Original Article

Acute Gastrointestinal Bleeding in Anticoagulated Patients: Prevalence and Predictors of Significant Endoscopic Lesions and Change of the Management

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Objective: Acute gastrointestinal [GI] bleeding is common in anticoagulant users. Optimal management regarding the role of endoscopy is lacking. This study aimed to elucidate the prevalence of significant endoscopic lesions and predictors of significant lesions and management change with endoscopy.

Materials and Methods: A retrospective cohort study of anticoagulated patients with GI bleeding who underwent endoscopy between January 2005 and December 2014 were reviewed and analyzed.

Results: There were 94 patients. Male and female were equal in number with a mean age of 71.6±10.8 years. Most (81.8%) received warfarin. Upper GI bleeding was the most common site (60.9%) followed by lower GI bleeding (28.2%), mid GI bleeding (5.5%) and undetermined (2.7%). Significant GI lesions were found in 62.7%. Peptic ulcer and colonic diverticulosis were the 2 most common causes (41.8% and 28.2%, respectively). Bleeding from coagulopathy occurred in 26.4%. Significant GI lesions led to the change of management in 53.6%, mostly with endoscopic therapy. Hematochezia (odds ratio [OR] 4.90, 95% confidence interval [CI] 1.22 to 19.50, p = 0.024) and INR <4 (OR 4.07, 95% CI 1.17 to 14.27, p = 0.028) were associated with significant GI lesions, while concomitant antiplatelets was negatively associated with significant lesions (OR 0.32, 95% CI 0.12 to 0.88, p = 0.027). Hematochezia at presentation (OR 3.64, 95% CI 1.27 to 10.53, p = 0.016) and no use of antiplatelets (OR 0.28, 95% CI 0.09 to 0.89, p = 0.031) were associated with the change of management.

Conclusion: Significant GI lesions were present in two-third of anticoagulated patients who had acute GI bleeding and led to the change of management in one-third. Hematochezia, INR <4 and no concomitant antiplatelets predicted significant GI lesions. Hematochezia and no concomitant antiplatelets predicted the change of management, mostly with endoscopic therapy.

Keywords: Anticoagulant, Endoscopy, Gastrointestinal bleeding, Predictor, Outcome

J Med Assoc Thai 2018; 101 [Suppl. 4]: S135-S142
Website: http://www.jmatonline.com

Warfarin, unfractionated heparin [UFH], low molecular weight heparin [LMWH] and novel oral anticoagulants [NOACs] are the anticoagulants used for the prevention and treatment of various thromboembolic diseases e.g., patients with atrial fibrillation, prosthetic heart valves and venous thromboembolism. Despite the advances in treatment monitoring, patients who receive warfarin remain having an increased risk of major bleeding by 0.3 to 0.5% per year[1]. Although NOACs have fewer major bleeding complications compared to warfarin[2,3], the risk remains existing.

Acute gastrointestinal [GI] bleeding is a life-threatening complication and becomes the most common site of bleeding in 20 to 63% of anticoagulated patients[1,4-6]. The most common cause of upper gastrointestinal bleeding [UGIB] is peptic ulcer in 45 to 60% of patients[1,4,7]. The prevalence of lower [LGIB] and mid [MGIB] gastrointestinal bleeding are less clear, though there were some reports of bleeding diverticulosis[1,4] and asymptomatic colorectal cancer[8].

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How to cite this article: Nawarawong N, Pongprasobchai S, Tanwandee T. Acute Gastrointestinal Bleeding in Anticoagulated Patients: Prevalence and Predictors of Significant Endoscopic Lesions and Change ofthe Management. J Med Assoc Thai 2018;101;Suppl.4:S135-S142.

Since Asian patients including Thai are believed to have lower prevalence of colonic angioectasia but higher prevalence of ulcers[9], possibly from unreported over-the-counter non-steroidal anti-inflammatory drugs, [NSAIDs] use, thus, the etiology and manage-ment of GI bleeding among anticoagulated Asian patients might differ from those in the Westerns.

The optimal management of GI bleeding in anticoagulated patients, particularly the role of endoscopy is unclear and challenging. The causes of bleeding in such patients can be either from the intrinsic GI lesions, the anticoagulation effect, or both, making the benefits of endoscopy (to diagnose or stop bleeding) become less. It is also unknown whether endoscopy really helps manage the patients. Last, anticoagulated patients usually have multiple co-morbidities and are at high-risk for endoscopy. Thus, the decision to perform endoscopy is usually based on physician's individual judgment to weigh between benefits and risks of endoscopy. Taken together, it would be best if we could predict that which patients would get benefits from endoscopy, i.e. changing the management after endoscopy.

The present study aims to elucidate the prevalence, sites and causes of significant GI lesions in anticoagulated patients who had GI bleeding, toidentify clinical predictor of significant GI lesions and predictors of having management change from the endoscopy.

Materials and Methods

Patients

This is a retrospective cohort study approved by the Siriraj Hospital Institutional Review Board. Medical records of all patients ≥15 years old with acute GI bleeding (i.e. hematemesis, blood on nasogastric aspirate, melena or hematochezia) who received anticoagulant therapy including warfarin, UFH, LMWH and NOAC in Siriraj Hospital, Bangkok, Thailand between January 2005 to December 2014 were reviewed.

Inclusion criteria were patients with acute GI bleeding while receiving anticoagulant therapy and underwent appropriate endoscopy according to the presentation which are: esophagogastro-duodenoscopy [EGD] in case of hematemesis; EGD plus colonoscopy in case of melena or maroon stool; colonoscopy with/without EGD in case of hematochezia. Subjects were excluded if endoscopy was not done or incomplete according to the above criteria.

Data collection and definitions

Clinical data

Data were collected on age, gender, type of received anticoagulant, clinical presentations, comorbid diseases, concomitant use of antiplatelets or NSAIDs, site of bleeding and outcomes including, rebleeding, surgery and death.

Clinical important bleeding was defined by a drop of systolic blood pressure >20 mm Hg or a drop of hemoglobin (Hb) >2 g/dL within 24 hours after presentation[10].

Rebleeding was defined as an evidence of hematemesis, melena or hematochezia within 30 days after the onset of initial GI bleeding.

Undetermined cause of bleeding was labeled in patients with suspected MGIB (negative EGD/colonoscopy), whom video capsule endoscopy [VCE] or balloon-assisted enteroscopy [BAE] were not performed.

Laboratory data

Data were collected on Hb level at baseline and at presentation and level of anticoagulation at the time of GI bleeding.

Level of anticoagulation were classified as: overdose, INR >4 in warfarin user and PTT ratio >2.5 in heparin user[11,12]; high therapeutic dose, INR 2 to 3 in warfarin user and 2 to 2.5 in heparin user.

Endoscopic data

Endoscopic findings were classified as:

Significant causative lesions[9,13]: carcinoma, adenomatous polyp ≥1.5 cm or ≥1 cm with bleeding stigmata, 1 vascular ectasia ≥8 mm or ≥5 sites, GERD LA grade C to D, erosive gastritis/duodenitis (≥50 erosions ≥1 mm), gastric ulcer, duodenal ulcer or small bowel ulcer ≥1 cm or 2 sites ≥0.5 cm or ulcer with stigmata of recent hemorrhage [SRH], colonic ulcer ≥1 cm, active ileitis or colitis, diverticulosis with SRH or without other explainable bleeding cause.

Significant non-causative lesions were lesions that do not explain clinical bleeding but need treatment or follow-up, such as small gastrointestinal stromal tumor [GIST], advanced colonic adenoma.

In significant lesions: normal, nonerosive gastritis, hemorrhagic spots, blood stain mucosa, ulcer, vascular lesion or colonic polyps which were not fit the criteria for significant lesions.

Presumed bleeding from coagulopathy was

diagnosed if patients had insignificant endosopic lesions and anticoagulant overdose according to above criteria.

Endoscopic findings that change management: (1) lesions that needed endoscopic therapy including SRH (adherent clot, nonbleeding visible vessel [NBVV], oozing, spurting), angiodysplasia, Dieulafoy's lesion, bleeding diverticulosis or (2) lesions that needed specific medical therapy, e.g. cytomegalo virus esophagitis or colits, tuberculous colitis, etc (3) lesions that required surgery, e.g. tumor.

Statistical analysis

Statistical analysis used SPSS version 20.0. Demographic data and result of endoscopy were analyzed using descriptive statistics and presented as number, percent, mean and standard deviation. Clinical predictors of significant causative endoscopic lesions were analyzed using Chi-square or Fischer-exact tests for categorical variables and Student t-test or Mann-Whitney U test for continuous variables. Logistic regression analysis was used to identify independent predictors and presented as odds ratio [OR] and *p*-value. The *p*-value of <0.05 was considered statistically significant.

Results

During the study period, there were 2,171 patients receiving anticoagulants and 212 (9.8%) had GI bleeding. Endoscopy was performed in 105 patients (49.5%). Eight patients were excluded due to; 6 had incomplete endoscopic evaluation and 2 had incomplete history. Therefore, 94 patients were finally included in the study, 8 patients (8.5%) had more than 1 bleeding episode and 8 patients (8.5%) had rebleeding (range 1 to 2 times). The total bleeding episodes were 110 episodes.

Patients' characteristics

The baseline information of 94 patients is shown in Table 1. Male and female were equal in number with mean age of 71.6±10.8 years. Most patients have atrial fibrillation (60.6%) and valvular heart disease (38.3%). Of the 110 bleeding episodes, most (81.8%) occurred while receiving warfarin. Levels of anticoagulation were in overdose in 62.7% and 34.5% had concomitant use of antiplatelets.

Clinical manifestations and type of endoscopy

The clinical manifestations and types of endoscopy performed within 110 bleeding episodes are shown in Table 2. Approximately 56% of patients had melena as a presenting symptom and 64.5% had clinical important bleeding. EGD alone was performed in 54.5%, colonoscopy alone in 15.5% and combined EGD and colonoscopy in 24.5% of patients. UGIB was more common (60.9%) than LGIB (28.2%), and MGIB (5.5%).

Table 1. Characteristics of 94 patients

Characteristics	n (%)
Age (years)	71.6±10.8
Gender, n (male: female)	94 (47:47)
Comorbid diseases	
Atrial fibrillation	57 (60.6)
Valvular heart diseases	36 (38.3)
Stroke	29 (30.9)
Vascular thrombosis	26 (27.7)
Anticoagulant	
Warfarin	90 (81.8)
UFH	15 (13.6)
LMWH	4 (3.6)
NOAC	1 (0.9)
Level of anticoagulant*	
Therapeutic	25 (22.7)
High therapeutic	10 (9.1)
Overdose	70 (62.7)
Antiplatelet	38 (34.5)
Aspirin	29 (26.4)
Aspirin + clopidogrel	5 (4.5)
Clopidogrel	4 (3.6)

LMWH = low molecular weight heparin; NOAC = novel oral anticoagulants; UFH = unfractionated heparin
Data are expressed as number (%) or mean ± SD.
* Assessed only in warfarin and heparin group (n = 105)

Endoscopic findings

Significant GI lesions were detected in 69 of the 110 patients (62.7%), 29 patients (26.4%) had presumed bleeding from coagulopathy. Detail of each type of lesions is shown in Table 3. There are 8 patients who incidentally found lesions which needed intervention but might not explain bleeding (5 patients with more than 3 colonic polyps or polyps with high grade dysplasia, 1 patient with TB ileitis and 1 with asymptomatic gastric GIST).

EGD demonstrated significant lesions in 41 patients (45%) whereas colonoscopy did so in 28 patients (56%). Details of significant endoscopic findings were shown in Table 4. Peptic ulcer diseases were the most common lesions detected by EGD (32.2%)

Table 2. Clinical manifestations, type of endoscopy performed and sites of bleeding of 110 episodes

Parameters	n (%)
Clinical presentations	
Hematemesis	18 (16.4)
Hematochezia	32 (29.1)
Melena	62 (56.4)
Clinical important bleeding	71 (64.5)
Endoscopy	
EGD alone	60 (54.5)
Colonoscopy alone	17 (15.5)
Flexible sigmoidoscopy alone	3 (2.7)
EGD + colonoscopy	27 (24.5)
EGD + flexible sigmoidoscopy	3 (2.7)
Single balloon enteroscopy	4 (3.6)
Video capsule endoscopy	6 (5.5)
Final site of bleeding	
Upper	67 (60.9)
Lower	32 (28.2)
Mid	8 (5.5)
Undetermined	3 (2.7)

EGD = esophagogastroduodenoscopy

whereas colonic diverticulosis and ulcer were most common lesions detected by colonoscopy (14%).

Predictors of significant GI lesions and the change of management after endoscopy

Univariate and multivariate analyses of the possible factors associated with significant GI lesions and change of management after endoscopy are shown in Table 5 and Table 6, respectively. In the multivariate analysis, hematochezia (OR 4.90, 95% CI 1.22 to 19.5, $p = 0.024$) and INR <4 (OR 4.07, 95% CI 1.17 to 14.27, $p = 0.028$) associated with significant GI lesions, while concomitant use of anti-platelets negatively did (OR 0.32, 95% CI 0.12 to 0.88, $p = 0.027$). Hematochezia associated with the management change (OR 3.64, 95% CI 1.27 to 10.53, $p = 0.016$), whereas concomitant use of anti-platelets associated with no management change after endoscopy (OR 0.28, 95% CI 0.09 to 0.89, $p = 0.031$).

Impact on management and outcomes

Overall, there were 37 from 110 bleeding episodes that endoscopy led to the change of management. This comprised of 33.6% of all patients or 53.6% of those with significant GI lesions. The most common management changes were endoscopic therapy (32 patients, 86%), followed by medical therapy (3 patients, 8%) and surgery (3 patients, 8%). Despite the change of management, patients, however, remained having significantly higher rate of rebleeding, but similar rates of surgery and death compared to patients without changing management after endoscopy (Table 7).

Discussion

Acute GI bleeding is common among users of anticoagulants, no matter it is warfarin, UFH, LMWH or NOACs[1-3]. The initial management for such patients is primarily the reversal of anticoagulation. However, the optimal role of endoscopy in these patients is less clear. To perform endoscopy routinely in anticoagulated patients with acute GI bleeding may not be appropriate due to the concern of patient's risk from the underlying diseases and quite often, the endoscopic result was negative, nonspecific and does not change any following treatment. Thus, the decision to perform endoscopy in this group of patients is usually based on both the physicians and patients in case by case basis. Furthermore, there is no standard recommendation with this regard.

In the present study, the authors found that approximately 10% of patients who received anticoagulants had acute GI bleeding. UGIB was the most common site (60%) of bleeding with peptic ulcer asthe most common cause (43%). LGIB was less common (28%) and most from colonic diverticulosis and ulcers. MGIB comprised of 5.5% and cause was finally undetermined in 2.7%. This picture was comparable to the other previous studies that demonstrated GI bleeding in 12% of patients who took warfarin[7], UGIB as the most common site of GI bleeding[14] and peptic ulcer as the most common cause (45 to 60%)[1,4]. There was quite limited data on the prevalence of LGIB and MGIB. Recent Japanese study on patients who were on warfarin and NOACs reported the prevalence of LGIB and MGIB to be 50% and 7%, respectively[14], which quite differed from ours, particularly the prevalence of LGIB (50% vs. 28%). The reason is unclear. Finally, previous studies reported a 17 to 30% prevalence of GI bleeding of undetermined cause[1,4] or with normal EGD and colonoscopy[15]. These frequencies markedly differ from that of our study (2.7%), probably because our study classified a separated group of "presumed bleeding from coagulopathy" (26%). This group of patients had normal or insignificant GI lesions but did have anticoagulation overdose level. The authors felt that it was reasonable to presume this setting as bleeding from coagulopathy rather than labeling it as

Table 3. Prevalence of each type of GI lesions in 110 bleeding episodes

Type of lesions	n (%)	Detail of lesions	n (%)
Significant causative lesions	69 (62.7)	Peptic ulcer	28 (25.5)
		Vascular lesions	5 (4.5)
		Colonic diverticulosis	7 (6.3)
		Malignancy	6 (5.5)
		Polyps	3 (2.7)
		Colonic ulcer	7 (6.3)
		Radiation colitis	3 (2.7)
		Miscellaneous*	10 (9.1)
Significant non-causative lesions	8 (7.3)	Advanced adenoma or ≥3 colonic polyps	5 (4.5)
		Tuberculous ileitis	1 (0.9)
		Colitis	1 (0.9)
		Asymptomatic gastric GIST	1 (0.9)
Presumed bleeding from coagulopathy	29 (26.4)	Mild erosive or nonerosive gastritis	13 (37.1)
		Small ulcers	9 (25.7)
		Normal/blood stained mucosa	6 (17.0)
		Small vascular lesions	4 (11.4)
		Small colonic polyps	2 (1.8)
		Mild reflux esophagitis	1 (2.9)
Insignificant lesions	7 (6.3)	Erosive gastritis	3 (2.7)
		Nonerosive gastritis	3 (2.7)
		Small gastric ulcer	1 (0.9)
Undetermined	5 (4.5)		

GIST = gastrointestinal stromal tumor
* Mallory-Weiss tear, reflux esophagitis, duodenal diverticulum, CMV esophagitis, post sphinterotomy bleeding, post polypectomy bleeding

Table 4. Detail of significant lesions according to the types of endoscopy

Type of endoscopy	Significant lesion, n (%)	Detail of lesions	n (%)
EGD (n = 90)	40 (44)	Peptic ulcer	28 (31.1)
		Vascular	2 (2.2)
		Malignancy	2 (2.2)
		Miscellaneous*	8 (8.9)
Colonoscopy or sigmoidoscopy (n = 50)	28 (56)	Colonic diverticulosis	7 (14)
		Colonic ulcers	7 (14)
		Malignancy	3 (6)
		Polyps	3 (6)
		Vascular lesions	3 (6)
		Radiation colitis	3 (6)
		Post polypectomy bleeding	2 (4)
Single balloon enteroscopy (n = 4)	1 (25)	Jejunal GIST	1 (25)

GIST = gastrointestinal stromal tumor
* Mallory-Weiss tear, reflux esophagitis, duodenal diverticulum, CMV esophagitis, post sphinterotomy bleeding

undetermined cause of bleeding as other's[1,4].

The decision to perform EGD, colonoscopy, or both is normally relied on the patient's presentations. In the present study, both EGD and colonoscopy had

Table 5. Univariate and multivariate analyses of factors associated with significant GI lesions

Factors	Significant lesions (n = 69)	Insignificant lesions (n = 41)	Univariate analysis			Multivariate analysis		
			OR	95% CI	*p*-value	OR	95% CI	*p*-value
Male	36 (51.4)	19 (46.3)	0.85	0.39 to 1.86	0.692			
Age (year)	69.6±11.5	73.0±10.3			0.156			
Antiplatelet use	18 (26.1)	20 (52.6)	0.35	0.15 to 0.79	0.011	0.32	0.12 to 0.88	0.027
Hematochezia	27 (84.4)	5 (15.6)	4.36	1.53 to 12.6	0.006	4.90	1.22 to19.5	0.024
Hemoglobin (g/dL)	7.8±2.8	7.1±2.3						
<8 g/dL	35 (56.5)	27 (43.5)	2.08	0.92 to 4.68	0.077			
INR	4.75±3.2	7.59±3.0						
<4	22/57 (38.6)	4/33 (12.1)	4.58	1.41 to 12.73	0.011	4.07	1.17 to 14.27	0.028

CI = confidence interval; INR = international normalized ratio; OR = odds ratio; SD = standard deviation
Data are expressed as number (%) or mean ± SD.

Table 6. Univariate and multivariate analyses of factors associated with the change of managementafter endoscopy

Factors	Management change (n = 37)	Management unchanged (n = 73)	Univariate analysis			Multivariate analysis		
			OR	95% CI	*p*-value	OR	95% CI	*p*-value
Male	18 (48.6)	37 (50.7)	1.09	0.49 to 2.39	0.840			
Age (year)	73.2±10.2	66.1±11.6						
Anti-platelet use	6 (16.2)	32 (43.8)	0.25	0.09 to 0.67	0.004	0.28	0.09 to 0.89	0.031
Hematochezia	18 (48.6)	14 (19.2)	3.99	1.67 to 9.52	0.001	3.64	1.27 to 10.53	0.016
Hemoglobin (g/dL)	7.8±2.8	7.1±2.3						
<8 g/dL	18 (48.6)	44 (60.3)	1.60	0.72 to 3.55	0.245			
INR	4.8±3.2	7.6±3.0						
<4	11/26 (42.3)	15/64 (23.4)	1.64	0.66 to 4.04	0.284			

CI = confidence interval; Hb = hemoglobin; INR = international normalized ratio; OR = odds ratio; SD = standard deviation
Data are expressed as number (%) or mean ± SD.

Table 7. Impact of the change of management on patients' outcomes in the 110 episodes of bleeding

Outcomes	Change of management with endoscopy		OR	95% CI	*p*-value
	Yes (n = 37)	No (n = 73)			
Rebleeding	10 (27)	2 (2.7)	13.18	2.70 to 63.93	0.000
Surgery	3 (8.1)	0	NA	NA	0.036
Death	1 (4.2)	3 (4.3)	0.97	0.09 to 9.80	1.000

CI = confidence interval; NA = not assessable; OR = odds ratio

high diagnostic yields (44% and 56%, respectively). The most common etiologies identified by both routes were similar to GI bleeding in general, which are peptic ulcer and colonic diverticulosis. However, colonic ulcers were also common, probably due to the occurrence of colonic ischemia or acute hemorrhagic rectal ulcer syndrome, which commonly occur in the setting of multiple comorbid inpatients like ours.

The present study showed that appropriate endoscopy (based on presentation) could identify

significant GI lesions in two-third of the patients and would change the management in one-third, particularly with endoscopic therapy. There were 7% of patients of which endoscopy discovered incidental significant lesions i.e., as advanced adenoma, GIST and tuberculous ileitis, though they were not the causes of bleeding. This might be another advantage of the endoscopy in this setting. Unfortunately, even after discovery of significant lesions and having management change with endoscopic therapy, the outcomes of the patients remained unsatisfactory, i.e. very high rebleeding rate (27%), confirming the treatment difficulty among this group of patients. Nevertheless, mortality after management change (4%) seemed to be low enough, compared to those without management change or results from other studies[4,7].

In the present study, we could identify 3 predictors for the presence of significant GI lesions, i.e. hematochezia, INR of <4 and no concomitant antiplatelets and also identify 2 predictors for the change of management change from endoscopy, i.e. hematochezia and no concomitant antiplatelets. The presentation of hematochezia usually indicated LGIB or severe UGIB, thus it is reasonable to predict significant GI lesions than others. Patients with INR <4 were more likely to bleed from intrinsic GI lesion rather than the effect of coagulopathy[16] leading to the higher detection rate of significant GI lesions. Although one retrospective study[7] found no difference in the frequency of detected lesions and the need of endoscopic therapy between patients with INR >4 and those with INR 2-3, the present study included gastritis as a positive lesion and showed significantly more gastritis in the INR >4 group (35%) than the INR 2-3 group (9%). In fact, the findings of so called gastritis may be observed in many patients with coagulopathy and was classified as insignificant lesion in the present study. If discarding this gastritis cases, the positive lesions in the INR >4 group might become lower than the INR 2-3 group and consistent with the result of the present study. Similarly, the concomitant use of antiplatelets was predictor of no significant GI lesions probably because the combined antiplatelets and anticoagulant would increase the systemic bleeding effects themselves without the need of intrinsic GI lesions.

There were many limitations of the present study. First was the selection bias because included patients were only those who could underwent endoscopy according to the physicians' evaluation and decision. Thus, patient who were too sick or risky for endoscopy or those whose bleeding was minimal might not undergo endoscopy. However, we believed that this study more reflected the real life practice. Second, the level of anticoagulation was not possible in many patients due to the use of LMWH or NOAC. Third, some patients who were suspicious of MGIB, i.e. negative EGD/colonoscopy did not further investigate the small bowel. Thus, some patients in the undetermined group might actually have MGIB. Last, this is a retrospective study conducted in a university hospital setting, therefore, the results may not be generalized to other outlying hospitals. A prospective study is required to confirm our results. Further study is also needed to verify the usefulness of the 3 predictors in the selection of appropriate anticoagulated patients for endoscopy.

Conclusion

Significant GI lesions were present in two-third of anticoagulated patients who had acute GI bleeding and bleeding from coagulopathy occurred in one-fourth. Endoscopy led to the change of management in one-third. Peptic ulcers and colonic diverticulosis were the 2 most common causes. Hematochezia, INR <4 and no concomitant antiplatelets predicted significant GI lesions. Hematochezia and no concomitant antiplatelets predicted management change after endoscopy.

What is already known on this topic?

Acute GI bleeding is common among anticoagulated patients. The most common causes are gastritis, peptic ulcer, colonic diverticulosis and normal endoscopy. The prevalence of bleeding from coagulopathy without intrinsic GI lesion is unknown. Whether endoscopy led to the change of management is unclear.

What this study adds?

Bleeding from coagulopathy occurred in one-fourth. Endoscopy led to the change of management in one-third. Hematochezia, INR <4 and no concomitant antiplatelets predicted significant GI lesions. Hematochezia and no concomitant antiplatelets predicted management change after endoscopy.

Potential conflicts of interest

None.

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