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Temporal trends and risk factors of gastrointestinal bleeding in patients with left ventricular assist devices: a nationwide analysis 2008-2017

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Abstract

Background Left ventricular assist devices (LVADs) are indicated for patients with end-stage heart failure and require systemic anticoagulation. Gastrointestinal (GI) bleeding is a major adverse event following LVAD implantation. There is paucity of data on healthcare resource utilization in patients with LVAD and the risk factors of associated bleeding, despite the increase in GI bleeding. We investigated the in-hospital outcomes of GI bleeding in patients with continuous-flow (CF) LVAD.

Methods This was a serial cross-sectional study of the Nationwide Inpatient Sample (NIS) in the CF-LVAD era from 2008-2017. All adults admitted to hospital with a primary diagnosis of GI bleeding were included. GI bleeding was diagnosed by ICD-9/ICD-10 codes. Patients with CF-LVAD (cases) and without CF-LVAD (controls) were compared using univariate and multivariate analyses.

Results A total of 3,107,471 patients were discharged with a primary diagnosis of GI bleeding during the study period. Of these, 6569 (0.21%) had CF-LVAD-related GI bleeding. Overall, bleeding angiodysplasia accounted for the majority (69%) of LVAD-related GI bleeding. There was no statistical difference in mortality, but the length of hospital stay increased by 2.53 days (95% confidence interval [CI] 1.78-2.98; P<0.001) and the mean hospital charge per stay increased by $25,980 (95%CI 21,267-29,874; P<0.001) in 2017 compared to 2008. The results were consistent after propensity score matching.

Conclusion Our study highlights that patients with LVAD admitted to the hospital for GI bleeding experience longer hospital stays and greater healthcare costs that warrant risk-based patient evaluation and careful implementation of management strategies.

Keywords Endoscopy, heart failure, gastrointestinal bleeding, angiodysplasia, left ventricular assist devices

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Conflict of Interest: None

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Introduction

Left ventricular assist devices (LVADs) have been shown to improve survival and reduce morbidity in patients with advanced or end-stage heart failure [1,2]. Currently, the accepted indications for their use are as a bridge to heart transplantation, or as destination therapy in patients not eligible for heart transplantation [3]. There are 2 primary types of LVADs: first-generation pulsatile-flow devices and second-generation continuous-flow devices (CF-LVADs). CF-LVADs have largely replaced the first-generation devices and account for more than 90% of all implanted LVADs in the current era [4]. Since their approval by the US Food and Drug Administration (FDA) in 2008-2017, more than 17,000 CF-LVADs have been implanted in the United States [4,5].

A major adverse event associated with LVADs is gastrointestinal (GI) bleeding [6]. The overall incidence of GI bleeding in patients with CF-LVADs ranges from 18-40% [7,8]. However, there is a paucity of data relating to contemporary trends of LVAD-related GI bleeding. The aim of this study was to analyze the temporal trends and outcomes of LVAD-related

GI bleeding using the National Inpatient Sample database (NIS). This is the first study to analyze the trends of LVAD-related GI bleeding in this manner using the NIS.

Materials and methods

Study design and database description

This was a serial cross-sectional analysis of adult patients with LVADs hospitalized from 2008-2017 with GI bleeding in acute-care hospitals across the United States. The NIS is maintained by the Agency for Healthcare Research and Quality (HCUP). It is the largest publicly available all-payer inpatient database in the United States [9]. NIS contains de-identified hospital and patient level information, including demographics, length of hospital stay (LOS) and total hospital charges. The cost of individual hospitalizations was calculated by multiplying the total charge by the specific cost-to-charge ratio. The hospital cost-to-charge ratio is a standardized hospital datum that refers to the all-payer inpatient costs and charges reported by hospitals to the center for Medicare and Medicaid services. A consumer price index was used appropriately to adjust for inflation and convert to 2017 dollars. NIS contains up to 36 secondary diagnoses and 25 procedure codes for NIS 2017, using the International Classification of Diseases (see below). NIS is a compilation of 35 million inpatient admissions each year from 1000 hospitals representative of all non-federal acute-care hospitals nationwide. The NIS database is drawn from all states participating in HCUP, representing approximately 97% of the US population.

Study patients

The NIS-HCUP database was queried from 2008-2017 using the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) and 10th Revision, Clinical Modification (ICD-10-CM) diagnosis and procedure codes. We elected to initiate our analysis from 2008, the year HeartMate II, the most widely used LVAD, was approved by the FDA, till January 2017 [4].

Only patients with a primary diagnosis of GI bleeding as well as a secondary diagnosis of LVAD using ICD-9-CM (2008-September 2015) or ICD-10-CM (October 2015 onwards) were included in the study. Data on demographics, etiological factors, adverse events and predictors of GI bleeding were extracted using the respective ICD-9-CM and ICD-10-CM codes. GI bleeding was diagnosed according to the ICD-9/ICD-10 codes for drop in hemoglobin level, melena, hematochezia, hematemesis or guaiac-positive stool. This study was exempt from institutional review board approval given the de-identified nature of the NIS database and its public availability.

Study variables

Patients' demographic variables, including age, sex, race, median household income for patient's zip code (quartiles) and insurance status, were provided within the NIS for each hospitalization. Hospital size was categorized into small (1-299 beds), medium (300-499), or large (500+), based on an algorithm developed by HCUP [10]. Comorbidities for risk adjustment were derived from the Agency for Healthcare Research and Quality's comorbidity measures, based on the Deyo adaptation of the Charlson Comorbidity Index (CCI) for administrative data [11]. Patients were assigned a score of 0-4 based on the total number of comorbidities. To avoid multicollinearity, we excluded congestive heart failure and coagulopathy from the comorbidity index [12,13].

Among all admissions for GI bleeding, patients with CF-LVAD implants were identified based on the presence of ICD-9-CM and ICD-10-CM codes V43.21 and Z95.811, respectively, for heart assist devices. To restrict this group to only patients with CF-LVADs, we used the respective ICD-9 and ICD-10 codes to exclude other therapeutic measures, such as artificial heart, biventricular assist devices and heart transplantation. Patients with GI bleeding and CF-LVADs were defined as cases, and patients with GI bleeding but without CF-LVADs served as controls.

Outcomes

The primary outcome measure was healthcare resource utilization in patients with an LVAD admitted for GI bleeding. Secondary outcome measures included mortality, adverse events, and predictors of GI bleeding. Hospital resource utilization was defined collectively by requirement for intervention, LOS, and mean hospitalization charges. Adverse events included acute renal failure requiring hemodialysis, shock, and mechanical ventilation requiring intensive care unit admission.

Exclusions

The following exclusion criteria were applied: (a) age under 18 or patients with missing age; (b) patients transferred from an outside hospital, since the duration and adverse events of a prior hospitalization were not known; (c) all codes describing positive pregnancy status; (d) patients with a history of cirrhosis or variceal bleeding, because cirrhosis is a contraindication for LVAD implantation [14].

Statistical analysis

Statistical analysis was performed using STATA, version 16.0 (StataCorp., College Station, Texas, US). This software permits analysis to produce nationally representative

unbiased results, variance estimates and P-values. Weighting of patient-level observations was implemented. A univariate screen was initially performed to calculate unadjusted odds ratios (OR), and a multivariate logistic regression model was then built by including all confounders found to be significant on univariate analysis (using a cutoff P-value of 0.2), to calculate adjusted odds ratios (aOR). Logistic regression was used for binary outcomes and linear regression for continuous outcomes. Proportions were compared using the chi-square test and continuous variables using the Student's *t*-test. A P-value <0.05 was considered statistically significant for all outcomes. For outcomes of interest, adjustments were made using univariate analysis of covariance (ANCOVA) by the general linear model. Adjustments were made for the following variables: age, sex, race, median income, urban/rural hospital, hospital size and CCI. The mean cost of stay was adjusted for inflation by comparison to December 2017. To test whether missing data could introduce bias into the study, we assumed that data were not missing at random and applied the multivariate imputation by chained equations (MICE) method obtained from sequential multivariable models with fully conditional specifications [15]. Overall, 20 imputed data sets were formed using information from all the covariates in the database, as well as other covariates used in regression models, without missing information. The results with and without imputation were not statistically different. Hence, results without imputation are reported.

Results

Trend analysis

There were a total of 3,107,471 discharges with a primary diagnosis of GI bleeding during the study period. For all patients, hospitalizations for a primary discharge diagnosis of GI bleeding increased by 29.8% (95% confidence interval [CI] 27.6-29.9; P<0.001) from 2008-2017 (Fig. 1A). The number of hospital admissions for patients with LVADs increased by 91.6% (95%CI 90.4-93.6; P<0.001) in 2017 compared to 2008. There was a total of 6569 (8.36% of all LVAD hospitalizations) admissions for LVAD patients with a primary diagnosis of GI bleeding. The admissions for GI bleeding secondary to LVAD increased by 95.5% (P<0.001) in 2017 compared to 2008 (Fig. 1B).

Univariate analysis

On univariate analysis risk factors associated with GI bleeding in patients with LVAD were male sex (77.65% vs. 52.23%, P<0.001), age > 60 years (72.16% vs. 73.72%, P=0.0036), African American (25.49% vs. 15.54%, P=0.0065), Medicare insured (71.76% vs. 67.39%, P<0.001), treated at a teaching hospital (96.86% vs. 66.29%, P<0.001), large hospital size (88.63% vs. 48.87%, P<0.001), and CCI≥4 (66.02% vs. 34.41%, P<0.001) (Table 1). GI bleeding with LVAD vs. GI bleeding without LVAD had a significantly higher rate of comorbid conditions, such as chronic obstructive pulmonary disease (27.48% vs. 17.36%, P<0.001), coronary artery disease (CAD) (56.47% vs. 29.86%, P<0.001), atrial fibrillation (26.27% vs. 08.40, P<0.001), chronic kidney disease (CKD) (05.10% vs. 01.17%, P<0.001), and Stage 5 CKD/end-stage renal disease (41.96% vs. 31.23%, P=0.005) (Table 1).

Patients who had GI bleeding with LVAD compared to GI bleeding without LVAD underwent upper endoscopy (82.35% vs. 72.96%, P=0.0015) and colonoscopy (27.06% vs. 18.74%, P<0.001) more frequently. Those who had GI bleeding with LVAD vs. GI bleeding without LVAD were also more likely to undergo enteroscopy (34.47% vs. 25.17%, P=0.001) during hospitalization (Table 1). GI bleeding with LVAD vs. GI bleeding without LVAD less frequently underwent upper endoscopy within 24 h of admission (35.29% vs. 46.42%, P<0.001) and enteroscopy similarly within 24 h of admission (14.47% vs. 16.03%, P=0.50) (Table 1).

GI bleeding with LVAD vs. GI bleeding without LVAD had higher resource utilization including LOS >7 days (51.76% vs. 15.05%, P<0.001) and blood transfusion (73.12% vs. 48.31%, P<0.001) (Fig. 2).

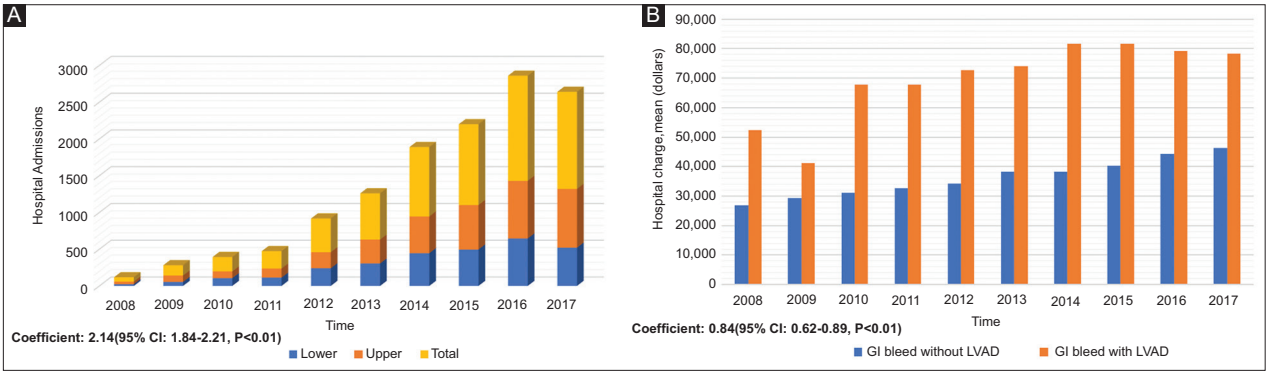

Figure 1 Trend analysis of hospital admissions for gastrointestinal (GI) bleeding and hospital charges in patients with a left ventricular assist device (LVAD). (A) Trend of hospital admissions for upper and lower GI bleeding in patients with an LVAD from 2008-2017. (B) Trend of mean hospital charge for hospitalized patients with GI bleeding with and without LVAD from 2008-2017
CI, confidence interval

Table 1 Demographics, hospital characteristics, site, patient characteristics, and timing of endoscopy in patients with gastrointestinal (GI) bleeding

Demographics	GI bleeding with LVAD		GI bleeding without LVAD		P-value
	N=1320 (%)		N=408,870 (%)		
	n	%	n	%	
Sex					<0.001
Male	1025	77.65	212,611	52.23	
Female	295	22.35	192,169	47.77	
Age					0.0036
18-40	15	01.18	20,893	05.11	
41-60	352	26.67	86,558	21.17	
>60	953	72.16	310,419	73.72	
Race					0.0065
White	818	61.96	272,348	66.61	
African American	336	25.49	65,538	15.54	
Hispanic	83	06.27	37,452	09.16	
Other	83	06.27	35,572	08.70	
Hospital teaching status					<0.001
Non-teaching	41	03.14	137,830	33.71	
Teaching	1279	96.86	271,040	66.29	
Hospital size					<0.001
Small	10	0.78	80,138	19.60	
Medium	140	10.59	128,917	31.53	
Large	1170	88.63	199,815	48.87	
Charlson comorbidity index					<0.001
1	52	03.92	109,577	26.80	
2	224	16.99	83,205	20.35	
3	172	13.07	75,396	18.44	
4	872	66.02	140,692	34.41	
Length of stay					<0.001
<7 days	637	48.24	343,451	84.95	
8-14 days	502	38.04	49,554	12.17	
15-21 days	109	08.24	8014	01.96	
>21 days	74	05.49	3761	0.92	
Nutrition status					0.2648
BMI 20-30	243	18.42	102,177	24.99	
BMI 30-40	729	55.26	176,264	43.11	
BMI>40	347	26.32	130,429	31.90	
Protein calorie malnutrition					0.2390
Moderate	21	01.57	11,326	02.77	
Severe	47	03.53	9608	02.35	
Weekend admissions	228	17.25	100,000	24.46	0.005
Patient characteristics					
COPD	363	27.48	70,980	17.36	<0.001
Pulmonary embolism	98	07.45	28,335	06.93	0.7368
VTE/DVT	16	01.18	8300	02.03	0.3394
Acute MI	17	01.31	4375	01.77	0.4844
CAD	744	56.47	12,209	29.86	<0.001
Arrhythmia	16	01.18	6460	01.58	0.6056
Atrial fibrillation	347	26.27	34,345	08.40	<0.001
CKD	66	05.10	4784	01.17	<0.001
Stage 1-2	481	36.47	5446	13.32	0.0024
Stage 3-4	40	03.14	25,391	06.21	0.2960
Stage 5 or ESRD	554	41.96	127,690	31.23	0.0084
DM	5	0.39	4293	01.05	
NASH	5	0.39	13,656	03.34	

(*Contd...*)

Table 1 *(Continued)*

Demographics	GI bleeding with LVAD		GI bleeding without LVAD		P-value
	N=1320 (%)		N=408,870 (%)		
	n	%	n	%	
Site of GI bleeding					
Upper GI bleed	800	59.22	263,185	64.37	0.033
Lower GI bleed	520	37.54	145,685	35.63	0.526
Intervention					
EGD	1082	82.35	298,311	72.96	0.0015
EGD within 1 day of admission	466	35.29	189,797	46.42	0.0014
Enteroscopy	455	34.47	102,912	25.17	0.0010
Enteroscopy within 1 day of admission	191	14.47	65,542	16.03	0.5037
Colonoscopy	356	27.06	76,622	18.74	<0.001

Univariate analysis of patients with and without continuous-flow left ventricular assist devices (LVADs) in the Nationwide Inpatient Database in 2017

Bed size categories are based on hospital beds and are specific to the hospital's location and teaching status. Bed size assesses the number of short-term acute beds in a hospital. SE standard error

[a]The cell's value is not displayed. As per data agreements with observations in any given cell of analyzed data is below 10. AHRQ, researchers cannot report any statistics where the number of observations in any given cell of analyzed data is below 10

BMI, body mass index; COPD, chronic obstructive pulmonary disease; VTE, venous thromboembolism; DVT, deep venous thrombosis; MI, myocardial infarction; CAD, coronary artery disease; CKD, chronic kidney disease; ESRD, end-stage renal disease; DM, diabetes mellitus; NASH, nonalcoholic steatohepatitis; EGD, esophagogastroduodenoscopy; n, total number of patients

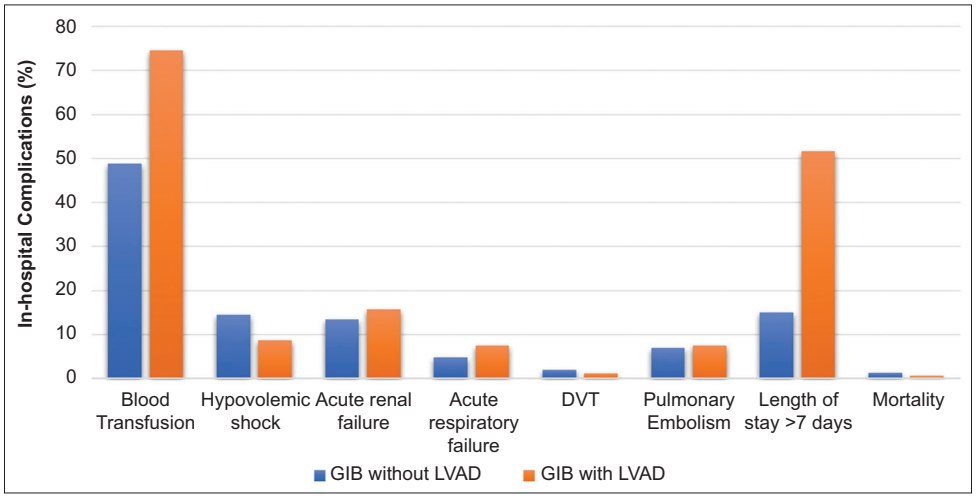

Figure 2 Primary and secondary outcomes in patients with gastrointestinal bleeding (GIB): univariate analysis of patients with and without continuous flow left ventricular assist devices (LVADs) in the Nationwide Inpatient Database in 2017, represented in %
DVT, deep vein thrombosis

Causes of GI bleeding

The etiology of GI bleeding with LVAD vs. GI bleeding without LVAD was angiodysplasia (68.57% vs. 11.81%, P<0.001), angiodysplasia of the stomach and duodenum (40.76% vs. 6.83%, P<0.001), or angiodysplasia of the colon (27.71% vs. 4.98%, P<0.001). GI bleeding with LVAD vs. GI bleeding without LVAD secondary to peptic ulcer disease (8.26 vs. 38.35%, P<0.001), gastritis/duodenitis (5.45% vs. 12.32%, P=0.002), diverticulosis of colon with hemorrhage (7.42% vs. 22.10%, P<0.001), hemorrhage of rectum and anus (1.59% vs. 07.82%, P<0.001), Dieulafoy's lesion (8.71% vs. 1.81%, P=0.032), Dieulafoy's lesion of the stomach and duodenum (6.06% vs. 1.49%, P=0.021), and Dieulafoy's lesion of the distal small bowel (2.65% vs. 0.32%, P=0.003) (Table 2). When specific ICD-9-CM and ICD-10-CM codes were available for differentiating upper vs. lower GI bleeding, trend analysis demonstrated that the increment in LVAD patients with upper GI bleeding was more pronounced than in those with lower GI bleeding (coefficient: 2.14, 95%CI 1.84-2.21; P<0.001). LOS increased by 2.53 days (95%CI 1.78-2.98; P<0.001), mean hospital cost for each stay increased by $25,980 (95%CI 21,267-

Table 2 Location and etiology of gastrointestinal (GI) bleeding in patients with and without continuous flow left ventricular assist devices (LVADs) in the Nationwide Inpatient Sample (NIS) in 2017

Source of GI bleeding	GI bleed with LVAD		GI bleed without LVAD		P-value
	N=1320		N= 408,870		
	n	%	n	%	
Esophagus[a]	-	0.00	21,634	05.29	-
Peptic ulcer disease	109	08.26	158,755	38.85	<0.001
Gastritis/duodenitis	72	05.45	50,400	12.32	0.024
Dieulafoy lesion	115	08.71	7,402	01.81	0.037
Stomach and duodenum	80	06.06	6,106	01.49	
Distal small bowel	35	02.65	1,296	0.32	
Angiodysplasia	905	68.57	48,319	11.81	<0.001
Stomach and duodenum	538	40.76	27,927	06.83	
Colon	367	27.71	20,392	04.98	
Diverticulosis of colon with hemorrhage	98	07.42	90,368	22.10	<0.001
Hemorrhage of rectum and anus	21	1.59	31,992	07.82	<0.001

[a]The cell's value is not displayed. As per data agreements with observations in any given cell of analyzed data is below 10. AHRQ, researchers cannot report any statistics where the number of observations in any given cell of analyzed data is below 10. Agency for Healthcare Research and Quality researchers cannot report any statistics where the number of observations in any given cell of analyzed data is below 10

29,874; P<0.001), and the total cost increased by 150 million dollars (95%CI 138-169 × 10^6; P<0.001) (Fig. 1B).

Independent predictors of mortality, total charge, and LOS

The results of a multivariate outcome analysis are presented in Tables 3 and 4. Multivariate linear regression analysis was performed after adjusting for patient and hospital-level confounders, demographics, hospital characteristics, comorbidities and secondary causes of GI bleeding. Multivariate analysis demonstrated that GI bleeding with LVAD was associated with a longer LOS by 4.10 days (coefficient: 0.383, 95%CI 0.094-0.671; P=0.002) and higher hospital charges by $25,980 (coefficient: 7139, 95%CI 5973-7521; P<0.001) compared to GI bleeding without LVAD (Table 3).

Independent predictors of GI bleeding with LVAD, were age >40 years (OR 8.74, 95%CI 2.88-11.61; P<0.001), male sex (OR 3.05, 95%CI 2.37-4.30; P<0.001), longer LOS >7 days (OR 2.95, 95%CI 2.25-3.86; P<0.001), history of GI bleeding (OR 27.65, 95%CI 21.20-36.06; P<0.001), CAD (OR 2.62, 95%CI 2.00-3.44; P<0.001), and CKD stage 3 or higher (OR 3.15, 95%CI 2.37-4.18; P<0.001) (Fig. 3).

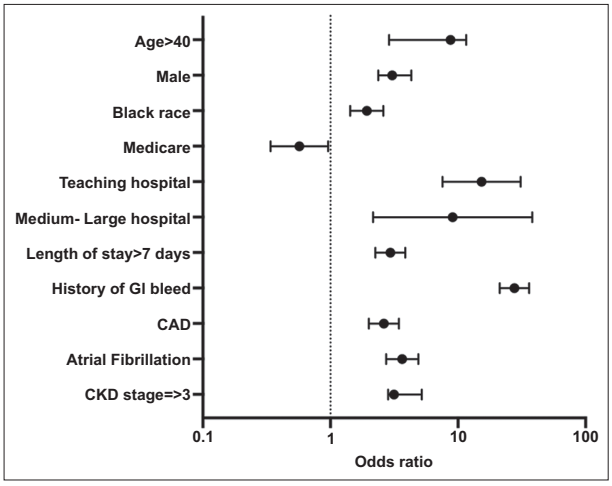

Figure 3 Forest plot for independent predictors of gastrointestinal (GI) bleeding in patients with continuous-flow left ventricular assist devices (LVADs) in the Nationwide Inpatient Sample in 2017
CAD, coronary artery disease; CKD, chronic kidney disease

Discussion

In this large, multi-institution, population-based study we observed that hospital admissions for GI bleeding in adult patients with LVAD had nearly doubled in the decade of the study. This increase in hospital admissions was associated with a higher cost of healthcare resource utilization and no significant change in mortality. Angiodysplasias were the most common cause of bleeding in this group of patients. Older age, male sex, black race, and a history of CAD, CKD, or prior GI bleeding were associated with a higher risk of bleeding.

The pathophysiology of luminal GI bleeding in patients with LVAD is multifactorial. The interaction between blood and CF-LVAD leads to an acquired von Willebrand disease wherein the shear forces created by the LVAD result in proteolysis of von Willebrand factor (vWF) multimers and subsequent impaired platelet adhesion [16-18]. Mucosal hypoperfusion due to reduced arterial pulsatility causes regional hypoxia with subsequent arteriovenous dilation and formation of angiodysplasias [19]. Cardiac transplantation in these patients leads to reversal of these changes and normalization of vWF

Table 3 Independent predictors of in-hospital gastrointestinal (GI) bleeding in patients with continuous-flow left ventricular assist devices (LVADs)

Outcomes	Adjusted odds ratio	95%CI	P-value
Sex			
Female	Reference		
Male	3.05	2.37-4.30	<0.001
Age			
18-40	Reference		
41-60	8.74	2.88-11.61	<0.001
>60	3.52	2.25-7.02	<0.002
Race			
White	Reference		
African American	1.93	1.43-2.60	<0.001
Hispanic	1.01	0.60-1.70	0.829
Other	0.83	0.49-1.39	0.431
Hospital teaching status			
Non-teaching	Reference		
Teaching	15.30	7.55-30.98	<0.001
Hospital size			
Small	Reference		
Medium	9.08	2.16-38.22	0.003
Large	46.49	11.55-187.1	<0.001
LOS			
<7 days	Reference		
8-14 days	2.95	2.25-3.86	<0.001
15-21 days	2.65	2.55-4.22	<0.001
>21 days	2.98	2.70-5.19	<0.001
History of previous GI bleed			
CAD	27.65	21.20-36.06	<0.001
Atrial fibrillation	2.62	2.00-3.44	<0.001
CKD stage ≥3	3.65	2.73-4.88	<0.001
(GFR <60 mL/min)	3.15	2.83-5.20	<0.001

Multivariate logistic regression analysis of patients with GI bleeding and LVAD in the Nationwide Inpatient Database in 2017. Private insurance includes HMO

GI, gastrointestinal; PUD, peptic ulcer disease; n, number of patients; VTE, venous thromboembolism; DVT, deep venous thrombosis; CAD, coronary artery disease; CKD, chronic kidney disease; GFR, glomerular filtration rate; LOS, length of stay; n, total number. OR, odds ratio; CI, confidence interval; LVAD, left ventricular assist device

levels, as previously reported by Uriel *et al* [20]. Another factor contributing to the occurrence of bleeding in these patients is the use of antiplatelet and antithrombotic therapy [21].

Using data from the NIS databases from 2009-2011, Abbas *et al* [22] reported that the hospital admission for GI bleeding in patients with LVAD was 8%. While we observed a similar percentage of admissions during that time period, the total number of GI bleeds amongst patients with LVAD increased by a factor of twenty from 2008-2017. The likely reasons for these findings include an increase in the number of implanted LVADs every year and recurrent bleeding episodes in the same patient with LVAD, given persistent risk factors such as vWF deficiency and continued use of anticoagulation. Notably, the increment in upper GI bleeds over the study period was greater than that in lower GI bleeds.

Our analysis suggests that the GI bleed-related mortality in patients with LVAD did not change significantly during the study period. It was, however, associated with greater morbidity at the patient level, and with a higher cost of healthcare resource utilization at the national level. The number of endoscopic procedures and blood transfusions, the LOS, and the total cost of hospitalization increased progressively during the period of this study. Apart from bleeding-related morbidity, there may be other clinical implications of bleeding in this group of patients. A higher transfusion burden risks allosensitization that may be relevant in patients who have LVAD implanted as a bridge to cardiac transplantation [23]. Withholding anticoagulation during the admission for GI bleeding risks pump thrombosis and other thromboembolic sequelae [24]. Additionally, the most common source of bleeding in this patient population is GI angiodysplasias, which often bleed intermittently, have high re-bleeding rates, and for which medical management is currently limited [25].

A careful strategy to identify patients at risk of bleeding is thereby required. From our large nationwide study, we have elucidated risk factors that increase the odds of GI bleeding in patients with LVAD. These include older age, male sex, black race, and a history of CAD, CKD, atrial fibrillation or prior GI bleeding. These results are slightly different from those obtained by Draper *et al* [26] in their systematic review, but similar to those obtained in a recent study by Yin *et al* [27]. A risk-based approach may guide clinicians in implementing treatment choices in an individualized and informed manner. Novel techniques using a low-intensity anticoagulation protocol or increased LVAD pulsatility may be used selectively, weighing the risks and benefits [28,29]. Newer, third-generation LVADs (i.e., HeartMATE 3™, Abbott) with

Table 4 Independent predictors of total hospital charges and length of hospital stay in gastrointestinal (GI) bleeding

Variables	Total hospital charge ($)			Length of hospital stay (days)		
	Coefficient	95%CI	P-value	Coefficient	95%CI	P-value
Age						
18-40	Reference					
41-60	2869.49	1167-4571	<0.001	0.224	0.157-0.290	<0.001
>60	1844.99	5.755-3684	0.049	0.313	0.243-0.382	<0.001
Sex						
Female	Reference					
Male	2713.87	2014-3413	<0.001	-0.048	-0.083-0.110	0.006
Race						
White	Reference					
Black	545.52	-913.51-2004 8925-	0.464	0.176	-0.176-0.087	<0.001
Hispanic	10758.94	12593	<0.001	-0.008	-0.061-0.457	0.776
Other	4914.24	2851-6977	<0.001	-0.026	-0.081-0.027	0.336
Hospital region						
Northeast	Reference					
Midwest	-8161.38	-12570--3752	<0.001	-0.0560	-0.164-0.052	0.311
Southern	-4399.66	-8971-172	0.059	-0.0234	-0.134-0.087	0.678
Western	16092.75	10101-22084	<0.001	-0.164	-0.297--0.031	0.015
Median income in patient zip code						
$1–$38,999	Reference					
$39,000–$47,999	-1165.45	-3634-1303	0.355	0.034	-0.060-0.129	0.478
$48,000–$62,999	-835.62	-3413-1743	0.526	0.676	-0.0781-0.120	0.676
$63,000 and above	5407.98	944-9871	0.018	0.828	-0.098-0.1224	0.828
LVAD	7139	5973-7521	0.017	0.383	0.094-0.671	0.009
Weekend admission	1747	973-2521	0.001	0.138	0.107-0.168	<0.001
Insurance status						
Self-pay/Uninsured	Reference					
Medicare	758.31	-1150-2667	0.436	0.052	-0.118-0.1491	0.201
Medicaid	-954.43	-2271-363	0.156	-0.151	-0.053-0.337	<0.001
Private insurance	-1835.69	-3479-191	0.029	-0.161	-0.175-0.105	<0.001
Hospital teaching status						
Non-teaching	Reference					
Teaching	2737	999-4475	0.002	0.158	0.126-0.191	<0.001
Hospital size						
Small	Reference					
Medium	3605.57	1472-5739	0.001	0.098	-0.058-0.138	<0.001
Large	4231.11	2039-6422	0.001	0.204	0.164-0.244	<0.001
Acute MI	21283.69	11511-31056	<0.001	0.525	0.132-0.919	0.009
CAD	1619.43	685-2553	0.001	0.115	-0.083-0.147	<0.001
Atrial fibrillation	2336.86	467-6367	0.023	0.113	-0.067-0.160	<0.001
PE/VTE	375.27	-1173-1924	0.635	0.150	0.082-0.218	<0.001
CKD stage 3 or higher	2866.4	2076-3656	0.001	0.133	0.088-0.177	<0.001
Diabetes mellitus	347.95	-452-1148	0.394	0.069	0.035-0.105	<0.001
COPD	2202.24	1146-3258	0.001	0.190	0.142-0.238	<0.001
Colonoscopy	2607	247-4966	0.030	0.175	0.081-0.268	<0.001
Enteroscopy	1831	-307-3970	0.093	0.073	-0.011-0.157	0.088
Marijuana	6686	-1689-15063	0.118	-0.058	-0.308-0.191	0.646

Linear regression analysis of patients in the Nationwide Inpatient Database in 2017. Private insurance includes HMO

OR, odds ratio; CI, confidence interval; LVAD, left ventricular assist device; COPD, chronic obstructive pulmonary disease; PE, pulmonary embolism; VTE, venous thromboembolism; MI, myocardial Infarction; CAD, coronary artery disease; CKD, chronic kidney disease; n, total number of patients

electromagnetic centrifugal flow have recently been shown to have a lower incidence of GI bleeding and other hemocompatibility-related complications [30]. A combination of these techniques and risk-stratification strategies may help reduce the incidence and healthcare burden of LVAD-related GI bleeding.

The strengths of our study lie in the sheer size of our patient sample and the period of the study. Our analysis encompasses the nationwide sample of CF-LVADs since their approval in 2008. ICD codes for GI bleeding used in the analysis are highly specific and have been previously validated to have high accuracy [31]. Our analysis is, however, limited by its retrospective design. We were not able to estimate re-bleeding rates as NIS is limited to in-hospital data and longitudinal follow-up information is unavailable. The type of enteroscopy (whether device-assisted or video capsule) is not discernible from the procedure codes. The ICD codes for type of anticoagulation used and adjunctive therapy (such as hemostatic clips, cautery or hemospray) used during the endoscopy are not available in the NIS database. Nevertheless, this paper adds valuable data to the current literature on GI bleeds in patients with LVAD.

To conclude, GI bleeding in patients with LVADs is an important cause of morbidity and healthcare resource utilization in the United States. Its rising number of hospital admissions warrants risk-based patient evaluation and careful implementation of management strategies in patients with advanced heart failure.

Summary Box

What is already known:

- The left ventricular assist device (LVAD) is a bridge to heart transplant in patients with advanced or end-stage heart failure
- LVAD patients require lifelong anticoagulation
- Gastrointestinal (GI) bleeding is a common major adverse event associated with LVADs
- Angiodysplasia of the GI tract is one of the common etiologies of GI bleeding in patients with LVADs

What the new findings are:

- There was a rising trend in the hospital admissions for LVAD-associated GI bleeding from 2008-2017 (increase by 95.5%)
- The increase in hospital admissions was associated with a higher cost of healthcare resource utilization and no significant change in mortality in patients with LVAD-associated GI bleeding
- Approximately 70% of LVAD-associated GI bleeding is secondary to angiodysplasia
- Independent risk factors for LVAD-associated GI bleeding were older age, male sex, black race, and a history of coronary artery disease, chronic kidney disease, or prior GI bleeding

References

1. Miller LW, Pagani FD, Russell SD, et al; HeartMate II Clinical Investigators. Use of a continuous-flow device in patients awaiting heart transplantation. *N Engl J Med* 2007;**357**:885-896.
2. Slaughter MS, Rogers JG, Milano CA, et al; HeartMate II Investigators. Advanced heart failure treated with continuous-flow left ventricular assist device. *N Engl J Med* 2009;**361**:2241-2251.
3. Gopinathannair R, Cornwell WK, Dukes JW, et al. Device therapy and arrhythmia management in left ventricular assist device recipients: a scientific statement from the American Heart Association. *Circulation* 2019;**139**:e967-e989.
4. Kirklin JK, Pagani FD, Kormos RL, et al. Eighth annual INTERMACS report: special focus on framing the impact of adverse events. *J Heart Lung Transplant* 2017;**36**:1080-1086.
5. U.S. Food & Drug Administration. Thoratec HeartMate® II LV AS. Summary of safety and effectiveness data. Available from: https://www.accessdata.fda.gov/cdrh_docs/pdf6/P060040b.pdf [Accessed 3 January 2023].
6. Genovese EA, Dew MA, Teuteberg JJ, et al. Incidence and patterns of adverse event onset during the first 60 days after ventricular assist device implantation. *Ann Thorac Surg* 2009;**88**:1162-1170.
7. Harvey L, Holley CT, John R. Gastrointestinal bleed after left ventricular assist device implantation: incidence, management, and prevention. *Ann Cardiothorac Surg* 2014;**3**:475-479.
8. Aggarwal A, Pant R, Kumar S, et al. Incidence and management of gastrointestinal bleeding with continuous flow assist devices. *Ann Thorac Surg* 2012;**93**:1534-1540.
9. Introduction to the HCUP nationwide inpatient sample (NIS). Rockville, MD: agency for healthcare research and quality. Available from: https://www.hcup-us.ahrq.gov/db/nation/nis/NIS_Introduction_2016.jsp [Accessed 3 January 2023].
10. Khera R, Krumholz HM. With great power comes great responsibility: big data research from the National Inpatient Sample. Circulation: Cardiovascular Quality and Outcomes. 2017 Jul;10:e003846.
11. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol* 1992;**45**:613-619.
12. Zidek JV, Wong H, Le N, Burnett R. Causality, measurement error and multicollinearity in epidemiology. *Environmetrics* 1996; **7**:441-451.
13. Singh G, Albeldawi M, Kalra SS, Mehta PP, Lopez R, Vargo JJ. Features of patients with gastrointestinal bleeding after implantation of ventricular assist devices. *Clin Gastroenterol Hepatol* 2015;**13**:107-114.e1.
14. Miller LW, Guglin M. Patient selection for ventricular assist devices: a moving target. *J Am Coll Cardiol* 2013;**61**:1029-1221.
15. Vassileva CM, McNeely C, Mishkel G, Boley T, Markwell S, Hazelrigg S. Gender differences in long-term survival of Medicare beneficiaries undergoing mitral valve operations. *Ann Thorac Surg* 2013;**96**:1367-1373.
16. Geisen U, Heilmann C, Beyersdorf F, et al. Non-surgical bleeding in patients with ventricular assist devices could be explained by acquired von Willebrand disease. *Eur J Cardiothorac Surg* 2008;**33**:679-684.
17. Baldauf C, Schneppenheim R, Stacklies W, et al. Shear-induced unfolding activates von Willebrand factor A2 domain for proteolysis. *J Thromb Haemost* 2009;**7**:2096-3105.
18. Malehsa D, Meyer AL, Bara C, Strüber M. Acquired von Willebrand syndrome after exchange of the HeartMate XVE to the HeartMate II ventricular assist device. *Eur J Cardiothorac Surg* 2009; **35**:1091-1093.
19. Suarez J, Patel CB, Felker GM, Becker R, Hernandez AF, Rogers JG. Mechanisms of bleeding and approach to patients with axial-flow

left ventricular assist devices. *Circ Heart Fail* 2011;**4**:779-784.
20. Uriel N, Pak SW, Jorde UP, et al. Acquired von Willebrand syndrome after continuous-flow mechanical device support contributes to a high prevalence of bleeding during long-term support and at the time of transplantation. *J Am Coll Cardiol* 2010;**56**:1207-1213.
21. Cushing K, Kushnir V. Gastrointestinal bleeding following LVAD placement from top to bottom. *Dig Dis Sci* 2016;**61**:1440-1447.
22. Abbas A, Mahmoud A, Ahmed M, Aranda J Jr, Klodell CT Jr, DraganovPV. Gastrointestinal bleeding during the index hospitalization for mechanical circulatory support devices implantation, a nationwide perspective. *Dig Dis Sci* 2017;**62**:161-174.
23. Drakos SG, Stringham JC, Long JW, et al. Prevalence and risks of allosensitization in HeartMate left ventricular assist device recipients: the impact of leukofiltered cellular blood product transfusions. *J Thorac Cardiovasc Surg* 2007;**133**:1612-1619.
24. Stulak JM, Lee D, Haft JW, et al. Gastrointestinal bleeding and subsequent risk of thromboembolic events during support with a left ventricular assist device. *J Heart Lung Transplant* 2014;**33**:60-64.
25. Jackson CS, Strong R. Gastrointestinal angiodysplasia: diagnosis and management. *Gastrointest Endosc Clin N Am* 2017;**27**:51-62.
26. Draper KV, Huang RJ, Gerson LB. GI bleeding in patients with continuous-flow left ventricular assist devices: a systematic review and meta-analysis. *Gastrointest Endosc* 2014;**80**:435-446.
27. Yin MY, Ruckel S, Kfoury AG, et al. Novel model to predict gastrointestinal bleeding during left ventricular assist device support. *Circ Heart Fail* 2018;**11**:e005267.
28. Netuka I, Ivák P, Tučanová Z, et al. Evaluation of low-intensity anti-coagulation with a fully magnetically levitated centrifugal-flow circulatory pump-the MAGENTUM 1 study. *J Heart Lung Transplant* 2018;**37**:579-586.
29. Botterbusch CN, Monticone P, Illouz E, Burg B, Polverelli L, Snyder T. Getting past the spin: The CorWave LVAD, a membrane wave pump providing physiologic pulsatility without high shear. *J Heart Lung Transplant* 2019;**38**:S345.
30. Mehra MR, Uriel N, Naka Y, et al; MOMENTUM 3 Investigators. A fully magnetically levitated left ventricular assist device - final report. *N Engl J Med* 2019;**17**:1618-1627.
31. Li F, Hinton A, Chen A, et al. Left ventricular assist devices impact hospital resource utilization without affecting patient mortality in gastrointestinal bleeding. *Dig Dis Sci* 2017;**62**:150-160.