CONSENSUS STATEMENT

AN ISHLT CONSENSUS STATEMENT ON STRATEGIES TO PREVENT AND MANAGE HEMOCOMPATIBILITY RELATED ADVERSE EVENTS IN PATIENTS WITH A DURABLE, CONTINUOUS-FLOW VENTRICULAR ASSIST DEVICE

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Life expectancy of patients with a durable, continuous-flow left ventricular assist device (CF-LVAD) continues to increase. Despite significant improvements in the delivery of care for patients with these devices, hemocompatability-related adverse events (HRAEs) are still a concern and contribute to significant morbility and mortality when they occur. As such, dissemination of current best evidence and practices is of critical importance. This ISHLT Consensus Statement is a summative assessment of the current literature on prevention and management of HRAEs through optimal management of oral anticoagulant and antiplatelet medications, parenteral anticoagulant medications, management of patients at high risk for HRAEs and those experiencing thrombotic or

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bleeding events, and device management outside of antithrombotic medications. This document is intended to assist clinicians caring for patients with a CF-LVAD provide the best care possible with respect to prevention and management of these events.
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KEYWORDS:
hemocompatibility; continuous-flow ventricular assist device; thrombosis; hemorrhage; vitamin K antagonists; antiplatelet medications; anticoagulation

Durable, continuous-flow left ventricular assist devices (CF-LVADs) have become a mainstay in the care of patients with American College of Cardiology Stage D heart failure. Per a recent Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) report (2022), 81% of CF-LVAD patients are designated as long-term therapy, with > 90% receiving a CF-LVAD with full magnetic levitation in the year 2021.[1] Life expectancy while on support continues to increase, with current survival at > 80% at 1 year and > 50% at 5 years. The increasing number of patients with a CF-LVAD who are living for long periods of time increases the importance of the prevention of thrombotic and bleeding (i.e., hemocompatibility) events (HRAEs). Despite incremental improvement in the rates of bleeding and thrombosis over the past 15–20 years of device experience, these HRAEs continue to afflict durable CF-LVAD recipients. Adverse events like gastrointestinal bleeding (GIB), hemolysis, and thrombotic events—such as pump thrombosis and stroke—still extend beyond the peri-operative period and contribute to significant morbidity. For this reason, knowledge of current best evidence and practices in the prevention and management of HRAEs is increasingly crucial to the longitudinal management of CF-LVAD patients.

METHODS

This consensus document was developed in accordance with the International Society of Heart and Lung Transplantation (ISHLT) Standards and Guidelines committee document development policies. The consensus committee members were selected to represent the diversity and multidisciplinary nature of the society and were approved by the ISHLT Standards and Guidelines committee. Each member contributed to the literature searches, developed content, reviewed the final consensus statements, and approved the final manuscript.

The writing group reviewed all peer-reviewed publications pertaining to strategies to prevent HRAEs (i.e., management of antithrombotic therapies, device management, surgical issues, etc.) in patients with a HM2 and HM3 CF-LVAD (Abbott, Chicago, IL) and the HeartWare HVAD System (Medtronic, Minneapolis, MN), as these devices comprise the majority of CF-LVADs placed during the past 15 years. This document was written as a summative assessment of the current literature with accompanying expert opinion, rather than guidelines written with specific levels of evidence. This document is intended to assist physicians, surgeons, pharmacists, nurses, and other providers who manage these patients.

Coagulation effects of continuous flow left ventricular assist devices

The current generation of CF-LVADs are rotary pumps that use electromagnetic and mechanical forces to pump blood into the aorta. These rotary pumps cause damage to the blood cells and lead to hemolysis due to the shear stress.[2] The factors to be considered in this process are rotor speed, exposure time, surface texture, blood viscosity, flow patterns, preload, and afterload.

In contrast to healthy endothelium that resists thrombosis, artificial surfaces—like that of the device—promote clotting.[3] This complex series of interconnected processes include protein adsorption, adhesion of platelets, leukocytes, and red blood cells, thrombin generation, and complement activation. Fibrinogen is a plasma protein that initially deposits on artificial surfaces, including the CF-LVAD surface. Other adhesive proteins, including fibronectin and von Willebrand factor (vWF), also bind to the surface and together with fibrinogen mediate platelet adhesion. Though CF-LVADs are made of hemocompatible biomaterials like titanium alloy products that are relatively inert and prevent platelet adhesion, they are not completely resistant to thrombosis.[4] The adsorbed proteins also mediate the attachment of cells

like platelets, leukocytes, and red blood cells to artificial surfaces. The adherent platelets become activated, further amplifying adhesion to pro-thrombotic proteins, aggregation on the artificial surface, and platelet thrombus formation.

In addition, the shear forces and the continuous blood flow also activate platelets.[5] The activation of platelets involves a complex interaction of protein receptors, leukocytes, endothelial proteins, glycoproteins, microparticles, interleukin and adhesion molecules.[6,7] The exposure of plasma proteins, fibrinogen, and vWF to the surface of the metallic pump may result in platelet adhesions.[8,9] The leukocytes and endothelial cells release microparticles that trigger vascular inflammation that further amplifies coagulation.[10] Lastly, the complement system is also activated after blood encounters artificial surfaces, which further escalates thrombin generation. Given the activated platelet function and the coagulation activation in patients with durable CF-LVAD therapy, long-term anti-thrombotic therapy is warranted to prevent adverse events.

ORAL ANTICOAGULANTS

Chronic oral anticoagulants

Vitamin K antagonists

Vitamin K antagonists (VKA) have been and continue to be the mainstay of thrombotic prophylaxis in CF-LVAD patients since the first dischargeable devices were utilized decades ago. The 4-hydroxycoumarins are the primary anticoagulants used worldwide and include warfarin, dicumarol, phenprocoumon, and acenocoumarol. For the purpose of this document, this class of medications will be referred to generically as VKAs.

Despite the known limitations of these medications—include variable dose response as well as significant drug and dietary interactions—nearly all contemporary CF-LVAD patients will require a VKA.

International normalized ratio (INR) targets

Anticoagulation management strategies in CF-LVAD have historically been highly variable depending upon center practices. In a large retrospective, single center analysis of 249 patients implanted with either a HM2 or HVAD device, sub- or supra-therapeutic International Normalized Ratio (INR) values were associated with adverse clinical outcomes.[11] In this series, INRs < 1.5 had a high rate of thrombotic events, defined as pump thrombosis and ischemic stroke (0.4 events per patient-year). Conversely, INR values > 3.5 were associated with a high rate of hemorrhagic events (1.4 events per patient-year). The authors concluded that the optimal INR was 2.6, with a goal range of 2.0–3.2. Data analyzed from the HVAD ENDURANCE trial further elucidates the impact of INR on adverse events after CF-LVAD implant. In an analysis of stroke after CF-LVAD implantation, investigators found that INR < 2.0 was associated with ischemic events.[12]

The HM3 also has a provision for an alternative INR range of 1.7–2.3, which may be considered in patients with concern for bleeding.[13] This recommendation stems from a pilot study evaluating the feasibility of low-intensity anticoagulation in HM3 devices (MAGENTUM-1) 6 weeks after implantation.[14] Fifteen patients were treated with an initial INR goal of 2–3 for 6 weeks followed with an INR goal of 1.5–1.9 for 6 months after implantation with no hemolysis events reported. One patient had a suspected gastrointestinal bleeding event. This is a promising examination of lowered anticoagulation targets without an increase in hemocompatibility related adverse events (HRAEs) in this patient population.

Based upon available data and manufacturer recommendations[13,15] an INR goal of 2.0–3.0 appears appropriate for most durable CF-LVAD patients with caveats for intensifying or lowering INR goals in patients that develop HRAEs related to their devices and anticoagulation therapy.

Time in therapeutic range

While much of the literature surrounding routine anticoagulation in durable CF-LVAD patients has been focused on INR goals, a more important measure of anticoagulation effectiveness is time in therapeutic range (TTR). In published literature evaluating warfarin therapy in atrial fibrillation, the reported TTR is 55–64%.[16,17] However, data from the CF-LVAD population suggests that TTR is much less, usually around 46%.[18] The optimal TTR in the CF-LVAD population is unknown; however, it stands to reason that a higher TTR should result in fewer HRAEs. Prior research has identified that increased age and distance from clinic are positively associated with TTR, whereas female sex, type II diabetes, and prior warfarin use are negatively associated with TTR.[19]

In an evaluation of TTR that compared usual care (UC; $n = 44$) to patient self-testing (PST; $n = 11$) with pharmacist management, TTR was significantly higher in the PST group compared to UC (44% vs 31%, $p = 0.026$).[20] Clinical outcomes were not statistically different between groups; however, the PST group is quite small in this analysis. Another center retrospectively analyzed their durable CF-LVAD patient population ($n = 51$) for overall TTR, as well as TTR surrounding clinical events. The overall TTR was 52%, and patients that suffered a bleeding event were more likely to spend a higher amount of time with supra-therapeutic INRs (41 vs 17%; $p = 0.007$).[21]

TTR was evaluated retrospectively in both HVAD and HM2 patients ($n = 30$) during periods of thrombus and thrombus-free intervals.[22] In the month preceding a thrombotic event, the TTR for INR goals 2–3 was 11.4% lower than during the control period (47.7% vs 59.1%; $p = 0.029$). The MAGENTUM-3 trial also measured TTR, noting a high number of INRs within the augmented INR target of 1.5–1.9 (mean TTR 75.3 +/– 9%).[14]

Based upon available data, there appears to be an association with poorly controlled VKA therapy (as measured by TTR) and adverse clinical outcomes. A case series described a multidisciplinary effort to improve TTR in durable CF-LVAD patients.[23] The initiative consisted of several process changes, including standardized INR goals and integration of a clinical pharmacist as a consultant to the care team. Mean TTR improved from 29.7 ± 11% to 60 ± 21.4% ($p < 0.0001$). Rates of HRAE were not different between pre- and post-implementation groups.

Home self-testing, or point-of-care testing (POCT), has been shown to increase the likelihood of therapeutic INR values in CF-LVAD recipients.[24] In an analysis of 48 patients (50% HVAD, 16.7% HM2, 33.3% HM3) those tested daily had a higher percentage of therapeutic INRs compared to patients tested thrice weekly (73.5% vs 68.4%; $p = 0.006$). Patients with high TTR (> 70%) had a higher freedom from neurologic events and hemorrhagic strokes. Another single center analysis of home self-testing in CF-LVAD patients ($n = 15$) resulted in a mean TTR of 78.1 ± 14.3%.[25] While home self-testing is a tool that can aid in improving anticoagulation metrics, the challenge lies in the ability of providers to manage an increase in INR readings and insurance coverage for frequent testing.

Direct oral anticoagulants

The only completed trial to date that has tested a direct oral anticoagulant (DOAC) in patients with a mechanical heart valve showed that dabigatran was associated with an excess of thromboembolic and bleeding events compared with warfarin.[26] As a result, VKAs remain the standard of care in those patients, as well as patients with atrial fibrillation and concomitant moderate-to-severe mitral stenosis. For this reason, there has been hesitancy to use DOACs in CF-LVAD patients.

Dabigatran use was investigated in 7 HM2 LVAD patients who had significant bleeding events while on warfarin. Its use was found to be safe and effective in that cohort, without an increase in pump thrombosis, but with significantly lower rates of major bleeding.[27] More recently, in a single center retrospective study of 7 patients supported by either a HM2 or HVAD who were switched to apixaban or rivaroxaban after warfarin failure, there was no reported increased risk of pump thrombosis or bleeding complications in the Factor Xa inhibitor group compared to the warfarin group.[28] The most robust analysis for DOACs in the durable CF-LVAD setting comes from a pilot study randomizing 30 HVAD patients to dabigatran vs VKA. This study was terminated early due to increased thromboembolic events in the dabigatran group, which was almost certainly due to the inadequate doses of dabigatran used in this analysis.[29] Recently, there was a retrospective analysis that compared apixaban ($n = 15$) and warfarin ($n = 20$) in HM3 patients. At 6 months, thrombotic complications and death were not different between the groups, while the apixaban group had clinically lower rates of bleeding complications (5% vs 30%).[30]

While the limited evidence is too scant to recommend DOACs for durable CF-LVAD patients at this time, the therapeutic advantages of these agents highlight the need for large prospective studies of DOAC use in HM3 recipients. Fortunately, there is an ongoing randomized trial comparing the hemocompatibility of warfarin to apixaban in HM3 patients.[31]

Oral anticoagulants in pediatric patients

While DOACs are gaining increasing interest for CF-LVAD anticoagulation in adults, organized data in pediatric patients does not yet exist. There are anecdotal reports of apixaban use in pediatric HM3 patients, but no publication of these results to date.

Key points

- Vitamin K Antagonists (VKAs) remain the oral anticoagulant of choice for patients with a durable CF-LVAD.
- The most commonly utilized initial INR goal is 2-3 for patients with a HM2, HeartWare HVAD, or HM3 CF-LVAD.

- INR goals may need to be adjusted in response to bleeding or thrombotic events that occur while on device support.
- Time in therapeutic INR range (TTR) appears to be lower in patients with a CF-LVAD and has been associated with bleeding and thrombotic events. Efforts to improve TTR (such as identification of risk factors for low TTR, home self-testing, and multidisciplinary management strategies) are encouraged.
- Given the ongoing uncertainty regarding safety and efficacy of DOACs, their use is very infrequent in CF-LVAD patients at this time.

ORAL ANTIPLATELET MEDICATIONS

Measured effects of CF-LVAD on platelet activation

Early studies of patients with CF-LVAD support resulted in elevations in several markers of platelet activation. In one study of 2 CF-LVAD patients, CD62 and CD63 levels were increased up to 30% compared to pre-operative levels. However, these patients were also noted to have decreased thrombin-induced platelet response. It was theorized that the use of aspirin and unfractionated heparin during CF-LVAD support resulted in this decline in thrombin-induced platelet binding.[32] Elevated levels of CD62 and CD63 in CF-LVAD patients promote the formation of platelet monocyte complexes which may further increase platelet adhesion and thrombus formation.[33] However, more recent studies of both axial flow and centrifugal flow pumps showed no significant change in either platelet count or platelet activation. Evaluation of first-generation axial flow CF-LVADs also failed to show elevated circulating activated platelets.[34] Additionally, comparison of different centrifugal flow LVADs demonstrated similar levels of P-selectin, GPIIb/IIIa and monocyte platelet aggregates, indicating equivalent levels of platelet activation.[35]

All CF-LVADs have been shown to induce acquired von Willebrand syndrome (AvWS) which likely has a significant role in non-surgical bleeding.[36–38] Current data demonstrates less impact on the high molecular weight multimers (HMWM) (the more active form of von Willebrand Factor [vWF]) with centrifugal flow compared to axial flow LVADs.[39] Comparison of various CF-LVADs have noted differences in the size of vWF multimers formed, level of vWF activity, and the level of coagulation factor VIII (FVIII) activity, though the data are not consistent and therefore offer limited insight into the hemocompatibility variability between devices.[38,40]

Platelet function testing in CF-LVAD patients

There are a number of point-of-care and laboratory-based assays for evaluating platelet function.[41] Light transmission aggregometry has been used to assess whether or not the HM2 LVAD influenced basal platelet activity. In a small study of 24 prospectively enrolled patients, these investigators found that while acquired von Willebrand deficiency was common, platelet function was only slightly diminished compared with normal controls.[42]

The assessment of aspirin hyporesponsiveness or resistance via platelet function testing has also been studied in CF-LVAD cohorts. In a retrospective review of platelet responsiveness to aspirin of 85 HM2 patients by use of the VerifyNow Aspirin test, 19 (22%) were found to be non-responsive (aspirin responsiveness units > 550). Non-responders had aspirin doses incrementally increased early after CF-LVAD placement until responsiveness was achieved. Using this strategy, freedom from bleeding and suspected/confirmed pump thrombosis were not different between the patients based on aspirin responsiveness.[43]

While some have proposed clinical algorithms to titrate antiplatelet therapies based upon platelet function testing,[42] none have been validated prospectively in large samples.

Key points

- No single marker of platelet activity has been correlated with adverse events in CF-LVAD, thus none are routinely utilized in patient management at this time.
- Aspirin resistance has been documented in patients with a CF-LVAD, although its clinical significance is uncertain.

ANTIPLATELET AGENTS

Aspirin

Dose range data

HeartMate 2

In a single-center, retrospective study of HM2 patients who received aspirin 81 mg daily (low dose, $n = 18$) or 325 mg daily (high dose, $n = 70$), high dose aspirin patients had an adjusted hazard ratio of 3.4 (95% CI 1.2–9.5) for hemorrhagic events compared to low dose aspirin ($p = 0.02$).[44] Specifically, GI bleed (37% vs 17%), epistaxis (11% vs 6%), and intracranial hemorrhage (7% vs 0%) occurred more in the high dose group. Survival free from hemorrhagic events at 1 year was 46% vs 78% for aspirin 325 mg vs 81 mg, respectively ($p = 0.004$). Overall thrombotic events were the same between groups (HR 1.9 [95% CI 0.2–15.7]; $p = 0.54$); only patients receiving 325 mg of aspirin experienced pump thrombosis events (6%). While an aspirin dose of 81–325 mg daily is recommended by the manufacturer for patients with a HM2 device, it is unclear that doses at the higher end of this range are more beneficial.[13]

HVAD

In post-hoc analyses of the ADVANCE and HVAD CAP trials, aspirin dose ≤81 mg was found to be a risk factor for pump thrombosis (odds ratio 2.28)[45] and ischemic CVA (hazard ratio 6.8).[46] Somewhat counterintuitively, low dose aspirin was also a risk factor for hemorrhagic stroke, potentially the consequence of ischemic CVAs that underwent hemorrhagic transformation.

More recently, a single-center, retrospective analysis grouped HVAD patients by having received "per protocol" aspirin (PP; 162 mg or 325 mg) or "dose reduced" aspirin (DR; 81 mg or 0 mg). Of the 66 patients who survived the implant hospitalization, the composite endpoint of pump thrombosis or ischemic stroke occurred more frequently in the DR group (8 events [29%] vs 2 events [5%], HR 4.9, 95% CI 1–23; $p = 0.045$). Patients alive at 1 year ($n = 50$) had similar composite endpoint findings (HR 9.6, 95% CI 1.2–7.9; $p = 0.037$), driven by a higher incidence of ischemic CVA (22% vs 0%, $p < 0.05$).[47]

Manufacturer recommendations are to utilize an aspirin dose of > 81 mg/day in HVAD patients, and the above summarized data would support this recommendation.[15]

HeartMate 3

The effect of aspirin dose on HRAEs in HM3 patients was assessed in a post-hoc analysis of the MOMENTUM 3 study.[48] Patients who received 81 mg aspirin (low dose, $n = 180$) were compared to high dose patients who received 325 mg ($n = 141$). No differences were found in survival free of hemorrhagic or thrombotic adverse events including any specific subtype of HRAE. Survival was also similar between groups. In view of this data and known bleeding risk with all durable CF-LVADs, if used, an aspirin dose of 81–100 mg should be sufficient for HM3 patients. The ARIES-HM3 trial (discussed below) calls into question the routine use of any dose of ASA in patients with a HM3 CF-LVAD.

Antiplatelet agents in pediatric CF-LVAD patients

Data on the role aspirin use in the pediatric LVAD population remains very limited. The EXCOR Pediatric VAD Investigational Device Exemption (IDE) study enrolled 68 children implanted in North America. Timing of initiation and dose of aspirin varied by patient age and was determined using the Edmonton Anticoagulation and Platelet Inhibition Protocol. Antiplatelet therapy was generally initiated at 48 hours post-EXCOR VAD implant and after initiation of heparin. Specifically, aspirin was started after chest tube removal at a dose of 1 mg/kg/day divided twice daily with dose adjustment according to thromboelastography (TEG) assay and platelet mapping parameters.[49] The antiplatelet regimen for the HM3 population in the ACTION trial included only aspirin, although the dose was not specified.[50]

Key points

- In patients with a HM2 CF-LVAD, evidence suggests low dose aspirin (81-100 mg) may reduce bleeding events compared to higher dose aspirin (325 mg) without increasing thrombotic complications.
- In patients with a HVAD, several post-hoc and retrospective studies suggest aspirin doses of ≤81 mg are associated with increased rates of pump thrombosis and ischemic stroke. Therefore, doses > 81 mg/day are preferred.

- In patients with a HM3 CF-LVAD, prospective, randomized, controlled trial data indicates that use of aspirin confers no benefit in reduction of thrombotic events and significantly increases the risk of bleeding. The routine use of aspirin is likely to diminish significantly moving forward.
- There is no evidence of a difference in HRAEs between HM3 patients receiving low (i.e., 81 mg) and high (325 mg) dose aspirin; thus, if aspirin is prescribed, lower doses within this range should be utilized.
- In pediatric CF-LVAD patients, aspirin initiation and dosage vary by age, device, and institutional practices. Aspirin use is reasonable in this setting, however the independent impact of its use on HRAEs has not been determined.

P2Y12 inhibitors

Gallo et al. conducted a single center study on antiplatelet therapy management after thrombotic and hemorrhagic events in patients supported with CF-LVAD.[51] The study included 231 patients with 161 (70%) supported with HM2 and 70 (30%) supported with HVAD. Hemorrhagic and thrombotic events were reported for 3 groups: (A) ASA 325 mg ($n = 115$), (B) ASA 81 mg ($n = 82$), (C) DAPT with ASA 81 mg and P2Y12 inhibitor (clopidogrel 75 mg) once daily ($n = 34$). Patients with thrombotic complications were switched to DAPT ($n = 34$) or continued ASA 325 mg ($n = 11$). The indications for DAPT were coronary stent placement (2.5%), pump thrombosis (15%) and ischemic stroke (2%). Most of the patients who were switched to DAPT were supported with HM2. The addition of second antiplatelet agent decreased thrombotic events without increasing bleeding events in this study.

P2Y12 inhibitors in pediatric patients

Data on the safety of dual antiplatelet therapy with P2Y12 inhibitors in children with CF-LVADS is lacking; use varies by centers.

Key points

- Dual antiplatelet therapy (DAPT) with aspirin and either clopidogrel, prasugrel, or ticagrelor is not routinely indicated in CF-LVAD patients unless there is markedly increased thrombotic risk, prior history of pump thrombosis or very recent coronary revascularization.
- The choice of, and indication for second antiplatelet agent in addition to aspirin may be based on individual center experience, preference and/or protocol.
- There are no structured analyses of the use of clopidogrel, prasugrel, or ticagrelor in addition to aspirin in pediatric patients with a CF-LVAD, thus no conclusions can be drawn with respect to the safety and efficacy of DAPT at this time.

Empirically withholding aspirin

HeartMate 2

In HM2 patients, warfarin monotherapy has been associated with similar rates of thrombotic complications (6% incidence of both pump thrombosis and ischemic stroke) and with less bleeding (19% overall bleeding, 4% hemorrhagic stroke) when compared to warfarin plus aspirin.[52] In another small ($n = 76$ patients) single center retrospective study of HM2 patients, the use of warfarin monotherapy was not associated with an increased risk of composite outcome of death, bleeding events, and thrombotic events (53% vs 59%, respectively, $p = 0.64$).[53] Similarly, no significant difference in bleeding events (34% vs 43%, respectively, $p = 0.48$) nor any thrombotic events (9% vs 11%, respectively, $p = 1.00$) were noted with warfarin alone compared with warfarin and ASA. In an as-treated analysis of the PREVENT II trial of HM2 patients receiving warfarin and either ASA ($n = 34$) or placebo ($n = 31$) started within 48 hours of implant, no significant differences in non-surgical bleeding (placebo: 38 [95% CI: 21.6–55.9]; ASA: 44 [95% CI: 27.4–60.8]) and thromboembolic events (placebo: 12.9 [95% CI: 1.1–24.7]; ASA: 8.8 [95% CI: 0.0–18.4]) were seen at 6 months. These results, however, should be interpreted with caution owing to an early termination of this study due to futility of enrollment because of other ongoing clinical trials.[54]

HeartMate 3

In a single-center analysis, 43 HM3 patients were placed on warfarin and aspirin (81 mg) within 7 days of implant and later converted to warfarin monotherapy after either a bleeding event occurred or 3 months had passed, whichever occurred first.[55] One year event-free survival was significantly better on warfarin monotherapy than with the combination of aspirin and warfarin (97% vs 65%, $p = 0.018$). During the study period no pump thrombosis or ischemic strokes occurred in the warfarin monotherapy group and there was no significant difference in median lactate dehydrogenase levels for the 3 consecutive months before and after discontinuation of aspirin. In a multicenter, retrospective observational study 7 HM3 patients were discharged from index hospitalization on warfarin alone due to early bleeding events or high risk of bleed (HAS BLED score ≥ 4). When compared with 23 patients discharged on warfarin and aspirin over a median follow-up period of 645 days, this small group of patients suffered significantly less bleeding events (0%) than those in the aspirin group (39%). No thrombotic events occurred in either group.[56] Another small ($n = 81$), retrospective, single-center study comparing warfarin alone to warfarin plus aspirin after HM3 placement demonstrated no increase in overall HRAEs and a reduction in the secondary endpoint of bleeding in the warfarin alone group.[57]

Given the significant interest in the risk vs benefit of aspirin in HM3 patients, the Antiplatelet Removal and Hemocompatibility Events With the HM3 Pump IDE (ARIES-HM3) Study was conducted. Six hundred and twenty-eight patients immediately-post HM3 LVAD placement at 51 hospitals around the world were randomized to receive VKA (goal INR 2–3) and either ASA 100 mg PO daily or placebo. The primary composite endpoint of survival free of non-surgical (> 14 days after implant) major HRAEs occurred in 68.1% of patients receiving ASA and 74.2% of those receiving placebo at 12 months, which met pre-defined criteria for non-inferiority of the placebo treatment. The probability of a non-surgical bleeding event at 24 months was 30% in the placebo group and 42.4% in the ASA group (HR 0.67, 95% CI, 0.50–0.92, $p = 0.01$). There was no difference in the rate of thrombotic events between groups and no documented instances of pump thrombosis in either arm despite enrollment of patients with significant thrombotic risk factors such as concomitant atrial fibrillation, DM, and/or history of vascular events. Patients assigned to placebo were hospitalized for 47% fewer days over the duration of the study than those who received ASA, resulting in a 41% reduction in the cost of caring for bleeding episodes. This study challenges current guideline recommendations favoring the use of ASA in patients with a HM3 LVAD; as such, the use of ASA in this setting will likely decrease significantly moving forward.[58]

Withholding of antiplatelet agents in pediatric patients

Data on the safety of aspirin discontinuation in children with CF-LVADS is lacking and varies by centers.

Key points

- Empiric warfarin monotherapy may be considered in carefully selected HM2 patients with perceived low thrombotic and/or high bleeding risk.
- Discontinuation of aspirin may be considered in HM2 patients who experience bleeding events while on device support.
- The use of aspirin after HM3 LVAD has not been proven to be beneficial in preventing thrombotic events and is associated with increased risk of bleeding.

PARENTERAL ANTICOAGULANT MEDICATIONS

Post-operative bridging to therapeutic INR

Unfractionated heparin (UFH)

Early experience with UFH bridging compared to no-bridging in the immediate post-operative period demonstrated that thrombotic events were exceedingly low regardless of strategy chosen, but bleed rates were significantly higher in patients who received fully therapeutic UFH.[59] The general consensus for UFH titration is APTT 40–60 seconds in patients < 48 hours post-operatively, and APTT 60–80 seconds after 48 hours post-operatively.[60–62] Device manufacturers have specific recommendations for commencement and up-titration of UFH.[13,15]

Low-molecular weight heparin (LMWH)

Studies comparing LMWH to UFH following CF-LVAD insertion have demonstrated that LMWH had no significant differences in thrombotic complications or short-term mortality, a non-significant trend towards lower bleeding and a significant reduction in post-operative length of stay.[63] However, half-life prolongation in renal impairment, lack of a complete reversal agent, and being more challenging to titrate than UFH may make LMWH less preferable than UFH in postoperative bridging.

It has been suggested that LMWH should start within 48 hours of surgery, although may be delayed up to postoperative day 4 due to severe bleeding or awaiting decannulation of additional mechanical circulatory support.[64] Conservative initial doses of LMWH are recommended, such as 0.5 mg/kg subcutaneous (SC) enoxaparin twice daily or 60 units/kg SC dalteparin twice daily, targeting an anti-Xa 0.2–0.4 units/ml at 4 hours post-dose. Clinical discretion should guide dose reduction in patients with impaired renal function or at higher risk of bleeding.

Bivalirudin

Retrospective data indicates that post-operative bridging with the direct thrombin inhibitor bivalirudin does not differ in thrombotic or bleeding complications when compared to a no-bridging strategy,[65] but may increase overall bleeding rates when compared to UFH.[66] Internationally, bivalirudin dosing strategies vary widely, and are often adjusted at clinician's discretion for bleeding, additional extracorporeal support, and renal impairment with or without renal replacement therapy. An initial rate of 0.3 mg/kg/hour (5 mcg/kg/min) without bolus dosing, targeting APTT 70–100 seconds or activated clotting time (ACT) 180–220 seconds, appears to demonstrate adequate anticoagulation without statistically significant differences in short-term outcomes, when compared to UFH.[67]

Argatroban

Data for immediate postoperative bridging using the direct thrombin inhibitor argatroban following CF-LVAD insertion is limited. The recommended initial dose is 2 mcg/kg/min. However, a more conservative initial dose of 0.5–1.0 mcg/kg/min targeting APTT of 45–90 seconds, depending on the risk of bleeding and/or presence of cardiac, hepatic or other organ dysfunction, has demonstrated adequate anticoagulation without significantly increased bleeding risk in post-operative CF-LVAD patients.[68–70] A more recent case series using low-dose argatroban (0.2–0.42 mcg/kg/min) further demonstrated adequate anticoagulation without increased risk of bleeding in patients being bridged post-operatively following CF-LVAD insertion.[71] Careful consideration needs to be given to dosing and monitoring of argatroban, as there is currently no specific reversal agent and no effective clearance via renal replacement therapy.[68] Table 1 summarizes the bleeding and thrombotic events associated with the use of DTIs as immediate post-operative bridging agents.

Post-operative bridging in pediatric patients

Much of the available pediatric bridging experience comes from the use of the Berlin Heart Excor (BHE), the only pediatric-specific FDA-approved device. Use of the BHE has been associated with high bleeding and thrombotic complications (up to 30%).[49,72–74] One protocol recommended UFH infusion initiated on postoperative day 1 or 2, without a bolus, targeting anti-Xa concentrations 0.35–0.5 units/ml (corresponding APTT = 1.5–2.5 times the patient-specific baseline value) and a thromboelastography (TEG) R-time of 8–15 minutes as long as there is no bleeding and platelets are > 20,000/mm.[3,73]

The Advanced Cardiac Therapies Improving Outcomes Network (ACTION) group developed a protocol using bivalirudin for managing BHE based on clinical experience and expert opinion of ACTION member sites, acknowledging the limited data for bivalirudin in pediatric patients. This protocol recommends bivalirudin initiation if bleeding < 2 mL/kg/hour x 4 hours, APTT within 15 seonds of baseline or institutional normal values, INR < 1.3, fibrinogen > 200 and platelets > 100,000. The dosing is higher than the reported dosing for thrombosis treatment, with the initial rate being 0.3 mg/kg/hour (adjusted for renal insufficiency). APTT target is 50–60 seconds in the first 72 hours, then 60–80 seconds for standard risk and 70–90 seconds for patients at high risk of thrombosis.[75] A post-approval surveillance outcome study from the ACTION registry showed bivalirudin as the primary anticoagulant in 92% of patients, and stroke incidence decreased by 44% compared to the original BHE study.[76]

Table 1 Bleeding and Thromboembolic (TE) Outcomes Associated with Post-Operative Direct Thrombin Inhibitor Bridging Following CF-LVAD Insertion

Direct thrombin inhibitor	Study	Study type	Number of patients	Initial dose	Monitoring target	Outcome
Bivalirudin	Pieri et al. 2014	Observational, retrospective case series	12	0.025 mg/kg/hour	aPTT 45-60	Two cases minor bleeding, no major bleeding or TE events
	Kantorovich et al. 2016	Retrospective cohort comparison	139	0.04 mg/kg/hour	Prescriber discretion	Trend towards lower bleeding compared to heparin; no significant difference in TE compared to no bridging
	Ljajikj et al. 2017	Retrospective cohort comparison	47	Intraoperative bolus of 0.25-0.5 mg/kg, continuous infusion of 0.25-0.5 mg/kg/hour (4.2-8.4 mcg/kg/min)	ACT 180-220	Comparable results to intra-operative and post-operative heparin
	Milenkovich et al. 2020	Retrospective cohort comparison	51	N/A	N/A	No difference in early bleeding (< 96 hours), higher rates of overall bleeding compared to heparin
Argatroban	Pappalardo et al. 2012	Retrospective case series	27	0.02-0.42 mcg/kg/min	aPTT 45-80	No significant major bleeding events

ACT, activated clotting time; aPTT, activated partial thrombin time; CF-LVADs, continuous-flow left ventricular assist devices; TE, thromboembolic events.

Regarding intracorporeal devices, the HVAD and HM3 LVAD have been used mainly in children with weight > 25–30 kg due to device size and need to tolerate device flows. Parenteral anticoagulation administration is similar to adult patients. Limited experience of the HM3 LVAD in 35 adolescents and young adults at 9 centers, reported by the ACTION group, showed no uniformity in anticoagulation management. Most (77.8%) used UFH for bridging, others used LMWH or bivalirudin. This study reported no stroke or pump thrombosis and minimal bleeding.[50]

Laboratory monitoring

APTT vs anti-Xa monitoring of unfractionated heparin

APTT and anti-Xa levels can be significantly discordant in LVAD patients, especially when aPTT is very high.[77–79] Therapeutic aPTT levels have been shown to correlate to subtherapeutic anti-Xa levels (when measured concomitantly) in patients with a durable CF-LVAD.[77] Similarly, a therapeutic anti-Xa level has commonly been correlated to a supratherapeutic aPTT.[80] Little evidence supports the *clinical* superiority of one assay vs the other in terms of hard outcomes such as HRAEs. It may be prudent to choose the assay used for a given patient or scenario based on an assessment of risk and benefit. For example, it may be reasonable to use aPTT for routine post-operative bridging with UFH in an uncomplicated patient, since down-titration of UFH in response to an aPTT that is high may potentially limit post-operative bleeding risk. Conversely, in a patient with concern for thromboembolic complications, anti-Xa monitoring may help ensure the adequacy of anticoagulation.[79]

Monitoring of LMWH and fondaparinux

A generally accepted standard for measuring anti-Xa for LWMH is as a peak value (approximately 4 hours post dose), preferably after 2–3 doses. An anticoagulation goal intensity of 0.15–0.4 IU/ml has been reported in both immediate post-operative and chronic outpatient bridging scenarios.[63,64,80,81] Different brands of anti-Xa assay may vary significantly, especially at lower concentrations (< 0.35 IU/ml).[82] The measurement of anti-Xa effect should be performed by a technique calibrated to the associated drug. Fondaparinux-calibrated assays are rarely accessible, thus clinicians can consider using the LMWH method, as correlation is quite strong yet lower than the LMWH value.[83]

Key points

- Either aPTT or anti-Xa assay is reasonable to use in the titration of UFH bridging infusions. There is no evidence supporting the superiority of one assay vs the other. Clinicians should consider the patient's bleeding and thromboembolic risks when selecting one assay over the other in each clinical situation.
- Anti-Xa assays (preferably calibrated to the specific agent) are reasonable to ensure dosing of LMWH or fondaparinux has safely achieved therapeutic effect in patients deemed to be at high risk of HRAEs.

Special consideration: Heparin allergy (HIT)

In patients who develop acute heparin-induced thrombocytopenia (HIT) while awaiting CF-LVAD placement, there is limited information on treatment approaches, and most data have been derived from case reports.[84] The use of UFH in acute and subacute HIT during temporary mechanical circulatory support or cardiac surgery is associated with an increased risk of thrombotic events.[85] If delay of surgery is not deemed prudent, patients with acute HIT or subacute HIT have been reported to undergo one of the following treatments during CF-LVAD implantation: (1) intraoperative anticoagulation with bivalirudin[86] or argatroban,[70] (2) preoperative and/or intraoperative plasmapheresis,[87] (3) intraoperative UFH in combination with a potent antiplatelet agent (abciximab[88] or cangrelor[89]), (4) combination of the above[90] (Table 2).

Data supporting parenteral bridging in patients with HIT on chronic CF-LVAD support are scarce. One study reported successful heart transplant and safe re-exposure to UFH during cardiopulmonary bypass in 4 patients supported on CF-LVAD who had acute or remote HIT.[85] More research is needed to find the optimal bridging therapy for these patients.

Peri-procedural/outpatient bridging of subtherapeutic INR

The decision on whether to bridge a patient with CF-LVAD depends on the patient's bleeding vs thrombotic risk and can vary widely across centers both in the INR threshold for bridging, and on the type of invasive procedures that require it. Low-risk procedures such as dermatologic, dental, or cataract surgery can likely be safely performed without cessation of warfarin. However, there is no uniform guideline regarding a "safe" INR threshold for other procedures such as cardiac catheterization or gastrointestinal endoscopy, so the decision should be made at the clinician's discretion and practices may vary across mechanical circulatory support centers.

Bridging for subtherapeutic INR

Bleeding or thrombotic risk scores with which to assess the risk/benefit ratio of bridging in CF-LVAD patients are scarce. The UTAH Bleeding Risk Score identified age > 54 years, previous bleeding, coronary artery disease, chronic kidney disease, severe right ventricular dysfunction, mean pulmonary artery pressure < 18 mm Hg, and fasting glucose > 107 mg/dl to be independent predictors of gastrointestinal bleeding in CF-LVAD patients,[91] which may be applicable to decisions about bridging. The "threshold" INR value to initiate bridging therapy varies and may be dependent on device, ranging from 1.5 to 1.8.[81,92]

Choice of bridging agent

UFH has greater historical familiarity, while the subcutaneous options (LMWH, fondaparinux) can provide greater accessibility and possibly shorter time to initiation since they can be administered in the outpatient setting. Notably, an enoxaparin dose of ~ 1 mg/kg subcutaneously twice daily has been associated with increased bleeding risk.[93] It is reasonable to modify or lower LMWH dose to reduce bleeding events, particularly in high-risk patients.[81,92]

Table 2 Selected Case Reports of Anticoagulant Use in Patients with HIT Undergoing CF-LVAD Implantation

Study	Data source	Context/Type of MCS	HIT-oriented treatment	Outcomes
Zucker et al. 2010	Single center Retrospective	Patients with acute or remote HIT underwent CF-LVAD implant ($n = 8$) (and heart transplant)	Preoperative argatroban Intraoperative UFH	3 thromboembolic events in CF-LVAD patients 30-day survival 75% among CF-LVAD patients
Hillebrand et al. 2015	Single center Retrospective	7 patients with HIT and emergent ECLS received HM2 ($n = 5$) or HVAD ($n = 2$) LVAD	UFH was switched to argatroban while on ECLS and during CPB, argatroban continued post-op for bridging to warfarin	1 died of multiorgan failure 6 had intact neurological function 4 needed post-op re-exploration for bleeding Overall survival 57.1%
Ljajikj et al. 2017	Single center Retrospective Propensity-matched	Patients on ECLS received CF-LVAD implantation	Bivalirudin ($n = 21$) UFH ($n = 36$)	Similar rates of surgical re-exploration between bivalirudin (19%) and UFH (16.7%) ($p = 0.8$)
Lee et al. 2018	Single center Retrospective	6 patients with HIT undergoing durable LVAD implantation	Intraoperative abciximab + UFH Abciximab stopped 15 minutes after UFH reversal with protamine Postoperative platelet transfusion	-No thromboembolic complication -1 patient had chest exploration + RVAD for bleeding
Gernhofer et al. 2018	Single center Retrospective	1 patient with HIT received HM3 LVAD	Preoperative bivalirudin Intraoperative cangrelor + UFH Cangrelor stopped 10 minutes before protamine Postoperative platelet transfusion Postoperative bivalirudin bridging to warfarin	No thrombotic or bleeding complication
Maffei et al. 2020	Single center Retrospective	2 patients with HIT underwent CF-LVAD implantation	Preoperative plasmapheresis Postoperative bivalirudin	1 patient with postoperative bleeding
Naqvi et al. 2022	Single center Retrospective	4 patients with HIT underwent HM3 LVAD implantation	Preoperative plasmapheresis Intraoperative UFH Postoperative bivalirudin as bridge to warfarin	2 patients with postop bleeding 1 died of multiorgan failure unrelated to HIT therapy

CF-LVADs, continuous-flow left ventricular assist devices; ECLS, extracorporeal life support; HIT, heparin-induced thrombocytopenia; HM3, HeartMate 3; MCS, mechanical circulatory support; UFH, unfractionated heparin.

Fondaparinux, an anticoagulant that binds ATIII and inhibits factor Xa, has been used successfully for bridging in case reports of patients with HIT.[81,94]

Special consideration: Patients with chronic kidney disease

Patients with CrCl ≤ 30 ml/min who require bridging should receive UFH instead of LMWH or fondaparinux due to impaired renal drug clearance and increased bleeding risk. If LMWH or fondaparinux is used, anti-Xa monitoring specifically for LMWH or fondaparinux is recommended, and fondaparinux dose should be reduced by 50% in patients with CrCl 30–50 ml/min.[95]

Key points

- Patients with a history of or at high risk of thromboembolic events while on CF-LVAD should receive parenteral anticoagulant bridging therapy when INR is subtherapeutic (thresholds vary by individual centers).
- Both UFH and LMWH are reasonable bridging options. LMWH is preferable for patients managed in the outpatient setting. Fondaparinux is reasonable to use as a bridging agent in patients with HIT.
- Dosing in patients with increased bleeding risk:
  Enoxaparin 0.5 mg/kg SC BID (CrCl > 30 ml/min), or
  UFH started at 5–10 units/kg/hour (titrate to APTT 40–60 seconds, or anti-Xa level of 0.15–0.35 IU/ml, or
  Fondaparinux 2.5 mg (weight < 50 kg), 5 mg (50–100 kg), 7.5 mg (> 100 kg) SC daily (CrCl > 30 ml/min).
- Dosing in patients with increased thrombotic risk:
  Enoxaparin 1 mg/kg SC BID (CrCl > 30 ml/min), though may consider lower dose to minimize bleeding risk, or
  UFH started at 10 units/kg/hour (titrate to APTT 40–60 seconds, or anti-Xa level of 0.15–0.35 IU/ml), or
  Fondaparinux 5 mg–7.5 mg SC q24 hours (CrCl > 30 ml/min).
- Dosing in patients with renal insufficiency:
  Avoid LMWH or fondaparinux and use UFH if CrCl ≤ 30 ml/min.
  For CrCl 30–50 ml/min, fondaparinux may be used with caution at 50% dose reduction, with consideration for anti-Xa monitoring.

MANAGEMENT OF ANTITHROMBOTIC THERAPIES IN PATIENTS AT HIGH RISK OF HRAES

The spectrum of HRAEs results from the complex interplay of multiple pathophysiologic processes that include but is not limited to (1) direct effect of the shear forces on the rheological properties of the blood components both at the tissue-VAD interface as well as systemically in the circulatory system; (2) alteration in the microcirculation due to change in pulsatility of the blood column; (3) activation of the inflammatory and angiogenesis pathways and (4) non-linear physiologic effects on the coagulation cascade during drug therapy to balance bleeding vs thrombotic risks.[96]

Using a tiered hemocompatibility score, the continuous-flow centrifugal HM3 was shown to have greater freedom from HRAEs when compared to axial continuous flow devices (i.e., the HM2).

Hypercoagulable states

Thrombophilia or hypercoagulable states, both congenital and acquired, have been increasingly recognized causes of HRAEs in patients with a CF-LVAD. Despite an incidence of hypercoagulable states of 15% in a prospective multi-center clinical study with adherence to a strict protocol for pump implantation and medical management, the prevalence of hypercoagulable states was not statistically different between patients with and without pump thrombosis.[97] The authors suggested that the hypercoagulable states represent a heterogeneous group of disorders that differ in their composite thrombotic risk and a systematic evaluation that includes both clinical as well as laboratory assessment will lead to individualized approaches to risk assessment. Congenital hypercoagulable states such as Factor V Leiden mutation causing HRAEs have been reported.[98] Several

acquired hypercoagulable states leading to HRAEs have been reported, such as antiphospholipid antibody syndrome,[99] plasmatic hypercoagulation,[100] heparin-induced thrombocytopenia,[98] thrombocytopenia,[101] elevated Factor VIII activity and idiopathic thrombocytopenic purpura (ITP).[98]

In a single-center retrospective study, 20 of 167 LVAD patients (11.9%) were identified with a hypercoagulable state (the majority of which were acquired) which was associated with a lower event-free survival.[102] Patients with a hypercoagulable state had higher occurrence of deep venous thrombosis (DVT) and subarachnoid hemorrhage. In another single-center study of 286 CF-LVAD patients implanted over a 5-year period, 12 patients had a significant hematologic condition (5 patients with ITP, 1 with Factor V Leiden, 1 with elevated Factor VIII, 2 with HIT and 3 with undefined hypercoagulable state) predisposing them to HRAEs.[98] Patients with prior history of a hypercoagulable state had higher risk for bleeding, thrombotic and neurologic events during device support, leading to early mortality.

Key point

- Hypercoagulable states are common in patients with a CF-LVAD; whether they directly correlate to incident thrombotic events is unclear.

Presence of thrombotic risk factors

Patient-related risk factors

Non-modifiable risk factors for pump thrombosis include age at implant, female gender, higher body mass index and non-O blood type,[103] in addition to psychosocial issues, such as limited support, limited cognition, substance abuse, severe psychiatric disease and repeated non-compliance.[104] The presence of prothrombotic comorbidities such as atrial fibrillation, right sided dysfunction,[103] pulmonary disease,[103] and previous gastrointestinal bleed (GIB)[105] have also been shown to increase thrombotic risk.

Modifiable risk factors for thrombotic events include tobacco use, bacteremia, early previous pump thrombosis,[106] pump infection, and hypertension.[107,108] The timing on the occurrence of stroke and death with earlier devices seems bimodal, being the highest risk immediately post-implant and at 9–12 months. By contrast, the HM3 demonstrates early stroke risk that seems to diminish over time. Infection, regardless of its source, is an independent predictor of multiple stroke types (including ischemic and hemorrhagic) during both the early and late period after implantation.[108] Patients with central venous pressure < 12 mm Hg, pulmonary artery wedge pressure < 18 mm Hg, and cardiac index > 2.2 liter/min/m^2 have shown greater freedom from HRAEs, an effect thought to be due to improved flow dynamics, although the precise mechanistic link to HRAEs is unknown.[109] Significant aortic insufficiency 3 months after LVAD placement was shown in a small study to be associated with HRAEs, although the onset and progression of AI was not known.[110] In addition, decoupling of pulmonary artery diastolic pressure and pulmonary capillary wedge pressure (leading to worsening right heart failure) was associated with HRAEs, likely due to pump stasis, hepatic congestion with consequent dysregulation of inflammatory and coagulation cascade and development of arteriovenous malformations.[111]

Device-related risk factors

Improvements to both the design of the CF-LVADs and better understanding of their management have shown progress towards reducing the risk of thrombotic events. The MOMENTUM 3 trial demonstrated the superiority of the HM3 over the HM2 for the composite outcome of disabling stroke and reoperation for pump thrombosis at 6 months.[112] The effect was sustained at 2 years,[113] making the HM3 the device with the highest freedom from stroke at 1 year (when compared with HMII and HVAD).[114]

Hemocompatibility outcomes in pediatric patients with durable, continuous-flow LVADs (HVAD and HM2) have been published in a recent Pediatric Interagency Registry for Mechanical Circulatory Support (Pedimacs) Annual Report. In patients with a median age of 14.9 years, these devices showed an early (i.e., within 3 months of implant) bleeding rate of 14 per 100 patient years and a late (> 3 months from implant) bleeding rate of 2 per 100 patient years.[115] There were 3 early strokes and 1 late per 100 patient years. An analysis of 50 pediatric patients (median age: 12.9 years) with a HVAD showed a 14% rate of bleeding and 4% rate of stroke during a median 71 days on device support.[116]

Risk mitigation strategies

The empiric management of antithrombotic therapies in patients at high risk of HRAEs is evolving. The presence of either thrombotic or bleeding risk factors may prompt clinicians to customize the antithrombotic therapy of a specific patient, but there is no validated algorithm to guide clinicians at this time. Prediction models used in other disease states (such as the $CHADS_2$, CHA_2DS_2-VASC, HAS-BLED, and $HEMORR_2HAGES$ scores) have not proven to be predictive in patients with a CF-LVAD.[107,117] As a result, antithrombotic adjustments are generally made only in reaction to a newly-developed HRAE.

Key points

- Awareness of non-modifiable and modifiable risk factors for thrombotic events may help the clinician decide on the appropriateness of empiric adjustment of antithrombotic medications.
- Modifiable thrombotic risk factors should be avoided (or treated when possible) as a means of reducing the incidence of thrombotic events.
- Evidence on the safety and efficacy of empiric intensification of the antiplatelet and/or anticoagulant regimen of a patient with a CF-LVAD and known thrombotic risk factors is limited.

History of/high risk of bleeding

Patient-related risk factors

The most common risk factor for bleeding events is excessive anticoagulation. High INR values are associated with hemorrhagic events (adjusted HR 1.66, 95% CI 1.43–1.93), with the highest bleeding rate occurring with INRs > 3.5.[11] A higher baseline INR has also been associated with bleeding events,[118] which may reflect underlying liver dysfunction or right sided heart failure and secondary liver congestion. Lastly, whether bridging therapy with unfractionated or low molecular weight heparin is associated with increased bleeding has led to conflicting results, with some studies showing increase bleeding risk when used as bridge for low INR,[93,119] while others did not.[120] Other factors associated with bleeding in patients with a CF-LVAD include use of antiplatelet medications (aspirin, clopidogrel), thrombocytopenia or platelet dysfunction (induced by the CF-LVAD or from other causes), acquired von Willebrand syndrome, impaired renal function, ECMO support pre-LVAD implantation and infectious complications. A recent meta-analysis reporting a pooled prevalence rate of GIB of 24.4%, failed to show a statistically significant association between GIB and risk factors such as age, gender, hypertension, chronic kidney disease and diabetes.[121] More research is needed to understand the interplay between device and patients' factors leading to bleeding.

Device-related factors

In a recent INTERMACS analysis, rates of gastrointestinal bleeding differed between the different devices. The lowest incidence within the first year after device placement was seen in patients with a HM3 at 12%; the highest incidence of 25% occurred in patients with a HM2.[114] The HVAD was intermediate, with an incidence of 20% in the first year after implant.[114] Bleeding events with CF-LVADs are frequent due to anticoagulation, acquired von Willebrand syndrome created by shear stress, and reduced pulsatility. The HM3 was engineered with these aspects in mind, using a magnetic levitated rotor to reduce shear stress and an intermittent low speed to promote aortic valve opening. The MOMENTUM 3 trial demonstrated improved hemocompatibility of the HM3 pump compared to the HM2,[113,122,123] with marked reduction in de-novo pump thrombosis and stroke rates, but only a modest decrease in bleeding complications,[113,124] which remain worrisome.[125,126] Thus, addressing the ongoing risk of bleeding, especially non-surgical mucosal bleeding (e.g. gastrointestinal bleeding) remains of outmost importance. A patient-specific approach based on perceived bleeding risk may be necessary in decisions to empirically deescalate antithrombotic therapy in the absence of large trials.

Risk mitigation strategies

Observational studies in patients implanted with the HM3 who suffer bleeding have suggested a signal of reduced subsequent bleeding events with withdrawal of aspirin. Post-hoc analyses on the effectiveness of 2 different

doses of aspirin within the HM3 arm of the MOMENTUM 3 trial,[48] with both groups using anticoagulation targeted to an INR of 2.0–3.0, showed that the usual dose aspirin (325 mg daily) was similar to low-dose aspirin (81 mg daily) in terms of survival free from HRAEs (non-surgical bleeding, pump thrombosis, stroke, and peripheral arterial thromboembolic events) at 2 years (43.4% vs 45.3%, $p = 0.94$). There were also no differences in survival free from hemorrhagic (usual-dose: 54.4% vs low-dose: 51.7%, $p = 0.42$) events. Two small reports of patients implanted with the HM3 and maintained on warfarin monotherapy [INR 2–3] after aspirin discontinuation, mostly due to bleeding, failed to demonstrate any sign of increased thrombotic complications, while a third using no aspirin after HM3 (regardless of risk factors) demonstrated reduced rates of bleeding.[56,57,127] As noted earlier in the document, these initial findings led to the investigation of whether antiplatelet therapy could be avoided in an effort to reduce bleeding complications in the Antiplatelet Removal and Hemocompatibility Events with the HM3 Pump (ARIES-HM3) trial. The omission of ASA was associated with significant reductions in all non-surgical bleeding, including moderate, severe, and gastrointestinal.[58]

Key points

- Awareness of non-modifiable and modifiable risk factors for bleeding events may help the clinician decide on the appropriateness of empiric adjustment of antithrombotic medications.
- INR control (with a focus on minimizing INRs > 3.5) is critical to prevention of bleeding events in patients with a CF-LVAD.
- Removal of aspirin from the antithrombotic regimen of patients with a HM2 may reduce overall rates of bleeding and may be reasonable for patients with perceived high risk of bleeding at the time of CF-LVAD placement.
- Removal of aspirin from the antithrombotic regimen of patients with a HM3 reduces rates of bleeding with no increase in thrombotic events and should be considered for all patients except those with abnormally high thrombotic risk factors.

MANAGEMENT OF THROMBOTIC EVENTS

Pharmacologic management of pump thrombosis

Anticoagulation with parenteral unfractionated heparin and direct thrombin inhibitors

Intensification of anticoagulation with parenteral UFH may assist in the prevention of clot progression and/or thromboembolism. Unrandomized studies have also demonstrated some benefit from use of direct thrombin inhibitors (DTIs), including bivalirudin and argatroban.[128] The hypothesis is that DTIs, which inhibit both free and clot-bound thrombin, may provide a more effective mechanism of anticoagulation in patients with PT, yet well-powered studies are lacking. In a study of 57 patients with HVAD thrombosis, patients treated initially with bivalirudin ($n = 16$) had fewer recurrent thrombotic/hemolytic episodes than those ($n = 26$) who received UFH alone.[129] Other case series demonstrate similar findings.[130,131] Argatroban, a reversible direct thrombin inhibitor with hepatic clearance, is also an option but has very limited data in CF-LVAD patients.[128]

Intravenous antiplatelet agents

The administration of intravenous antiplatelet therapy alone or in addition to standard anticoagulation has demonstrated largely negative outcomes in small samples of patients with high clinical suspicion of PT.[128] In a study of 27 nonrandomized patients on HM2 or HVAD support, parenteral eptifibatide used alone ($n = 10$) or in addition to intravenous anticoagulation ($n = 17$) failed to demonstrate improved outcomes.[132] Another small case series demonstrated high bleeding, intraparenchymal cerebral hemorrhage and mortality rates with use of eptifibatide for suspected pump thrombosis.[133]

Thrombolytics

In carefully selected patients who have failed escalation of anticoagulation are not transplant or re-operative CF-LVAD candidates, systemic or localized intracavity administration of thrombolytic therapy may be considered.

Thrombolytics have demonstrated variable success (11–82%) in treating CF-LVAD PT, and data are largely from case series with large potential for patient selection bias.[128,134] The high variability of the results is likely related to the different pathophysiologies driving PT, especially across different pump flow configurations, as well as patient selection and duration of PT. Patients with recurrent hemolysis likely have some degree of chronic PT. Chronic, denatured clot (typical of that seen on the HM2 bearing or inflow pannus) often results from thermal degradation and tends to be composed of denatured proteins and fibrin that recombinant tissue plasminogen activator (rTPA) and other thrombolytics fail to degrade.[135] Additionally, thrombolytic therapy is associated with hemorrhagic complication and/or embolic events (19–50%).[128] It is recommended that a baseline computed tomography of the head, type and screen, and coagulation parameters (INR, fibrinogen, PTT, and hemoglobin) be obtained prior to administration of thrombolytics with intensive care unit and close blood pressure and neurologic monitoring undertaken.

Different protocols and thrombolytics (rTPA, tenecteplase and alteplase) have been used for PT management, with no clearly superior agent.[106,134,136,137] Catheter directed intraventricular administration of thrombolytics reduces the cumulative dose given and exposes the thrombus to high concentrations of drug, but skilled technique is required.[138] Conversely, systemic thrombolytics increase the risk of bleeding complications.

Long-term management of patients with pump thrombosis

Following medical or surgical treatment of CF-LVAD PT, it is key to investigate potential contributions to PT, such as an infection, non-compliance with antithrombotic medications, device malpositioning, etc. In addition, anticoagulation targets and antiplatelet therapy doses should be reassessed. There are no good data to support an INR goal above 2–3, aspirin escalation above 325 mg/day, addition of clopidogrel, or routine platelet-function monitoring.[2,138]

Key points

- In CF-LVAD patients hospitalized for significant hemolysis, first-line therapy in stable patients consists of oral antiplatelet therapy and escalation of anticoagulation with unfractionated heparin or a direct thrombin inhibitor, with close monitoring of LDH and signs of bleeding.
- Device exchange should be considered in long-term therapy CF-LVAD patients with reasonable operative risk who fail to respond to parenteral anticoagulation and/or those with significant hemodynamic instability, irrespective of long-term therapy or bridge to transplant intent.
- Intravenous antiplatelet agents have not been shown to be beneficial in the management of pump thrombosis and may increase risk of harm.
- Thrombolytic therapy for the treatment of PT is carries significant risk and should be deployed only in patients who fail (or are not candidates for) the above management strategies.

Pharmacologic management of ischemic cerebrovascular events in patients on durable left ventricular assist device support

Risk factors for ischemic neurologic events include preoperative patient characteristics such as patient age, female sex/body surface area, and prior history of atrial fibrillation and/or stroke, as well device related factors including device model, elevated mean arterial blood pressure (MAP) and history of device infection, hemolysis, or pump thrombosis. Stroke frequencies have been derived from major clinical trials and the INTERMACS registry and are depicted in Table 3. As device technology has evolved into the third generation, hemocompatibility and stroke rates have improved.

Pharmacologic management of thrombotic neurologic events

Acute stroke assessment and imaging in durable CF-LVAD patients should follow established expert recommendations for non-CF-LVAD patients, with the exception of utilization of MRI (Dawson 2022).[140–142] Since many CF-LVAD patients are not thrombolytic candidates due to concomitant oral antithrombotic medications, the

Table 3 Frequency of Stroke in CF-LVAD Patients from Major Trials/Registries[139]

Trial	Device	Incidence
INTERMACS Registry – 1 year follow-up	All LVADs	~10%
REMATCH (DT) Trial – 2 years follow-up	HeartMate XVE	10%
HeartMate II (BTT) trial – 6 months follow-up	HeartMate II	8.3%
HeartMate II (DT) trial – 2 years follow-up	HeartMate II	17%
ENDURANCE trial (DT)	HeartWare HVAD	30%
MOMENTUM 3 Trial (BTT or DT)	HeartMate 3	10%

BTT, bridge to transplant; CF-LVAD, continuous-flow left ventricular assist device; DT, destination therapy; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support: HM2, HeartMate 2; HM3, HeartMate 3.

decision to transfer a CF-LVAD patient to the implanting CF-LVAD center prior to initial emergency evaluation should be individualized for the patient with considerations including the initial center's ability to assess blood pressure, maintain safe CF-LVAD equipment function (including dangers of MRI and power failure), and the center's ability to rapidly provide mechanical thrombectomy and/or urgent surgical intervention for secondary intracranial bleeding.

Blood pressure control

Given the challenges with BP assessment, best practices support arterial line placement for accurate and constant BP assessment in the CF-LVAD patient. There are no data to support any ideal BP goal in CF-LVAD patients with acute ischemic stroke (AIS). In patients with medical conditions mandating tighter BP control (such as CF-LVAD therapy) the general recommendation is to reduce BP by 15–20% over 24 hours. While the recommended CF-LVAD BP in absence of neurologic insult is a MAP 75–90 mm Hg, hypotension in patients with AIS can lead to cerebral ischemia, especially in the setting of notable vasogenic edema. Once patients are neurologically stable, resumption of oral antihypertensive and traditional guideline directed heart failure therapies may be reasonable in stable CF-LVAD patients without hypotension for long-term stroke secondary prevention.[142]

Intravenous tissue plasminogen activator

A presenting INR > 1.7 will likely exclude most CF-LVAD patients from IV thrombolytic therapy.[143] The safety of reversing INRs for thrombolytic candidacy is not known; there are data to suggest that using prothrombin complex concentrates in the non-LVAD population to normalize INRs in stroke patients may actually enhance coagulation and/or worsen neurological deficits, leading Japan and the European Stroke Organisation to advise against this practice. Patients receiving IV thrombolytic therapy require tight BP control before and at least 24 hours after thrombolytic therapy to reduce the risks of cerebral hemorrhage. Because there is no Food and Drug Approval recommendation for intraarterial thrombolytic therapy, most current recommendations favor mechanical thrombectomy with stent retrievers over attempts at intraarterial lysis.[141,144]

Antiplatelet agents

Since some CF-LVAD patients will be on aspirin therapy upon admission, this therapy is often maintained. In CF-LVAD patients with AIS taking 81 mg aspirin without a prior bleeding event, it may be reasonable to discuss escalation of aspirin dose (to 162–325 mg daily), even in the short term. In those not on ASA at time of AIS, it is reasonable to add ASA to warfarin moving forward, although no data clearly indicates that this strategy is beneficial. There are no data to support the routine addition of clopidogrel or dipyridamole to the therapeutic regimen of CF-LVAD patients with AIS.

Anticoagulation

The CF-LVAD population has unique considerations including potential active pump thrombosis (or risk of new pump thrombosis), however the antithrombotic benefits of routine UFH use during acute stroke should be weighed against its potential risks. In a study of 19 patients with AIS on durable CF-LVAD support, hemorrhagic

transformation occurred in 6 (32%) of the 19 patients, 17 of whom received uninterrupted anticoagulation therapy in the acute stroke setting.[145] Thus, close neurologic monitoring with daily computed tomography is reasonable for those CF-LVAD maintain on anticoagulation for AIS.

Key points

- Close monitoring of blood pressures using an arterial line is appropriate for CF-LVAD patients presented with confirmed or suspected ischemic stroke.
- Interdisciplinary collaboration between neurology, advanced heart failure, and critical care specialists is needed to define blood pressure targets before and after neurologic intervention to avoid the potential complications of cerebral ischemia or hemorrhage from over and under treatment of systemic hypertension, respectively.
- Initiation or resumption of aspirin therapy is reasonable for CF-LVAD patients following stabilization from an ischemic stroke. Increase in aspirin dose in those on prior aspirin therapy (maximum 325 mg aspirin/day) may be considered.
- The risk vs benefit of continuing anticoagulation in the setting of acute stroke must be individualized for the patient based on neurologic infarct size, patient clinical stability, underlying pump function, pump or aortic root thrombosis risk, and hemolysis history.
- Close neurologic monitoring of CF-LVAD patients on anticoagulation therapy who have suffered ischemic neurologic insult should be employed given the increased risk of hemorrhagic transformation of infarcted neurologic tissue.

MANAGEMENT OF BLEEDING EVENTS

Background

Among CF-LVAD patients, major bleeding remains the most common HRAE, affecting 33% of patients within the first year of implant, with gastrointestinal bleeding accounting for approximately 50% of these events.[146]

Causes of CF-LVAD-related bleeding are multifactorial and include the need for chronic antithrombotic therapy, most commonly with a VKA and single antiplatelet therapy, as well as CF-LVAD-induced physiologic derangements including acquired von Willebrand Syndrome and the development of arteriovenous malformations.[36,60,147,148]

Management of antithrombotic therapy around bleeding events depends on several patient-related factors including the severity of bleeding, the level and type of current antithrombotic therapy, and the risk of thromboembolic events associated with the CF-LVAD in question.[149]

Reversal of antithrombotic therapy

Minor bleeding may be treated with temporary interruption in anticoagulant and/or antiplatelet therapy without administration of a reversal agent. In the setting of overt bleeding which occurs while the CF-LVAD patient is on antithrombotic therapy and which requires transfusion or surgical intervention, antithrombotic therapy should be held and reversal of antithrombotics should be considered. For reversal of VKA, reversal strategies may include administration of vitamin K_1 with or without fresh frozen plasma (FFP) or prothrombin complex concentrates (PCC). While not a direct reversal agent, recombinant activated factor VII (rFVIIa) may also be considered as a hemostatic agent and will be discussed in more detail below.

Vitamin K_1

In general, interruption of VKAs is not sufficient to treat severe bleeding and administration of vitamin K_1 (phytonadione) is required. Oral administration of vitamin K_1 bypasses infusion reactions seen with intravenous or subcutaneous administration but takes substantially longer for onset (6–10 hours) and peak effect (24–48 hours) when compared to intravenous administration. Therefore, oral vitamin K_1 may be considered in patients without

active or life-threatening bleeding and who do not require urgent intervention, but who may be at high risk of bleeding due to excessive levels of anticoagulation as indicated by INR.

For more rapid reversal, vitamin K_1 should be administered intravenously. Intravenous vitamin K_1 administration results in increased vitamin K-dependent coagulation factors (II, VII, IX, X) after 1–2 hours with a peak effect around 12 hours. A low-dose (1 mg) intravenous vitamin K_1 results in similar reduction of INR values compared with 5 mg oral vitamin K $_1$ after 24 hours.[150] A high-dose (e.g. 5 mg or more) intravenous vitamin K_1 can be used for the management of life-threatening bleeding, together with either PCC or FFP. In general, intravenous vitamin K_1 should not be used as monotherapy in the setting of acute severe bleeding.[149,151,152] Subcutaneous administration of vitamin K1 is not recommended due to erratic and unpredictable absorption.

The administration of intravenous vitamin K_1 for the treatment of severe bleeding should always be balanced against the risk of thromboembolic events. Jennings et al. retrospectively studied anticoagulation reversal strategies in a cohort of 122 LVAD patients, 80% with a HM2 LVAD and 20% with an HVAD.[153] In 25 patients, 38 anticoagulation reversal events occurred. The indication for reversal was mainly acute hemorrhage (19 of 38 events). Reversal was attempted with vitamin K_1 in all patients (mean dose 10 $\pm$ 8 mg, given orally in 18 patients, intravenously in 16 patients), together with FFP (60%), PCC (5%) and/or rFVIIa (8%). Within 30-day of follow-up, 2.6% (1/38) of the patients experienced a thromboembolic event. More recently, low-dose vitamin K_1 was compared to a more conservative strategy of "watchful waiting" for LVAD patients requiring INR reversal prior to endoscopy. The use of low-dose vitamin K_1 was equally safe and more efficacious in achieving INR < 2.[154]

Vitamin K in pediatric patients

Yu et al. reported anticoagulation reversal with PCC and vitamin K_1 in children with an HVAD ($n = 4$) in the setting of emergent neurosurgical intervention. Vitamin K_1 (0.1–0.22 mg/kg) was administered to 3 patients on warfarin in combination with other agent(s).[155] All 3 patients achieved an INR of 1.5 or lower. No patient experienced device thrombosis.

Prothrombin complex concentrates and fresh frozen plasma

In addition to vitamin K_1, FFP or PCC can be administered for the treatment of severe bleeding in CF-LVAD patients. It is important to note that PCC has 3 different formulations including 3-factor PCC, 4-factor PCC, and activated PCC. Four-factor PCC contains concentrated vitamin-K dependent clotting factors II, VII, IX and X, as well as smaller quantities of protein C and S, antithrombin, and heparin. Activated PCC contains similar clotting factors to 4-factor PCC though the factor VII content is in activated form. For the purpose of this document, we will use the term PCC to refer to these products interchangeably as most publications include a variety of PCC products. The decision of which product to give may be based on availability, cost, and safety profile.

In recent years, PCC has become an attractive alternative for VKA reversal over FFP given shorter administration times, smaller infusion volumes, more rapid reversal of INR, and avoidance of transfusion-associated adverse events.[156,157] Importantly, in non-LVAD patients with major bleeding, PCC and FFP are associated with similar thrombotic risk.[156]

There are no randomized controlled trials investigating the efficacy and safety of FFP or PCC in CF-LVAD patients with bleeding complications. The majority of the studies investigating FFP and PCC in CF-LVAD patients are related to peri-operative bleeding at the time of CF-LVAD implant[158–161] or anticoagulation reversal before heart transplantation.[162–166] In a recent study of 170 patients, the use of FFP at the time of CF-LVAD placement (vs no FFP) is associated with an increased risk of mortality (HR per unit FFP 1.08 [95% CI 1.04–1.12]).[161] PCC use at the time of CF-LVAD implant is generally given as an FFP-sparing product for reasons cited above. Retrospective reviews comparing PCC to standard of care or traditional management have not been able to demonstrate a blood sparing effect.[159,160] Importantly, the risk of pump thrombosis with PCC appears to be low.[158,159] These reviews offer conflicting results on the incidence of non-LVAD thrombotic events. The largest retrospective review of PCC use in CF-LVADs reported a DVT incidence of 10.3% within 30 days vs 0% seen in patients who did not require PCC.[159] Smaller series did not report an increase in thrombotic events in patients who received PCC.[158,160]

In a few retrospective case series, the safety and efficacy of PCC in CF-LVAD patients presenting with a bleeding has been reported.[167–170] In a retrospective cohort study, 37 continuous flow CF-LVAD patients (HM2 and HVAD) received 49 administrations of PCC for INR reversal for various reasons including major bleeding, minor bleeding, and/or urgent or elective surgeries.[168] A multidisciplinary team (anticoagulation specialist, hematologist, member of the CF-LVAD team) determined the dose of PCC based on clinical indication for reversal, current INR, and target INR. Mean

dosage of PCC in the group with major bleeding was 30 units/kg and decreased the mean INR from 2.9 to 1.6 (32% of the patients also received intravenous vitamin K_1). The mean dose of PCC in the elective surgery group was 17 units/kg which decreased mean INR from 2.9 to 1.7. Within 30 days, no adverse events (pump thrombosis, stroke, venous embolism, arterial thrombosis, or myocardial infarction) were observed. Wong and colleagues compared traditional INR reversal ($n = 10$) with PCC-assisted reversal ($n = 10$) with no reversal ($n = 11$) in CF-LVAD patients with intracranial hemorrhage.[167] The latter cohort of patients was not reversed as risk was believed to outweigh the benefit, typically occurring in patients with hypercoagulable history and/or those with very small intracranial hemorrhage volume and minimal to no neurological deficits. The mean dosage of PCC utilized in this study was 20.5 units/kg (range 5.5–28 units/kg), frequently resulting in an administered dose which was lower than the FDA-approved dose. Successful reversal was achieved earliest in patients who received PCC-assisted reversal, with no thrombotic complications identified. Of note, the authors also concluded that in select patients who may be high risk of thrombotic complications and low risk for hemorrhagic expansion, holding the VKA without active reversal, also appeared to be a safe and effective management strategy.

Firm conclusions regarding FFP and PCC are limited by the non-controlled nature of the studies, small samples, and often-times higher acuity/more severely ill patients in the PCC groups. Additionally, these trials included almost exclusively patients with HM2 or HVAD which carry a higher thrombotic risk than the HM3.

Prothrombin complex concentrates/fresh frozen plasma in pediatric patients

In the pediatric CF-LVAD patient population, evidence for the use of PCC is limited to case series and small retrospective studies. Yu reported the successful use of PCC 25 units/kg in the setting of acute management of neurosurgical intervention for hemorrhage and stroke in pediatric CF-LVAD patients on warfarin in combination with other agents.[155] All patients survived to transplant and were discharged home. FFP has also been reported to be used for management of bleeding or anticoagulation reversal in pediatric durable CF-LVAD patients at varying doses, and in combination with other agents with overall successful outcomes.[155,171–174]

Key points

- Given the limitations of the evidence on the use of PCC in CF-LVAD patients presenting with bleeding, no firm guidance regarding preferred dosing can be provided.
- In CF-LVAD patients presenting with intracranial hemorrhage, dosing strategies ranging from low dose (11–16 units/kg) to standardized PCC dosing based on the patients' initial INR (25 units/kg for INR 2–4; 35 units/kg for INR 4–6; 50 units/kg for INR > 6) have been shown to be effective.
- Time permitting, dose of PCC should be determined based on a patient-specific assessment of risks and benefits through a multidisciplinary collaboration of CF-LVAD physicians, hematology specialists, neurologists (when applicable) and/or pharmacists.

Recombinant factor VIIa

Recombinant activated factor VII is believed to independently stimulate clotting and platelet activity both through TF and TF-independent mechanisms.[175] Bruckner and colleagues published the largest case series of rFVIIa use in adult CF-LVAD patients.[176] In this single-center study, rFVIIa was administered to 62 patients, most often due to refractory surgical bleeding at the time of CF-LVAD implant, exchange, or removal. The authors compared events in patients who received "low-dose" (1.2 mg or approximately 20 mcg/kg) rFVIIa with "high-dose" (single or repeat dosing totaling 30–70 mcg/kg). Blood product transfusions were reduced in both groups after the administration of rFVIIa. Thrombotic events occurred in 22.6% of patients and included stroke, DVT, MI, PE, vascular occlusion, and ventricular thrombus. Notably, the rates of thrombosis were higher in the high-dose rFVIIa group (36.7%) compared with the low-dose group (9.4%).

Recombinant factor VIIa in pediatric patients

With regards to pediatric durable CF-LVAD patients, there is limited data regarding the utilization and dosing of rFVIIa, thus no recommendations can be made.

Key points

- With the availability of PCC, rFVIIa should be limited in CF-LVAD patients due to concern for thrombotic risk.
- Recombinant factor VIIa (rFVIIa) may be considered for refractory bleeding when all reversible causes of bleeding have been corrected. A "low dose" (i.e., ~20 mcg/kg) is preferred.

Antiplatelet reversal

Given lack of therapeutic options, patients on aspirin who present with acute bleeding are most commonly managed by withholding therapy. This practice may be reasonable due to the fact that approximately 30% of patients are considered aspirin resistant.[177] Since aspirin irreversibly binds to platelets, platelet inhibition may be present for the life of the platelets (~10 days) however platelet function may recover as soon as 20% of cyclooxygenase activity has been restored which may occur in 2 days.[178]

In pediatric patients, there is inconclusive evidence to recommend antiplatelet reversal. Case reports and case series report either continuing, holding, or administering platelets.[155,173,174]

Key points

- In adult and pediatric patients, the use and dose of intravenous vitamin K_1 depends on the severity of the bleeding and the need for sustained reversal of anticoagulation.
- In adult CF-LVAD patients that experience a minor bleeding with high INR levels, low-dose oral or intravenous vitamin K_1 can be considered in addition to temporary interruption of VKAs.
- In adult CF-LVAD patients that experience a major or life-threatening bleeding, high-dose (5–10 mg) intravenous vitamin K_1 should be administered in combination with other anticoagulation reversal agents (PCC of FFP).
- When urgent INR reversal is indicated, PCC may be preferred over FFP due to more rapid reversal. It is ideal to discuss a patient's individual risk of thrombotic events and the indication and dose of PCC and FFP for the management of bleeding in a multidisciplinary team (including an anticoagulation specialist, hematologist, member of the CF-LVAD team).
- There is insufficient evidence to inform decisions around the use of rFVIIa in contemporary CF-LVADs. Other agents such as PCC and FFP should be used preferentially. If rFVIIa is required for refractory bleeding, the lowest effective dose (≤20 mcg/kg) should be used.
- In pediatric patients with a durable CF-LVAD requiring acute bleeding management, collaboration of the multidisciplinary team (including an anticoagulation specialist, hematologist, pharmacist, and members of the CF-LVAD team) will assist in arriving at an appropriate strategy for each patient. Consideration should be given to holding anticoagulation, and if urgent reversal is indicated, the utilization of vitamin K, PCC and or FFP in light of patient's risk of thrombotic complications.

Minimization of antithrombotic therapy

Currently, all commercially available continuous flow LVADs carry recommendations for use with VKA plus aspirin for antithrombotic therapy; this may change given the recently published results of ARIES-HM3. However, there is limited data to guide attempts at minimization of antithrombotic therapy in certain populations and in particular circumstances.

In the US arm of a multicenter, observational study, CF-LVAD patients who had a reduction in their antithrombotic therapy in response to a bleeding event with either de-escalation to VKA alone, use of aspirin alone, or no antithrombotic therapy at all did not have a reduction in future bleeding events and may have been predisposed to a higher risk of thrombotic complications.[179] One group retrospectively studied a mixed cohort of HM2 and HVAD patients who had antiplatelet therapy reduced in response to bleeding events.[51] Decreasing aspirin dose in this setting reduced subsequent bleeding events without increasing thrombotic complications.

In those patients supported with an HVAD, data from the bridge to transplant approval study and the subsequent continuing access protocol has identified aspirin doses ≤ 81 mg as a predictor of both hemorrhagic and ischemic cerebrovascular accidents.[46] Additionally, recent single-center retrospective data evaluating aspirin at 162–325 mg vs ≤81 mg daily was suggestive of a trend towards more ischemic stroke and pump

thrombosis in the dose-reduced aspirin group, with no benefit in regard to HRAEs, rendering many practitioners reticent to reduce or remove ASA in patients with an HVAD.[47]

As noted in earlier sections of this document, 2 small, single center analyses of patients with a HM3 showed no excess in HRAEs when ASA was stopped due to bleeding[55,56]; this strategy may be safe and reasonable moving forward. Increasingly, patients with a HM3 CF-LVAD may no longer be receiving ASA at all, which will reduce the number of patients presenting with bleeding events and the need for de-escalation of their existing antithrombotic therapy.

Key points

- Patients with CF-LVAD who have had a bleeding episode may be at risk for downstream thrombotic events if antithrombotic therapy is minimized; shared decision making should be employed when determining optimal antithrombotic therapy.
- There is no data to suggest the safety of minimization of antithrombotic therapy in patients with a HVAD, while there may be potential harm. These patients should remain on aspirin doses greater than 81 mg daily plus a VKA (with target INR $\geq$ 2.0.) unless a multidisciplinary decision based on patient-specific factors determines that a reduced strategy is appropriate.
- In patients with a HM3 CF-LVAD who have had a significant bleeding event, a lower INR target of 1.5–1.9 may be considered, however the long-term rates of thrombotic events with this strategy are unknown.
- HM3 patients with a significant bleeding event on any dose of aspirin (81–325 mg) should be strongly considered for indefinite discontinuation of aspirin.
- Given variability in anticoagulation protocols currently being utilized in pediatric patients with a durable CF-LVAD (i.e., Edmonton, Stanford, ACTION), it is difficult to provide antithrombotic minimization strategies.

OTHER INTERVENTIONS TO MINIMIZE HRAES

Device management

Surgical positioning

The position of the inflow cannula in the left ventricular cavity is of utmost importance. Even though thrombi formation is caused by a variety of factors, such as pump type and flow, infection, anticoagulation and blood pressure, the size of the LV is not negligible. Low flow with stasis at the LV apex is significantly increased with positioning of the inflow cannula near the lateral wall compared to a central implantation of the cannula at the apex. Therefore, placement of the inflow cannula towards mitral valve should be the goal during inflow cannula positioning.[180]

The PREVENT study showed that HM2 pump position at implant had a significant impact on the event-free survival and the incidence of adverse events at 6 months. An extreme angle of the inflow cannula relative to the pump and to the vertical plane of the mitral valve axis was identified as an independent risk factor (hazard ratio = 3.6; 95% confidence interval = 1.5–8.9; $p = 0.006$) for pump thrombosis when adjusting for differences in pump speed and anticoagulation.[181] Deep pump pocket creation, parallel placement of the inflow cannula to septum, avoidance of right ventricle compression by the outflow graft and pump fixation after optimal positioning before chest closure are the 4 key principals.[182] HVAD or HM3 implantation are quite similar, and for both pumps the inflow cannula should be parallel to the interventricular septum and directed towards the position of the mitral valve.

Weight gain or loss and ventricular remodeling can lead to a change of the position of CF-LVAD components inside the patient's body. Regular assessment of the inflow cannula's position by X-ray or echocardiography should be performed to control the position of the inflow cannula.[183] In general, evaluation of pump position through imaging (chest X-ray, TEE, CT) during routine visits in the outpatient clinic is well-advised with thorough evaluation of conservative therapy options in cases of inflow thrombosis to avoid surgical revision.

Continuous-flow LVAD speed management

Continuous flow left ventricular assist device speed needs to be adapted to each individual patient depending on their weight, height, and size in consideration of calculated cardiac output. In CF-LVAD ramp testing, speed is first reduced, and echocardiographic and hemodynamic data are obtained. The speed is then increased while repeat

echocardiographic and hemodynamic data are obtained at each pump speed. Using this data, the appropriate CF-LVAD speed (targeting a pulmonary capillary wedge pressure (PCWP) < 18 mm Hg, central venous pressure < 12 mm Hg, and cardiac index > 2.2 liter/min/m^2) can be determined.[184] Echocardiography is used to determine the optimal CF-LVAD speed that allows intermittent aortic valve opening and neutral interventricular septum position without increased aortic or tricuspid regurgitation or RV dilation. There is no increased risk for clinically relevant bleeding complications after speed optimization. Hemoglobin levels remain unchanged. Speed optimization enables at least intermittent aortic valve opening without the development of increased aortic regurgitation.[185] Speed optimization should be addressed during routine follow-up visits.

Outflow graft placement/movement

Low flow alarms or clinical signs of low flow are often evidence of outflow graft obstruction.[186] Outflow graft kinking and twisting should primarily be avoided. Clockwise rotation of the pump at the time of implantation can enable placement of the outflow graft at a greater angle. Another option is to resect one part of the graft and add an end-to-end anastomosis. This would require full heparinization and cardiopulmonary bypass.[187] In a retrospective single-center study, Agrawal et al. showed that ~6% of their LVAD patients developed hemodynamically significant outflow graft obstruction with a mean time of graft obstruction onset of 2 years after LVAD implantation. Clinical presentations of outflow graft obstruction were low estimated LVAD pump flow (95%), heart failure signs/symptoms (90%), or both (85%), with 59% of the patients progressing to cardiogenic shock. Almost 80% of the obstructions were caused by external compression.[188] All their patients were treated with a percutaneous stent placement in the outflow graft. Surgical replacement of the graft is the most decisive strategy for true outflow graft thrombosis, although percutaneous stenting can be considered as an alternative in selected cases. Here the use of a cerebral protection system should also be considered.[189,190] During implantation of the CF-LVAD, partial filling of the LV while still on cardiopulmonary bypass can expand the outflow graft and assist with correct sizing of the length to prevent kinking or narrowing.[191] This can be achieved off-pump with filling the outflow graft with water under pressure. An additional CT angiogram with 3-dimensional reconstruction during follow-up visits allows for assessment of the course of the outflow conduit.

Key points

- Central positioning of the inflow cannula in the LV directed to the mitral valve orifice is ideal.
- Periodic evaluation of pump position through imaging (chest X-ray, TEE, CT) during routine visits in the outpatient clinic is reasonable.
- Thorough evaluation of conservative therapy options in inflow thrombosis may help to avoid surgical revision.
- Speed optimization should be addressed during follow-up visits in patients with ongoing signs/symptoms of heart failure.
- Surgical replacement of the graft is the safest strategy for outflow graft thrombosis, with percutaneous stenting as a minimally invasive alternative.

Blood pressure management

While early data in axial flow and hydrodynamic centrifugal flow pumps suggested a correlation between elevated BP and thromboembolic complications, newer data challenges the causality of these associations and cautions against overtreatment of BP. [97,125,192,193] Furthermore, low arterial pulse pressure due to continuous flow poses a significant challenge in accurately measuring systemic BP due to diminished oscillatory flow during the cardiac cycle.[194] In ambulatory patients, automated BP cuffs often fail to detect the BP due to diminished oscillatory blood flow. Therefore, opening Doppler pressure measured by a Doppler ultrasound has become the standard method for measuring BP outside of the ICU and typically falls somewhere between the MAP and systolic blood pressure (SBP). In patients lacking a palpable pulse, the opening Doppler pressure more closely approximates the MAP. However, in patients with a palpable pulse, the opening Doppler pressure will be closer to the SBP, and a cuff pressure will yield a more accurate MAP using the calculation MAP = (SBP + [2 x DBP])/3. Therefore, when taking a BP measurement in a CF-LVAD patient, it is important to first note whether the palpable pulse is present or absent to avoid overtreating BP in the event the opening Doppler pressure corresponds to the SBP rather than the MAP.[195]

The optimal range of systemic BP for patients on CF-LVAD support has been an area of intense focus over the past 10 years as survival has improved and attention has turned toward minimizing clinical adverse events, including stroke and pump thrombosis. A recent analysis of data from the MOMENTUM 3 study of a fully magnetically levitated CF-LVAD HM3 compared to HM2 showed no direct association between BP and stroke. In the analysis, device type was the most significant driver of stroke with HM3 having a 3.3 times lower stroke rate than HM2. [125] A recent analysis of the INTERMACS registry demonstrated decreased survival among CF-LVAD-supported patients with BP within the lowest and highest quartiles (average Doppler pressure ≤80 mm Hg and ≥ 105 mm Hg and average MAP ≤ 75 mm Hg and ≥ 90 mm Hg, respectively). Interestingly, the risk of stroke by BP category (low, normal, high, and very high) depended on how BP was measured. Blood pressure by MAP or opening Doppler pressure was not associated with stroke when assessed as a continuous variable. Patients with low and very high average Doppler pressures were at the lowest risk for stroke compared to average Doppler pressure 81–100 mm Hg. Finally, when blood pressure was assessed according to SBP, there was a significant association between higher average SBP (HR 1.07 per 10 mm Hg increase, $p = 0.001$), with patients with high and very high SBP (≥108 mm Hg) having the highest risk of stroke (log rank $p < 0.001$).[193] Taken together, the available evidence suggests that maintaining a Doppler pressure 80–100 mm Hg in non-pulsatile patients and a calculated MAP 75–90 mm Hg in pulsatile patients are needed to maximize survival and possibly to reduce thromboembolic events, although more randomized, controlled data is needed. Clinical trials in CF-LVADs are generally not prescriptive about medications used to achieve suggested BP targets, but available data suggests that HF Guideline Directed Medical Therapy agents should be utilized to manage BP in CF-LVAD patients who can tolerate these medications.

Key points

- In non-critically ill CF-LVAD patients, the presence of a pulse should be assessed. For non-pulsatile patients, an opening Doppler pressure should be measured with a target of 80–100 mm Hg. For pulsatile patients, an automatic cuff pressure should be obtained, and the calculated MAP (SBP + 2 x DBP)/3) should be maintained between 75–90 mm Hg.
- Care should be taken to avoid overtreating BP in patients on CF-LVAD support. Opening Doppler pressure < 80 mm Hg and MAP < 75 mm Hg should be avoided.
- Guideline-directed medical therapies for heart failure including neurohormonal blockade should be utilized to maintain BP targets.

Left atrial appendage ligation/Cox Maze procedure

For all patients on contemporary CF-LVAD oral anticoagulation is recommended; therefore, being off anticoagulation is not the desired therapeutic aim of any adjunct surgical procedure conducted at the time of CF-LVAD placement. A single center report investigating the effect of left atrial appendage closure found that left atrial appendage closure at the time of CF-LVAD implantation is associated with a decreased risk of thromboembolic events independent of the presence of atrial fibrillation.[196]

In an INTERMACS analysis of 3,909 patients with CF-LVAD, atrial fibrillation was not associated with an increase in thromboembolic events or decrease in survival.[197] A meta-analysis including 6,351 patients found no effect of atrial fibrillation on thromboembolic events, stroke, or pump thrombosis.[198] A recent large single-center report with 696 patients also showed that atrial fibrillation in CF-LVAD patients had no impact on survival, pump thrombosis or thromboembolic events.[199] Enriquez et al. investigated the different entities of atrial fibrillation and observed no increased mortality or increase of thromboembolic events in patients with paroxysmal atrial fibrillation. Persistent atrial fibrillation was independently associated with increased mortality and heart failure hospitalizations, but not death alone.[200]

Further work on understanding of the effects of unloading on electro-anatomical remodeling and the positive and negative effects of CF-LVAD implantations on atrial fibrillation are needed before more invasive strategies like Cox-maze procedure can be routinely recommended at the time of CF-LVAD implantation.

Key point

- Given limited data, the utility of ablation techniques or left atrial appendage closure/exclusion at the time of LVAD implantation are uncertain.

CONCLUSION

Durable, continuous-flow LVADs will continue to be integral to improving the longevity and quality of the lives of patients with advanced HF for the foreseeable future. Improvements in device design and patient management have reduced the overall number of HRAEs and contributed to prolonged life expectancy while on device support. This Consensus Statement captures the current best evidence and practices in the management of antithrombotic therapies and should serve as a guide to reducing and managing HRAEs for clinicians who care for these patients. While more research is always needed, the clinical research and experience captured in this document represent significant practice improvements over the past 15-20 years and have laid the path for ongoing work towards a future state where HRAEs are infrequent.

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