Cardiovascular Therapeutics

Dabigatran for Mechanical Valves

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Over 100,000 patients in the United States undergo heart valve replacement each year.¹ Although both bioprosthetic and mechanical valves may be used, mechanical valves have the advantage of greater durability. This potential benefit is offset, however, by a much higher risk of thromboembolic complications and the need for lifelong anticoagulation.² Historically, warfarin has been the anticoagulant of choice for these patients. However, warfarin therapy is less than ideal; it has the potential for numerous drug–drug and drug–food interactions and high interpatient variability that necessitates frequent blood draws and international normalized ratio (INR) monitoring. The recent development of target-specific oral anticoagulants (TSOACs) such as dabigatran, rivaroxaban, and apixaban provides potential alternatives for valve prophylaxis. To date, however, dabigatran is the only TSOAC that has been studied in a comparative trial with warfarin in patients with mechanical valves, and unfortunately the results have been disappointing. This article will review the evidence and concerns about the use of dabigatran in patients with mechanical valves.

Dabigatran etexilate is a prodrug for the direct thrombin inhibitor dabigatran.³ Dabigatran binds to thrombin and inhibits the conversion of fibrinogen to fibrin. The drug has a desirable pharmacokinetic profile with a rapid onset of action. Peak plasma levels are achieved approximately 2 hours after dosing, and steady state is typically achieved within 3 days. Elimination is primarily renal, with 80% of the drug excreted unchanged. With continuous dosing, the half-life is approximately 14 hours, thus enabling twice-daily dosing. Currently approved by the US Food and Drug Administration (FDA) for stroke prophylaxis in atrial fibrillation (AF), the recommended dose for patients with normal renal function is 150 mg twice daily (bid). Dosage reduction to 75 mg bid is recommended when the creatinine clearance is 15 to 30 mL/min. Patients with more severe renal failure should not receive dabigatran. One of the major

advantages of dabigatran as well as the other TSOACs is the more predictable dose response that eliminates the need for routine laboratory monitoring.

CLINICAL EFFICACY OF DABIGATRAN

Dabigatran was initially approved by the FDA for stroke prevention in AF on the basis of the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY).⁴ In this comparative trial of 18,113 patients at moderate to high risk for stroke, dabigatran 150 mg bid was found to be superior to warfarin (target INR, 2-3) for the prevention of stroke or systemic embolism (relative risk [RR], 0.66; 95% CI, 0.53-0.82; $P = .003$). The annual rate of intracranial hemorrhage was also lower with dabigatran (0.10% vs 0.38%; $P < .001$). Conversely, there was a higher annual rate of major gastrointestinal bleeding with dabigatran (1.51% per year vs 1.02% per year; RR, 1.50; 95% CI, 1.19-1.89; $P < .001$). As a result of these findings, the current guidelines from the American College of Chest Physicians (ACCP) recommend dabigatran as an alternative to warfarin for AF patients with moderate to high risk of stroke who cannot or prefer not to take warfarin.⁵ Although many patients with AF also have valvular heart disease, the RE-LY trial excluded patients with valvular heart disease and prosthetic heart valves. Thus, the FDA-approved indication for dabigatran is limited to nonvalvular AF.

EFFICACY IN PATIENTS WITH MECHANICAL VALVES

Initial findings from animal studies conducted in pigs suggested that dabigatran might be effective for preventing thrombus formation in humans with mechanical heart valves.^{6,7} Despite these encouraging results, however, concerns have been raised by several case reports of patients taking dabigatran off-label for mechanical valve prophylaxis. Atar et al described 2 patients with bileaflet mechanical mitral valves who had been maintained on therapeutic warfarin

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for several years without complication.⁸ After switching to dabigatran, both patients developed fatal valve thrombosis within 1 to 2 months. Three additional patients have been described, 2 with a mechanical aortic valve and 1 with a mechanical mitral valve, who experienced valve thrombosis on dabigatran.^{9,10} One patient experienced an embolic stroke, and the other 2 patients required repeat surgery but survived.

The only prospective trial to date assessing the comparative effectiveness of dabigatran and warfarin for patients with mechanical valves was the Randomized, Phase II Study to Evaluate the Safety and Pharmacokinetics of Oral Dabigatran Etxilate in Patients after Heart Valve Replacement (RE-ALIGN).¹¹ The study cohort included adults ≤ 75 years of age with mechanical bileaflet valves (aortic, mitral, or both). Among the patients, 80% had undergone valve implantation within the past 7 days and 20% had received a valve more than 3 months before randomization. Analysis was conducted separately for these 2 patient groups: This was a dose ranging study that used a dosing algorithm for dabigatran based on a pharmacokinetic model from the RE-LY trial. The initial doses were 150, 220, or 300 mg of dabigatran twice daily based upon renal function. Subsequent dosage adjustments were made to achieve a trough plasma level of ≥ 50 ng/mL. Warfarin was adjusted to an INR of 2-3 or 2.5-3.5 depending upon the patient's thromboembolic risk. Patients were followed for 12 weeks.

RE-ALIGN was terminated early after enrollment of only 252 patients because of an excess of both thromboembolic and bleeding events among patients receiving dabigatran. Dose adjustment or discontinuation of dabigatran was required in 32% of the patients. Ischemic or unspecified stroke occurred in 9 (5%) dabigatran patients compared to no patients in the warfarin group. The majority of thromboembolic events occurred within the first 90 days in the group that had recently undergone valve surgery. Major bleeding was also increased, occurring in 7 patients (4%) and 2 patients (2%), respectively. All major bleeding episodes occurred in the early postoperative group and were pericardial in location.

Several possible reasons for the lack of efficacy of dabigatran in RE-ALIGN have been proposed.^{11,12} Trough plasma levels of dabigatran during the first 4 weeks of the study were actually lower than expected. In view of the poor oral bioavailability of dabigatran, it is possible that absorption was delayed or reduced in the early postoperative period. It should be noted that the early postimplantation period is

highly inflammatory and thrombogenic. For patients being initiated on warfarin, bridging therapy is generally used until a therapeutic INR is obtained. Thus, it is possible that the fixed dose of dabigatran did not achieve adequate plasma levels fast enough to prevent thrombi from forming. However, because thromboembolic events occurred in patients with both lower and higher plasma levels, this does not fully explain the results. It has also been suggested that differences in the mechanisms of action for dabigatran and warfarin may at least partially explain the discordant findings. In AF, thrombi typically form in the left atrial appendage where flow rates and shear forces are typically low and blood stasis triggers the release of thrombin. In mechanical valve patients, thrombin is released in response to tissue factor from injury during implantation and exposure of blood to the artificial valve surfaces. The majority of thrombi tend to form along the sewing ring, which does not endothelialize for several weeks. Warfarin would likely be more effective in preventing these thrombi, because the drug inhibits factor VII that mediates tissue factor release as well as factors IX, X, and thrombin that mediate contact pathway-induced coagulation.

FDA COMMUNICATIONS

Based on the findings of RE-ALIGN, the FDA issued a safety advisory against the use of dabigatran in patients with mechanical valves and a requirement to add a contraindication to the product labeling.¹³ Patients taking dabigatran for mechanical valves are urged to talk with their physician but not stop taking the drug on their own. Although the contraindication does not specifically apply to bioprosthetic heart valves, in view of the absence of data, the FDA warns that dabigatran use in these patients cannot be recommended.

IMPLICATIONS FOR PRACTICE

Mechanical heart valves are associated with an increased risk of thromboembolism.² Among the three types of mechanical valves, the risk is highest with the caged-ball, intermediate with the tilting-disk, and lowest with the bileaflet design. Valves implanted in the mitral position are associated with greater risk than those in the aortic position, which has higher blood flow rates. Without antithrombotic therapy, the risk of thromboembolism with a mechanical valve has been estimated in various studies to be 4 to 23 events per 100 patient years. Warfarin is estimated

to reduce this risk to approximately 1 event per 100 patient years.¹⁴

The TSOACs are increasingly being used in patients with AF, a condition common among those who also have valvular heart disease. Many patients prefer these agents due to the more predictable dose response, lack of laboratory monitoring, and lower risk of drug–drug interactions. Thus, the ability to continue these agents in patients with both AF and valve replacements would be highly desirable. In the case of dabigatran, the paucity of evidence leaves many questions unanswered. Specifically, studies are needed to determine whether an alternative dosing regimen such as higher or more frequent doses with or without bridging may increase efficacy while maintaining an acceptable bleeding risk. The most appropriate timing for initiation of prophylaxis after the procedure also needs to be determined. The efficacy and safety of these newer agents when combined with single or dual antiplatelet therapy will also need to be examined, because many patients in this population will be taking these drugs.

For now, patients who have been taking dabigatran or other TSOACs for other indications prior to valve replacement surgery will need to be transitioned to warfarin. Due to the slow onset of warfarin, conversion will require overlap of the 2 drugs.¹⁵ For patients with normal renal function (creatinine clearance ≥ 50 mL/min), warfarin should be started 3 days before discontinuing dabigatran. For those with reduced renal function (creatinine clearance 30–50 mL/min), a 2-day overlap is suggested. In more urgent cases, heparin may be preferred for bridging during the initiation of warfarin. Recommendations for mechanical valve prophylaxis are provided by both ACCP¹⁶ and the American College of Cardiology/American Heart Association (ACC/AHA).¹⁷ These guidelines recommend long-term warfarin maintained at an INR of 2.5–3.5 (target, 3.0) for patients with a mechanical mitral valve and 2.0–3.0 (target, 2.5) for those with an aortic valve.

SUMMARY

Effective long-term oral anticoagulant therapy is required in patients who have received mechanical heart valves to reduce the risk of thromboembolism. Patients with mechanical heart valves are at high risk for cardioembolic stroke due to thrombus formation on the valve's surface. Numerous factors impact the overall risk for thrombosis, including the valve posi-

tion, valve design, and additional patient risk factors such as AF or prior history of thromboembolism.

Based on the findings of the only prospective study to date, dabigatran should not be used for mechanical valve prophylaxis due to a risk of higher thromboembolic events and excess bleeding. Nonetheless, it is important to keep in mind that this study does not definitively prove a total lack of efficacy of dabigatran for valve prophylaxis but rather demonstrates that the dosing strategy used was ineffective. It is also possible that other TSOACs such as the factor Xa inhibitors rivaroxaban and apixaban might prove beneficial, but unfortunately no studies have been completed.

Thus, for the foreseeable future, warfarin remains the only viable oral anticoagulant for prophylaxis in patients with mechanical heart valves. In view of the large number of patients with valvular disease, the complexity of taking warfarin, and the potential advantages of the newer agents, additional studies are clearly justified to further determine the effectiveness of alternative agents. Due to the high potential for serious and often fatal outcomes in these patients when prophylaxis is inadequate, it is imperative that pharmacists keep abreast of emerging information and monitor patients closely for appropriate therapy.

REFERENCES

1. Lloyd-Jones D, Adams RJ, Brown TM, et al. Executive summary: Heart disease and stroke statistics—2010 update: A report from the American Heart Association. *Circulation*. 2010;121:948–954
2. Leiria TLL, Lopes RD, Williams JB, et al. Antithrombotic therapies in patients with prosthetic heart valves: Guidelines translated for the clinician. *J Thromb Thrombolysis*. 2011;31:514–522.
3. Ellis CR, Kaiser DW. The clinical efficacy of dabigatran etexilate for preventing stroke in atrial fibrillation patients. *Vasc Health Risk Manag*. 2013;9:341–362.
4. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009;361(12):1139–1151. [Erratum published in *N Engl J Med*. 2010;363(19):1877.]
5. You JJ, Singer DE, Howard PA, et al. Antithrombotic therapy for atrial fibrillation antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2012;141(Suppl):e531S–575S.
6. McKellar SH, Abel S, Camp CL et al. Effectiveness of dabigatran etexilate for thromboprophylaxis of mechanical heart valves. *J Thorac Cardiovasc Surg*. 2011;141:1410–1416.

7. Schomburg JL, Medina EM, Lahti MT, Bianco RW. Dabigatran versus warfarin after mechanical mitral valve replacement in the swine model. *J Invest Surg.* 2012;25: 150-155.
8. Atar S, Wishniak A, Shturman A, et al. Fatal association of mechanical valve thrombosis with dabigatran. *Chest.* 2013;144:327-328.
9. Stewart RA, Astell H, Young L, White HD. Thrombosis on a mechanical aortic valve whilst anti-coagulated with dabigatran. *Heart Lung Circ.* 2012;21:53-55.
10. Price J, Hynes M, Labinaz M, Ruel M, Boodhwani M. Mechanical valve thrombosis on dabigatran. *J Am Coll Cardiol.* 2012;60:1710-1711.
11. Eikelboom JW, Connolly SJ, Brueckmann M, et al; for the RE-ALIGN Investigators. Dabigatran versus warfarin in patients with mechanical heart valves. *N Engl J Med.* 2013;369:1206-1214.
12. Hylek EM. Dabigatran and mechanical heart valves – not as easy as we hoped. *N Engl J Med.* 2013;369:1264-1266.
13. Drug safety communication: Pradaxa (dabigatran etexilate mesylate) should not be used in patients with mechanical prosthetic heart valves. Silver Spring, MD: Food and Drug Administration; December 19, 2012. <http://www.fda.gov/Drugs/DrugSafety/ucm332912.htm>. Accessed November 7, 2013.
14. Cannegieter SC, Rosendaal FR, Briet E. Thromboembolic and bleeding complications in patients with mechanical heart valve prostheses. *Circulation.* 1994;89:635-641.
15. *Pradaxa* [product information]. Ridgefield, CT: Boehringer Ingelheim. Revised December 2013.
16. Whitlock RP, Sun JC, Fries SE, et al. Antithrombotic and thrombolytic therapy for valvular disease. 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest.* 2012;141(Suppl):e576S-e600S.
17. Bonow RO, Carabello BA, Chatterjee K, et al. 2008 focused update incorporated into the ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol.* 2008;52:e1-e142. ■