Non-Valvular Atrial Fibrillation: The Overlooked Concepts and Challenges of Novel Oral Anticoagulants

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EDITORIAL

Atrial Fibrillation (AF) is the most common sustained cardiac arrhythmia with a high prevalence in the elderly population [1]. AF is associated with substantial morbidity and mortality, particularly due to stroke and thromboembolism [2].

As a progressive atrial myopathy, the etiopathogenesis of AF is multifactorial. For example, valvular heart disease are found in 30% of AF patients and in mitral stenosis and/or regurgitation chronic atrial stretch is a well known pathophysiological factor in the occurrence of AF [1,3,4]. Indeed, mitral valve prolapse with or without regurgitation, calcification of the mitral annulus, tricuspid valve diseases, and idiopathic dilatation of the right atrium have been associated with a high incidence of AF. Also AF can be a late manifestation of aortic valve diseases causing left ventricular hypertrophy [1].

In the recent ACCF/AHA/HRS guidelines the term non-valvular atrial fibrillation (NVAF) 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 [1]. The 2012 focused update of the European Society of Cardiology (ESC) Guidelines for the management of AF define the term valvular AF as AF that is related to rheumatic valvular disease (predominantly mitral stenosis) or prosthetic heart valves [2]. According to these definitions we should consider patients with mitral and tricuspid regurgitation, calcification of the mitral annulus and aortic valve diseases as NVAF. However, there is a significant relation between these valvular diseases and AF as mentioned above. Although no satisfactory or uniform definition of these terms (valvular or non-valvular) exists, the major clinical trials [5-7] were designed in the basis of these conflicting and perhaps insufficient definitions. All of these studies included patients with NVAF but there is no a clear explanation about the definition of NVAF. The Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonist for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) trial [5] excluded patients with hemodynamically significant mitral valve stenosis and prosthetic heart valve (annuloplasty with or without prosthetic ring, commissurotomy and/or valvuloplasty) whereas the Randomised Evaluation of Long Term Anticoagulation Therapy (RE-LY) trial [6] excluded patients with a history of heart valve disorder (i.e., prosthetic valve or hemodynamically relevant valve disease) and the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial [7] excluded patients with moderate or severe mitral stenosis and prosthetic valve heart valve.

At this point we have to answer this question: Is there any clear reason to define the other AF related valvular heart diseases such as aortic valve disease, tricuspid valve disease and mitral regurgitation as NVAF?

In a recent meta-analysis of 4 randomized trials involving 42,411 patients who received the newer anticoagulants and 29,272 who received warfarin, the Novel Oral Anticoagulants (NOAC) dabigatran, rivaroxaban, apixaban, and edoxaban protects against stroke or systemic embolism better than warfarin and had comparable safety profiles [8].

Heidbuchel and colleagues [9] published a practical guide on the use of NOACs in patients with non-valvular AF. However, several important caveats and research priorities to optimise the use of the NOACs in AF remain. In patients who are prescribed a NOAC, a rapid and reliable measurement of the anticoagulant effect of the NOACs and as well as a defined therapeutic range are not available. Although the effectiveness and safety of an antidote to dabigatran (aDabi-Fab) has been demonstrated in a rat model of anticoagulation [10], in humans there is currently no specific antidote for the treatment of NOAC associated major bleeding. Because there is a lack of consensus, the management of patients with intracranial haemorrhagie (ICH) who are taking NOACs is very challenging. Some animal studies suggest that Prothrombin Complex Concentrates (PCC) can prevent expansion of dabigatran associated-ICH [11] and PCC, fresh frozen plasma, and Factor VIII can prevent expansion of rivaroxaban-associated ICH [12]. Therefore, in patients with life-threatening bleeding the administration of PCC or activated PCC is soley based on these.
scarce experimental data. An another important caveat that needs to clarify which assay condition and coagulation parameter optimally useful in monitoring of patients treated with PCC and other haemostatic agents.

The management of Acute Coronary Syndrome (ACS) in AF patients on NOAC is not clearly defined. It is unknown whether Percutaneous Coronary Intervention (PCI) is safe in NOAC treated patients without bridging and without additional periprocedural heparin, since all clinical trials have suggested interruption of NOAC treatment at PCI. After ACS it is also unknown whether dual or single antiplatelet therapy plus warfarin or NOAC or vice versa [9]. In post ACS patients with high risk the addition of apixaban, at a dose of 5 mg twice daily, to antiplatelet therapy significantly increased major and fatal bleeding risk including ICH, without clear evidence of reduction ischemic events including stroke [13]. In another ACS study low-dose rivaroxaban (2.5 and 5 mg twice daily) on top of dual antiplatelet therapy reduced the risk of the composite end point of death from cardiovascular causes, myocardial infarction or stroke and increased the risk of major bleeding and ICH but not the risk of fatal bleeding [14].

In patients taking a NOAC who experience acute ischemic stroke, except some isolated case reports of dabigatran [15-17] there is no evidence based data about thrombolysis in stroke patients taking NOACs. In these patients the optimal time to start or re-start anticoagulation therapy is also uncertain.

AF prevalence rises exponentially with age and nearly half of people with AF are older than 75 years [1]. There are many potential disadvantages of the NOACs in the elderly population including twice daily dosage regimen, the lack of a rapid and reliable monitoring option, the relatively short duration of action, food and drug interaction, excretion mainly by the kidney and the lack of an antidote [9].

In patients with mechanical prosthetic heart valve life-long oral anticoagulation is considered to be essential. However, these patients were excluded in the major clinical trials of the NOACs [5-7]. In the Randomised, Phase II Study to Evaluate the Safety and Pharmacokinetics of Oral Dabigatran Etxeílata in patients after Heart Valve Replacement (RE-ALIGN) trial [18] the use of dabigatran in patients with mechanical heart valves was associated with increased rates of thromboembolic and bleeding complications, as compared with warfarin, thus showing no benefit and an excess risk. However, an another invito study showed that high dose rivaroxaban (300 ng/ml, as achieved with oral administration of 20 mg), but not low dose rivaroxaban (30 ng/ml) is as effective as enoxaparin and unfractioned heparin in preventing thrombus formation on mechanical heart valves [19]. Although the results of the Kaeberich et al.’s [19] study are encouraging further studies are needed in this regard.

In conclusion the current arbitrary definition of NVAF should be clearly defined and large prospective studies should be designed to clarify the use of NOACs in different patient population as mentioned above.

REFERENCES
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