Antiplatelet and anticoagulation strategies for left ventricular assist devices

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Abstract: Left ventricular assist devices (LVAD) have revolutionized the management of advanced heart failure. However, complications rates remain high, among which hemorrhagic and thrombotic complications are the most important. Antiplatelet and anticoagulation strategies form a cornerstone of LVAD management and may directly affect LVAD complications. Concurrently, LVAD complications influence anticoagulation and anticoagulation management. A thorough understanding of device, patient, and management, including anticoagulation and antiplatelet therapies, are important in optimizing LVAD outcomes. This article provides a comprehensive state of the art review of issues related to antiplatelet and anticoagulation management in LVADs. We start with a historical overview, the epidemiology and pathophysiology of bleeding and thrombotic complications in LVADs. We then discuss platelet and anticoagulation biology followed by considerations prior to, during, and after LVAD implantation. This is followed by discussion of anticoagulation and the management of thrombotic and hemorrhagic complications. Specific problems, including management of heparin-induced thrombocytopenia, anticoagulant reversal, novel oral anticoagulants, artificial heart valves, and noncardiac surgeries are covered in detail.

Keywords: Heart failure (HF); left ventricular assist devices (LVAD); anticoagulation; antiplatelet

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Introduction

"When the blood leaves its contact with normal intima and endocardial surfaces and flows over a foreign surface of any kind, it undergoes abnormal changes, and the longer this contact continues, the more severe become the changes." These were reflections of Dr. Michael DeBakey in 1971 as he described the first left ventricular assist device (LVAD) implants in the 1960s. He concluded "Mechanical assistance for long-term support or possible total replacement of the biologic heart therefore remains unachieved insofar as a satisfactory blood interface is concerned. The blood interface is perhaps the most critical problem yet to be solved in the development of an artificial heart." (1). Since that time, advances in VAD technology now allow patients to live a near-normal life at home for years on device therapy. However, issues of biocompatibility, hemostasis and thrombosis remain central in VAD design and patient management.

Historical overview

The advent of cardiopulmonary bypass (CPB) in the 1950s paved the way for mechanical circulatory support (MCS) and artificial heart programs in the 1960s. Early LVADs were large, paracorporeal, and required patients to remain

in the hospital until transplant. A variety of antithrombotic regimens were tested.

A major change in the LVAD landscape came with the REMATCH trial where patients with advanced heart failure (HF) ineligible for transplantation treated long-term with the Heartmate Vented Electric device had 48% reduction in mortality compared to medical management. For this pulsatile device, only aspirin was required for antithrombotic therapy. Bleeding and thrombotic complications were common, including 0.56 non-neurologic bleeding events per patient year (EPPY), 0.14 EPPY for peripheral embolism, 0.46 EPPY for perioperative bleeding, 0.06 EPPY LVAD thrombosis, and 0.75 EPPY for device malfunction (2).

The next major advance occurred with the advent of continuous flow (CF) devices. These devices required systemic anticoagulation. Compared to the Heartmate XVE, the Heartmate II had higher survival free from disabling stroke or need for device replacement. Bleeding, overall stroke, and pump thrombosis rates were not significantly different (3). The current generation Heartmate 3 has shown higher survival free of disabling stroke compared to Heartmate II (4).

The scope of the problem

Despite the survival advantage of LVAD over medical, the frequency and severity of adverse events (AE) represent a limitation of this therapy (2-9) (*Table 1*). The freedom to first occurrence of major AE (including infection, device malfunction, stroke, bleeding or death) at 6 months post-implantation is approximately 40% (10). The most frequent AEs are bleeding and thromboembolism episodes (11). AEs in LVAD patients lead to recurrent hospitalizations with an estimated 218 hospital admissions per 100 patients at 1 year post-implant (12). The balance between bleeding and thrombosis is vital in the management of patients supported by LVAD and represent a challenge to advanced HF cardiologists. Patient do not typically fit a "bleeder" or "clotter" profile, but they rather move along the bleeding/thrombotic spectrum. The interplay between bleeding and thrombotic event has been clearly demonstrated, with

Table 1 Bleeding and thromboembolic complications from clinical trials of LVADs

Clinical trial	Characteristics	Adverse events related to coagulation	
		Bleeding	Thrombosis
REMATCH Trial (2) (2001), PF	Mean age 68 y/o	Non-neurologic: 0.56	Neurologic dysfunction: 0.39
	68 patients received PF LVAD	Peri-operative: 0.46	Peripheral embolism: 0.14
	1-year survival 52%		Pump thrombosis: 0.06
	OMT group 1-year survival 25%		Device Malfunction: 0.75
HM-2 BTT (5) (2007), CF-Axial	Mean age 50 y/o	Bleeding requiring surgery: 0.78	Embolic stroke: 0.13
	133 patients received CF HM-2	Bleeding requiring 2pRBC: 2.09	TIA: 0.1
	Survival at 1 year 68%	Hemorrhagic stroke: 0.05	Peripheral embolic: 0.15
			Pump thrombosis: 0.03
			Hemolysis: 0.06
HM-2 DT (3) (2009), CF-Axial	Mean age 64 y/o	Bleeding requiring surgery: 0.23	Embolic stroke: 0.06
	134 patients received HM-2	Bleeding requiring PRBC: 1.66	Total stroke: 0.13
	Survival at 2-year 58%	Hemorrhagic stroke: 0.07	Pump thrombosis: 0.02
HM-2 Post approval (6) (2011), CF-Axial	131 patients received HM-2	Bleeding: 1.44	Embolic stroke: 0.06
	Survival at 1 year 85%	Hemorrhagic stroke: 0.01	Total stroke: 0.08
			Peripheral embolism: 0.01
			Venous thromboembolic: 0.09
			Hemolysis: 0.04

Table 1 *(continued)*

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Clinical trial	Characteristics	Adverse events related to coagulation	
		Bleeding	Thrombosis
ENDURANCE TRIAL (7) (2017), HVAD *vs.* HM-2; CF (Centrifugal *vs.* Axial)	Mean age 64 y/o (HVAD)	Bleeding requiring surgery	Embolic stroke
	Mean age 66 y/o (HM-2)	HVAD: 0.13	HVAD: 0.17
	Composite endpoint 2 years	HM-2: 0.14	HM-2: 0.06
	HM-2 59%	Bleeding requiring 4U PRBC	Total stroke
	HVAD 55%	HVAD: 0.11	HVAD: 0.29
		HM-2: 0.14	HM-2: 0.09
		Gastrointestinal bleeding	Pump thrombosis
		HVAD: 0.56	HVAD: 6.4%
		HM-2: 0.98	HM-2: 10.7%
		Hemorrhagic stroke	
		HVAD: 0.11	
		HM-2: 0.03	
Post approval HM-2 (8) (2014), CF (Axial)	247 patients received HM-2	Bleeding requiring surgery: 0.09	Embolic stroke: 0.031
	Survival at 2 years 61%	Bleeding req PRBC: 0.84	Total stroke: 0.083
		Hemorrhagic stroke: 0.052	TIA: 0.08
			Pump thrombosis: 0.024
			Hemolysis: 0.06
ADVANCE TRIAL (9), HVAD BTT	Age 53 HVAD	Bleeding requiring surgery: 0.26	Embolic stroke: 0.11
	HM-2 52	Bleeding requiring >4 PRBC: 0.12	TIA: 0.08
	140 patients received HVAD	Gastrointestinal Bleeding: 0.23	Pump thrombosis: 0.03
	499 HM-2		High power events: 0.02
	Survival at 1 year		Hemolysis: 0.06
	HVAD 86%		Arterial thromboembolism: 0.06
	HM-2 85%		Venous thrombosis: 0.1
MOMENTUM-3 TRIAL (4) (2019), CF (Centrifugal *vs.* Axial)	Mean Age	Any bleeding	Total stroke
	HM-3 59 y/o (516 patients)	HM3: 0.61	HM-3: 0.08
	HM-2 60 y/o (512 patients)	HM2: 0.95	HM-2: 0.18
	Combined primary endpoint (survival free of stroke or pump exchange)	Gastrointestinal bleeding	Disabling stroke
	HM-3 76.9%	HM3: 0.31	HM-3: 0.04
	HM-2 64.8%	HM2: 0.49	HM-2: 0.07
			Pump thrombosis
			HM-3: 0.01
			HM-2: 0.12

CF, continuous flow; PF, pulsatile flow; HM-2, Heartmate II; HM-3, Heartmate 3; HVAD, Heartware HVAD; BTT, bridge to transplant; PRBC, packed red blood cells; TIA, transient ischemic attack.

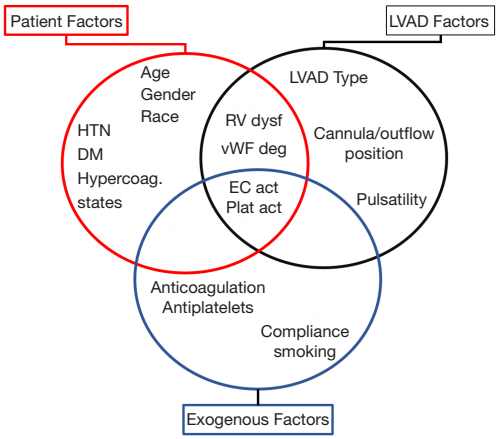

Figure 1 Interrelations between patient, LVAD and exogenous factors that lead to specific predisposition to thrombotic or bleeding events. DM, diabetes mellitus; HTN, hypertension; RV, right ventricle; vWF, von Wilebrand Factor; deg : degradation; EC act, endothelial cell activation; Plat act, platelet activation; LVAD, left ventricular assist device.

an increased risk of thromboembolic event following an episode of bleeding (13,14) or an increased risk in bleeding episode as a result of a prior thrombotic event (15-17). In addition, infections (18,19) and right ventricular failure (20,21) have also been associated with increased risk for bleeding or thromboembolic events.

Pathophysiology of bleeding and thromboembolic complications

Factors predisposing to bleeding or thrombotic events can be related to the patient, the LVAD or external factors (*Figure 1*). The interplay between these factors determines whether a patient experiences a bleeding or thrombotic episode.

LVAD-related factors

Device type is directly related to the frequency of bleeding/thrombotic events. Pulsatile LVADs had high rates of stroke, thromboembolic events, and device malfunction but no significant gastrointestinal bleeding (GIB) (2). The development of axial CF LVADs represented a significant improvement in technology, and frequency of device malfunction and thromboembolic events decreased significantly (5). However, with the loss of pulsatility the development of arteriovenous malformations (AVM) and recurrent GIB became an important problem (22). The introduction of the smaller centrifugal CF-LVAD (Heartware HVAD) broadened the utilization of LVADs, but with some concerns about increased frequency of strokes (7). The newest device, the HM3 has advantages over previous axial 2nd generation devices with a very low frequency of pump thrombosis and a decreased frequency of disabling stroke with no changes in the frequency of GIB (4). Given the lower thromboembolic events, the HM3 has shifted the pendulum, and clinicians are now focusing on lower anticoagulation and antiplatelet protocols in an effort to decrease the frequency of GIB (23,24). The variations in hemorrhagic or thrombotic events seen with different LVADs depends on multiple factors including LVAD hemocompatibility, which refers to the thrombotic response induced by the device on contact with blood. Multiple factors affect the hemocompatibility of the LVAD, including platelet activation due to shear stress (25), endothelial cell activation (26), degradation of von Willenbrand factor (27) and oxidative stress (28). LVADs differ in their ability to affect each of these parameters (29-31). In addition to LVAD itself, other parameters such as pulsatility (32) play an important role in the development of bleeding/thrombotic episodes.

Patient-dependent factors

Patient-related factors are also important in the development of hemorrhagic or thromboembolic events. Nonmodifiable factors include age, gender, and genetic polymorphisms. Advanced age is associated with increased frequency of both hemorrhagic and thrombotic events (33,34). Female gender is associated with an increased risk of stroke (35). Hypercoagulable states are associated with increased in thromboembolic neurological events and mortality (36,37). Modifiable risk factors are also important. Hypertension is associated with hemorrhagic and ischemic strokes (19,38,39). Some reports have suggested that diabetes mellitus (40) and atrial fibrillation (41) may also be associated with thromboembolic events. As mentioned earlier, infections (18,19) and right ventricular dysfunction (20,21) with increased systemic venous pressures are associated with cerebrovascular events and GIB respectively.

Exogenous factors

Other factors influencing the development of bleeding or thrombotic events relate to the intensity and strategy of anticoagulation and antiplatelet therapy. Compliance with medications, interactions with other medications or drugs

as well as the use of tobacco (19) could affect the frequency of thrombotic/bleeding effects.

The interaction of pump, patient and external factors will create a unique combination in an specific individual, which requires individualized approaches prevent bleeding/thrombotic events. For example, genetic variations are associated with differential responses to warfarin, aspirin, and clopidogrel, and identification of these patients early on could be an strategy to prevent bleeding/thromboembolic events (42).

Platelet activation, clotting cascade and antiplatelet and antithromobotic agents

Patients supported by LVADs require a combination of antiplatelet and antithrombotic agents. Physiologically the hemostatic system has a close interaction between platelets and clotting factors. Exposure of platelets to any foreign material will initiate their activation which is characterized by structural and functional changes that result in adhesion, degranulation and aggregation leading to the formation of a platelet rich plug (43). Simultaneously, the intrinsic and extrinsic pathways will be activated converging on the activation of Factor X which catalyze the formation of thrombin from prothrombin. Thrombin will promote the conversion of fibrin from fibrinogen. Thrombin can also potently activate platelets. Fibrin will stabilize the platelet plug and lead to clot formation. Shear stress is increased in LVAD supported patients which predisposed to platelet activation (25) and to Von Wilebrand factor degradation (27), leading to an increased risk for both clotting and bleeding. *Figure 2* summarizes this physiology and pharmacological targets.

Pre-implant antiplatelet and anticoagulation management

Many patients with HF require anticoagulants/antiplatelet drugs for coronary artery disease, stents, atrial fibrillation, left ventricular thrombus, or deep venous thrombus. Only a few studies inform anticoagulation or antiplatelet management prior to LVAD implantation. The 2019 EACTS consensus statement on long-term MCS suggests withdrawal of dual antiplatelet therapy and/or vitamin K antagonists and use use of short-acting intravenous anticoagulation for bridging prior to LVAD (44).

Typical antiplatelet management would be to continue aspirin until the day of surgery and discontinue ticagrelor, clopidogrel, or prasugrel 3, 5 or 7 days before surgery respectively (45-47). There is higher risk of tamponade or chest reexploration for bleeding when surgery is performed within 24 hours after clopidogrel discontinuation. After 1–4 days of discontinuation, this risk continuously diminishes, although the risk of transfusion remains high. Ticagrelor's bleeding profile is similar to clopidgrel. Prasugrel, however, carries substantial higher risk of bleeding post cardiac surgery, and should be avoided in patients who are heart transplant or LVAD candidates. In the case of recent percutaneous coronary intervention (PCI), bridging with GPIIb/IIIa inhibitors may be considered, but there could be residual risk for stent thrombosis (48-51). Eptifibatide and Tirofiban should be discontinued at least 4 hours prior surgery, longer if significant renal dysfunction is present. Cangrelor, an intravenous antiplatelet drug with half life under 5 minutes and elimination independent of renal or liver function, may also be used to bridge patients to LVAD (52).

Outpatients taking a novel oral anticoagulant (e.g., dabigatran, apixaban, rivaroxaban) should be transitioned to coumadin or bridged with heparin/enoxaparin. If the patient is on coumadin and undergoing elective LVAD, bridging with unfractionated heparin (UFH) is recommended (53). Low molecular weight heparin (LMWH) should be discontinued 12 hours prior to surgery, and fondaparinux 24 hours prior to surgery. A longer interval may be necessary for patients with impaired renal function.

For urgent/emergent cases on patients receiving warfarin, prothrombin complex concentrates (PCC) may be considered to reverse Vitamin K antagonist effect (54,55). A Cochrane systematic review on PCCs in non-LVAD cardiac operations demonstrated that PCC use does not reduce mortality or PRBC transfusion requirements but reverses vitamin K-induced coagulopathy without the need for transfusion of fresh frozen plasma (55).

LVAD implantation: intraoperative anticoagulation management

The standard approach to LVAD implantation is utilizing cardiopulmonary bypass (CPB), and UFH remains the most commonly used anticoagulant during CBP due to its short half life and existence of a reversal agent, protamine. Bolus administration of UFH based on weight is monitored by activated clotting time (ACT) target range from 400 to 500 seconds, "maximally activated level". Despite this widely accepted level of anticoagulation, there is no clear consensus on the accurate calculation of this initial dose of UFH. Options for calculating the initial heparin bolus

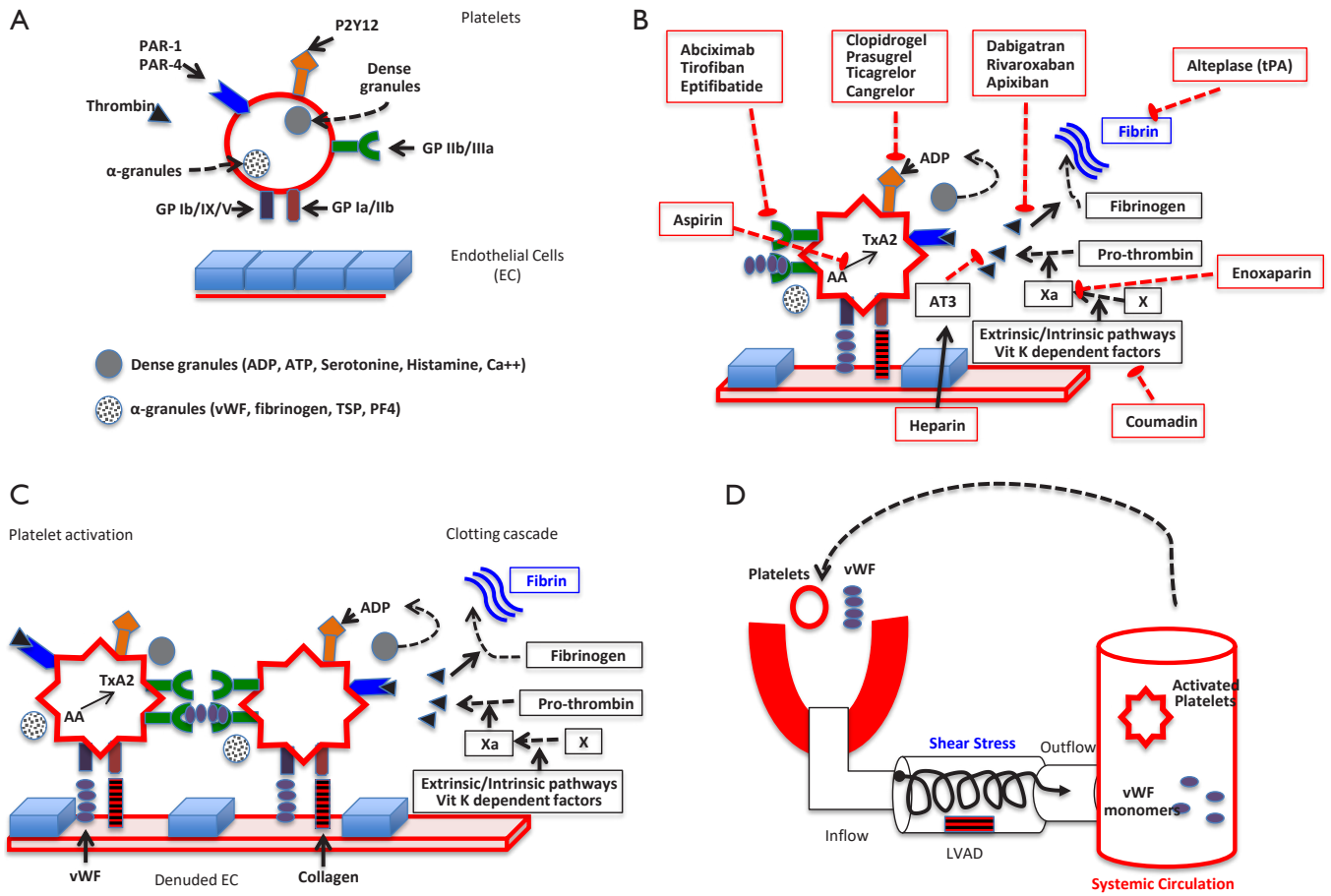

Figure 2 Platelet and Clotting cascade in LVAD patients. (A) Inactive platelets and its receptors and granules. (B) Hemostatic response to denuded endothelium. Panel depicts platelet activation (adhesion, aggregation, degranulation) and their interaction with the clotting cascade. (C) Depicts the multiple pharmacological targets to interfere with platelet function and clotting cascade. (D) Depicts the LVAD as a source of shear stress and foreign material that leads to platelet activation, vWF degradation. LVAD, left ventricular assist device; AA, arachidonic acid; ADP, adenosine diphosphate; AT3, antithrombin 3; GP, glycoprotein; LVAD, left ventricular assist device; vWF, von Willebrand factor.

include a fixed, weight-based dose, (e.g., 300 IU/kg), or use of point-of-care tests that measure the whole blood sensitivity to heparin using an associated dose response. ACT should be monitored at regular intervals during CPB. The Society of Thoracic Surgeons (STS) guideline recommends ACT above 480 seconds during CPB (56). At the end of surgery, heparin is reversed with the calculated protamine reversal dose based on a titration to existing heparin in the blood. Level of anticoagulation is measured by ACT, point-of-care testing using protamine titration of heparinized blood samples, and thromboelastography with or without heparinase. Comparisons of these three methods suggest that ACT-based measurement of residual heparin effect is the least accurate (57,58). A meta-analysis of standard weight-based versus titrated protamine dosing favors titrated dose protamine for heparin reversal because of less postoperative blood loss and decreased packed red blood cell transfusion (59). It is reasonable to limit the ratio of protamine/heparin to less than 2.6 mg protamine per 100 units heparin because total doses above this ratio inhibit platelet function, prolong ACT, and increase the risk of bleeding (60).

Management of heparin induced thrombocytopenia (HIT)

Insufficient data exists regarding the management of acute/subacute HIT prior to MCS. CPB requires full anticoagulation, and the use of heparin in the setting of

acute HIT (thrombocytopenia and positive heparin/platelet factor 4 antibody by enzyme-linked immunosorbent assay) is concerning because of the risk of thrombosis.

The 2012 College of Chest Physicians (ACCP) HIT guidelines recommend use of bivalirudin over non-heparin anticoagulants or heparin plus antiplatelet agents in patients with acute HIT (thrombocytopenic, HIT antibody positive) or subacute HIT (HIT antibody positive, normal platelets) who require urgent cardiac surgery. For patients requiring nonurgent surgery, it is recommended to wait until thrombocytopenia has resolved and HIT antibodies are negative. In patients with history of HIT but undetectable antibodies requiring cardiac surgery, brief intraoperative-only heparin challenge is recommended. In patients with history of HIT in whom antibodies are still present, nonheparin anticoagulation is recommended (61).

However, in practice, the choice of anticoagulant during CPB in patients with HIT is not well defined, with several potential strategies: delaying surgery until HIT antibodies are negative (typically ~100 days after heparin cessation), intraoperative anticoagulation with direct thrombin inhibitor (DTI) such as argatroban or bivalirudin, use of heparin and intravenous antiplatelet agents(short-acting antiplatelet therapy potentially attenuates HIT antibody-induced platelet activation), and plasmapharesis. Irreversibility of intravenous DTIs makes these agents less appealing (62-66).

A few studies have reported on plasmapharesis prior to cardiac surgery. In one single-center study of 11 patients, plasma exchange was performed with fresh-frozen plasma replacement using a 1.3 plasma volume exchange. Plasmapharesis was performed before heparinization if patient was stable, but otherwise heparin was given, CBP initiated to stabilize patient, and plasmapheresis performed during CPB. Heparin is removed during plasmapheresis so additional heparin infusion was required. After a single plasmapheresis treatment, titers were reduced by 50–85%. Six of 9 patients had negative titers after treatment, and the other three who had particularly high titers at baseline had reduced titers without clinical HIT (67)

Ramu *et al*. described a case-series of 4 patients requiring CPB with acute HIT, 2 of whom underwent heart transplantation (68). The strategy in this study involved pre-operative therapeutic plasma exchange until HIT ELISA turned negative, followed by intra-operative heparin. Post-operatively, patients were treated with non-heparin anticoagulants (bivalirudin or argatroban) bridged with warfarin. This approach successfully avoided non-heparin anticoagulants intra-operatively while preventing complications such as thrombosis and bleeding.

More evidence is required in this area to recommend one strategy over another, and HIT remains a significant perioperative management challenge.

Perioperative antiplatelet and anticoagulation management

Manufacturer guidelines exist regarding perioperative antiplatelet and anticoagulation management (*Table 2*) (69-71) but there are institutional variations.

Once UFH is started, the target anticoagulation range intially remains lower and is gradually increased during subsequent days [e.g., postoperative day 1–2 activated partial thromboplastin time (aPTT) goal of 40–60 seconds, and increase aPTT goal to 60–80 seconds on post-operative day 2–3] Anti-Xa monitoring is increasing in utility given discordance between aPTT and anti-Xa levels in LVAD patients with international normalized ratio (INR) above 1.8 (72).

Regarding antiplatelet therapy, recent clinical trials involving HVAD, HeartMate II and HeartMate 3 have recommended 81–325 mg daily aspirin (73). P2Y12 inhibitors can be considered in aspirin allergic patients. European centers that have treated patients with anticoagulation only (median INR 2.31) after HeartMate II implantation reported similar rates of bleeding and thrombotic complications compared to those treated with aspirin and anticoagulation at 2 years (74). In addition, a placebo-controlled trial of placebo or aspirin 81 mg daily after HeartMate II™ (PREVENT II) was performed in the US (36). At 6 months, the proportions of non-surgical bleeding, stroke, thromboembolic events, or ischemic or hemorrhagic strokes did not differ between placebo and ASA groups. At 12 months, more major bleeding events had occurred in the ASA compared to the placebo group but stroke remained comparable (75). The 2012 AHA Scientific Statement and 2013 ISHLT guidelines recommend both antiplatelet and anticoagulants in CF-LVADs (73,76).

Whether UFH bridging should be used after LVAD implantation has been an area of debate. Consensus guidelines recommend beginning UFH once chest tube output has decreased and gradually increasing the target to the therapeutic range (34,73). Although the field initially moved away from postoperative heparin because of reports of increased postoperative hemorrhage, the increased HeartMate II thrombosis rates led to a re-examination of

Table 2 LVAD manufacturer recommendations

	Perioperative heparin	Antiplatelet initiation	Anticoagulation Initiation	Maintenance regimen
Heartmate II (69)	If no persistent bleeding, begin bridging with unfractionated heparin or LMWH within 48 hours of device implant with a goal PTT of 40–45 sec in the first 48 hours, followed by titration up to PTT 50–60 by 96 hours	Once no evidence of bleeding, initiate ASA therapy (81–325 mg daily) 2 to 5 days post HMII implantation	Initiate warfarin within 48 hours to obtain a goal INR of 2.0–2.5 by POD 5–7, then discontinue heparin	Maintain the patient throughout LVAD support on aspirin and Coumadin with a goal INR of 2.0–2.5
Heartware (70)	Begin low-dose heparin at 10 units/kg/hr on postoperative day one to a target PTT of 40–50 seconds. Prior to initiation of anticoagulation, chest tube drainage should be less than 40 mL/hr for approximately three hours; the HCT should be stable without the need for transfusion of blood products, and coagulation factors approaching normal. Gradually increase the heparin dosage to maintain the aPTT in a range of 50–60 seconds	Aspirin should be started at a dose such as 325 mg/d within 24 hours after implant if no postoperative bleeding complications. If ASA alone chosen, check for ASA resistance is recommended to establish the dose or to select an alternative. For patients who are aspirin sensitive or intolerant, clopidogrel at doses of 75–150 mg/day (after a load of 300 mg)	Warfarin should be started within 4 days post-op and titrated to maintain an INR of 2.0 to 3.0	Maintain anticoagulation for INR range of 2.0–3.0 Daily aspirin dose should be >81 mg and platelet inhibition should be evaluated and adjust ASA mono-therapy accordingly or consider combination therapy such as ASA 81 mg plus Aggrenox (ASA plus extended-release dipyridamole) or daily ASA 81 mg plus Plavix 75 mg
Heartmate 3 (71)	Begin IV heparin after 12–24 hours or when chest tube drainage is less than 50 mL/hr over a 2–3 hours period: • Initially titrate to a PTT of 45–50 for 24 hours (1.2–1.4 times control) • After 24 hours, increase heparin and titrate to PTT 50–60 (1.4–1.7 times control) • After another 24 hours, increase heparin and titrate to PTT 55–65 (1.5–1.8 times control)	On postoperative day 2–3, initiate ASA 81–100 mg QD	On postoperative day 3–5, once there is no evidence of bleeding and the chest tubes have been removed, begin warfarin (overlapping with the heparin). Discontinue heparin after obtaining an acceptable, stable INR. The INR should be maintained in the range of 2.0–3.0	Maintain the patient throughout support on aspirin and warfarin

PT, prothrombin time; PTT, partial thromboplastin time; LMWH, low molecular weight heparin; HMII, Heartmate II; INR, international normalized ratio.

heparin bridging (77,78). Ninety-five percent of patients received UFH in the PREVENTion of HeartMate II Pump Thrombosis trial. Pump thrombosis occurred in 1.9% of patients who received heparin bridging, maintained adequate pump speeds (≥9,000 revolutions per minute) and had all surgical recommendations followed, compared with 8.9% of other patients (P<0.01) (79). Thus, heparin bridging is recommended after LVAD implantation to bridge to therapeutic vitamin K antagonist (VKA) anticoagulation.

Anticoagulation management of patient with LVAD at the time of transplant

LVAD patients undergoing transplantation require full anticoagulation reversal before transplant. Vitamin K alone is not sufficient (80). Historically, fresh-frozen plasma (FFP) and low-dose 3 factor prothrombin complex concentrates (3F-PCCs) have most commonly been used for warfarin reversal before heart transplantation. After the introduction of 4F-PCC, this agent has gained significant popularity in perioperative anticoagulant reversal. 4F-PC is derived from human plasma and contains factors II, VII, IX, X, protein C, protein S, antithrombin III, and heparin (therefore 4F-PCC contraindicated in HIT) (81). 4F-reverses anticoagulation effects of VKA faster and with smaller volumes than FFP (82,83). In a randomized study of anticoagulated patients needing urgent procedures, Goldstein *et al.* reported effective haemostasis in 78 (90%) patients in the 4F-PCC group *vs.* 61 (75%) patients in the FFP group. Rapid INR reduction (≤1.3 at 0.5 h after infusion end) occurred in 48 (55%) patients in the 4F-PCC group *vs.* eight (10%) patients in the FFP group (83). However, a 2019 retrospective study showed significantly higher risk of thromboembolic events in patients receiving 4F-PCC compared to FFP (17.7% *vs.* 2.7%, P<0.001) for urgent warfarin reversal, raising concern for use of such products in the perioperative period (84).

Consensus guidelines from the American College of Cardiology recommend the use of FFP for the immediate reversal of anticoagulation in the setting of major bleed only when 4-factor PCC is not available (80). The dose of 4F-PCC depends on the INR at the time of administration and the patient's body weight (if INR 2 to 4: 25 U/kg, INR 4 to 6: 35 U/kg, INR >6: 50 U/kg; max dose 5,000 U in patients over 100 kg), and 4F-PCC should be co-administered with vitamin K.

A recent single-center, retrospective study of 106 patients undergoing heart transplantation before and after implementation of a PCC-based preoperative warfarin reversal protocol revealed that the use of PCC decreases the need for FFP compared with the traditional approach of vitamin K and FFP (6 versus 8 units, P=0.002) (85). Of the PCC cohort, 47 received 3F-PCC and 10 received 4F-PCC. All patients receiving 4F-PCC achieved an INR <1.5 at the time of surgery, whereas 35 of 47 (74.5%) patients receiving 3F-PCC achieved this INR goal. Additionally, the study reported a significant reduction in reversal time in the 4F-PCC group compared to the 3F-PCC group (1.1±1.0 *vs.* 3.4±3.3 h, P<0.001). 4F-PCC dosing was adjusted based on initial INR and repeat INR at 15 minutes after infusion. This step-wise approach allowed use of lower doses of 4F-PCC than other studies and the FDA-labeled dose, which may be important in avoiding venous thromboembolism events.

Warfarin considerations

Maintenance of INR within therapeutic range is recommended for patients on warfarin and CF-LVADs, and time in therapeutic range (TTR) correlates with clinical outcomes (86). However, high TTR is difficult to achieve despite intense monitoring by LVAD teams, and a meta-analysis of 5 studies showed TTR of only 46.6% in CF-LVADs (87). Low TTR may contribute to bleeding and thromboembolic complications.

There are substantial institutional variations in who manages a LVAD patient's warfarin: implanting center VAD coordinator/physician, implanting center anticoagulation clinic, outside anticoagulation clinic, non-LVAD clinician. A single-center study of 55 patients reported that anticoagulation managed by clinical pharmacists using patient self-tested (PST) point-of-care (POC) INR was associated with higher TTR (44.4%*vs.* 30.6%, P=0.026) compared to usual care with no difference in bleeding or thrombotic outcomes (88). In another single-center study, 26 patients whose warfarin managed by pharmacists in the first 3 months after LVAD had significantly higher TTR than historical controls (89). Others however, have reported no difference in INRs and clinical outcomes irrespective of the type of provider managing the patient's INR (90). A centralized interdisciplinary anticoagulation management system that integrates inpatient and outpatient management and has standardized guidelines may also improve anticoagulation management (91).

The inconvenience and cost of frequent laboratory visits

for INR checks has led to adoption in some centers of PST with home POC INR machines. While generally adequate, concerns about quality control, precision, and accuracy remain. In a single-center study of 50 LVAD patients who underwent simultaneous POC and core lab INR testing found a median INR difference of 0.39 between the methods, with the POC test consistently overestimated INR, leading to concerns about inadequate anticoagulation in those with low-normal readings on POC tests (92). Another multicenter study of paired (but not simultaneous) POC and lab INR tests showed no statistically significant differences between either method, particularly when measured within 4 hours of each other (93).

Novel oral anticoagulants

Given the aforementioned issues with warfarin, there has been interest in novel oral anticoagulants (NOACs) in LVAD patients. Pollari reported a patient with recurrent GI bleeds on warfarin who was switched to apixaban without any bleeding or thromboembolic complications in the ensuing year (94). Another patient with resistance to vitamin K antagonists was treated with dabigatran without bleeding or thromboembolic complications until explant for recovery (95). A single-center study of 7 patients showed no increase in thrombotic complications and lower incidence of major bleeding with dabigatran compared with acenocoumarol (96). In contrast, a randomized controlled trial of 30 Heartware patients randomized to dabigatran or phenprocoumon was terminated early because of excess thromboembolic events (50%) in the dabigatran group (97). A single-center series of 7 patients who had "failed" warfarin therapy with TTR of 30% were switched to apixaban or rivaroxaban, with lower thromboembolic or bleeding complications on NOACs (98). Given safety concerns, NOACs are not currently recommended as primary anticoagulation in LVADs.

Pump thrombosis (PT)

LVAD PT is a major LVAD complication with substantial morbidity and is the most common reason for device replacement. The etiology is complex, with patient-related, device-related, and management-related factors (99). For the Heartmate II device, there was a substantial increase in PT during 2011–2013, which resulted in intense investigation as to the contributing factors and management strategies, with some reversal of PT rates by 2014 (100,101). A large proportion of the published literature on PT management pertains to the Heartmate II device and may not necessarily be applicable to other devices. PT risk is device dependent, and Heartmate III has a significantly more favorable PT profile than Heartmate II (1.4% *vs.* 13.9% at 2 years) (4).

Small case series have reported variable degrees of success in treating PT with augmented or alternate anticoagulation, antiplatelet therapies, and thrombolysis (11,102). Larger and aggregate studies report approximately 50% success of medical therapy in resolving PT, with similar success rates in Heartmate II and HVAD. A pooled analysis showed significant major bleeding risk of ~29% in those receiving thrombolytics and 12% in those receiving non-thrombolytics (102). In a combined analysis of data from three experienced centers, mortality at 6 months in those treated medically was 48% compared to under 20% in those treated with pump exchange or transplantation (103). Early surgical pump exchange, often performed via subcostal approach, is the definitive and gold standard therapy for PT in patients who are surgical candidates (12). For nonsurgical candidates, anticoagulant and antiplatelet therapy may be individualized, based on presenting symptoms, clinical stability, and laboratory parameters such as INR at the time of pump thrombosis.

Given the challenges of treating PT, prevention is paramount. In addition to non-modifiable patient-related factors, management-related factors, such as mean arterial pressure >90 mmHg, aspirin dose ≤81 mg daily, and INR ≤2 were risk factors for pump thrombosis in the Heartware ADVANCE study (104). In the Heartmate II PREVENT trial, adherence to recommended surgical techniques, heparin bridging after implantation, maintaining MAP <90 and INR 2–2.5, and running pump speed >9,000 was associated with a low rate of PT (79).

Bleeding complications

Among the more challenging situations in LVAD management include decisions on cessation and resumption of anticoagulation and antiplatelet therapies in patients who have had hemorrhagic complications. International guidelines provide only general recommendations (99).

Intracranial hemorrhage

Intracranial hemorrhage (ICH) is a devastating complication with 50% early mortality and substantial disability in survivors.

A few studies have examined in detail antithrombotic management strategies after ICH in LVAD patients. In a single center study of 36 patients who developed ICH while on pulsatile and CF LVADs, warfarin was withheld in 61% and aspirin was withheld in 47%. Anticoagulation was reversed with FFP in 61% and platelets were administered in 39%. No acute thromboembolic events were seen. Aspirin was resumed after a median of 6 days and warfarin resumed after a median of 10.5 days with no recurrent bleeds. Patients with subdural hemorrhage (SDH) and subarachnoid hemorrhage (SAH) had better outcomes than those with intraparenchymal hemorrhage (IPH) (105). Another single center study of 27 LVAD patients with ICH, those with IPH had a higher rate of anticoagulant (90%) and antiplatelet (50%) reversal than those with SDH or SAH. Antiplatelet resumption occurred at mean of 6 days and anticoagulation at a mean of 3.4 days in this group. No patients had LVAD thrombosis with anticoagulation reversal (106). Wong and colleagues evaluated 31 patients with ICH and demonstrated no thromboembolic events in those who received PCC. Also, patients with small bleeds (mean ICH volume 0.4 cm^3) were managed conservatively without active reversal, with no increased hemorrhage (107). In another single center study of 405 LVAD patients, ICH occurred in 39 (10%). Among these, 27 received antithrombotic reversal (PCC, Vitamin K, and/or FFP). Eight of the 27 had inadequate coagulopathy reversal (INR GE 1.4). ICH expansion or death before repeat imaging occurred in 38% of patients with inadequate coagulopathy reversal *vs.* 30% of patients with adequate coagulopathy reversal. One thrombotic event (deep venous thrombosis) occurred with reversal. Antithrombotics were resumed in all 17 survivors (12 resumed warfarin + antiplatelet, 4 resumed antiplatelet, of whom 1 crossed to the warfarin + antiplatelet group, and 2 resumed warfarin alone). The median time to resumption was 8 days for aspirin and 14 days for warfarin. There were 4 recurrent intracranial hemorrhages in the group (2 ICH (intracerebral hemorrhage), 1 SDH, 1 SAH), none of which were fatal. Three of the 4 recurrent ICH were in the aspirin + warfarin group, and two ICH occurred during heparin-warfarin bridge. There was a trend for more thrombotic events in the antiplatelet alone resumption group. The median time to ischemic stroke was 428 days after antithrombotic resumption and median time to recurrent hemorrhagic stroke was 7 days after antithrombotic resumption. The authors conclude in LVAD patients with ICH, anticoagulation reversal, preferably with PCC appears to be safe, the timing of anticoagulation resumption may need to be extended to 30 days after index event given early risk of recurrent hemorrhage, and heparin bridge should be avoided (103).

Gastrointestinal bleeding

Gastrointestinal bleeding (GIB) occurs in 12–25% of patients in the first year after LVAD (12). Rates of GIB in LVAD patients are substantially higher than in other populations on antiplatelets or anticoagulants. The pathophysiology of GIB on LVAD is multifactorial and includes acquired Von Willebrand syndrome, angiodysplasias likely related to low pulsatility, altered nitric oxide metabolism, and right ventricular (RV) dysfunction (21,108). In addition to adjustment of antiplatelet and anticoagulant agents, other management approaches with variable success include pump speed adjustment to induce pulsatility, volume, inotropes, and VAD management to treat RV dysfunction, octeotride, vWF concentrate, desmopressin, danazol, thalidomide, ACE inhibitors, and estrogen (108,109). Finally, transplantation when available is a highly effective intervention for people with recurrent GIB (110).

The 2013 ISHLT MCS guidelines provided, in the absence of adequately powered studies, several consensus (level of evidence C) recommendations for management of GIB in LVAD patients. These included cessation of anticoagulant/antiplatelet drugs until bleeding resolves in the absence of pump dysfunction, reversal of anticoagulation in the setting of elevated INR and clinically significant GIB, and resumption of antiplatelet and anticoagulation therapy after resolution of a first episode of GIB. For recurrent GIB without a source or source not amenable to treatment, it was recommended that the dose, intensity, or even the use of antiplatelet drugs or warfarin should be re-evaluated (73). The 2020 guideline update notes that reducing speed to induce pulsatility may decrease GIB risk.

Decisions regarding antiplatelet and anticoagulation management are institution-specific and generally made on an individualized basis based on severity of bleeding, endoscopic findings and risk of recurrence, history of prior GIB, and risk or history other thrombotic complications. Recurrent GIB risk remains significant despite cessation of anticoagulation or antiplatelet agents. In an important analysis of 100 patients with HM II LVAD and prior bleeding complications, reduced antithrombotic therapy with warfarin only (38%), aspirin only (28%), or no antithrombotic agents (34%) was still associated with 71 bleeding events within 1 year of reduced antithrombotic,

and the most common event was GIB (22) with comparable rates across the three antithrombotic subgroups. Importantly stroke occurred in 6% and pump thrombosis in 7% in the year after initiation of reduced antithrombotics (14).

LVAD and artificial valves

Patients with aortic and mitral valve disease or prior valve replacements may develop advanced HF requiring LVAD therapy. Limited experience suggests that for pre-existing bioprosthetic or mechanical mitral valves, no surgical modification is required (111). Heparin should be started early, as soon as no significant postoperative bleeding is observed. Aspirin should INR target should be 2.5–3.5 for patients with mechanical mitral valve and current generation CF LVADs. Pre-existing mitral regurgitation usually requires no therapy and generally expected to improve after LVAD, although this is increasingly being recognized as a complicated matter, with intense ongoing investigation (112).

Aortic insufficiency impairs LVAD function. For pre-existing aortic insufficiency, valve oversewing, leaflet repair, or bioprosthetic aortic valve replacement is recommended. Mechanical aortic valves risk valve and root thrombus and should not be implanted. Patients with pre-existing mechanical aortic valves may be treated with patch closure or replacement with a bioprosthetic aortic valve.

LVAD and noncardiac surgery

Patients on LVAD therapy may require non-cardiac surgery, which can usually be safely performed, but there are unique antiplatelet or anticoagulant considerations. The nature of surgical intervention being performed (e.g., neurosurgical *vs.* endoscopic or dermatologic) as well as patient's individual bleeding and thrombotic history influence the management strategy. For elective surgeries, active reversal (e.g., Vitamin K, PCC, FFP, platelet transfusions) is generally not performed, but passive reversal, often combined with a heparin or enoxaparin bridge is a common approach (113). For urgent or emergent procedures, the nature of the surgical problems, anticipated surgery, and pre-existing bleeding and thrombotic profile dictate the most appropriate approach and is best done collaboratively with the surgeon and the LVAD team.

Conclusion

Bleeding and thromboembolism are key complications of LVADs. A thorough understanding of device, patient, and management, including anticoagulation and antiplatelet therapies are important in optimizing VAD outcomes.

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Footnote

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