Atrial fibrillation, valvular heart disease, and use of target-specific oral anticoagulants for stroke prevention

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This editorial refers to ‘Clinical characteristics and outcomes with rivaroxaban vs. warfarin in patients with non-valvular atrial fibrillation but underlying native mitral and aortic valve disease participating in the ROCKET AF trial’†, by G. Breithardt et al. on page 3377.

With the introduction of the target-specific oral anticoagulants (TSOAs), primary and secondary stroke prevention in atrial fibrillation (AF) has been revolutionized. Large randomized clinical trials and subsequent meta-analyses have clearly demonstrated that these agents have at least comparable if not superior efficacy and cause no more or even less major bleeding than vitamin K antagonists.1–5 The improved safety profile of these new compounds is particularly reflected by the significantly reduced risk of intracranial bleeds in comparison with warfarin, a property which all TSOAs have in common.6

Because of the historical studies on stroke prevention in patients with AF, all of the pivotal trials of TSOAs were conducted in patients with non-valvular AF, defined as patients with AF without rheumatic valve disease (mainly severe/moderate mitral stenosis) and/or without prosthetic heart valves. All other types of valve disease such as mitral regurgitation, aortic regurgitation, or aortic stenosis, for example, were allowed to be included in these trials. However, the historical term ‘non-valvular AF’ recently used in TSOA studies has created some confusion and led to concerns about the use of the TSOAs in patients with AF and valvular abnormalities. The recently published European and North American recommendations for management of AF have defined valvular AF as AF related to rheumatic valve disease (predominantly mitral stenosis) or to prosthetic heart valves,7 or as AF occurring in the absence of rheumatic mitral stenosis, mechanical or bioprosthetic heart valves, or mitral valve repair.8 The rationale behind these definitions was the generally accepted higher risk of thrombo-embolic stroke associated with these conditions.

Whereas rheumatic valvular disease is nowadays less frequently observed—at least in developed countries—many patients suffering from AF have other valve abnormalities. The ROCKET AF investigators have now presented their post-hoc analysis of AF patients with ‘significant valvular disease’ who were randomized to treatment with rivaroxaban or warfarin.9 Patients with valvular AF, defined as AF in patients with moderate/severe mitral stenosis and/or prosthetic heart valves, had been excluded from ROCKET AF. The authors are to be congratulated for their in-depth analysis of this important subset of patients. Their report represents the first full-length article on this topic which should be viewed in the light of two preliminary similar reports, one from the ARISTOTLE trial comparing apixaban with vitamin K antagonist therapy10 and one from the RE-LY trial comparing dabigatran with warfarin.11

The study by Breithardt et al. offers insights into three clinically important issues.7 The first issue relates to the clinical characteristics of subjects who had significant valvular disease. Overall, 14% of the ROCKET patients had some form of significant valvular disease compared with 26% in the ARISTOTLE trial10 and 22% in RE-LY.11 Not unexpectedly, valvular disease in the majority of patients consisted of mitral regurgitation (90%), followed by aortic regurgitation (25%) and aortic stenosis (11%; more than one valve could be affected). Similar numbers were seen in the dabigatran11 and the apixaban experience.10 In ROCKET AF, patients with valvular disease were older than individuals without, and had more comorbidities such as congestive heart failure, prior myocardial infarction, prior coronary artery bypass graft surgery, renal impairment, and peripheral arterial disease. The same differences in baseline characteristics between patients with and without valvular disease were observed in the other two trials.10,11 Despite these differences, in the ROCKET AF trial stroke rates were similar in patients with or without valvular disease after adjustment for important baseline criteria; similar to the findings in the RE-LY trial.11 In contrast, in the ARISTOTLE trial, the rate of stroke and systemic embolism...
was higher in patients with valvular disease when compared with patients without valvular abnormalities. Importantly, however, major or non-major clinically relevant bleeds were more frequent in patients with than without valvular disease in the ROCKET AF, RE-LY, and ARISTOTLE trials.

The second issue obviously relates to the efficacy of rivaroxaban as compared with warfarin. The risk of stroke or systemic embolism with rivaroxaban vs. warfarin was consistent among patients with [hazard ratio (HR) 0.83, 95% confidence interval (CI) 0.55–1.27] and without valvular disease (HR 0.89, 95% CI 0.75–1.07), with an interaction P-value of 0.76. Consistent efficacy in both patient subsets was also reported for dabigatran and apixaban, indicating that the advantages of TSOAs over warfarin for stroke prevention are consistently preserved in patients with and without valvular disorders (Figure 1). These findings are very important and have major implications for the practising physician since patients with AF with valvular abnormalities are very common in clinical practice.

The third issue relates to safety, i.e. the risk of bleeding. As already noted, overall bleeding risk was higher in patients with valvular disease in all three TSOA trials. Breithardt and colleagues

![Figure 1](https://academic.oup.com/eurheartj/article-abstract/35/47/3323/2293192)

**Figure 1** Risk for stroke or systemic embolism (SSE) in patients treated with rivaroxaban, dabigatran (two doses), or apixaban compared with warfarin in patients with or without valvular disease (upper half). Risk for major bleeding events in patients treated with rivaroxaban, dabigatran (two doses), or apixaban compared with warfarin in patients with or without valvular disease (lower half).
report a higher rate of major or non-major clinically relevant bleeding in patients with valvular disease who were assigned to rivaroxaban vs. warfarin (HR 1.25, 95% CI 1.05–1.49). This difference was not found in patients without valvular disease (HR 1.01, 95% CI 0.94–1.10; interaction P-value 0.034). In a set of careful subanalyses, the investigators ruled out a significant influence of co-morbidities such as heart failure or the use of concomitant antiplatelet therapy, for example, on this interaction between bleeding and valvular heart disease. Despite the differences observed in the treatment effect of rivaroxaban vs. warfarin on bleeding events, the rates of intracranial haemorrhage were significantly lower in patients receiving rivaroxaban than in patients receiving warfarin with and without valvular disease. The reason for this increase in risk for extracranial bleeding events with rivaroxaban in the subset of patients with valvular disease remains speculative. For both dabigatran and apixaban, there was no significant interaction between valvular disease and bleeding risk,\textsuperscript{10,11} highlighting an important difference among the TSOAs. Despite that, the play of chance can also explain, in part, these findings, since multiple comparisons were performed in a relatively small subgroup of patients.

What were the major lessons learned from this ROCKET AF sub-study and from similar post-hoc explorations of other TSOA trials? The practising physician now has a better understanding of the term ‘non-valvular AF’ which predominantly excludes patients with rheumatic valve disease (mainly severe/moderate mitral stenosis) and/or with prosthetic heart valves. These two disease entities will remain a domain of vitamin K antagonist therapy for stroke prevention particularly after one study has failed to show benefit of dabigatran in patients with prosthetic heart valves.\textsuperscript{12} Importantly, patients with AF and other valvular abnormalities are seen frequently in clinical practice (most commonly with mitral regurgitation), and are by definition considered as non-valvular AF patients who are suitable to be anticoagulated with any of the TSOAs in a similar fashion to individuals with AF without any valvular heart abnormalities. As individuals who have AF and valvular disease are generally older and have more advanced disease states and more co-morbidities, they deserve meticulous care, and particular attention must be paid not only to the anticoagulation strategy, but also to their overall treatment. The higher bleeding risk in patients with valvular disease treated with rivaroxaban as compared with warfarin observed in ROCKET AF is a puzzling finding where the underlying mechanisms behind it deserve additional research.

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\textbf{References}\n


