A Multicenter Study of Left Ventricular Assist Device-Related Gastrointestinal Bleeding

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INTRODUCTION: Continuous left ventricular assist devices (LVADs) offer hemodynamic support in advanced and decompensated heart failure but are often complicated by gastrointestinal bleeding (GIB) in medically fragile patients.

METHODS: We performed a retrospective analysis of 475 consecutive patients who underwent LVAD implantation at the Massachusetts General Hospital and Tufts Medical Center from 2008 to 2019 and identified 128 patients with clinically significant GIB. Clinical characteristics of each bleeding event, including procedures and interventions, were recorded. We examined LVAD patients with overt and occult presentations to determine diagnostic endoscopic yield and analyzed predictors of recurrent GIB.

RESULTS: We identified 128 unique patients with LVAD implantation complicated by GIB. No significant difference was observed based on study center, underlying cardiomyopathy, race/ethnicity, serum indices, and medications used. Overt bleeders presented more commonly during LVAD implantation admission ($P = 0.001$) than occult bleeders. Occult bleed presentations had only 1 lower and no middle GI bleed source identified, despite similar workups to overt bleeds. Destination therapy (e.g., among nontransplant candidates) LVAD implantation (odds ratio 2.38, 95% confidence interval 1.05–5.58) and a history of GIB (odds ratio 3.85, 95% confidence interval 1.29–12.7) were independently associated with an increased risk of recurrent GIB-related hospitalization.

DISCUSSION: Our findings confirm a high rate of GIB, especially in destination LVAD patients, and show a low diagnostic yield for colonoscopy and middle GI bleed assessments in LVAD patients with occult bleeds. Overt bleeding was more common and associated with vascular malformations. Although endoscopic interventions stopped active hemorrhage, GIB often recurred.

INTRODUCTION

There are approximately 6.5 million adults in the United States diagnosed with heart failure (1). Left ventricular assist devices (LVADs) are mechanical circulatory support systems for patients with end-stage heart failure refractory to medical therapy, with 27,298 devices implanted between 2010 and 2019 (2,3). Although originally designed as a temporary bridge to transplant, LVADs are increasingly being used as life-prolonging (i.e., destination or palliative) therapy in patients not suitable for transplant. Major bleeding and infection continue to be the leading adverse events in this population, with 50% of these major bleeding episodes being gastrointestinal (GI) (2,4–6). With the widespread use of newer generation continuous-flow LVADs, the incidence of GI bleeding (GIB) in these patients has increased, with a reported incidence ranging from 17.6% to 40% and a 9% mortality rate (6,7). Lack of physiologic pulsatile laminar flow resulting in angiodysplasia, acquired von Willebrand syndrome, need for therapeutic anticoagulation, and impaired platelet aggregation are some of the proposed mechanisms of GIB in this population (7,8). The need for uninterrupted therapeutic anticoagulation for optimal functioning of the device makes managing GIB particularly challenging. GIB in this population has shown to increase length of hospital stay (9,10). Identifying risk factors predisposing patients to GI bleeds may help develop more efficient monitoring, diagnosis, and treatment for

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these complex patients (11–13). We report a large 2-center study of the risk factors that result in recurrent GIB in patients who have undergone successful LVAD implantation, to examine bleeding presentation types and interventions and propose an algorithm for the management of LVAD-associated GIB.

METHODS

Study population

We conducted a multicenter retrospective cohort study of all consecutive patients who underwent LVAD implantation at the Massachusetts General Hospital and Tufts Medical Center incorporating data from the Interagency Registry for Mechanically Assisted Circulatory Support and adding a more detailed review of the GI issues (14). The study protocol was reviewed and approved by the institutional review board of each participating institution (2019A008821). All adult patients aged 18 years or older who underwent LVAD implantation from February 2008 to January 2019 were included in our study.

Outcome assessment

We retrospectively reviewed 475 consecutive patients who underwent LVAD implantation at each site during the study period. We then identified patients admitted for initial or recurrent GIB, defined as having occult blood-positive stool, iron deficiency anemia, hematemesis, melena, hematochezia, or other blood loss in the digestive tract, after LVAD implantation. All patients who had clinically significant bleeding or anemia, which could have represented bleeding, underwent endoscopy at some time. Patients with known clinically significant bleeding events presenting to outside unaffiliated institutions were transferred to the home institution for completion of their workup. This created a cohort of 128 unique LVAD patients with GIB who were then analyzed as overt compared with occult bleeding, then by patients with a single admission for GIB (n = 77) and patients with recurrent bleeding across 2 or more admissions (n = 51). Recurrent bleeding was defined as individuals with an LVAD in place experiencing a bleeding event requiring hospitalization within a 11-year period after hospitalization for index bleed.

Data collection

We used a secure, Health Insurance Portability and Accountability Act-compliant data management system, the Research Electronic Data Capture electronic database. The longitudinal data set contained comprehensive deidentified patient information such as demographics; clinical characteristics including cardiomyopathy, serum indices at presentation, medication usage (e.g., aspirin, clopidogrel, warfarin, proton pump inhibitors, and angiotensin-converting enzyme inhibitors [ACEis] or angiotensin receptor blockers [ARBs]), history of previous GIB before LVAD implantation, and hospitalization; and admission laboratory data. Index bleed was defined as GIB requiring hospitalization after LVAD implantation or a bleeding event during LVAD implantation admission. We collected data on GIB during initial implantation and any recurrent GIB after index hospitalization for overt bleeds (confirmed with symptoms of melena, hematochezia, bright red blood per rectum, hematemesis) or occult bleeds (determined by hemoglobin drop >1 g/dL, a positive fecal occult blood test, or the presence of iron deficiency anemia that was deemed to warrant endoscopic evaluation). We also noted the characteristics of the bleeding event, including the etiology and location of the bleeding, and the time interval to endoscopic intervention. Bleeding locations

were defined as upper (esophagus through mid-duodenum), middle (mid-duodenum through terminal ileum), lower (large intestine), and unknown. Diagnostic finding was classified as (i) no bleeding seen, (ii) bleed of unclear etiology, and (iii) bleed and definite diagnosis. All clinical and endoscopic data were analyzed and extracted from the institutional electronic health records.

Statistical analysis

Patients were analyzed based on the presentation of their bleeding post-LVAD implantation and whether clinical outcomes varied by single or recurrent admission for suspected GIB. For comparing data between groups, we used the χ^2 or Fisher exact test for categorical measures and the Student t test for continuous measures. Continuous variables are expressed as means $\pm$ SDs, and categorical variables are expressed as numbers and proportions. A 2-sided P value of <0.05 was considered statistically significant. We used univariable and multivariable logistic regression analyses to calculate odds ratios (ORs) and their 95% confidence intervals (CIs) to identify independent predictors of recurrent presentations for suspected GIB. All analyses were performed using Stata Statistical Software version 11.0 (Stata, College Station, TX, 2009).

RESULTS

Baseline patient characteristics

Of the 475 consecutive patients who underwent LVAD implantation during the study period at either site, we identified 128 unique patients (25% of total) who had GIB. In total, there were 237 hospitalizations with an average length of stay of 24 days. The mean age at the time of initial GIB hospitalization was 60 ± 12 years, and most of the patients were male (78%) (Table 1). Patients more often had destination therapy compared with bridge to cardiac transplantation. There were no significant differences between patients with overt and occult bleeding, except that overt bleeding was more likely to require investigation during implantation admission (P = 0.001). Forty-four patients (34%) had bleeding during initial implantation hospitalization. Of all the patients identified with GIB , 51 (40%) required admission for recurrent bleeding. A history of GIB pre-LVAD implantation was more common among patients with recurrent GIB compared with those admitted just once (24% vs 8%). All patients with bleeding or a history of bleeding were on some form of acid-reducing therapy. Although anticoagulation was usually carefully controlled during bleeding events, patients were not fully reversed, and thromboembolic events were not observed. No patients were operated on or died directly because of their GIB.

Sources of overt and occult GIB

Most of the patients presented with an overt bleed on initial presentation, 93 (73% of total GIB) compared with 35 (27% of total GIB) patients who presented with an occult bleed. Among the occult bleeding patients, 34% upper GI bleed sources were identified and only 3% lower GI bleed. No middle GI bleeds and 54% unknown bleed locations were noted (Table 2). In comparison, overt bleeding patients had a similar percentage of upper GI bleed sources (32% vs 34%), but a much higher proportion of lower sources (25% vs 3%) and middle sources (13% vs 0%) and a lower percentage of unknown locations (27% vs 54%). Overt bleeders did undergo a higher number of middle GI bleed assessments, which included video capsule endoscopy (VCE), enteroscopy (push, single-balloon), computed tomography

Table 1. Baseline patient characteristics

	Overall (n = 128)	Overt (n = 93)	Occult (n = 35)	P value
Age at first GI bleed hospitalization, yr, mean (SD)	60 (12)	61 (11)	58 (15)	0.22
Female, n (%)	28 (21.9)	18 (19.4)	10 (28.6)	0.26
Study center, n (%)				
MGH	40 (31.3)	32 (34.4)	8 (22.9)	0.29
Tufts	88 (68.8)	61 (65.6)	27 (77.1)	
Reason for LVAD, n (%)				
BTT	53 (41.4)	35 (37.6)	18 (51.4)	0.16
Destination	75 (58.6)	58 (62.4)	17 (48.6)	
Initial LVAD indication, n (%)				
Nonischemic	63 (49.2)	44 (47.3)	19 (54.3)	0.48
Ischemic	65 (50.8)	49 (52.7)	16 (45.7)	
Race, n (%)				
White	108 (84.4)	76 (81.7)	32 (91.4)	0.18
Black	9 (7.0)	8 (8.6)	1 (2.9)	0.26
Asian	2 (1.6)	2 (2.2)	0 (0)	0.38
Other/Hispanic	9 (7.0)	7 (7.5)	2 (5.7)	0.72
Baseline indices, mean (SD)				
Hemoglobin (g/dL)	7.1 (1.5)	7.1 (1.5)	7.1 (1.5)	0.83
INR	2.6 (1.3)	2.5 (1.3)	2.8 (1.5)	0.33
Platelets (10^9/L)	190 (94)	185 (88)	204 (103)	0.32
Creatinine (mg/dL)	1.5 (0.8)	1.50 (0.9)	1.52 (0.5)	0.95
Albumin (g/dL)	2.92 (1.3)	2.88 (1.3)	3.04 (1.3)	0.51
Medications at admission, n (%)				
Aspirin	121 (94.5)	88 (95)	33 (94)	0.94
Clopidogrel	10 (7.8)	7 (8)	3 (9)	0.84
Warfarin	120 (93.8)	86 (92)	34 (97)	0.33
Proton pump inhibitor	92 (71.9)	69 (74)	23 (66)	0.34
ACEis/ARBs	62 (48.4)	46 (49)	16 (46)	0.70
Bleeding during initial LVAD implantation	44 (34)	40 (43)	4 (11)	0.001
Location of bleed, n (%)				0.001
Upper	42 (33)	30 (32)	12 (34)	
Middle	12 (9)	12 (13)	0 (0)	
Lower	24 (19)	23 (25)	1 (3)	
Unknown	44 (34)	25 (27)	19 (54)	
Procedures, n (%)	253	190	61	0.11
EGD	109 (85)	76 (82)	33 (94)	0.05
Colonoscopy	70 (55)	54 (58)	16 (46)	0.74
Middle GI bleed assessment	74 (58)	60 (65)	12 (36)	0.07
Single admission	77 (60)	57 (61)	20 (57)	1
History of GIB (before LVAD), n (%)	6 (4.7)	4 (4.3)	2 (5.7)	
Recurrent hospitalization	51 (40)	36 (39)	15 (43)	0.67
History of GIB (before LVAD), n (%)	12 (24)	9 (25.0)	3 (20.0)	

Middle GI bleed assessments included VCE, enteroscopy (push, single-balloon), CTA, tagged red blood cell scans, and interventional radiology-directed angiography. Polytomous variables may not add to 100% because of rounding. The χ^2 or Fisher exact test was used for categorical measures and the Student t test for continuous measures.
ACEi, angiotensin-converting enzyme inhibitor; ARBs, angiotensin receptor blockers; BTT, bridge to transplantation; CTA, computed tomography angiogram; EGD, esophagogastroduodenoscopy; GI, gastrointestinal; GIB, gastrointestinal bleeding; INR, international normalized ratio; LVAD, left ventricular assist device; MGH, Massachusetts General Hospital; VCE, video capsule endoscopy.

Table 2. Bleeding locations and procedures completed based on bleed presentation

	Overall (n = 128)	Overt (n = 93)	Occult (n = 35)	*P* value
Bleeding during initial LVAD implantation	44 (34)	40 (43)	4 (11)	0.001
Location of bleed, n (%)				0.001
Upper	42 (33)	30 (32)	12 (34)	
Middle	12 (9)	12 (13)	0 (0)	
Lower	24 (19)	23 (25)	1 (3)	
Unknown	44 (34)	25 (27)	19 (54)	
Procedures, n (%)	253	190	61	0.11
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Middle GI bleed assessments included VCE, enteroscopy (push, single-balloon), CTA, tagged red blood cell scans, and interventional radiology-directed angiography. Polytomous variables may not add up to 100% because of rounding. The χ^2 or Fisher exact test was used for categorical measures and the Student *t* test for continuous measures. CTA, computed tomography angiogram; EGD, esophagogastroduodenoscopy; GI, gastrointestinal; LVAD, left ventricular assist device; VCE, video capsule endoscopy.

angiogram, tagged red blood cell (RBC) scans, and interventional radiology (IR)-directed angiography. Ten of 12 tagged red cell scans were positive. Procedural workup, including the number of colonoscopies, was similar in both groups ($P = 0.11$). However, overt bleeders underwent fewer esophagogastroduodenoscopy (EGD) procedures ($P = 0.05$). In occult bleeding patients, 12 assessments for middle GIB sources did not localize a bleeding site in any case. There were 51 patients who had bleeding recurrence and required hospitalization. Of these, the location of bleeding was unidentified in 65% of recurrent admissions compared with 29% in index presentation (Table 3). When a bleeding site was known in subsequent hospitalization, it was frequently localized in the stomach and duodenum (35%).

Clinical predictors for recurrent GIB
Univariable and multivariable logistic regression analyses were performed on clinical predictors of recurrent GIB-related

Table 3. Location of GI bleeding for patients with single and recurrent hospital admission

Location of bleed	Single admission (N = 77), n (%)	Recurrent admission (N = 51), n (%)
Esophagus	5 (6.5)	0 (0)
Stomach	19 (25)	18 (35)
Duodenum (D1, D2)	5 (6.5)	10 (20)
Duodenum (D3, D4)	2 (2.6)	4 (7.8)
Jejunum	3 (3.9)	8 (16)
Ileum	5 (6.5)	0 (0)
Small bowel—nonspecific	1 (1.3)	4 (7.8)
Colon	6 (7.8)	11 (22)
Rectum	5 (6.5)	4 (7.8)
Unable to identify the source	22 (29)	33 (65)

GI, gastrointestinal.

hospital admissions inclusive of age, sex, study site, reason for LVAD implantation, aspirin use, ACEi or ARB therapy, and a history of pre-LVAD GIB. Of these clinical predictors, history of pre-LVAD GIB was associated with an increased risk of recurrent post-LVAD GIB-related hospitalizations (OR 3.85, 95% CI 1.29–12.7) (Table 4). Destination therapy LVAD implantation was also associated with a more than 2-fold increased odds of hospitalization because of recurrent GIB. The choice of anticoagulation did not affect the frequency of recurrent bleeding.

Lesion types for recurrent GIB
There were 161 unique bleeding events identified for the 51 recurrent bleeding patients. Sources of GIB were localized using a combination of techniques including EGD, colonoscopy, enteroscopy (push and single-balloon), VCE, tagged RBC scan, computed tomography angiogram, and catheter angiography with IR. The type of bleeding lesion could be identified in most of the single bleeding events (64.9%) and in recurrent bleeders (53.4%). Of the identified lesion types on index bleed, 20% were due to ulcers and 16% were due to arteriovenous malformations (AVMs) (Table 5). Patients with recurrent bleeding were much more likely to remain undiagnosed (47%). GIB from an ulcer was greater among patients with a single bleed compared with patients with recurrent bleed ($P = 0.02$).

Interventions
A variety of interventions were used during endoscopy for the initial bleed, which were highly effective in stopping current bleeding. However, especially in patients with AVMs, these interventions were not effective in preventing recurrent bleeding. In total, there were 72 interventions used to manage and treat GIB in 59 patients. Twenty-eight interventions (36%) were in patients who had a single admission and received 1 or multiple therapeutic interventions, compared with 44 (86%) in the recurrent admission group (Table 6). Most cases (96%) of active bleeding lesions were controlled during the procedure principally by endoclips and those with peptic ulcers infrequently rebled. The proportion of patients who received clips, however, was 2 times greater in the recurrent admission group than those on index presentation.

Table 4. Univariable and multivariable logistic regression analyses of clinical predictors for recurrent gastrointestinal bleeding-related hospital admission

	Univariable odds ratio (95% CI)	P value	Multivariable odds ratio (95% CI)	P value
Age	1.03 (1.00–1.07)	0.054	1.02 (0.98–1.06)	0.37
Female sex	0.53 (0.20–1.28)	0.17	0.66 (0.23–1.85)	0.44
Tufts study site	0.85 (0.40–1.84)	0.68	1.07 (0.6–2.55)	0.88
Destination therapy	2.71 (1.29–5.93)	0.01	2.38 (1.05–5.58)	0.04
Aspirin use	2.07 (0.46–14.5)	0.38	1.13 (0.19–9.07)	0.89
Prior GIB	3.59 (1.29–11.0)	0.02	3.85 (1.29–12.7)	0.02
ACEis/ARBs	2.12 (1.04–4.40)	0.04	1.82 (0.82–4.09)	0.14

The χ^2 or Fisher exact test was used for categorical measures and the Student t test for continuous measures.
ACEis, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; CI, confidence interval; GIB, gastrointestinal bleeding.

Patients with rebleeding hospitalizations were also more frequently treated with argon plasma coagulation compared with the single-admission group (14% vs 4%) and have vascular malformations. Of the treated overt bleeds, 29 (74%) were managed by clips and 6 (15%) were treated with argon plasma coagulation. Clips were also the primary intervention for 8 occult bleeds (89%). Other interventions including band ligations, IR coiling/embolization, and thermal interventions were less frequently used across both groups. Recurrent bleeders, primarily those with

AVMs, were 3 times more likely to have received clips combined with a second modality than patients who had a single GIB-related hospitalization (22% vs 7%). We had an insufficient number of patients receiving octreotide for analysis.

DISCUSSION

This large observational study analyzes GIB in continuous-flow LVAD patients, investigating clinical patterns that can inform the clinical evaluation and management of these complex patients. Our findings confirm a high rate of GIB, especially in destination patients, and show a low diagnostic yield for colonoscopy and middle GI bleed assessments in LVAD patients who present with occult bleeding (15–18). Overt bleeding was more frequent and may originate from anywhere in the GI tract. GIB frequently recurred and often was associated with vascular malformations. Although endoscopic interventions stopped active bleeding during the procedure, they were not demonstrated to prevent future bleeding. Destination therapy LVAD implantation (OR 2.38, 95% CI 1.05–5.58) and a history of GIB (OR 3.85, 95% CI 1.29–12.7) were independently associated with an increased risk of recurrent GIB-related hospitalization (19). The evaluation of occult initial bleed presentations had only 1 lower GI bleed source

Table 5. Identified lesion types for single and recurrent bleeding patients

Lesion type	Single bleed (n = 77), n (%)	Recurrent bleed (n = 161), n (%)	P value
Ulcer	15 (19.5)	13 (8.1)	0.02
AVM	12 (15.6)	40 (24.8)	0.15
Dieulafoy	7 (9.1)	9 (5.6)	0.46
Gastritis (erosive, hemorrhagic)	4 (5.2)	9 (5.6)	1
Polyp	1 (1.3)	1 (0.6)	0.55
Diverticular	1 (1.3)	1 (0.6)	0.55
Hemorrhoid	2 (2.6)	2 (1.2)	0.60
Duodenitis	0 (0)	1 (0.6)	1
Esophagitis	0 (0)	0 (0)	1
Ischemic colitis	4 (5.2)	2 (1.2)	0.10
Ischemic enteritis	1 (1.3)	2 (1.2)	1
Adenocarcinoma	1 (1.3)	1 (0.6)	0.55
GAVE	0 (0)	5 (3.1)	0.18
Polypectomy	1 (1.3)	0 (0)	0.33
Iatrogenic	1 (1.3)	0 (0)	0.33
Mallory-Weiss tear	0 (0)	0 (0)	1
Unknown lesion	27 (35.1)	75 (46.6)	0.12

The χ^2 or Fisher exact test was used for categorical measures and the Student t test for continuous measures.
AVM, arteriovenous malformation; GAVE, gastric antral vascular ectasia.

Table 6. Identified intervention and rate of recurrence

Intervention type	Single admission, n (%)	Recurrent admission, n (%)	P value
Clips	17 (22.1)	23 (45.1)	0.01
APC	3 (3.9)	7 (13.7)	0.09
Banding	1 (1.3)	0 (0)	1
Epinephrine injection	0 (0)	0 (0)	N/A
IR coiling/ embolization	1 (1.3)	0 (0)	1
Thermal intervention	1 (1.3)	3 (5.9)	0.30
Multiple	5 (6.7)	11 (21.6)	0.03

The χ^2 or Fisher exact test was used for categorical measures and the Student t test for continuous measures.
APC, argon plasma coagulation; IR, interventional radiology; N/A, not available.

and no middle GI bleed sources identified, despite relatively similar workups to overt bleeds.

Based on this experience, we propose an approach for initial LVAD-associated GIB. It is important to note that if a patient is presenting with a recurrent GI bleed, this approach should be informed by the prior endoscopic evaluation (19,20). If a patient has an overt GI bleed presentation that is not hematemesis (e.g., melena, hematochezia, or bright red blood per rectum) with a significant hemoglobin drop (>2 points) from baseline, we recommend performing a colonoscopy, and if unrevealing, for a source followed by a push enteroscopy in one anesthesia session. If these tests are all negative, we advise endoscopically deploying a video capsule to assess for more distal small bowel sources that may ultimately warrant deep balloon enteroscopy intervention or IR. The data support colonoscopy in patients with melena as part of the initial workup because of the propensity for right-sided colonic bleeding (from AVMs) to present in this way. This strategy of performing both enteroscopy and colonoscopy in either order can also help minimize LVAD time off therapeutic anticoagulation and the need for multiple anesthesia sessions (21,22). Although we report a relatively large series, it is retrospective and unstructured. Consequently, these recommendations must be viewed as tentative until controlled trials can be performed. Alternative strategies performing early tagged red cell scans or VCE to guide further workup need to be considered.

In patients with suspected occult GI bleed, if there is a significant hemoglobin drop (>2 points) from baseline that requires transfusion of at least 1 unit of packed red blood cells, we advise starting workup with EGD given the reasonably high rate (34%) of upper sources in this group, but not to proceed directly to colonoscopy or further small bowel bleed assessment given the very low yield of these tests based on our observations. In suspected occult GI blood loss cases with persistent downtrend in hemoglobin levels and multiple transfusion requirements, further evaluation with colonoscopy and capsule endoscopy or tagged RBC scan should be considered. This refinement of other recommendations needs independent validation and would help optimize both diagnostic and therapeutic yields while minimizing LVAD time off therapeutic anticoagulation and the number and duration of anesthesia sessions in these tenuous patients (19,23,24). In patients with suspected occult blood loss who underwent endoscopic evaluation, we suspect that a significant portion of the unknown bleed source patients (54%) had an alternative etiology to their anemia. Possible other etiologies in LVAD patients would include chronic low-grade hemolysis, anemia of chronic disease, and chronic kidney disease.

Recurrent GIB is common in these patients and is a major source of both patient morbidity and healthcare-associated costs (25). These bleeding events result in additional admissions that can span weeks requiring multiple endoscopic procedures and numerous transfusions. Earlier studies have largely been smaller, single-center investigations focused primarily on the low rates of endoscopic diagnostic yield. Previous studies have identified several factors that predict recurrent bleeding, including initial bleed hospitalization length of stay, male sex, international normalized ratio (INR) at index bleed, whether an endoscopic intervention was performed, destination therapy LVAD status, and LVAD speed (16,22). Our study identified older age, lower hemoglobin at presentation, destination therapy LVAD status, and most notably GI bleeds pre-LVAD implantation as risk factors of recurrent GIB events. A history of pre-LVAD GIB was associated with a 3-fold increase in risk of recurrent post-LVAD GIB-related hospitalizations. These advanced heart failure patients

often already have low flow to their gut mucosa, which can promote angiogenesis before undergoing LVAD implantation. Patients who have bled before implantation likely have a predisposition toward AVM formation, which is by far the most identified cause of recurrent GIB in our population.

An understanding of the risk factors of recurrent GI bleed at the time of LVAD implantation could be useful to plan and optimize medical and endoscopic management. Others have proposed earlier cessation of aspirin or lowering of INR goals, maximizing ACEi or ARB usage when able, and earlier initiation of octreotide. ACEi/ARB use has been shown to have an association with reducing AVM-associated bleeding, although our data do not demonstrate a decrease in recurrent bleeding (23,26). Octreotide has shown promise in the treatment of recurrent LVAD GIB (24,27,28).

Because of the high frequency of bleeding and bleeding vascular malformations, one might consider using earlier VCE during bleeding events (29,30). In patients presenting with supratherapeutic INRs more than 3, capsule endoscopy on admission may be especially useful in gathering more data to guide decision making on the type of endoscopic evaluation to pursue while waiting for INR to drift down to a safe range for endoscopy. Endoscopic management of AVM-associated bleeding is especially challenging because there can be multiple lesions in different locations including the small bowel (31,32). Endoscopic interventions for preventing rebleeding overall were disappointing, and further study of antiangiogenetic medications such as Avastin or thalidomide may be rewarding.

Anticoagulation undoubtedly contributes to the frequency and clinical significance of GIB. One might reasonably consider whether the increased risk of bleeding is exceeded by the decrease in thromboembolic events. Other observational reports from Interagency Registry for Mechanically Assisted Circulatory Support demonstrate a significant risk of thromboembolic disease and a critical value of effective anticoagulation (2,33).

Our study is limited by its retrospective medical record-based data. Control groups for optimal comparison are not available. Data from other hospitals where patients receive some of their care are often incomplete or unavailable, although patients most often return to the medical center for most of their care after LVAD placement. Consistent diagnostic and endoscopic approaches were not used over several years and in the 2 institutions. Patients who did not undergo endoscopic examination were excluded, which we used as a marker of a clinically significant bleeding event. Furthermore, in retrospect, it is difficult to ascertain whether the patients with unknown bleed sources had true GIB or anemia of an alternative etiology.

Our findings confirm a high frequency of GIB after LVAD placement and a higher rate in destination LVAD patients (3,28). We found a low diagnostic yield for colonoscopy and middle GI bleed assessments in LVAD patients who present with suspected occult bleeds and proposed a management algorithm for index GI bleeds based on an initial stratification of whether the bleed is overt or occult. In overt bleeders that are not a clear upper GI bleed source (i.e., hematemesis), we suggest colonoscopy and subsequent push enteroscopy, followed by capsule endoscopy placement, all in 1 anesthesia session (32,34). In occult bleeders that have a significant hemoglobin drop from baseline and need for at least 1 blood transfusion, we would advise performing EGD, but reserving colonoscopy and small bowel bleed assessments for patients with persistent requirement for multiple transfusions. Recurrent GIB remains especially challenging in this group of patients, and early identification of at-risk individuals, those with

a history of pre-LVAD implantation GIB and destination LVAD status, could allow for more deliberate preimplantation endoscopy programs that may improve the quality of their care.

CONFLICTS OF INTEREST

Guarantor of the article: James M. Richter, MD, MA.
Specific author contributions: J.D., A.K., and J.M.R.: study concept and design. J.D., A.K., M.B.R., and J.B.H.: acquisition of data. L.H.N., J.D., and A.K.: analysis and interpretation of data. J.D., A.K., L.H.N., and J.B.H.: drafting of the manuscript. J.M.R.: critical revision of the manuscript. L.H.N.: statistical analysis. M.J.S. and J.M.R.: study supervision.
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Study Highlights

WHAT IS KNOWN

✔ Left ventricular assist devices (LVADs) are used for a bridge to transplantation and destination therapy.

✔ Gastrointestinal bleeding (GIB) is a frequent complication of LVAD placement.

WHAT IS NEW HERE

✔ This is the largest, multicenter study to date to explore the risk factors that result in recurrent GIB in patients with LVAD implantation.

✔ History of pre-LVAD GIB was associated with a 3-fold increase in risk of recurrent post-LVAD GIB-related hospitalizations.

✔ LVAD patients who presented with occult bleeds showed a lower diagnostic yield for colonoscopy and middle GIB assessments.

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