

Platelet Inhibition With Ticagrelor for Left Ventricular Assist Device Thrombosis

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Although considered standard therapy for Stage D heart failure since 2008, the continuous, axial flow HeartMate II (HMII) left ventricular assist device (LVAD) has recently been associated with unexpected rise in rates of pump thrombosis.¹ With an incidence of 0.01 to 0.11 events per patient-year, LVAD thrombosis responds to intensification of antithrombotic therapy with unfractionated heparin (UFH), dual antiplatelet therapy with or without thrombolytics or glycoprotein IIb/IIIa inhibition in <50% of cases, and is associated with nearly 50% 6-month mortality.¹ Therefore, surgical pump exchange or urgent transplantation remains the treatment of choice despite potential high risk and cost. Herein, we report the first successful experience using the potent P2Y₁₂ ADP receptor inhibitor ticagrelor in addition to UFH and aspirin (acetylsalicylic acid [ASA]) to treat LVAD thrombosis and avoid pump exchange in 4 patients with confirmed or suspected HMII thrombosis.

Methods and Definitions

With institutional Institutional Review Board approval, we reviewed medical records of 4 consecutive patients admitted to the cardiac intensive care unit at our institution with confirmed or suspected LVAD thrombosis. LVAD thrombosis was diagnosed in the presence of abrupt elevations of serum lactate dehydrogenase (LDH) to >900 mg/dL without (suspected LVAD thrombosis) or with (confirmed LVAD thrombosis) 1 of the following: (1) abnormal LVAD flows or power surges, (2) clinical symptoms of heart failure, or (3) supporting echocardiographic ramp study. We determined antiplatelet activity using VerifyNow P2Y₁₂ assay, with values >230 P2Y₁₂ reaction units (PRU) indicating nonresponder status. Patients were treated clinically using standard doses of medications based on clinical preference.

Patient 1

A 28-year-old black man had HMII implanted as destination therapy for nonischemic cardiomyopathy before 7 days. Postsurgical course was complicated by slowly increasing LDH with peak of 980 U/L, requiring maintenance of UFH

in addition to ASA 325 mg daily, dipyridamole, later switched to clopidogrel. Because LDH remained elevated and PRU was 321, ticagrelor was started (180 mg load and 90 mg twice daily) instead of clopidogrel. Five days later, LDH decreased (Figure) and he was discharged on ASA, ticagrelor, and warfarin. At 7-month follow-up, there was no bleeding or device thrombosis with LDH of 286 U/L.

Patient 2

A 66-year-old black man with HMII for 947 days as destination therapy for nonischemic cardiomyopathy had a history of bleeding gastrointestinal arteriovenous malformations that required discontinuation of antiplatelet therapy. During the previous year, he had 3 admissions for asymptomatic LDH elevations with subtherapeutic international normalized ratios that resolved with UFH. In this index hospitalization, he presented with hematuria, worsening heart failure, LDH of 2951 U/L, and serum creatinine of 2.96 mg/dL. He was given ASA, clopidogrel, UFH, milrinone, and intra-aortic balloon pump. Because his PRU was 294, clopidogrel was changed to ticagrelor. On day 12, abciximab was given for 48 hours without success and he underwent attempted pump exchange on hospital day 15. In the operating room, the device was deeply embedded in adhesions. The surgeon noted that the urine was clearer and, given the risk of surgery, elected to abort the procedure. Over the next days, LDH started to decrease progressively, renal failure and heart failure symptoms resolved. He was discharged on ticagrelor, aspirin, and warfarin and at 9-month follow-up had no bleeding or hemolysis with LDH of 228 U/L. At month 12, he opted for hospice because of progressive right ventricular failure.

Patient 3

A 47-year-old white man with HIV had a HMII as destination therapy for 757 days without previous complications. During an asymptomatic clinic follow-up, his international normalized ratio of 1.8 and LDH 1196 U/L despite ASA 81 mg, clopidogrel 75 mg, and warfarin daily. On admission, his rotations per minute were 9400 and serum creatinine of 0.94 mg/dL. He

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was initially given UFH, ASA, and clopidogrel, but because PRU was 280, ticagrelor was substituted for clopidogrel. LDH decreased within 24 hours and he was discharged on day 6 with LDH of 450 U/L on ASA, ticagrelor, and warfarin. At 6-month follow-up, there was no bleeding or device thrombosis with LDH of 275 U/L.

Patient 4

A 46-year-old black man with nonischemic cardiomyopathy had HMII as destination therapy for 300 days. He was on clopidogrel, dipyridamole, and warfarin because of ASA allergy. On admission, he had New York Heart Association Class II symptoms, international normalized ratio of 2.1, LDH of 1373 U/L, and PRU of 164. Despite adequate platelet inhibition, we decided to substitute ticagrelor for clopidogrel and add UFH. Computed tomography revealed malpositioning of the inflow cannula, which was abutted against the left ventricular septum. LDH decreased within 5 days to baseline of 546 U/L and he was discharged on ticagrelor and subcutaneous enoxaparin but readmitted a week later undergoing LVAD exchange.

Discussion

In this pilot experience, we report short-term resolution of suspected pump thrombosis with the use of the potent P2Y₁₂ ADP inhibitor ticagrelor in combination with UFH and ASA. Importantly, we also show that continuation of ticagrelor, aspirin, and warfarin was associated with 6-month survival free from bleeding or thrombosis in 3 of 4 patients, of whom 2 had prior episodes of pump thrombosis. Our findings highlight the generally under-recognized role of platelet inhibition in the pathogenesis and management of LVAD thrombosis and raise the possibility that the recent increase in HMII pump thrombosis may be partially explained by lack of sufficient platelet inhibition in these patients.

Temporal changes in antiplatelet therapy help support this hypothesis. Starling et al¹ reported a sharp inflection in frequency of pump thrombosis in 3 large volume centers that began in March 2011, although data from the Food and Drug Administration's manufacturer and user facility device experience (MAUDE) database suggest that this actually started about a year earlier.² In their in-depth review, Mehra et al³ noted several secular changes in management that occurred predating this period: (1) avoidance of postoperative heparin bridging, (2) lower international normalized ratio targets, and (3) lower rotations per minute settings to allow aortic valve opening. One correlation that was conspicuously absent was the change from dual antiplatelet therapy to single antiplatelet therapy after reports of higher risk of gastrointestinal bleeding that also occurred around that time. This led to discontinuation of dipyridamole by most programs around the country, while some questioned the need at all for antiplatelet therapy. Although temporally compelling, the causative relationship between the intensity of antiplatelet therapy and advent of increased pump thrombosis is confounded by many factors and requires further study.

Although the exact mechanism of thrombus formation within continuous flow LVADs is not clear, collective observations from explanted LVADs have demonstrated the presence of white (ie, platelet rich) and red (ie, red blood cell rich)

clots within different areas of the device. White clot is firm and tightly adherent to the bearing or rotor, develops over longer time, and is typically caused by platelet activation from arterial shear stress and device generated heat. In contrast, red thrombus develops faster when there is flow stagnation, is soft and more mobile with a tendency to embolize. Although a recent abstract analyzing the composition of 10 clots from explanted LVADs found red clots in 9 and white clots in 1⁴, general experience, including our own, support an equally frequent if not higher incidence of white clots within explanted devices.

Based on current knowledge and this pilot experience, we propose a new paradigm to explain the role of antiplatelet therapy in pump thrombosis. Initially, for reasons that are related to engineering and design characteristics of the HMII, heat generated by the device in the presence of preserved platelet function causes deposition of platelet-rich thrombi around the bearing or rotor.¹ This deposit, once present, may lay quiescent with appropriate antiplatelet therapy, anticoagulation, and ideal hemodynamic conditions. Alternatively, abnormal hemodynamics or interruption of thrombotic prophylaxis (as occurs during episodes of gastrointestinal bleeding, for example) results in recurrent platelet activation, facilitated by higher levels of shear stress caused by the fibrin-coated rotor or bearing. Without sufficient platelet inhibition, accelerated de novo formation and expansion of white clot occur. This now rapidly expanding white thrombus and creates progressive flow stagnation within the device causing increased flow impediment and exacerbation of hemolysis. Aggressive platelet inhibition, such as obtained by the potent P2Y₁₂ inhibitor ticagrelor, may disrupt this process.

Lastly, in this small series, there was no bleeding suggesting the use of ticagrelor in LVAD patients, a population with notoriously high-bleeding risk. Ticagrelor is a reversible P2Y₁₂ inhibitor with a shorter half-life found to decrease major adverse cardiovascular events compared with clopidogrel in patients with acute coronary syndromes in clinical trials without increasing major bleeding.

This report is limited by our small sample of 4 patients, only 1 of which had confirmed pump thrombosis. Also, the use of ticagrelor with warfarin is off-label and not approved by the Food and Drug Administration.

In conclusion, potent platelet inhibition with ticagrelor in combination with ASA and heparin anticoagulation was successfully used in HMII LVAD thrombosis to normalize LDH levels, ameliorate symptoms, and avoid pump exchange without higher risk of bleeding. Randomized clinical trials are necessary to confirm these findings.

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Disclosures

Dr Oliveira is a member of Abiomed (advisory board, honorarium) and Alnylam Pharmaceuticals (advisory board, honorarium). Dr Simon is a member of Medtronic Vascular (advisory board, honorarium) and Cordis/Johnson & Johnson (advisory board, honorarium). The other authors report no conflicts.

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KEY WORDS: platelet aggregation inhibitor ■ thrombosis ■ ticagrelor ■ ventricular assist device

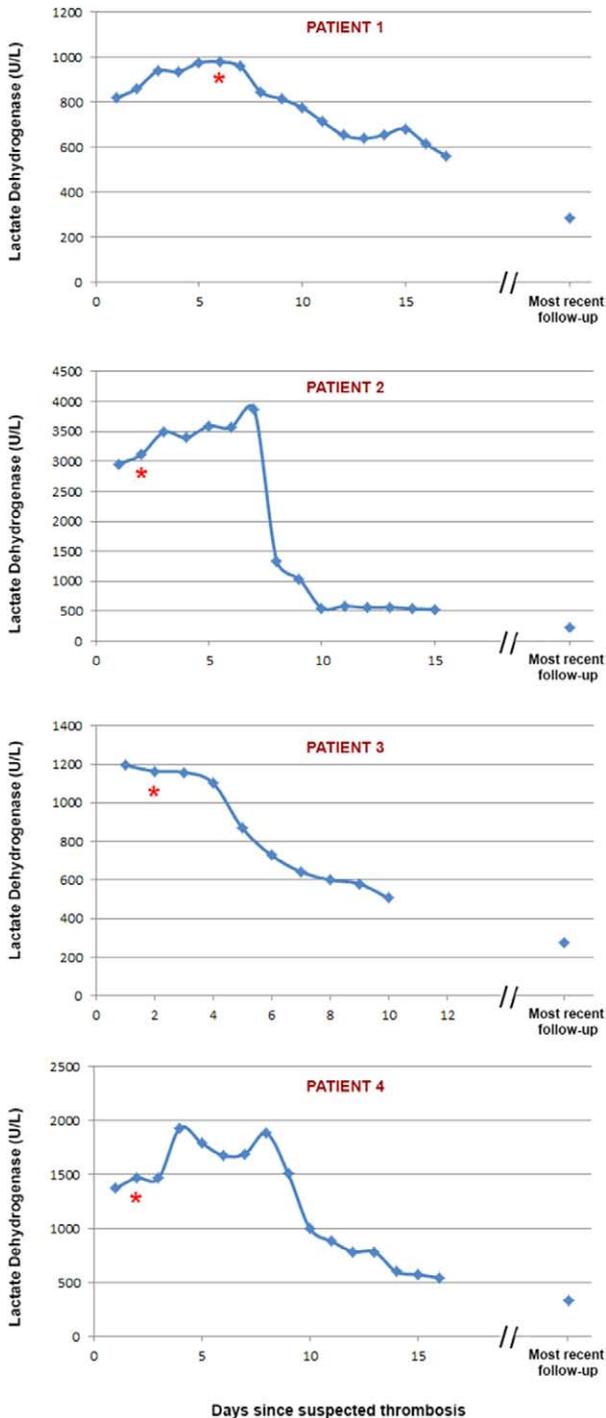


Figure. Lactate dehydrogenase trend in patients 1 to 4. Red star indicates starting day of ticagrelor treatment.

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