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Lessons from the trials

# RE-ALIGN: First trial of novel oral anticoagulant in patients with mechanical heart valves – The search continues

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## BACKGROUND

Over 4 million people worldwide have received a prosthetic heart valve, and an estimated 300,000 valves are being implanted every year.<sup>1</sup> Prosthetic heart valves improve quality of life and survival of patients with severe valvular heart disease, but the need for antithrombotic therapy to prevent thromboembolic complications in valve recipients, poses challenges for clinicians and patients.<sup>1</sup> Post-operative oral vitamin K antagonists, such as warfarin, are prescribed universally.<sup>2</sup> Some disadvantages of warfarin are its narrow therapeutic range, pharmacological and food interactions, and the need for frequent monitoring and dose adjustments.<sup>3</sup> New generation anticoagulants are more pharmacologically stable and do not require monitoring, although they have not been used as yet for the management of prosthetic heart valves.<sup>1</sup>

Novel oral anticoagulants (NOACs), including oral direct thrombin inhibitors and oral factor Xa inhibitors, have come to the fore in prevention of stroke in patients with atrial fibrillation (AF). Kaba and his colleagues<sup>4</sup> reviewed recent trials which presented compelling evidence for the safety and efficacy of these NOACs versus warfarin for this population of patients. NOACs are currently preferred over warfarin for stroke prevention in AF by both the recent ESC guidelines update and ACCP 9 guidelines.<sup>5</sup> Dabigatran etexilate (dabigatran) is a direct oral thrombin inhibitor, which has been shown in the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) study to be more effective than warfarin in patients with non-valvular atrial fibrillation with a better safety profile.<sup>6,7</sup>

RE-ALIGN™ was a multicentre, prospective, randomized, phase II dose-validation study, with blinded end-point adjudication, funded by Boehringer Ingelheim Pharmaceuticals, Inc. (BIPI). The primary end points of the study being trough plasma level of dabigatran, with additional efficacy and safety outcomes including; systemic embolism, valve thrombosis, bleeding, and death. The trial started recruiting at the end of 2011 with the aim of validating a new regimen for the administration of dabigatran to prevent thromboembolic complications in patients with mechanical heart valves. The trial was conducted at 39 centers in 10 countries.<sup>8</sup>

RE-ALIGN ran for 12 weeks, at the end of which, participants could choose to stop the study drug and switch to a non-study vitamin K antagonist, or they could choose to enroll in an extension trial (RE-ALIGN-EX). Participants in the extension trial continued to receive the assigned study drug for a planned interval of up to 84 months.

Patients were eligible for inclusion if they were between the ages of 18 and 75 years and had one of the following: mechanical valve replacement in the aortic or mitral position or both within the past 7 days (population A), or mechanical mitral valve (with or without aortic replacement) more than 3 months before randomization (population B). The trial had several exclusion criteria, including: prior prosthetic heart valve or aortic root replacement, valve replacement in tricuspid or pulmonary

<http://dx.doi.org/10.5339/gcsp.2014.13>

Submitted: 23 April 2014  
Accepted: 28 April 2014  
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position, clinically-relevant paravalvular leaks, endocarditis, history of hemorrhagic stroke, high risk for bleeding, hepatitis or abnormal liver functions, and CrCl <40 mL/min.

A total of 405 patients were originally planned, but the study was halted after recruitment of 252 patients. On the basis of safety data review, the data and safety monitoring board recommended discontinuation of the study because of unacceptable thromboembolic and bleeding event rates in the dabigatran group. There were no cases of stroke in the warfarin group, while in the dabigatran group, stroke occurred in 9 patients (5%). Two patients died in the warfarin group versus one patient in the dabigatran group. Valve thrombosis without clinical symptoms was detected in 5 patients, all of whom were in the dabigatran group (3%). The composite of stroke, transient ischemic attack, systemic embolism, myocardial infarction, or death occurred in 4 patients (5%) in the warfarin group and 15 patients (9%) in the dabigatran group. Most thromboembolic events among patients in the dabigatran group occurred in population A. Episodes of major bleeding occurred in 2 patients (2%) versus 7 patients (4%), and bleeding of any type occurred in 10 patients (12%) versus 45 patients (27%) in warfarin and dabigatran groups, respectively. A consistent pattern of increased bleeding events in the dabigatran group was evident in both populations. However, all major bleeding occurred in patients who underwent randomization within 1 week after cardiac surgery (population A). All 252 participating patients discontinued the assigned study drug and were switched to a non-study vitamin K antagonist.

#### WHAT HAVE WE LEARNED?

The authors should be congratulated for such an important attempt to find a solution for the continuing problem of thromboembolic and bleeding complications, associated with the use of warfarin, in patients with mechanical heart valves – especially in developing countries where a massive and rapidly-increasing burden of valvular heart disease exists.

The RE-ALIGN trial was a well-designed and conducted study. However, the dosing algorithm for dabigatran was based on a pharmacokinetic model developed in the RE-LY trial, which studied the characteristics of dabigatran in a different population. It is of interest to note that most thromboembolic events occurred among patients of the dabigatran arm when it was the initial anticoagulant, with fewer events occurring in patients who started dabigatran after 3 months of warfarin therapy. This might be due to inadequate plasma levels of the dabigatran during the first few weeks after surgery, which might have allowed for early formation of blood clots that were not clinically manifested until later. Therefore, patients of the dabigatran arm might have required a higher initial trough plasma levels. However, increasing the dose can lead to increased bleeding episodes, which was already higher in this group.

In conclusion, the RE-ALIGN study did not support the use of dabigatran as an alternative to warfarin in patients with mechanical heart valves. However, these disappointing results should not negate other future trials to study alternative NOACs.

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