Gastrointestinal Bleeding on Continuous-Flow Left Ventricular Assist Device therapy

Yoav Hammer MD[1], Abbas Bitar MD[1], Keith D Aaronson MD MS[1]

[1] Division of Cardiovascular Disease, Michigan Medicine - University of Michigan, Ann Arbor, Michigan, USA.

Corresponding author:

Yoav Hammer, MD

Division of cardiovascular medicine, University of Michigan hospital.

1500 E Medical Center Drive, Ann Arbor, MI, 48109-5853

Email: yoavhamer@gmail.com, hyoav@med.umich.edu.

Tel - (888) 287-1082.

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Abstract

While technological advances in the field of continuous-flow left ventricular assist device (CF-LVAD) are constantly being made, CF-LVAD recipients are still subjected to a relatively high rate of LVAD-related adverse events, with post-LVAD gastrointestinal bleeding (GIB) being the most common one. GIB is associated with a significant impairment in quality of life, multiple hospital admissions, blood transfusion requirements and possibly death. Furthermore, of those patients who bled once, many will experience recurrent GIB events, which further aggravates their discomfort. While some medical and endoscopic treatment options are available, evidence regarding their benefit remains largely equivocal, with all related studies based on data from registries rather than clinical trials. Although having a major impact on LVAD recipients, an effective and validated pre-implant screening options to predict GIB events post-implant are scarce. This review focuses on the etiology, incidence, risk factors, treatment options and the effect of new generation devices on post-LVAD GIB.

Key words – continuous-flow left ventricular assist device, gastrointestinal bleeding, arteriovenous malformations, Heartmate 3.

Introduction

The field of durable mechanical circulatory support (MCS) has progressed substantially over the past 5 years. The introduction of the newer generation Continuous Flow LVADs (CF-LVADs) have contributed significantly to patient survival and salvaged numerous patients with advanced HF who were not eligible for heart transplant or couldn't wait for one (1). While historically LVADs were implanted mainly as a Bridge to transplant (BTT) indication, 81.1% of LVADs were implanted as destination therapy (DT) in 2021 (2). HeartMate 3™ (HM3), a fully magnetically levitated centrifugal pump, is the newest device available, and has been shown to further improve outcomes of this patient population (2,3).

Improved survival, quality of life and functional capacity are realized despite a substantial burden of LVAD complications, including thromboembolic events, infections and non-surgical bleeding events, particularly gastrointestinal bleeding (GIB). While the incidence of thromboembolic events has dropped significantly with the improved hemocompatibility pump profile of the HeartMate 3, non-surgical bleeding, mainly GIB,

continues to be a common occurring event post LVAD implant (4). In this review, we discuss the incidence, etiology, risk factors, treatment, and prevention of GIB in LVAD patients.

Incidence and outcomes

While the prevalence of GIB in LVAD patients varies significantly between different studies, depending on device type and year of study (1,3,5,6), latest INTERMACS annual report estimates the incidence of post-LVAD GIB at 18%, 23% and 27% at 1, 2, and 3 years post LVAD implantation, respectively, in the years 2017-2021 (2).

Although GIB events can occur at any time after LVAD implantation, the risk is higher in the early post-implant period (within 2 years of implantation) (2,7). Moreover, patients admitted for GIB once, have a 20-30% risk for another bleeding episode resulting in hospitalization (8). Recurrent and debilitating GIB in CF-LVAD patients affect quality of life and may negatively impact their heart transplant candidacy. Although with frequent GI bleeding episodes patients can be up listed to higher UNOS listing status, when these bleeding episodes require transfusions, some patients will develop anti-HLA antibodies, which may undermine their chance of getting transplanted in a timely manner (9).

Gastrointestinal bleeding in LVAD patients may originate in any part of the gut. Thirty-three percent of culprit lesions will be found in the upper GI tract and 25% in the lower GI tract, however in 42% of cases no source of bleeding can be clearly identified (10). Of those cases with an identifiable culprit, over 50% result from arteriovenous malformations (AVMs), most in the upper GI tract (11). Other causes may include Dieulafoy lesions, peptic ulcer disease, bowel ischemia, radiation proctitis, neoplasia, diverticulosis, or hemorrhoids (12).

Gastrointestinal bleeding in LVAD patients is associated with more frequent hospitalizations, thromboembolic (TE) events and healthcare related costs (13-16). While some studies found a relationship between mortality and GIB in CF-LVAD patients (10,17), others have not (13,18).

Pathophysiology

As post-LVAD GIB has rarely been reported in patients who were supported by the old generation pulsatile assist devices, it is the continuous flow nature of the pump which is thought to be responsible for this phenomenon (19). Furthermore, removal of LVAD for the purpose of orthotopic heart transplant (OHT) was shown to dramatically reduce the rate of such events (9,20). Multiple mechanisms have been described in relation to GIB in CF-LVAD patients. The most common and accepted ones have been related to anticoagulant and antiplatelet therapies, an acquired von Willebrand syndrome and AVM formation (21-23).

Use of anticoagulant and antiplatelet medications –

The chronic use of anticoagulant and antiplatelet medications contributes to higher risk for bleeding events, GIB among those. However, patients with CF-LVAD have higher bleeding rates than do patients exposed to these agents in other settings (e.g., mechanical valves for example) (24). Moreover, many CF-LVAD patients with GIB present with subtherapeutic or normal international normalized ratio (INR) at the time of bleeding. This suggests that medication therapy is not the sole or even the most dominant factor leading to these events.

Acquired Von Willebrand (vW) syndrome

The acquired vW syndrome was initially described by Heyde et al and Warkentin et al in patients with aortic stenosis (AS) (25,26), and was found later to also be a fundamental component in the mechanism of GIB in CF-LVAD patients as well (21,22). Von Willebrand factor (vWF) is a high molecular weight multimer (HMWM) which binds factor VIII and serves as an important modulator in hemostasis. In patients with acquired vW

syndrome, shear stress on blood elements traveling through the rapidly spinning CF-LVAD rotor results in massive degradation of this vWF into inactive low molecular weight fragments, making the patient subjected to bleeding events, most commonly from AVMs located in the GI tract.

AVM formation due to lack of pulsatility

As the incidence of GIB is significantly higher in CF-LVAD compared with earlier generation pulsatile LVADs (19), the lack of pulsatility has been investigated as a possible contributor. Since blood flows continuously through CF-LVADS, pulsatility is usually markedly reduced, with any remaining minimal pulsatility through residual native cardiac function. As a result, the aortic valve is less frequently opened, what leads in turn to a further reduction in pulse pressure. This low pulse pressure is thought to result in GI hypoperfusion, vasodilatation and hypoxia, which trigger the release of angiogenic factors (13,23,27), which are thought to play a role in CF-LVAD related GIB. A recent study by Patel et al. reported a higher prevalence of AVMs in patients with HFrEF in general, with an even higher incidence in those with a higher NYHA class. This observation promotes the theory that those angiogenic factors do not necessarily promote new AVMs formation after LVAD implantation, but rather increase the tendency to bleed in pre-formed AVMs (28).

Risk stratification

Multiple studies have tried to establish risk factors associated with GIB post LVAD implantation. However, these studies have all been relatively small, and their findings have not always been reproducible (10,29-34). Factors found to be associated with GIB in patients with CF-LVAD are listed in **Table 1**. Yin et al. recently published the Utah score (17) for predicting the probability of GIB in patients with CF-LVAD. Three hundred fifty-one patients implanted between 2004-2017 were included, of which 120 (34%) had GIB after a median follow up of 196 days. Independent predictors of GIB were age > 54, history of previous bleeding, coronary artery disease (CAD), chronic kidney disease (CKD), mean pulmonary artery pressure < 18mmhg and fasting glucose > 107 mg/dl. Using those predictors, a score was created, and patients were stratified into low, medium or high risk for GIB. High risk patients according to this score had an 83% probability of GI bleeding at 3 years. Currently the Utah score is the only available model to predict GIB in CF-LVAD, although it has not been validated in other studies. While this score performed very well in the index study, it is based on data from a modest number of patients at two centers in same state and pertains only to older generation axial and centrifugal pumps, which are either much less frequently or no longer implanted. A robust and updated model from a comprehensive national registry of newer generation CF-LVAD's that could predict a patient's likelihood to bleed, based

on preoperative patient characteristics, could have important implications on patient selection for LVAD and subsequent management.

Diagnosis and management

Any history of melena, hematochezia, hematemesis, or coffee ground vomiting should prompt a quick evaluation for GIB. In some cases, the initial suspicion might arise from a decrease in serum hemoglobin accompanied by a positive fecal occult blood test, without obvious signs of bleeding. Because of the complex nature of these events, admitting the patient for evaluation is warranted. Most AVM related GIB events would resolve spontaneously within four days, and on average, one bleeding episode will require the administration of four packed red blood cell units (35). GIB in LVAD patients might be a complex event, with many challenges imposed on the provider. These events should be treated by experienced providers and managed with a multidisciplinary approach. Currently, there is not a widely accepted, standardized protocol for managing GIB in LVAD recipients, and practice varies among different institutions.

Endoscopic evaluation and management

While endoscopic evaluation is the most common method of investigation, it sometimes fails to reveal a clear source. The diagnostic yield of conventional endoscopic evaluation in this patient population is estimated at 60%, with upper endoscopy having the highest yield (36,37). Patients with hemodynamic instability should be resuscitated promptly in the intensive care unit prior to endoscopic evaluation.

Endoscopic diagnostic and treatment options include esophagogastric duodenoscopy (EGD), colonoscopy, push enteroscopy, double-balloon enteroscopy, and video capsule endoscopy (VCE). In most cases, the initial procedures in the evaluation will be an EGD, a colonoscopy, or both, depending on patient presentation. Coffee ground vomiting and hematemesis are strongly suggestive of an upper GIB source, while hematochezia is strongly suggestive of a lower one. Although melena suggests an upper GI origin in most cases, it can also result from a "high" lower GI origin. If EGD and colonoscopy have not yielded a source, VCE would be the next step in most cases. While EGD allows visualization of the proximal upper GI tract only (up to first part of jejunum), VCE holds the ability to visualize the entire small intestine and identify AVMs/polyps in that region. Although VCE is the only endoscopic modality which cannot be deployed therapeutically, it is an important diagnostic tool in obscure GIB. Once a source of bleeding had been recognized, it could be treated locally by thermal coagulation therapy or hemostatic clips (38). In case of a deeper upper GI source, a push enteroscopy or a double balloon enteroscopy might be warranted, in order to

reach the bleeding source. As mentioned before, in about 40% of cases, there will be no identified source of the bleed. In cases of an active and ongoing GIB, a tagged RBC scan (if bleeding rate ≥ 0.1-0.5 ml/min) and angiography (if bleeding rate ≥ 0.5 ml/min) may be considered (39). **Figure 1** summarizes the diagnostic and therapeutic approach to GIB in patients with CF-LVAD.

Medical management

Systemic medical therapy has become an eminent part of treatment and prevention strategies. Possible non-invasive strategies include rotor speed reduction, withholding anticoagulant and antiplatelet therapy and administration of several medications. Currently, all data regarding medical therapy in this patient population are derived from observational studies, with no randomized clinical trials performed.

Reducing or holding anticoagulation and anti-platelet medications

Anticoagulation and antiplatelet therapy, most often warfarin and aspirin, are standard of care in patients with CF-LVAD. Lowering or holding the dose of anticoagulation therapy and holding antiplatelet therapy for severe or recurrent bleeding are common first steps in the treatment of these patients. However, these approaches tip the balance towards the thrombotic side, and might result in a devastating TE event. Furthermore,

clinical scenarios in which newly prescribed medications such as antibiotics for driveline infection and amiodarone for arrhythmias are common in LVAD patients, and may increase the risk of drug interactions with Warfarin. Currently, there are no widely accepted guidelines to guide providers on how to manage this issue, and a personalized approach is usually taken, with great variability between different centers.

The literature regarding the safety of reduced antithrombotic prophylaxis in this population is conflicting. The TRACE study evaluated the option of reduced therapy both in Europe and in the USA. In the European arm, 101 patients with HM2 were treated with Warfarin only and no antiplatelet therapy, with a target INR of 2.3-2.5. Ninety-two percent of those patients were treated with this regimen based on a center standard of care or due to physician preference, and not due to past bleeding events. At 2 years, freedom from bleeding, ischemic stroke, hemorrhagic stroke, and pump thrombosis after initiation of Warfarin only therapy was 81% ± 6%, 96% ± 2%, 94% ± 3%, and 94% ± 3%, respectively. Given the combination a relatively low risk of bleeding and stroke/pump thrombosis, the authors concluded that this strategy may help to reduce the incidence of major bleeding without increasing the risk of thromboembolic events (40). In the US arm, 100 patients with HM2 were treated with either warfarin only (38%), aspirin only (28%), or no anti-thrombotic agent at all (34%). The main difference from the European study population was that in the US arm, 82% of patients were treated with a reduced regimen because of past bleeding events. Freedom from

ischemic stroke at 1 year was 93.8% ± 2.5%, and freedom from device thrombosis was 92.7% ± 2.7%. Bleeding event occurred in 52% of patients. Although TE event rate was overall low, it was higher than observed in the European arm and in previously described cohorts on a full antithrombotic regimen. The authors concluded that reduced therapy is achievable but might increase the risk of TE events (41). A study by Stulak et al demonstrated an increased risk of TE events in CF-LVAD patients who had an episode of GIB. Although the exact mechanism was not known, the authors concluded that it is likely that a reduction in anticoagulant and antiplatelet management might have contributed to this risk (15). While clear evidence regarding the efficacy of reducing anticoagulant therapy in older generation CF-LVADs is lacking, recent papers examining this question in HM3 patients revealed more favorable results. In an observational single-center study by Lim et al, stopping aspirin in 53 out of 80 HM3 recipients resulted in lower GIB rates, while no significant difference in either mortality or TE events was observed (42). An additional retrospective single-center study by Marshall et al also reported a lower bleeding rate but similar TE event rate in patients treated with a reduced antithrombotic therapy (defined as the discontinuation of aspirin, warfarin, or both), compared with those on standard antithrombotic regimen (43).

In summary, Patients admitted for GIB and have an INR above their target should be treated with holding warfarin until bleeding stops and INR returns to advisable value. Reversal agents to counter the effect of warfarin may increase the risk of experiencing

TE events, and therefore should be administered with great caution, according to the specific clinical circumstances. In patients who bleed with an INR in the usual therapeutic range (2.0-3.0), lowering the target INR and/or holding antiplatelet therapy may be considered.

Medications for primary prophylaxis

Angiotensin-Converting Enzyme Inhibitor/Angiotensin receptor blockers (ACEI/ARB)

In addition to the multiple mechanisms by which ACEI/ARB exert their beneficial effect on patients with HF, they have also been known to downregulate the action of transforming growth factor β (TGF-β), VEGF and angiopoietin-2. A few studies investigated the hypothesis that downregulation of these factors might reduce angiogenesis and thus reduce the occurrence and bleeding from AVMs. In 2017, Houston et al. published the first study to suggest a reduction in GIB rate in CF-LVAD patients receiving an ACEI or ARB. In this retrospective analysis of 131 patients with an HVAD or HM2, the rate of GIB in those patients who were not treated with ACEI/ARB was significantly higher (48%) compared with those who were treated (24%). Logistic regression hazards model demonstrated that treatment with ACEI or ARB therapy resulted in an odds ratio of 0.29 for GIB (44). In 2019, Converse et al. validated this observation, by reviewing 111 patients with HM2 and demonstrating a 57% reduction in

GIB in those patients who were treated with ACEI or ARB and a 63% reduction in the risk of AVM-related GIB. They were also able to demonstrate that when the mean daily post-operative lisinopril-equivalent ACE inhibitor/ARB dose was >5 mg, the risk of major GIB decreased in a dose-threshold manner (45). Neither the Houston nor the Converse study adjusted for propensity to receive an ACE inhibitor or ARB. Brinkley et al. published an analysis from the ISHLT IMACS registry, in which 11,494 patients with CF-LVAD were reviewed with regards to ACEI/ARB and mineralocorticoid receptor antagonist (MRA) therapy, using propensity score matching to adjust for differences in baseline characteristics related to the use of ACEI/ARB. In this analysis, ACEI/ARB treatment was associated with a significantly reduced GIB rate (HR of 0.88) and reduced mortality (HR of 0.72) (46). However, not all studies were able to establish a clear relation between GIB and ACEI/ARB therapy. In a recent analysis from INTERMACS by Jennings et al, ACEI/ARB did not demonstrate a protective effect against GIB (47). Vukelic et al similarly could not demonstrate a clear relation between ACEI/ARB and GIB in CF-LVAD patients (48). Three recent meta-analysis examined the relation between ACEI/ARB treatment and GIB in LVAD patents. Two of them concluded that this treatment did mitigate GIB (OR 0.35 [0.22-0.56] and 0.58 [0.34-0.98]) (49,50), while the other did not (HR:0.46 [0.16-1.3] (51). In summary, although evidence is equivocal, it appears that ACEI/ARB might provide certain protection from GIB events, and their use seems reasonable. As none of the mentioned studies,

including those in the meta-analyses were randomized clinical trials, a definitive

judgement as to benefits of ACEI/ARB with respect to GIB can't be made.

Digoxin

Digoxin inhibits hypoxia-inducible factor 1-alpha (HIF-1a), a transcription factor that

upregulates vascular endothelial growth factor (VEGF) and angiopoietin-2, thus

reducing angiogenesis in the GI tract. Vukelic et al. demonstrated a 2-fold reduction in

GIB events in LVAD patients treated with digoxin (16% vs 33%) in 199 CF-LVAD

patients, especially if the bleeding was presumed to be of AVM origin (48). Later, El-

Rafei et al. analyzed 649 patients with CF-LVAD (12% with HM3), and found that

digoxin was associated with a 34% less GIB. Furthermore, the GIB rate was even lower

when the analysis was confined to patients with AVM-related GIB (52). Digoxin has a

relatively narrow therapeutic window, and thus drug levels should be monitored.

Omega-3 fatty acids

Omega-3 fatty acids possesses anti-inflammatory and antiangiogenic properties. In a

paper published by Imamura et al., 30 patients with CF-LVAD were treated with 4 g/d of

omega-3s for approximately one year. When compared to the patients who were not

treated with omega-3s, those who were had a significantly higher chance for being free

of GIB (97% versus 73%) at one year (53). The mechanism of action remains obscure but may be related to reductions in TNF-α, with subsequent suppression of angiopoietin-2 expression. Omega-3 fatty acids are not known to have significant side effects, except for occasional dyspepsia.

Proton pump inhibitors (PPI)

Hickman et al. retrospectively examined the effect of PPIs on 30-day bleeding rate in patients who underwent an LVAD implantation and demonstrated a reduced HR for GIB of 0.18 in patients who were treated with PPI (54). While the benefits in the immediate post-operative period are evident, there is no clear evidence that PPIs reduce the rate of GIB in LVAD patients beyond this period.

Hemodynamic adjustments –

Increased right heart pressure has been reported as a risk factor for GIB in this patient population (30,55). Although there is no clear evidence that hemodynamic optimization in patients with elevated right sided filling pressures genuinely reduces GIB, it is considered a reasonable measure to take.

As mentioned earlier, one possible mechanism for the increased rate of GIB in CF-LVAD compared with older generation pulsatile devices is the lack of pulsatility. Pump speed reduction results in an increased left ventricular volume and pressure, which leads to a more powerful ventricular contraction and opening of the aortic valve (AV), thus creating a pulse. Several studies have examined this hypothesis. Wever-Pinzon et al evaluated the proportion of pulsatility in patients with HM2 LVAD and reported more GIB in patients with lower PI (i.e., less pulsatility)(13). Muthiah et al demonstrated recovery of vWF profile after improving pulsatility (evaluated by AV opening on echocardiography) in patients with HeartWare Ventricular Assist Device (HVAD) (56). However, this practice is not performed routinely in contemporary practice (unless the left ventricle is underfilled), as speed reduction might impair LV unloading, which in turn might result in HF exacerbation and thrombotic events. Furthermore, a benefit of this manipulation on the newer generation HM3 LVAD has not been demonstrated. Patients with refractory GIB who do not respond to endoscopic or conventional medical therapy might be candidates for this approach (36).

Medications for secondary prophylaxis

Octreotide

Octreotide, a somatostatin analogue, reduces splanchnic blood flow and gastric acid secretion in the upper GI tract , and has been used to treat AVM-related GIB in non-LVAD patients (57). It can be administered via injection, either as a short or a long-acting formulation. In recent years, several studies have examined the efficacy and safety of this agent in CF-LVAD recipients. A multicenter study by Shah et al. evaluated 52 HM2 patients who were treated with octreotide after a first GIB event and found those patients to have a significantly reduced risk of rebleeding compared with a matched historical control cohort (58). Juricek et al. evaluated 30 CF-LVAD patients with recurrent GIB and demonstrated a significantly reduced frequency of GIB following treatment with octreotide (59). In a similar study by Wilson et al., 32 CF-LVAD patients with recurrent GIB had fewer GIB events with octreotide (4.3 vs. 0.9 events/year) (60). Although octreotide use can be associated with adverse events (mainly GI symptoms), those events are mostly of mild nature, and would not typically result in drug discontinuation (61). Furthermore, in the above-mentioned studies, there were no adverse events reported (59,60). To date, octreotide has not been studied for primary prevention of GIB in LVAD patients.

Thalidomide

Thalidomide is an anti-angiogenic, orally administer medication that may prevent formation and bleeding from AVMs by suppression of VEGF. Anecdotal reports have

demonstrated reduced rates of GIB when thalidomide has been used for secondary prevention in LVAD patients with recurrent and intractable GIB (62-65). Thalidomide however has a relatively high rate of side effects, including birth defects, TE events, neuropathy and liver failure, and thus should be considered only in patients with recurrent and refractory GIB that cannot be treated with other modalities. The risk of TE event is particularly relevant in CF-LVAD patients, especially with older generation devices. Hence, thalidomide is not recommended in CF-LVAD patients with a history of pump thrombosis, and antithrombotic therapy should not be stopped in a CF-LVAD patient treated with thalidomide (63).

Estrogen based Hormonal therapy

Estrogen-based hormonal therapy has been used for secondary prophylaxis of bleeding AVMs in non-LVAD patients (66,67), possibly via improving vascular endothelium integrity. However, a multicentered, placebo-controlled, randomized controlled trial in 72 non-LVAD patients failed to show a significant reduction in bleeding with estrogen (68). Data regarding estrogen-based hormonal therapy in LVAD patients consists only of case reports (69). Furthermore, the possible risk of TE events raises major concerns in this patient population.

Danazol

Danazol is a synthetic steroid with anti-estrogenic properties that reduces endometrial bleeding in women (70). By possibly inhibiting endothelial permeability, danazol was examined as a possible mitigator in LVAD patients with recurrent GIB in 2 studies. Schettle et al. observed fewer hospitalizations and transfusion needed following initiation of danazol in 19 CF-LVAD patients with recurrent GIB (71). In a similar retrospective single-arm study of 30 LVAD recipients with recurrent GIB, Mathur et al. reported shorter hospital length of stay and fewer blood units transfused during subsequent hospitalizations for GIB (72). Given the limited evidence for its benefit, and because of concern for possible liver injury, danazol should not be used routinely, and further studies should continue to evaluate its efficacy.

Doxycycline

Doxycycline is a widely used antibacterial medication. In an in-vitro study on 8 healthy humans conducted by Bartoli et al., doxycycline significantly inhibited the action of ADAMTS-13, which serves as a vWF protease, leading to reduced vWF degradation and enhanced function (73). In a later study by the same author, blood samples were

collected from 31 CF-LVAD patients. Blood samples from LVAD patients who had GIB from presumed AVMs had more vWF degradation fragments compared with LVAD patients who bled from a non-AVM origin. The authors conclude that a theoretical basis exists for possible use of doxycycline in GIB in CF-LVAD patients (74). However, at present there is no clinical evidence supporting the use of doxycycline for prevention of recurrent bleeding in LVAD patients.

Desmopressin

Desmopressin is a vasopressin analogue that is currently used in patients with bleeding diathesis such as hemophilia A, type 1 von Willebrand disease or uremic bleeding or (75). Desmopressin exerts its haemostatic effect by inducing vWF formation, and thus had been suggested to potentially be beneficial in CF-LVAD patients. A case report by Hollis et al. in a HM2 patient with refractory GIB found that inhaled desmopressin (150 µg nasal inhalation 3 times per week) substantially reduced hospital admissions and transfusion requirements (76). Further studies are needed.

Bevacizumab

Bevacizumab (Avastin) is a humanized monoclonal antibody against VEGF that confers potent anti-angiogenic properties. Asleh et al. recently reported a pilot study of IV

Bevacizumab in 5 CF-LVAD patients with recurrent GIB, and demonstrated a significant reduction in blood product requirements, hospital admissions and endoscopies. No major adverse effects were noted (77). This promising option warrants further investigation.

Table 2 summarizes available medical treatments for GIB in CF-LVAD patients, along with mechanism of action, level of evidence and main side effects.

The era of HeartMate 3^{TM} (HM3)

In 2017, the US Food and Drug administration approved the implantation of HM3 LVAD in patients with advanced HF, based on the favorable results of the MOMENTUM 3 trial (78). In 2019, Mehra et al published the final report of the MOMENTUM 3 trial, which demonstrated superiority of HM3 over HM II for the primary outcome of freedom from disabling stroke and need for reoperation to replace or remove a malfunctioning device (3). The use of HM3 has increased significantly in the last few years, and in 2021, HM3 represented 92.7% of LVADs implanted in the US, according to the latest INTERMACS report (2).

As a fully magnetically levitated centrifugal pump, HM3 is designed to reduce shear stress on blood elements and avert pump thrombosis. It has wide blood flow passages

and thus reduces friction between blood elements and pump surfaces. This pump is also programmed for periodic cycling of rapid changes in rotor speed, and thus creates an artificial pulse. This fixed pulse is thought to reduce stasis in the pump (78,79). Although early reports could not demonstrate a clear reduction of GIB with HM3 compared with HM II, the final report of MOMENTUM3 trial did show a significant reduction in GIB events in patients with HM3 (24.5% of patients with HM3 vs 30.9% of patients with HM II) (3). This reduction in GIB events might be related to several factors – first, the reduction in shear stress is thought to ameliorate the degradation of high-molecular-weight multimers of Von Willebrand factor (21). Second, the artificial pulse is thought to reduce the tendency to form new AVM in GI tract of LVAD patients (13). Third, since patients with HM3 tend to have less thrombotic events, physician behavior might also be related to this GIB reduction, possibly by prescribing lower doses of anticoagulant and antiplatelet medications. Nonetheless, there is still a significant residual risk of GIB in patients with HM3, and therefore the need for better strategies to reduce GIB remains.

Better information on the risks and benefits of withholding antiplatelet therapy in HM3 recipients will soon be forthcoming. Recognizing the much lower risks of pump thrombosis and ischemic stroke with the HM3 than with earlier continuous flow devices, the ARIES study (NCT04069156) randomized 628 patients newly implanted with a HM3

to either warfarin plus aspirin arm or warfarin with placebo. Results are expected in autumn 2023.

Gaps in knowledge

Although common, there are still many aspects of post-LVAD GIB which remain obscure. First, we still lack the fundamental understanding of the complex pathomechanism of this phenomenon, which in turn limits our ability to properly prevent or treat these events. Next, while multiple treatment options exist, most studies regarding the efficacy of such treatment options are still largely equivocal, with no randomized trials available. Next, most data regarding post-LVAD GIB stem from old generation devices, which are mostly unavailable today, and therefore novel studies evaluating this phenomenon in patients with the newer generation and less thrombogenic HM3 LVAD are of necessity. Last, a tool to stratify the risk for developing post-LVAD GIB according to pre-implant characteristics could have an impact on the stratification process before LVAD implantation, the need for possible primary prophylactic therapy, and the intensity of anticoagulation a specific patient requires.

Conclusions and future directions

GIB remains a significant limitation of durable-CF LVADs, resulting in frequent rehospitalization and impairing recipients' health-care related quality of life. GIB in patients with CF-LVAD is a complex phenomenon related to a combination of host, pump, and medical factors. While technological efforts in pump technology have directly and indirectly contributed to reduced GIB, we as providers should aspire for a better understanding of the mechanisms of GIB and investigate novel treatment options. Future directions should focus on obtaining more robust evidence regarding the available medical treatment options for secondary prophylaxis of recurrent GIB. Given the lower incidence of pump thrombosis and thromboembolic events with the HM3 (relative to older generation pumps), future studies should explore primary prevention strategies for GIB, particularly if these could be targeted to patients at highest risk for GIB. The development of a stratifying tool for the risk of post-LVAD GIB according to pre-implant characteristics could have important implications on these patients.

Figure legend

Figure 1 – Suggested algoritm for the management of gastrointestinal bleeding in patients with CF-LVAD. LVAD: left ventricular assist device; HF: heart failure; GI: gastrointestinal; EGD: esophagogastric duodenoscopy; VCE: video capsule endoscopy; IR: interventional radiology.

Declaration of Interest: none declared.

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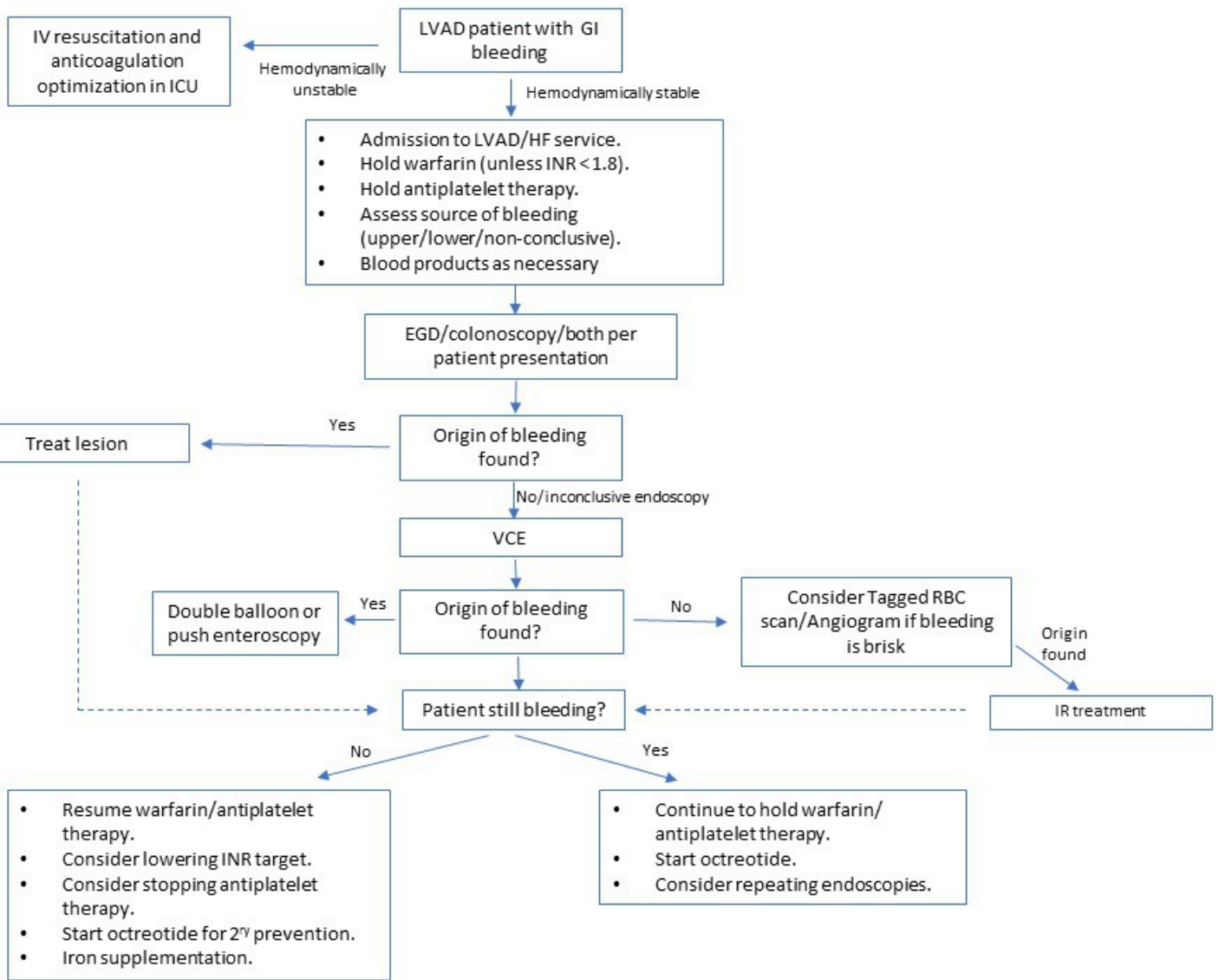
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IV resuscitation and anticoagulation optimization in ICU

Hemodynamically unstable

LVAD patient with GI bleeding

Hemodynamically stable

- Admission to LVAD/HF service.
- Hold warfarin (unless INR < 1.8).
- Hold antiplatelet therapy.
- Assess source of bleeding (upper/lower/non-conclusive).
- Blood products as necessary

EGD/colonoscopy/both per patient presentation

Yes

Treat lesion

Origin of bleeding found?

No/inconclusive endoscopy

VCE

Yes

Double balloon or push enteroscopy

Origin of bleeding found?

No

Consider Tagged RBC scan/Angiogram if bleeding is brisk

Origin found

Patient still bleeding?

IR treatment

No

Yes

- Resume warfarin/antiplatelet therapy.
- Consider lowering INR target.
- Consider stopping antiplatelet therapy.
- Start octreotide for 2^{ry} prevention.
- Iron supplementation.

- Continue to hold warfarin/ antiplatelet therapy.
- Start octreotide.
- Consider repeating endoscopies.

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