10-1-2019

Hemostatic complications associated with ventricular assist devices.

Talal Hilal

James O Mudd
Heart Failure and Transplantation Cardiology, Providence Sacred Heart Medical Center & Children's Hospital, Spokane, WA, USA

Thomas G DeLoughery

Received: 15 March 2019 | Accepted: 8 May 2019

DOI: 10.1002/rth2.12226

REVIEW ARTICLE

rpth research & practice in thrombosis & haemostasis

Hemostatic complications associated with ventricular assist devices

Talal Hilal MD[1] | James Mudd MD[2] | Thomas G. DeLoughery MD, MACP, FAWM[3,4,5]

[1]Division of Hematology/Oncology, Mayo Clinic Cancer Center, Mayo Clinic, Phoenix, Arizona

[2]Center for Advanced Heart Disease and Transplantation, Providence Sacred Heart Medical Center, Spokane, Washington

[3]Division of Hematology/Medical Oncology, Knight Cancer Center, Oregon Health & Science University, Portland, Oregon

[4]Division of Laboratory Medicine, Department of Pathology, Oregon Health & Science University, Portland, Oregon

[5]Division of Hematology/Oncology, Department of Pediatrics, Oregon Health & Science University, Portland, Oregon

Correspondence
Thomas G. DeLoughery, Hematology L586, Oregon Health and Science University, 3181 SW Sam Jackson Park Road, Portland, OR 97201-3098.
Email: delought@ohsu.edu

Abstract

Hemostatic complications are common in patients with ventricular assist devices. The pathophysiologic mechanisms that lead to dysregulated hemostasis involve complex interactions between device surface, sheer stress, and blood flow. These factors lead to various manifestations that require a thorough understanding of the interplay among platelets, coagulation factors, and red cells. In this article, we review the pathophysiology of hematologic complications (bleeding, acquired von Willebrand disease, heparin-induced thrombocytopenia, hemolysis, stroke and pump thrombosis), the clinical manifestations, and the management of each. We summarize the evidence available for management of these entities and provide a pragmatic clinical review.

KEYWORDS

heart-assist devices, hemostasis, heparin-induced thrombocytopenia, thrombosis, ventricular assist devices, von Willebrand diseases

Essentials

- Hemostatic complications associated with ventricular assist devices (VADs) are common, and multiple manifestations can coexist in the same patient.
- Pump thrombosis is a devastating complication that typically requires surgical management.
- Acquired von Willebrand disease is an underdiagnosed manifestation associated with VADs that can complicate anticoagulant management.
- Maintaining a balance between bleeding and thrombosis risks is key to managing patients with VADs.

1 | INTRODUCTION

Over the past 2 decades, the use of ventricular assist devices (VADs) has increased dramatically. The first VADs were used in acutely ill patients as a bridge to transplant; more recently, left VADs are implanted in patients for end-stage chronic heart failure as destination therapy (ie, long-term use). With the increased use of VADs, a greater understanding and appreciation of the unique hemostatic complications associated with these devices has developed. In this review, we discuss the types of VADs currently in use and

their indications. The pathophysiology and clinical manifestations of coagulation defects seen in patients with VADs will be discussed, followed by management strategies of patients with these complications.

2 | VENTRICULAR ASSIST DEVICES

The burden of chronic heart failure (HF) is significant, with >870 000 new cases diagnosed in the United States per year and a lifetime risk of developing HF of 1 in 5 for men and women after the age of 40.[1] Despite advances in our understanding of this syndrome, mortality remains high, with a 50% mortality rate 5 years after diagnosis, which is higher than several common malignancies.[2–4] Moreover, the number of individuals who progress to end-stage HF remains large, with few durable long-term treatment strategies. Great strides have been made in medical and device therapy for HF; however, the prevalence of HF continues to rise, with estimates of a 46% increase by 2030 with total costs estimated at almost $70 billion.[1] Beyond medical therapy, heart transplant remains the best therapy for end-stage HF with actuarial survival approaching 14 years.[5] However, few individuals are candidates for this treatment, and the demand far exceeds the supply.

Mechanical circulatory support has been in evolution since the National Institutes of Health first started the artificial heart program in the 1960s. VADs are a manifestation of the program, serving now as destination therapy—treatment that supports the existing heart, not just until a heart transplant but also for the remainder of the patient's life. VADs have dramatically improved patients' overall survival and quality of life. In addition to technical improvements in device design, there has been a shift in patient selection from critically ill patients in shock to patients with advanced class III-IV HF.[6] Since 2005, data from >15 000 patients have been entered into the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS).[6] Outcomes are generally good, with enhanced survival (1-year survival of 80%) and improved function and quality of life.[7]

The first generation of devices used pulsatile technology with integrated valve regulated flow. The first randomized trial, the REMATCH (Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure) trial, demonstrated a survival advantage of the pulsatile VAD over optimal medical treatment.[8] Second- and third-generation devices have addressed device durability issues by removing valve-regulated flow and moving to axial and centrifugal technology using blood as the bearing fluid. As such, the REMATCH II trial was conducted 10 years after REMATCH using the axial continuous-flow HeartMate II (Thoratec Corp., Pleasanton, CA); it showed improved overall survival and reduction in adverse events compared to the pulsatile HeartMate XVE.[9] The US Food and Drug Administration (FDA) subsequently approved the HeartMate II device as destination therapy. It resulted in improved morbidity and mortality compared to first-generation devices, providing a more stable platform for patients with end-stage HF awaiting transplant or those who are transplant ineligible.[10–12]

The HeartMate 3 centrifugal continuous-flow device is the most recent VAD engineered to improve hemocompatibility and reduce shear stress. It was compared with the HeartMate II in the MOMENTUM3 (Multicenter Study of MagLev Technology in Patients Undergoing Mechanical Circulatory Support Therapy With HeartMate 3) trial, and showed superiority over the HeartMate II in the composite end point of disabling stroke and reoperation rate for pump thrombosis at 6 months after implantation, with an event-free survival at 6 months of 86.2% in the centrifugal-flow pump group and 76.8% in the axial-flow pump group. There was no difference in death or disabling stroke between the groups, but reoperation for pump malfunction was less frequent in the centrifugal-flow pump group than in the axial-flow pump group.[13] This device is approved for use in the European Union and was approved by the FDA in October 2018 for use as short-term and long-term therapy for patients with advanced refractory HF. The ENDURANCE (The HeartWare Ventricular Assist System as Destination Therapy of Advanced Heart Failure) trial similarly assessed the safety and effectiveness of the centrifugal-flow left VAD—HeartWare HVAD (Medtronic, Dublin, Ireland)—relative to a control, axial-flow left VAD in patients with advanced heart failure. The primary end point of survival at 2 years free from disabling stroke or device removal for malfunction or failure in the intention-to-treat population showed that the HeartWare centrifugal-flow device was noninferior to the control device.[14]

From these trials, it was clear that VADs are associated with significant morbidity and mortality; morbidities include bleeding, infection, pump thrombosis, and stroke. An analysis of US registry data of cumulative event rates in 8644 patients found that approximately 29% experienced bleeding events and 17% experienced neurologic complications (stroke and hemorrhage).[15] Therefore, comorbid conditions are important in candidate selection, and prior clotting disorders or bleeding diatheses are important considerations. Inability to tolerate anticoagulation due to prior bleeding events on oral anticoagulants remains a contraindication to VAD support. Additional comorbidities such as renal and hepatic dysfunction, prior chest surgery, peripheral arterial disease, and diabetes mellitus are important considerations for optimal candidate selection and timing of VAD implant.

3 | PATHOPHYSIOLOGY OF HEMATOLOGIC COMPLICATIONS

The placement of a VAD can lead to a variety of hematologic complications. The etiology of these complications is due to both the presence of a large foreign body (nonendothelial surface) and increased shear forces acting on flowing blood and its cellular components. Conceptually, there is a "VAD triad" analogous to Virchow's triad consisting of the interactions of (1) artificial surface, (2) blood alterations, and (3) the effects of abnormal flows (Figure 1). The major blood components that are affected by the presence of a VAD are coagulation factors, platelets, and erythrocytes.

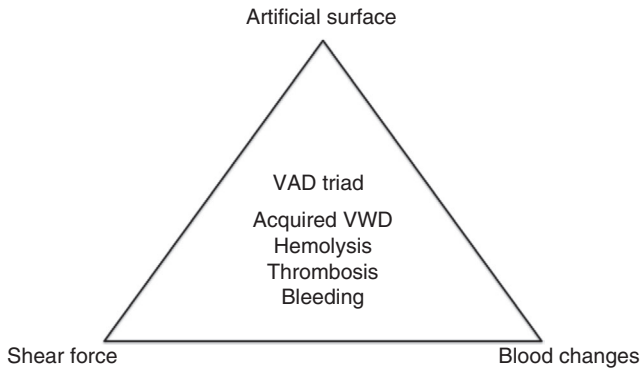

FIGURE 1 VAD Triad

3.1 | Coagulation factors

When placed, the VAD presents a large area of a nonendothelial surface to flowing blood. Plasma protein absorption by the surface is the first thing to occur.[16] These proteins include fibrinogen and contact pathway proteins (factor XII, kallikrein and high-molecular-weight kininogen). Fibrinogen can offer binding sites for platelets, leading to the formation of platelet aggregates. The binding of the contact system proteins to the surface leads to activation of coagulation by generating factor IXa, which can then lead to thrombin generation.[17] Studies have shown that with VAD placement there is depletion of contact pathway proteins over the first 2 weeks, suggesting activation with resultant protein depletion.[18]

3.2 | Platelets

Platelets become activated both by interactions with the nonendothelial surface and by the high shear forces. The nonendothelial surface introduced can activate platelets directly, independently of fibrinogen or contact system proteins. In an in vitro study, 15 minutes after blood was exposed to a surface, 5 to 16 platelets per 1000 μm were deposited—with this number increasing by 40% to 50% with the applied shear force.[19] The presence of a rapidly rotating pump is another surface reaction that can lead to very high shear forces, much more than those found in normal circulation; this can lead to alterations in von Willebrand protein, platelets, and erythrocytes.[20] In the above-mentioned in vitro model, levels of platelet factor 4 (PF4)—a marker of platelet activation—were increased within 120 minutes.[21] High shear unfolds von Willebrand protein, exposing platelet-binding sites. Platelets bind and become activated, recruiting more platelets to bind to von Willebrand proteins, resulting in the formation of platelet thrombi.[22] One would hypothesize that activation of platelets can lead to platelet deposition in the inner linings of the thrombus. However, a histopathologic analysis of thrombi from the HeartMate II VAD showed that the inner rings of the thrombus were rich in fibrin and von Willebrand factor (VWF). Platelets were found in the outer rings, suggesting that they may have a role in thrombus growth as well.[23]

The presence of a nonendothelial surface can also be a source of platelet dysfunction. In one study, 69% of patients with VADs had impaired ristocetin-induced platelet aggregation and decreased activity of plasma VWF, presumably due to lack of high-molecular-weight VWF multimers.[24] Finally, the vast majority of VAD patients are on antiplatelet agents, and those agents will augment platelet dysfunction.[25] Clinically, the platelet function assays are abnormal in all patients, likely reflecting both platelet dysfunction and acquired von Willebrand disease (aVWD).[26,27]

3.3 | Erythrocytes

Erythrocytes do not tolerate the high shear forces found in VADs and can be disrupted. The magnitude of the shear force needed to disrupt erythrocytes is 15 times higher than that required to unfold von Willebrand protein and 3 times higher than that required to activate platelets, so only a limited amount of VAD blood flow leads to red cell destruction.[20] Routinely, with VAD placement there is an increase in hemolysis due to presence of focal areas of very high shear. However, this hemolysis is markedly accentuated with the formation of pump thrombi.[28] Presence of thrombin in the blood flow leads to local areas of very high shear, with resultant erythrocyte destruction and clinically evident hemolysis.

4 | CLINICAL HEMATOLOGIC MANIFESTATIONS

4.1 | Acquired von Willebrand disease

The high shear stress associated with VADs leads to aVWD. Von Willebrand protein is synthesized as a dimer that then polymerizes to form ultra-large multimers over 20 000 kD in size. When released from endothelial cells, these ultra-large multimers are large enough to allow spontaneous binding and aggregation of platelets. As spontaneous platelet aggregation is undesirable in normal circumstances, von Willebrand protein undergoes cleavage by ADAMTS-13, resulting in formation of high-molecular-weight (HMW) multimers. The multimers are <20 000 kD in size but are the most effective in promoting hemostasis.

Von Willebrand protein usually circulates in a folded-up configuration, but under shear stress it can extend into long strings.[29] This unfolding exposes the von Willebrand A2 domain, which is a site for ADAMTS-13 cleavage, leading to loss of the most hemostatically effective HMW multimers. In addition, high levels of shear forces can lead to physical breakdown of HMW multimers, which further adds to the aVWD.[30] The onset of aVWD after VAD placement is rapid, often occurring immediately after surgery.[31,32] In an in vitro model, the onset of aVWD was within 2 hours of starting blood flow through the device, demonstrating the rapidity of protein degradation.[21] The aVWD appears to last as long as the VAD is in place—even up to 80 months. The resolution of aVWD is also rapid after VAD removal—often within 1 week.[33]

On laboratory testing, the levels of von Willebrand protein are markedly elevated, but ratio of von Willebrand activity to protein are markedly lower, <0.7, reflecting the loss of the HMW multimers.[34] Multimer analysis demonstrates that the levels of the HMW fractions are decreased by 30%, with a concomitant rise in the medium- and low-molecular-weight fractions.[26] Studies reveal that decreased or absent HMW multimers are very common, occurring in virtually all patients with a VAD.[33] However, the level of VWF activity of protein is not the only explanation for clinical bleeding seen in patients with VADs.[35] In one prospective study, 27% of patients with loss of HMW multimers had bleeding complications.[27]

4.2 | Hemolysis

Hemolysis is a common phenomenon seen after implantation of a VAD. In clinical practice, hemolysis can be an early marker of thrombosis, and routine monitoring for changes in plasma free hemoglobin and/or lactate dehydrogenase (LDH) help to diagnose potential thrombus development. Patients may have asymptomatic changes in these serum markers, and a careful assessment of pump parameters and markers of ventricular unloading through noninvasive or invasive means is important in deciding either to increase anticoagulation, to administer thrombolytics, or to proceed to pump exchange. One particular form of mechanical circulatory support (MCS) associated with hemolysis is the Impella device, which is increasingly used in cardiogenic shock. The rate of hemolysis is approximately 60% in patients who require long-term (>24 hours) support.[36]

Free hemoglobin is routinely used to assess erythrocyte destruction. False-positive results can be seen when hemolysis occurs during blood sampling and in high bilirubin states, such as in hepatic dysfunction from right ventricular heart failure, drugs, or sinusoidal endothelial dysfunction.[37] Haptoglobin, a protein synthesized by the liver, binds free hemoglobin in states of hemolysis and is usually depleted. However, reduced synthesis due to liver impairment can result in low levels of haptoglobin without hemolysis. An increase in LDH of >2.5 times the upper limit of normal can be indicative of early device thrombosis.[11]

Free hemoglobin is normally filtered through the glomerulus and actively reabsorbed in proximal tubule cells, where it is catabolized with release of iron in the form of hemosiderin. When the reabsorption capacity of the kidney is exceeded, hemoglobinuria occurs.[38] This can lead to acute renal failure during severe episodes of intravascular hemolysis. Furthermore, chronic intravascular hemolysis can lead to hemosiderin deposition in the proximal tubule and Fanconi syndrome.[39]

Other clinical manifestations of intravascular hemolysis are related to local and systemic nitric oxide deficiency, resulting in endothelial dysfunction. In animal models, nitric oxide has been shown to inhibit platelet aggregation and adhesion by increasing cyclic guanine monophosphate levels.[40] In deficiency states, such as nitric oxide scavenging by hemoglobin, platelet aggregation increases, as shown in studies of healthy volunteers.[41] Nitric oxide also has a role in smooth-muscle regulation.[38] This was demonstrated by administration of hemoglobin preparations to healthy human volunteers, resulting in abdominal pain, esophageal spasms, and dysphagia.[42]

The seventh INTERMACS annual report showed that patients who required a pump exchange had a worse survival compared to patients who did not require a pump exchange.[6] However, this likely reflects poor outcomes once refractory hemolysis develops regardless of whether patients undergo pump exchange. In another study, patients treated with medical therapy intensification had worse outcomes than patients who underwent pump exchange (1-year freedom from stroke or death of 49.5% and 87.5% in the medical and surgical cohorts, respectively; $P = 0.027$.[43]

4.3 | Thrombosis

Despite many efforts put in place to make the VAD surface less thrombogenic as well as the use of aggressive anticoagulation techniques, thrombotic complications remain the most feared VAD-related complications with rates of 7% to 16% per year.[44,45]

4.3.1 | Stroke

Strokes occur with an incidence ranging from 7% to 10% per year according to one meta-analysis.[46] Studies consistently show that about 50% of strokes in this setting are embolic and 50% are hemorrhagic.[47,48] The etiology of embolic strokes is assumed to be formation of thrombi in the pump, which are then the source of the emboli, as they have direct access to the arterial outflow. However, it is important to recognize that patients with HF may have atrial fibrillation and prior left ventricular mural thrombi, both of which may be sources of thrombus formation. Hemorrhagic strokes may be primary brain bleeds or hemorrhagic transformation of embolic strokes. Strokes are an adverse prognostic indicator, with a case fatality rate of 13% and double the risk of death over the long term.[45,49] International normalized ratio (INR) control appears to be important, as strokes are increased with INR <1.5 to 2.0, and hemorrhagic strokes increase with INR >3.0.[50]

4.3.2 | Pump thrombosis

The other devastating thrombotic complication of VAD placement is pump thrombosis. Rates vary in the literature but range from 5.5% to 12%.[51] Diagnosis of early thrombosis can be subtle, but 4 early signs are pump power elevation, a rise in LDH, evidence of hemolysis, or new heart failure symptoms.[52] A rise in LDH is a sensitive and early sign of pump thrombosis.[53] Thrombi in the pump disrupt blood flow, causing an increase in shear forces and red cell destruction, which leads to a marked increase in LDH levels—often >1000 μ/L.[51,54,55] Pump findings include increased power need or the finding that increasing power to the pump does not increase blood flow.[54]

Imaging with echocardiography or computed tomography can show either signs of thrombosis or changes in blood flow suggestive of obstruction to flow that may be consistent with thrombosis in

the pump. The pump ramp test looks to evaluate whether increasing pump speed leads to decreased left ventricular volume or unloading of the ventricle. In a normal-functioning VAD, the increased speed would lead to "draining" of the ventricle, but if the flow is blocked, this decrease in ventricular size is blunted. Falling blood pressure and cardiogenic shock are late signs.

The rate of pump thrombosis for the patients with a HeartMate II VAD was noted to be increased in many centers in 2013.[11] The etiology for this is not known, but speculation ranges from subtle changes in the pump design and preparation to less intense anticoagulation or to no heparin bridging after pump placement. An analysis of this device in the INTERMACS registry found an increase in pump exchange due to thrombosis from 2009 to 2012.[56] Indeed, pump design may also play a role in prevention. The HeartMate 3, a fully magnetically levitated centrifugal continuous-flow pump with a change in speed every 2 seconds as a means to wash the rotor, showed lower rates of pump thrombosis compared to the HeartMate II.[13]

4.4 | Heparin-induced thrombocytopenia

The combination of heparin exposure and increased platelet activation places patients with VADs at risk for heparin-induced thrombocytopenia (HIT). HIT is a platelet activation syndrome mediated by antibodies to heparin-PF4 protein complexes that activate platelets and lead to thrombocytopenia and thrombosis. One difficulty in assessing both patients and the literature on HIT incidence is the presence of frequent false-positive anti-PF4 antibodies, evaluated by PF4 ELISA, in this setting as with any cardiac surgery population.[55] Studies do show high rates of PF4 antibody formation in the 50% range, but the rate of finding platelet-activating PF4 antibodies is 10%, which is higher than in cardiac surgery or other high-risk settings.[57–60] The presence of platelet-activating PF4 antibodies does markedly increase the risk of thrombosis.

The most sensitive sign of HIT is a ≥50% fall in the platelet count.[59] In assessing the VAD patient at risk for HIT, one needs to keep other causes of thrombocytopenia in mind, such as recent surgery or infections. The 4Ts score is a pretests clinical scoring system that takes into account the degree of thrombocytopenia, timing of platelet count fall, other causes of thrombocytopenia, and thrombosis, and has been shown to have a high negative predictive value (ie, low-probability 4Ts score essentially excludes HIT) in a systematic review and meta-analysis.[61] Furthermore, one study has shown that combining 4Ts clinical score with the PF4 ELISA test increases sensitivity and specificity.[62] In patients with thrombocytopenia and a high 4Ts score, especially with new thrombosis, blood should be drawn for PF4 ELISA testing. If the ELISA test is positive, patients need to be changed to an alternative anticoagulation. Given the high false-positive rate, anti-PF4 antibodies need to be confirmed with heparin-induced platelet activation testing (serotonin release assay), which is specific for HIT.[61]

The first step in treatment of HIT is to avoid heparin. Alternatives for anticoagulation include argatroban, bivalirudin, or fondaparinux.[63,64] For patients with renal insufficiency, argatroban is the preferred choice. Clearance of argatroban is decreased in hepatic disease, and the dose is typically decreased as well. Given its long half-life, renal clearance, and lack of validated methods for monitoring, fondaparinux is not routinely used in patients with MCS. Our preferred choice is therefore bivalirudin unless a patient has severe renal insufficiency.

4.5 | Bleeding

Bleeding can occur in up to 80% of patients with VADs, with a meta-analysis reporting an overall rate of 30% (10% of which are fatal).[45] There are several patterns of bleeding. There is an early increased incidence of bleeding with or after surgery requiring reoperation in 14% to 30% of patients.[65–67] Factors that put patients at risk for surgical bleeding include anticoagulation before surgery and renal and/or liver dysfunction due to heart failure. Other risk factors for surgical bleeding are older age and cardiogenic shock.[65,68]

The need for long-term combination antiplatelet and antithrombotic therapy is a risk factor for bleeding. In addition, aVWD and platelet dysfunction are also risk factors for bleeding. Finally, changes in blood flow due to the VAD, especially continuous-flow models, may lead to anatomic causes of bleeding. In the late postoperative period, bleeding is usually from the gastrointestinal (GI) tract or intracranial. The most serious site of bleeding is intracranial hemorrhage, with rates of 1% to 9% per year being reported.[69] In a pediatric series, the rate was 17%, with most patients dying of the intracranial bleed.[70]

The most common site of bleeding is the GI tract, with up to 5% to 40% suffering this complication.[71–74] The site of bleeding can be anywhere in the GI tract and is often a challenge to diagnose, as it may be related to diffuse angiodysplasia. Studies showed an 8.7% to 38% rate of ulcers and gastritis, presumably due to both antiplatelet agents and stress.[72,75] Arteriovenous malformations are a particular source of bleeding, especially in patients with continuous-flow pumps.[72] With the advent of continuous-flow devices, the risk of GI bleeding was noted to increase—in some studies >10-fold over pulsatile flow devices.[71] In these patients, the site of bleeding was found to be arteriovenous malformation, with a rate of 20% to 60% being reported.[76] Given the association of continuous-flow pumps and arteriovenous malformation, it has been hypothesized that the lack of pulse pressure is a key risk factor for the development of abnormal vasculature. Supporting this idea is the increased risk of arteriovenous malformations seen in other disease states marked by lack of pulse pressure such as aortic stenosis.[77] Theories on etiologies for arteriovenous malformations range from an increased sympathetic tone leading to smooth-muscle relaxation and vessel dilation to hypoperfusion resulting in local hypoxia and vascular dilation.[73,75] Other postulated mechanisms include the impact VWF may have on vascular integrity, including the possibility that VWF fragments may be proangiogenic (Table 1).[78]

TABLE 1 Hematologic manifestations and their management

	Signs	Treatment	Long-term
Pump thrombosis	Increase LDH or plasma free hemoglobin, hemolysis, new or worsening heart failure, failed pump ramp test	Heparin Eptifibatide Thrombolytics (intravenous or intraventricular) Surgery preferred (pump replacement)	Increase INR range 2.5-3.5 Increase aspirin dose to 325 mg/daily
Heparin-induced thrombocytopenia	Thrombosis, thrombocytopenia without alternative explanation (drug-induced, sepsis)	Argatroban Bivalirudin	Avoid heparin products
Bleeding	Depends on site of bleed and severity	Warfarin: prothrombin complex concentrate Antiplatelet agents • Aspirin: 1 plateletpheresis unit • Other agents: 2 plateletpheresis units	Reduce INR goal to 1.5-2.0 (if moderate bleed), or halt (if severe bleed) Risk/benefit discussion

INR, international normalized ratio; LDH, lactate dehydrogenase.

5 | MANAGEMENT STRATEGIES

5.1 | Bleeding

Life-threatening major hemorrhage is managed with immediate reversal of anticoagulation using prothrombin complex concentrate for warfarin[79] and platelet transfusions to reverse the antiplatelet effect. The role of von Willebrand replacement is controversial given that any infused factor is likely to be rapidly degraded.[15] It has been proposed that reducing pump speed may help, as this may lessen shear forces and degradation of VWF. However, even with reduced pump speed, the shear forces generated are still an order of magnitude greater than physiologic levels and von Willebrand degradation still occurs. For patients with GI bleeding, where most studies show the majority of the bleeding lesions are in the upper tract, esophagogastroduodenoscopy (EGD) is the first diagnostic approach. If EGD is negative, a pill endoscopy is an option to image the small bowel, which is often the site of arteriovenous malformations.[66,75] For patients with frankly bloody stools, colonoscopy is the first choice for evaluation.

Mild to moderate bleeding requires an individualized assessment to identify the best approach for management. Epistaxis or mild GI bleeding can be managed by holding aspirin. Another approach is to lower the INR goal; however, it has been shown that lessening of anticoagulation may lead to thrombosis. Having a GI bleed is also a 7.4-fold risk factor for stroke, perhaps due to the need to decrease or halt anticoagulation.[72]

Longer-term management of bleeding patients is less settled, as patients often rebleed after the first event.[72] Reduction of anticoagulation should be considered only for patients with recurrent severe bleeding. However, even off anticoagulation, the rate of rebleeding approaches 40%.[80] There are anecdotes about the use of octreotide to control bleeding from arteriovenous malformations, but results are contradictory, and again this should be reserved for patients for whom there are no other options to control bleeding.[81,82] There are preliminary promising data for omega-3 fatty acids, where the use of 4 g daily resulted in lower rates of GI bleeding (3%) compared to 22% in a retrospective control group, but these results need to be confirmed in a randomized clinical trial.[83]

5.2 | Anticoagulation

Antithrombotic therapy with both anticoagulation and antiplatelet agents is crucial in preventing thrombotic complications in VAD patients. It was once standard that patients after VAD placement be treated with heparin until warfarin achieves a therapeutic INR. Now it is not uncommon to find heparin being held in this period to decrease early postoperative bleeding rates.[84–87] However, this lack of heparin has led to recent concern of an association with increased risk of pump thrombosis. It may be prudent to limit holding heparin to patients at high risk of bleeding, such as those with previous GI bleeding or other risk factors for hemorrhage.[84]

Given the role of platelet activation by surfaces and shear, aspirin is started when surgical bleeding stops. There is no consensus on dosing, with recommendations ranging from 81 to 325 mg depending on centers.[87] One center has reported decreased stroke risk with 325-mg dosing, but other studies show increased bleeding.[65] Conversely, a small study eliminated the use of aspirin and used warfarin with an INR of 2 to 2.5 with low thrombosis and bleeding rates. This provocative finding will need to be confirmed by larger studies.[88]

Warfarin is started with varied INR goals among centers as well as consideration of patient risk factors for either bleeding or thrombosis.[45] Most INR goals are in the 2 to 3 range, but many centers using HeartMate II will drop this to 1.5 to 2.5 based on data showing less bleeding with no increase in thrombosis with INRs in this range.[84,89] Studies show that with HeartMate II patients, the highest rate of thrombosis was with INRs <1.5, but the rate was still high with INRs of 1.5 to 2.0. Bleeding increases slightly with INRs >2.5 to 3.0 but increases substantially with INRs >3.5.[49] One challenge with warfarin is that, due to illness and polypharmacy, these patients have may have unstable INRs. The time in therapeutic range for VAD patients is only 30% to 50%.[65] This time in range is considerably lower than that reported in atrial fibrillation patients, and this instability of anticoagulation may add to both bleeding and thrombosis risk.

Traditionally, heparin is monitored by the activated partial thromboplastin time (APTT). However, this test can be affected by warfarin, high factor VIII due to underlying inflammation, and hemolysis. Recent studies have shown that the APTT underestimates heparin requirements for VAD patients when compared to heparin levels measured by anti-Xa activity.[90] One of the factors responsible for this discrepancy is residual warfarin effect. It has been shown that for every 1.0-unit rise in INR >1, the APTT increases by 16 seconds, which can lead to falsely high APTTs.[91] Elevations of LDH >1000 also interfere with the APTT assay. For patients who are taking or have recently taken warfarin and for those with high LDHs, using heparin levels via the anti-Xa assay may result in more accurate heparin dosing and does not lead to an increased risk of bleeding despite supratherapeutic APTTs.

The direct oral anticoagulants (DOACs) have been shown in the setting of venous thromboembolism and atrial fibrillation to be just as effective as warfarin with lesser rates of bleeding, including intracranial hemorrhage and fatal bleeding. Given the lack of need for monitoring as well as no food and minimal drug interaction, the DOACs are attractive for the replacement of warfarin in VAD patients. A small study of 7 patients using dabigatran showed no excess rate of bleeding or thrombosis.[92] However, a single-center, randomized trial of dabigatran vs. warfarin was terminated early due to increased thromboembolic events associated with dabigatran.[93] Furthermore, given the negative experience with dabigatran use in mechanical heart valves, routine use cannot be recommended until ongoing clinical trials are completed.

5.3 | Pump exchange

Treatment of pump thrombosis is primarily surgical, involving exchange of the pump or urgent cardiac transplant when feasible. While the patient is being evaluated, initial medical therapy consisting of heparin is started, but this alone is considered insufficient to treat pump thrombosis.[15,51,54] Some groups have tried adding glycoprotein IIb/IIIa inhibitors, usually eptifibatide, for 24 to 48 hours, but this can be complicated by bleeding and stroke. A large study using eptifabatide 0.1 to 2.0 μg/kg/min with no bolus showed only a 17% success rate and a mortality rate of 41% with a 63% rate of bleeding.[94] Thrombolytics have also been tried with a variety of dosing protocols, ranging from a 100-mg bolus of tissue-type plasminogen activator (t-PA) to an intraventricular infusion of 1 mg/min, which can limit the total amount of thrombolytics infused.[54,95] A novel approach uses a low-dose infusion of a bolus of 3 mg and then a 5- to 6-hour infusion of t-PA at 3 mg/h.[54] However, the results of medical therapy are poor, with studies showing only 23% to 50% success and high rates of complications: 10% to 15% stroke, 65% bleeding, and 17% to 52% mortality.[51,52] Data for surgical replacement are better, with only 0% to 6.5% early mortality, making this the therapy of choice.

The key to prevention of pump thrombosis is adequate anticoagulation. INRs must be monitored frequently to keep patients in the therapeutic range. For patients with a history of pump thrombosis, it is prudent to aim for a higher INR range of 2.5 to 3.5. Some also have advocated increasing the aspirin dose to 325 mg/d.

6 | PERIOPERATIVE MANAGEMENT FOR NONCARDIAC SURGERY

As discussed previously, all patients with a left VAD will likely be maintained on anticoagulation. In patients undergoing noncardiac surgery, appropriate anticoagulation bridging should be undertaken. Warfarin should be discontinued 2 to 5 days preoperatively and a heparin infusion initiated until the morning of the planned procedure.[96,97] For patients with a history of HIT, both argatroban and bivalirudin are recommended for bridging. In some cases, patients with an increased risk of bleeding due to platelet dysfunction and aVWD may be safely taken to surgery without bridging if there is concern for hemorrhage intra- or postoperatively.[98]

In the postoperative setting, anticoagulation should be resumed when the risk of postoperative bleeding is deemed acceptable.[99] It is generally recommended that heparin be used in this setting if there are no contraindications, but some case series have suggested that warfarin may be resumed without the need for heparin.[85] Timing of resumption of antiplatelet therapy is variable, but most published experiences suggest that aspirin can be resumed 1 week postoperatively.[100] The management of bleeding in the postoperative period depends on the cause and source of bleed. Surgical causes may need operative correction and management. However, bleeding unrelated to the operation remains common (eg, GI bleeding) and must be monitored postoperatively.[101]

7 | SUMMARY

VADs remain an important modality in the treatment of advanced HF for those who cannot wait or are not candidates for heart transplantation. The balance of bleeding and thrombosis is complex, and a multitude of patient and device characteristics can shift this balance. Careful assessment of bleeding and thrombotic risks should occur prior to VAD implant. The perioperative phase is a complex time that often results in activation of blood components and may set the stage for future bleeding and/or thrombotic events, which carry increased risks of morbidity and mortality.

RELATIONSHIP DISCLOSURE

The authors report nothing to disclose.

AUTHOR CONTRIBUTIONS

TH, JM, and TGD reviewed the literature and wrote the manuscript.

ORCID

Talal Hilal https://orcid.org/0000-0001-8249-4128

Thomas G. DeLoughery https://orcid.org/0000-0002-5790-4700

REFERENCES

1. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, et al. Heart disease and stroke statistics–2015 update: a report from the American Heart Association. Circulation. 2015;131:e29–322.
2. Roger VL, Weston SA, Redfield MM, Hellermann-Homan JP, Killian J, Yawn BP, et al. Trends in heart failure incidence and survival in a community-based population. JAMA. 2004;292:344–50.
3. Levy D, Kenchaiah S, Larson MG, Benjamin EJ, Kupka MJ, Ho KK, et al. Long-term trends in the incidence of and survival with heart failure. N Engl J Med. 2002;347:1397–402.
4. Stewart S, MacIntyre K, Hole DJ, Capewell S, McMurray JJ. More "malignant" than cancer? Five-year survival following a first admission for heart failure. Eur J Heart Fail. 2001;3:315–22.
5. Lund LH, Edwards LB, Kucheryavaya AY, Benden C, Christie JD, Dipchand AI, et al. The registry of the International Society for Heart and Lung Transplantation: thirty-first official adult heart transplant report–2014; focus theme: retransplantation. J Heart Lung Transplant. 2014;33:996–1008.
6. Kirklin JK, Naftel DC, Pagani FD, Kormos RL, Stevenson LW, Blume ED, et al. Seventh INTERMACS annual report: 15,000 patients and counting. J Heart Lung Transplant. 2015;34:1495–504.
7. Raffini L. Anticoagulation with VADs and ECMO: walking the tightrope. Hematology Am Soc Hematol Educ Program. 2017;2017:674–80.
8. Rose EA, Moskowitz AJ, Packer M, Sollano JA, Williams DL, Tierney AR, et al. The REMATCH trial: rationale, design, and end points. Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure. Ann Thorac Surg. 1999;67:723–30.
9. Slaughter MS, Rogers JG, Milano CA, Russell SD, Conte JV, Feldman D, et al. Advanced heart failure treated with continuous-flow left ventricular assist device. N Engl J Med. 2009;361:2241–51.
10. Miller LW, Pagani FD, Russell SD, John R, Boyle AJ, Aaronson KD, et al. Use of a continuous-flow device in patients awaiting heart transplantation. N Engl J Med. 2007;357:885–96.
11. Starling RC, Moazami N, Silvestry SC, Ewald G, Rogers JG, Milano CA, et al. Unexpected abrupt increase in left ventricular assist device thrombosis. N Engl J Med. 2014;370:33–40.
12. Aaronson KD, Slaughter MS, Miller LW, McGee EC, Cotts WG, Acker MA, et al. Use of an intrapericardial, continuous-flow, centrifugal pump in patients awaiting heart transplantation. Circulation. 2012;125:3191–200.
13. Mehra MR, Naka Y, Uriel N, Goldstein DJ, Cleveland JC Jr, Colombo PC, et al. A fully magnetically levitated circulatory pump for advanced heart failure. N Engl J Med. 2017;376:440–50.
14. Rogers JG, Pagani FD, Tatooles AJ, Bhat G, Slaughter MS, Birks EJ, et al. Intrapericardial left ventricular assist device for advanced heart failure. N Engl J Med. 2017;376:451–60.
15. Connors JM. Anticoagulation management of left ventricular assist devices. Am J Hematol. 2015;90:175–8.
16. Annich GM. Extracorporeal life support: the precarious balance of hemostasis. J Thromb Haemost. 2015;13(suppl 1):S336–42.
17. Maas C, Renne T. Regulatory mechanisms of the plasma contact system. Thromb Res. 2012;129(suppl 2):S73–6.
18. Himmelreich G, Ullmann H, Riess H, Rosch R, Loebe M, Schiessler A, et al. Pathophysiologic role of contact activation in bleeding followed by thromboembolic complications after implantation of a ventricular assist device. ASAIO J. 1995;41:M790–4.
19. Schaub RD, Kameneva MV, Borovetz HS, Wagner WR. Assessing acute platelet adhesion on opaque metallic and polymeric biomaterials with fiber optic microscopy. J Biomed Mater Res. 2000;49:460–8.
20. Fraser KH, Zhang T, Taskin ME, Griffith BP, Wu ZJ. A quantitative comparison of mechanical blood damage parameters in rotary ventricular assist devices: shear stress, exposure time and hemolysis index. J Biomech Eng. 2012;134:081002.
21. Dassanayaka S, Slaughter MS, Bartoli CR. Mechanistic pathway(s) of acquired von willebrand syndrome with a continuous-flow ventricular assist device: in vitro findings. ASAIO J. 2013;59:123–9.
22. Casa LD, Deaton DH, Ku DN. Role of high shear rate in thrombosis. J Vasc Surg. 2015;61:1068–80.
23. Baumann Kreuziger L, Slaughter MS, Sundareswaran K, Mast AE. Clinical relevance of histopathologic analysis of HeartMate II thrombi. ASAIO J. 2018;64:754–9.
24. Klovaite J, Gustafsson F, Mortensen SA, Sander K, Nielsen LB. Severely impaired von Willebrand factor–dependent platelet aggregation in patients with a continuous-flow left ventricular assist device (HeartMate II). J Am Coll Cardiol. 2009;53:2162–7.
25. Cowger JA, Romano MA, Shah P, Shah N, Mehta V, Haft JW, et al. Hemolysis: a harbinger of adverse outcome after left ventricular assist device implant. J Heart Lung Transplant. 2014;33:35–43.
26. Meyer AL, Malehsa D, Budde U, Bara C, Haverich A, Strueber M. Acquired von Willebrand syndrome in patients with a centrifugal or axial continuous flow left ventricular assist device. JACC Heart Fail. 2014;2:141–5.
27. Crow S, Chen D, Milano C, Thomas W, Joyce L, Piacentino V 3rd, et al. Acquired von Willebrand syndrome in continuous-flow ventricular assist device recipients. Ann Thorac Surg. 2010;90:1263–9; discussion 9.
28. Birschmann I, Dittrich M, Eller T, Wiegmann B, Reininger AJ, Budde U, et al. Ambient hemolysis and activation of coagulation is different between HeartMate II and HeartWare left ventricular assist devices. J Heart Lung Transplant. 2014;33:80–7.
29. Springer TA. von Willebrand factor, Jedi knight of the bloodstream. Blood. 2014;124:1412–25.
30. Bartoli CR, Restle DJ, Zhang DM, Acker MA, Atluri P. Pathologic von Willebrand factor degradation with a left ventricular assist device occurs via two distinct mechanisms: mechanical demolition and enzymatic cleavage. J Thorac Cardiovasc Surg. 2015;149:281–9.
31. Heilmann C, Geisen U, Beyersdorf F, Nakamura L, Benk C, Berchtold-Herz M, et al. Acquired von Willebrand syndrome in patients with ventricular assist device or total artificial heart. Thromb Haemost. 2010;103:962–7.
32. Heilmann C, Geisen U, Beyersdorf F, Nakamura L, Trummer G, Berchtold-Herz M, et al. Acquired Von Willebrand syndrome is an early-onset problem in ventricular assist device patients. Eur J Cardiothorac Surg. 2011;40:1328–33.
33. Geisen U, Brehm K, Trummer G, Berchtold-Herz M, Heilmann C, Beyersdorf F, et al. Platelet secretion defects and acquired von Willebrand syndrome in patients with ventricular assist devices. J Am Heart Assoc. 2018;7. pii: e006519.
34. Leebeek FW, Eikenboom JC. Von Willebrand's disease. N Engl J Med. 2016;375:2067–80.
35. Uriel N, Pak SW, Jorde UP, Jude B, Susen S, Vincentelli A, et al. Acquired von Willebrand syndrome after continuous-flow mechanical device support contributes to a high prevalence of bleeding during long-term support and at the time of transplantation. J Am Coll Cardiol. 2010;56:1207–13.
36. Badiye AP, Hernandez GA, Novoa I, Chaparro SV. Incidence of hemolysis in patients with cardiogenic shock treated with impella percutaneous left ventricular assist device. ASAIO J. 2016;62:11–4.
37. Heilmann C, Geisen U, Benk C, Berchtold-Herz M, Trummer G, Schlensak C, et al. Haemolysis in patients with ventricular assist devices: major differences between systems. Eur J Cardiothorac Surg. 2009;36:580–4.
38. Rother RP, Bell L, Hillmen P, Gladwin MT. The clinical sequelae of intravascular hemolysis and extracellular plasma hemoglobin: a novel mechanism of human disease. JAMA. 2005;293:1653–62.

39. Clark DA, Butler SA, Braren V, Hartmann RC, Jenkins DE Jr. The kidneys in paroxysmal nocturnal hemoglobinuria. Blood. 1981;57:83–9.
40. Radomski MW, Palmer RM, Moncada S. The anti-aggregating properties of vascular endothelium: interactions between prostacyclin and nitric oxide. Br J Pharmacol. 1987;92:639–46.
41. Schafer A, Wiesmann F, Neubauer S, Eigenthaler M, Bauersachs J, Channon KM. Rapid regulation of platelet activation in vivo by nitric oxide. Circulation. 2004;109:1819–22.
42. Murray JA, Ledlow A, Launspach J, Evans D, Loveday M, Conklin JL. The effects of recombinant human hemoglobin on esophageal motor functions in humans. Gastroenterology. 1995;109:1241–8.
43. Levin AP, Saeed O, Willey JZ, Levin CJ, Fried JA, Patel SR, et al. Watchful waiting in continuous-flow left ventricular assist device patients with ongoing hemolysis is associated with an increased risk for cerebrovascular accident or death. Circ Heart Fail. 2016;9. pii: e002896.
44. Felix SE, Martina JR, Kirkels JH, Klopping C, Nathoe H, Sukkel E, et al. Continuous-flow left ventricular assist device support in patients with advanced heart failure: points of interest for the daily management. Eur J Heart Fail. 2012;14:351–6.
45. Baumann Kreuziger LM, Kim B, Wieselthaler GM. Antithrombotic therapy for left ventricular assist devices in adults: a systematic review. J Thromb Haemost. 2015;13:946–55.
46. Backes D, van den Bergh WM, van Duijn AL, Lahpor JR, van DD, Slooter AJ. Cerebrovascular complications of left ventricular assist devices. Eur J Cardiothorac Surg. 2012;42:612–20.
47. Vogler EA, Siedlecki CA. Contact activation of blood-plasma coagulation. Biomaterials. 2009;30:1857–69.
48. Harvey L, Holley C, Roy SS, Eckman P, Cogswell R, Liao K, et al. Stroke after left ventricular assist device implantation: outcomes in the continuous-flow era. Ann Thorac Surg. 2015;100:535–41.
49. Boyle AJ, Russell SD, Teuteberg JJ, Slaughter MS, Moazami N, Pagani FD, et al. Low thromboembolism and pump thrombosis with the HeartMate II left ventricular assist device: analysis of outpatient anti-coagulation. J Heart Lung Transplant. 2009;28:881–7.
50. Nassif ME, LaRue SJ, Raymer DS, Novak E, Vader JM, Ewald GA, et al. Relationship between anticoagulation intensity and thrombotic or bleeding outcomes among outpatients with continuous-flow left ventricular assist devices. Circ Heart Fail. 2016;9:e002680.
51. Mehra MR, Stewart GC, Uber PA. The vexing problem of thrombosis in long-term mechanical circulatory support. J Heart Lung Transplant. 2014;33:1–11.
52. Stulak JM, Sharma S, Maltais S. Management of pump thrombosis in patients with left ventricular assist devices. Am J Cardiovasc Drugs. 2015;15:89–94.
53. Uriel N, Han J, Morrison KA, Nahumi N, Yuzefpolskaya M, Garan AR, et al. Device thrombosis in HeartMate II continuous-flow left ventricular assist devices: a multifactorial phenomenon. J Heart Lung Transplant. 2014;33:51–9.
54. Bartoli CR, Ailawadi G, Kern JA. Diagnosis, nonsurgical management, and prevention of LVAD thrombosis. J Card Surg. 2014;29:83–94.
55. Ravichandran AK, Parker J, Novak E, Joseph SM, Schilling JD, Ewald GA, et al. Hemolysis in left ventricular assist device: a retrospective analysis of outcomes. J Heart Lung Transplant. 2014;33:44–50.
56. Kirklin JK, Naftel DC, Kormos RL, Pagani FD, Myers SL, Stevenson LW, et al. Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) analysis of pump thrombosis in the HeartMate II left ventricular assist device. J Heart Lung Transplant. 2014;33:12–22.
57. Schenk S, El-Banayosy A, Prohaska W, Arusoglu L, Morshuis M, Koester-Eiserfunke W, et al. Heparin-induced thrombocytopenia in patients receiving mechanical circulatory support. J Thorac Cardiovasc Surg. 2006;131:1373–81.
58. Koster A, Huebler S, Potapov E, Meyer O, Jurmann M, Weng Y, et al. Impact of heparin-induced thrombocytopenia on outcome in patients with ventricular assist device support: single-institution experience in 358 consecutive patients. Ann Thorac Surg. 2007;83:72–6.
59. Warkentin TE, Greinacher A, Koster A. Heparin-induced thrombocytopenia in patients with ventricular assist devices: are new prevention strategies required? Ann Thorac Surg. 2009;87:1633–40.
60. Koster A, Loebe M, Sodian R, Potapov EV, Hansen R, Muller J, et al. Heparin antibodies and thromboembolism in heparin-coated and noncoated ventricular assist devices. J Thorac Cardiovasc Surg. 2001;121:331–5.
61. Cuker A, Gimotty PA, Crowther MA, Warkentin TE. Predictive value of the 4Ts scoring system for heparin-induced thrombocytopenia: a systematic review and meta-analysis. Blood. 2012;120:4160–7.
62. Demma LJ, Winkler AM, Levy JH. A diagnosis of heparin-induced thrombocytopenia with combined clinical and laboratory methods in cardiothoracic surgical intensive care unit patients. Anesth Analg. 2011;113:697–702.
63. Benken ST, Tillman N, Dajani S, Shah A, Thomas T. A retrospective evaluation of fondaparinux for confirmed or suspected heparin-induced thrombocytopenia in left-ventricular-assist device patients. J Cardiothorac Surg. 2014;9:55.
64. Pieri M, Agracheva N, Di Prima AL, Nisi T, De BM, Isella F, et al. Primary anticoagulation with bivalirudin for patients with implantable ventricular assist devices. Artif Organs. 2014;38:342–6.
65. Baumann Kreuziger LM. Management of anticoagulation and antiplatelet therapy in patients with left ventricular assist devices. J Thromb Thrombolysis. 2015;39:337–44.
66. Suarez J, Patel CB, Felker GM, Becker R, Hernandez AF, Rogers JG. Mechanisms of bleeding and approach to patients with axial-flow left ventricular assist devices. Circ Heart Fail. 2011;4:779–84.
67. Goldstein DJ, Beauford RB. Left ventricular assist devices and bleeding: adding insult to injury. Ann Thorac Surg. 2003;75:S42–7.
68. Neill S, Engoren M, Kouatli Y, Shields TA, Jewell E, Pagani FD. Risk factors related to transfusion requirements in patients undergoing implantation of ventricular assist devices. J Cardiothorac Vasc Anesth. 2015;29:297–302.
69. Patel H, Madanieh R, Kosmas CE, Vatti SK, Vittorio TJ. Complications of continuous-flow mechanical circulatory support devices. Clin Med Insights Cardiol. 2015;9:15–21.
70. Niebler RA, Lew SM, Zangwill SD, Woods RK, Mitchell ME, Tweddell JS, et al. Incidence and outcome of pediatric patients with intracranial hemorrhage while supported on ventricular assist devices. Artif Organs. 2014;38:73–8.
71. Atluri P, Acker MA, Jessup M. The next decade in mechanical assist: advances that will help the patient and the doctor. Curr Opin Cardiol. 2011;26:256–60.
72. French JB, Pamboukian SV, George JF, Smallfield GB, Tallaj JA, Brown RN, et al. Gastrointestinal bleeding in patients with ventricular assist devices is highest immediately after implantation. ASAIO J. 2013;59:480–5.
73. Stulak JM, Lee D, Haft JW, Romano MA, Cowger JA, Park SJ, et al. Gastrointestinal bleeding and subsequent risk of thromboembolic events during support with a left ventricular assist device. J Heart Lung Transplant. 2014;33:60–4.
74. Harvey L, Holley CT, John R. Gastrointestinal bleed after left ventricular assist device implantation: incidence, management, and prevention. Ann Cardiothorac Surg. 2014;3:475–9.
75. Guha A, Eshelbrenner CL, Richards DM, Monsour HP Jr. Gastrointestinal bleeding after continuous-flow left ventricular

device implantation: review of pathophysiology and management. Methodist Debakey Cardiovasc J. 2015;11:24–7.
76. Demirozu ZT, Radovancevic R, Hochman LF, Gregoric ID, Letsou GV, Kar B, et al. Arteriovenous malformation and gastrointestinal bleeding in patients with the HeartMate II left ventricular assist device. J Heart Lung Transplant. 2011;30:849–53.
77. Loscalzo J. From clinical observation to mechanism – Heyde's syndrome. N Engl J Med. 2012;367:1954–6.
78. Starke RD, Ferraro F, Paschalaki KE, Dryden NH, McKinnon TA, Sutton RE, et al. Endothelial von Willebrand factor regulates angiogenesis. Blood. 2011;117:1071–80.
79. Lankiewicz MW, Hays J, Friedman KD, Tinkoff G, Blatt PM. Urgent reversal of warfarin with prothrombin complex concentrate. J Thromb Haemost. 2006;4:967–70.
80. Katz JN, Adamson RM, John R, Tatooles A, Sundareswaran K, Kallel F, et al. Safety of reduced anti-thrombotic strategies in HeartMate II patients: a one-year analysis of the US-TRACE Study. J Heart Lung Transplant. 2015;34:1542–8.
81. Aggarwal A, Pant R, Kumar S, Sharma P, Gallagher C, Tatooles AJ, et al. Incidence and management of gastrointestinal bleeding with continuous flow assist devices. Ann Thorac Surg. 2012;93:1534–40.
82. Hayes HM, Dembo LG, Larbalestier R, O'Driscoll G. Management options to treat gastrointestinal bleeding in patients supported on rotary left ventricular assist devices: a single-center experience. Artif Organs. 2010;34:703–6.
83. Imamura T, Nguyen A, Rodgers D, Kim G, Raikhelkar J, Sarswat N, et al. Omega-3 therapy is associated with reduced gastrointestinal bleeding in patients with continuous-flow left ventricular assist device. Circ Heart Fail. 2018;11:e005082.
84. Toeg H, Ruel M, Haddad H. Anticoagulation strategies for left ventricular assist devices. Curr Opin Cardiol. 2015;30:192–6.
85. Slaughter MS, Naka Y, John R, Boyle A, Conte JV, Russell SD, et al. Post-operative heparin may not be required for transitioning patients with a HeartMate II left ventricular assist system to long-term warfarin therapy. J Heart Lung Transplant. 2010;29:616–24.
86. Feldman D, Pamboukian SV, Teuteberg JJ, Birks E, Lietz K, Moore SA, et al. The 2013 International Society for Heart and Lung Transplantation Guidelines for mechanical circulatory support: executive summary. J Heart Lung Transplant. 2013;32:157–87.
87. Hohner E, Crow J, Moranville MP. Medication management for left ventricular assist device thrombosis. Am J Health Syst Pharm. 2015;72:1104–13.
88. Litzler PY, Smail H, Barbay V, Nafeh-Bizet C, Bouchart F, Baste JM, et al. Is anti-platelet therapy needed in continuous flow left ventricular assist device patients? A single-centre experience. Eur J Cardiothorac Surg. 2014;45:55–9.
89. John R, Kamdar F, Eckman P, Colvin-Adams M, Boyle A, Shumway S, et al. Lessons learned from experience with over 100 consecutive HeartMate II left ventricular assist devices. Ann Thorac Surg. 2011;92:1593–9.
90. Sieg A, Mardis BA, Mardis CR, Huber MR, New JP, Meadows HB, et al. Developing an anti-Xa-based anticoagulation protocol for patients with percutaneous ventricular assist devices. ASAIO J. 2015;61:502–8.
91. Kearon C, Johnston M, Moffat K, McGinnis J, Ginsberg JS. Effect of warfarin on activated partial thromboplastin time in patients receiving heparin. Arch Intern Med. 1998;158:1140–3.
92. Terrovitis JV, Ntalianis A, Kapelios CJ, Vakrou S, Diakos N, Katsaros L, et al. Dabigatran etexilate as second-line therapy in patients with a left ventricular assist device. Hellenic J Cardiol. 2015;56:20–5.
93. Andreas M, Moayedifar R, Wieselthaler G, Wolzt M, Riebandt J, Haberl T, et al. Increased thromboembolic events with dabigatran compared with vitamin K antagonism in left ventricular assist device patients: a randomized controlled pilot trial. Circ Heart Fail. 2017;10. pii: e003709.
94. Tellor BR, Smith JR, Prasad SM, Joseph SM, Silvestry SC. The use of eptifibatide for suspected pump thrombus or thrombosis in patients with left ventricular assist devices. J Heart Lung Transplant. 2014;33:94–101.
95. Kiernan MS, Pham DT, DeNofrio D, Kapur NK. Management of HeartWare left ventricular assist device thrombosis using intracavitary thrombolytics. J Thorac Cardiovasc Surg. 2011;142:712–4.
96. Ficke DJ, Lee J, Chaney MA, Bas H, Vidal-Melo MF, Stone ME. Case 6-2010: noncardiac surgery in patients with a left ventricular assist device. J Cardiothorac Vasc Anesth. 2010;24:1002–9.
97. Morgan JA, Paone G, Nemeh HW, Henry SE, Gerlach B, Williams CT, et al. Non-cardiac surgery in patients on long-term left ventricular assist device support. J Heart Lung Transplant. 2012;31:757–63.
98. Barbara DW, Wetzel DR, Pulido JN, Pershing BS, Park SJ, Stulak JM, et al. The perioperative management of patients with left ventricular assist devices undergoing noncardiac surgery. Mayo Clin Proc. 2013;88:674–82.
99. Eckhauser AE, Melvin WV, Sharp KW. Management of general surgical problems in patients with left ventricular assist devices. Am Surg. 2006;72:158–61.
100. Garatti A, Bruschi G, Colombo T, Russo C, Milazzo F, Catena E, et al. Noncardiac surgical procedures in patient supported with long-term implantable left ventricular assist device. Am J Surg. 2009;197:710–4.
101. Roberts SM, Hovord DG, Kodavatiganti R, Sathishkumar S. Ventricular assist devices and non-cardiac surgery. BMC Anesthesiol. 2015;15:185.

How to cite this article: Hilal T, Mudd J, DeLoughery TG. Hemostatic complications associated with ventricular assist devices. *Res Pract Thromb Haemost*. 2019;3:589–598. https://doi.org/10.1002/rth2.12226