Defining non-valvular atrial fibrillation while selecting anticoagulation therapy

Recently, there have been major advances in the anticoagulation treatment options available to use in patients presenting with atrial fibrillation (Saraf et al, 2014). New oral anticoagulants are an alternative to vitamin K antagonists for the prevention of stroke in patients with non-valvular atrial fibrillation. However, non-valvular atrial fibrillation is not clearly defined in updated National Institute for Health and Care Excellence guidelines (Jones et al, 2014). To define this group of non-valvular atrial fibrillation patients, a deeper understanding of inclusion and exclusion criteria for all the related trials is needed.

Who was in and who was out?

Patients with mechanical heart valves or haemodynamically significant mitral stenosis were excluded from all three major trials for new oral anticoagulants – RE-LY (for dabigatran) (Connolly et al, 2010), ROCKET AF (for rivaroxaban) (Hacke et al, 2011), and ARISTOTLE (for apixaban) (Granger and Alexander 2011).

In terms of precise exclusion (or defining patients with valvular atrial fibrillation), each trial differed: the ROCKET-AF excluded patients with haemodynamically significant mitral stenosis or patients with a prosthetic heart valve (annuloplasty with or without prosthetic ring, commissurotomy and/or valvuloplasty), the RE-LY trial excluded patients with a history of heart valve disorder (i.e. prosthetic valve or haemodynamically relevant valve disease) and the ARISTOTLE trial excluded patients with moderate to severe mitral stenosis or patients with a prosthetic heart valve.

Furthermore the RE-ALIGN trial (Eikelboom et al, 2013), a study to evaluate the safety of oral dabigatran *vs* warfarin in patients after heart valve replacement, was stopped early because patients taking dabigatran were more likely to experience strokes, myocardial infarction and thrombus formation on the mechanical heart valves than patients taking warfarin. There was also more bleeding after valve surgery in the dabigatran group, thus dabigatran is contraindicated for use in patients with mechanical heart valves.

Similar drug safety and efficacy information is lacking for the other two new oral anticoagulants – rivaroxaban and apixaban – in patients with mechanical heart valves. None of the new oral anticoagulants have been studied in patients with bioprosthetic heart valves. None of the above mentioned three major trials included pregnant or lactating women, children, patients with reversible causes of atrial fibrillation, or patients with severe hypertension (systolic blood pressure >180 mmHg or diastolic blood pressure >100 mmHg). Patients with a recent stroke, with significant liver disease, and complex patients with multiple comorbidities were also excluded from all trials.

American Heart Association guidelines for the management of patients with atrial fibrillation (January et al, 2014) defined 'non-valvular atrial fibrillation' as atrial fibrillation in the absence of rheumatic mitral stenosis, a mechanical or bioprosthetic heart valve and mitral valve repair. The description of rheumatic mitral stenosis in the American Heart Association guidelines also remains unclear; however, after careful review of the trials, one may concur that it refers to 'haemodynamically' significant rheumatic mitral stenosis (relying on clinical history and echocardiographic findings). Also, it is not yet clear if patients with other types of significant valvular heart disease (non-rheumatic significant mitral stenosis, moderate to severe aortic stenosis, severe mitral regurgitation and severe tricuspid regurgitation) should be referred to as having 'non-valvular' or 'valvular' atrial fibrillation for the consideration of anticoagulation.

Conclusions

As new oral anticoagulants have been approved for use by the National Institute for Health and Care Excellence and prescriptions for these are on the rise across the UK, a cautious approach to patient selection should be adopted, as a large cohort of this patient population with atrial fibrillation will be in the unclearly defined (valvular or non-valvular) category. The safest current practice would be to consider time-tested warfarin for anticoagulation for this unclear group of patients with atrial fibrillation. This could be introduced in the form of local checklists when considering new oral anticoagulants in patients with non-valvular atrial fibrillation. **BJHM**

KEY POINTS

- Three new oral anticoagulants (dabigatran, rivaroxaban and apixaban) have been endorsed by the National Institute for Health and Care Excellence as an alternative to warfarin therapy in patients with 'non-valvular' atrial fibrillation.
- 'Non-valvular' atrial fibrillation remains unclearly defined by trials and guidelines.
- A cautious approach to patient selection should be adopted for the use of these new non-vitamin K antagonist oral anticoagulants.

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