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Stroke prevention strategies in patients with atrial fibrillation and heart valve abnormalities: perceptions of 'valvular' atrial fibrillation: results of the European Heart Rhythm Association Survey

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The purpose of this European Heart Rhythm Association (EHRA) Survey was to assess the perceptions of 'valvular' atrial fibrillation (AF) and management of AF patients with various heart valve abnormalities in daily clinical practice in European electrophysiology (EP) centres. Questionnaire survey was sent via the Internet to the EHRA-EP Research Network Centres. Of the 52 responding centres, 42 (80.8%) were university hospitals. Choosing the most comprehensive definition of valvular AF, a total of 49 centres (94.2%) encountered a mechanical prosthetic heart valve and significant rheumatic mitral stenosis, 35 centres (67.3%) also considered bioprosthetic valves, and 25 centres (48.1%) included any significant valvular heart disease, requiring surgical repair in the definition of valvular AF. Only three centres (5.8%) would define valvular AF as the presence of any (even mild) valvular abnormality. None of the centres would use non-vitamin K antagonist oral anticoagulants (NOACs) in AF patients with mechanical prosthetic valves, only 5 centres (9.8%) would use NOACs in patients with significant mitral stenosis, 17 centres (32.7%) would consider the use of NOACs in patients with bioprosthetic valves, and 21 centres (41.2%) would use NOACs in patients with a non-recent transcatheter valve replacement/implantation, while 13 centres (25.5%) would never consider the use of NOACs in AF patients with even mild native heart valve abnormality. Our survey showed marked heterogeneity in the definition of valvular AF and thromboprophylactic treatments, with the use of variable NOACs in patients with valvular heart disease other than prosthetic heart valves or significant mitral stenosis, indicating that this term may be misleading and should not be used.

Keywords Valvular atrial fibrillation • Mechanical prosthetic valves • Bioprosthetic valves • Transcatheter valve replacement/implantation • Non-valvular atrial fibrillation • Stroke prevention • Oral anticoagulation • EHRA survey • EP wire

Introduction

High risk of stroke without oral anticoagulant (OAC) therapy, in patients with atrial fibrillation (AF) and mechanical prosthetic heart valves or significant (rheumatic) mitral stenosis, has been well known, but these patients were not included in the historical trials, comparing vitamin K antagonists (VKAs) vs. placebo for stroke prevention in AF.[1] The pivotal trials on the efficacy and safety of non-vitamin K oral anticoagulants (NOACs) for stroke prevention in AF also excluded such patients, but used variable inclusion criteria, regarding other heart valve abnormalities.[2–5]

Thromboembolic risk (as well as the risk of OAC-associated bleeding) in AF patients with heart valve abnormalities other than prosthetic mechanical heart valves or significant mitral stenosis is less well known, but recent work suggests that the CHA2DS2-VASc score can assist risk stratification.[6] Along with variable definitions of 'valvular' AF used in the literature and contemporary clinical practice, this may create uncertainty among physicians regarding the use of OAC in many AF patients.

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The purpose of this European Heart Rhythm Association (EHRA) Scientific Initiatives Committee EP Wire Survey was to assess the perception of 'valvular' AF and management of AF patients with various heart valve abnormalities in daily clinical practice in European electrophysiology (EP) centres.

Methods and results

This survey was based on a questionnaire sent via the Internet to the EHRA-EP Research Network Centres. Of the 52 responding centres, 42 (80.8%) were university hospitals and 10 centres (19.2%) were private hospitals or other non-academic centres.

Diagnostic criteria and definition of valvular atrial fibrillation

Figure 1A shows the criteria that responding centres considered as diagnostic for valvular AF. While most centres would diagnose valvular AF in the presence of rheumatic mitral valve stenosis (50 centres, 96.2%) or a prosthetic mechanical heart valve (48 centres, 92.3%), other heart valve abnormalities were variably encountered (*Figure 1A*).

Most centres would consider not only the rheumatic aetiology but also the sclerotic or other valvular disease as a criterion for the diagnosis of valvular AF (39 centres, 75.0%), but would diagnose valvular AF only in patients with haemodynamically significant valve disease (36 centres, 69.2%). However, around a half of the responding centres would diagnose valvular AF only in the presence of mitral valve disease or a heart valve stenosis (*Figure 1B*).

We asked the EP Network Centres to choose the most comprehensive descriptive definition of valvular AF among the alternatives shown in *Figure 2*, implying that all AF patients not fitting the definition should be regarded and treated as having non-valvular AF. Only three centres (5.8%) would define valvular AF as the presence of any (even mild) valvular abnormality (*Figure 2*). Overall, 49 centres (94.2%) encountered a mechanical prosthetic heart valve and significant rheumatic mitral valve stenosis, 35 centres (67.3%) considered a bioprosthetic heart valve in addition to the two former conditions, and 25 centres (48.1%) also included any significant valvular heart disease, requiring surgical repair in the definition of valvular AF.

Antithrombotic therapies for stroke prevention in atrial fibrillation patients with a prosthetic heart valve

None of the responding centres would use a NOAC for stroke prevention in AF patients with a prosthetic heart valve (*Figure 3A*), but all would use a VKA, and 10 centres (19.2%) would combine a VKA with aspirin either routinely (1 centre, 1.9%) or in patients with mitral mechanical valve (2 centres, 3.9%) or a mechanical valve

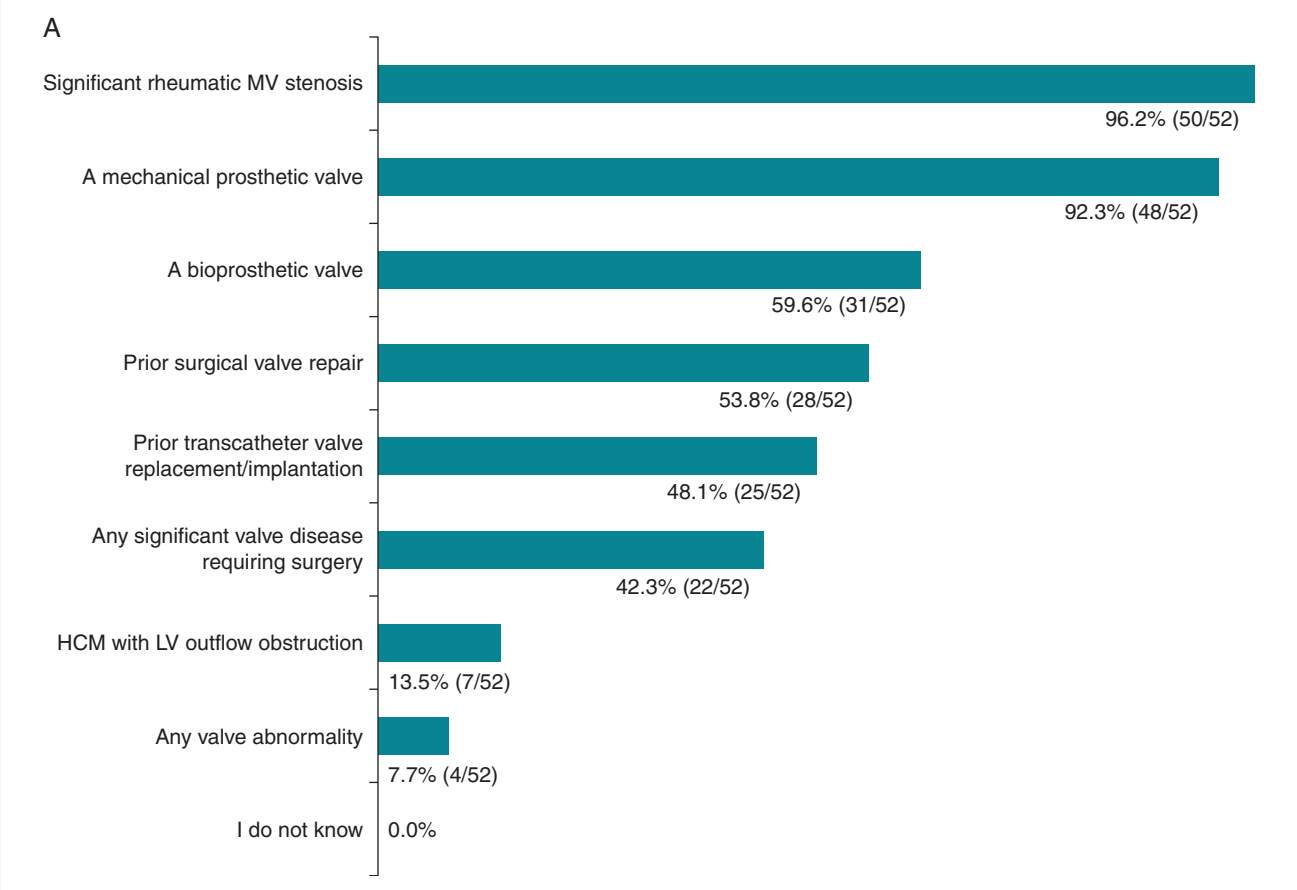

Figure 1 (*A*) Diagnostic criteria for valvular AF. (*B*) The relevance of native heart valve disease characteristics for the diagnosis of valvular AF. AF, atrial fibrillation; MV, mitral valve; HCM, hypertrophic cardiomyopathy; LV, left ventricular.

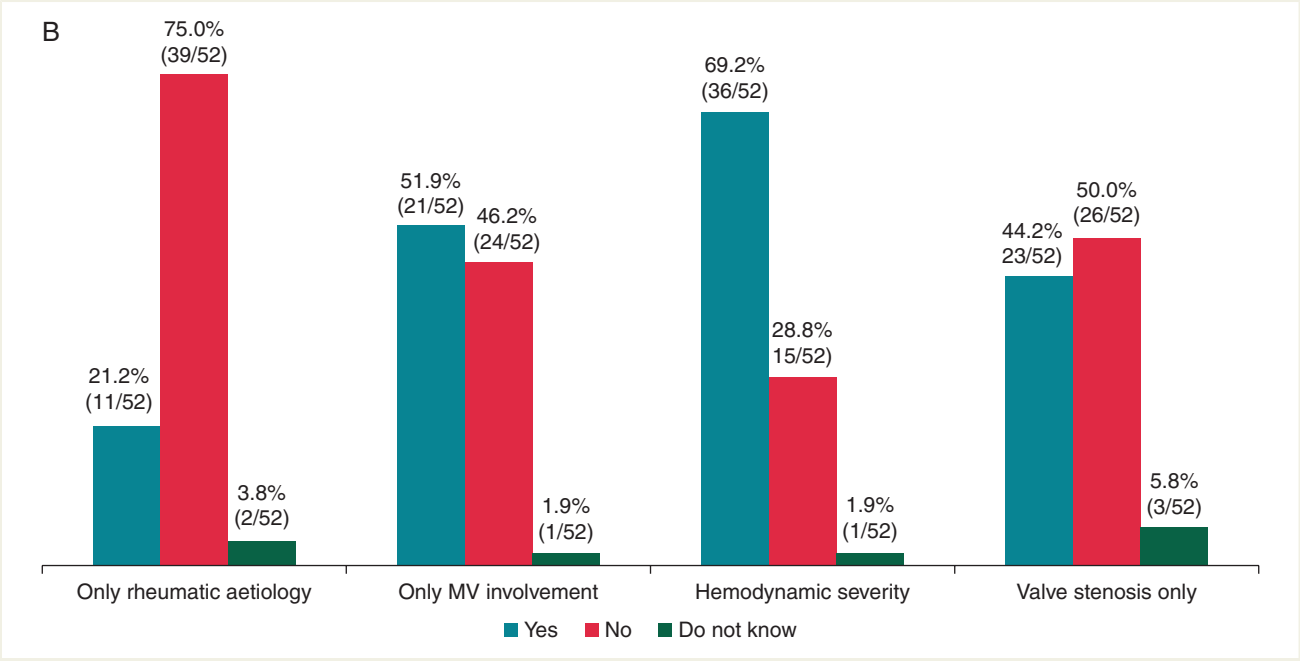

Figure 1 *Continued.*

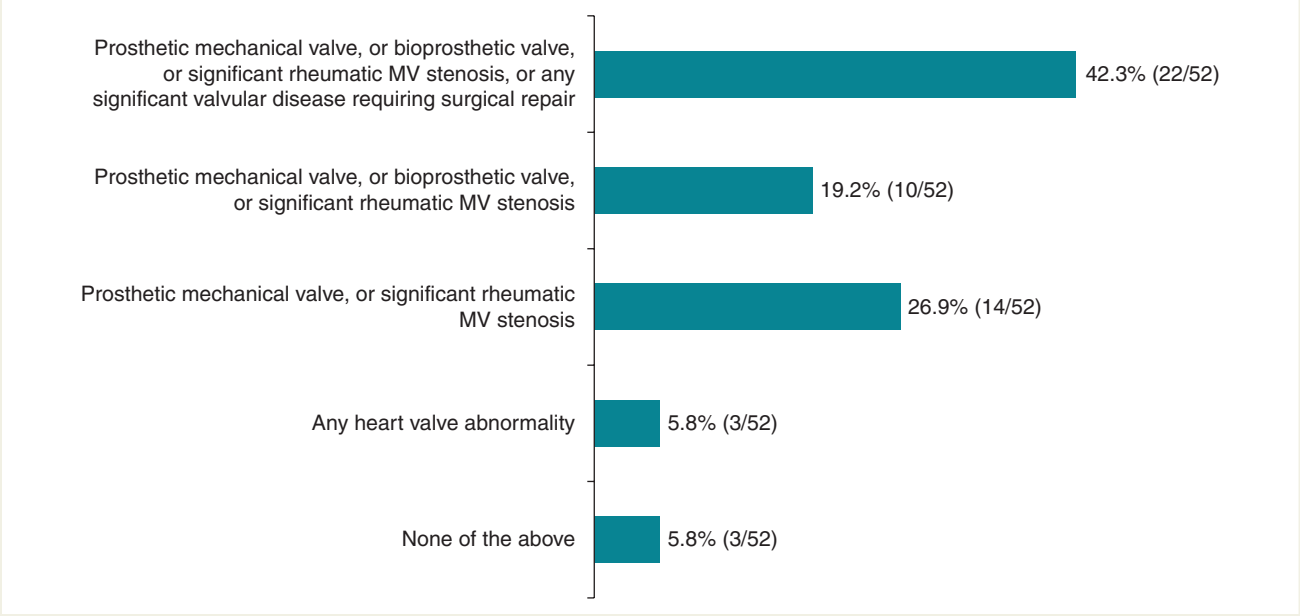

Figure 2 The definition of valvular AF (implying that AF patients not fitting the definition should be treated as having non-valvular AF). AF, atrial fibrillation; MV, mitral valve.

and history of prior stroke/TIA (7 centres, 13.5%). There was heterogeneity regarding the choice of antithrombotic therapy in AF patients with a bioprosthetic valve or those with a non-recent transcatheter valve replacement/implantation (*Figure 3A*). Of note, none of the centres would opt for a combination of antiplatelet drugs without oral anticoagulation in AF patients with a prosthetic heart valve.

The use of oral anticoagulant in atrial fibrillation patients with a native heart valve disease

In AF patients with a native valve abnormality and established indication for OAC use due to the presence of one or more conventional stroke risk factors, such as age ≥75 years, hypertension,

prior stroke and heart failure, 13 centres (25.5%) would never use NOACs in the presence of any native valve disease, and only 9 centres (17.7%) would preferably use NOACs instead of VKAs in patients with mitral valve stenosis. Although more centres preferred NOACs to VKAs in patients with other valve abnormalities (i.e. mitral regurgitation, or aortic, tricuspid or pulmonary valve disease), the use of NOACs was generally more likely in patients with mild-to-moderate heart valve abnormality than in those with moderate-to-severe valvular disease (*Figure 3B*).

In AF patients with a native heart valve disease and no conventional stroke risk factors, 17 centres (33.3%) would not use any OAC, while other centres would consider the use of OAC in patients with mitral valve stenosis (29 centres, 56.9%), mitral regurgitation (15 centres, 29.4%), aortic valve stenosis (11 centres, 21.6%), aortic regurgitation (12 centres, 23.5%), a tricuspid valve disease (10 centres, 19.6%) or a pulmonary valve abnormality (11 centres, 21.6%), while in 1 centre (2.0%) there was no strict policy for such patients.

Once the decision to use a NOAC has been made, 38 centres (74.5%) would choose the drug according to individual patient risk profile, 4 centres (7.8%) had no particular policy regarding the choice of a NOAC and 9 centres (17.7%) would preferentially use a particular NOAC. Overall, 38 centres (74.5%) considered the available evidence on the use of NOACs in patients with valvular AF as insufficient for clinical decision-making, 12 centres (23.5%) felt the evidence provided sufficient clinical guidance and 1 centre (2.0%) had no particular preferences towards the issue.

Discussion

This EP Wire provided an insight into the perception of 'valvular' AF and management of AF patients with various heart valve abnormalities in European daily clinical practice. The main findings of this survey are: (i) considerable variability in the criteria used for the diagnosis of valvular AF, (ii) variable definitions of valvular AF and (iii) variable antithrombotic treatments of these patients, in particular with regard to the use of NOACs for stroke prevention in AF patients with various heart valve abnormalities other than a prosthetic mechanical heart valve. This heterogeneity may reflect confusion among treating physicians regarding the use of OACs in valvular AF due to the lack of high-quality data, and could potentially translate into a suboptimal stroke prevention treatment in many AF patients presenting with various heart valvular conditions.

Diagnostic criteria and definition of valvular atrial fibrillation

While significant rheumatic mitral valve stenosis and a mechanical prosthetic heart valve were the most uniformly acknowledged diagnostic criteria for valvular AF, bioprosthetic valves, prior surgical valve repair, a history of transcatheter valve replacement or significant valvular disease requiring surgery were also considered as diagnostic for valvular AF by many centres in our study (*Figures 1A* and *2*). In addition, 75% of centres would not consider only the rheumatic aetiology (but also a sclerotic or other valve disease aetiology), 60% of centres would consider the severity of valve disease, and

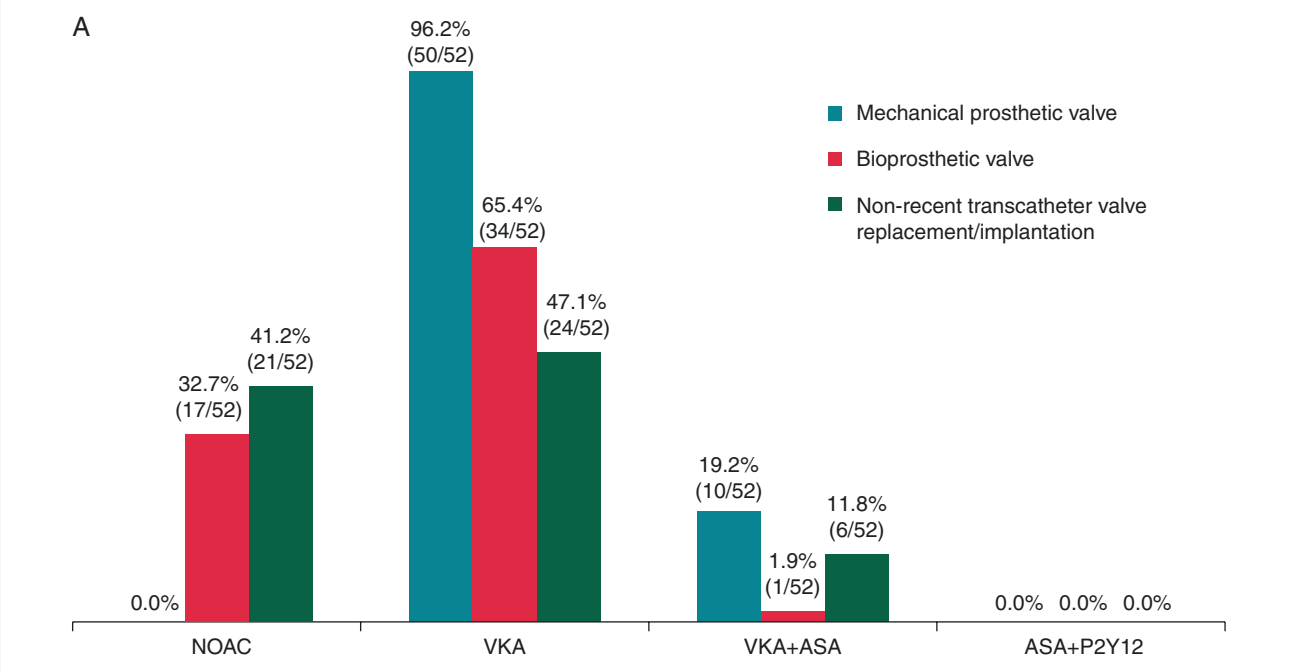

Figure 3 (*A*) Antithrombotic therapy for stroke prevention in AF patients with prosthetic heart valves. *Multiple answers were enabled; hence the sum of percentages does not necessarily equal 100%. (*B*) The use of NOACs for stroke prevention in patients with AF and a native heart valve abnormality. Light blue bars represent mild-to-moderate respective heart valve disease, and dark blue bars represent moderate-to-severe respective heart valve disease. Multiple answers were enabled. AF, atrial fibrillation; NOAC, non-vitamin K antagonist oral anticoagulant; VKA, vitamin K antagonist; ASA, acetyl-salicylic acid; P2Y12, platelet P2Y12 receptor inhibitors.

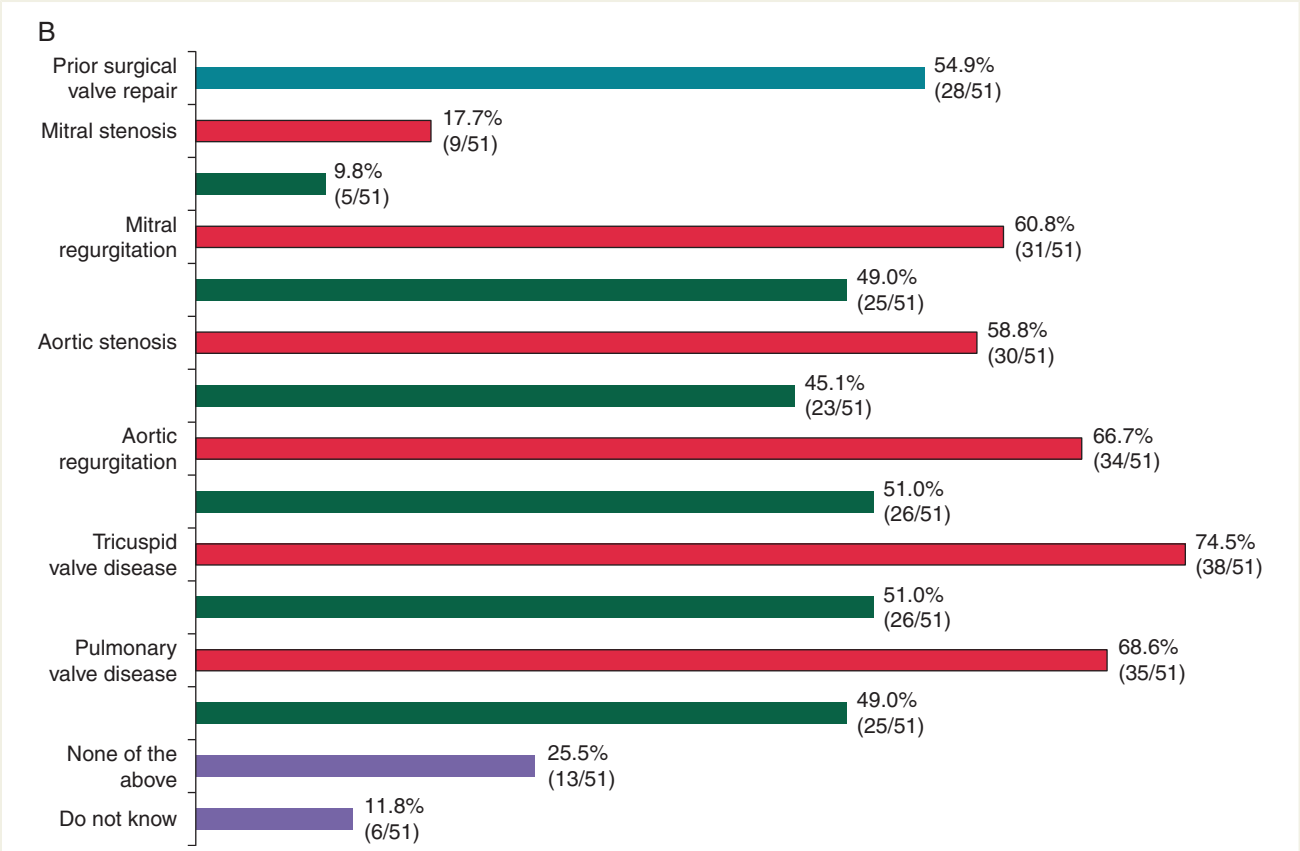

Figure 3 *Continued.*

around a half of the responding centres would also diagnose valvular AF in patients with valvular disease not involving mitral valve, or only in the presence of a valve stenosis.

This heterogeneity is probably due to the variable definitions of valvular AF used in AF guidelines[7,8] and stroke prevention trials.[1–5] For example, in the European AF guidelines, the term valvular AF refers to AF in patients with prosthetic heart valves or rheumatic valvular disease (predominantly mitral stenosis), while the US guidelines define valvular AF as AF in patients with rheumatic mitral stenosis, a mechanical or bioprosthetic heart valve or mitral valve surgical repair.[7,8] The pivotal NOAC trials on stroke prevention in AF consistently excluded patients with mechanical prosthetic heart valves or significant mitral valve stenosis. Patients with bioprosthetic valves were included only in the ENGAGE-AF study[5] (edoxaban), but no *post hoc* analysis of ENGAGE-AF patients with heart valve abnormalities has been published yet. The ENGAGE-AF, ROCKET-AF[2] (rivaroxaban) and ARISTOTLE[3] (apixaban) trials included patients with a history of surgical valve repair (i.e. annuloplasty with or without a prosthetic ring, commissurotomy, or valvuloplasty), while the RE-LY trial[4] (dabigatran) included only patients with mild-to-moderate native valve disease.

Overall, the *post hoc* analyses of NOAC trials showed that AF patients with heart valve abnormalities, other than a prosthetic valve or significant mitral valve stenosis, had more cardiovascular comorbidities (e.g. coronary artery disease and heart failure) than those without valvular disease. Nonetheless, the efficacy of apixaban, dabigatran and rivaroxaban was similar, irrespective of the presence or absence of valvular heart disease, and the only significant safety interaction was shown with rivaroxaban [in patients with valvular heart disease, the rate of major or clinically relevant non-major bleeding was higher in the rivaroxaban than in the warfarin arm (19.8 vs 16.8%, interaction $P = 0.034$)].[2] Importantly, the rates of intracranial bleeding were consistently lower with all NOACs than those of warfarin, irrespective of the valvular heart disease status.[2–4]

Implications for atrial fibrillation thromboprophylaxis

Given that all four NOACs have been approved for stroke prevention in patients with non-valvular AF, the diagnosis of valvular AF would exclude the option of NOAC use for stroke prevention in such patient. Indeed, NOACs are not recommended for stroke prevention in AF patients with mechanical prosthetic valves,[9] based on the RE-ALIGN study which showed higher rates of stroke, valve thrombosis and major bleeding with titrated-dose dabigatran compared with warfarin in patients with prosthetic mechanical heart valves.[10] However, more data are needed to inform clinical decision-making regarding AF patients with significant mitral valve

stenosis or bioprosthetic heart valves or those with a transcatheter valve replacement/implantation.

In our study, none of the respondents would use NOACs in AF patients with mechanical prosthetic valves, while only 18 and <10% of centres would use NOACs in patients with mild-to-moderate and moderate-to-severe mitral stenosis, respectively (*Figure 3B*). Of note, conduction of a randomized trial investigating NOACs in patients with significant mitral stenosis (without or with AF) has been recently advocated, based on the absence of scientifically plausible rationale for considering NOACs inferior to VKAs (particularly to poorly controlled VKA treatment) in patients with mitral stenosis.[11]

Nearly a third of centres in our study would use NOACs in AF patients with a bioprosthetic heart valve, and even more centres (41%) would consider the use of NOACs in AF patients with a history of non-recent transcatheter valve replacement/implantation (*Figure 3A*). Of note, in a 'real-world' AF cohort, including 549 patients with a valve bioprosthesis, the presence or location of bioprosthetic valve was not significantly associated with increased risk of stroke, while the use of OAC (VKAs) was significantly related to a lower risk of stroke.[6] Also, the ongoing randomized trials, investigating the use of apixaban (the ATLANTIS trial, NCT02664649) or rivaroxaban (the GALILEO trial, NCT02556203) post-transcatheter valve implantation, are expected to add some information regarding such patients with AF.

Although more data are needed to inform the optimal stroke prevention treatment in AF patients with bioprosthetic heart valves, transcatheter valve replacement/implantation and mitral valve stenosis, the aforementioned *post hoc* analyses of pivotal NOAC trials provide sufficient evidence on the outcomes of AF patients with various native valve abnormalities randomized to a NOAC vs. warfarin. Nonetheless, 25.5% of centres in our study would never consider the use of NOACs in AF patients with any native heart valve abnormality, and the proportion of centres, favouring NOACs over VKAs for native heart valve abnormalities, decreased with increasing severity of the respective valve disease (*Figure 3B*). Since many 'real-world' AF patients may have mild-to-moderate or significant valvular heart disease not precluding the use of NOACs for stroke prevention, our findings support the notion that the term 'valvular' AF is a misnomer which should not be used in clinical practice, or the term valvular AF should be more rigorously defined.[12]

Conclusion

Our survey showed marked heterogeneity in the definition of valvular AF and variable thromboprophylactic strategies in AF patients with valvular heart disease other than prosthetic heart valves or significant mitral stenosis. Many physicians may be reluctant to use NOACs even in AF patients with mild-to-moderate native heart valve abnormalities. The term valvular AF may be misleading and hence should not be used in clinical practice.

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