Antithrombotic Treatment for Left Ventricular Assist Devices: One Does Not Fit All

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Abstract

As the prevalence of heart failure is increasing globally, left ventricular assist devices (LVADs) have become essential therapeutic options in managing advanced heart failure. This review explores the development of LVAD technology, with a focus on the shift from pulsatile to continuous-flow devices, particularly the HeartMate 3, the most advanced generation of LVADs. The evolution in design has significantly enhanced patient survival and quality of life. However, hemocompatibility-related adverse events (HRAEs)—such as pump thrombosis, ischemic and hemorrhagic strokes, and gastrointestinal bleeding—remain major clinical challenges. Striking the delicate balance between preventing thromboembolic events and minimizing hemorrhagic risks remains critical in LVAD patient management. Current therapeutic strategies typically involve long-term anticoagulation with vitamin K antagonists and antiplatelet therapy, though optimal management must be individualized based on patient-specific factors and device characteristics. Emerging alternatives, including low-dose anticoagulation, direct oral anticoagulants such as apixaban, and aspirin-free regimens, offer promising potential to reduce adverse outcomes. This review also highlights the role of innovative mechanical designs in minimizing shear stress and alternative treatments in preventing complications like gastrointestinal bleeding. Despite these advancements, personalized treatment strategies are critical, as no single therapeutic regimen fits all LVAD recipients. Ongoing research into both device technology and pharmacological therapies is essential to further reduce HRAEs and improve long-term outcomes for LVAD patients.

Keywords

- left ventricular assist device
- hemocompatibility-related adverse event
- antithrombotic treatment
- antiplatelet therapy

Introduction

Heart failure (HF) has an estimated worldwide prevalence of 56.2 million individuals,[1] and it is still increasing. In 2019, The Heart Failure Association ATLAS reported data for 13 European countries, with a median prevalence of HF of 17.20 (interquartile range [IQR]: 14.30–21) per 1,000 people and a median annual incidence of 3.20 (IQR: 2.66–21) per 1,000 person-years, ranging from <2.0 in Italy to $\geqq 6.0$ in Germany.[2] The 5-year survival rate is less than 50% after diagnosis.[3,4] Heart transplantation (HT) is considered the optimal therapy for advanced HF, but donor shortage and strict selection criteria limit its use.[1,5]

In this context, left ventricular assist devices (LVADs) have emerged as a therapeutic alternative. The intended goals of therapy include short-term assistance, either "bridge to

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transplant" (BTT), the most frequent indication in Europe (EU) (66%),[6] or "bridge to candidacy," and long-term assistance, also known as "destination therapy" (DT) for patients who are not eligible for HT, the latter accounting for 73% of the indications in the United States from 2018 to 2022.[5]

The use of continuous-flow LVAD (CF LVAD) in appropriate candidates has improved survival, functional capacity, and quality of life for patients with end-stage HF.[6] HeartMate 3 (HM 3; Abbott, Chicago, Illinois, United States) is nowadays the only available device for clinical use approved by the regulatory agencies in the European Union (EU) and the United States.[7] According to the observational extended follow-up study of the MOMENTUM 3 trial,[8] it has a 5-year survival of 58.4% in the United States and 54 to 63.3% in European-based cohorts.[6,9] Nevertheless, hemocompatibility-related adverse events (HRAEs; pump thrombosis, hemorrhagic or ischemic stroke, and gastrointestinal [GI] bleeding)[10,11] continue to contribute to mortality and morbidity in assisted patients.[12] Therefore, optimal antithrombotic treatment is one of the important goals to be reached in the future.

LVAD Generations

Mechanical circulatory support (MCS)-implanted devices include LVADs, VADs used as right ventricular support (RVAD), biventricular support (BiVAD), and total artificial hearts (TAHs).[13] This review will focus on LVADs, as they are the most commonly implanted devices.

The goal of MCS research, starting in 1964 with the formation of the Artificial Heart Program,[14] was initially to develop a mechanical pump able to assist the left ventricle (LV) by pumping blood from the LV to the aorta, without major thrombosis, and enable patients to survive until a donor heart became available.[15]

The first LVADs were large pulsatile, pneumatically driven devices designed to mimic rhythmic cardiac activity and had limited durability.[15] Due to the limitations in miniaturization, the focus of research shifted toward developing electrically powered devices.[16] In 1999, the REMATCH trial[17] compared optimal medical therapy with a vented electric LVAD in advanced HF patients ineligible for HT. The improvement of survival at 1 year in the LVAD group (52 vs. 25% in the medical therapy group, $p = 0.002$) led to the approval of the HeartMate vented electric LVAD (HeartMate VE) for DT[15] after its former approval as BTT. The HeartMate XVE was then successfully designed to improve pump reliability and durability.[18] Despite improvements in survival with the HeartMate XVE (61% at 1 year),[19] adverse events (infection, neurological dysfunction, or pump failure) still affected about half of the patients.[15]

The second generation of LVADs was designed as continuous-flow pumps, categorized into axial-flow devices (HeartMate II, Thoratec Corporation, San Diego, California, and Jarvik 2000, Jarvik Heart, Inc., New York, New York, United States) and centrifugal-flow devices (HeartWare, HeartWare International, Framingham, Massachusetts, United States).

Continuous-flow pumps were much smaller (suitable for smaller patients including women), and they had a single internal rotor less prone to dysfunction.[15] They showed superior durability and better neurological outcomes compared with pulsatile pumps.[20] This generation contributed to improved survival of LVAD-implanted patients, with 1- and 2-year survival of 73.1 and 69.1%, respectively, and a median patient survival of 46.5 months (95% confidence interval [CI]: 44.7–48.2 months).[21] These devices were the most frequently implanted between 2010 and 2014 in the United States[21] before their use declined (1.8% of implanted devices in the United States in 2019).

Axial-flow pumps improved patient comfort with less pump failure and improved clinical outcomes, including lower risk of thromboembolic events.[22] Initially, centrifugal-flow devices were found to be noninferior to axial-flow pumps with respect to the incidence of disabling stroke or the need for device replacement, but they were associated with a higher risk of ischemic and hemorrhagic stroke (29.7 vs. 12.1%, $p < 0.001$).[23] Due to safety issues (pump malfunction), increased risk of mortality, and neurological adverse events, Medtronic stopped the sale of the HeartWare in 2021 after the implantation of several thousand patients worldwide.[24]

The HM 3 represents the third generation of LVADs. It received the CE mark in Europe for short- and long-term support in 2015, followed by FDA approval in 2017. The HM 3 utilizes centrifugal flow technology but with a fully magnetically levitated rotor (MagLev LVAD), eliminating mechanical contact between internal components and blood, thereby reducing the risk of mechanical failure and shear stress.[25] The HM 3 incorporates intrinsic pulsatility into the continuous flow, simulating periodic pulses every two seconds by briefly slowing down and speeding up the rotor speed. A shift to nearly exclusive implantation of MagLev LVAD occurred, representing 77.7% of LVAD implants in 2019[21] and 99.8% in 2022.[5]

In the MOMENTUM 3 randomized controlled trial,[26] Mehra et al compared the mechanical-bearing axial continuous-flow pump, Heartmate II (HM II) ($n = 512$), with the MagLev centrifugal continuous-flow pump, HM 3 ($n = 516$). Results showed that the HM 3 was superior with regard to 2-year survival free of disabling stroke or need for reoperation to replace or remove a malfunctioning device (76.9 vs. 68.8%, relative risk, 0.84; 95% CI: 0.78–0.91; $p < 0.001$).[26] Also, the number of events per patient-year for stroke, major bleeding and GI bleeding were lower in the MagLev pump group.[26]

Survival, again, improved, as showed in the 2023 annual report from the Society of Thoracic Surgeons (STS) Interagency Registry for Mechanically Assisted Circulatory Support (Intermacs). During the period 2018 to 2022, MagLev LVAD recipients exhibited significantly higher 1- and 5-year survival of 86 and 64%, respectively, than those receiving non-MagLev devices.[5]

Despite these encouraging results, the patient's quality of life remains affected by adverse events and mortality.[8] Rehospitalization occurs in more than half of the LVAD patients.[5]

The next part of this review will focus only on MagLev LVAD, namely, HM 3. It will cover advancements in hemocompatibility, HRAEs, and current strategies for antithrombotic and antiplatelet treatments.

Hemocompatibility

Hemocompatibility is a key factor in the interaction between a foreign material or device and the patient's blood. To achieve optimal hemocompatibility, the design goals of the HM 3 were to minimize the degree of shear force acting on blood components, to reduce the biomaterial–blood interface area, and to enhance continuous blood flow with an artificial pulse.[25] Despite these advances, the nonphysiological blood flow dynamic (continuous laminar flow with minimal pulsatility) contributes to HRAEs. The reduced pulsatility is associated with numerous alterations such as endothelial dysfunction, the release of proinflammatory factors, the rise of reactive oxygen species, a decreased nitric oxide bioavailability, platelet activation, and changes in the vascular bed (increased permeability, vascular smooth muscle proliferation, and dysregulated tone).[27,28] The high shear stress associated with continuous flow can also lead to von Willebrand factor (vWF) abnormalities. These abnormalities have been described in some studies as a decrease of large vWF multimers (acquired von Willebrand disease [vWD] type 2A) due to mechanical destruction,[29] cleavage of large vWF multimers by ADAMTS-13 (as indicated by a drop of ADAMTS-13 level), and platelet-dependent mechanisms.[30] These factors contribute to the increased hemorrhagic risk associated with the use of LVAD.

HRAEs during LVAD Assistance

Thrombosis and bleeding are among the most frequent deleterious complications occurring in patients with LVAD. Major bleeding is the second most common adverse event (after infection), affecting 17% of patients with MagLev devices in the first 90 days postimplantation and another 17% in the period beyond 90 days.[5] The most frequent bleeding complications include GI bleeding and hemorrhagic stroke. Thrombotic complications predominantly include ischemic stroke and pump thrombosis. HRAEs were reported as the third cause of death in the 5-year follow-up of the MOMENTUM 3 trial patients, with an attributed mortality rate of 3.9%,[8] and are also responsible for rehospitalization and morbidity.[5]

Hemorrhagic and Ischemic Stroke

Ischemic and hemorrhagic strokes remain significant causes of death in LVAD patients.[27] Even though continuous-flow devices have drastically improved patients' outcomes over the last two decades, 9.6% of MagLev patient's deaths are still attributed to neurological dysfunction.[5] The MOMENTUM 3 trial showed a significantly improved stroke-free survival at 2 years for HM 3 compared with HM II, with stroke rates of 9.9 versus 19.4%, respectively (hazard ratio, 0.42; 95% CI, 0.30–0.57, $p < 0.001$).[26] A secondary analysis of the MOMENTUM 3 trial confirmed the better neurologic outcome at 5 years with an occurrence of any stroke of 0.050 events/patient-year in the HM 3 group compared with 0.136 events/patient-year in the HM II group (rate ratio: 0.37, 95% CI: 0.27–0.50, $p < 0.01$).[8] In the 2023 Intermacs report, stroke occurred in 5% in the early period ($\leqq$90 days following implantation) and in another 4% in the late period.[5]

Under continuous flow, the arterial baroreceptors are unloaded, leading to an increase in neurohumoral and sympathetic activation, with consequently a chronic elevation of mean arterial pressure, a rightward shift of the cerebral autoregulation curve, and a reduction of the dilator capacity of the cerebral vascular bed.[27] However, the altered cerebral autoregulation in the context of continuous-flow devices is not well established, and there is conflicting evidence showing a preserved autoregulation during implantation and in the early postoperative period[31] as well as later.[32]

The multiple detrimental effects of reduced pulsatility and vWF degradation are predisposing factors for stroke.[27] Intravascular hemolysis can also lead to the activation of platelets (ADP release by damaged red blood cells) and the hemostatic system and may enhance clot stability.[33] Finally, infectious complications increase the risk of stroke through inflammation and septic emboli.[27]

Strategies to minimize both hemorrhagic and ischemic stroke risks are adequate antiplatelet therapy, close monitoring of anticoagulation, and strict blood pressure control (mean arterial pressure: 75–90 mm Hg).[34]

Pump Thrombosis

Pump thrombosis is a severe HRAE, and it is associated with significant morbidity and mortality.[35] The thrombotic risk is partly linked to the type of LVAD pump and its design. The rate of pump thrombosis with HM II began to increase in 2011. A pooled analysis from three experienced LVAD centers confirmed this trend, reporting an 8.4% (95% CI, 5.0–13.9) incidence of confirmed pump thrombosis within 3 months.[35] Contributing factors to this rise were thought to be the adoption of lower anticoagulation strategies (to prevent GI bleeding which was also a concern), particular pump-related settings (lower speed), and lack of adherence to recommended implantation techniques (i.e., pump below the diaphragm, inflow cannula parallel to the septum, outflow graft position right of the sternal midline, and pump fixation).[36] In the PREVENT trial (prospective, multicenter, single-arm), strict adherence to antiplatelet therapy combined with anticoagulation, and to other components of a structured surgical implant technique and postoperative hemodynamic management, was associated with a significant reduction in pump thrombosis risk at 6 months (1.9 vs. 8.9%; $p < 0.01$).[36]

Innovations in pump design allowed for a decrease in the rate of pump thrombosis.[37] As described in a computational fluid dynamics model, HM 3 compared with HM II minimizes the shear force on blood components due to the wide blood-flow gaps, has a lower hemolysis index, and alternates the speed every 2 seconds, changing blood flow to eliminate the presence of recirculation and stasis zones.[25] The design of HM 3 is also believed to allow the preservation of vWF by reducing shear stress and platelet activation.[30] In the MOMENTUM 3 trial, suspected or confirmed pump thrombosis at 2 years

occurred in 1.4% of patients ($n = 7$), significantly lower than for axial pump (13.9%, $n = 70$).[26] Similarly, in the 2023 Intermacs report, 5-year freedom from device malfunction/pump thrombosis was significantly higher for HM 3 compared with non-MagLev devices (83 vs. 54%, $p < 0.0001$).[5]

There are several other thrombotic risk factors, non-modifiable and modifiable. Non-modifiable factors include age at implant, female gender, higher body mass index, non-O blood type, some psychosocial issues (e.g., limited support, repeated non-compliance), the presence of a prothrombotic state, atrial fibrillation, dysfunction of the right ventricle, pulmonary disease, and finally history of GI bleeding.[38] Modifiable factors include tobacco use, bacteremia, pump infection, and hypertension.[38] Shear-mediated platelet activation and cytokine-mediated endothelial cell inflammatory activation may contribute to thrombosis by enhancing the adhesion of platelets to the inflamed endothelium and platelet prothrombotic function.[39]

Pump thrombosis can be highlighted by biological (elevated lactate dehydrogenase, plasma-free hemoglobin rise, and hemoglobinuria) or technical anomalies (increased pump power), or by clinical symptoms suggestive of new ongoing HF.[36] Interestingly, the detection of loss of circadian fluctuations of the pump power using time-frequency analysis of the LVAD logfiles[40] or accelerometer signal changes in the third-harmonic and non-harmonic amplitude[41] have been identified as new tools allowing early detection of pump thrombosis, prior to clinical manifestation or symptoms. Initial treatment, in case of hemodynamic stability, should consist of systemic intravenous anticoagulation with unfractionated heparin (Class I, level of evidence C).[34,36] For patients who are candidates for surgery, pump replacement is the definitive therapy (Class I, level of evidence C), with urgent transplantation as an alternative if the expected wait time for HT is short (Class IIa, level of evidence C).[34] In carefully selected patients, systemic or intraventricular thrombolytic therapy can be considered as an initial strategy over pump replacement (Class IIa, level of evidence C).[34] The safety and efficacy of glycoprotein IIb/IIIa inhibitors have not been established in this setting.[34]

Gastrointestinal Bleeding

Approximately 50% of cases of bleeding have a GI etiology.[21] In the MOMENTUM 3 trial, 24.5% of patients suffered from GI bleeding, a significantly lower rate than for HM II patients (30.9%).[26]

The etiology of GI bleeding is mostly attributed to the presence of vascular architecture abnormalities (angiodysplasias) in the small bowel and vWF degradation.[42] The pathophysiology related to GI bleeding in the context of CF LVAD consists of extrinsic (pharmacological) and intrinsic factors (related to LVAD).[43] Anticoagulation and antiplatelet therapy (extrinsic factors) increase the bleeding risk, but they are not the underlying cause of GI bleeding.[43] Intrinsic factors are secondary to the non-physiological, continuous blood flow and the foreign interface of the LVAD.[43] The presence of angiodysplasias is the result of a constant hypoperfusion, due to lower intraluminal pressure combined with an increased sympathetic tone, and hypoxia of the GI tract mucosa, stimulating the release of angiogenic factors.[43,44]

Acquired vWD has been attributed to the degradation of the large vWF multimers by ADAMTS-13[30,43,45]; however, current evidence does not completely support this mechanism. High shear stress seems the primary mechanism for inducing a conformational change in vWF that becomes hyperadhesive and activated. This results in the binding and activation of platelets, and also the promotion of angiogenesis.[46] Acquired vWD contributes to the high prevalence of bleeding during long-term support and at the time of transplantation.[47] Finally, acquired platelet dysfunction (antiplatelet agents and high shear stress exposure) and modulation of platelet microRNAs induced by LVAD are other contributing factors.[47,48]

In the 2023 Intermacs report, GI bleeding occurred in 8% of patients in the early period following implantation ($\leqq$90 days), and in 11% in the late period.[5] Over 5 years, patients implanted with a MagLev device showed a higher freedom from GI bleeding compared with the non–MagLev-implanted patients (72 vs. 60%, $p < 0.0001$).[5]

Future strategies to reduce the rate of GI bleeding will rely not only on technological advancements in LVADs but also on the pharmacological properties of specific drugs and innovative therapeutic approaches.

The EVAHEART (EVAHEART Inc, Houston, Texas, United States) is an LVAD, approved in 2010 by the Japanese Pharmaceuticals and Medical Devices Agency, designed to reduce vWF degradation by increasing pulsatility and reducing shear stress.[27] This device caused significantly less vWF degradation than the HM II in a mock circulatory loop with whole human blood.[49] A prospective observational study evaluated its effectiveness between 2011 and 2013.[50] Interestingly, over the 96 patients implanted with EVAHEART, no GI bleeding occurred. This new evolution in pump design seems promising to reduce GI bleeding, and the ongoing COMPETENCE trial will provide further insights by comparing EVAHEART 2 with HM 3.[51]

Pharmacologically available interesting agents include digoxin, octreotide, thalidomide, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and hormone therapy. A detailed description of their potential to reduce GI bleeding is beyond the scope of this review, but interestingly, the use of the readily available and cheap drug, digoxin, was associated with a reduction of GI bleeding in retrospective trials testing its impact on clinical outcomes in LVAD patients.[52–54] One potential explanation is the suppression of neo-angiogenesis through inhibition of the hypoxia-inducible factor-1α, which is a mediator of angiopoietin-2-induced angiodysplasias.[53]

Finally, a pilot study assessed the safety of infusing umbilical cord lining stem cells to improve vascular stability by addressing angiogenesis dysregulation, which is believed to contribute to bleeding in LVAD patients.[55] Despite including only nine patients, the study indicated a trend toward reduced GI bleeding.[55,56] This study highlights cell therapy as a promising research direction to improve hemocompatibility.

Antithrombotic Treatment Following Implantation

As stated, bleeding and thrombosis are still of the two most common complications in patients assisted with LVAD. The primary concern in the early postoperative period is bleeding; hence, "hemostasis management is a key priority."[34] Coagulopathy should be corrected early in the postoperative phase (Class IIa, level of evidence C), and targeted hemostatic intervention algorithms should be applied to achieve appropriate haemostasis.[34] Careful introduction of anticoagulant and antiplatelet therapy is necessary to achieve the desired therapeutic effect without increasing the risk of bleeding. Evidence regarding the introduction of anticoagulants is low and recommendations are based mostly on expert opinion. According to the 2023 International Society of Heart and Lung Transplantation guidelines, a heparin bridge (with unfractionated heparin) should be started within the first 24 hours after surgery if hemostasis is adequate and chest tube output is less than 50 mL/hour for several hours.[34] A targeted activated partial thromboplastin time (aPTT) between 40 and 60 seconds is recommended; however, as the normal range of aPTT is dependent on the reactive used by the laboratory, this range could vary depending on institutional and local protocols. Anti-Xa activity monitoring may be useful in specific situations where a prolonged aPTT is not associated with increased bleeding risk (preanalytical issue, factor XII deficiency, pre-kallikrein deficiency, interaction with C-reactive protein).[57] Vitamin K antagonist (VKA) therapy should be initiated when chest tubes are removed or by postoperative day 2, according to local hospital protocols.[34]

Long-Term Antithrombotic Treatment

As for the immediate postoperative period, evidence concerning long-term antithrombotic treatment following LVAD implantation is lacking, and most recommendations are based on expert consensus.

Long-term anticoagulation is recommended with VKA to maintain the international normalized ratio (INR) within a specific range specified by the manufacturer for each device (Class I, level of evidence B).[34,38] For HM 3 devices, the recommended target of INR is 2.0 to 3.0.[26] As for other indications for anticoagulation, maximizing the time interval during which the patient is within the INR target is challenging. It has been demonstrated in patients with atrial fibrillation that the mean time in therapeutic range (TTR) is $\sim 65\% \pm 20\%$.[58] In a 2017 meta-analysis on LVAD patients receiving warfarin, Martinez et al analyzed a total of 270 patients with follow-up ranging from 9 to 76 person-years. The weighted mean TTR was only 46.6% (95% CI: 36–57.3%, $I^2 = 94\%$), illustrating the difficulty of managing VKA anticoagulation in LVAD patients.[59] A retrospective study on HeartWare devices showed that a low TTR was associated with significantly lower 2-year survival (61.7%) compared with moderate and high TTR (72.4 and 75.1%, respectively; $p = 0.001$), and with higher rates of HRAEs.[60] Still, VKA therapy remains the recommended long-term treatment following LVAD implantation.[34,38]

As mentioned in the consensus document developed in accordance with the International Society of Heart and Lung Transplantation, the INR target may need to be adjusted in response to bleeding or thrombotic events occurring during LVAD support.[38]

In the pilot study MAGENTUM I, Netuka et al tested low-intensity warfarin anticoagulation (INR: 1.5–1.9) combined with aspirin in patients with HM 3 device, following an initial 6-week post-implantation period of standard anticoagulation (INR: 2.0–3.0) combined with aspirin.[61] No thrombotic events occurred during the 6-month follow-up, suggesting that low-intensity anticoagulation is achievable and may be safe in the context of HM 3 during the first 6 months of postimplantation. Further large-scale trials are necessary to confirm this finding. Interestingly, the TTR was $75.3 \pm 8.6\%$, during the low-intensity phase, which was much higher than the TTR reported by Martinez et al.[59,61] The strict follow-up performed in clinical trials may have contributed to the improved TTR and outcome in this pilot study.

Direct oral anticoagulants (DOACs) have several advantages over VKA, including rapid onset and offset of action, fixed dosing, less drug or dietary interactions, and no need for repetitive coagulation monitoring.[62] DOACs have a direct and targeted anticoagulant effect by inhibiting free and complex-bound clotting factor X (-xabans) or II (dabigatran). One of the first DOACs to be tested in a prospective randomized, open-label, single-center study in the context of LVADs was dabigatran.[63] Patients assisted with HeartWare devices were randomized to receive either VKA or dabigatran in addition to aspirin. The study had to be interrupted for safety reasons because of a higher rate of thromboembolic events in the dabigatran arm. DOACs became contraindicated for LVADs and for mechanical heart valves following another phase II study that was prematurely interrupted for the same issue.[64]

Even so, researchers have not given up on the potential of DOACs in this field, and have concentrated their efforts on another, possibly more promising molecule, the anti-Xa agent apixaban. In the ARISTOTLE trial, apixaban was compared with warfarin in patients with atrial fibrillation. Apixaban was superior in preventing stroke and systemic embolism and caused less bleeding (massive bleeding, hemorrhagic stroke).[65] In a retrospective study, apixaban was also associated with lower rates of GI bleeding compared with warfarin,[66] which may be particularly relevant to LVAD-associated bleeding.

Apixaban's anticoagulant effect was assessed in an ex-vivo mock loop model with a HeartWare device. It performed similarly to warfarin and better than dabigatran.[67] VKA and apixaban target coagulation before the initiation of the common pathway, as opposed to dabigatran which acts more distally in the pathway of the clotting cascade. Remembering that each molecule of factor Xa generates ~1,000 molecules of thrombin, a more proximal inhibition on the pathway might be more effective.[68] One interesting proposition from Aimo and colleagues, to improve -xaban

anticoagulation in the field of LVAD, would be to measure factor Xa activity in animals receiving warfarin (with an INR target of 2–3), and to search for the anti-factor Xa dose that achieves similar trough-and-peak factor Xa levels.[68]

In a phase 2, open-label trial, Shah et al compared apixaban to warfarin in patients assisted with a MagLev LVAD, and assessed the safety and freedom from a composite primary outcome of death or major HRAEs (stroke, device thrombosis, major bleeding, aortic root thrombus, and arterial non-central nervous system thromboembolism).[12] LVAD recipients were randomized in a 1:1 ratio to receive low-dose aspirin with either apixaban (5 mg, twice daily) or warfarin. A total of 30 patients were included (14 warfarin and 16 apixaban). The primary outcome did not occur in any patient in the apixaban group at 24 weeks and did occur in two patients (14%) in the warfarin group. This study showed that alternative anticoagulation with apixaban is feasible without an excess of HRAEs or mortality and supports the development of an appropriately powered clinical trial to assess the efficacity and safety of apixaban for patients with LVADs.

The DOT-3 randomized trial also demonstrated the safety of using apixaban (with or without aspirin) in a small number of HM 3 patients for up to 6 months, with no thromboembolic events reported in the DOAC groups. Moreover, patients on apixaban had successful HT.[69] However, the associated hemorrhagic risk on DOAC compared with VKA in the case of transplantation should be assessed on a prospective and broad basis before considering its inclusion in the management of BTT patients.

The ongoing ApixiVAD study (registered in the Australian New Zealand Clinical Trials Registry ACTRN12621000956808) is a multicenter, international, open-label, randomized, controlled, non-inferiority pilot trial. It aims to include 50 BTT or DT HM 3 patients. This trial will assess the safety of apixaban 2.5 mg twice daily compared with the standard of care with VKA.[70] Mortality, thromboembolic events, major bleeding (including operative bleeding), immediate transplant outcomes, and patients' quality of life related to anticoagulation will be assessed and the results should provide further information on the safety and feasibility of apixaban anticoagulation.

Antiplatelet Therapy

Antiplatelet therapy is recommended with VKA following LVAD implantation, even if solid evidence of efficacy and safety is lacking.[71] The 2023 International Society of Heart and Lung Transplantation guidelines state that antiplatelet therapy should be initiated in the postoperative period in the intensive care unit (Class I, level of evidence C) and that chronic antiplatelet therapy with aspirin may be used in addition to VKA (Class I, level of evidence C).[34] Aspirin is the most common antiplatelet agent used in this context.[34] Therapy is started between postoperative days 1 and 3 with the dosage ranging from 81 to 325 mg, depending on the local hospital practice.

Platelet function assays may be used to direct the dosing and number of antiplatelet drugs (Class IIb, level of evidence C).[34] A retrospective study in the context of HM 3 investigated the usefulness of aspirin titration based on the antiplatelet effect monitored by the Verify Now Aspirin test (Accumetrics Inc., San Diego, California, United States). The study found that increasing aspirin doses in non-responders to achieve responsiveness demonstrated a similar rate of pump thrombosis and freedom from thrombotic complications compared with the patients who were initially responsive.[72] It may be reasonable to consider escalation of antiplatelet therapy in patients who have thrombotic events with documented compliance to VKA and aspirin (Class IIb, level of evidence C).[34] Dual-antiplatelet therapy with aspirin and a P2Y12 inhibitor (clopidogrel, prasugrel, or ticagrelor) is not routinely indicated for LVAD patients unless there is a markedly increased thrombotic risk, a prior history of pump thrombosis or very recent coronary revascularization.[38]

Regarding the dosage of aspirin, there is no evidence of benefit on the rate of HRAEs in HM 3 patients receiving a high dose of aspirin compared with a low dose of aspirin; thus, it is recommended to use the lower doses.[38] In an exploratory analysis of the patients implanted with HM 3 from the MOMENTUM 3 trial, two groups were compared based on the aspirin dose: a low-dose group (81 mg, $n = 180$) and a usual-dose group (325 mg, $n = 141$).[73] The primary endpoint was survival free from HRAEs, including non-surgical bleeding, pump thrombosis, stroke, and peripheral arterial thromboembolic events. At 2 years, the proportion of patients who survived without HRAEs was similar between the low-dose and usual-dose groups (45.3 vs. 43.4%, $p = 0.94$) and it was also the case for freedom from hemorrhagic events (51.7 vs. 54.4%, $p = 0.42$).[73] This suggests either that the full aspirin effect is already achieved with an 81-mg dose or that aspirin is not required to prevent thrombosis in patients implanted with HM 3.[74]

The usefulness of aspirin has been questioned. First, the impact of aspirin with VKA compared with VKA alone on thrombin generation seems of low intensity in the context of LVAD.[75] Then, there is growing evidence of the increased bleeding risk associated with aspirin treatment in LVAD patients, without a positive effect on thromboembolic events. In a prospective study, including 53 LVAD patients with a median duration of support of 324 days (IQR: 226–468), 25 bleeding events were recorded (47% of the patients).[76] Coagulation tests showed that the INR was in the targeted interval, with a median of 2.51 (IQR: 1.98–2.97), and that there was a significant decrease of vWF:Ag and vWF:CB after the implant. Aspirin contributed significantly to bleeding events in the background of acquired vWD and its withdrawal significantly reduced bleeding recurrence.[76] Other studies supported the contribution of aspirin to bleeding in HM 3 patients and the safety and efficacy of an aspirin-free antiplatelet regimen in reducing HRAEs.[77,78]

Recently, an international, double-blind, randomized controlled trial, ARIES-HM3, investigated this issue.[71] HM 3-implanted patients were randomized in a 1:1 ratio to receive aspirin 100 mg combined with VKA or placebo combined with VKA. The primary composite outcome to assess the non-inferiority of placebo was survival free of major nonsurgical HRAEs (including stroke, pump thrombosis, major

bleeding, or arterial peripheral thromboembolism) at 12 months. The principal secondary endpoint was the incidence of nonsurgical bleeding events. A total of 589 patients were analyzed, 271 in the placebo group and 273 in the aspirin group. At 12 months, 74% of the patients in the placebo group reached the primary outcome compared with 68% in the aspirin group. These findings demonstrate the non-inferiority of the placebo with an absolute between-group difference of 6.0% improvement in event-free survival with placebo ([lower 1-sided 97.5% CI, −1.6%]; $p < 0.001$). Very interestingly, Mehra et al also showed that the avoidance of aspirin was associated with reduced nonsurgical bleeding events (relative risk, 0.66 [95% CI, 0.51–0.85]; $p = 0.002$) with no increase in stroke or other thromboembolic events. These results challenge the actual guideline of antiplatelet treatment in the context of LVAD, and the use of aspirin in this setting will likely decrease in the future.[38]

Finally, in the case of thrombotic or hemorrhagic HRAEs with or without recurrence, treatment may be tailored based on the patient's bleeding or thrombotic risk, even though no validated algorithm currently exists to guide clinicians.[38] Shah et al developed a multistate model to help clinicians estimate the dynamic risk of an adverse event (GI bleeding, stroke, and death) occurring in HM 3 patients in the next 30 days. The model includes 39 variables, to predict risk of GI bleeding (16 variables), stroke (10 variables), and death (19 variables). It has been developed and validated using the population of HM 3 patients included in the MOMENTUM 3 trial. During the validation process, the model was able to predict GI bleeding and death with moderate accuracy (AUC: 0.73 and 0.76, respectively), but accuracy was low for stroke prediction (AUC: 0.6).[79] This model might help the clinician decide on the modification of ongoing treatment, but it has yet to be validated in real-world HM 3 patients and its impact on the incidence of adverse outcomes will need to be studied.

An interesting treatment algorithm has been proposed by Consolo et al to reduce anticoagulation or antiplatelet therapy to avoid bleeding recurrence in HM 3 patients.[80] Depending on the anticoagulation status (INR <4 vs. INR >4), and the type of bleeding (mucosal/GI/occult anemia vs. retroperitoneal/muscle hematoma vs. intracranial), different adjustments of the antithrombotic regimen are suggested with the interruption of aspirin combined or not with a stepwise reduction of the INR target.[80]

Conclusions

The evolution in LVAD design has led to a decrease in HRAEs for the latest generation, represented by the HM 3. Bleeding adverse events, mostly GI bleeding, remain a major concern. In HM 3 patients, the use of aspirin had not been proven to be beneficial and there is growing evidence supporting its removal. VKA anticoagulation with strict and frequent INR monitoring is recommended within a specific INR range specified by the manufacturer. Clinical trials on apixaban like the ongoing ApixiVAD study will provide further information regarding the safety and feasibility of treating HM 3 implanted patients with this DOAC.

Finally, clinicians should remember that one treatment does not fit all LVAD recipients and that anticoagulation and antiplatelet therapy should be adapted based on the individual patient's bleeding and thrombotic risk.

Conflicts of Interest

AO-G has no conflict of interest.

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