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Peer-reviewed Case Series

Cangrelor: Safe and Effective for Left Ventricular Assist Device Thrombosis

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Abstract

Pump thrombosis is a devastating complication of left ventricular assist device implantation as it increases the risk of mortality and morbidity. Early and effective treatment is important to prevent the progression of the clot and to avoid the surgical need for pump exchange or heart transplant. The current strategies of intensifying anticoagulation therapy are not consistently effective and carry significant bleeding risks. Cangrelor is a new pharmacological agent that has been utilized as an antiplatelet agent in several cardiac procedures. In this case series, we describe the use of cangrelor for left ventricular assist device thrombosis in five patients. Cangrelor appears to be a potentially safe and effective alternative strategy.

Background

Left ventricular assist devices (LVADs) have changed the outlook of end-stage heart failure by improving the quality of life of patients and their survival rates. However, the use of LVAD systems is not free of adverse events; pump thrombosis is known to be one of the major related complications. Even though the incidence of pump thrombosis has decreased with the newer magnetically levitated technology, thrombosis treatment continues to be therapeutically challenging with the other types of LVAD. In particular, the Heartmate II (HMII, Abbott, Abbott Park, IL) and Heartware ventricular assist device (HVAD, Medtronic, Minneapolis, MN) systems present challenges in the management of pump thrombosis. Even though HMII is now rarely implanted due to the approval of the HeartMate 3 device (HM3, Abbott, Abott Park, IL), many patients with a HMII continue to be followed.

A thrombosis can develop in any part of the LVAD, including the inflow canula, the pump itself or the outflow canula. Different strategies have been used in the management of LVAD thrombosis, including surgical and pharmacological therapies. Pharmacological therapy is the preferred initial management strategy in patients who are hemodynamically stable. Most of the pharmacological regimens are based on expert opinions and consensus statements, and they are institution specific. Various treatment regimens like increasing the goal international normalization ratio (INR) target, monotherapy with either heparin, direct thrombin inhibitor, glycoprotein IIb/IIIa inhibitors (GPIIb/IIIa), thrombolytics or a combination of the above have been used with varying success in resolving pump thrombosis.[1] However, increasing the level of anticoagulation increases the risk of bleeding complications like gastrointestinal bleeding and intracranial hemorrhage. If patients undergo pump exchange or heart transplantation (HT), there is an increased risk of perioperative bleeding with higher anticoagulation levels. Early management that is based on the trend of one of the hemolysis markers, lactate dehydrogenase (LDH), can avoid the need for pump exchange.[2]

However, medical management is not always successful or possible; thus, surgical interventions (pump exchange and HT) or, in futile cases, palliative care become the only options. Therefore, an alternative pharmacological agent that is effective in treating pump thrombosis with less bleeding complications is the ideal solution. Cangrelor, an antiplatelet agent has newly emerged as one such agent.[3] We hereby describe five cases with seven episodes of pump thrombosis treated with cangrelor along with heparin.

Case Series Description

Case 1

A 63-year-old male with ischemic cardiomyopathy was implanted with a HMII in June 2017. He developed pump thrombosis a few months later and had to

undergo a pump exchange after failing medical management and developing a subarachnoid hemorrhage on heparin and GPIIb/IIIa inhibitors. He was readmitted three months later with increased shortness of breath and an elevated LDH of 1055 Units/L (normal range of LDH at our institution is 140-271 Units/L), putting him at risk for another episode of pump thrombosis. Cangrelor was initiated when LDH levels increased to 1332 Units/mL, and free hemoglobin (Hgb) increased to 333 mg/dL on heparin alone. Cangrelor was chosen over eptifibatide at this time due to a concern regarding his previous development of subarachnoid hemorrhage while on eptifibatide.

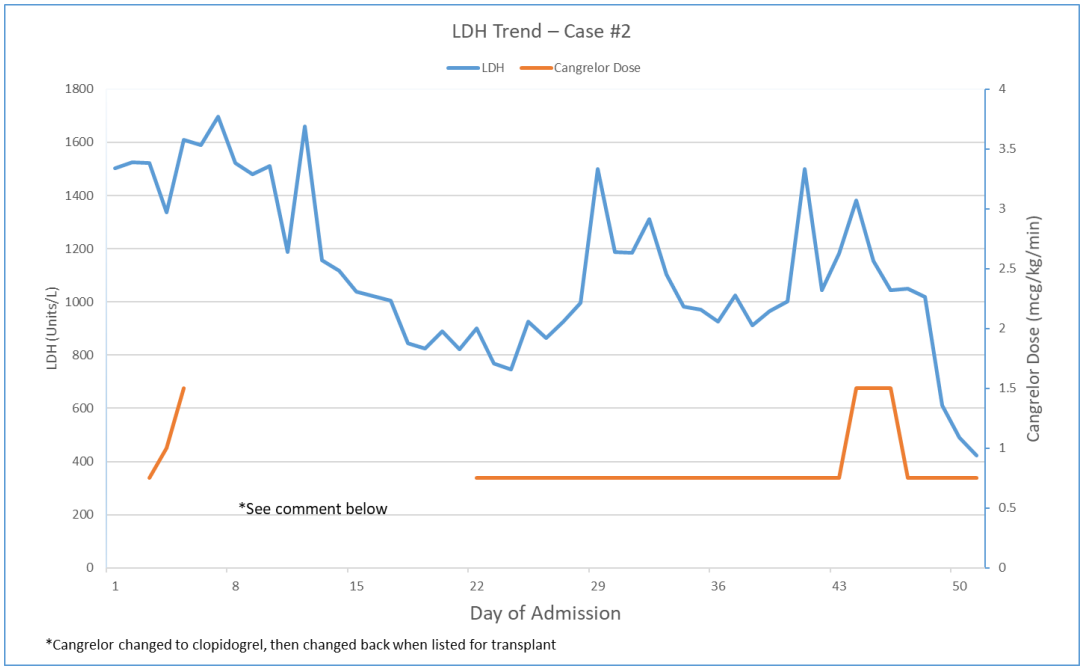
Cangrelor was started at a high rate of 4 mcg/kg/min. The dosage was reduced to a maintenance rate of 0.75 mcg/kg/min after nearly 24 hours as there was a significant decrease in free Hbg (333 to 33mg/dL). The cangrelor drip remained at a maintenance rate of 0.75 mcg/kg/min for 23 days, and LDH levels responded favorably (Figure 1). There was a rebound increase in LDH; thus, the drip was titrated up to 1.5 mcg/kg/min in increments of 0.25 mcg/kg/min, then titrated back down once LDH began to fall again. Thromboelastography with platelet mapping was done routinely to assess platelet percent inhibition and aggregation and guided the titration of the dose. Cangrelor was eventually stopped after 64 days when a suitable donor was determined. The patient underwent a successful HT without any bleeding complications. At the one-year follow-up appointment, the patient was doing well.

Figure 1. *The lactose dehydrogenase (LDH, Units/L) trend and cangrelor dose (mch/kg/min) in Case #1.*

Case 2

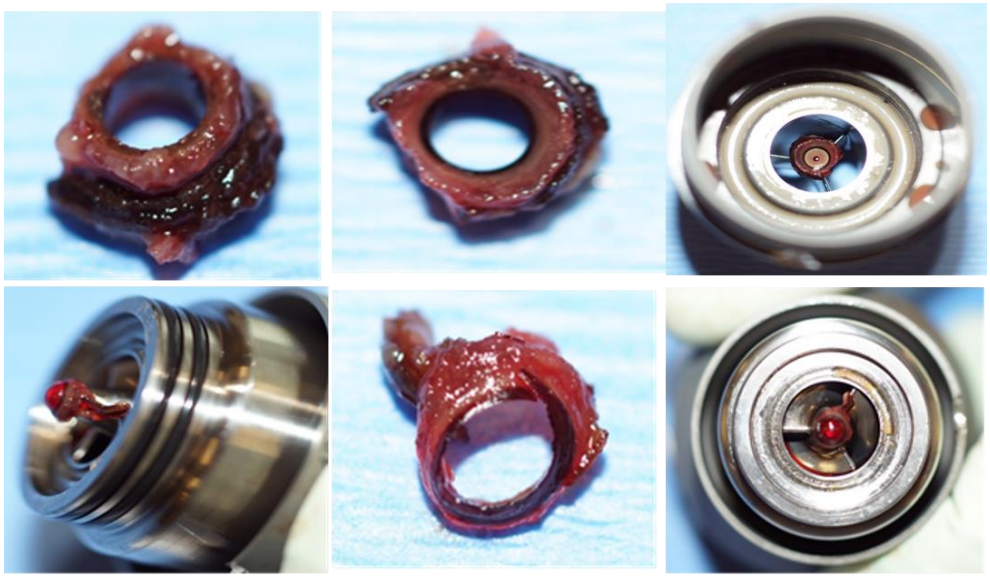
A 56-year-old female with a history of ischemic cardiomyopathy underwent the placement of a HMII in July of 2016. She had her first episode of pump thrombosis in 26 months later (October 2018) and was managed medically on heparin and GPIIb/IIIa (eptifibatide) infusions. Five months later (March 2019), she had another episode of elevated LDH to 1503 units/L (baseline LDH of 500-700 Units/L) and was started on heparin and eptifibatide. LDH levels did not decrease as expected; thus, the eptifibatide was switched to cangrelor (0.75 mcg/kg/min). The infusion of cangrelor was interrupted due to various reasons, and the patient was maintained on clopidogrel. When the patient was ultimately listed for heart transplantation, cangrelor was reinstated. She was maintained on cangrelor and heparatin for approximately 25 days once she was listed. The patient continued to have intermittent episodes of hemolysis, and the cangrelor infusion rate was titrated based on the labs and ranged from 0.75 mcg/kg/hour to 1.5 mcg/kg/hour until the time of transplant. The use of cangrelor avoided the need for urgent pump exchange as well as the use of longer-acting, irreversible antiplatelet agents while awaiting a HT. The patient did not experience any further bleeding or clotting events. The patient did not experience any further bleeding or clotting events. She underwent a successful HT and was doing well at the one-year follow-up appointment.

Figure 2. *The lactose dehydrogenase (LDH, Units/L) trend and cangrelor dose (mch/kg/min) for Case #2.*



The analysis of the explanted LVAD showed a laminated ring thrombus surrounding the bearing cup of the inlet stator (Figure 3).

Figure 3: *Images of a laminated ring thrombus surrounding the bearing cup and ball of the inlet stator of Case 2*



Case #3

A 39-year-old female with peripartum cardiomyopathy who received a HMII in February of 2017, required an LVAD exchange in 13 months later (March 2018) secondary to pump thrombosis. She was readmitted three months post-LVAD exchange (June 2018) after presenting with an LDH of >2500 U/L and was successfully treated medically with eptifibatide and heparin. She was discharged on aspirin, ticagrelor, and warfarin with a higher INR goal (2.5-3.5).

She was again readmitted 13 months post-LVAD exchange (January 2019) with an LDH of >1500 U/L. She was not deemed to be a candidate for another LVAD exchange or HT due to socioeconomic reasons. Due to suspected pump thrombosis, she was placed on a heparin drip, and cangrelor was initiated at a rate of 0.75 mcg/kg/min. Her LDH dropped to 650U/L in just two days (Figure 4). She was placed back on warfarin, ticagrelor, and aspirin and discharged from the hospital.

The same patient was readmitted a month later (February 2019), again with an LDH of nearly 1400 U/L. The ticagrelor was placed on hold, and a heparin drip was started in addition to eptifibatide. No significant decrease in LDH was observed despite almost 96 hours of eptifibatide, and her free hemoglobin peaked at 107 mg/dL. She was then switched to a cangrelor drip at an aggressive rate of 4 mcg/kg/min. Her LDH dropped by >400 U/L within the first 24 hours of starting cangrelor and returned to baseline after just 72 hours on the cangrelor drip (Figure

5). Cangrelor was then discontinued, she was placed back on her home regimen and discharged.

Figure 4 *: The lactose dehydrogenase (LDH, Units/L) trend and cangrelor dose (mch/kg/min) for Case #3's admission 13 months post-LVAD exchange (January 2019).*

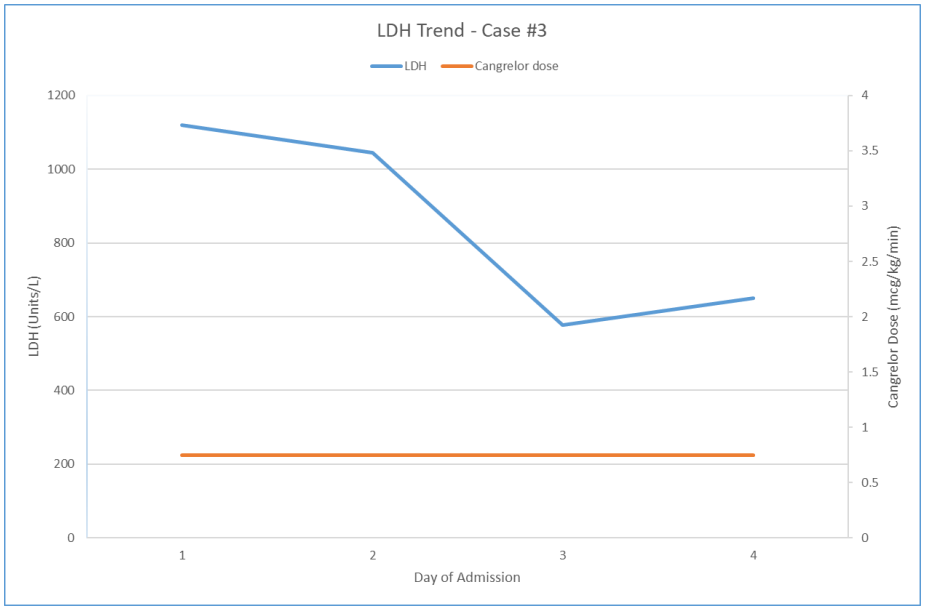
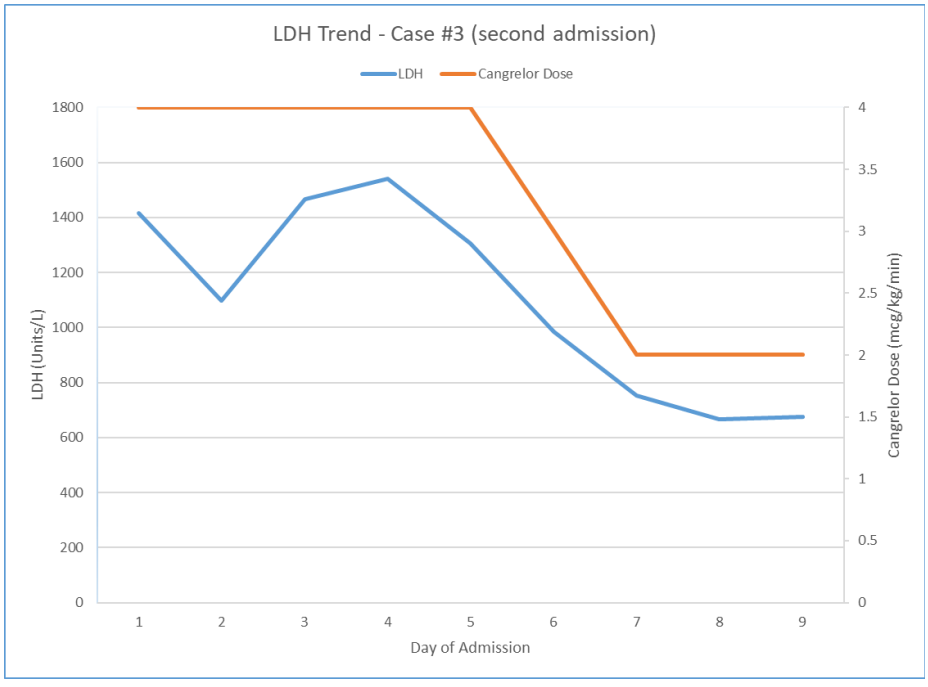


Figure 5: *The lactose dehydrogenase (LDH, Units/L) trend and cangrelor dose (mch/kg/min) for Case #3's admission 14 months post-LVAD exchange (February 2019)*

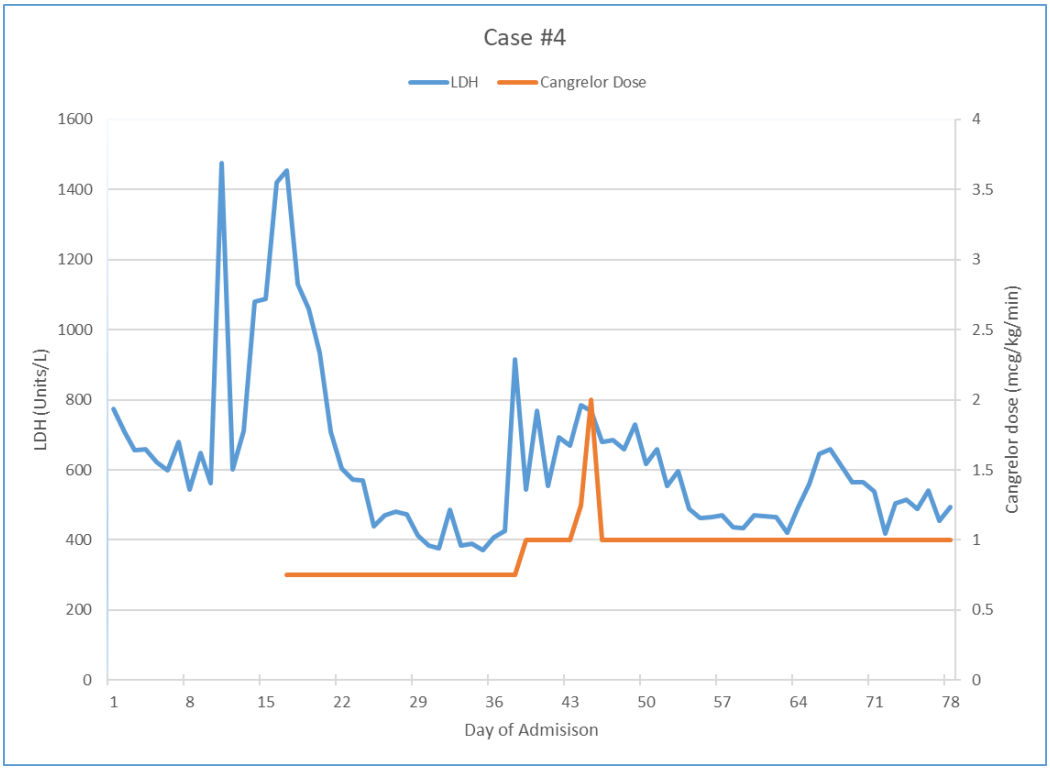


She had one more episode of pump thrombosis, which was again treated with cangrelor with good results. She is alive without any further episodes of pump thrombosis and currently doing well.

Case #4

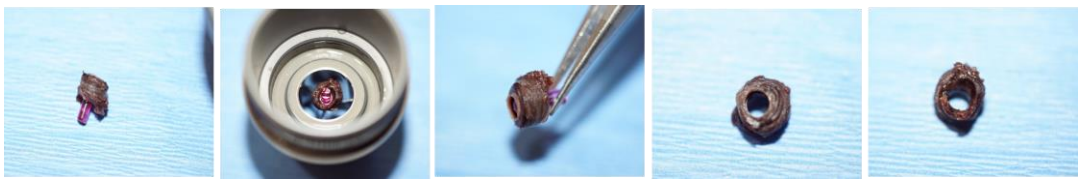
A 57-year-old male with a HMII was admitted six months post-LVAD implantation with suspected pump thrombosis. The patient had noticed tea-colored urine for about a week before admission, and his LDH was at 3200U/L with a corresponding free Hgb of 290mg/dL. Both LDH and free Hbg started trending down once he was initiated on a heparin drip, full dose aspirin, and ticagrelor. After reaching a plateau, his LDH spiked again up to 1500U/L. Cangrelor was initiated, and the LDH began to trend down (Figure 6). Rate adjustments were made to the cangrelor infusion in response to slight elevations in LDH, but he remained on a rate of 1 mcg/kg/min for most of his hospitalization with stabilized LDH levels.

Figure 6. *The lactose dehydrogenase (LDH, Units/L) trend and cangrelor dose (mch/kg/min) for Case #4.*



A suitable donor heart was found, and he received a HT two months later. Unfortunately, he suffered complications from HT and died six weeks after the transplant. The explanted pump had a thrombus ring attached to the inlet bearing cup and ball (Figure 7).

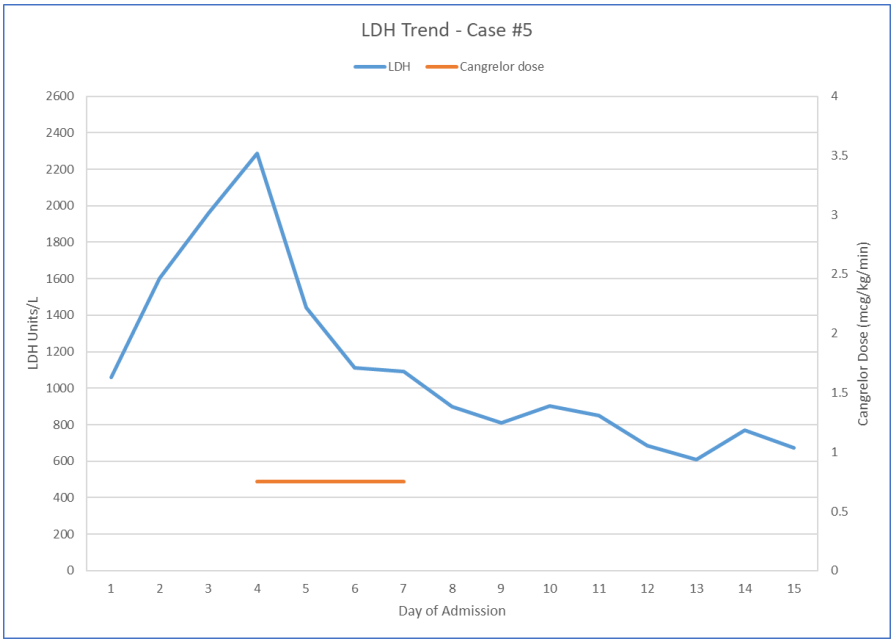
Figure 7: *A thrombus ring is attached to the inlet bearing cup and ball in Case #4.*



Case #5

A 56-year-old female received a HMII as destination therapy in 2015. She underwent a successful pump exchange twice (January 2017 and September 2019) due to LVAD thrombi. She was admitted seven months post-exchange (May 2020) with cough, fatigue, an elevated LDH of 1060 Units/L, and a free Hgb of 26 mg/dl. There was a concern for recurrent LVAD thrombosis. Log files showed a power spike and pulsatility index event. Her INR on admission was supratherapeutic at 4.45, and she had been taking her home dose of aspirin 81mg and persantine 75mg three times a day. A heparin drip was initiated; however, LDH continued to trend up and peaked at 2287 Units/L. Hence, cangrelor was started at 0.75mcgm/kg/min. Upon initiation of cangrelor, the patient's LDH dropped significantly and continued to fall until the day of discharge (Figure 8). Her free Hgb returned to normal, and she was eventually able to transition to oral therapy with ticagrelor in addition to aspirin. Her warfarin was restarted with a goal INR of 2.5-3.5, and the heparin drip was discontinued.

Figure 6. *The lactose dehydrogenase (LDH, Units/L) trend and cangrelor dose (mch/kg/min) for Case #5.*



She was discharged in a stable condition. However, the patient presented three weeks later with another episode of pump thrombosis and underwent an LVAD exchange to the HM3 through an open sternotomy.

Discussion

Cangrelor is a reversible P2Y12 inhibitor that is structurally and functionally similar to ticagrelor, which rapidly blocks adenosine diphosphate-mediated platelet aggregation.[4] Its antiplatelet effects are seen within two minutes of administration. As an additional benefit, it has an extremely short half-life of approximately 3-4 minutes, with pharmacokinetics independent of organ function. After cangrelor is discontinued, platelet function restores to normal within an hour.[5] It is approved for use as an adjunct to percutaneous coronary intervention to reduce the risk of periprocedural myocardial infarction, repeat coronary revascularization, and stent thrombosis in patients not previously treated with a P2Y12 inhibitor. Recent publications have described the use of cangrelor in the LVAD population in addition to heparin for other indications like a history of heparin-induced thrombocytopenia or as a bridge to LVAD implementation in a patient with a recent stent.[6,7]

Medical management of pump thrombosis typically can include heparin, a thrombolytic, a GPIIb/IIIa inhibitor, or a direct thrombin inhibitor such as bivalirudin or argatroban. Therapies may be used alone or in combination. The use of escalated therapies, such as the addition of GPIIb/IIIa inhibitors, has been more successful than heparin alone in several cases; unfortunately, there is also a higher rate of bleeding seen with these agents.[2]

The use of potent P2Y12 inhibitors for the management of LVAD pump thrombosis has only been described in two case series to date.[3,8] Oliveira et al. described five cases in which substitution of ticagrelor for clopidogrel in the setting of suspected pump thrombosis resulted in the reversal of LDH elevation, HF symptoms (when present), and resolution of other signs of hemolysis in all five patients.[8] Four of the patients remained without bleeding or hemolysis complications on long-term follow up (6-12 months). Unfortunately, the long half-life of ticagrelor makes it less appealing if a patient must undergo a surgical procedure or were to bleed, due to its lack of reversibility. Cangrelor's quick onset to platelet inhibition accompanied by an extremely short half-life and reversible platelet inhibition offers a great benefit over the current strategies used in this setting.

The other case series evaluated the use of cangrelor in four patients with five episodes of suspected pump thrombosis.[3] Cangrelor successfully reversed the signs of pump thrombus in three episodes, while two patients went on to require pump exchange. No major bleeding events occurred during the cangrelor infusions.

In our case series, the combination of cangrelor and heparin was successful in treating the pump thrombosis in all cases. Heparin alone or the combination of

heparin and GP IIb/IIIa was not effective in this series. The use of cangrelor enabled three patients (Cases 1, 2, and 4) to be successfully bridged to HT for many days without any bleeding complications or end-organ damage. Two of the three patients underwent transplant successfully without major perioperative bleeding. Upon review of the explanted pump, there was evidence of a small amount of thrombus (Case 4). Case 3 & 5 received LVADs as destination therapy. We avoided pump exchange despite multiple episodes of pump thrombosis in Case 3. Despite the successful treatment of the initial episode of pump thrombosis with cangrelor and heparin, the patient later required an exchange to the HM3 device.

The meta-analysis by Dang et al. reported that 40% of patients with continuous-flow devices do not respond to non-thrombolytic therapy to treat pump thrombosis. Hence, medical management of pump thrombosis, especially in HMII patients, is often temporizing.

The cangrelor dose was titrated in all the patients and was individualized based on their LDH trend, thromboelastogram analysis, and clinical presentation. Further increases in cangrelor rates would not likely provide any additional therapeutic benefit if maximal ADP platelet inhibition had already been reached. Therefore, we used thromboelastography with platelet mapping (TEG 5000 Thrombelastograph Hemostasis Analyzer system, Haemonetics®, Braintree, MA) to assess platelet percent inhibition and aggregation. These results were utilized to evaluate the effect of cangrelor initiation and dose titration on adenosine diphosphate (ADP) inhibition. No major or minor bleeding episodes were noted in any of the patients. Currently, in our institution, we have adopted the routine use of cangrelor for pump thrombosis if heparin alone is not sufficient.

Of note, two of the patients described here had been receiving ticagrelor before presentation (Case 3 & 4). Pharmacokinetic data have shown cangrelor to exert a more potent effect on platelet inhibition earlier than ticagrelor. Still, equal platelet inhibition was seen as soon as four hours after the percutaneous intervention. One hypothesis could be that titration of the cangrelor drip based on LDH response allowed for a more individualized approach to inhibiting platelet function when compared to the standard dosing of ticagrelor (90mg twice daily). Unless patients previously on ticagrelor had issues with compliance or absorption, the benefit of using cangrelor over ticagrelor remains unclear.

Cangrelor, in combination with heparin, was a potentially effective alternative strategy to treat pump thrombosis without major bleeding complications in this case series. More work is needed to understand the optimal dosing and timing of cangrelor and correlation with the thromboelastogram analysis. However, applicability of cangrelor as a management strategy for centrifugal-flow devices will require further evaluation. Although randomized prospective trials are needed to shed more light on this, cangelor appears to be a promising new pharmacological agent.

Acknowledgment

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