A randomized controlled trial comparing efficacy of early video capsule endoscopy with standard of care in the approach to nonhematemesis GI bleeding (with videos)

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Background and Aims: Patients presenting with nonhematemesis GI bleeding (NHGIB) represent a diagnostic challenge for physicians. We performed a randomized controlled trial to assess the benefits of deployment of a video capsule soon after admission in the management of patients presenting with melena, hematochezia, or severe anemia compared with standard of care management.

Methods: Patients admitted with NHGIB were randomized and placed into 1 of 2 study groups. In the experimental group, patients ingested a video capsule soon after admission to the hospital. These patients had further endoscopic workup based on the findings from the capsule. Patients in the control group underwent endoscopic evaluation (ie, upper endoscopy, capsule endoscopy, and/or colonoscopy) to identify the source of bleeding as directed by the attending gastroenterologist's interpretation of their clinical presentation. The primary endpoint for this study was the rate of localization of bleeding during hospitalization.

Results: Eighty-seven patients were included in this study: 45 randomized to the standard of care arm and 42 to the early capsule arm. A bleeding source was localized in 64.3% of the patients in the early capsule arm and in 31.1% of the patients in the standard of care arm ($P < .01$). The likelihood of endoscopic localization of bleeding over time was greater for patients receiving early capsule endoscopy compared with those in the standard of care arm (adjusted hazard ratio, 2.77; 95% confidence interval, 1.36-5.64).

Conclusions: For patients admitted to the hospital for NHGIB, early capsule endoscopy is a safe and effective alternative for the detection of the source of bleeding. (Clinical trial registration number: NCT02442830.) (Gastrointest Endosc 2019;89:33-43.)

(footnotes appear on last page of article)

Hospitals in the United States admit approximately 350,000 patients every year for GI bleeding at an annual total cost of approximately 2.5 billion dollars.[1-3] For patients presenting with hematemesis, management routinely involves EGD.[4] For patients presenting with nonhematemesis GI bleeding (NHGIB; ie, melena, hematochezia, or symptomatic iron deficiency anemia) the algorithm for management is less clear, but traditionally patients undergo EGD or colonoscopy based on the presumed location of bleeding. If initial tests are negative, then additional procedures may be performed to locate the source of bleeding.

Patients presenting with NHGIB may have a source of bleeding anywhere within the GI tract. In 20% of these patients, a definitive diagnosis is not identified by the end of a conventional workup.[5] Patients who remain

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undiagnosed at the end of their hospitalization are frequently readmitted with recurrent bleeding, leading to more procedures and additional costs.[6]

For patients in whom a bleeding source has not been identified after a conventional workup, video capsule endoscopy (VCE) is considered to investigate the small bowel.[7] This device images the esophagus, stomach, duodenum, and right side of the colon and can be administered without preparation.[8] A recent innovation now allows for real-time viewing of what the capsule is visualizing without waiting for completion of the study.[9]

For patients with hematemesis there is evidence that early use of VCE can act as a screening tool for whether patients require admission. In this algorithm, if there are signs of recent bleeding on VCE, patients are admitted and undergo endoscopy. Those patients without findings on VCE are discharged for further outpatient evaluation.[10] The results of this study are promising and suggest that early administration of VCE can change the management of GI bleeding.

We hypothesize that for patients admitted for NHGIB, early VCE will improve localization of the bleeding source compared with standard of care. By providing an evaluation of the GI tract closer to the time of presentation, VCE would provide an efficient method to localize the bleeding source. We performed a randomized controlled trial to examine this hypothesis.

METHODS

Trial design

We performed a parallel, randomized, controlled trial from April 2015 to July 2017 at the University of Massachusetts Medical School in Worcester, Massachusetts. The institutional review board approved this study, which was registered with ClinicalTrials.gov (NCT02442830). Patient recruitment ended after the required sample size had been exceeded. All authors had access to the study data and approved the final manuscript. Full details of the study protocol can be found in the Appendix 1, available online at www.giejournal.org.

Patients

Patients were screened in the emergency department or soon after admission to the hospital. Patients were eligible to be included in this study if they were at least 18 years old, able to provide informed consent, hemodynamically stable (defined as blood pressure >100/60 mm Hg or pulse <100 beats per minute at the time of consent), and admitted for evaluation of new-onset NHGIB. Patients were excluded if they were pregnant, had a history of gastroparesis, had signs of infection, had dysphagia, had bleeding concerning for hemorrhoids, had an allergy to metoclopramide or erythromycin, had a code status of do not resuscitate, had Crohn's disease, had a history of abdominal radiation or intestinal surgery, had an implanted cardiac device, had findings concerning for an acute abdomen, or if they had an American Society of Anesthesiologists score of 4 or greater.

Randomization

A computer program generated a code associating study numbers with group assignments, either standard of care or early capsule. We used an allocation concealment scheme using sequentially numbered, opaque, sealed envelopes. Study personnel opened envelopes containing cards (associating the group assignment to the patient's study number) after patient consent was obtained. Study personnel and medical teams were not blinded to group allocation after consent.

Interventions

Patients randomized to the early capsule arm ingested an EC-S10 VCE (Olympus Corp, Tokyo, Japan) within 10 minutes of consent. Immediately after ingestion of the VCE, a research staff member activated the real-time viewer on the RE-10 recorder (Olympus Corp) to look for blood in the stomach. If blood was found, the gastroenterology consult team was notified. If no blood was seen, the real-time viewer was rechecked 60 minutes later to ensure the capsule had entered the small bowel. If the capsule remained in the stomach, the patient was given intravenous metoclopramide, 10 mg, or intravenous erythromycin, 125 mg. The real-time viewer was checked 8 hours later (or the following day if the capsule was ingested after 12:00 pm) to ensure cecal transit. If cecal transit occurred (or if the capsule battery had expired) the recording was downloaded via a computer workstation using Endocapsule software 10 (Olympus Corp).

Gastroenterologists with expertise in VCE (D.R.C., K.B., and C.M.) did an initial read within 1 hour of download and immediately notified the gastroenterology team of the findings. The gastroenterology team performed further endoscopic examinations at their own discretion. If the VCE was negative, the gastroenterology team performed further examinations to identify the source of bleeding at their own discretion.

For patients randomized to the standard of care arm, the consulting gastroenterologist chose which procedures to perform and when to perform them based on their interpretation of the patient's presentation. A patient requiring VCE was given the same type of Olympus capsule used in the early capsule arm. Readings were performed by the same gastroenterologists interpreting examinations in the early capsule arm. Results were provided with the same degree of expediency.

Patients in both arms received blood transfusions, intravenous fluids, proton pump inhibitor therapy, and other nonendoscopic treatments at the discretion of their primary teams. Patients included in the study were

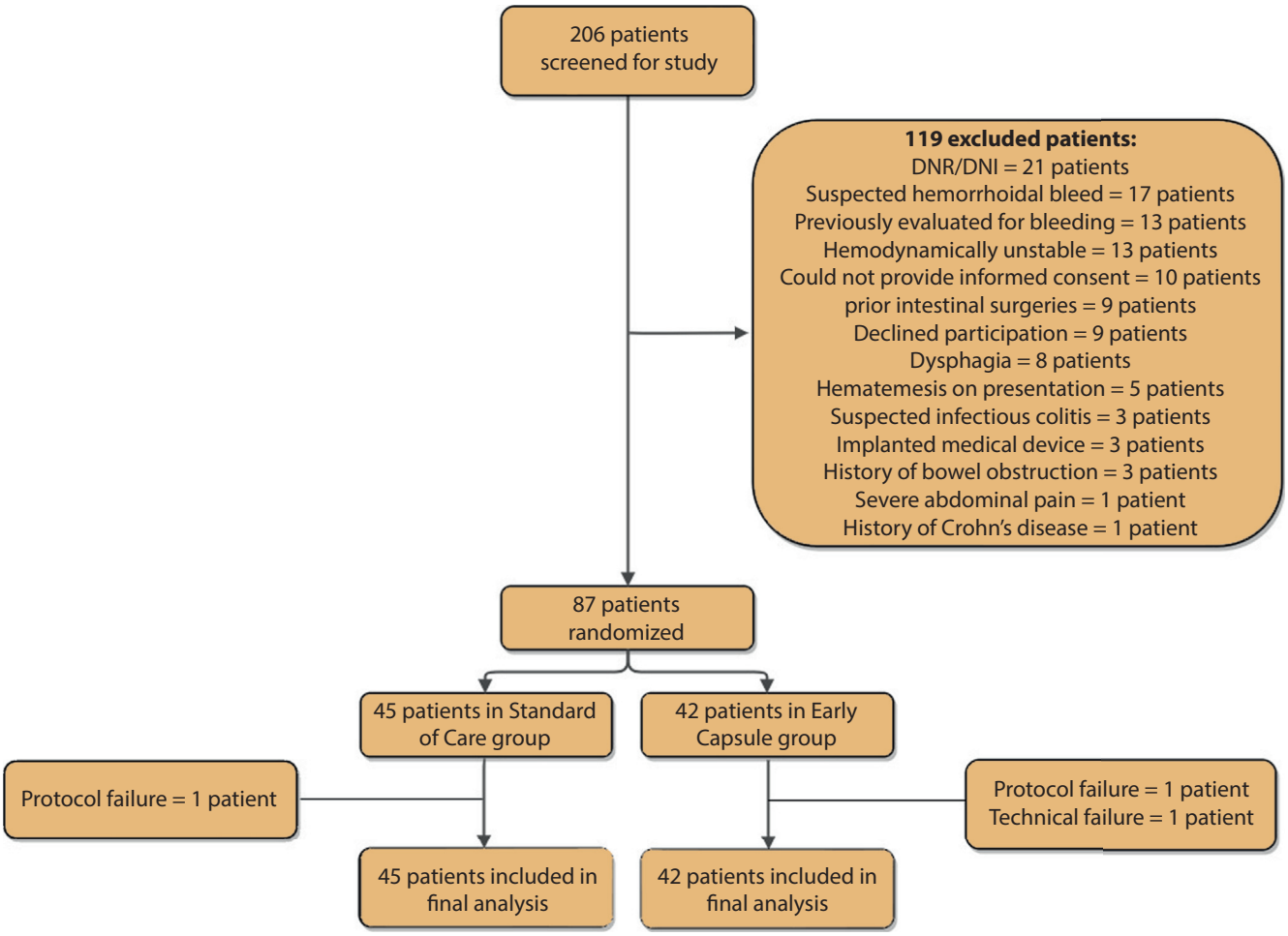

Figure 1. Number of patients screened, included, randomized, and analyzed according to intention-to-treat protocol. *DNR/DNI*, Do not resuscitate/do not intubate.

monitored throughout their hospitalization and for 30 days after discharge.

Outcomes

The primary outcome for this study was the rate of localization of bleeding during hospitalization. Localization of bleeding was defined as identification of blood or a lesion with high-risk stigmata of recent hemorrhage (SRH).[11] Bleeding was localized to 1 of 3 areas: foregut (esophagus to second portion of the duodenum), midgut (ampulla of Vater to the ileocecal valve), or colon (cecum to rectum). The most proximal location where bleeding or bleeding source was identified was considered the anatomic location of bleeding. Secondary outcomes included overall rate of localization of bleeding by the end of admission, anatomic location of bleeding or the bleeding source, rate of endoscopic therapy, rate of readmission, rate of diagnosis of vascular lesions (defined as Dieulafoy lesions or angioectasias), rate of recurrent bleeding within 30 days of discharge, rate of all-cause mortality within 30 days of hospitalization, cumulative direct hospital costs by the end of admission, and overall rate of identifying the etiologic diagnosis.

Diagnoses were classified as definitive or presumptive. Definitive diagnoses were those associated with high-risk SRH. A lesion was considered a presumptive diagnosis if it was associated with low-risk SRH, moderate to severe mucosal abnormalities, or if blood was found near where the lesion was identified and no other potential etiologies were found.

Statistical analysis

We planned the study as a superiority trial and estimated the probability of localization of bleeding during hospitalization in the early capsule arm to be 2 times greater than that of the standard of care arm (ie, estimated hazard ratio [HR] of 2.00). We found no prior studies similar to our methodology, so prior experience at our institution guided the estimation of effect. Power analysis revealed that for this effect size to be detected (80% chance) as significant at the 5% level, a sample of at least 72 patients (36 per group) was required.

Patient characteristics were described as means with standard deviation or as proportions. Time to localization and time to first procedure were described using medians with interquartile range. Hospital costs were described in U.S. dollars.

Independent variables selected for analysis included those previously suggested as prognostic indices for NHGIB.[12,13] Variables chosen for analysis included gender, race, age, vital signs at admission, use of anticoagulants, use of nonsteroidal anti-inflammatory drugs (eg, aspirin and ibuprofen), use of a $P2Y_{12}$ inhibitor (eg, clopidogrel), factors that contribute to the Glasgow-Blatchford Score,[14] and type of bleeding at admission (ie, hematochezia, melena, or symptomatic anemia).

Univariate analyses involved Wilcoxon-Rank sum tests for continuous variables and χ^2 or Fisher exact tests for binary variables. A Kaplan-Meier survival analysis with a log-rank test compared the cumulative incidence of endoscopic localization of bleeding for the 2 groups. For multivariate analyses, independent variables with a difference at $P < .10$ after univariate analysis or those noted to be unevenly distributed between the 2 cohorts were included as covariates. Cox proportional hazard and logistic regression analysis were described using HRs and odds ratios (ORs), respectively, plus the 95% confidence interval (CI). A $P < .05$ was significant. Statistical analysis was performed using STATA 13 (StataCorp, College Station, Tex). An interim analysis was performed 1 year after the commencement of the trial to assess effect size and for adverse events.

Role of the funding source

Olympus Corporation (Tokyo, Japan) provided an unrestricted grant for this trial and was not involved in trial design, manuscript preparation, statistical analysis, or decision to submit the manuscript for publication

RESULTS

Patients

Of the 87 patients randomized in the study, 45 were allocated to the standard of care group and 42 were allocated to the early capsule group. In the standard of care group, there was 1 protocol failure involving a patient who was supplied an SB3 capsule (Medtronic, Sunnyvale, Calif). In the early capsule group, 1 patient received a capsule that was faulty and unable to transmit images to the recorder. There was also a protocol failure involving a patient who was included after undergoing a workup at another hospital before admission. Through an intention-to-treat protocol, all 87 patients were included in the final analysis (Fig. 1).

Table 1 demonstrates the baseline characteristics of the 87 patients included in the analysis. Between the study groups, baseline characteristics were similar; however, more patients in the standard of care group used nonsteroidal anti-inflammatory drugs (60.0% vs 28.6%; $P < .05$) and had a history of heart failure (17.8% vs 2.4%, $P < .05$).

TABLE 1. Baseline patient characteristics by study group

	Early capsule group (n = 42)	Standard of care group (n = 45)
Male	23 (54.7)	28 (62.2)
Race		
White	36 (85.7)	42 (93.3)
Black	3 (7.2)	1 (2.2)
Hispanic	3 (7.1)	2 (4.4)
Age, y	67.0 ± 12.6	70.4 ± 16.4
Home medications		
Anticoagulation agents	9 (21.4)	11 (24.4)
NSAIDs	12 (28.6)	27 (60.0)
$P2Y_{12}$ inhibitor	7 (16.7)	6 (13.3)
Vital signs at admission		
Heart rate at admission, beats/min	77.7 ± 13.2	82.9 ± 15.4
Systolic blood pressure at admission, mm Hg	124.4 ± 21.9	125.3 ± 21.4
History of heart failure	1 (2.4)	8 (17.8)
History of cirrhosis	4 (9.5)	4 (8.9)
Recent syncope	4 (9.5)	2 (4.5)
Glasgow-Blatchford score	8.4 ± 4.2	9.7 ± 3.7
Laboratory data at admission		
Blood urea nitrogen, mmol/L	1.7 ± 1.3	1.9 ± 1.3
Prothrombin time, s	15.3 ± 9.5	15.8 ± 11.4
Hemoglobin, g/dL	9.4 ± 3.0	9.1 ± 2.1
Type of bleeding at admission		
Melena	26 (61.9)	34 (75.6)
Hematochezia	11 (26.1)	9 (20.0)
Symptomatic anemia	5 (11.9)	2 (4.4)

Values are n (%) or mean ± standard deviation.
NSAIDS, Nonsteroidal anti-inflammatory drugs.

Outcomes

A bleeding source was localized in 14 patients (31.1%) in the standard of care arm and in 27 patients (64.3%) in the early capsule arm. In the standard of care arm, of the 14 patients with localization of bleeding, 64.3% had bleeding localized by EGD, 28.6% had bleeding localized by VCE, and 7.1% had bleeding localized by colonoscopy. In the early capsule arm, of the 27 patients with localization of bleeding, no patients had bleeding localized by EGD, 92.6% had bleeding localized by VCE, and 7.4% had bleeding localized by colonoscopy. Of the patients who had localization of bleeding, 9.3% in the early capsule group and 4.4% in the standard of care group did not have an etiologic diagnosis.

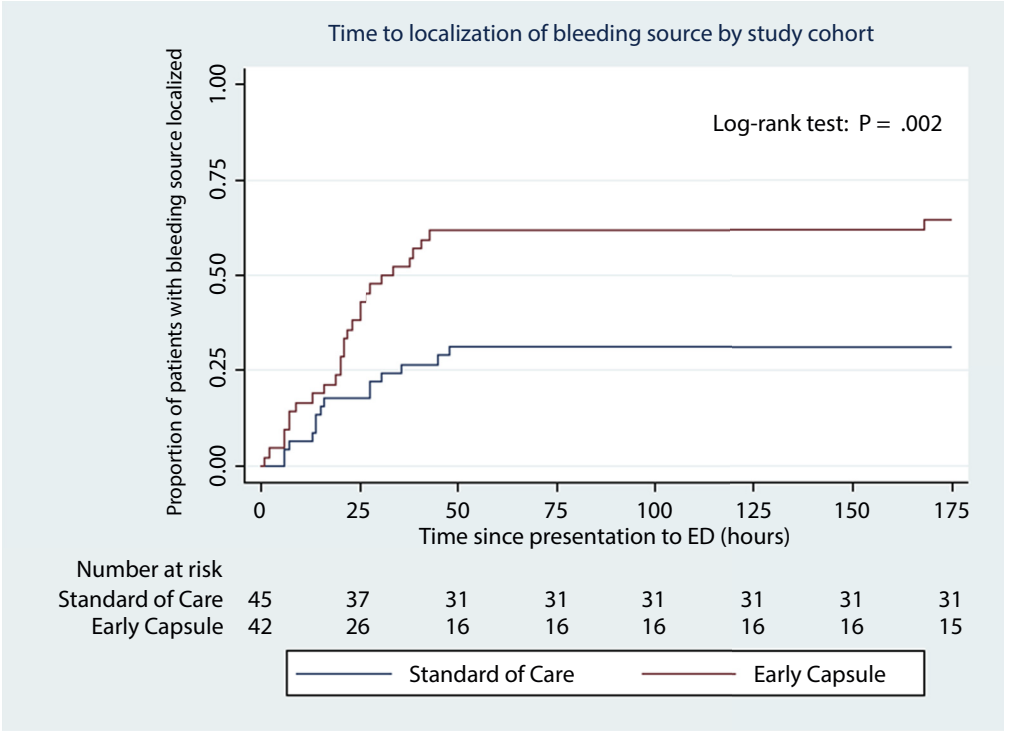

Figure 2. Kaplan-Meier analysis of cumulative incidence of localization of bleeding source after presentation to the emergency department (ED) by study cohort.

The median times to localization of bleeding for the standard of care and early capsule groups were 16 and 21 hours, respectively. The median times to first procedure (including VCE) for the standard of care and early capsule groups were 21 hours (interquartile range, 15-28) and 6 hours (interquartile range, 4-17), respectively. There were no procedural adverse events in either group.

Kaplan-Meier curves comparing cumulative incidence of localization of bleeding between the 2 cohorts were significantly different (log-rank test, $P = .002$; Fig. 2). Table 2 demonstrates univariate and multivariate Cox proportional hazard analysis of factors that contribute to localization of bleeding during hospitalization. Multivariate analysis demonstrated that early capsule endoscopy (HR, 2.77; 95% CI, 1.36-5.64), admission serum blood urea nitrogen (HR, 1.01; 95% CI, 1.00-1.02), and patient age (HR, 1.04; 95% CI, 1.01-1.06) were the only independent predictors of rate of localization of bleeding over time (Table 2).

Table 3 demonstrates univariate and adjusted logistic regression analysis of factors that contribute to overall localization of bleeding. Multivariate analysis demonstrated that randomization to the early capsule group (OR, 5.28; 95% CI, 1.74-16.06) and age (OR, 1.06; 95% CI, 1.02-1.11) were the only independent parameters associated with localization of bleeding by the end of hospitalization.

Univariate and logistic regression analyses (adjusted for nonsteroidal anti-inflammatory drug use and history of heart failure) for additional outcomes according to study cohort are demonstrated in Table 4. Compared with the standard of care group, the odds were significantly higher that patients in the early capsule group would have bleeding localized to the colon (adjusted OR, 4.09; 95% CI, 1.12-15.00), a diagnosis by the end of admission (adjusted OR, 2.67; 95% CI, 1.04-6.86), and a vascular lesion diagnosed as the source of bleeding (adjusted OR, 10.73; 95% CI, 1.60-72.11). There was no significant difference in the rate of all-cause mortality between the 2 cohorts (Table 4).

Analysis of anatomic localization of bleeding according to type of bleeding at presentation is demonstrated in Table 5. Significantly more patients in the early capsule group admitted with melena had localization of bleeding to the midgut or colon compared with patients in the standard of care group (26.9% vs 5.9%, $P = .02$). The etiologic diagnosis profile of both cohorts is demonstrated in Table 6.

The average cumulative direct cost of hospitalization per patient in the early capsule group and the standard of care group were not significantly different (9579 vs 9174 U.S. dollars, $P = .77$). Examples of active bleeding visualized on VCE are shown in Figure 3A-D and Videos 1 and 2.

DISCUSSION

This is the first randomized controlled trial to demonstrate the efficacy of early VCE in the management of patients admitted for NHGIB. Compared with conventional

TABLE 2. Univariate and multivariate Cox proportional hazard analysis of factors contributing to localization of bleeding over time

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Early capsule	2.63 (1.38-5.04)	.003	2.77 (1.36-5.64)	.005
Male gender	.63 (.35-1.17)	.151		
Age	1.02 (1.00-1.05)	.027	1.04 (1.01-1.06)	.009
Race				
White	1.24 (.44-3.49)	.678		
Black	.90 (.22-3.75)	.890		
Hispanic	.74 (.18-3.06)	.676		
Home medications				
Anticoagulation agents	.62 (.28-1.42)	.265		
NSAIDs	.65 (.35-1.23)	.191	.92 (.47-1.80)	.798
$P2Y_{12}$ inhibitor	1.33 (.59-2.99)	.496		
Vital signs at admission				
Heart rate	1.00 (.98-1.03)	.676		
Systolic blood pressure	1.00 (.99-1.02)	.791		
History of heart failure	.36 (.09-1.49)	.158	.39 (.09-1.77)	.221
History of liver cirrhosis	.44 (.11-1.83)	.258		
Recent syncope	1.97 (.70-5.55)	.198		
Laboratory data at admission				
Blood urea nitrogen	1.01 (1.00-1.02)	.030	1.01 (1.00-1.02)	.008
Prothrombin time	1.00 (.97-1.03)	.906		
Hemoglobin	1.00 (.88-1.13)	.997		
Type of bleeding at admission				
Melena	1.26 (.64-2.48)	.498		
Hematochezia	1.02 (.50-2.08)	.954		
Anemia	.44 (.11-1.85)	.266		

Covariates included in multivariate analysis were those found to be associated with time to localization of bleeding on univariate analysis ($P < .10$) plus NSAID use and history of heart failure.

HR, Hazard ratio; *CI*, confidence interval; *NSAIDS,* nonsteroidal anti-inflammatory drugs.

workup, an algorithm based on early VCE was superior for localizing bleeding during hospitalization.

Localization of bleeding in this study was defined as identifying the most proximal area of blood in the GI tract or identifying a lesion demonstrating high-risk SRH. Localization of bleeding was the primary outcome for this study because it is precise, objective, and can guide future interventions if definitive management by endoscopy is not achieved. For example, if a patient has no etiologic diagnosis identified by endoscopy but bleeding is localized to the right side of the colon, then future interventions (eg, surgery or angiography) can be directed to that area. Likewise, the importance of detection of SRH in GI bleeding is well established, because endoscopic hemostasis of lesions demonstrating high-risk SRH reduces recurrent bleeding, need for surgery, and mortality.[15-19] Along with improved localization of bleeding for patients receiving early capsule endoscopy, there was also a higher rate of identifying the etiologic diagnosis of bleeding compared with patients in the standard of care arm. Despite this, the study did not demonstrate a significant difference in rate of recurrent bleeding, readmission, or mortality between the 2 cohorts.

A significant difference found between the 2 cohorts was the rate of identification of vascular lesions as the source of bleeding. Vascular lesions are uncommon causes of acute GI hemorrhage, accounting for only 2% to 8% of nonvariceal upper GI bleeds.[20] In the early capsule cohort of this study, vascular lesions represented 19.0% of the causes of bleeding (compared with 4.4% in the standard of care arm). One reason for this discrepancy is that early VCE detected bleeding more frequently than the standard of care, thereby providing a target area in which to search for the responsible lesion. This is important, given that vascular lesions are small, bleed intermittently, and do not leave mucosal signatures associated with high-risk SRH as may be seen with ulcers.

TABLE 3. Comparison of variables by successful localization of bleeding source

	Bleeding source Localized (n = 41)	Bleeding source not localized (n = 46)	Univariate analysis	Multivariate analysis	
			P value	Odds ratio (95% confidence interval)	*P* value
Randomization to early capsule group	27 (65.9)	15 (32.6)	.002	5.28 (1.74-16.06)	.003
Male	21 (51.2)	30 (65.2)	.186		
Race					
White	37 (90.2)	41 (89.1)	1.000		
Black	2 (4.9)	2 (4.3)	1.000		
Hispanic	2 (4.9)	3 (6.5)	1.000		
Age, y	72.5 ± 12.5	65.4 ± 15.8	.053	1.06 (1.02-1.11)	.007
Home medications					
Anticoagulation agents	7 (17.1)	13 (28.3)	.216		
NSAIDs	15 (36.6)	24 (52.2)	.144	.66 (.23-1.87)	.437
$P2Y_{12}$ inhibitor	7 (17.0)	6 (13.0)	.599		
Vital signs at admission					
Heart rate at admission, beats/min	80.9 ± 17.0	80.0 ± 12.1	.769		
Systolic blood pressure at Admission, mm Hg	125.5 ± 23.2	124.3 ± 20.1	.822		
History of heart failure	2 (4.9)	7 (15.2)	.163	.21 (.03-1.56)	.126
History of cirrhosis	2 (4.9)	6 (13.0)	.272		
Recent syncope	4 (9.8)	2 (4.3)	.415		
Laboratory data at admission					
Blood urea nitrogen, mmol/L	2.1 ± 1.3	1.6 ± 1.3	.027	1.02 (1.00-1.04)	.112
Prothrombin time, s	15.6 ± 11.1	15.5 ± 9.9	.953		
Hemoglobin, g/dL	9.3 ± 2.4	9.2 ± 2.8	.934		
Admitting symptom					
Hematochezia	10 (21.7)	10 (24.4)	.769		
Melena	29 (70.7)	31 (67.4)	.737		
Symptomatic anemia	2 (4.9)	5 (10.9)	.439		

Values are n (%) or mean ± standard deviation. Univariate analysis involved Wilcoxon rank sum tests for continuous variables and χ^2 or Fisher's exact tests for categorical variables. Covariates included in multivariate analysis were those found to be associated with time to localization of bleeding on univariate analysis ($P < .10$) plus NSAID use and history of heart failure.

NSAIDS, Nonsteroidal anti-inflammatory drugs.

In current practice, it is difficult for endoscopists to know whether an angioectasia seen on endoscopy is the source of bleeding because the endoscopic appearance of an angioectasia that bled and stopped compared with that of an angioectasia that never bled is often the same.[21,22] Bleeding vascular lesions, however, are at a higher risk of recurrent bleeding compared with nonbleeding vascular lesions.[23] Thus, identification and treatment of such lesions is key in preventing recurrent bleeding.

Although early VCE improved localization of bleeding compared with standard of care, examination of the midgut by VCE was not a major contributing factor. In our study, a midgut source of bleeding was identified in 4.4% of patients in the early capsule arm compared with 2.2% of patients in the standard of care arm. Unexpectedly, more patients in the early capsule group compared with patients in the standard of care group had localization of bleeding in the colon (31.0% vs 8.8%, respectively). In patients presenting with melena, significantly more patients in the early capsule group were found to have sources of bleeding in the midgut or colon compared with the standard of care group. In addition to being diagnosed with diverticular bleeds, patients in the early capsule arm were also found to have vascular lesions in the right side of the colon as the source of bleeding. In comparison, patients receiving standard of care had no vascular lesions diagnosed as the source of bleeding in the colon. By providing early visualization of the midgut and right side of the colon, early capsule endoscopy is valuable in identifying lesions distal to the foregut that may stop bleeding by the time traditional flexible endoscopic procedures are initiated. This is

TABLE 4. Analysis of secondary outcomes by study cohort

	Early capsule group (n = 42)	Standard of care group (n = 45)	Univariate analysis *P* value	Adjusted odds ratio (95% confidence interval)	*P* value
Endoscopies performed during hospitalization					
Video capsule endoscopy	42 (100.0)	14 (31.1)	N/A		
EGD	21 (50.0)	34 (75.6)	.014	.39 (.14-1.07)	.067
Colonoscopy	17 (40.5)	15 (33.3)	.490		
Enteroscopy	1 (2.4)	0 (.0)	.483		
Anoscopy	0 (.0)	1 (2.2)	1.000		
Anatomic location of bleeding source					
Foregut	12 (28.6)	9 (20.0)	.351		
Midgut	2 (4.8)	1 (2.2)	.608		
Colon	13 (31.0)	4 (8.8)	.014	4.09 (1.12-15.00)	.033
Diagnosis by end of admission	29 (69.0)	21 (46.7)	.035	2.67 (1.04-6.86)	.041
Presumptive	17 (40.5)	9 (20.0)	.037	2.67 (.95-7.47)	.062
Definitive	12 (28.6)	12 (26.7)	.843		
Vascular lesion diagnosed as source of bleeding	9 (21.4)	2 (4.4)	.017	10.73 (1.60-72.11)	.015
Therapeutic intervention performed	11 (26.2)	13 (28.9)	.778		
All-cause mortality within 30 days after discharge	1 (2.4)	2 (4.4)	1.000		
Recurrence of bleeding within 30 days after discharge	0 (.0)	4 (8.9)	.117		

Values are n (%). Univariate analysis involved Wilcoxon rank sum tests for continuous variables and χ^2 or Fisher exact tests for categorical variables. Multivariate analysis pursued for outcomes found to be different between study cohorts after univariate analysis.

TABLE 5. Analysis of anatomic localization of bleeding by study cohort

	Early capsule group (n = 42)	Standard of care group (n = 45)	*P* value
Patients with melena	26	34	
Bleeding localized to foregut	11 (42.3)	9 (26.5)	.197
Bleeding localized to midgut	2 (7.7)	1 (2.9)	.574
Bleeding localized to colon	5 (19.2)	1 (2.9)	.076
No localization of bleeding	8 (30.8)	23 (67.6)	.009
Patients with hematochezia	11	9	
Bleeding localized to foregut	1 (9.1)	0 (.0)	.353
Bleeding localized to midgut	0 (.0)	0 (.0)	1.000
Bleeding localized to colon	7 (63.6)	2 (22.2)	.092
No localization of bleeding	3 (27.3)	7 (77.8)	.070
Patients with symptomatic anemia	5	2	
Bleeding localized to foregut	0 (.0)	0 (.0)	1.000
Bleeding localized to midgut	0 (.0)	0 (.0)	1.000
Bleeding localized to colon	1 (20.0)	1 (50.0)	.464
No localization of bleeding	4 (80.0)	1 (50.0)	.464

Values are n (%). Univariate analysis involved χ^2 or Fisher exact tests.

particularly important in patients presenting with melena who likely will not have a colonoscopy until after a negative upper endoscopy and after undergoing a bowel prep. This could result in a delay during which time bleeding may cease, making it more difficult to identify the causative lesion.

One hypothesis for why early VCE may have resulted in improved localization of bleeding relates to timing. In our

TABLE 6. Etiologic diagnoses of patients in each cohort

	Early capsule group (n = 42)	Standard of care group (n = 45)
Foregut lesions, presumptive/definitive (total %)		
Esophageal ulcer	1/0 (2.4)	0/1 (2.2)
Gastroduodenal ulcer	3/4 (16.7)	6/6 (26.7)
Gastropathy/duodenopathy	4/0 (9.5)	0/0 (.0)
Gastric angioectasia	0/1 (2.4)	0/0 (.0)
Duodenal Dieulafoy lesion	0/0 (.0)	0/1 (2.2)
Duodenal angioectasia	0/2 (4.8)	0/1 (2.2)
Midgut lesions, presumptive/definitive (total %)		
Small bowel angioectasia	1/2 (7.1)	0/0 (.0)
Colorectal lesions, presumptive/definitive (total %)		
Diverticulosis	6/0 (14.3)	2/0 (4.4)
Colonic angioectasia	1/1 (4.8)	0/0 (.0)
Dieulafoy lesion	0/1 (2.4)	0/0 (.0)
Cecal ulcer	0/1 (2.4)	0/1 (2.2)
Colorectal cancer	0/0 (.0)	0/2 (4.4)
Internal hemorrhoids	0/0 (.0)	1/0 (2.2)
Ischemic colitis	1/0 (2.4)	0/0 (.0)
No diagnosis	13 (31.0)	24 (53.3)

Diagnoses were further classified as either definitive or presumptive based on findings during endoscopy.

study, the median time to ingestion of the VCE in the early capsule arm was 6 hours, whereas the median time to first procedure for the standard of care arm was 21 hours. Several studies have investigated the role of early endoscopy for the management of GI bleeding to see what the benefits and risks may be.[24-26]

A study by Nagata et al[27] demonstrated that early colonoscopy benefits patients admitted with acute lower GI bleeding. This study demonstrated that early colonoscopy increased detection of SRH, increased rate of therapeutic intervention, and decreased length of hospitalization. In another study, Kumar et al[28] analyzed the effect of urgent EGD on management of acute, nonvariceal, upper GI bleeding. The study demonstrated that urgent EGD increased mortality, recurrent bleeding, and need for further procedures. The proposed reason behind this result is that patients are not adequately resuscitated before undergoing urgent endoscopy and are at a higher risk of adverse events. The benefit of our algorithm is that this risk is mitigated given that VCE can be performed at bedside quickly but requires no preprocedural sedation or preparation. This allows for early visualization of the GI tract without putting the patient at risk of adverse procedural events.

Despite differences in outcomes related to localization of bleeding, there was no difference in the direct hospital costs for the admissions between study groups. Although no immediate difference is seen, it is possible that improved localization of bleeding may prevent or shorten future admissions, thereby lessening long-term costs for the health system and for the patient. Further study into the long-term financial benefits of the early capsule algorithm should be performed to test this principle.

Our study has important limitations to consider. One limitation is that this study was performed in a single center and the study population was relatively homogenous, which may limit the generalizability of our results. Regarding methodology, a significant limitation is that we did not blind study personnel to group allocation after randomization. To limit observer bias we chose a primary outcome that was objective (ie, visualization of bleeding or detection of high-risk SRH). A limitation of using this composite outcome, however, is that although detection of SRH is an established clinical outcome, the composite outcome of localization of bleeding has not been validated as being associated with important clinical measures (eg, recurrent bleeding, length of hospitalization, or mortality).

In summary, early VCE is a beneficial alternative to management of patients presenting with NHGIB. This randomized controlled trial demonstrates that early VCE allows for localization of bleeding sooner and more frequently than the current standard of care, and because VCE does not require preparation or procedural sedation, patients are not at increased risk of adverse procedure-related events. Further study should assess whether early capsule endoscopy is cost-effective and

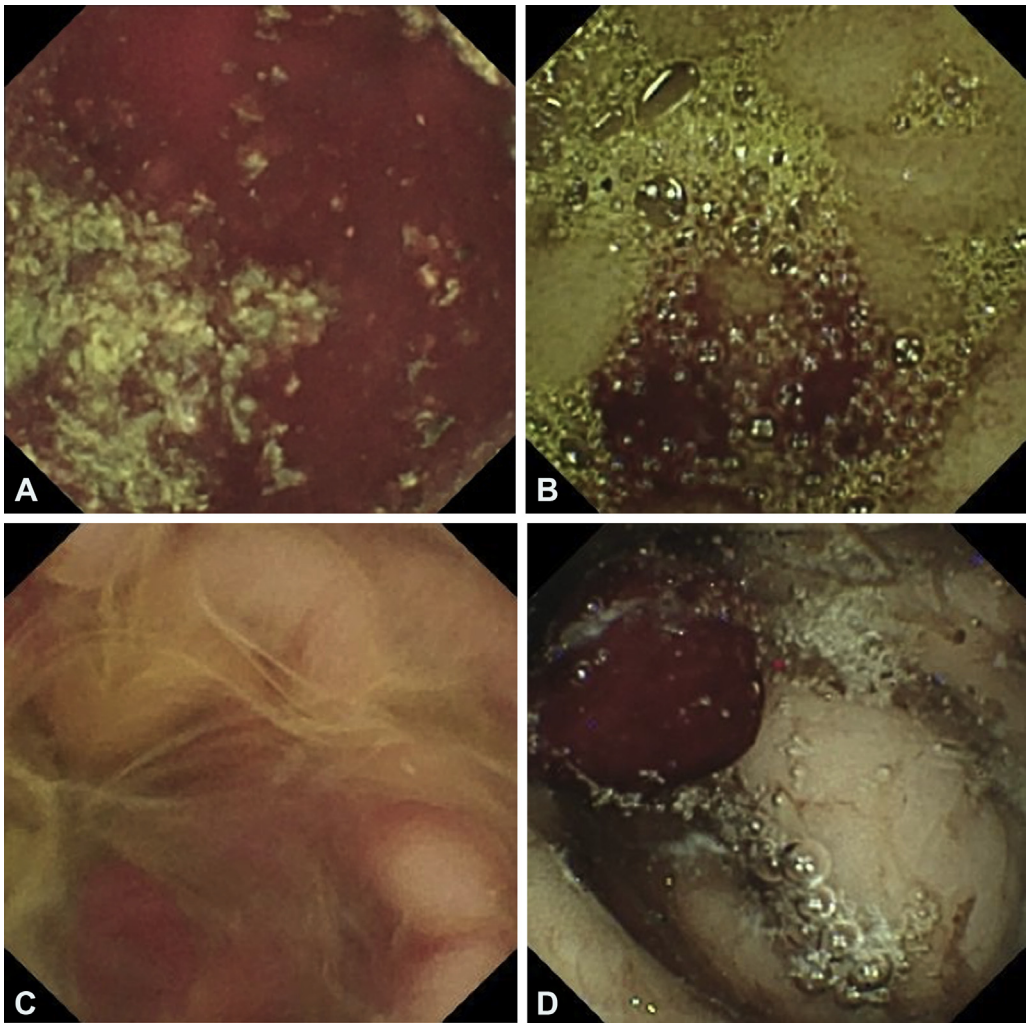

Figure 3. Examples of bleeding localized by video capsule endoscopy. **A,** Active cecal bleeding. Colonoscopy revealed a cecal Dieulafoy lesion. **B,** Actively bleeding gastric angioectasia. **C,** Fresh bleeding in the duodenum. Upper endoscopy revealed a duodenal angioectasia. **D,** Active bleeding identified in the stomach. Upper endoscopy revealed portal hypertensive gastropathy as the source of bleeding.

can decrease rates of recurrent bleeding, readmission, and mortality.

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Abbreviations: CI, confidence interval; HR, hazard ratio; NHGIB, nonhematemesis GI bleeding; OR, odds ratio; SRH, stigmata of recent hemorrhage; VCE, video capsule endoscopy.

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APPENDIX 1

1) TITLE

A randomized controlled trial comparing efficacy of early video capsule endoscopy to standard of care in the approach to gastrointestinal bleeding

2) OBJECTIVES

The objectives of this study are to test whether there are statistically significant differences between the conventional workup of non-hematemesis gastrointestinal bleeding by endoscopy compared with deployment of a video capsule as the first test followed by the most appropriate endoscopic procedure based on findings, if needed.

3) INCLUSION AND EXCLUSION CRITERIA

Inclusion criteria:

- Age greater than 18 years old
- New onset of melena or hematochezia
- Able to sign consent
- Hemodynamically stable (ie, blood pressure >100/60 or pulse <100 at the time of consent)
- ED must plan to admit patient to the hospital or Clinical Decision Unit.

Exclusion criteria:

- Adults unable to consent
- Individuals who are not yet adults (infants, children, teenagers)
- Pregnant women
- Prisoners
- Prior history of gastroparesis
- Prior history of intestinal surgery
- Prior history of Crohn's disease
- Concern for infectious colitis
- Non-English speaking
- Evidence of dysphagia at the time of presentation
- Presence of bright red blood per rectum
- Allergy to metoclopramide or erythromycin
- Code status of DNR/DNI or CMO
- Prior history of abdominal radiation
- Presence of ICD or pacemaker or other implanted electronic devices
- Abdominal pain suggesting an acute abdomen or obstruction. In clinical practice, only patients with crampy abdominal pain due to Crohn's disease, previous intestinal surgery and a previous history of radiation therapy require a patency capsule or CT enterography before capsule endoscopy.
- Patients who cannot undergo surgery

4) STUDY ENDPOINTS

The primary outcome for this study is the rate of endoscopic localization of bleeding over time. We defined localization of bleeding as a composite outcome of endoscopic visualization of bleeding (melena, coffee grounds, or bright red blood) or lesion(s) with associated high-risk stigmata of recent hemorrhage (SRH).

Secondary outcomes included overall rate of localization of bleeding, anatomic location of bleeding, rate of endoscopic therapy, rate of diagnosis, readmission rate, rate of identification of vascular lesions (defined as Dieulafoy lesions or angioectasias) as the source of bleeding, 30-day rate of re-bleeding, and 30-day rate of all-cause mortality.

5) PROCEDURES INVOLVED

Screening

Patients presenting to the emergency room with non-hematemesis gastrointestinal bleeding (defined as melena, hematochezia, or symptomatic anemia) were first identified by a member of the emergency department staff.

Once a potential research subject was identified a page was sent to a member of the research team (ie, research staff member, gastroenterology fellow on call, or gastroenterology attending on call) from the emergency department. In addition to this, the clinical research coordinator or gastroenterology fellow screened the emergency department triage software for patients who were listed as having non-hematemesis gastrointestinal bleeding.

Once a subject was identified, the subject was seen and examined by the gastroenterology fellow and attending as per standard of care and asked to participate in the study.

Randomization

If inclusion/exclusion criteria are met, the consent discussion took place and only if the subject agreed and consent was obtained, then the subject was randomized to the "Early Capsule Group" or "Standard of Care Group." All patients in the "Early Capsule group" received a video capsule. Only some of the patients in the "Standard of Care Group" received the capsule as indicated by what is considered the standard workup.

Patients were assigned study ID numbers consecutively by the order of which they are enrolled in our study. For the Randomization Process we utilized the Randomization Module within the REDCap database which allows researchers to randomly assign study participants into specific study groups. The Randomization Module allowed us to attach particular Study ID numbers randomly to particular groups.

Prior to the start of the study, a code was generated to associate a study number with group assignment – Standard of Care or Early Capsule. We used an allocation concealment scheme using sequentially numbered, opaque, sealed envelopes. Each envelope carried a card associating a group assignment with a study number. Cards were placed in opaque envelopes by research personnel uninvolved with the consent process of our study. Study personnel opened envelopes only after consent was obtained. Study personnel and medical teams were not blinded to group allocation following consent.

Patients randomized to the "Early capsule group" had a video capsule deployed as soon as possible after presentation to the emergency department, once the consent process had taken place, eligibility had been confirmed, and the subject had met the standard of care guidelines for preparation before capsule ingestion.

Standard preparation for capsule ingestion means that a patient cannot eat for 10 hours prior to deployment of the capsule. Therefore, patients in our study were asked when they had last eaten. If patients reported that they have not eaten anything over the past 10 hours the capsule was deployed immediately. If, however, patients reported that they had eaten something over the past 10 hours we took note of when they believe they last ate and deployed the capsule 10 hours after the time that they last ate.

Procedure

Capsules were swallowed with a small (4-12 oz.) amount of water. As noted above, patients did not have the capsule deployed until it had been confirmed that 10 hours had passed since the patient had last eaten. Patients were allowed to take medications up to two hours prior to ingesting the capsule (which is standard of care).

Immediately following ingestion of the VCE a research staff member used the capsule's Real-Time Viewer (RTV) to inspect for blood in the stomach. At 40 to 60 minutes following VCE ingestion, a staff member again used the RTV to confirm that the capsule has entered the small bowel. If the capsule at that time was still in the stomach a prokinetic agent (either metoclopramide or erythromycin) was used to help push the capsule into the duodenum.

Four hours after ingestion, a staff member used the RTV to again check for blood. This the mean small intestinal transit time of the small intestine. If the VCE is in the cecum, the study will be stopped and data will be downloaded to the workstation and processed into a video. If the VCE had not reached the cecum, at 4 and 8 hours after ingestion, a staff member will again check the RTV to see if blood is present and/or the ileocecal valve had been passed. Data from the capsule recorder were then downloaded to a workstation as soon as possible.

The PI or sub-investigator then reviewed the video of the capsule recording [it takes about 5 minutes to establish if there is bleeding and where it is coming from. More detailed analysis will take about 15 minutes]. As soon as the capsule recording had been reviewed the PI or sub-investigator informed the patient's attending gastroenterologist as to where the bleeding is coming from or that bleeding is not seen ideally within 1 to 4 hours from the time of stopping the capsule recording.

Depending on the findings a recommendation was made as to the next most appropriate test. If blood was found in the esophagus, stomach or duodenum an upper endoscopy was recommended. If blood is seen in the small intestine, it was recommended that the subject next have a push enteroscopy, deep enteroscopy, or angiography. If blood was found in the right side of the colon, colonoscopy was recommended. If the capsule study was not diagnostic and no blood is seen in the GI tract and there is no ongoing hematochezia, the subject will be placed in ED observation for up to 23 hours and evaluated for potential discharge and follow-up by gastroenterology as an outpatient.

For most subjects, the capsule will pass in a bowel movement within 24 to 72 hours of ingestion.

Patients randomized to the "Standard of Care" group had an upper endoscopy, colonoscopy, and additional capsule or small bowel enteroscopy depending on the subject's presentation and the results of the workup performed by the gastroenterology team. For patients requiring a video capsule endoscopy as part of "conventional workup," the patients were provided the same Olympus video capsule that was used in the "Early Capsule" group. Further management would be as standard of care. These subjects will be discharged on the recommendation of the attending hospitalist after completion of treatment.

Review and follow-up

During hospitalization, data was recorded from the electronic medical record including patient medical history, patient medication lists, lab values, times and types of procedures (e.g. upper endoscopy, enteroscopy, colonoscopy), time from entry to ED to time to localization of bleeding, admission disposition (i.e. clinical decision unit, regular floor, ICU), time of discharge. Patients were also followed for 30 days following discharge to assess for episodes of re-bleeding. All of this information was linked to the subject's study ID number. This data collection was for research purposes only.

6) DATA MANAGEMENT

- Power analysis: For sample size determination, we planned the study as a superiority trial and we estimated the probability of localization of bleeding over time in the Early Capsule arm to be two times greater than that of the Standard of Care arm (ie, estimated hazard ratio of 2.00). We found that no prior published studies were similar enough to our methodology, so we used prior experience at our institution to guide the estimation of effect. Sample size calculation and power analysis

were performed using a Log-rank Freedman method. The power analysis revealed that in order for this effect size to be detected (80% chance) as significant at the 5% level, a sample of at least 72 patients (36 per group) would be required.

- Statistical analysis: Patient characteristics and demographics were described as means with standard deviation (SD) or as proportions. Time to localization and time to first procedure were described using medians with interquartile range (IQR).
- Univariate analyses involved Wilcoxon-Rank sum tests for continuous variables and Chi-square or the Fisher Exact tests for binary variables. A Kaplan-Meier survival analysis with a Log-rank test was performed to compare the cumulative incidence of endoscopic localization of bleeding for the two groups over time. A univariate and multivariate Cox proportional hazard analysis was performed to assess the effect of variables on the probability of localization of bleeding over time. A logistic regression analysis was performed and adjusted for covariates to assess the effect of variables on overall odds of localization of bleeding. For multivariate analyses, independent variables with a difference at $P<.10$ following univariate analysis or those noted to be unevenly distributed between the two cohorts following randomization were included as covariates. Cox proportional hazard analysis and logistic regression analysis were described using hazard ratios (HR) and odds ratios (OR), respectively, plus the 95% confidence interval (CI) with the associated P value. A P value of less than .05 was considered to be significant. Statistical analysis was performed using STATA 13 (StataCorp; College Station, Texas).
- Steps were taken to secure data: All clinical data from individual subjects will be de-identified and given a study number. The study number will serve as a link between the data and the subject's identifiable information. RedCAP online encrypted database will be used to store the dataset. The database will only be accessed by the primary investigator and research assistants.
- Data were exported for analysis as a de-identified data set. The de-identified dataset (which would be absent of any PHI) would be transferred in a password-encrypted email to the external sponsor.
- The external sponsor – Olympus Corporation – will have access only to the de-identified data set and will not have access to the study key with identifying health information.
- Identifier keys were destroyed once primary data analysis is complete.

7) PROVISIONS TO MONITOR THE DATA TO ENSURE THE SAFETY OF SUBJECTS*

Throughout the course of the included patients participation in this study they were followed for signs of adverse events to medication administration or for complications of capsule endoscopy. Adverse events were documented. Any adverse events that occurred were reviewed by the study staff and the Primary Investigator within one week.

8) VULNERABLE POPULATIONS

No vulnerable populations were enrolled.

9) MULTI-SITE RESEARCH

Not applicable – single site research.

10) COMMUNITY-BASED PARTICIPATORY RESEARCH

Not applicable – not community-based participatory research.

11) SHARING OF RESULTS WITH SUBJECTS

Study results were not expected to be shared with individual subjects and subjects will not be identified in any publications; however, de-identified results may be published in publicly available journals.

12) SETTING

Initial screening of subjects will be performed in the Emergency Room at the University of Massachusetts-University Campus. Review of video capsule recordings will occur at the GI endoscopy clinic at the same campus.

13) RESOURCES AVAILABLE

The Principal Investigator is a board-certified gastroenterologist with extensive experience at reading video capsules. He oversaw all aspects of the research to ensure it was conducted correctly and that all staff were properly trained on their roles and responsibilities. He was assisted by sub-investigators who are physicians (attendings, fellows, and/or residents) in the Department of Medicine and Emergency Medicine.

Gastroenterology fellows and Medicine residents were used to screen potential candidates for this study once they were notified by the paging process described previously. All fellows and residents had appropriate CITI training and were be added to the list of project personnel prior to interacting with or obtaining consent from subjects. They were responsible for reviewing the inclusion and exclusion criteria with the subject and with obtaining consent for the capsule endoscopy if the subjects agree to take part in the study.

For subjects who agree to take part in the study, Gastroenterology fellows and residents were also tasked with administering the capsule and with following the results on the RTV as described previously. Fellows and residents performing this task had appropriate training and experience in administering the capsule. The Principal Investigator reviewed the training of the fellows and residents and personally demonstrated to them how to administer the capsule. The Principal Investigator was available for any questions that may come up if a fellow or resident has difficulty initiating the capsule. The decision to order prokinetics came after the fellows and residents have discussed using those agents with the Principal Investigator.

Subinvestigators had the responsibility to upload videos to the ShareFile environment using the capsule workstation as described. They communicated capsule findings from the Primary Investigator and Sub-investigator to the primary team members regarding recommendations of further workup and procedures based on the recordings.

14) CONFIDENTIALITY

Study data and information were stored securely at the study center. All data and information were considered confidential. No identifying information will be used in any report or publication generated from this study. All information gathered was placed directly into an online encrypted database. This included identifier information (ie, medical record numbers) as well as study data. The data from this database was then exported to a data analysis software and was de-identified. Data analysis on the exported data set was then performed.

15) ECONOMIC BURDEN TO SUBJECTS

All costs associated with the emergency department stay, hospital admission, and associated testing (including but not limited to endoscopy procedures) were paid by the subject or insurance and the subject was responsible for all co-pays, deductibles, etc. These are all standard of care procedures.

For those in the early capsule group, the cost of using the prokinetic medications (if necessary) was paid by the subject or insurance as this is part of the standard of care procedures for their emergency department admission and assessment. Any subsequent intervention will be billed to the subject or insurance.

The cost of the video capsule and its reading, both for the early capsule group and any subject in the standard of care group who receives a video capsule, was paid for by the study and not billed to the subject or insurance.

16) DRUGS OR DEVICES

The video capsule that was used in this study is the Olympus small intestinal capsule endoscopy system (EC-10 System). This system has been cleared by the FDA under 510(k) approval number K123421. This is a capsule imaging system intended for visualization of the small intestine mucosa. This is the FDA cleared labeling. There is no requirement for timing in the FDA labeling. The video capsules was locked in our study coordinator's office. Handling and administration of the capsules was performed by study staff members who have been trained and have experience in the tasks related to the video capsules.

The two prokinetic agents that were used as part of this study if capsule retention occurred were metoclopramide and erythromycin. Metoclopramide is labeled for use in gastroparesis and not gastrointestinal bleeding. Erythromycin is not approved as a prokinetic agent; however, both drugs are often used in the hospital setting for the purposes of emptying the stomach of blood in patients with gastrointestinal bleeding.