Acute Coronary Syndrome of Embolic Origin in a Patient on Direct Thrombin Inhibitor Three Years After Mechanical Mitral Valve Replacement

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Highlights
Dabigatran was shown to be inferior to warfarin for patients with mechanical heart valves. However it was postulated that its inferiority was limited to early post-operative period where the valves had not been adequately endothelialized. We present a case where thromboembolic acute coronary syndrome developed in a patient six months after switching from warfarin to dabigatran, despite three years after mechanical mitral valve replacement. We propose an alternative explanation for dabigatran failure.

Keywords: Acute coronary syndrome; thromboembolism; anticoagulation

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Patients with mechanical prosthetic heart valves are at higher risks of systemic thromboembolization parried by long-term anticoagulation with warfarin. Despite warfarin, these patient has a thromboembolic risk of approximately 0.7 to 1.0 percent per patient per year [1].

The conventional anti-coagulant warfarin acts by depleting functional vitamin K reserves from the liver, and hence reducing the hepatic synthesis of coagulation factors II, VII, IX, and X [2]. The newer anti-coagulating agent Dabigatran is a specific, reversible, direct thrombin inhibitor that inhibits both free and fibrin-bound thrombin [3]. It has a fast onset of action, predictable and good anti-coagulation efficacy and safety profile, negating the need for routine coagulation monitoring [3]. Dabigatran was shown to be non-inferior to warfarin in terms of preventing thromboembolism and its bleeding risks for patients with non-valvular atrial fibrillation [4]. However compared to warfarin, dabigatran had resulted in excessive thromboembolic events as well as bleeding events when used on patients with mechanical heart valves in the RE-ALIGN trial [5].

We present a case of a 55 year-old woman who suffered from chronic rheumatic heart disease with mitral stenosis. She underwent two percutaneous balloon mitral valvotomies at age 33 and age 47 respectively and subsequently a mitral valve replacement with a St. Jude Medical bi-leaflet mechanical valve at age 51. She was put on warfarin ever since then.

At age 54, she developed recurrent subconjunctival hemorrhage. She sought medical advice from another cardiologist outside of our hospital, who advised her to discontinue warfarin and started her on dabigatran at a dose of 110mg twice daily, later increased to 150mg twice daily given her normal creatinine clearance. Six months after starting on dabigatran, she presented with acute chest pain. Electrocardiography showed dynamic ST-T segment changes over leads V1 to V2, and Troponin I level was raised to 17 ng/mL. Transesophageal echocardiography revealed a functioning prosthetic mitral valve and no intracardiac thrombus. Coronary angiogram showed a focal thrombus at the distal part of the left circumflex artery (Figure 1A). Otherwise, there were no atherosclerotic changes in all three coronary arteries. Balloon dilatation using a 1.5mm balloon was performed to the lesion, from which the thrombus migrated further downstream (Figure 1B). Stenting was not performed in view of the suspected embolic origin of the thrombus and small vessel size. She was discontinued with dabigatran and resumed on warfarin. She remained well since thereafter for more than 1 year.
This coronary occlusion was almost certain to be embolic in origin as a discrete thrombus typical of embolus was identified in the culprit vessel during the time of coronary angiography, which migrated readily upon balloon dilatation. In addition, all segments of all coronary arteries were free from any atherosclerotic change and she had no other atherosclerosis risk factors.

In the Re-ALIGN trial [5], investigators argued that most thromboembolic events happened in patients who had mechanical heart valve replacements less than three months prior to commencement of dabigatran. Hence those patients were at highest risk of thromboembolism due to incomplete endothelialization of mechanical heart valves, where contact pathway-induced coagulation could be so intense that local dabigatran was overwhelmed. On the contrary warfarin would be more effective because of its inhibition of both tissue factor–induced coagulation (via depletion of factor VII) and contact pathway–induced coagulation (via depletion of factor IX), as well as inhibiting the synthesis of factor X and thrombin in the common pathway. However in our case the patient had received mechanical heart for more than three years, presumably adequately endothelialized. Yet she suffered from thromboembolic complication after switching to dabigatran for six month.

A more plausible explanation for the inferior clinical outcomes of dabigatran is that thrombin itself exhibits anti-coagulant activity [6]. When thrombin is bound to surface thrombomodulin it will expose the cleavage site. This will cleave protein C to give activated protein C that interferes with cofactors V and VIII thus converting pro-coagulant thrombin to an anticoagulant [6]. When dabigatran inhibits thrombin, it also inhibits its anti-coagulant properties and may give rise to thromboembolic activities. If this argument holds, other newer oral anti-coagulant like rivaroxaban, apixaban and edoxaban which have no anti-thrombin activity, can possibly be non-inferior to warfarin for patients with mechanical heart valves. In fact high dose rivaroxaban showed promising results in a pre-clinical study [7].

This case illustrates the harmful effect of dabigatran compared to warfarin in patients with mechanical heart valves even if the mechanical heart valve is presumed to be adequately endothelialized years after surgery.