Non-vitamin K oral anticoagulants in ‘valvular’ atrial fibrillation: a call for action

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This editorial refers to ‘Non-vitamin K antagonist oral anticoagulants in atrial fibrillation accompanying mitral stenosis: the concept for a trial’ by R. De Caterina and A.J. Camm, on page 6–11.

Non-vitamin K oral anticoagulants in valvular atrial fibrillation

Non-vitamin K oral anticoagulants (NOACs) have become the standard of care for stroke prevention in patients with non-valvular atrial fibrillation (AF), based on the impressive efficacy and safety data demonstrated in four independent large-scale clinical trials.1–6 However, while the general concept and recommendations for the use of NOACs are being well conceived, the term ‘non-valvular’ has caused substantial confusion in daily clinical practice.7 First, its definition is not uniform across different guidelines. While the most recent ESC Guideline update in 2012 defines ‘valvular AF’ as rheumatic valvular disease (predominantly mitral stenosis) or prosthetic heart valves,5 current AHA/ACC/HRS Guidelines in addition explicitly include bioprosthetic valves and mitral valve repair.8 The second problem relates to the fact that the exclusion criteria due to valvular disease were not uniform across different NOAC trials. For example, the exclusion criteria in the ROCKET-AF trial were prosthetic heart valve or haemodynamically significant mitral stenosis, whereas in the ENGAGE-AF TIMI 48 trial, these were moderate or severe mitral stenosis, or a mechanical heart valve (whilst bioprosthetic heart valves and/or valve repair were allowed).2,4 As a result, uncertainty persists among practicing physicians whether a given patient with valvular heart disease is eligible for NOAC treatment. As a result, patients with valvular disorders other than the ones mentioned above, including frequently encountered entities such as aortic stenosis or mild-to-moderate mitral regurgitation, were often denied NOACs based on the perception that they were suffering from valvular AF. Indeed, this issue has been elegantly unveiled in a recent reappraisal by De Caterina and Camm.9 Also, recent subgroup analyses from ROCKET-AF and ARISTOTLE have indicated that patients with such lesions had a comparable efficacy and safety when treated with NOACs and vitamin K antagonists (VKAs).10,11 While available evidence hence suggests that these patients may be anticoagulated with NOACs, individuals with relevant mitral stenosis as well as those with mechanical heart valves were consistently excluded from all NOAC trials. For these patients, VKA treatment remains the standard of care—for now.

Non-vitamin K oral anticoagulants in mitral stenosis

In this issue of Europace,12 the authors take a strong stand, proposing a randomized clinical trial to investigate the superiority of NOACs over standard of care for prevention of stroke and systemic embolism in patients with rheumatic mitral stenosis. Their conclusive stream of arguments in favour of such a trial runs along several lines. (i) Although increasingly rare in Western countries, rheumatic heart disease remains a major healthcare issue in the developing world and newly industrialized countries, including large populations in China, India, and Mexico. Owing to the high incidence of thromboembolism, stroke related to AF in patients with mitral stenosis is affecting a large number of individuals worldwide. (ii) Current standard of care for these patients, i.e. anticoagulation with VKAs, is associated with several drawbacks, including inability to reach adequate time in the therapeutic range. As a result, these individuals either derive no benefit—and potential harm—from VKAs or are a priori transferred to an inferior treatment strategy such as antiplatelet agents (mostly aspirin). (iii) There is no scientifically plausible hypothesis why NOACs should be inferior in patients with mitral stenosis, particularly if compared with poorly controlled VKA treatment—as is the case for most of these patients.

Based on this, the authors suggest conducting an open label randomized clinical trial investigating a once-daily NOAC against the ‘standard of care’ (aspirin or VKA) in patients with moderate to
Learning from previous disappointing results

Another crucial aspect to consider will be NOAC dosing, which has panned out to be the most important factor for hitting the ‘sweet spot’ between efficacy and safety. In fact, this is not only evident from the pivotal NOAC trials in AF, but also for other indications such as NOACs in patients with acute coronary syndrome (ATLAS-TIMI 51 vs. APPRAISE-2), as well as in the long-term prevention of venous thromboembolism (e.g. EINSTEIN-EXT vs. AMPLIFY-EXT). In our view, performing a well-designed phase II dose-finding study may turn out to be time (and money) well invested. Should the proposed Phase III study of NOACs in mitral stenosis patients unexpectedly turn out negative, this will likely shut the door—potentially forever—for NOACs for this indication.

Indeed, this is exactly what happened to NOACs on the other side of valvular AF, i.e. in patients with mechanical heart valves. The RE-ALIGN trial investigating dabigatran for this indication had to be prematurely terminated due to excess in bleeding as well as thromboembolic complications in the NOAC arm.13 Is this indicative of failure of NOAC therapy in patients with mechanical valves? There are several reasons to believe that it is not, and that in fact design-related factors substantially contributed to these findings. Indeed, dabigatran doses used in this study were extrapolated from the RE-LY trial as well as from preclinical animal data, resulting in doses ranging from 150 to 300 mg bid administered in RE-ALIGN—hence equal to or substantially higher than those given in RE-LY. However, the pathogenesis of thrombus formation is likely to be different post valve replacement, thereby rendering the extrapolation of doses and target values subject to various factors which are difficult to control for. Potentially, a more thorough evaluation of the target dose for dabigatran in the setting of a dedicated Phase II study may have led to different doses to be chosen for RE-ALIGN, and may have avoided some of the negative results.

Another important trial-related downside relates to the recruited patient population. Indeed, including the majority of patients (80%) in the immediate post-operative period (3–7 days post-surgery), hence in a phase of increased risk of bleeding and thromboembolism during which bridging therapy with unfractionated heparin is normally used to tailor anticoagulation to the individual patient, likely resulted in a difficult population to investigate a new drug for a new indication. It is not surprising that the majority of complications occurred in just these patients. Randomizing patients after 3–6 months, hence in a stable post valve replacement period, would likely have been associated with much less ‘noise’ and would have more relevantly been able to determine the real efficacy and safety of dabigatran in this patient population.

As a result of RE-ALIGN, NOACs are contraindicated in all patients with mechanical valves. However, it is plausible that in differently selected patients (i.e. mid-term and not immediately after valve surgery) treated with the appropriate NOAC dose (i.e. well-studied Phase II), NOACs may be non-inferior if not superior to VKAs in patients with mechanical valves. Nevertheless, it is highly unlikely that such a trial will be conducted or sponsored in the near future, based on the negative findings of RE-ALIGN.

Hence, we fully agree that an outcome trial of NOACs in patients with mitral stenosis is necessary and should be conducted. Learning from previous disappointments and adapting the strategy to conduct such a trial will be of crucial importance to turn it into success, and to eventually allow for these patients to profit from NOACs for this new indication.

Conflict of interest: J.S. reports receiving consulting and lecture fees from Amgen, Astra-Zeneca, Attirec, Bayer, Biotronik, Biosense Webster, Boehringer-Ingelheim, Boston Scientific, Bristol-Myers Squibb, Daiichi-Sanyko, Cook Medical, Medtronic, Pfizer, Sanofi-Aventis, Sorin, St. Jude Medical, and Zoll. He also reports grant support through his institution from Bayer, Biotronik, Daiichi-Sanyko, Medtronic, and St. Jude Medical. He is co-director of CorXL. D.A. reports receiving consulting and lecture fees from Amgen, Astra-Zeneca, Bayer Healthcare, Boehringer-Ingelheim, Bristol-Myers Squibb, Cardiome, MSD, Novartis, Pfizer, Roche-Diagnostics, Sanofi-Aventis, and Vifor Pharma.

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