SCIENTIFIC EDITORIAL

Fondaparinux in atrial fibrillation — old dog, new tricks?

Fondaparinux dans la fibrillation atriale : on n’apprend pas à un vieux singe à faire des grimaces

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The modern approach to managing atrial fibrillation (AF) is now very much patient-centred and symptom directed [1]. Symptomatic, persistent AF can be unrelenting and result in a significant reduction in the patient’s quality of life. To alleviate these symptoms, besides provision of adequate rate-limiting agents, clinicians may alternatively offer rhythm control, for example, cardioversion to bring about restoration of sinus rhythm. Nevertheless, the risk of peri-cardioversion thromboembolism is high.

Thus, guidelines demand for utilisation of oral anticoagulation, traditionally Vitamin K antagonist (VKA, eg. warfarin) with a minimum of therapeutic anticoagulation (INR 2.0—3.0) for 3 weeks pre-cardioversion then for a minimum of 4 weeks post-cardioversion, but continued longer term where stroke risk factors are evident [2]. The use of transoesophageal echocardiography can potentially avoid pre-cardioversion anticoagulation and expedite cardioversion by excluding atrial thrombus, but the need for post-cardioversion anticoagulation still remains.

Until recently, VKAs and unfractionated heparin (UFH) were the only available anticoagulants, but their use was hampered by the need of close monitoring and adherence to a tight therapeutic range (be it international normalised ratio, INR, or activated partial thromboplastin time, aPTT) [3,4]. With VKAs, there is also the recognition that good quality anticoagulation control (as reflected by the time in therapeutic range (TTR) is necessary, to minimise the risks of thromboembolism and bleeding [5]. Fondaparinux, on the
other hand, is an indirect Factor Xa inhibitor, that is effective in treatment for both venous thrombosis and acute coronary syndrome [6,7]. Thus, the question remains: is fondaparinux an effective anticoagulant in patients with AF?

In this issue of Archives of Cardiovascular Diseases, Cohen et al. investigate the use of fondaparinux in the setting of electrical cardioversion of AF. The safety of fondaparinux in transoesophageal echocardiography-guided electric cardioversion of atrial fibrillation (SAFE-AF) study was an international phase II pilot study, involving 349 patients with AF who were scheduled to undergo electric cardioversion [8]. During the course of the study, transoesophageal echocardiogram was used to establish the absence of thrombus in left atrium or corresponding atrial appendage, prior to randomisation to fondaparinux or VKA (plus UFH) arm. Subsequent electric cardioversion was done, with post-procedural anticoagulation for 4 weeks and outpatient follow-up period of up to 90 days.

The chief purpose of this phase II trial was to establish the safety of use of fondaparinux in AF patients undergoing cardioversion, thus the primary endpoint of combined rate of ischaemic stroke, thromboembolism, bleeding events and death during treatment phase is of particular interest. This study demonstrated relatively higher primary endpoint event rate (1.7% versus 1.2%) with fondaparinux compared to VKA. Bleeding rates were also higher with fondaparinux compared to VKA, 1.7% versus 0.6%.

When compared to a previous study, the Anticoagulation in Cardioversion Enoxaparin (ACE) trial [9], the absolute rate of combined safety and efficacy event rate in fondaparinux was significantly lower (2.8% enoxaparin and 4.8% VKA), together with more modest major bleeding rate (0.8% enoxaparin and 2.4% VKA). Nevertheless, with such a small sample size in each treatment arm and without more data from the VKA group, such as the TTR, it is difficult to establish if the seemingly higher primary endpoint and bleeding rate in the fondaparinux group was due to chance or as a reflection of better oral anticoagulation control in VKA group.

These results should put in context with the recently published Xplore the efficacy and safety of once-daily oral rivaroxaban for the prevention of cardiovascular events in patients with non-valvular atrial fibrillation scheduled for cardioversion (X-VerT) study [10]. X-VerT compared VKA with rivaroxaban, a selective factor Xa antagonist, and the primary composite endpoint rate (including stroke, systemic thromboembolism, myocardial infarction and death) was 0.51% with rivaroxaban versus 1.02% with VKA, with a safety endpoint rate (fateful and major bleeds) of 0.61% versus 0.80% for rivaroxaban compared to VKA, respectively. Other reassuring data for the non-VKA oral anticoagulants (NOACs) come from post-hoc analyses of their phase 3 trials, showing similar efficacy and safety of dabigatran and apixaban compared to warfarin, when used peri-cardioversion [11,12].

Hence, although the SAFE-AF study was novel, it was small and underpowered. However, it did suggest that fondaparinux use in AF was associated with a low rate of systemic thromboembolism in return for a modest major bleeding risk, as compared to the combined VKA and UFH treatment. Nonetheless, the performance of fondaparinux pales in comparison to more contemporary oral anticoagulants, as demonstrated in the X-VerT study.

Second, amongst those patients whom thrombus had been discovered, 4 weeks of mandatory anticoagulation use was given to allow for dissolution of thrombus. Indeed, the sustained use of fondaparinux brought about a higher proportion of thrombus clearance as compared to VKA (76.8% versus 50%), although not statistically significant (P = 0.24). Conversely, some anecdotal case reports [13,14] have even suggested that off-label treatment with fondaparinux may bring about formation of atrial thrombus. Therefore, although the use of fondaparinux to promote left atrial thrombus dissolution may appear plausible, one should still practise caution when using it as an alternative anticoagulant over VKA or UFH.

Third, when comparing fondaparinux with VKA, the use of fondaparinux had a shorter mean duration of hospital stay, 5.9 days versus 8.1 days. This perhaps reflects the pharmacokinetics and dynamics of VKA, and the time taken for INR to reach therapeutic range (especially since this would be influenced by many clinical risk factors [15]) and could have probably resulted in prolongation of inpatient stay among VKA users.

In conclusion, the SAFE-AF study has established the idea that an injectable, indirect factor Xa inhibitor (fondaparinux) may potentially be a safe and effective anticoagulant in AF patients prior to cardioversion. The once-daily injection is definitely an attractive option over twice daily low-molecular weight heparin or continuous UFH infusion. Nevertheless, with the advent of plethora of NOACs, the role of injectable anticoagulants has diminished. This is further exacerbated by the lack of robust data from large prospective randomised controlled trials.

With the recent publication of the X-VerT study (relating to rivaroxaban), other open-labelled trials involving NOACs in the peri-cardioversion period are ongoing, for example, the EMANATE trial (with apixaban) and ENSURE-AF (with edoxaban). These trials may potentially reinforce the preponderance of NOAC use over VKA or injectable anticoagulants. For now, NOACs have certainly streamlined the approach to anticoagulation for AF cardioversion, and by avoiding the delays with VKAs to achieve therapeutic anticoagulation, they are therefore here to stay.

Disclosure of interest

Yee C. Lau and Richard A. Brown have no conflict of interest to declare.

Gregory Y.H. Lip has served as a consultant for Bayer, Astellas, Merck, Sanofi, BMS/Pfizer, Daiichi-Sankyo, Biotronik, Medtronic, Portola and Boehringer Ingelheim and has been on the speakers bureau for Bayer, BMS/Pfizer, Boehringer Ingelheim, Daiichi-Sankyo, Medtronic and Sanofi Aventis.

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