

Anticoagulation for Mechanical Heart Valves Will Oral Factor Xa Inhibitors Be Effective?

Noel C. Chan, Jeffrey I. Weitz, John W. Eikelboom

The global burden of valvular heart disease, which currently affects more than 100 million people, is growing with the aging population.¹ Severe valvular heart disease is associated with major morbidity and mortality and often necessitates surgical valve replacement with a mechanical or a tissue valve. If the risk of surgery is prohibitive, transcatheter valve replacement is another option.²

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Although mechanical heart valves (MHV) are more durable than tissue valves, they are more thrombogenic. Consequently, patients with MHV require long-term anticoagulation with vitamin K antagonists, such as warfarin.^{2,3} Although effective, warfarin has well-known limitations, including multiple drug and food interactions, and the challenges of coagulation monitoring and maintaining the international normalized ratio within the therapeutic range. Indeed, variability in the international normalized ratio is a major independent predictor of reduced survival in patients with MHV.⁴ Consequently, there is a need for effective anticoagulants for MHV patients with better pharmacological profiles than warfarin.

Direct oral anticoagulants have replaced warfarin for many indications.⁵ These agents include dabigatran, which inhibits thrombin, and rivaroxaban, apixaban and edoxaban, which inhibit factor Xa. Despite the proven efficacy and safety of direct oral anticoagulants in the prevention of stroke in patients with atrial fibrillation, and in the prevention and treatment of venous thromboembolism, the unfavorable results of the RE-ALIGN (Randomized, Phase II Study to Evaluate the Safety and Pharmacokinetics of Oral Dabigatran Etexilic acid in Patients after Heart Valve Replacement) trial prompted the FDA to issue black-box warnings against the use of direct oral anticoagulants in patients with MHV.⁶ In the RE-ALIGN trial, dabigatran etexilate was titrated up to a maximum dose of 300 mg twice daily (BID) to achieve a trough level above 50 ng/mL. Despite this targeted dosing, dabigatran was associated with a trend for an excess of ischemic strokes and a significant increase in major bleeds compared with dose-adjusted warfarin, leading to early termination of the trial.⁶ The higher dabigatran doses likely explain the increased bleeding, but even

with these higher doses, dabigatran was less effective than warfarin at preventing clotting on MHV.

Why did dabigatran fail for this indication when it was successful in others? The failure likely reflects the fact that unlike the situation in atrial fibrillation and venous thromboembolism where thrombosis is initiated by tissue factor, clotting on MHV is triggered via activation of the contact system, resulting in the local generation of thrombin in concentrations that overwhelm those of dabigatran (Figure).⁷ One molecule of factor Xa triggers the generation of 1000 molecules of thrombin. Therefore, it is possible that by inhibiting upstream to thrombin, oral factor Xa inhibitors, such as apixaban, may be better than dabigatran for suppressing clotting on MHV.

In this issue, Lester et al⁸ lend credence to this hypothesis, and report that oral or intravenous apixaban prevented clotting to a similar extent as warfarin dose-adjusted to an international normalized ratio of 2 to 3 in a porcine heterotopic aortic valve model. Because of the rapid clearance of orally administered apixaban in pigs, an oral dose of 1 mg/kg BID was required to maintain the antifactor Xa activity above 0.6 IU/mL throughout the dosing interval. The intravenous apixaban regimen was designed to mimic the exposure obtained when apixaban is given to humans at a dose of 5 mg BID. After 30 days, the mean thrombus weight on the explanted valves was 1422.9 mg in the controls (n=4), not given any anticoagulant. In contrast, the mean thrombus weights were 357.5 and 247.1 mg in the oral apixaban (n=5) and warfarin (n=3) groups, respectively. After 14 days, the mean thrombus weight was only 61.1 mg in the group (n=4) given intravenous apixaban. Using a similar porcine model, others have reported that oral rivaroxaban (2 mg/kg BID) is superior to subcutaneous enoxaparin (2 mg/kg BID) in preventing valve thrombosis, supporting the hypothesis that factor Xa is an appropriate target for attenuating clotting on MHV.⁹

Does this mean that apixaban can be safely used instead of warfarin in humans with MHV? Although promising, the findings need to be interpreted with caution. First, the sample size (n=16) was small, so that efficacy comparisons with warfarin are underpowered. Second, the oral apixaban regimen administered in this study is a higher dose than that used in humans. Although the intravenous infusion regimen more closely mimicked apixaban dosing in humans, thrombus weight measurements were confounded by earlier assessment at day 14 instead of day 30. Finally, although the pig heterotopic aortic valve model is often used to test the efficacy of anticoagulants, it is uncertain whether the results from this model can be translated to humans. For instance, dabigatran was more effective than enoxaparin for preventing valve thrombosis in this model, but failed in humans in the RE-ALIGN study.^{6,10}

The RE-ALIGN trial results have improved our understanding of the mechanism of clotting on MHV. There is

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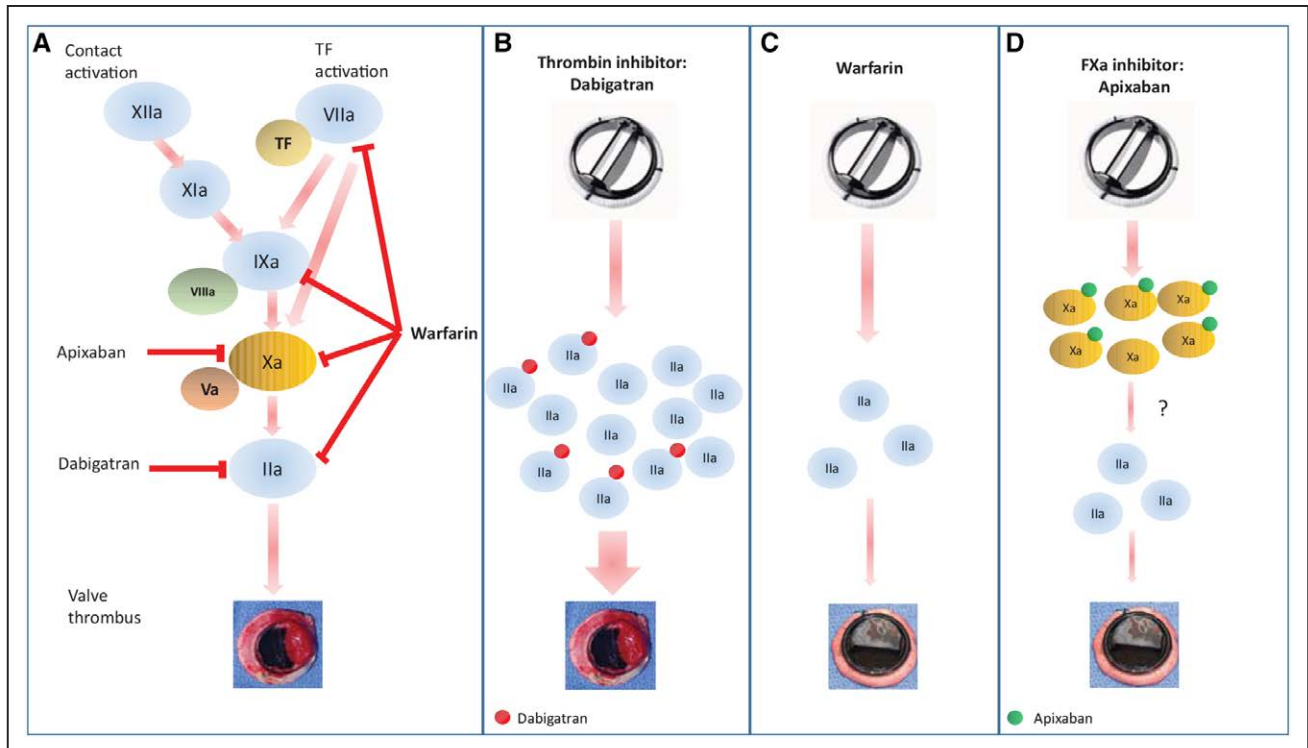


Figure. Mechanisms of mechanical heart valve thrombosis and the differential effects of anticoagulants on thrombin generation. **A**, Mechanical heart valves (MHV) trigger clotting via both the tissue factor (TF) and the contact pathway. Surgical implantation exposes TF, which binds factor VIIa (VIIa) to form extrinsic tenase and results in activation of factor X (X) and factor IX (IX). In the presence of factor VIIIa (VIIIa), factor IXa (IXa) incorporates into intrinsic tenase to further promote factor Xa (Xa) generation. Xa and Va then form the prothrombinase complex, which converts prothrombin to thrombin (IIa), and leads to clotting by converting fibrinogen to fibrin. Thrombin generation induced by TF is downregulated by tissue factor pathway inhibitor, which first binds and inhibits VIIa and then inhibits VIIa bound to TF. The valve leaflets and suture ring initiate clotting via contact activation. On these surfaces, factor XII (XII) undergoes auto-activation to form XIIa. The latter amplifies its own generation via the prekallikrein–kallikrein system (not shown), and also activates factor XI (XI), which then activates IX, thus generating intrinsic tenase and amplifying Xa and IIa generation. The sites of action of warfarin, Xa inhibitors such as apixaban, and thrombin inhibitors, such as dabigatran are shown. **B**, By triggering contact activation, MHV lead to the generation of thrombin in concentrations that exceed those of dabigatran, which inhibits thrombin in a stoichiometric manner. **C**, In contrast, by reducing the levels of the vitamin K–dependent clotting factors (VII, IX, X, and II), warfarin suppresses Xa and thrombin generation. **D**, Because each Xa molecule can generate 1000 molecules of thrombin, Xa inhibition by apixaban may attenuate thrombin generation to a similar extent as warfarin provided that the apixaban concentrations are sufficiently high throughout the day to prevent breakthrough thrombin generation.

mounting evidence that the root cause of thrombosis on blood-contacting medical devices is activation of factor XII.¹¹ This explains why coating such devices with corn trypsin inhibitor, a potent and specific inhibitor of factor XIIa, or knocking down the levels of factor XII or factor XI with antisense oligonucleotides prevents such clotting.^{12,13} In the absence of oral inhibitors of factor XII or XI, oral factor Xa inhibitors may be the next best choice. Although the preclinical results with apixaban and rivaroxaban are promising, clinical trials are needed to assess their use in patients with MHV. The key issue will be determining the critical threshold of factor Xa inhibition required to prevent clotting on MHV and identifying oral dosing regimens capable of achieving them. From being restricted to warfarin, we now have the knowledge and tools to devise better and more convenient anticoagulant regimens for patients with MHV, but considerably more work remains to be done.

Disclosures

None.

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