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Chapter 3

Gastrointestinal Bleeding with Continuous Flow Left Ventricular Assist Devices (LVADs)

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Additional information is available at the end of the chapter

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1. Introduction

Continuous flow left ventricular assist devices (CF-LVADs) have emerged as the standard of care for patients in advanced heart failure. The two common CF-LVADs in use are the FDA approved HeartMate II® (Thoratec Inc.) and the currently investigational HVAD™ (HeartWare Inc.). These CF-LVADs are being used as a bridge-to-transplant (BTT) and also as destination therapy (DT) (for those ineligible for heart transplant) [1, 2]. The clinical use of these newer devices has resulted in improved outcomes [3] including significantly reduced complication rates with improved durability compared to the first generation pulsatile design pumps [2]. However, with this new technology, a new set of complications have arisen including the increased incidence of Gastrointestinal (GI) bleeding [4, 5, 6, 7].

2. Definition

Patients are considered to have GI bleeding if they have one or more of the following symptoms: guaiac-positive stools, hematemesis, hematochezia, melena, active bleeding or blood within the GI tract at the time of endoscopy or colonoscopy, drop in hematocrit or patients hemoglobin level decreases by more than or equal to 1g/dl which necessitates transfusion of packed red blood cells [4, 5].

3. Incidence

Several studies done on CF-LVADs have shown varying rates of GI bleed ranging from 15% to 50% [Table 1]. One series showed that CF-LVADs have nearly four times the incidence of bleeding compared to the pulsatile devices [8].

Author	Study Population	Device	BTT / DT	GI Bleed Incidence	Results
Letsou et al. J Heart Lung Transplant 2005;24:105-109 [9]	21	JARVIK 2000	21 / -	3 (14%)	• All three cases were secondary to AVMs in the GI tract.
Stern et al. J Card Surg 2010;25:352-356 [7]	33	HM II® (20)/ HM XVE® (9)/ VentrAssist® (4)	19 / 14	8 out of 20 HM II® patients (40%)	• GI bleed was noticed only in patients with HM II® LVAD. • 3 patients (38%) had rebleeds • Mean time to first GI bleed was 87 days. • Source of bleed was identifiable in only 6(35%) patients.
Uriel et al. J Am Coll Caridol 2010;56:1207-1213 [10]	79	HM II®	64 / 15	24 (30.3%)	• Aim of the study was looking at bleeding from all cause. • GI bleed analysis was secondary.
Demirozu et al. J Heart Lung Transplant 2011;30:849-53 [5]	172	HM II®	-	32 (19%)	• AVMs were source of bleeding in 10 (32%) patients. • Median time to first GI bleed was 40 days. • All 4 patients with a previous history of GI bleed, bled again.
John et al. Ann Thorac Surg 2011;92:1593-1600 [11]	130	HM II®	102 / -	18 (17.6%)	• Analysis of GI bleed was not the primary end point of the study.
Morgan et al.	86	HM II®	54 / 32	19 (22.1%)	• Previous history of GI bleed was an independent

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Author	Study Population	Device	BTT / DT	GI Bleed Incidence	Results
J Heart Lung Transplant 2012;31:715-718 [6]					predictor of future GI bleeds (OR 2.24). • Patients with previous history of GI bleed, bled more (p=0.01) • All recurrent bleeds were from the same site.
Aggarwal et al. Ann Thorac Surg 2012;93:1534-1540 [4]	101	HM II®	7 / 94	23 (22.8%)	• Previous history of GI bleeds (OR 22.7), elevated INR (OR 3.9) and low platelets (OR -0.98) were independent predictors of future GI bleeds. • Most common cause of bleeding was gastric erosions followed by AVMs. • Recurrent bleed was more common in elderly patients. • Octreotide did not impact clinical outcomes.

GI – Gastrointestinal; AVM – Arteriovenous Malformation; HM II® – HeartMate II®; HM XVE – HeartMate XVE®; BTT – Bridge to Transplant; DT – Destination Therapy; INR – International Normalized Ratio; HMW vWF – High Molecular, LVAD- Left ventricular assist device, Weight vonWillebrand Factor; OR – Odds Ratio

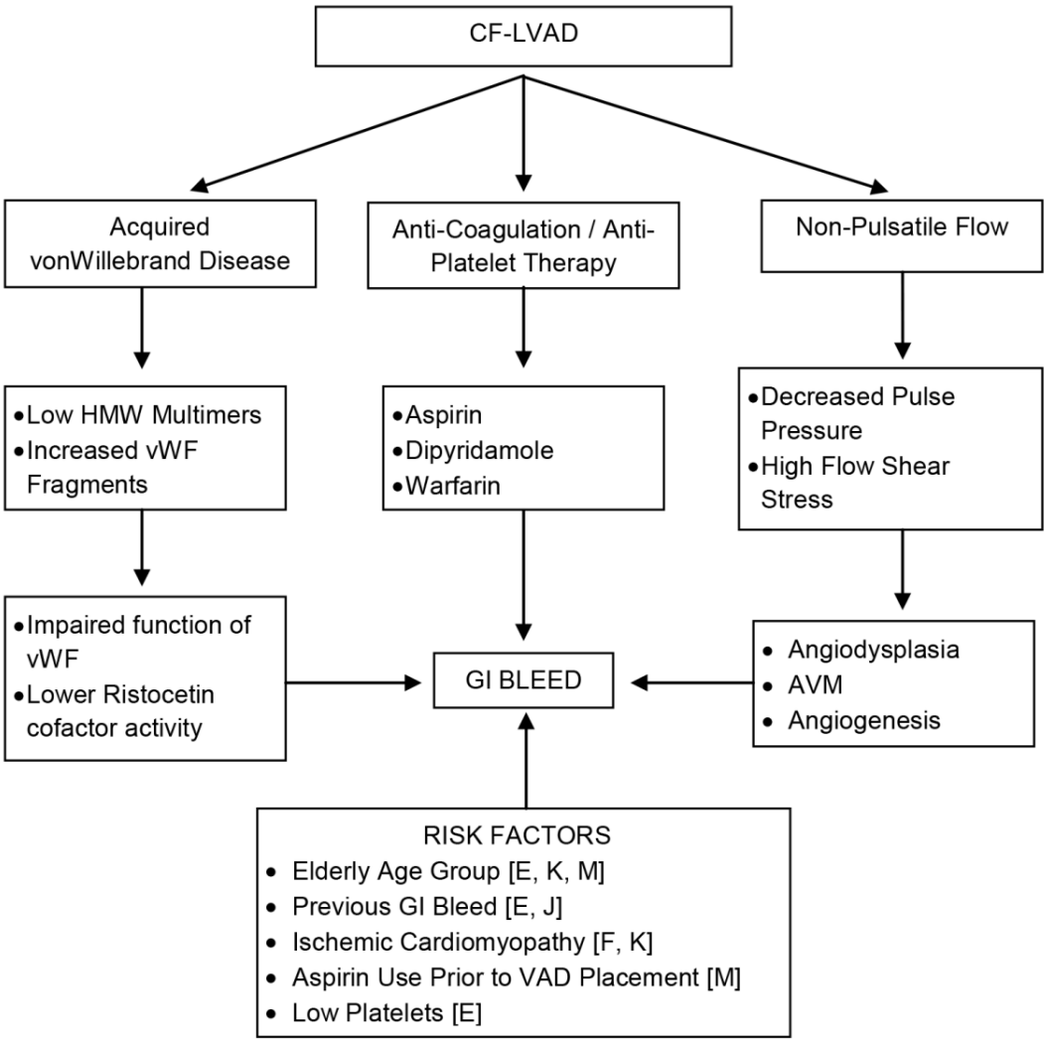
Table 1. Studies evaluating GI bleed in LVAD patients

4. Pathophysiology

The first generation of LVADs (HeartMate I®) utilized a pulsatile flow mechanism that did not necessitate anticoagulation like the newer second generation pumps. Reports of GI bleeding do however exist with this device [12, 13]. Since the advent of the newer CF-LVADs, the incidence of GI bleed has increased. Multiple mechanisms for this have been proposed: coagulopathy, lack of pulsatility, acquired vonWillebrand syndrome (AvWS) or other risk factors (low platelet count, increased age and a previous history of GI bleed) (Fig. 1.).

Patients with CF-LVADs have state physiologically similar to aortic stenosis because of the narrow pulse pressure [4, 14]. Heyde et al. [15, 16] suggested this physiology resulting in distension of the sub-mucosal venous plexus of GI tract eventually leading to angiodysplasia, arteriovenous malformations (AVMs) and bleeding. An alternative mechanism that has been suggested describes decreased perfusion of the GI and intestinal mucosa due to low pulse

pressure, causing mucosal ischemia and the formation of friable new vessels that are likely to bleed [5]. Several other theories have also been proposed for the relation between aortic stenosis like flow pattern and GI bleeding. Boley and colleagues [17] suggested that increased intraluminal pressure with muscular contraction may result in dilated mucosal veins that favor development of AV communication which may bleed when exposed to trauma or stress. Alternatively a neurovascular cause proposed by Cappell and colleagues [18] indicates that increased sympathetic tone results in smooth muscle relaxation and development of angiodysplasia.



HMW – High Molecular Weight; vWF – VonWillebrand Factor; AVM – ArterioVenous Malformation

Figure 1. Pathophysiology of GI bleeding in CF-LVAD

There is a substantial alteration of the prothrombotic profile in patients with CF-LVADs. The integrity of vascular endothelium, as evidenced by border protein expressions such as vonWillebrand Factor (vWF), is partially dependent on the stretch and distension created by the pulsatile flow. This plays an important homeostatic role in areas of high sheer stress such

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as GI AVMs [19, 20, 21]. One mechanism that was initially noted by Uriel et al. [10] was the development of AvWS as supported by depletion of high molecular weight vWF. CF-LVADs have impellar-like mechanism which creates high sheer stress environment and causes elongation and unfolding of the vWF multimers resulting in exposure to metalloproteases that cleaves it to form smaller vWF multimers similar to what happens when blood flows across a stenotic aortic valve [22, 23]. Sixty percent of patients with low HMW vWF experienced bleeding. Klovaite et al. [19] demonstrated the impact of CF-LVAD on vWF dependent platelet aggregation. They showed that almost 70% of the patients had impaired ristocetin-induced platelet aggregation. These labs return to normal baseline values post heart transplant which suggests that the hemodynamics of CF-LVADs have a significant role to play [10, 14].

5. Contributing factors

Major bleeding events are seen more frequently in older population and in those with ischemic cardiomyopathy as their underlying etiology for heart failure [10] (Fig. 1.). One of the most significant contributing factors is a previous history of GI bleed with the most likely source of bleed being the same site as the previous bleed [4]. Those with multiple episodes of bleeding tend to be significantly older than those with a single episode of bleed [4]. These patients need to be evaluated carefully preceding LVAD implantation because of their elevated risk profile. The duration of LVAD implantation does not appear to play a significant role as bleeding occurs at varying time intervals ranging from 8 to 18 months. Recent study by Aggarwal et al. [4] showed that an INR value at the upper limit of goal increased the risk of GI bleed compared to the lower limit, although this was not statistically significant. Platelets counts were also significantly lower in those with GI bleed according to the same study [4].

6. Classification of GI bleed

Bleeding is classified as either upper GI (proximal to the ligament of Treitz, which includes the esophagus, stomach and duodenum) or lower GI (distal to the ligament of Treitz, which includes the jejunum, ileum and colon) based on the site of bleed. Most common causes are vascular malformations like AVM and Dieulafoy lesions accounting for 30 - 40% and 15 - 20% respectively and peptic ulcer disease accounting for 10 - 15%. The location and types of lesions causing GI bleed are listed in Table 2 as seen from 4 different studies on this topic [4, 5, 7, 24].

7. Management

Management of a LVAD patient with GI bleed utilizes a multi-disciplinary approach. Main goals of initial assessment should be to evaluate the location and severity of bleed, hold any anti-coagulants and resuscitate to maintain stable hemodynamics (Fig. 2.).

Upper GI
Gastric / Duodenal AVM
Gastric / Duodenal Dieulafoy Lesions
Hemorrhagic Gastritis
Esophageal / Gastric / Duodenal Ulcers
Gastric Polyps
Gastric Angiodysplasia
Mallory Weiss Tear
Cameron's Ulcers
Lower GI
Jejunal / Colonic AVMs
Small Bowel Angiodysplasia
Diverticulosis
Cecal / Rectal Ulcers
Ischemic Colitis
Sigmoid Polyp
Hemorrhoids
Drive-Line Erosions of the Colon

Table 2. Location of GI bleeding after CF-LVAD

7.1. Laboratory investigations

Blood counts with hemoglobin and hematocrit along with platelet count need to be evaluated and compared with patient's most recent baseline value to assess severity of the bleed. Bleeding profile of the patient should also be obtained to assess level of coagulopathy.

7.2. Blood products

These include transfusion of packed red blood cells, platelets, cryoprecipitate and fresh frozen plasma as clinically indicated. The latter is usually given if there is evidence of active bleeding especially with supratherapeutic PT/INR. Transfusion requirements averaged 2 - 4 units of packed red blood cell per bleeding patient as shown in multiple studies [4, 5, 7].

7.3. Pharmacotherapy

7.3.1. Anticoagulants / antiplatelets

The current standard of treatment involves immediate discontinuation of antiplatelets and anticoagulants including aspirin, dipyridamole and warfarin. Although discontinuation of anticoagulants poses a risk for development of device thrombosis and subsequent systemic embolus, the true incidence of this adverse event is low. This has been attributed to be sintered titanium lining the inner surface of these devices [20, 25]. There are cases that have reported discontinuation of anticoagulants (in recurrent GI bleeders) for prolonged periods (up to 12 months) without any incidence of thrombus formation [26]. Anticoagulants are temporarily withheld and are restarted after complete resolution of bleeding. Patients with previous history or at high risk of thrombosis might require bridging (till INR reaches therapeutic range) with unfractionated or low molecular weight heparin, while being closely monitored for signs of bleeding.

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7.3.2. Proton Pump Inhibitors (PPI)

High dose antisecretory therapy with proton pump inhibitors like omeprazole, pantoprazole significantly reduce the rate of bleeding and rebleeding from GI ulcers [27]. PPI therapy also promotes hemostasis in lesions other than ulcers by neutralizing gastric acid which leads to stabilization of the clots [28]. Oral and intravenous PPI therapy also decreases rebleeding rate, the length of hospital stay and need for blood transfusion in patients [29, 30].

7.3.3. Octreotide

This is a synthetic somatostatin analogue that is usually used in the treatment of variceal bleeding but has been shown to reduce the risk of bleeding due to non-variceal causes as well [31]. It has been used in some centers with mixed reports. It acts by inhibiting gastric acid, decreasing gut hormones as well as constricting splanchnic and portal circulation. It also inhibits growth factors such as endothelial growth factors, basic fibroblast growth factor, and insulin-like growth factor-1 and is responsible for suppression of angiogenesis [32]. It can be administered either as a continuous infusion or subcutaneous injection [33]. Aggarwal and colleagues [4] demonstrated that octreotide administration did not significantly impact the length of hospital stay, requirements for blood transfusion, rebleeding rates or mortality. However these results could have been skewed because the predominant cause of the GI bleeding in their study population was gastric erosions with AVMs a close second.

7.4. Diagnostic modalities

There are multiple diagnostic modalities available to investigate and visualize the source of GI bleed. However, the source of bleed might not be identifiable in all cases. One study reported the possibility of not being able to locate the site of bleed at 65% of their study population [24].

7.4.1. Esophagogastroduodenoscopy (EGD)

This allows direct visualization of the esophagus, stomach and the proximal duodenum. EGD also permits us to perform intervention if needed at a site of bleeding which could be an AVM or Dieulafoy lesion. Elmunzer et al. [24] demonstrated that on average 3.3 endoscopic procedures were necessary for each patient before the cause of bleeding was established and several require an additional procedure prior to achieving complete hemostasis. Complications for this procedure include bowel perforation, bleeding, aspiration pneumonia and complication related to sedation.

7.4.2. Colonoscopy

This procedure provides us with direct visualization of the mucosa of the cecum, colon and rectum. Advantages include its ability to localize the site of bleed and the potential for interventional therapy. Some gastroenterologists do not recommend any bowel preparation since blood is a cathartic while others prefer an enema or a quick bowel preparation with balanced electrolyte solution [34]. The cecum can be reached in 95 % of patients presenting with lower GI bleed which may be sufficient enough as most lesions are found distal to the

cecum [34]. Complications of this procedure include bowel perforation, bleeding, infection and complications secondary to sedation.

7.4.3. Small bowel Video Capsule Endoscopy (VCE)

This provides a non-invasive diagnostic imaging of the small intestine that cannot be visualized with an EGD. The overall yield for obscure GI bleeding has been reported to be in the range of 45 – 70% with one meta-analysis showing the diagnostic yield of VCE (63%) to be significantly higher than deep bowel enteroscopy (26%) [35]. In about 16% of cases it does not reach the cecum within the recording time due to various reasons that can cause the bowel motility to slow down [36]. The main disadvantage with this study is that it is not possible to intervene therapeutically. There is some concern that the wireless signal transmission from capsule may be disturbed by the electromagnetic field of the VAD. The opposite may also be of concern where the signals may interfere with the functioning of the VAD and ICD [37, 38]. However, patients have undergone these procedures without complications.

7.4.4. Tagged RBC bleeding scan

Radionuclide imaging study can detect blood loss occurring at a rate of 0.1 – 0.5 ml/min. It is more sensitive than angiography but less specific [44]. The major disadvantage is that this can only localize the bleed to a general area in the abdomen and not a precise location. Tagged RBC scan should typically be performed prior to angiography to determine if bleeding is sufficient enough to increase the diagnostic yield of an angiogram and allow for selective angiography of appropriate vessels. Patients with a negative bleeding scan are most likely to have a negative angiogram [45].

7.4.5. Mesenteric angiogram

Angiography requires active blood loss of 1 – 1.5 ml/min for a bleeding site to be visualized [42]. This procedure is very specific but sensitivity varies depending on the pattern of bleeding. Advantages with this procedure are accurate anatomic localization of bleed and the fact that it does not need any bowel preparation. It permits therapeutic intervention with catheter directed vasopressin infusion and transcatheter embolization. The frequency of a negative arteriogram can be reduced if radionuclide imaging is used to screen for active bleeding [43]. Disadvantages include the inability to use this with renal insufficiency. Complications include worsening of renal function, infarction, bleeding.

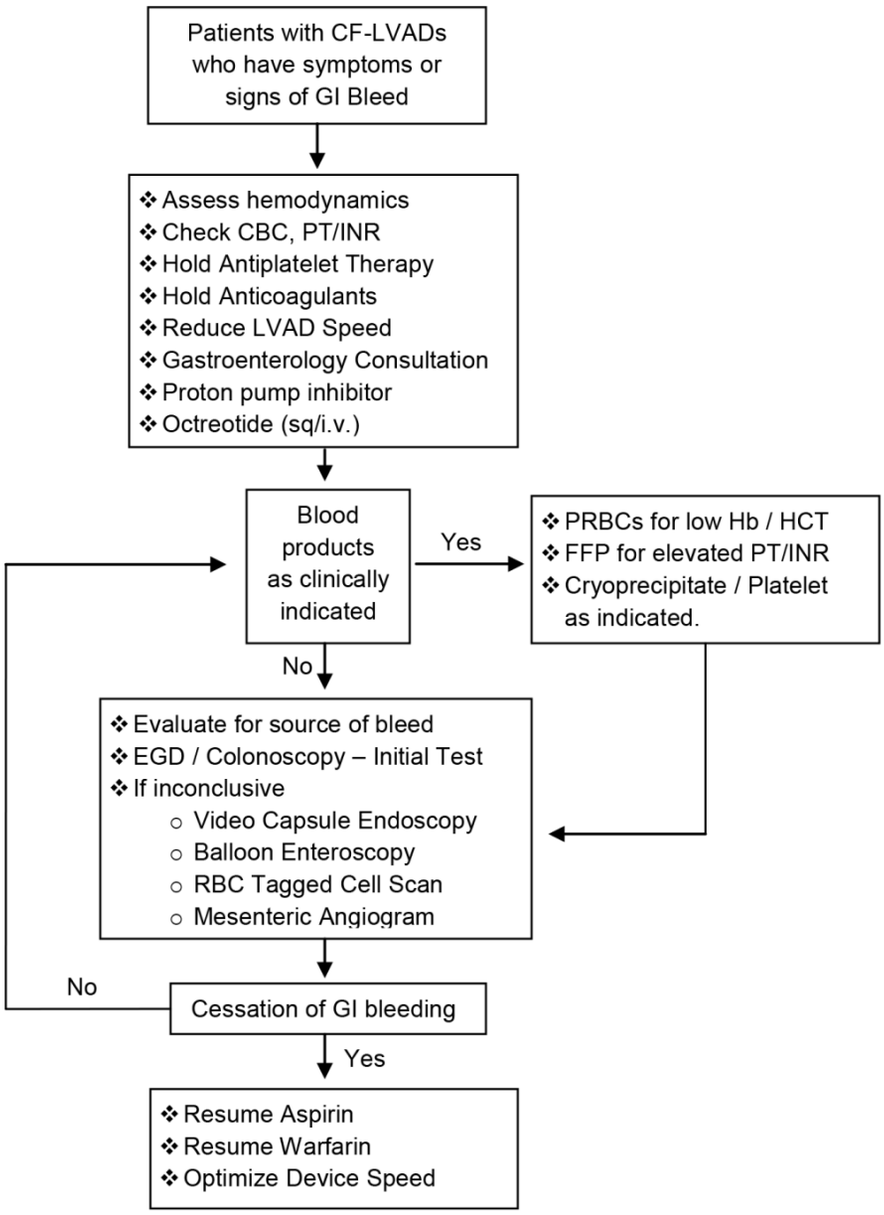
7.4.6. Deep bowel enteroscopy

Deep small bowel enteroscopy permits visualization and intervention till upto 60 cm of the proximal jejunum. The procedure is approached from the mouth (anterograde) or from the anus (retrograde) depending on whether the lesion is found in the first 60 % of VCE or in the last 40 % [39]. The diagnostic yield of balloon assisted enteroscopy ranges from 40 – 80 % with therapy being performed in 20 – 55 % of patients [40, 41]. Complications of this procedure include pancreatitis, bowel perforation, bleeding, and aspiration pneumonia.

http://dx.doi.org/10.5772/56010

7.5. Device management

The usual speeds of a LVAD pump are maintained at 8800 – 10000 rpm (for axial flow HM II®) and 2800 – 3200 rpm (for centrifugal flow HVAD™). In a patient with GI bleed, a common practice is to reduce the VAD pump speed to generate pulsatility. Speed adjustment should ideally be performed under echocardiographic monitoring in order to achieve the lowest possible speed safely while ensuring adequate left ventricular unloading [4]. This however might not be possible at time in patients with severe bleeding



CBC – Complete Blood Count; PT – Prothrombin Time; sq - Subcutaneous ; i.v. - Intravenous; Hb - Hemoglobin; HCT-Hematocrit; EGD – Esophagogastroduodenoscopy; PRBC – Packed Red Blood Cell

Figure 2. Management of GI bleeds in CF-LVADs

7.6. Intervention

Endoscopic interventional technique includes cauterization, injection, and clipping of a visible vessel, while intervention with mesenteric angiography involves transcatheter coil embolization. It is possible to perform a Deep Bowel Push Enteroscopy as a diagnostic and therapeutic procedure potentially guided by results of the capsule endoscopy. This is a somewhat invasive procedure but a good alternative to the more invasive surgical laparotomy. Very rarely surgical procedures like partial gastrectomy or bowel resection are required after multiple failed attempts at other non-surgical treatment options.

7.7. Anticoagulation post GI bleed

Aspirin is usually restarted after cessation of GI bleeding and ensuring hemodynamic stability. Re-initiation of warfarin along with aspirin is variable and depends on the severity of the GI bleed, endoscopic appearance of culprit lesion and other comorbidities (e.g. prosthetic heart valve). Goal INR for those anticoagulated with warfarin post GI bleed is aimed at the lower end of the therapeutic range (1.5 – 2 for HM II® and 2 – 3 for HVAD™) [4, 46].

7.8. Recurrence of GI bleed

Recurrence is more common in patients restarted on warfarin in combination with aspirin compared to those on aspirin alone. It is more common in the elderly and almost 60% of these recurrences are from the same site of bleed as the original source [4]. The predominant cause is usually gastric angiodysplasia [7]. After resuscitation and management of the bleed, the practice of restarting anticoagulation with warfarin varies widely and depends on patient comorbidities and physician preference. If it is restarted, goal INR is usually maintained close to lower end of normal for the specific LVAD type [4, 46]. Few preventive strategies being promoted include (i) maintaining LVAD pump speed at the lowest possible safe range under echocardiographic guidance to reduce flow and gain relative pulsatility, (ii) maintain INR at the low end of the recommended range for the respective devices in patients at high risk of GI bleed, (iii) close outpatient monitoring (more frequent than usual outpatient monitoring) of INR, hemoglobin and platelets, (iv) having a low threshold for diagnostic endoscopic evaluation in patients suspected of having GI bleeding.

8. Future directions

The significance of the role played by anticoagulants in causing GI bleeding along with altered hemodynamics and AvWS is not clearly discernable. Patient specific anticoagulation may be required tom improve clinical outcomes. Studies have shown that genetic polymorphisms in cytochrome P450 2C9 (CYP2C9) and vitamin K epoxide reductase gene (VKORC1) affect the pharmacokinetics and pharmacodynamics of warfarin [47]. Warfarin genotyping has been proven to reduce hospitalization rates including those due to GI bleeding [48] but has not been evaluated in this particular population with CF-LVADs.

The use of direct thrombin inhibitors like dabigatran, and Factor Xa inhibitors like apixaban and rivaroxaban has been approved for stroke prophylaxis in non-valvular atrial fibrillation [49, 50,

http://dx.doi.org/10.5772/56010

51]. No studies have been done testing the efficacy of these newer anticoagulants in patient with CF-LVADs. Future trials could be directed towards this to look for suitable alternatives to warfarin.

The use of thalidomide for GI bleeding secondary to vascular malformation that is refractory to endoscopic or medical therapy has been mentioned in literature. Thalidomide has anti-inflammatory, immunomodulatory and anti-angiogenic properties along with the capability to inhibit vascular endothelial growth factor (VEGF), a key component in the formation of vascular endothelium in the early stages of angiogenesis [52]. In a study by Ge et al. [53], it has shown to be an effective and safe method for treating and preventing recurrent GI bleeding for a period of up to 1 year. Lenalidomide, a thalidomide analogue that is more potent with lesser side effects is being evaluated for the same. There have not been any case reports regarding the use of thalidomide or its analogue in GI bleeding with CF-LVADs.

Another new avenue for treatment of GI bleed in LVAD patients involves the possible use of Factor VIII concentrates that contain both Factor VIII and vWF (Haemate P / Humate-P) for AvWS. Cushing et al. [54] reported a single case where transfusion of Factor VIII resulted in a significant decrease in the requirement for blood component transfusion. Once the treatment was initiated, the levels of vWF activity and Factor VIII levels improved dramatically. Future studies could investigate this possibility as a novel therapeutic strategy.

The likelihood of establishing pulsatile flow, even if intermittently with CF-LVADs has to be entertained in the future. If change in hemodynamics with continuous flow rather than pulsatile flow is a major contributor for GI bleeding then this might help reduce the number of events in the future. Newer devices may have this capability built in to switch back and forth between the two pump modes.

9. Conclusion

GI bleeding from CF-LVADs is gaining prominence with increasing use of CF-LVADs as a BTT or DT in those with refractory heart failure. At the present time there is no clear evidence that indicates a distinctive way in which to treat all GI bleeds. Management strategy depends on the patient's clinical picture, aggressive supportive measures and timely intervention.

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