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EVALUATION OF GI BLEEDING AFTER IMPLANTATION OF LEFT VENTRICULAR ASSIST DEVICE

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Abstract

Background—Left ventricular assist devices (LVADs) have revolutionized management of end stage heart failure (ESHF). However, unexpectedly high rates of gastrointestinal bleeding (GIB) have been described, and etiologies and outcome remain unclear.

Objective—To determine the prevalence, etiology and outcome of GIB in LVAD recipients.

Design—Retrospective case series.

Setting—Tertiary care academic university hospital.

Patients—154 ESHF patients (55.4 yr, 122 M/32F) with LVADs implanted over a 10 year period.

Interventions—None

Main outcome measurements—Overt or occult GIB prompting endoscopic evaluation ≥7 days after LVAD implant.

Results—Over a mean of 0.9 ± 0.1 yrs of follow-up, 29 patients (19%) developed 44 GIB episodes. Patients with GIB were older and anticoagulated before device implant ($p \leq 0.02$ for each). GIB was overt (n=31) rather than occult (n=13), and most presented with melena (n=22, 50%); hemodynamic instability was observed in 13.6%. Each bleeding episode required 2.1±0.1 diagnostic or therapeutic procedures, and a source was localized in 71%. Upper endoscopy provided highest diagnostic yield, peptic bleeding (n=14) and vascular malformations (n=8) dominated findings. Endoscopy was safe and well tolerated. Overall mortality was 35%, none directly from GIB.

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Limitations—Retrospective design.

Conclusions—Rates of GIB with LVADs are higher than that seen in other patient populations, including those on anticoagulation and antiplatelet therapy. GIB episodes are mostly overt and predominantly from the upper GI tract. Endoscopy is safe in the LVAD population.

INTRODUCTION

Over five million people are affected by congestive heart failure (CHF) in the United States, with a quarter of these developing end stage heart failure (ESHF).(1) Medical therapies have significantly reduced morbidity and mortality, but heart transplantation remains the criterion standard for management.(1, 2) Given the large discrepancy between demand for heart transplants and donor organ supply, mechanical circulatory support (i.e. left ventricular assist devices, LVADs) has evolved rapidly over the past two decades. (3–5). Overall survival after 1 year of LVAD support can be as high as 72%; more than twice that seen with optimal medical therapy.(4) First generation LVADs were based on a pulsatile mechanism, compressed air driving a pump for pressure driven flow. However, poor reliability, high rates of infection and need for extensive surgical dissection during implantation led to development of continuous flow LVADs, which are smaller, do not require a large drive line, and are more reliable than pulsatile LVADs.(6, 7) Thromboembolic complications are countered by antithrombotic therapy, most commonly with a combination of aspirin and warfarin.(4)

The long term implications of lack of pulsatile blood flow on organ function are not well understood. Early animal studies showed that non-pulsatile blood flow adversely affected renal and hepatic perfusion, but limited studies after continuous flow LVAD implantation suggest preservation and even improvement of hepatic and renal function.(8–11) Several investigators have recently reported rates of luminal gastrointestinal bleeding (GIB) as high as 40% in patients after continuous flow LVADs.(12–18) These reports have left many unanswered questions regarding the risk factors for GIB during LVAD support, the role and safety of endoscopy, and outcomes in this population.

The aim of this retrospective study was to determine the prevalence, etiology and outcome of GIB in patients receiving LVAD support, and to assess the safety and efficacy of gastrointestinal endoscopy in this population.

METHODS

Patients

Adult patients (>18 yr) who had either HeartMate XVE (HM XVE, pulsatile flow) or HeartMate II (HM II, continuous flow) LVAD implantation (Thoratec, Pleasanton, CA) for ESHD over a 10 year period (2001–2010) were identified from our institutional database. Patients were excluded if they died in the operating room during LVAD implantation or if only a right ventricular assist device was placed. The review of clinical data for the purpose of this study was approved by the Institutional Review Board at Washington University School of Medicine.

LVAD implantation

LVADs were implanted as a bridge to transplant (BTT) or as destination therapy (DT) in patients deemed not to be transplant candidates. From 2001 to May 2005, HM XVE, a pulsatile LVAD, was used exclusively. After the continuous flow HM II became available, our institution transitioned to this device, which was used exclusively in the last 4 years of the study period.

All patients were anticoagulated postoperatively with unfractionated heparin or bivalirudin, and later transitioned to oral warfarin, with a goal international normalized ratio (INR) of 2–3. Aspirin 81 to 325 mg was used universally. Clopidogrel and/or dipyridamole were added at the discretion of the attending cardiologist and cardiac surgeon in select patients. All patients were maintained on intravenous proton pump inhibitor (PPI) until they were transferred out of the intensive care unit (ICU), after which further PPI administration was at the discretion of the treating cardiologist and cardiac surgeon.

Gastrointestinal bleeding

For the purpose of this study, GIB was defined as: a) the development of *overt bleeding* from the upper or lower GI tract as reported by treating or emergency room physicians, or 2) *occult bleeding*, with a ≥2 gram/dL drop in hemoglobin from recorded baseline values and hemoccult positive stool with no alternative explanation for anemia. Bleeding events within 7 days after LVAD implantation were deemed procedure related and were excluded. GIB was classified as early (within 8–30 days after LVAD implantation) and late (>30 days). In patients with multiple GIB events, a new episode of GIB was defined as bleeding >30 days from the initial event. A potential source of bleeding on endoscopy was defined as a lesion in the luminal GI tract with stigmata or recent bleeding (active bleeding, adherent clot, non-bleeding visible vessel, pigmented material at lesion base) in patients with overt bleeding, or any luminal GI tract lesion known to cause blood loss in patients with occult bleeding. Hemodynamic instability was defined as clinically significant end organ hypoperfusion requiring emergent blood transfusion and/or vasopressor support.

Endoscopy

All endoscopic procedures were performed in the inpatient endoscopy suite or intensive care unit. Conscious sedation (fentanyl, midazolam) or monitored anesthesia (including propofol) was administered at the discretion of the endoscopist and consulting anesthesiologist, and no set protocol was in place for choosing one method over the other. Heart rate, pulse oximetry and LVAD flow parameters were monitored at frequent intervals during the procedure. When endoscopic therapy was required for control of bleeding, injection (1:10,000 epinephrine), thermal therapy (bipolar or monopolar electrocautery, argon plasma laser), or mechanical therapy with homeostatic clips were utilized. Video capsule endoscopy was performed in select patients when recommended by the GI consult service; in all instances, records of prior imaging were reviewed to document absence of obstructing bowel lesions. Procedure notes on all endoscopic procedures were reviewed as part of data collection for this study.

Radiologic Studies

Radiologic studies were performed when endoscopy was unrevealing or when bleeding was not endoscopically controlled. Radionuclide bleeding studies were performed after IV administration of in vitro Tc-99m labeled red cells. Patients with a positive bleeding study or with rapid bleeding and hemodynamic compromise were referred for visceral angiography, performed under the direction of the attending interventional radiologist.

Data Collection

Demographics, clinical features of CHF, prior GIB, and comorbid medical illnesses were recorded from electronic medical records. With GIB presentations, hemodynamics, units of packed red blood cells transfused, ICU admission, nadir hemoglobin, INR and platelet count were recorded at presentation, discharge, and each subsequent GIB presentation. When applicable, cause of death was determined from our institution's electronic medical record and LVAD registry.

Statistical analysis

The Shapiro-Wilk test was used to assess normality of data. Normally distributed data are reported as mean ± standard error of the mean, skewed data as median and interquartile range. Grouped continuous variable data were compared using two-tailed Student's t test. Intergroup comparisons were made using the Chi-squared test and Fisher's exact test where appropriate. A p value of <0.05 was required for statistical significance in each instance. Bleeding event rate per 100 patient-years was calculated and modeled with a Poisson regression having LVAD type as the independent variable, number of bleeding events as the dependent variable, and log patient years as the offset. All analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, NC).

RESULTS

Between 2001 and 2010, 154 patients (55.4±0.87 years old, 79.2% male) underwent LVAD implantation (pulsatile HM XVE in 27.3%, continuous flow HM II in 72.7%). Of these, 29 patients (18.8%) developed 44 episodes of GIB during a mean of 0.9 ±0.1 years (range 0.1–2.8 years) of follow-up, after exclusion of one GIB event in the immediate post-operative period. Patients who developed GIB were older, more likely to have been anticoagulated before LVAD implantation, and more likely to have received an LVAD for DT rather than BTT (p<0.02 for each, Table 1), but PPI use and prior GIB were similar regardless of GIB. Etiology of ESHF (ischemic vs. non-ischemic cardiomyopathy) and indications for LVAD (DT vs. BTT) were similar between HM XVE and HM II devices.

GIB events occurred after a mean of 159.3±25.8 days after LVAD implantation. Only 20.4% of GIB episodes occurred in the first month (within 8–30 days). Two-thirds of the GIB events occurred in outpatients and prompted hospital admission; in 14 instances (31.2 %), bleeding started in hospitalized patients. Most episodes of GIB were overt, presenting mainly as melena (Table 2). Bleeding occurred while anticoagulated in 77.3% (Table 3), when median INR was 2.0 (IQR 1.8–2.5). Only 13.6% were hemodynamically unstable, and admission to the ICU was only necessary in 5 instances (11.4%). The median duration of bleeding was 3.5 days (interquartile range, IQR 2–10 days), with mean nadir hemoglobin level of 7.3±0.2 g/dL (decline of 2.9±0.25 g/dL from baseline). Patients were given transfusions of 3.0 (IQR 2–4) units of packed red blood cells per bleeding event.

Endoscopy

Coagulation parameters were corrected (INR<1.5, PTT< 30) in all patients before endoscopy (Table 3). One patient with obscure occult bleeding declined endoscopy. The time interval to the first endoscopic procedure was 2.04±0.25 days, 1.63±1.5 for overt bleeding and 3.0 ±0.49 for occult bleeding (p=0.01). Monitored anesthesia (involving propofol administration) was administered by ICU staff or an anesthesiologist in 44%; the remainder were administered conscious sedation (fentanyl, midazolam) by the endoscopist. A total of 82 endoscopic procedures and 8 radiologic procedures were performed (mean 2.1± 0.1 procedures per bleeding event). The need for repeat endoscopic procedures was higher (2.7±1.1 endoscopic procedures per bleeding event) when a source for bleeding was identified, compared with 1.8±0.9 procedures per bleeding event when no etiology for GIB could be found (p=0.002). Conscious sedation and monitored anesthesia were well tolerated, with no cardiac or pulmonary complications related to sedation. The sole endoscopic complication was a duodenal ulcer perforation after 3 attempts at hemostasis with monopolar electrocautery. There were no adverse events related to capsule endoscopy. A source for bleeding was localized in 71.5% of bleeding events (Table 2). Upper endoscopy provided highest diagnostic yield with a definitive source in 20 of 35 procedures (Figure 1, p<0.05 compared with colonoscopy and enteroscopy), peptic bleeding (n=14) and vascular

malformations (n=5) dominated findings. Testing for *Helicobacter pylori* (histology, CLO test or serology) was undertaken in all patients with peptic bleeding but only 2 (14.3 %) had evidence of infection. The number of capsule endoscopy procedures performed (5) was limited.

HM II LVAD

Because only the HM II LVAD is currently in use, events specific to this device were separately analyzed (Table 2). There was a trend toward a higher incidence of GIB with continuous flow (HM II) compared with pulsatile (HM XVE) LVADs (34 events/100 patient years with HM II, and 27 events/100 patient yearswith HM XVE, p=0.64). All 10 bleeding events which occurred off anticoagulation were in HM II patients. Proportions of patients with each final diagnosis were not different from the entire cohort; vascular lesions were seen only with HM II. Diagnostic yields from each procedure performed were also comparable (Table 2).

Management

Endoscopic hemostatic therapy was attempted and was initially successful in 9 instances (all cases HM II, all performed for upper gut bleeding lesions). Therapy was performed using a thermal device (heater probe) in 2 instances, argon plasma coagulation in 3, and hemostatic clip in 4 instances; epinephrine injection was used as an adjunct in 3 instances. Six of the patients undergoing endoscopic hemostatic therapy rebled from the same source despite PPI therapy. One patient underwent successful surgery for treatment of a perforated duodenal ulcer. In 5 bleeding episodes, radionuclide red blood cell scans were obtained, and correctly localized the site of bleeding in 60.0%. Visceral angiography was undertaken during three bleeding events, and was negative in all instances. Anticoagulation was resumed at discharge in 23/34 (67.6%) of subjects who were anticoagulated before the onset of GI bleeding (Table 3).

Recurrent GI bleeding

Eleven patients, all with HM2 LVADs, developed 15 recurrent GIB events (38.5% of GIB events in HM 2 group), with a mean of 1.5±0.2 recurrent bleeding events per patient. In 73% of instances, the recurrent GIB event presented with the same symptoms as the initial event. The etiology of bleeding was the same on recurrence in 7 patients, and different in 2 patients (duodenal vascular lesion, ischemic colitis in one, and peptic ulcer, jejunal vascular lesion in the other); an etiology for bleeding could not be established in the remainder (2 patients) with recurrent bleeding. There were no episodes of recurrent GIB in patients supported by HM XVE.

DISCUSSION

In the largest study to date monitoring GIB after LVAD implantation, we report an unusually high rate of GIB during LVAD support in patients with ESHF. The 19% incidence of GIB in LVAD patients is higher than the 1.5–8% incidence typically observed in patients on triple antithrombotic therapy (aspirin, clopidogrel, warfarin or equivalent) for cardiovascular disease.(19) Further, we report that GIB episodes are mostly overt and identified bleeding sources are predominantly from the upper GI tract. Our results indicate that a thorough endoscopic evaluation can identify an etiology for GI bleeding in over 70% of cases, and upper endoscopy has the highest diagnostic value. Finally our experience demonstrates that diagnostic and therapeutic endoscopy, including capsule endoscopy, is safe in the LVAD population.

The high rate of GI bleeding observed in our study is consistent with findings from prior smaller case series. (12, 17, 18) Specifically, Stern et al. reported that an etiology for GIB could not be identified in 65% of cases; however, of only 17 GIB events, none were attributed to PUD [14]. Similarly, Crow et al. report no PUD related bleeds in their 101 patient cohort, despite demonstrating a potential etiology for GIB identified in 75% of patients. Both studies provide few details regarding the nature of GIB events and subsequent work up. In our cohort, an etiology for GIB was identified in 70% of patients, which concurs rates reported with antithrombotic therapy (70–80%) [16, 17, 18]. Further, patients on antithrombotic therapy have upper GI tract bleeding sites >50% of the time, with which our findings are consistent. Finally, our proportions of PUD (32%) are concordant with rates seen with antithrombotic therapy (20–50%) [17, 18]. The high rates of PUD bleeding in these patients has been attributed to nonsteroidal anti-inflammatory drug (NSAID) induced damage to the upper GI tract mucosa coupled with NSAID ± thiopyridine induced platelet inhibition and anticoagulation.(19, 20) We therefore conclude that an upper endoscopic examination is the best initial test in LVAD patients presenting with acute GIB, and provides the highest likelihood of finding a source for the bleed.

Our finding of the lack of protection afforded by PPI use to GIB in our patient population is surprising, because data from randomized controlled trials suggest that the addition of PPI to antiplatelet therapy decreases the risk of GIB by more than 60% in individuals who are at average risk and by as much as 89% in those with history of GIB.(21, 22) Further, our rate of Helicobacter pylori positivity was extremely low. Taken together, these findings lead us to speculate that non-traditional factors likely have a significant role in the pathogenesis of ulceration and GIB in patients being supported by LVADs. We note that higher rates of GIB have been reported with continuous flow LVADs compared with pulsatile devices; a similar trend can be seen in our data.(12, 17) This observation may suggest alterations in GI mucosal and vascular biology with continuous flow that may lower mucosal protection against gastric acid. It is also possible that autoregulation of intestinal blood flow is compromised with lack of pulsatile flow, similar to that observed in normotensive critically ill patients with stress ulcers, 50% of whom have evidence of splanchnic hypoperfusion despite normal blood pressure.(23) This hypothesis is also consistent with animal studies by Yasue et al. suggesting that ischemic mucosal damage in the stomach occurs even in the absence of gastric acid.(24)

Other investigators have proposed that the high rate of bleeding in continuous flow LVADs is from a defect in thrombogenesis brought on by nonpulsatile blood flow.(25) Patients can develop decreased levels of high molecular weight von Willebrand factor (vWF), which are critical for platelet adhesion. Levels can be low enough to support the diagnosis of acquired vWF syndrome.(25, 26), potentially from high shear forces encountered in the continuous flow LVAD that resolve after transplant.(25). This insult, combined with pharmacologically induced platelet dysfunction, could significantly increase the risk of GIB in patients with pre-existing gastrointestinal pathology, similar to Heyde's syndrome in patients with aortic stenosis.(27, 28) Our study was not geared to test these concepts, but we propose that impaired mucosal perfusion combined with an acquired bleeding diathesis may be responsible for the increased GIB risk in continuous flow LVADs. Given the observed lack of protection afforded by PPIs, adjunctive mucosal protective agents such as sucralfate or misoprostol need to be investigated. Furthermore, given the fact that an acquired vWF deficiency may contribute to bleeding during LVAD support, the current approach of using antiplatelet and anticoagulation therapy may need to be reconsidered in favor of vitamin K antagonists or oral direct thrombin inhibitors.

Our study does have some limitations. The retrospective nature of the study may have led us to underestimate the true incidence of GIB. Second, the pulsatile and continuous flow

LVAD groups were not balanced. Despite this we observed a trend toward a higher rate of GIB in the HM II group. Third, the workup of GIB was not standardized; a source could have been identified if a more aggressive endoscopic workup was pursued, as can be the case with obscure GIB in the general population.(29) However, given the relatively slow and benign course of GIB in most patients in our series, the conservative approach of observation and support with iron or transfusion therapy appears to be adequate for clinical management when GI bleeding remains obscure after bidirectional endoscopy. Finally, we did not assess splanchnic perfusion or vWF activity and can only speculate on the pathogenesis of GIB during LVAD support.

In conclusion, we report that the rate of GIB after LVAD implantation is significantly higher than that seen after anticoagulation or antiplatelet therapy for cardiovascular conditions. The majority of GIB episodes during LVAD support are overt and from the upper GI tract, peptic erosions and ulcers dominating the etiology when a bleeding source was identified. A thorough endoscopic evaluation can identify an etiology for GIB in over 70% of cases; with upper endoscopy (followed by push enteroscopy, if negative) offering the highest upfront diagnostic yield. Further prospective studies are needed in this population to elucidate the mechanisms leading to GIB, as well as evaluate novel therapeutic approaches.

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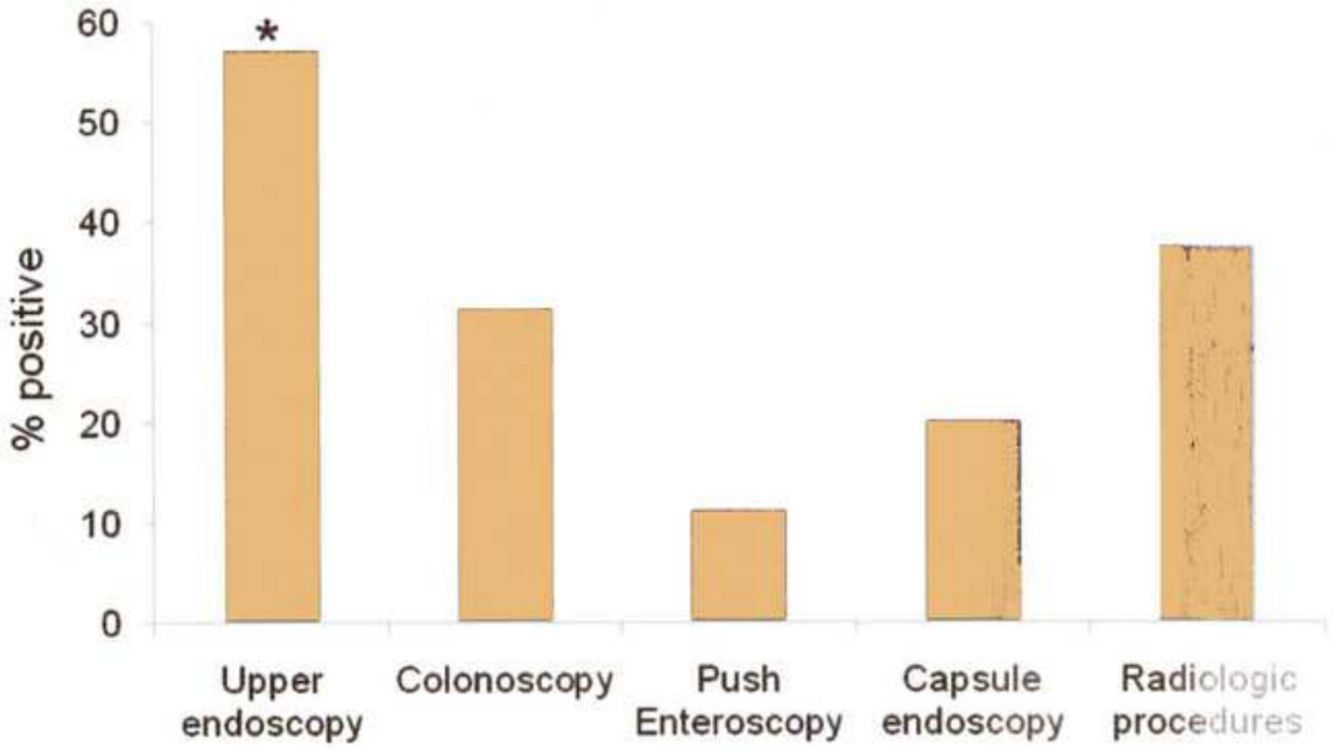

Figure 1.

Diagnostic yield of endoscopic and radiologic procedures performed for the evaluation of gastrointestinal bleeding in patients with LVADs. Upper endoscopy had the highest yield for a source of bleeding, significantly higher than that seen with colonoscopy or enteroscopy. The number of capsule endoscopy (5) and radiologic procedures (8) performed were limited. (*$p<0.05$ compared to colonoscopy and enteroscopy)

Table 1

Clinical Characteristics of Study Patients

	All patients ***n=154***	**GIB** ***n=29***	**No GIB** ***n=125***	**p-value**
Age (± SEM)	55.4±0.87 years	61.2±1.5	54.1±1.1	0.0003
Gender	122 M/ 32 F	26 M/ 3 F	96 M/29 F	
Etiology of CHF				NS
Ischemic	89 (57%)	16 (55%)	73 (57%)	
Nonischemic	65(43%)	13 (45%)	52 (43%)	
Therapy type				0.015
Bridge to transplant	105 (68%)	14 (48%)	91 (73%)	
Destination therapy	49 (32%)	15 (52%)	34 (27%)	
Prior GIB	5 (3%)	2 (7%)	3 (2%)	NS
Prior anticoagulation	93 (60%)	23 (79%)	69 (56%)	0.02
Antithrombotic therapy				
Warfarin	111 (72.1%)	20 (69%)	91 (72.8%)	NS
Aspirin	143 (92.9%)	28 (97%)	115 (92.0%)	NS
Clopidogrel	5 (3%)	1 (3%)	4 (3%)	NS
Dipyridamole	11 (7.7%)	2 (6.9%)	9 (7.2%)	NS
PPI use	113 (73%)	23 (79%)	90(73%)	NS
Mortality	55 (35%)	10 (34%)	45 (35%)	NS

GIB: gastrointestinal bleeding; PPI: proton pump inhibitor

Table 2

GI Bleeding Events by LVAD type

	All Patients ***n=44***	**HM II Device** ***n=39***
Occult	13 (29.5%)	11 (28.2%)
Overt	31 (70.5%)	28 (71.8%)
Melena	22	21
Hematochezia	6	5
Hematemesis	3	2
Mode of Localization		
EGD	20 (45.5%)	17 (43.6%)
Colon	10 (22.7%)	9 (23.1%)
Deep Enteroscopy	1 (2.3%)	1 (2.6%)
Not localized	13 (29.5%)	12 (30.8%)
Final Diagnosis		
Peptic Bleeding	14 (31.8%)	11 (28.2%)
Vascular Malformations	12 (27.3%)	12 (30.8%)
Colitis	3 (6.8%)	2 (5.1%)
Polyps	2 (4.5%)	2 (5.1%)
No diagnosis made	13 (29.5%)	12 (30.8%)

Table 3

Management Approach to Anticoagulation During Gastrointestinal Bleeding Episodes

Management Approach	All patients *n=34*	HM II device *n=29*
Acute Management		
Fresh frozen plasma	11 (32.4%)	8 (27.5%)
Vitamin K	1 (2.9%)	1 (3.5%)
Warfarin held only	22 (64.7%)	20 (69.0%)
Chronic Management		
Warfarin Continued	23 (67.7%)	19 (65.5%)
Warfarin Stopped	11 (32.3%)	10 (35.5%)