Antithrombotic Strategies and Device Thrombosis

Paul A. Gurbel, MD[a,*], Palak Shah, MD, MS[b], Shashank Desai, MD[b], Udaya S. Tantry, PhD[c]

KEYWORDS

• Device thrombosis • Antithrombotic therapy • Platelets • Warfarin • Aspirin • Bleeding

KEY POINTS

- Device thrombosis, thromboembolic events, and bleeding are major adverse events that contribute to the morbidity of left ventricular assist device (LVAD) therapy.
- Current guidelines for antithrombotic therapy are largely based on results of device trials that did not randomize patients to a particular antithrombotic strategy.
- Thrombotic and bleeding events often occur in the same patient over time and challenge the identification of optimal antithrombotic therapy strategies.
- Advances in antithrombotic therapy may result from randomized trials that embed laboratory assays that blueprint hemostasis pathways in LVAD patients.
- Emerging studies are attempting to link specific assay results to the occurrence of thrombotic and bleeding events that may also facilitate personalization of antithrombotic therapy.

INTRODUCTION

Left ventricular assist devices (LVADs) with continuous-flow pumps have emerged as a main therapeutic strategy during the last decade in patients with advanced refractory heart failure (HF). These LVADs are used as either a bridge to transplant (BTT) or destination therapy (DT) in patients who are considered ineligible for transplantation. Currently, the most widely used continuous-flow pump models include the HeartMate II (HMII) device (Abbott Laboratories, Abbott Park, IL) that uses an axial pump design as well as the HVAD (Medtronic, Minneapolis, MN) and the HeartMate 3 (Abbott Laboratories, Abbott Park, IL) that both use a centrifugal flow pump design. Because of the improved pump design and treatment strategies, newer-generation continuous-flow devices are associated with enhanced survival, functional capacity, and quality of life. With either strategy, the duration of expected VAD support continues to increase. However, the annual rate of device thrombosis along with infection, gastrointestinal bleeding, and stroke still remains high and

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[a] Interventional Cardiology and Cardiovascular Medicine Research, Inova Center for Thrombosis Research and Drug Development, Inova Heart and Vascular Institute, 3300 Gallows Road, Falls Church, VA 22042, USA; [b] Heart Failure and Transplantation, Inova Heart and Vascular Institute, 3300 Gallows Road, Falls Church, VA 22042, USA; [c] Inova Center for Thrombosis Research and Drug Development, Inova Heart and Vascular Institute, 3300 Gallows Road, Falls Church, VA 22042, USA

* Corresponding author.

E-mail address: Paul.Gurbel@inova.org

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significantly influences morbidity and mortality among these patients.[1]

Optimal antithrombotic therapy is very critical in patients treated with LVADs, because device thrombosis is strongly influenced by both platelet function and coagulation. The International Society for Heart and Lung Transplantation's (ISHLT) guidelines recommend antiplatelet therapy with aspirin and anticoagulation with warfarin in patients treated with LVADs.[2] These recommendations are based on opinions and protocols mandating these agents in clinical device trials but not on strong evidence from adequately powered randomized trials. Moreover, there are specific manufacturer recommendations for anticoagulation and antiplatelet therapy that differ from society guidelines.[3,4] In this article, the authors discuss multiple risk factors associated with device thrombosis, limitations of current antithrombotic therapy strategies, and future directions.

PATHOPHYSIOLOGY OF DEVICE THROMBOSIS

The underlying pathophysiology of device thrombosis is multifactorial and can be related to patient management (antiplatelet/anticoagulant therapy), patient characteristics, surgical implant technique, and device engineering. Device thrombosis is characterized by the development of thrombus/clot within the flow path of the pump, including the titanium inflow cannula, within the pump housing, on the rotor, or in the outflow graft. Thrombus can either originate in the pump itself or migrate from the left atrium/ventricle or from right-sided cardiac chambers through a septal defect and lodge into the pump components. Consequences of device thrombosis range from small thrombi formation without any clinical consequences to device malfunction with life-threatening hemodynamic impairment, cardiogenic shock, and death. Additional complications include peripheral thromboembolism, transient ischemic attack, and ischemic stroke with or without hemorrhagic complications.

Signs of device thrombosis include recurrent HF signs and symptoms, hemoglobinuria (tea-colored urine), along with laboratory markers of hemolysis, such as lactate dehydrogenase (LDH) levels greater than 2.5 times the upper limit of laboratory normal, a plasma free-hemoglobin concentration greater than 40 mg/dL, hemoglobinuria, anemia, or an elevated bilirubin level.[1,5–7] Of these findings, elevated LDH levels have been shown to be strongly correlated with hemolysis due to device thrombosis.[5] Power spikes and/or falsely elevated device flows (if clot on rotor) or flow reduction (if clot occluding inflow cannula) may be seen, but the sensitivity of these measures on interrogation is low.[6]

Two types of pump thrombi have been described: acute catastrophic red thrombi that predominantly consist of red cells trapped in the fibrin mesh. Red thrombus typically is soft and usually forms at the inlet and outlet stators. It may be associated with blood stasis due to flow conditions, ingested clot, or inadequate anticoagulation. White thrombi are rich in platelets with debris in fibrin mesh that typically forms over time. White thrombus generation depends on turbulent blood flow and heat generation and forms on the pump surface[8] (Fig. 1).

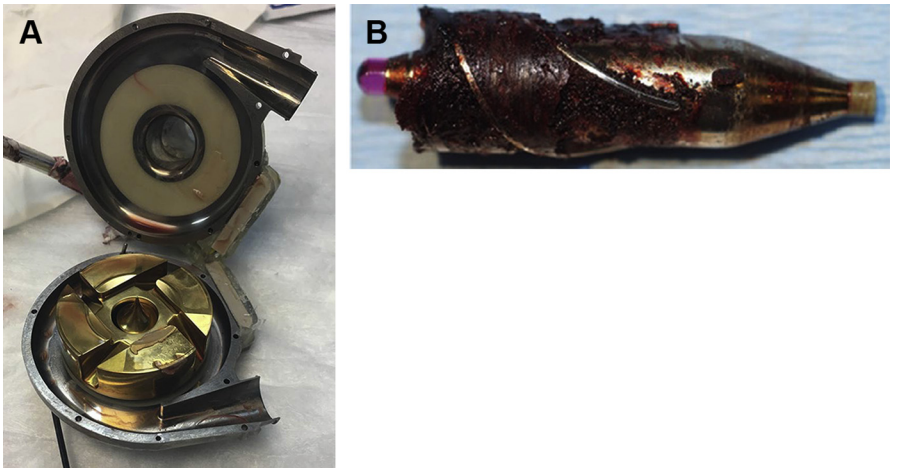

Fig. 1. White and red clot in the setting of device thrombosis. (*A*) White clot is rich in platelets with a fibrin mesh that typically forms overtime. (*B*) Red clot is rich in red blood cells that may be associated with blood stasis due to low-flow conditions, ingested clot, or inadequate anticoagulation.