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Original Article

A population based analysis of trends, risk factors and outcomes associated with gastrointestinal bleeding in patients with left ventricular assist devices

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Abstract: *Introduction:* Prior to the utilization of continuous flow (CF) devices in 2010, Gastrointestinal (GI) bleeding was a common adverse event related to left ventricular assist device (LVADs) that was found to be even more frequent when CF devices were first introduced. *Objective:* Given the drastic increase in the use of new CF-LVADs, we sought to determine if CF-LVADs are associated with an increased number of GI bleeds and higher mortality. *Methods:* We analysed the data from a national inpatient sample database using the ICD-9 procedure code for LVAD use in end-stage heart failure among patients > 18 years. The total sample consisted of 2,359 patients (M_{age}=55 ± 13.7 years). A majority of the sample was male (77%) and Caucasian (59%). *Results:* The Incidence of GI bleeding from 2010 to 2014 was 7.46% with no significant change in yearly incidence over five-year period (P=.793). After controlling for age, sex, and length of stay, multivariate logistic regression revealed that significant predictors of GI bleed were acute kidney injury (AOR=1.87, 95% CI=1.26, 2.80), peripheral vascular disease (AOR=1.77, 95% CI=1.02, 2.94), body mass index ≥ 25 (AOR=.46, 95% CI=.22, .87), hemiplegia or paraplegia (AOR=3.01, 95% CI=1.17, 7.05), moderate or severe liver disease (AOR=2.40, 95% CI=.97, 5.34), peptic ulcer disease (AOR=18.13, 95% CI=7.86, 42.38), surgical aortic valve replacement (AOR=2.46, 95% CI=1.12, 5.15), and venous thromboembolism (AOR=2.58, 95% CI=1.57, 4.15). *Conclusion:* The results of the study show that GI bleeding is highly prevalent in patients with LVADs and there was no improvement in rates of GI bleed over five years since the CF-LVADs were initially introduced and is associated with an increased likelihood of mortality.

Keywords: End-stage heart failure, mechanical circulatory support, national inpatient sample, continuous flow left ventricular assist device, cardiogenic shock

Introduction

Gastrointestinal (GI) bleed is one of the most common and serious adverse events related to the implantation of left ventricular assist devices (LVADs) in patients with end-stage heart failure [1-4]. Over the last few years, there has been an increased utilization of these devices due to improved mortality benefits in patients with cardiogenic shock [5, 6]. As the number of patients requiring circulatory devices support has increased and available donors has decreased, LVADs have become more permanent therapeutic options. LVADs can be divided into first, second, and third generation devices. The pulsatile flow (PF) pumps are first-generation devices that displayed a survival benefit over medical therapy, but resulted in high mortality and morbidity due to their large size and limited durability [6]. The continuous flow (CF) devices consist of second-generation (axial flow pumps) and third generation devices (centrifugal flow

pumps) that are smaller, more durable, and utilize the rotary-pump technology to provide blood flow with reduced pulsatility [7].

As LVAD therapy improves, it is important to identify and minimize the adverse effects associated with its usage. LVAD use is associated with an increased risk of hypercoagulability with varying frequencies of cerebrovascular disease, thromboembolism, pump thrombosis and hemorrhagic complications, with GI bleed being the most common. To prevent device related complications (e.g., thromboembolism), antiplatelet and anti-coagulation therapy have been utilized. Pathophysiology of GI bleed may be due to fibrinolytic pathway activation, consumption of coagulation proteins and use of anticoagulation and anti-platelet therapy to prevent thrombotic complications [8, 9]. In the second generation devices (axial flow pumps), the major cause of morbidity and mortality is due to non-surgical bleeding [8]. Bleeding is mainly seen in the first month of implantation and the risk can be augmented with existing comorbidities (e.g., aortic stenosis, renal failure, liver disease) and medications (e.g., nonsteroidal anti-inflammatory drugs, anti-platelets, anti-coagulants). CF-LVADs are more durable and have better survival rates as compared to PF-LVADs [5, 10, 11]. However, prior evidence has shown that CF-LVADs would be associated with an increase in GI bleeding because of narrow arterial pulse pressure, alterations of mucosal perfusion and administration of both Warfarin and antiplatelet agents in patients with non-pulsatile LVADs to minimize thrombotic risks [4, 8, 9]. Even though there is early evidence that these newer CF-devices might have benefits, there is a need to explore them further as evidence suggest an increased risk of GI bleed for CF devices compared to PF devices.

Since 2010, there has been an increasing shift away from PF-LVADs and towards CF-LVADs [7]. Although technological innovations associated with the development of second- and third-generation LVADs would presumably lead to improvements in patient-related outcomes, evidence is needed to determine whether these newer devices have increased benefits for patient functioning and are linked to lower rates of post-implant complications. In this study, we examine GI bleeding in patients with LVAD by comparing the incidence, trends, and inpatient mortality associated with GI bleeding over a five-year period following the introduction of CF-LVADs.

Methods

Data source

The National Inpatient Sample (NIS), which forms part of the Healthcare Cost and Utilization Project (HCUP) datasets, were obtained and analysed from 2010 to 2014. The NIS represents 20% of hospitalized patients from approximately 1,000 hospitals prior to 2012 and approximately 4,300 participating hospitals after 2012, with the exclusion of long-term acute care hospitals. All states that participate in the HCUP provide data to the NIS, which covers > 95% of the United States population and 94% of all community hospital discharges. The NIS database contains de-identified patient information containing demographics, discharge diagnoses, comorbidities, procedures, outcomes, and hospitalization costs. The Institutional Review Board of our University deemed this study exempt from formal review, as the datasets contained de-identified patient information. Datasets are available at https://www.hcup-us.ahrq.gov/nisoverview.jsp provided by the Agency for Healthcare Research and Quality.

Selection of study sample and covariates

We used the International Classification of Diseases, 9th Revision procedure code of 37.66 (i.e., Insertion of Implantable Heart Assist System), in any procedure field among patients aged 18 years or older. To minimize the possibility of data duplication, we excluded patients with an indicator of transfer to another acute-care facility. Patient characteristics included age, sex, race, health insurance, total cost of hospitalization, length of hospitalization, and geographic region of hospital admission. Comorbidities and complications were identified using ICD-9 codes in the diagnosis fields and procedures were identified using ICD-9 codes in the procedure fields. Race was classified as white, black, Hispanic, Asian or Pacific Islander, Native American, or unknown, as captured by hospital administration. We used medical comorbidities reported in the NIS datasets to generate the Charlson comorbidity index [12, 13]. Charlson comorbidity index scores were categorized as 0, 1, 2 or ≥ 3.

Statistical analysis

A series of comparative analyses were computed to identify trends in patient and hospital characteristics, comorbidities, in-patient mortality, and GI bleed. Differences between continuous variables were assessed using independent samples *t*-tests and one-way analysis of variance tests, whereas differences involving categorical variables were tested using the Chi-square test of independence or the Fisher's exact test. Predictors of GI bleed were examined using a hierarchical multivariate binary logistic regression analysis involving all eligible cases from 2010 to 2014. Patient characteristics (i.e., age, sex, and length of hospitalization) were entered in Step 1, whereas comorbidities were entered in Step 2. Based on our review of existing literature on GI bleed comorbidities, we included hemodialysis, acute kidney injury, peptic ulcer disease, renal disease, mild liver disease, and moderate to severe liver disease in Step 2 [11, 12, 14-16]. A series of preliminary bivariate logistic regression analyses indicated that mechanical ventilation, peripheral vascular disease, diabetes, body mass index ≥ 25, chronic obstructive pulmonary disease, hemiplegia or paraplegia, aortic stenosis, surgical aortic valve replacement, and venous thromboembolism yielded marginally significant (*p*s < .10) associations with GI bleed. Each of these comorbidities were also included in Step 2 of the multivariate analysis. Because ≤ .17% of the total sample were diagnosed a comorbidity of Von-Willebrand disease, transcatheter aortic valve replacement, dementia, HIV/AIDS, or metastatic solid tumor, these variables were omitted from the multivariate analysis. All statistical processing was performed in R (R Core Team, 2019) with Type I error rate set to 0.05.

Results

Demographics

We analysed the data from National inpatient sample database using *International Classification of Disease*-9 procedure code for LVAD use for end-stage heart failure among 2,359 patients aged 18 years or older (M_{age}=55 ± 13.7 years). A majority of the sample was male (77%) and Caucasian (59%).

Trends

There was no significant increase in the trends of GI bleed from 2010 to 2014 (*P*=.793), with a total incidence over the five-year period of 7.46%. GI bleed was associated with an increased likelihood of mortality, X^2 (1)=53.27, *P* < .001, OR=3.57, 95% CI=2.57, 4.93.

Length of stay and charlson co-morbidity

The mean length of stay among LVAD patients with GI bleed (M=53.64) was significantly higher compared to those without GI bleed (M=31.53), t (2355)=-11.03, P < .001. The mean total charges among LVAD patients with GI bleed (M=1,070,952.00) was higher compared to those without GI bleed (M=749,023.50), t (2334)=-8.17, P < .001. On further stratifying the sample by age groups, majority of the sample were in between the age group of 50-64 years (43%) followed by ≥ 65 years (27.21%). Mean Charlson co-morbidity score (M ± SD) was 2.88 ± 1.18. We see saw an increase in the Charlson score for comorbidities of ≥ 3 from 57.4% in 2010 to 64.6% in 2014 (**Table 1**). The most common cause of GI bleeding was angiodysplasia of stomach and intestine (**Table 2**).

Multivariate analysis

The hierarchical binary logistic regression analysis revealed a significant improvement in model fit for Step 2 compared to Step 1, ΔX^2 (15)=110.29, Nagelkerke ΔR^2=.11, *P* < .001. After statistically controlling for effects of age, sex, and length of hospitalization, comorbidities that emerged as significant predictors of GI bleed included acute kidney injury (AOR=1.87, 95% CI=1.26, 2.80, *P*=.002), peripheral vascular disease (AOR=1.77, 95% CI=1.02, 2.94, *P*=.034), body mass index ≥ 25 (AOR=.46, 95% CI=.22, .87, *P*=.026), hemiplegia and paraplegia (AOR=3.01, 95% CI=1.17, 7.05, *P*=.015), moderate or severe liver disease (AOR=2.40, 95% CI=.97, 5.34, *P*=.042), peptic ulcer disease (AOR=18.13, 95% CI=7.86, 42.38, *P* < .001), surgical aortic valve replacement (AOR=2.46, 95% CI=1.12, 5.15, *P*=.020), and venous thromboembolism (AOR=2.58, 95% CI=1.57, 4.15, *P* < .001). All other comorbidities included in the model were not significantly associated with GI bleed (*p*s > .05) (**Table 3**).

Discussion

Using a nationally representative NIS database of US hospital admissions from 2010 to 2014, our observations support the following conclu-

Table 1. Characteristics of Left Ventricular Assist Device recipients for index admission by year

Variable	Year					*p*-value	Total
	2010	2011	2012	2013	2014		
Total LVADs	380	426	482	523	548		2359
Gastrointestinal bleed	24 (6.32%)	35 (8.22%)	40 (8.30%)	38 (7.27%)	39 (7.12%)	.793[b]	176 (7.46%)
Mortality	61 (16.05%)	83 (19.48%)	83 (17.22%)	88 (16.83%)	88 (16.06%)	.653[b]	403 (17.08%)
Age (years), *M* ± *SD*	53.69 ± 13.64	55.31 ± 14.11	55.18 ± 13.69	54.41 ± 13.92	56.38 ± 13.25	.037[a]	55.07 ± 13.73
18-34	49 (12.89%)	45 (10.56%)	48 (9.96%)	58 (11.09%)	45 (8.21%)		245 (10.39%)
35-49	70 (18.42%)	80 (18.78%)	99 (20.54%)	112 (21.41%)	99 (18.07%)		460 (19.50%)
50-64	176 (46.32%)	177 (41.55%)	203 (42.12%)	215 (41.11%)	241 (43.98%)		1012 (42.90%)
≥ 65	85 (22.37%)	124 (29.11%)	132 (27.39%)	138 (26.39%)	163 (29.74%)		642 (27.21%)
Male	291 (76.58%)	321 (75.35%)	372 (77.18%)	414 (79.16%)	414 (75.55%)	.615[b]	1812 (76.81%)
Race						.082[c]	
White	240 (63.16%)	268 (62.91%)	285 (59.13%)	291 (55.64%)	315 (57.48%)		1399 (59.30%)
Black	77 (20.26%)	77 (18.08%)	103 (21.37%)	122 (23.33%)	132 (24.09%)		511 (21.66%)
Hispanic	31 (8.16%)	29 (6.81%)	23 (4.77%)	30 (5.74%)	32 (5.84%)		145 (6.15%)
Asian or Pacific Islander	6 (1.58%)	7 (1.64%)	9 (1.87%)	5 (0.96%)	4 (0.73%)		31 (1.31%)
Native American	1 (0.26%)	3 (0.70%)	2 (0.41%)	1 (0.19%)	3 (0.55%)		10 (0.42%)
Other	14 (3.68%)	12 (2.82 %)	29 (6.02%)	29 (5.54%)	15 (2.74%)		99 (4.19%)
Unknown	11 (2.89%)	30 (7.04%)	31 (6.43%)	45 (8.60%)	47 (8.58%)		164 (6.95%)
Insurance						.003[c]	
Medicare	157 (41.32%)	199 (46.71%)	224 (46.47%)	236 (45.12%)	267 (48.72%)		1083 (45.91%)
Medicaid	41 (10.79%)	55 (12.91%)	62 (12.86%)	68 (13.00%)	64 (11.68%)		290 (12.29%)
Private	170 (44.74%)	144 (33.80%)	178 (36.93%)	195 (37.28%)	195 (35.58%)		882 (37.39%)
Uninsured	7 (1.84%)	5 (1.17%)	5 (1.04%)	7 (1.34%)	5 (0.91%)		29 (1.23%)
Other	5 (1.32%)	20 (4.69%)	8 (1.66%)	10 (1.91%)	10 (1.82%)		53 (2.25%)
Unknown	0 (0.00%)	3 (0.70%)	5 (1.04%)	7 (1.34%)	7 (1.28%)		22 (0.93%)
Hospital region						.289[b]	
Northeast	70 (18.42%)	105 (24.65%)	82 (17.01%)	101 (19.31%)	103 (18.80%)		461 (19.54%)
Midwest	89 (23.42%)	104 (24.41%)	124 (25.73%)	119 (22.75%)	138 (25.18%)		574 (24.33%)
South	156 (41.05%)	158 (37.09%)	203 (42.12%)	225 (43.02%)	235 (42.88%)		977 (41.42%)
West	65 (17.11%)	59 (13.85%)	73 (15.15%)	78 (14.91%)	72 (13.14%)		347 (14.71%)
Length of stay (days), *M* ± *SD*	30.93 ± 24.75	35.22 ± 27.58	33.23 ± 25.85	33.18 ± 24.59	33.12 ± 27.91	.250[a]	33.18 ± 26.23
Total charges (dollars), *M* ± *SD*	637,205.27 ± 274,142.86	746,387 ± 465,239.90	791,223.50 ± 531,433.50	820,904.50 ± 546,710.30	819,105.40 ± 544,305.30	< .001[a]	772,175.90 ± 498,689.70
Comorbidities							
Aortic stenosis	26 (6.84%)	22 (5.16%)	31 (6.43%)	31 (5.93%)	29 (5.29%)	.802[b]	139 (5.89%)
Von-Willebrand disease	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.19%)	1 (0.18%)	1.000[c]	2 (0.08%)
Surgical aortic valve replacement	14 (3.68%)	12 (2.82%)	12 (2.49%)	12 (2.29%)	16 (2.92%)	.775[b]	66 (2.80%)
Transcatheter aortic valve replacement	0 (0.00%)	0 (0.00%)	0.00%	1 (0.19%)	0 (0.00%)	.768[c]	1 (0.04%)

Venous thromboembolism	26 (6.84%)	37 (8.69%)	43 (8.92%)	42 (8.03%)	40 (7.30%)	.756[b]	188 (7.97%)
Atrial Fibrillation	132 (34.74%)	164 (38.50%)	183 (37.97%)	209 (39.96%)	244 (44.53%)	.039[b]	932 (39.51%)
Hypertension	72 (18.95%)	73 (17.14%)	88 (18.26%)	116 (22.18%)	113 (20.62%)	.301[b]	462 (19.58%)
Acute kidney injury	173 (45.53%)	236 (55.40%)	245 (50.83%)	300 (57.36%)	330 (60.22%)	< .001[b]	1284 (54.43%)
Ventricular arrhythmia	159 (41.84%)	193 (45.31%)	219 (45.44%)	234 (44.74%)	258 (47.08%)	.635[b]	1063 (45.06%)
Hemodialysis	27 (7.11%)	35 (8.22%)	33 (6.85%)	29 (5.54%)	39 (7.12%)	.608[b]	163 (6.91%)
Mechanical ventilation	123 (32.37%)	143 (33.57%)	142 (29.46%)	132 (25.24%)	158 (28.83%)	.049[b]	698 (29.59%)
Peripheral vascular disease	19 (5.00%)	26 (6.10%)	45 (9.34%)	37 (7.07%)	38 (6.93%)	.141[b]	165 (6.99%)
DM	89 (23.42%)	101 (23.71%)	141 (29.25%)	148 (28.30%)	157 (28.65%)	.123[b]	636 (26.96%)
DMCC	17 (4.47%)	15 (3.52%)	26 (5.39%)	32 (6.12%)	28 (5.11%)	.444[b]	118 (5.00%)
BMI ≥ 25	44 (11.58%)	56 (13.15%)	38 (7.88%)	87 (16.63%)	95 (17.34%)	< .001[b]	320 (13.57%)
COPD	182 (48.42%)	197 (46.24%)	235 (48.76%)	254 (48.57%)	278 (50.73%)	.745[b]	1148 (48.66%)
Acute myocardial infarction	110 (28.95%)	109 (25.59%)	129 (26.76%)	128 (24.47%)	149 (27.19%)	.626[b]	625 (26.49%)
Cerebrovascular disease	39 (10.26%)	31 (7.28%)	25 (5.19%)	49 (9.37%)	55 (10.04%)	.023[b]	199 (8.44%)
Dementia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.18%)	1.000[c]	1 (0.04%)
Rheumatoid disease	5 (1.32%)	6 (1.41%)	4 (0.83%)	8 (1.53%)	3 (0.55%)	.475[c]	26 (1.10%)
Mild liver disease	47 (12.37%)	81 (19.01%)	102 (21.16%)	89 (17.02%)	101 (18.43%)	.016[b]	420 (17.80%)
Hemiplegia or paraplegia	4 (1.05%)	5 (1.17%)	5 (1.04%)	4 (0.76%)	15 (2.74%)	.089[c]	33 (1.40%)
Renal disease	147 (38.68%)	170 (39.91%)	195 (40.46%)	206 (39.39%)	250 (45.62%)	.164[b]	968 (41.03%)
Moderate or severe liver disease	8 (2.11%)	8 (1.88%)	13 (2.70%)	11 (2.10%)	8 (1.46%)	.728[b]	48 (2.03%)
Metastatic solid tumor	2 (0.53%)	1 (0.23%)	0 (0.00%)	0 (0.00%)	1 (0.18%)	.259[c]	4 (0.17%)
Cancer	11 (2.89%)	9 (2.11%)	13 (2.70%)	13 (2.49%)	10 (1.82%)	.822[b]	56 (2.37%)
HIV/AIDS	1 (0.26%)	0 (0.00%)	2 (0.41%)	0 (0.00%)	0 (0.00%)	.163[c]	3 (0.13%)
Peptic ulcer disease	3 (0.79%)	5 (1.17%)	7 (1.45%)	4 (0.76%)	9 (1.64%)	.653[c]	28 (1.19%)
Charlson score, *M* ± *SD*	2.78 ± 1.19	2.77 ± 1.10	2.93 ± 1.24	2.86 ± 1.18	3.01 ± 1.17	.010[a]	2.88 ± 1.18
0	1 (0.26%)	0 (0.00%)	0 (0.00%)	2 (0.38%)	0 (0.00%)		3 (0.13%)
1	55 (14.47%)	51 (11.97%)	55 (11.41%)	63 (12.05%)	49 (8.94%)		273 (11.57%)
2	106 (27.89%)	135 (31.69%)	134 (27.80%)	142 (27.15%)	145 (26.46%)		662 (28.06%)
≥ 3	218 (57.37%)	240 (56.34%)	293 (60.79%)	316 (60.42%)	354 (64.60%)		1421 (60.24%)

Note. [a]One-way ANOVA, [b]Chi-square test of independence, [c]Fisher's exact test. LVAD, Left Ventricular Assist Device; DM, Diabetes without chronic complications; DMCC, Diabetes with chronic complications; BMI, Body Mass Index; COPD, Chronic obstructive pulmonary disease.

Table 2. Including ICD-9 codes and the rates of GI bleeding

GI Bleeding	Year					ICD-9 Code
	2010	2011	2012	2013	2014	
Bleeding esophageal varices	0	0	0	0	0	456.0, 456.2, 456.20
Gastroesophageal laceration-hemorrhage syndrome/Mallory Weiss tear	0	0	1	0	0	530.7
Ulcer of esophagus with bleeding	0	1	0	2	0	530.21
Esophageal hemorrhage	0	1	1	2	1	530.82
Gastric Ulcer with Hemorrhage/Perforation	1	4	3	3	1	531.0, 531.00, 531.01, 531.2, 531.20, 531.21, 531.4, 531.40, 531.41, 531.6, 531.60, 531.61
Duodenal Ulcer with Hemorrhage/Perforation	0	1	0	0	3	532.0, 532.00, 532.01, 532.2, 532.20, 532.21, 532.4, 532.40, 532.41, 532.6, 532.60, 532.61
Peptic Ulcer site unspecified with Hemorrhage/Perforation	0	0	0	0	0	533.0, 533.00, 533.01, 533.2, 533.20, 533.21, 533.4, 533.40, 533.41, 533.6, 533.60, 533.61
Gastrojejunal Ulcer with Hemorrhage/Perforation	0	0	0	0	0	534.0, 534.00, 534.01, 534.2, 534.20, 534.21, 534.4, 534.40, 534.41, 534.6, 534.60, 534.61
Gastritis with hemorrhage	0	2	4	0	4	535.01, 535.11, 535.21, 535.41, 535.51, 535.61, 535.71
Angiodysplasia of stomach and duodenum with hemorrhage	2	2	5	5	5	537.83
Dieulafoy lesion (hemorrhagic) of stomach and duodenum	1	1	0	2	1	537.84
Hematemesis	1	3	3	4	3	578.0
Blood in stool/Melena	10	6	13	9	11	578.1
Dieulafoy lesion (hemorrhagic) of intestine	2	0	0	0	0	569.86
Angiodysplasia of intestine with hemorrhage	0	4	2	5	4	569.85
Diverticulitis of colon with hemorrhage	0	0	0	0	0	562.13
Diverticulosis of colon with hemorrhage	1	2	2	1	2	562.12
Diverticulitis of small intestine with hemorrhage	0	0	0	0	0	562.03
Diverticulosis of small intestine with hemorrhage	0	0	0	0	0	562.02
Hemorrhage of gastrointestinal tract unspecified	6	11	10	11	12	578.9

ICD-9 International classification of disease-9.

Table 3. Multivariate binary logistic regression model of gastrointestinal bleed

Determinant	Gastrointestinal bleed (0=No, 1=Yes)	
	Estimate (*SE*)	AOR (95% CI)
Block 1		
Age	0.02 (0.01)*	1.02 (1.01, 1.04)
Sex		
Female	0.36 (0.19)	1.43 (0.97, 2.09)
Length of stay	0.02 (0.00)**	1.02 (1.01, 1.02)
Model X^2 (*df*)	93.33 (3)**	
Nagelkerke R^2	.09	
Block 2		
Acute kidney injury	0.62 (0.20)*	1.87 (1.26, 2.80)
Hemodialysis	0.17 (0.28)	1.18 (0.67, 2.02)
Mechanical ventilation	0.12 (0.19)	1.13 (0.78, 1.63)
Peripheral vascular disease	0.57 (0.27)*	1.77 (1.02, 2.94)
DM	-0.27 (0.22)	0.77 (0.50, 1.15)
BMI ≥ 25	-0.78 (0.35)*	0.46 (0.22, 0.87)
COPD	-0.05 (0.18)	0.95 (0.66, 1.35)
Mild liver disease	-0.11 (0.22)	0.89 (0.58, 1.36)
Hemiplegia or paraplegia	1.10 (0.45)*	3.01 (1.17, 7.05)
Renal disease	-0.22 (0.18)	0.80 (0.56, 1.14)
Moderate or severe liver disease	0.87 (0.43)*	2.40 (0.97, 5.34)
Peptic ulcer disease	2.90 (0.43)**	18.13 (7.86, 42.38)
Aortic stenosis	0.33 (0.32)	1.39 (0.72, 2.53)
Surgical aortic valve replacement	0.90 (0.39)*	2.46 (1.12, 5.15)
Venous thromboembolism	0.95 (0.25)**	2.58 (1.57, 4.15)
Model X^2 (*df*)	203.61 (18)**	
Nagelkerke R^2	.20**	

Note. *P < .05, **P < .001. AOR, adjusted odds ratio; DM, Diabetes without chronic complications; BMI, Body Mass Index; COPD, Chronic obstructive pulmonary disease.

sions. First, the total number of GI bleed due to CF-LVADs were similar to earlier studies with a total incidence of 7.46%. Second, in-hospital mortality was higher in patients with GI bleed as compared to those without GI bleed. Third, there was also an increase in the length of stay (LOS) and total charges with time in patients with GI bleed. A majority of the GI bleeding evident in this study was due to angiodysplasia of the stomach and duodenum, followed by angiodysplasia of intestine. With increasing demand and supply of LVADs, it is important to identify the specific risk factors that may help reduce complications.

Incidence of GI bleed and associated co-morbidities

The overall incidence of GI bleed in patients with LVADs from 2010 to 2014 was higher relative to incidence rates reported in earlier studies, suggesting that implementation of newer LVADs may be accompanied by an increased risk of GI bleed. In our study, there has been an increase in the trend of patients ≥ 65 years receiving LVADs from 22.4% in 2010 to 29.4% in 2014. Moreover, there was an 7.2% increase in patients with LVADs who had a Charlson score of ≥ 3 between 2010 and 2014, indicating an older and sicker population. The observed trends in relation to the incidence of GI bleed in this study is consistent with earlier studies [16]. The presence of GI bleeding was associated with a significantly higher in-hospital mortality as compared to those without GI bleed. In general, CF-LVADs are associated with decreased mortality. Among co-morbidities, peptic ulcer disease appeared to be the strong independent risk factor associated with GI bleed.

Total charges

The mean total charges among LVAD patients with hospital courses complicated by GI bleed was higher compared to those without GI bleed. This may be explained by the need for multiple blood transfusions, GI consult services, investigations to identify the source of bleeding, treatment, and increased LOS. GI bleeds leads to a higher health care costs, and when coupled with higher likelihood of mortality, results in an overall higher financial burden. If we take care to screen and monitor patients at increased risk for GI bleeding then we could reduce healthcare costs and lower mortality.

Mechanisms leading to angiodysplasia and Arteriovenous malformation (AVM)

Angioectasias are thin-walled, dilated, ectatic blood vessels which may or may not have an endothelial lining. They are most commonly

seen in elderly patients who have a history of renal failure and/or aortic stenosis (AS). Von Willebrand factor (VWF) multimers are cleaved to small fragments as they pass through a stenotic aortic valve which enhances the risk of bleeding [16]. VWF multimers play a role in platelet aggregation, clotting and prevention of bleeding in high-shear areas [15, 17]. Prior studies have shown that post aortic valve replacement, VWF multimers levels rise and GI bleeding stops [15]. Similar to AS, risk of bleeding associated with LVADs is related to platelet dysfunction through inhibition of von Willebrand factor and the use of anticoagulation. There is a substantially higher risk when both warfarin and aspirin are used in conjunction as compared to the use of warfarin alone. Patients with continuous or non-pulsatile flow LVAD may have a higher risk of GI bleeding due to the continuous nature of the pump and may result in VWF deformation. Under these conditions, patients with pre-existing gastrointestinal angiodysplasia would be at risk for gastrointestinal bleeding. The pulse pressure varies with the speed of the device. The narrow arterial pulse pressures seen in the CF devices cause hypoperfusion of the intestines, leading to vascular dilation and angiodysplasia secondary to hypoxia. Another proposed mechanism is that the narrow pulse pressure raises the intraluminal pressure, causing muscular contraction and dilating mucosal veins, leading to the formation of *AVM*. Based on the findings of Crow et al with 101 patients, non-pulsatile LVADs had a significantly higher rate of gastrointestinal bleeding compared to pulsatile devices [1]. However, the main drawback of this study was non-pulsatile device recipients received anticoagulation with warfarin and aspirin, whereas pulsatile device recipients received only aspirin without anticoagulation. According to Potapov et al, non-pulsatile LVAD can generate pulsatile flow in a few settings with improved cardiac contractility of the ventricles, which could decrease VWF deformation and reduce the chance of GI bleeding [18]. In a study by Kushnir et al, there was a higher rate of GIB with continuous-flow LVADs than with pulsatile devices [19]; with similar trends reported in other studies [1, 4]. Other mechanisms which could play a role in increasing the risk of GI bleed in patients with CF-LVADs might be related to the lowering of mucosal protection against gastric acid. These alterations of mucosal perfusion are due to a lack of pulsatile flow, brought on by non-pulsatile blood flow. There has been no evidence to show that prophylaxis with proton pump inhibitors provides mucosal protection in patients with LVADs. Thus, the need for mucosal protecting agents should be considered.

Antiplatelets and anticoagulation

It is challenging to decide on anticoagulation therapy as it enhances the risk of bleeding and withholding it leads to risk of thromboembolism. Caution must be exercised when holding anticoagulation and antiplatelet agents, but it is reasonable to discontinue antiplatelet therapy in patients with clinically significant GI bleeding. As prior studies have stated, bleeding is usually related to an underlying lesion and not just medications. Warfarin and antiplatelet agents are administered in patients with non-pulsatile LVADs to minimize thrombotic risks [9].

Management of GI bleeding

The first procedure performed in most cases with acute lower GI bleeding is colonoscopy, an approach that is both diagnostic and therapeutic [20, 21]. Traditional endoscopic methods may miss the source of bleeding so other techniques like wireless PillCam SB capsule may be beneficial as it can detect the intermittent nature of the bleeding [22]. There have been a few concerns regarding the disturbances in the electromagnetic field of LVAD with the signals of the capsule, though these results have not been confirmed [23]. Strategies to prevent recurrence of GI bleeding are medical management, endoscopic therapy (argon plasma coagulation), placement of endoscopic hemoclips, contact thermal therapy, surgical resection of the colon or replacement of the aortic valve with a bioprosthetic valve [14]. There are many treatment options associated with acquired VWD which include tranexamic acid, desmopressin acetate and factor VIII concentrates. There is no clear data available for the patients included in the NIS database regarding the prior use of proton pump inhibitors or gastrointestinal evaluation with endoscopy/colonoscopy to prevent GI bleeding. It is difficult to detect lesions like AVMs when they are not actively bleeding, and thus may be missed. Hence, prior endoscopy/colonoscopy is usually not recom-

mended as it can miss the non-bleeding AVMs [24]. Patients with life-threatening or recurrent GI bleed should be considered for heart transplant surgery at the earliest to avoid hemodynamic compromise. This would also reduce the risk of developing circulating antibodies and avoiding cellular rejection after heart transplantation as a result of multiple blood transfusions [25]. Moreover, it is important to be cognizant of the hemodynamic compromise that may occur with the administration of high-dose heparin during heart transplant surgery.

Future prospect studies

Larger validation studies are needed to compare the methods discussed here. Additional studies employing more robust methodological approaches are needed to determine whether patient outcomes of LVAD therapy differ from those associated with cardiac transplantation in patients at a higher risk of GI bleeding. Other factors researchers could consider include redesigning devices in an attempt to increase pulse pressure by minimizing axial flow, evaluation of VWF levels before and after continuous and pulsatile device placement, implementation of early GI consultative services in patients at a higher risk of GI bleed, and the use of endoscopies prior to implantation for risk stratification. Since PPIs were ineffective, alternative agents should be studied to see if there is any benefit.

Limitations

Despite being an informative database capable of providing information about a large sample size over a wide geographic distribution to analyse the health trends over time, NIS database has its own set of limitations. The sampling approach used in the NIS database is representative of the US population of in-patients with LVADs, but the findings may not be generalizable to populations in other countries. The data is cross-sectional and causality cannot be assumed. GI bleeding was identified from ICD-9 codes in secondary diagnoses fields. However, we could neither establish if these events were truly related to device implantation nor the exact timing of the occurrence of events. As this study was based upon a database, we could not differentiate PF versus CF-LVADs. However, considering the FDA pattern and utilization rates, we presumed most of them received CF devices from 2010 onwards [7]. There is a lack of information regarding the timing and severity of complications, co-morbidities, pre-operative risk, medications, echocardiogram data, laboratory data, and endoscopy results. A few of these limitations may be partially compensated by the large sample size and absence of reporting bias due to selective participation of specialized centers in trials and/or registries. The database also does not contain post-discharge data on long-term outcomes. Lastly, this cohort was defined using diagnosis codes and may be subject to misclassification, but this is unavoidable in administrative database analysis.

Conclusion

Earlier studies showed an increase in the rate of GI bleed in CF-LVADs when compared to pulsatile flow devices. However, our study has indicated that CF-LVADs display no improvement in rates of GI bleed over five years, but that there was an increased likelihood of mortality in patients with GI bleed. Considering GI bleed is associated with an increased likelihood of mortality in patients with LVAD, the findings of this study highlight the importance of balancing advancements in LVAD technology with the risk of adverse side effects. The implications of the findings are discussed, including the need to improve approaches for identifying patients that may be at higher risk of LVAD treatment complications.

Disclosure of conflict of interest

None.

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