only trial performed so far with an NOAC in patients with a mechanical prosthetic valve (only a few of whom had AF), where warfarin was more effective and safer than the relatively high doses of dabigatran that were used [50].

AF in the presence of a bioprosthetic heart valve or after valve repair appears to have a risk of thromboembolism that is not markedly different from other forms of ''non-valvular'' AF. On the basis of the limited preliminary evidence from trials with NOACs, there is no reported difference in efficacy or safety compared with warfarin, although it is likely that only a few patients with a bioprosthesis were actually included in the ARISTOTLE and ENGAGE-AF trials. Well-powered studies comparing NOACs and VKAs in this setting would be welcome.

De Caterina and Camm recently proposed the term ''mechanical and rheumatic mitral valvular AF'' (acronym: MARM-AF) as an accurate description of a disease entity worthy of being kept separate from other forms of AF, but with possible inner differences between the two conditions [51]. Similarly, Breithardt and Baumgartner indicated that it would be better if the terms valvular and non-valvular AF were abandoned. Instead, AF in the presence of a mechanical valve and AF in association with mitral stenosis should be highlighted as conditions with special needs for anticoagulation [74]. As long as no new term has been agreed upon, ''valvular AF'' will continue to be used, and refers solely to patients with mitral stenosis or artificial heart valves (and valve repair in the North American guidelines only). Patients with ''non-valvular AF'' may have other types of valvular heart disease. One should emphasize strongly that ''non-valvular AF'' does not exclude patients with some types of valvular heart disease from therapy with novel direct oral anticoagulants.

Disclosure of interest

L.F. Consultant for the companies Bayer, Boehringher Ingelheim, Medtronic, Novartis and sanofi-aventis. Speakers Bureau member for the companies Bayer, Boehringher Ingelheim and Boston Scientific.

All other authors declare that they have no conflicts of interest concerning this article.

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