



Mechanical heart valve thrombosis and novel oral anticoagulants: a word of caution

“Clinicians should ... stop off-label use of these agents until convincing data demonstrating safety and efficacy are available.”

KEYWORDS: guidelines ■ mechanical valve ■ oral anticoagulation ■ thrombosis

Oral anticoagulant therapeutic options are currently expanding, not only in drug types, but their clinical indications. Dabigatran etexilate (Pradaxa®) is a direct thrombin (IIa) inhibitor that has been approved for prevention of embolic stroke related to nonvalvular atrial fibrillation (AF) following results from the RE-LY trial, a study comparing dabigatran (110 or 150 mg twice daily) with warfarin in patients with nonvalvular AF, were published in 2009 [1,2]. RE-LY demonstrated similar rates of thromboembolic events in low-dose dabigatran versus warfarin, while higher doses of dabigatran showed even fewer thromboembolic events [2]. Along with other trials investigating new oral anticoagulants in patients with nonvalvular AF (RE-LY [2], ARISTOTLE [3], AVERROES [4], ROCKET-AF [5]), current national guidelines now have recommendations for the use of dabigatran, apixaban and rivaroxaban for prevention of stroke in nonvalvular AF patients and prevention of deep vein thrombosis following orthopedic surgery [1,6]; however, there is little information regarding the use of these medications in mechanical valve thromboprophylaxis. Thus, off-label use of these new drugs could lead to catastrophic complications, since their mechanism of anticoagulation does not mirror that of vitamin K antagonists.

New anticoagulants & mechanical valve thrombosis

■ Preclinical data

It is important to recognize that the mechanism of thrombus formation in nonvalvular AF is substantially different from that in the setting of mechanical heart valves. While the concern in AF relates to blood stasis due to a noncontractile atrium in patients with mechanical valves, there is a foreign body that can directly activate blood components and the coagulation cascade. It is

not surprising that even vitamin K antagonists are prescribed to achieve different therapeutic levels in patients with AF versus mechanical heart valves, particularly in the mitral position. Therefore, the dosing of the new anticoagulants will likely have to be tailored to the indication for anticoagulation.

There have only been a few preclinical models investigating the possible role of either dabigatran or rivaroxaban in mechanical valve thrombo-prophylaxis. McKellar and colleagues used an *in vivo* swine model whereby a modified bileaflet mechanical valved conduit (St Jude Masters Series, St Jude Medical, Inc., MN, USA) was implanted to bypass the ligated, native descending thoracic aorta to compare the amount of valve thrombosis at 30 days in a control group (no anticoagulation), a clinical group control (enoxaparin 2 mg/kg twice daily) and experimental group (dabigatran 20 mg/kg twice daily) [7]. Their short-term results demonstrated that dabigatran was as effective as enoxaparin in preventing modified heterotopic mechanical aortic valve thrombosis. There was no mortality difference between all groups. Conversely, Schomburg and colleagues used an orthotopic swine mechanical mitral valve replacement model (27 mm Carbomedics OptiForm™ Mitral Valve, Sorin, Vancouver, Canada), comparing control group (no anticoagulation), clinical control group (warfarin therapy) and experimental group (dabigatran therapy at 20 mg/kg twice daily) and demonstrated a significant survival benefit of the use of dabigatran when compared with warfarin therapy. However, thrombus presence at necropsy was found to be twice as high in the dabigatran group (80%) versus the warfarin group (40%; $p = 0.2$) [8]. Although *in vitro* studies demonstrated similar effectiveness of dabigatran or rivaroxaban to unfractionated heparin and low molecular weight heparin in



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thrombo-prophylaxis of mechanical valves [9,10], this more clinically relevant recent swine model was not able to recapitulate results found both *in vitro* and in McKellar's heterotopic swine model, even with ten-times the clinical dose of dabigatran, thereby limiting the role of dabigatran in mechanical valve-directed anticoagulation.

■ Clinical experience

Current literature regarding mechanical valve thrombosis in patients taking dabigatran include four case reports, two of which were presented to our institution [11]. However, the total number of mechanical valve patients taking newer anticoagulants is not known and therefore, the incidence of mechanical valve thrombosis is impossible to calculate. In our publication, we presented two cases where a change from chronic oral use of warfarin to dabigatran etexilate resulted in both aortic (case 1) and mitral (case 2) mechanical valve thrombosis, requiring emergent surgical valve replacement (reviewed by Price *et al.*) [11]. The other cases are presented below.

Case 3

Chu and coworkers presented a 78-year-old man who was switched from warfarin therapy, taken for 15 years after aortic valve replacement with a St Jude mechanical aortic valve, to dabigatran etexilate (150 mg twice daily) by his family physician. After 3 months, he began to experience shortness of breath and unstable angina. Echocardiography demonstrated severe prosthetic aortic valve dysfunction with severe stenosis and regurgitation due to a stuck leaflet. At surgery, the hinge mechanism in the aortic valve leaflet contained thrombus which was removed while the valve was left *in situ*. Warfarin was restarted postoperatively and the patient had an uneventful postoperative course, thereby not requiring a new prosthetic valve [12].

Case 4

Stewart and colleagues report a case of a posterior mechanical aortic valve leaflet thrombosis and cerebral embolization in a 62-year-old male taking dabigatran etexilate (150 mg twice daily) 9 months after switching from warfarin daily dosing (international normalized ratio: 2.5–3.0) [13]. After the RE-LY trial results were published in late 2009, the patient decided to switch from warfarin to start a higher dosing dabigatran regimen. After 9 months of therapy, the patient presented to hospital with left-sided weakness and was diagnosed with an embolic stroke on

CT head scan. An echocardiogram demonstrated a highly mobile mass on the posterior mechanical aortic valve leaflet consistent with thrombus. After phenindione (vitamin K antagonist) therapy for several weeks, the aortic valve appeared normal on echocardiography and the patient remained well at 12 months follow-up. Luckily, this patient did not require repeat surgical intervention since the thrombus did not seem to impede aortic valve function [13].

“Off-label use can lead to catastrophic complications, jeopardize patient care, and adversely affect the approval of these medications for new clinical indications.”

Based on the four cases above, it is clear that dabigatran can be associated with mechanical valve thrombosis. Although causation cannot be established, patients with mechanical valves in either the aortic or mitral position should not be treated with dabigatran, or other newer oral anticoagulants, as warfarin substitutes until convincing safety data are available. To date, there are no data from published clinical trials evaluating the use of these agents in mechanical valve patients. Because mechanical valve thrombosis and its sequelae can result in sudden death, it may be that the number of cases remain under-reported. Management of oral anticoagulation for mechanical valves is performed by many individuals including patients, family physicians, cardiologists, cardiac surgeons and other healthcare providers. All stakeholders in the care of these patients and the patients themselves need to be aware of the potential serious adverse events that can occur when changing anticoagulation regimens from vitamin K antagonists to one of the latest oral anticoagulants.

Dabigatran for mechanical valve thrombo-prophylaxis

■ RE-ALIGN trial

Based on preclinical data, the randomized, Phase II study to evaluate the safety and pharmacokinetics of oral dabigatran etexilate in patients after heart valve replacement (RE-ALIGN) was created and began enrollment in early 2012 [14,101]. This prospective, randomized, open-label, blinded end point Phase II study will compare dabigatran with warfarin in mechanical valve patients during a 12-week follow-up period. Their dosing regimens will mimic those seen in the RE-LY trial to achieve a trough drug level of at least

50 ng/ml with dabigatran dosing ranging from 150 to 300 mg twice daily. Also, there are two study design groups; in group 1, patients begin dabigatran at postoperative day 3–7 (recent surgery group), while in group 2 (remote surgery group), patients receive standard warfarin therapy for 3 months and are then randomized to dabigatran or warfarin therapy [14]. However, recent news from the RE-ALIGN Data Safety Monitoring Board and Boehringer Ingelheim, Ltd, indicates that group 1 (the in hospital surgical group) has been discontinued due to “lower than projected plasma levels of dabigatran in this population, and an imbalance in reports of thromboembolic events (primarily strokes)” [102]. With more case reports emerging around the globe demonstrating an association between patients experiencing mechanical valve thromboembolism after switching from warfarin to dabigatran, there is no surprise that the RE-ALIGN trial was completely stopped since Pradaxa users were more likely to experience strokes, heart attacks and blood clots on their mechanical valves. Just weeks after this, both the Committee for Medicinal Products for Human Use of the EMA and the US FDA have instated a contraindication (warning of use) of Pradaxa in patients with mechanical prosthetic heart valves [103,104].

Conclusion & future perspective

Even with several drug–drug interactions, the need for constant blood monitoring, and a

negative image as ‘rat poison’ therapy, warfarin has been the only effective oral anticoagulant for over 50 years. Consequently, it is not surprising that the medical community was enthusiastic about the introduction of dabigatran in 2009, followed quickly by rivaroxaban and apixaban, as new effective therapeutic options for the prevention of systemic thromboembolism in patients with nonvalvular AF [2–5]. It is becoming increasingly clear that these agents cannot be used at the currently approved doses for other indications, such as mechanical valve thrombo-prophylaxis. The data suggesting efficacy in this context is limited and several cases of catastrophic valve thrombosis have now been reported [11–13]. Clinicians should therefore stop off-label use of these agents until convincing data demonstrating safety and efficacy are available. Off-label use can lead to catastrophic complications, jeopardize patient care and adversely affect the approval of these medications for new clinical indications.

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