MECHANICAL VALVE THROMBOSIS ON RIVAROXABAN: ARE NOVEL ANTICOAGULANTS REALLY AN OPTION?

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Abstract

This is a case of a 54-year-old female with a history of mechanical aortic valve replacement who presented in cardiogenic shock. Her primary care provider started her on rivaroxaban for anticoagulation therapy. An urgent transesophageal echocardiogram revealed a significant gradient and thrombosis on one leaflet of the valve that was immobile. Given that she was not a surgical candidate, she underwent thrombolysis. However, she later died due to complications from the thrombotic valve. The utility of target-specific oral anticoagulants has yet to be established in clinical practice.

Case Report

A 54-year-old female with a prior surgical mechanical aortic valve replacement for severe aortic stenosis presented with respiratory failure and febrile illness concerning for sepsis. She had a history of a myocardial infarction requiring percutaneous coronary intervention to the right coronary artery, rheumatoid arthritis, obesity, hypertension, diabetes complicated by digital ulceration, and hyperlipidemia.

Her symptoms, characterized by dyspnea, commenced 2 weeks prior to presentation. She was initially evaluated by primary care and treated with diuretics for volume overload. Upon developing encephalopathy and fever, she was taken to the emergency department, where she was found to have hypoxic respiratory failure and suspected sepsis with a white blood cell count of 14 x $10^3/\mu L$, creatinine 1.4 mg/dL, and lactate 1.8 mmol/L. She was initially managed with mechanical ventilation, vasopressors, and broad-spectrum antibiotics.

The cardiology service was consulted for evaluation of troponin elevation and nonspecific ST changes in the inferior leads. During clinical exam, an absence of mechanical heart valve sounds was noted. A chest x-ray revealed a metal valvular ring consistent with a mechanical valve prosthesis. During chart review of medications, it was discovered that the patient's primary care provider was managing her condition using a target-specific oral anticoagulant, rivaroxaban, instead of warfarin. Since these findings were suspicious for prosthetic valvular thrombosis, an urgent transthoracic echocardiogram (TEE) was performed, revealing a gradient of 100 mm Hg across a mechanical aortic valve with an ejection fraction of 35% to 40%. Movement of only one leaflet was observed, and a thrombus was noted on the immobile leaflet. The calculated Society of Thoracic Surgeons mortality score for aortic valve replacement was high at 58%, so the patient was considered for urgent thrombolysis. She was started on a heparin infusion and received alteplase, a thrombolytic agent. A subsequent TEE following thrombolysis showed a reduction in gradient to 54 mm Hg without any clinical improvement in her condition. After an urgent cardiothoracic consult, the patient was considered inappropriate for emergency cardiothoracic surgery.

Eight hours following the administration of thrombolysis, the patient developed diagnostic inferior ST elevation but was determined to be inappropriate for surgical revascularization or percutaneous coronary revascularization. On day 2 of hospitalization, her vasopressor requirements increased. At that point she was deemed unlikely to survive this clinical event and was transitioned to comfort-oriented care.

Discussion

Target-specific oral anticoagulants (TSOACs) are FDA-approved for stroke prevention in nonvalvular atrial fibrillation and for prevention and treatment of deep vein thrombosis and pulmonary embolism. Many patients prefer TSOACs over warfarin because they do not require frequent blood draws, dose adjustments, or dietary modifications and have less potential for drug-drug interactions.

So far, dabigatran is the most-studied TSOAC in mechanical heart valves. Although initial studies from in vitro and animal models were promising, several published case reports have raised concerns about the efficacy of dabigatran in mechanical valves.[1-3] Dabigatran at a dose of 150 mg twice daily was the only TSOAC to be evaluated in mechanical heart valves in a phase II multicenter randomized clinical trial (RCT) by the RE-ALIGN investigators. Unfortunately, this study was discontinued prematurely due to an excess of thrombotic and bleeding events in the dabigatran group.[4] This led to an FDA advisory warning against the use of dabigatran in patients with mechanical heart valves.[5] No such advisory exists for rivaroxaban because it has not yet been studied in a large RCT. A recent in vitro study tried to determine why RE-ALIGN was unsuccessful. Their findings indicated that a clinical dose of roughly 620 mg twice daily would be required to achieve concentrations high enough to inhibit thrombus formation on mechanical valves. At these doses, the risk of major bleeding would likely be significantly higher.[6]

Several in vitro and animal models have been conducted with rivaroxaban as well. Low-dose (30 ng/mL) and high-dose (300 ng/mL) rivaroxaban was compared to unfractionated heparin (UFH) and enoxaparin in an in vitro study by Kaeberich et al.[7] The study examined thrombus weight on mechanical heart valves after being exposed to 1 hour of pulsatile flow. High-dose rivaroxaban was as effective as UFH or enoxaparin; however, low-dose rivaroxaban

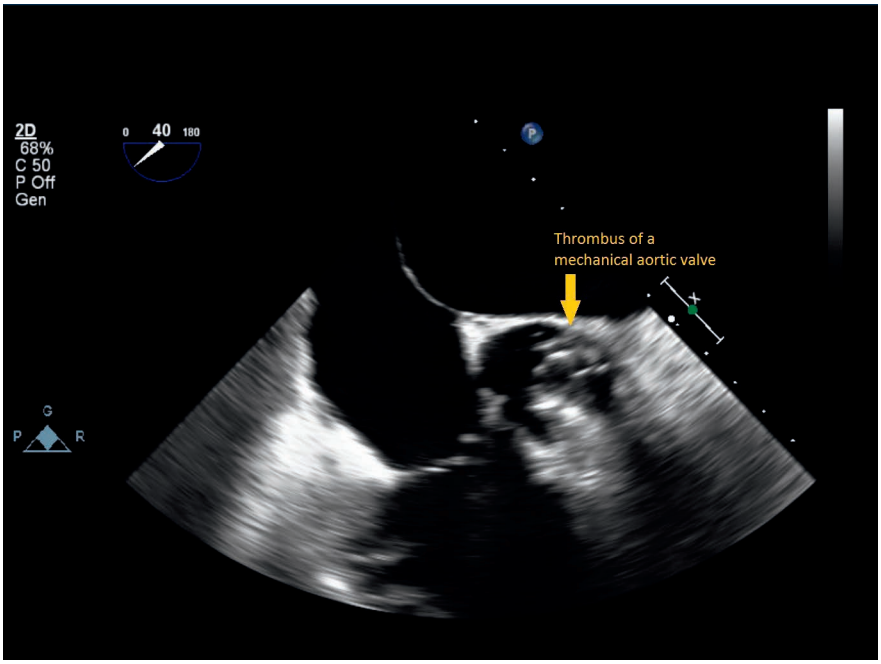

Figure 1. Midesophageal short-axis view of aortic valve with thick arrow pointing to mechanical aortic valve with thrombosis.

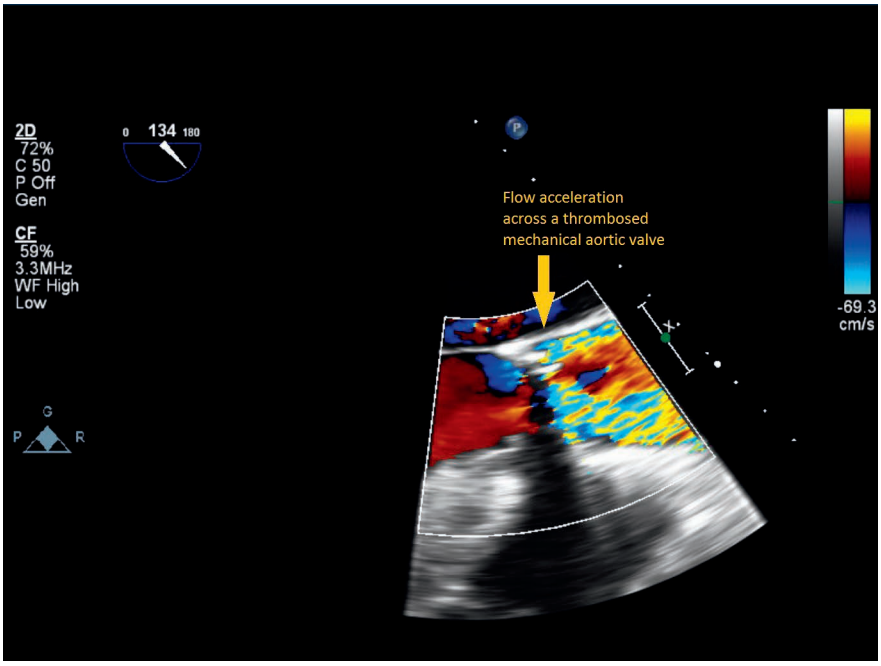

Figure 2. Midesophageal long-axis color Doppler view of aortic valve showing eccentic acceleration of velocity across the valve.

generated a large amount of thrombus. A study by Greiten et al.[8] evaluated the use of rivaroxaban in the porcine model. They implanted bileaflet mechanical valve conduits into 30 swine that were randomly assigned to one of three groups: rivaroxaban at 2 mg/kg twice daily, subcutaneous enoxaparin at 2 mg/kg twice daily, or no therapy. After 30 days, investigators measured thrombus formation on the valves using radiolabeled platelets. In the rivaroxaban group, there was less mean platelet deposition than in the enoxaparin or no-therapy groups. In addition, no hemorrhagic or thromboembolic complications were observed. However, as we have seen from the dabigatran studies, promising preclinical research does not necessarily translate to clinical application.

Based on our literature review, ours is the first reported case of a patient being treated off-label with rivaroxaban for a mechanical aortic valve. Similar to dabigatran, current doses of rivaroxaban used for stroke prophylaxis in patients with mechanical valves are associated with a high incidence of valve thrombosis and should not be used. Although the preclinical research with higher doses of rivaroxaban has been promising, its clinical utility needs further investigation.

Conflict of Interest Disclosure: The authors have completed and submitted the *Methodist DeBakey Cardiovascular Journal* Conflict of Interest Statement and none were reported.

Keywords: mechanical valve thrombosis, anticoagulation, oral anticoagulant, rivaroxaban, dabigatran

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