

EDITORIAL

# Anticoagulant Therapy for Mechanical Heart Valves — Unmet Need Persists

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**D**irect oral anticoagulants such as apixaban or dabigatran have revolutionized anticoagulant treatment. These drugs, which specifically inhibit either factor Xa or thrombin, respectively, are at least as effective as vitamin K antagonists (e.g., warfarin) in patients with atrial fibrillation or venous thromboembolism and have important safety advantages that include reduced risks of intracranial hemorrhage, fatal bleeding, and all-cause mortality.<sup>1-3</sup> They are also much easier to use because they are given in a fixed dose without routine laboratory monitoring of the anticoagulant effect and dose adjustment in the individual patient.

It was hoped these advantages would translate to patients with mechanical heart valves, who require life-long anticoagulant therapy to prevent valve-related thromboembolism. This hope has been deferred for the last 10 years based on the results of a phase II trial of dabigatran, which was terminated prematurely because of an excess of thromboembolic and bleeding events in patients given dabigatran compared with those who received warfarin.<sup>4</sup> Evidence-based guidelines therefore recommend anticoagulation using a vitamin K antagonist for all patients with mechanical heart valves.<sup>5</sup> These guidelines also state that the use of dabigatran is contraindicated, and the use of an anti-Xa direct oral anticoagulant has not been assessed and is not recommended.<sup>5</sup>

Now, the results of a new clinical trial by Wang et al.<sup>6</sup> have put the final nail in the coffin of hope for the use of a direct oral factor Xa inhibitor for anticoagulation in patients with a mechanical heart valve. Patients with an On-X mechanical aortic valve implanted at least 3 months previously were randomly assigned to receive 5 mg of apixaban twice daily or warfarin adjusted to achieve an international normalized ratio of 2.0 to 3.0. This trial was justified based on the reportedly lower thrombogenic nature of the On-X valve<sup>6</sup> and because an oral factor Xa inhibitor had not been evaluated in these patients.<sup>5</sup> The study was stopped early due to an excess of valve-related thromboembolic events in patients treated with apixaban. The incidence of thromboembolism was 4.2% per patient-year in the apixaban group versus 1.3% per patient-year in the warfarin group.<sup>6</sup> Thromboembolic stroke occurred in 14 patients (2.9%) given apixaban compared with none who received warfarin. The hope for an effective, safer, and easier-to-use alternative to warfarin has not been realized, and this unmet need persists.

Should a new clinical trial of a factor Xa or thrombin inhibitor be undertaken each time a new reportedly less thrombogenic mechanical heart valve is introduced into clinical practice? The answer is no. The risk is too great given two prior studies indicating failed

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effectiveness,<sup>4,6</sup> and the consequence for patients is devastating thromboembolism (e.g., stroke). Furthermore, recent laboratory studies<sup>7</sup> have advanced our understanding of the mechanisms by which mechanical heart valves induce thrombus formation and explain the ineffectiveness of apixaban and dabigatran observed in the clinical trials. In a series of elegant experiments,<sup>7</sup> Jaffer et al. studied thrombin generation induced by mechanical valve leaflets and sewing ring segments and evaluated the relative effectiveness of dabigatran, apixaban, rivaroxaban, and warfarin for inhibiting this thrombin generation using clinically relevant drug concentrations. Their results indicate three key inferences: targeted inhibition of thrombin using dabigatran, or of factor Xa using apixaban or rivaroxaban, is insufficient to block clotting induced by mechanical heart valves. First, concomitant inhibition of both factor Xa and thrombin is required. Second, warfarin is very effective because it inhibits both of these enzymes. Third, combined treatment with dabigatran and either apixaban or rivaroxaban is unlikely to be a viable solution because the drug concentrations required to inhibit thrombin generation to the same extent as warfarin at the recommended clinical effect (international normalized ratio, 2.5 or 3.0)<sup>5</sup> require doses that are substantially higher than those in current use and are therefore unlikely to be feasible in terms of safety.

Fortunately, new anticoagulants are on the horizon. Of particular relevance are the inhibitors of factor XI,<sup>8-10</sup> which inhibit both the contact activation of coagulation caused by mechanical valves and the propagation of clotting that is accelerated through feedback activation of factor XI by initial amounts of thrombin generated from tissue factor activation. Phase III trials are currently underway for several indications, for example, [NCT05757869](#) and [NCT05171049](#). For now, treatment with warfarin adjusted to achieve a target international normalized ratio of 2.5 or 3.0 remains the best practice to prevent thromboembolism for patients with mechanical heart valves.<sup>5</sup>

## Disclosures

Author disclosures are available at [evidence.nejm.org](https://evidence.nejm.org).

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