Impact of INR monitoring, reversal agent use, heparin bridging, and anticoagulant interruption on rebleeding and thromboembolism in acute gastrointestinal bleeding

Naoyoshi Nagata1, Toshiyuki Sakurai1, Shiori Moriyasu1, Takuro Shimbo2, Hidetaka Okubo1, Kazuhiro Watanabe1, Chizu Yoko1, Mikio Yanase1, Junichi Akiyama1, Naomi Uemura3

1 Department of Gastroenterology and Hepatology, National Center for Global Health and Medicine, Shinjuku, Tokyo, Japan, 2 Ohta Nishinouchi Hospital, Koriyama, Fukushima, Japan, 3 Department of Gastroenterology and Hepatology, Kohno-dai Hospital, National Center for Global Health and Medicine, Ichikawa, Chiba, Japan

Abstract

Background
Anticoagulant management of acute gastrointestinal bleeding (GIB) during the pre-endoscopic period has not been fully addressed in American, European, or Asian guidelines. This study sought to evaluate the risks of rebleeding and thromboembolism in anticoagulated patients with acute GIB.

Methods
Baseline, endoscopy, and outcome data were reviewed for 314 patients with acute GIB: 157 anticoagulant users and 157 age-, sex-, and important risk-matched non-users. Data were also compared between direct oral anticoagulants (DOACs) and warfarin users.

Results
Between anticoagulant users and non-users, of whom 70% underwent early endoscopy, no endoscopy-related adverse events or significant differences were found in the rate of endoscopic therapy need, transfusion need, rebleeding, or thromboembolism. Rebleeding was associated with shock, comorbidities, low platelet count and albumin level, and low-dose aspirin use but not HAS-BLED score, any endoscopic results, heparin bridge, or international normalized ratio (INR) ≥ 2.5. Risks for thromboembolism were INR ≥ 2.5, difference in onset and pre-endoscopic INR, reversal agent use, and anticoagulant interruption but not CHA2DS2-VASc score, any endoscopic results, or heparin bridge. In patients without reversal agent use, heparin bridge, or anticoagulant interruption, there was only one rebleeding.
event and no thromboembolic events. Warfarin users had a significantly higher transfusion need than DOACs users.

Conclusion
Endoscopy appears to be safe for anticoagulant users with acute GIB compared with non-users. Patient background factors were associated with rebleeding, whereas anticoagulant management factors (e.g. INR correction, reversal agent use, and drug interruption) were associated with thromboembolism. Early intervention without reversal agent use, heparin bridge, or anticoagulant interruption may be warranted for acute GIB.

Introduction
Acute gastrointestinal bleeding (GIB) in patients who are taking oral anticoagulants is expected to increase as the population ages\cite{1}. Endoscopy in this setting is a high-risk procedure\cite{2–4} in that it is associated with the potential for rebleeding\cite{4}. However, few data are available on the endoscopic and clinical outcomes of patients receiving anticoagulant therapy compared with those who are not\cite{5,6}.

The occurrence of acute GIB during anticoagulant therapy raises several difficulties related to the balance between bleeding risk and thromboembolic risk\cite{2,3,7}. These risks are probably related to patient background, endoscopic results, and anticoagulant management\cite{4,6,8,9}. However, which of these actually affect adverse outcomes remains unclear. Importantly, the issues of anticoagulant interruption, heparin bridge, and international normalized ratio (INR) correction during the pre-endoscopic period in the acute GIB setting have not been fully addressed in recent endoscopy guidelines from the United States, Europe, or Asia\cite{2,3,10}. Many gastroenterologists, therefore, likely limit the management of anticoagulated patients to their own experiences.

Recently, direct oral anticoagulants (DOACs) have been approved as alternatives to warfarin\cite{11}. While there may have been increasing recognition of GIB risk in patients on DOACs \cite{11–13}, limited data are available on differences in endoscopic results and adverse outcomes of GIB between DOAC and warfarin users\cite{14}.

The present study builds upon our previous work\cite{15} by adding GIB cases who received oral anticoagulants and newly collecting detailed data on baseline, anticoagulant management, and endoscopic and rebleeding outcomes accordingly. Because only 2%-6% of patients with acute GIB use anticoagulants\cite{16–18}, we reviewed a large number of GIB patients to (i) determine whether anticoagulated patients with acute GIB have adverse endoscopic and clinical outcomes compared with those not receiving anticoagulants, (ii) elucidate the risk factors for rebleeding and thromboembolism following endoscopy in anticoagulated patients; and (iii) explore differences in the endoscopic and clinical outcomes of GIB between DOACs and warfarin users and between those with upper and lower GI.

Material and methods
Study design, setting, and participants
We conducted a retrospective cohort study at the Department of Gastroenterology, National Center for Global Health and Medicine (NCGM), Japan. NCGM is the largest emergency hospital, with 900 beds, in the Tokyo metropolitan area. All clinical and endoscopic data analyzed
were extracted from a prospective electronic medical database (MegaOak online imaging system, NEC, Japan) and an electronic endoscopic database (SolemioEndo, Olympus, Japan), both of which contain searchable collection of records into which physicians or nurses prospectively input all clinical findings immediately after clinical evaluation or endoscopy[19,20]. Fig 1 illustrates the study flow of patient selection.

Between January 2009 and May 2016, we identified 1,483 consecutive patients with signs of acute, continuous, or frequent overt GIB (“hematochezia”, “red blood per rectum”, “melena”, “tarry stool”, or “hematemesis”) who were managed in hospital. We then reviewed the clinical and endoscopic data for each patient and excluded those who: (1) did not undergo endoscopy (n = 129); (2) had no overt bleeding within 3 days of endoscopy (n = 43); (3) had some missing clinical information (n = 14); or (4) were electively admitted with GIB (n = 39). This left a cohort of 1,267 patients with acute GIB who underwent endoscopy from which we analyzed data for 157 anticoagulated patients and 157 non-anticoagulated patients matched for age, sex, body mass index, outpatient onset, year of diagnosis, presenting shock, hematochezia, hemoglobin level, and drug use (NSAIDs, low-dose aspirin [LDA], and other antiplatelets).

The requirement for patient consent was waived because this was a retrospective study that was conducted without invasive procedures and data were anonymized and deidentified by the director of the clinical research division at our institution, who was not involved in this study, before our analysis. This study was approved by the ethics committee of the National Center for Global Health and Medicine (No. 1579) and was conducted in accordance with the provisions of the Declaration of Helsinki.

Comorbidities and medication

We collected data on the following background factors: signs of shock, presenting symptoms, history of GIB, co-morbidities, medications, and laboratory data related to GIB. Use of NSAIDs, LDA, non-aspirin antiplatelet drugs, warfarin, DOACs (dabigatran, rivaroxaban, apixaban and edoxaban), or proton pump inhibitors (PPIs) was defined as use within 1 month before admission. We evaluated 16 comorbidities using the Charlson comorbidity index[21]. CHA2DS2-VASc[22] and HAS-BLED[23] scores were calculated. After an episode of GIB, we collected data on anticoagulant management factors: INR in the pre-endoscopic period and use of reversal agent, heparin bridge, and drug interruption. Reversal agents included vitamin K, FFP, prothrombin complex concentrate (PCC), and recombinant activated factor VIIa. For heparin bridge, patients received prophylactic unfractionated heparin infusion intravenously. Only unfractionated heparin is used in Japan because low-molecular-weight heparin is not covered by the health care insurance system[24].

Clinical outcomes

The main outcomes of interest were rebleeding and thromboembolism within 90 days of endoscopy. Rebleeding was defined as significant overt bleeding along with unstable vital signs, or the need for a transfusion of ≥ 2 units of packed red blood cells in the first 24 h after onset or endoscopically verified GIB. We defined a thromboembolic event as having acute coronary syndrome, stroke, transient ischemic attack, pulmonary embolism, deep vein thrombosis, or arterial thromboembolism. Workup for thromboembolism included positive computed tomography, magnetic resonance imaging, coronary angiography, ventilation-perfusion scanning, and/or ultrasonography.
Patients with acute overt GIB (n = 1,483)
Patients with signs of acute, continuous, or frequent overt GIB ("hematochezia", "red blood pre rectum", "melena", "tarry stool", or "hematemesis") who were managed in hospital.

Clinical and endoscopic data for each patient was reviewed.

- Excluded patients (n = 216)
  - i) No endoscopy (n = 129)
  - ii) No overt bleeding within 3 days of endoscopy (n = 43)
  - iii) Missing clinical information (n = 14)
  - iv) Electively admission (n = 39)

Patients with acute overt GIB who underwent endoscopy (n = 1,267)
- Anticoagulated patients (n = 157)
- Non-anticoagulated patients (n = 1,110)

Non-anticoagulated cohort was matched with anticoagulated cohort for age, sex, body mass index, outpatient onset, year of diagnosis, presenting shock, hematochezia, hemoglobin level, and the use of NSAIDs, low-dose aspirin, and other antiplatelet drugs.

- Excluded patients (n= 953) Non-matched

- Anticoagulated GIB patients (n = 157)
- Non-anticoagulated GIB patients (n = 157)

Factors: patient background, endoscopic results, and anticoagulant management

Clinical outcomes: rebleeding and thromboembolism

Fig 1. Study flow. Abbreviation. GIB, gastrointestinal bleeding.

https://doi.org/10.1371/journal.pone.0183423.g001
Statistics
Categorical data were compared between the groups using the Chi-square test or Fisher’s exact test, as appropriate. Continuous data were compared with Wilcoxon’s rank-sum test. To determine the predictive factors of clinical outcomes, we conducted univariate logistic regression analysis. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated. In terms of anticoagulant management factors, we developed 4 types of propensity score for DOAC use, PT-INR (onset) ≥ 2.5, reversal agent use, heparin bridge, and anticoagulant interruption by using a logistic regression model for each treatment that included background factors shown to be different (p < 0.10) between treatment and non-treatment. Then, we conducted a multivariate analysis adjusted for the 4 types of propensity score to estimate the adjusted ORs for DOAC use, PT-INR (onset) ≥ 2.5, reversal agent use, heparin bridge, and anticoagulant interruption for clinical outcomes. A value of P < 0.05 was considered significant. All statistical analysis was performed using STATA version 14 software (StataCorp, College Station, TX).

Results
Background, endoscopy, and outcomes of anticoagulant users and non-users
The indications for anticoagulant use were as follows (Table 1): atrial fibrillation (n = 104), valvular replacement or valvular disease (n = 28), history of thromboembolism (n = 75); and ≥ 2 of these indications (n = 63). Baseline characteristics for both groups are shown in Table 1. The two groups were well matched for known risk factors, but compared with non-users, anticoagulated patients had significantly higher CHA2DS2-VASc scores, rates of atrial fibrillation and mechanical valve placement, prothrombin time (PT-INR) level, and use of PPIs. Endoscopic diagnosis or therapy is shown in Table 1: 108 patients (69%) underwent endoscopy within 24 h of onset in each group. Among anticoagulant users and non-users, 46.8% had upper sources and 53.2% had lower sources of GIB. The major cause of the bleeding was peptic ulcer disease for upper GIB and colonic diverticular bleeding for lower GIB. There were no significant differences between the two groups in terms of the rate of early endoscopy, upper or lower GIB, endoscopic diagnosis, endoscopic therapy need, transfusion need, rebleeding or thromboembolism. No endoscopy-related adverse events occurred in either group.

Risk factors for rebleeding and thromboembolism in anticoagulated patients
Factors associated with outcomes are shown in Tables 2–4. Significant predictors of rebleeding were found to be presenting shock, higher comorbidity index (including chronic kidney disease), platelet count < 10 (10^4/μl), and low-dose aspirin use at admission but not HAS-BLED score (Table 2). No significant predictors of thromboembolic event were found. No associations were found between any of the endoscopic factors (endoscopy timing, bleeding site, etiology, and therapy) and any of the outcomes (Table 3). INR level at onset or pre-endoscopy did not predict rebleeding, but INR level at onset was a significant predictor of thromboembolism (Table 4). No significant difference in rebleeding rate was seen between INR < 2.5 and ≥ 2.5, but INR ≥ 2.5 at onset was a predictor of thromboembolism. The difference in INR value between onset and pre- or post-endoscopy was significantly associated with thromboembolism but not rebleeding. Reversal agent use was significantly associated with thromboembolism but not rebleeding. Heparin bridging was not significantly associated with rebleeding or
Table 1. Baseline characteristics and outcomes of GIB patients compared between anticoagulant users and matched non-user controls (n = 314).

| Characteristic | Anticoagulant users (n = 157) | Matched non-users (n = 157) | P value |
|----------------|-----------------------------|-----------------------------|---------|
| Age, years     | 75.7 ± 10.6                 | 74.2 ± 11.5                 | 0.198   |
| Age > 70, years| 118 (75.2)                  | 117 (74.5)                  | 0.310   |
| Male           | 96 (61.2)                   | 96 (61.2)                   | 1.000   |
| BMI ≥ 25, kg/m²| 41 (26.1)                   | 31 (19.8)                   | 0.179   |
| Inpatient onset| 44 (28.0)                   | 33 (21.0)                   | 0.149   |
| **Signs or symptoms** |                      |                             |         |
| Shock²         | 32 (20.4)                   | 30 (19.1)                   | 0.777   |
| Hematemesis    | 25 (15.9)                   | 34 (21.7)                   | 0.194   |
| Tarry stool    | 68 (43.3)                   | 54 (34.4)                   | 0.105   |
| Hematochezia   | 84 (53.5)                   | 84 (53.5)                   | 1.000   |
| **Comorbidities or past-history** |                      |                             |         |
| Metabolic syndrome†| 122 (77.7)                   | 115 (73.3)                   | 0.359   |
| History of thromboembolism‡| 75 (47.8)                   | 65 (41.4)                   | 0.256   |
| History of GI bleeding| 34 (21.7)                   | 27 (17.2)                   | 0.318   |
| Charlson comorbidity index | 3.5 ± 2.7                   | 3.9 ± 3.6                   | 0.938   |
| CHA2DS2-VASc score | 2.7 ± 1.1                    | 2.4 ± 1.1                   | 0.023   |
| HAS-BLED score | 2.7 ± 1.2                   | 2.5 ± 1.2                   | 0.121   |
| Atrial fibrillation | 104 (66.2)                   | 7 (4.5)                     | <0.001  |
| Mechanical valve | 21 (13.4)                    | 0                            | <0.001  |
| Biological valve | 7 (4.5)                      | 1 (0.6)                     | 0.067   |
| **Baseline laboratory data** |                      |                             |         |
| Hemoglobin, g/dl | 10.3 ± 4.6                   | 9.7 ± 3.2                   | 0.417   |
| Platelets, 10⁹/μl | 30.9 ± 148.8                  | 20.7 ± 9.8                   | 0.129   |
| PT-INR         | 2.0 ± 1.2                   | 1.1 ± 0.2                   | <0.001  |
| PT-INR > 2.5   | 36 (22.9)                   | 10 (6.4)                    | <0.001  |
| Albumin, mg/dl | 3.5 ± 2.4                   | 3.1 ± 0.8                   | 0.141   |
| BUN, mg/dl     | 35.0 ± 22.4                 | 31.9 ± 33.5                 | 0.101   |
| Creatinine, mg/dl | 1.3 ± 1.3                   | 1.7 ± 2.3                   | 0.196   |
| **Medications** |                      |                             |         |
| NSAIDs         | 25 (15.9)                   | 25 (15.9)                   | 1.000   |
| Low-dose aspirin | 49 (31.2)                   | 44 (28.0)                   | 0.537   |
| Thienopyridine‖ | 9 (5.7)                      | 10 (6.4)                    | 0.813   |
| Other antiplatelets¶ | 10 (6.4)                    | 6 (3.8)                     | 0.305   |
| Proton-pump inhibitors | 78 (50.0)                   | 41 (26.1)                   | <0.001  |
| **Clinical outcome** |                      |                             |         |
| Early endoscopy | 108 (68.8)                   | 108 (68.8)                  | 1.000   |
| Bleeding sources, lower GI tract | 85 (54.1)                   | 82 (52.2)                   | 0.734   |
| **Upper source** |                      |                             |         |
| Peptic ulcer disease* | 47 (29.9)                   | 56 (35.7)                   | 0.279   |
| Mallory-Weiss syndrome | 6 (3.8)                      | 7 (4.5)                     | 0.777   |
| Post-endoscopic therapy | 7 (4.5)                      | 2 (1.3)                     | 0.173   |
| Esophageal ulcer | 4 (2.6)                      | 2 (1.3)                     | 0.684   |
| Angioectasia    | 2 (1.3)                      | 2 (1.3)                     | 1.000   |
| Varices (esophagus or stomach) | 0                             | 3 (1.9)                     | 0.248   |
| Other diagnosis** | 5 (3.2)                      | 4 (2.6)                     | 1.000   |
| **Lower source** |                      |                             |         |
| Colonic diverticular bleeding | 26 (16.6)                   | 29 (18.5)                   | 0.656   |

(Continued)
Table 1. (Continued)

| Diagnosis                        | Case (X%) | Control (X%) | p-value |
|----------------------------------|-----------|--------------|---------|
| Ischemic colitis                 | 10 (6.4)  | 13 (8.3)     | 0.516   |
| Other colitis                    | 2 (1.3)   | 5 (3.2)      | 0.448   |
| Colorectal cancer                | 5 (3.2)   | 3 (1.9)      | 0.723   |
| Radiation proctitis              | 0         | 2 (1.3)      | 0.498   |
| Angioectasia                     | 7 (4.5)   | 1 (0.6)      | 0.067   |
| Rectal ulcer                     | 7 (4.5)   | 8 (5.1)      | 1.000   |
| Inflammatory bowel disease       | 1 (0.6)   | 3 (1.9)      | 0.623   |
| Post-endoscopic therapy          | 13 (8.3)  | 5 (3.2)      | 0.052   |
| Hemorrhoids                      | 4 (2.6)   | 4 (2.6)      | 1.000   |
| Middle GIB                       | 8 (5.1)   | 8 (5.1)      | 1.000   |
| Other diagnosis***               | 2 (1.3)   | 0            | 0.498   |
| Unknown****                      | 1 (0.6)   | 1 (0.6)      | 1.000   |
| **Endoscopic therapy need**      | 64 (40.8) | 58 (36.9)    | 0.487   |
| Clipping                         | 55 (35.0) | 47 (29.9)    | 0.335   |
| Band ligation                    | 5 (3.2)   | 9 (5.7)      | 0.413   |
| Epinephrin injection therapy     | 3 (1.9)   | 3 (1.9)      | 1.000   |
| Hemostatic forceps               | 3 (1.9)   | 0            | 0.248   |
| Argon plasma coagulation         | 6 (3.8)   | 4 (2.6)      | 0.750   |
| Interventional radiology need    | 0         | 1 (0.64)     | 1.000   |
| Surgery need                     | 1 (0.6)   | 2 (1.3)      | 1.000   |
| Transfusion need                 | 83 (52.9) | 77 (49.0)    | 0.498   |
| Units of Transfusion need        | 3.7 ± 5.3 | 4.5 ± 9.4    | 0.708   |
| **Rebleeding**                   | 21 (13.4) | 25 (15.9)    | 0.523   |
| **Thromboembolism**              | 9 (5.7)   | 5 (3.2)      | 0.677   |
| Cardiovascular event             | 0         | 3 (1.9)      | 0.248   |
| Cerebrovascular event            | 4 (2.6)   | 1 (0.6)      | 0.371   |
| Pulmonary embolism or deep vein thrombosis‡‡ | 5 (3.2) | 1 (0.6) | 0.214 |

Values in parentheses are percentages. Values presented with a plus/minus sign are means ± SD. Bold values indicate statistical significance at P < 0.05.

1Shock was defined as decrease in systolic blood pressure to < 90 mmHg, paleness, cold sweats, dizziness, syncope, or unconsciousness.

2Metabolic syndrome was a clustering of ≥ 2 of the 4 following medical conditions: abdominal (central) obesity, hypertension, diabetes mellitus, and dyslipidemia.

3History of thromboembolism was defined as the presence of acute coronary syndrome, stroke, transient ischemic attack, pulmonary embolism, deep vein thrombosis, or arterial thromboembolism.

4Thienopyridine refers to the use of clopidogrel, prasugrel, ticagrelor, and ticlopidine. Other antiplatelets were cilostazol, dipyridamole, sarpogrelate hydrochloride, ethylicosapentate, dilaizep, limaprost, and beraprost.

5Deep vein thrombosis occurred in 1 anticoagulant user and in 1 control.

6Pepptic ulcer disease (n = 103) included gastric ulcer (n = 79) and duodenal ulcer (n = 26), and 2 patients had both gastric and duodenal ulcer. Five of the patients with gastric ulcer disease were subsequently identified as having gastric cancer based on histopathology.

7Other diagnosis of upper GIB included pancreatic cancer gastrointestinal invasion (n = 3), aneurysmal rupture to the stomach (n = 1), submucosal tumor of the stomach (n = 2), and bleeding from gastric polyp (n = 3).

8Other diagnosis of lower GIB bleeding was bleeding from colonic polyp (n = 2).

9Unknown source of bleeding (n = 2) was defined as a lesion where upper endoscopy and colonoscopy and/or capsule endoscopy or double-balloon endoscopy did not reveal the bleeding source.

Abbreviations: BMI, body mass index; PT-INR, prothrombin time-international normalized ratio; CHA2DS2-VASc, Congestive heart failure, Hypertension, Age ≥ 75, Diabetes mellitus, Stroke, Vascular disease, Sex female; HAS-BLED, hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratios (INR), elderly, drugs/alcohol concomitantly; BUN, blood urea nitrogen; NSAIDs, non-steroidal anti-inflammatory drugs.

https://doi.org/10.1371/journal.pone.0183423.t001
Table 2. Patient background factors associated with rebleeding and thromboembolism in anticoagulant users with acute GI bleeding (n = 157).

| Factor                      | Rebleeding event/ no event | Odds ratio (95% CI) | P   | Thromboembolic event/ no event | Odds ratio (95% CI) | P   |
|-----------------------------|----------------------------|---------------------|-----|-------------------------------|---------------------|-----|
| Age, years                  |                            |                     |     |                               |                     |     |
| Male                        | 13 (61.9) / 83 (61.0)      | 0.9 (0.4–2.7)       | 0.939 | 7 (77.8) / 89 (60.1)          | 2.3 (0.5–11.6)      | 0.304 |
| BMI ≥ 25, kg/m²             | 5 (23.8) / 36 (26.5)      | 0.9 (0.3–2.5)       | 0.796 | 3 (33.3) / 38 (25.7)          | 1.4 (0.3–6.1)       | 0.613 |
| In-patient onset            | 6 (28.6) / 38 (27.9)      | 1.0 (0.4–2.9)       | 0.952 | 2 (22.2) / 42 (28.4)          | 0.7 (0.1–3.6)       | 0.691 |
| Shock                       | 8 (38.1) / 24 (17.7)      | 2.9 (1.1–7.7)       | 0.036 | 3 (33.3) / 29 (19.6)          | 2.1 (0.5–8.7)       | 0.379 |
| Hematemesis                 | 3 (14.3) / 22 (16.2)      | 0.9 (0.2–3.2)       | 0.826 | 3 (33.3) / 22 (14.9)          | 2.9 (0.7–12.3)      | 0.157 |
| Tarry stool                 | 8 (38.1) / 60 (44.1)      | 0.8 (0.3–2.0)       | 0.605 | 5 (55.6) / 63 (42.6)          | 1.7 (0.4–6.5)       | 0.449 |
| Hematochezia                | 13 (61.9) / 71 (52.2)     | 1.5 (0.6–3.8)       | 0.409 | 3 (33.3) / 81 (54.7)          | 0.4 (0.1–1.7)       | 0.224 |
| Atrial fibrillation         | 16 (76.2) / 106 (77.9)    | 0.9 (0.3–2.7)       | 0.858 | 6 (66.7) / 106 (78.4)         | 0.6 (0.1–2.3)       | 0.418 |
| History of thromboembolism††| 12 (57.1) / 63 (46.3)     | 1.5 (0.6–3.9)       | 0.358 | 6 (66.7) / 69 (46.6)          | 2.3 (0.6–9.5)       | 0.254 |
| History of GI bleeding      | 5 (23.8) / 29 (21.3)      | 1.2 (0.4–3.4)       | 0.797 | 0 / 34 (23.0)                 | 0.3 (0–18)*         | 0.208 |
| Liver cirrhosis             | 1 (5.3) / 4 (2.9)         | 1.9 (0.2–17.6)      | 0.588 | 0/ 5 (3.4)                   | NA†                  | NA† |
| Chronic kidney disease      | 3 (15.8) / 5 (3.6)        | 5.0 (1.1–22.9)      | 0.039 | 1 (12.5) / 7 (4.7)            | 2.9 (0.3–26.9)      | 0.349 |
| Charlnor comorbidity index  | 4.8 ± 3.0 / 3.3 ± 2.6     | 1.2 (1.0–1.4)       | 0.024 | 4.3 ± 4.3 / 3.5 ± 2.6         | 1.1 (0.9–1.4)       | 0.362 |
| CHA2DS2-VASc                | 2.7 ± 0.8 / 2.7 ± 1.1     | 1.0 (0.7–1.5)       | 0.970 | 2.1 ± 0.9 / 2.7 ± 1.1         | 0.6 (0.3–1.1)       | 0.114 |
| HAS-BLED score              | 3.0 ± 1.2 / 2.6 ± 1.2     | 1.4 (0.9–2.0)       | 0.135 | 2.7 ± 1.0 / 2.7 ± 1.2         | 1.0 (0.5–1.8)       | 0.941 |
| Atrial fibrillation         | 12 (57.1) / 92 (67.7)     | 0.6 (0.3–1.6)       | 0.346 | 5 (55.6) / 99 (66.9)          | 0.6 (0.2–2.4)       | 0.489 |
| Mechanical valve            | 3 (14.3) / 18 (13.2)      | 1.1 (0.3–4.1)       | 0.895 | 2 (22.2) / 19 (12.8)          | 1.9 (0.4–10.0)      | 0.429 |

Values in parentheses are percentages. Values presented with a plus/minus sign are means ± SD.

*Exact logistic regression was performed. Bold values mean statistical significance at P < 0.05.

†There were no patients with outcomes and statistical analysis was not performed.

††History of thromboembolism was defined as the presence of acute coronary syndrome, stroke, transient ischemic attack, pulmonary embolism, deep vein thrombosis, or arterial thromboembolism.

Abbreviations: BMI, body mass index; CHA2DS2-VASc, Congestive heart failure, Hypertension, Age ≥ 75, Diabetes mellitus, Stroke, Vascular disease, Sex female; HAS-BLED, hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labor international normalized ratios (INR), elderly, drugs/alcohol concomitantly; BUN, blood urea nitrogen; NSAID, non-steroidal anti-inflammatory drugs; NA, not applicable; LDA, low-dose aspirin; PPI, proton-pump inhibitors; Inf, infinity.

https://doi.org/10.1371/journal.pone.0183423.t002
thromboembolism. All thromboembolic events occurred in anticoagulant interrupted patients before endoscopy. In patients without reversal agent use, heparin bridge, or anticoagulant interruption, there was only one rebleeding event and no thromboembolic events. Even after propensity score adjustment, the risk of DOAC use, PT-INR ≥ 2.5 at onset, heparin bridge, or anticoagulant interruption for any of the clinical outcomes remained unchanged compared with univariate analysis. Reversal agent use was not significantly associated with thromboembolism after propensity score adjustment (Table 5).

Table 4. Anticoagulant management factors associated with rebleeding and thromboembolism in anticoagulant users with acute GI bleeding (n = 157).

| Factor                                           | Rebleeding event/ no event | Odds ratio (95%CI) | P    | Thromboembolic event/ no event | Odds ratio (95%CI) | P    |
|--------------------------------------------------|---------------------------|--------------------|------|------------------------------|--------------------|------|
| DOAC use                                         | 5 (23.8)/ 37 (27.2)       | 0.8 (0.3–2.4)      | 0.744| 1 (11.1)/ 41 (27.1)          | 0.3 (0.04–2.7)     | 0.298|
| PT-INR (onset)                                   | 1.8 ± 0.8/ 1.9 ± 0.8      | 0.8 (0.4–1.5)      | 0.517| 2.6 ± 1.0/ 1.8 ± 0.7         | 3.1 (1.4–7.2)      | 0.008|
| PT-INR (pre-endoscopy)                           | 1.6 ± 0.7/ 1.7 ± 0.7      | 0.8 (0.4–1.6)      | 0.568| 2.1 ± 1.0/ 1.7 ± 0.7         | 1.8 (0.8–4.1)      | 0.139|
| PT-INR (onset) ≥ 2.5                             | 4 (19.1)/ 32 (23.5)       | 0.8 (0.2–2.4)      | 0.650| 6 (66.7)/ 30 (20.3)          | 7.9 (1.9–33.3)     | 0.005|
| PT-INR (pre-endoscopy) ≥ 2.5                     | 2 (9.5)/ 25 (18.4)        | 0.5 (0.1–2.1)      | 0.327| 3 (33.3)/ 24 (16.2)          | 2.6 (0.6–11.0)     | 0.201|
| Difference of INR value between admission and pre-endoscopy | 0.2 ± 0.3/ 0.2 ± 0.4 | 0.9 (0.3–3.1) | 0.974 | 0.5 ± 0.8/ 0.2 ± 0.4 | 3.7 (1.2–11.3) | 0.022 |
| Difference of INR value between onset and pre-endoscopy | 0.5 ± 0.8/ 0.5 ± 0.7 | 1.0 (0.5–2.0) | 0.897 | 1.3 ± 1.0/ 0.4 ± 0.7 | 3.2 (1.5–6.7) | 0.002 |
| Reversal agent (Vitamin K antagonist) use†       | 4 (19.1)/ 24 (17.7)       | 1.1 (0.3–3.6)      | 0.876| 4 (44.4)/ 24 (16.2)          | 4.1 (1.0–16.5)     | 0.045|
| Heparin bridging                                 | 7 (33.3)/ 42 (30.9)       | 1.1 (0.4–3.0)      | 0.822| 4 (44.4)/ 45 (30.4)          | 1.8 (0.5–7.1)      | 0.384|
| Anticoagulant interruption before endoscopy      | 19 (90.5)/ 97 (71.3)      | 3.8 (0.8–17.2)     | 0.081| 9 (100)/ 107 (72.3)          | 4.7 (0.7–inf)*     | 0.121|
| No reversal agent use, no heparin bridge, or no anticoagulant interruption | 1 (4.8)/ 36 (26.5) | 0.1 (0.02–1.1) | 0.058 | 0/ 37 (25) | 0.2 (0–1.6)* | 0.165 |

Values in parentheses are percentages. Values presented with a plus/minus sign are means ± SD.
*Exact logistic regression was performed. Bold values denote statistical significance at P < 0.05.
†Twenty-eight of patients received a reversal agent (Vitamin K) intravenously during the peri-endoscopic period; no patients received FFP, prothrombin complex concentrate, or recombinant activated factor VIIa.
Abbreviations: PT-INR, prothrombin time-international normalized ratio; Inf, infinity.

https://doi.org/10.1371/journal.pone.0183423.t004

https://doi.org/10.1371/journal.pone.0183423.t003

Table 3. Endoscopic factors associated with rebleeding and thromboembolism in anticoagulant users with acute GI bleeding (n = 157).

| Factor                             | Rebleeding event/ no event | Odds ratio (95%CI) | P  | Thromboembolic event/ no event | Odds ratio (95%CI) | P  |
|------------------------------------|---------------------------|--------------------|-----|-------------------------------|--------------------|-----|
| Early endoscopy (< 24 h)           | 13 (61.9)/ 90 (69.9)      | 0.7 (0.3–1.8)      | 0.466| 5 (55.6)/ 103 (69.6)           | 0.5 (0.1–2.1)      | 0.384|
| Lower GIB vs upper GIB             | 12 (57.1)/ 73 (53.7)      | 1.2 (0.5–2.9)      | 0.767| 3 (33.3)/ 82 (55.4)            | 0.4 (0.1–1.7)      | 0.210|
| Peptic ulcer bleeding              | 4 (19.1)/ 43 (31.6)       | 0.5 (0.2–1.6)      | 0.249| 4 (44.4)/ 43 (29.1)            | 2.0 (0.05–7.6)     | 0.335|
| Colonic diverticular bleeding      | 3 (14.3)/ 23 (16.9)       | 0.8 (0.2–3.0)      | 0.763| 0/ 26 (17.6)                   | 0.4 (0.01–2.4)*    | 0.523|
| Received endoscopic therapy        | 11 (52.4)/ 53 (39.0)      | 1.7 (0.7–4.3)      | 0.248| 4 (44.4)/ 60 (40.5)            | 1.2 (0.3–4.5)      | 0.817|
| Received endoscopic clipping       | 8 (38.1)/ 47 (34.6)       | 1.2 (0.5–3.0)      | 0.752| 3 (33.3)/ 52 (35.1)            | 0.9 (0.2–3.8)      | 0.912|
| Received endoscopic ligation       | 1 (4.8)/ 4 (2.9)          | 1.7 (0.2–15.5)     | 0.661| 0/ 5 (3.4)                    | 1.7 (0.04–13.1)*   | 0.959|

Values in parentheses are percentages. Values presented with a plus/minus sign are means ± SD.
*Exact logistic regression was performed. Bold values indicate statistical significance at P < 0.05.
Abbreviation. GIB, gastrointestinal bleeding.
Subgroup analysis of DOAC and warfarin users

Compared with warfarin users, DOAC users had a significantly higher rate of atrial fibrillation, higher levels of hemoglobin and albumin, lower levels of PT-INR and BUN, a lower rate of LDA use, and a higher rate of lower GIB (Table 6). No significant difference was found in the rate of early endoscopy, other endoscopic diagnosis, or other endoscopic therapy between the groups (Table 6). In terms of clinical outcomes, DOAC users received significantly fewer transfusions than warfarin users, and no significant differences were found in endoscopic therapy need, rebleeding, or thromboembolism between the groups (Table 6).

Subgroup analysis of patients diagnosed with upper and lower GIB

Compared with lower GI bleeders, there was a significantly higher rate of upper GI bleeders in elderly patients (> 70 years) and patients with shock, hematemesis, tarry stool, lower hemoglobin and albumin levels, or higher BUN level (Table 7). Upper GI bleeders were associated with a significantly higher rate of early endoscopy, endoscopic therapy need (particularly clipping), and transfusion need (Table 7).

Discussion

This study presents new information on the anticoagulant management for acute GIB. First, there were no apparent differences in endoscopic results or adverse clinical outcomes of GIB
Table 6. Baseline characteristics and outcomes of GIB compared between direct oral anticoagulant (DOAC) and warfarin users (n = 157).

| Characteristic                      | DOAC users (n = 42) | Warfarin users (n = 115) | P value |
|-------------------------------------|--------------------|--------------------------|---------|
| **Age, years**                      | 77.6 ± 7.7         | 75.0 ± 11.4              | 0.385   |
| Age > 70, years                     | 34 (81.0)          | 84 (73.0)                | 0.310   |
| **Male**                            | 23 (54.8)          | 73 (63.4)                | 0.321   |
| **BMI ≥ 25, kg/m²**                 | 13 (31.0)          | 28 (24.4)                | 0.404   |
| Inpatient onset                     | 11 (26.2)          | 33 (28.7)                | 0.757   |
| **Signs or symptoms**               |                    |                          |         |
| Shock                               | 6 (14.3)           | 26 (22.6)                | 0.252   |
| Hematemesis                         | 4 (9.5)            | 21 (18.3)                | 0.185   |
| Tarry stool                         | 19 (45.2)          | 49 (42.6)                | 0.769   |
| Hematochezia                        | 25 (59.5)          | 59 (51.3)                | 0.361   |
| **Comorbidities or past-history**   |                    |                          |         |
| Metabolic syndrome††                | 31 (73.8)          | 91 (79.1)                | 0.478   |
| History of thromboembolism††        | 25 (59.5)          | 50 (43.5)                | 0.075   |
| History of GI bleeding              | 11 (26.2)          | 23 (20.0)                | 0.405   |
| Charlson comorbidity index          | 3.4 ± 3.0          | 3.6 ± 2.6                | 0.315   |
| CHA2DS2-VASc score                  | 2.9 ± 0.9          | 2.6 ± 1.1                | 0.174   |
| HAS-BLED score                      | 2.8 ± 1.0          | 2.7 ± 1.2                | 0.635   |
| Atrial fibrillation                 | 34 (81.0)          | 70 (60.9)                | 0.018   |
| Mechanical valve                    | 5 (11.9)           | 16 (13.9)                | 0.743   |
| Biological valve                    | 2 (4.8)            | 5 (4.4)                  | 1.000   |
| **Baseline laboratory data**        |                    |                          |         |
| Hemoglobin, g/dl                    | 10.9 ± 2.9         | 10.1 ± 5.1               | 0.030   |
| Platelets, 10⁴/μl                   | 18.4 ± 6.8         | 35.5 ± 173.7             | 0.827   |
| PT-INR                              | 1.3 ± 0.3          | 2.2 ± 1.3                | <0.001  |
| PT-INR > 2.5                        | 3 (7.1)            | 33 (28.7)                | 0.005   |
| Albumin, mg/dl                      | 3.5 ± 0.6          | 3.4 ± 2.8                | 0.003   |
| BUN, mg/dl                          | 30.2 ± 27.1        | 36.7 ± 21.8              | 0.001   |
| Creatinine, mg/dl                   | 1.0 ± 0.4          | 1.4 ± 1.4                | 0.400   |
| **Medications**                     |                    |                          |         |
| NSAIDs                              | 6 (14.3)           | 19 (16.5)                | 0.735   |
| Low-dose aspirin                    | 8 (19.1)           | 41 (35.7)                | 0.047   |
| Thienopyridine                      | 2 (4.7)            | 7 (6.1)                  | 1.000   |
| Other antiplatelets§                | 1 (2.4)            | 9 (7.8)                  | 0.291   |
| Proton-pump inhibitors              | 23 (54.8)          | 55 (47.8)                | 0.442   |
| **Clinical outcome**                | DOAC users (n = 42) | Warfarin users (n = 115) | P value |
| Early endoscopy                     | 31 (73.8)          | 77 (67)                  | 0.412   |
| Bleeding sources, lower GI tract    | 29 (69.1)          | 56 (48.7)                | 0.023   |
| **Upper source**                    |                    |                          |         |
| Peptic ulcer disease*               | 9 (21.4)           | 38 (33.0)                | 0.160   |
| Mallory-Weiss syndrome              | 2 (4.8)            | 5 (4.4)                  | 1.000   |
| Post-endoscopic therapy             | 0                  | 7 (6.1)                  | 0.191   |
| Esophageal ulcer                    | 3 (2.6)            | 1 (0.9)                  | 1.000   |
| Angioectasia                        | 0                  | 2 (1.7)                  | 1.000   |
| Varices (esophagus or stomach)      | 0                  | 0                        | NA      |
| Other diagnosis**                   | 2 (4.8)            | 3 (2.6)                  | 0.610   |
| **Lower source**                    |                    |                          |         |
| Colonic diverticular bleeding       | 8 (19.1)           | 18 (15.7)                | 0.612   |

(Continued)
between anticoagulant users and non-anticoagulant users matched for age, sex, and important risk factors as controls. Second, only patient background factors were associated with rebleeding, whereas only anticoagulant management factors (e.g. INR correction, reversal agent use, and drug interruption) were associated with thromboembolism. Only one rebleeding event and no thromboembolic events occurred in patients without reversal agent use, heparin

Table 6. (Continued)

| Diagnosis                          | Group A | Group B | P-value |
|------------------------------------|---------|---------|---------|
| Ischemic colitis                   | 2 (4.8) | 8 (7.0) | 1.000   |
| Other colitis                      | 0       | 2 (1.7) | 1.000   |
| Colorectal cancer                  | 0       | 5 (4.4) | 0.325   |
| Radiation proctitis                | 0       | 0       | NA      |
| Angioectasia                       | 3 (7.1) | 4 (3.5) | 0.385   |
| Rectal ulcer                       | 1 (2.4) | 6 (5.2) | 0.676   |
| Inflammatory bowel disease         | 0       | 1 (0.9) | 1.000   |
| Post-endoscopic therapy            | 8 (19.1)| 5 (4.4) | 0.006   |
| Hemorrhoids                        | 2 (4.8) | 2 (1.7) | 0.290   |
| Middle GIB                         | 5 (11.9)| 3 (2.6) | 0.032   |
| Other diagnosis***                 | 0       | 2 (1.7) | 1.000   |
| Unknown****                        | 0       | 1 (0.9) | 1.000   |

Endoscopic therapy need

| Procedure                          | Group A | Group B | P-value |
|------------------------------------|---------|---------|---------|
| Clipping                           | 14 (33.3)| 41 (35.7)| 0.787 |
| Band ligation                      | 4 (9.5)  | 1 (0.9) | 0.018  |
| Epinephrin injection therapy       | 0       | 2 (6.1) | 0.565  |
| Hemostatic forceps                 | 0       | 3 (2.6) | 0.565  |
| Argon plasma coagulation           | 0       | 6 (5.2) | 0.193  |
| Combined therapy                   | 0       | 6 (5.2) | 0.193  |
| Interventional radiology need      | 0       | 0       | NA     |
| Surgery need                       | 0       | 1 (0.9) | 1.000  |
| Transfusion need                   | 17 (40.5)| 66 (57.4)| 0.072 |
| Units of transfusion needed        | 2.2 ± 3.1| 4.3 ± 5.9| 0.046 |

Rebleeding

| Diagnosis                          | Group A | Group B | P-value |
|------------------------------------|---------|---------|---------|
| Ischemic colitis                   | 2 (4.8) | 8 (7.0) | 1.000   |
| Other colitis                      | 0       | 2 (1.7) | 1.000   |
| Colorectal cancer                  | 0       | 5 (4.4) | 0.325   |
| Radiation proctitis                | 0       | 0       | NA      |
| Angioectasia                       | 3 (7.1) | 4 (3.5) | 0.385   |
| Rectal ulcer                       | 1 (2.4) | 6 (5.2) | 0.676   |
| Inflammatory bowel disease         | 0       | 1 (0.9) | 1.000   |
| Post-endoscopic therapy            | 8 (19.1)| 5 (4.4) | 0.006   |
| Hemorrhoids                        | 2 (4.8) | 2 (1.7) | 0.290   |
| Middle GIB                         | 5 (11.9)| 3 (2.6) | 0.032   |
| Other diagnosis***                 | 0       | 2 (1.7) | 1.000   |
| Unknown****                        | 0       | 1 (0.9) | 1.000   |

Values in parentheses are percentages. Values presented with a plus/minus sign are means ± SD. Bold values indicate statistical significance at P < 0.05.

1Metabolic syndrome was a clustering of at least two of the four following medical conditions: abdominal (central) obesity, hypertension, diabetes mellitus, and dyslipidemia.

2History of thromboembolism was defined as the presence of acute coronary syndrome, stroke, transient ischemic attack, pulmonary embolism, deep vein thrombosis, or arterial thromboembolism.

3Other antplatelets were cilostazol, dipyridamole, sarpogrelate hydrochloride, ethyl icosapentate, dilazep, limaprost, and beraprost.

*Peptic ulcer disease (n = 103) included gastric ulcer (n = 79) and duodenal ulcer (n = 26), and 2 patients had both gastric and duodenal ulcer. Five of the patients with gastric ulcer disease were subsequently identified as having gastric cancer based on histopathology.

**Other diagnosis of upper GIB included pancreatic cancer gastrointestinal invasion (n = 3), aneurysmal rupture to the stomach (n = 1), submucosal tumor of the stomach (n = 2), and bleeding from gastric polyp (n = 3).

***Other diagnosis of lower GIB bleeding was bleeding from colonic polyp (n = 2).

****Unknown source of bleeding (n = 2) was defined as a lesion where upper endoscopy and colonoscopy and/or capsule endoscopy or double-balloon endoscopy did not reveal the bleeding source.

Abbreviations: BMI, body mass index; PT-INR, prothrombin time-international normalized ratio; CHA2DS2-VASc, Congestive heart failure, Hypertension, Age > 75, Diabetes mellitus, Stroke, Vascular disease, Sex female; DOAC, direct oral anticoagulant; HAS-BLED, hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratios (INR), elderly, drugs/alcohol concomitantly; BUN, blood urea nitrogen; NSAIDs, non-steroidal anti-inflammatory drugs.

https://doi.org/10.1371/journal.pone.0183423.t006
Table 7. Baseline characteristics and outcomes of anticoagulant users compared between upper and lower GI bleeding (n = 157).

| Characteristic                  | Upper GIB (n = 72) | Lower GIB (n = 85) | P value |
|--------------------------------|--------------------|--------------------|---------|
| Age, years                     | 47 (65.3)          | 71 (83.5)          | 0.008   |
| Age > 70, years                | 73.9±11.2          | 77.2±9.8           | 0.046   |
| Male                           | 48 (56.5)          | 48 (66.7)          | 0.192   |
| BMI ≥ 25, kg/m²                | 21 (24.7)          | 20 (27.8)          | 0.662   |
| Inpatient onset                | 19 (22.4)          | 25 (34.7)          | 0.086   |
| **Signs or symptoms**          |                    |                    |         |
| Shock                          | 20 (27.8)          | 12 (14.1)          | 0.034   |
| Hematemesis                    | 23 (31.9)          | 2 (2.4)            | <0.001  |
| Tarry stool                    | 54 (75.0)          | 14 (16.5)          | <0.001  |
| Hematochezia                   | 8 (11.1)           | 76 (89.4)          | <0.001  |
| **Comorbidities or past history** |                 |                    |         |
| Metabolic syndrome             | 54 (75.0)          | 68 (80.0)          | 0.453   |
| History of thromboembolism     | 33 (45.8)          | 42 (49.4)          | 0.655   |
| History of GI bleeding         | 13 (18.1)          | 21 (24.7)          | 0.313   |
| Charlson comorbidity index     | 55 (76.4)          | 59 (69.4)          | 0.329   |
| CHA2DS2-VASc score             | 62 (86.1)          | 78 (91.8)          | 0.256   |
| HAS-BLED score                 | 39 (54.2)          | 49 (57.7)          | 0.662   |
| Atrial fibrillation            | 47 (65.3)          | 57 (67.1)          | 0.814   |
| Mechanical valve               | 8 (11.1)           | 13 (15.3)          | 0.443   |
| Biological valve               | 3 (4.2)            | 4 (4.7)            | 1.000   |
| **Baseline laboratory data**   |                    |                    |         |
| Hemoglobin, g/dl               | 8.8±2.9            | 11.5±5.4           | <0.001  |
| Platelets, 10^9/μl             | 20.0±9.0           | 40.1±202.1         | 0.224   |
| PT-INR                         | 2.1±1.3            | 1.9±1.1            | 0.140   |
| PT-INR > 2.5                   | 21 (29.2)          | 15 (17.7)          | 0.087   |
| Albumin, mg/dl                 | 3.1±0.6            | 3.8±3.2            | <0.001  |
| BUN, mg/dl                     | 44.9±25.1          | 26.6±18.1          | <0.001  |
| Creatinine, mg/dl              | 1.4±1.5            | 1.2±1.0            | 0.948   |
| **Medications**                |                    |                    |         |
| NSAIDs                         | 14 (19.4)          | 11 (12.9)          | 0.267   |
| LDA                            | 27 (37.5)          | 22 (25.9)          | 0.117   |
| Thienopyridine                 | 3 (4.2)            | 6 (7.1)            | 0.509   |
| Other antiplatelets            | 4 (5.6)            | 6 (7.1)            | 0.755   |
| PPIs                           | 32 (44.4)          | 46 (54.1)          | 0.227   |

**Clinical outcomes**

|                      | Upper GIB (n = 72) | Lower GIB (n = 85) | P value |
|----------------------|--------------------|--------------------|---------|
| Early endoscopy      | 60 (83.3)          | 48 (56.5)          | <0.001  |
| **Endoscopic therapy need** |            |                    |         |
| Clipping             | 37 (51.4)          | 27 (31.8)          | 0.013   |
| Band ligation        | 34 (47.2)          | 21 (24.7)          | 0.003   |
| Epinephrin injection therapy | 3 (4.2)    | 0                  | 0.094   |
| Hemostatic forceps   | 1 (1.4)            | 2 (2.4)            | 1.000   |
| Argon plasma coagulation | 2 (2.8)    | 4 (4.7)            | 0.688   |
| Combined therapy     | 4 (5.6)            | 2 (2.4)            | 0.414   |
| Interventional radiology need | 0              | 0                  | NA      |
| Surgery need         | 0                  | 1 (1.2)            | 1.000   |
| Transfusion need     | 51 (70.8)          | 32 (37.7)          | <0.001  |

(Continued)
bridge, or anticoagulant interruption. Third, some endoscopic results and clinical outcomes differed between DOAC and warfarin users or between those with upper and lower GIB.

In agreement with our findings, Choudari et al\[5\] found no significant differences in endoscopy therapy need or rebleeding between anticoagulant users and non-anticoagulated users. Konstanticos et al\[6\] reported differences in transfusion need and mortality between anticoagulant users and non-matched controls with upper GIB. Our study also showed a similar rate of early endoscopy, detailed etiology of GIB, and endoscopy-related adverse events (0%) between the two groups, suggesting that early endoscopy can be safe for anticoagulated as well as non-anticoagulated GI bleeders.

The ASGE guideline recommends that INR $< 2.5$ is reasonable to perform endoscopic therapy\[2\]; however, the evidence for this is not well established. We found here that any INR category level—including INR $\geq 2.5$—and a continuous INR value were not significant risk factors for rebleeding. Wolf et al\[8\] showed that neither a continuous INR value nor INR category was a predictor of rebleeding. Rubin et al\[25\] found that the rebleeding rate in patients with supratherapeutic INR ($\geq 4.0$) were not significantly different from those with INR 2.0–3.9. Taken together with our results, endoscopy in acute GIB would appear to be effective even in patients with elevated INR before the procedure. However, we found that INR $\geq 2.5$ at onset was a significant predictor of thromboembolism. We believe this means that rapid correction of INR during the peri-endoscopic period in patients with INR $\geq 2.5$ at onset confers increased risk. Because the ASGE guideline recommends performing endoscopic therapy in GI bleeding patients with INR $< 2.5$\[2\], many physicians quickly reduce the INR level in the peri-endoscopic period, especially in patients with INR $\geq 2.5$ at onset. We also speculate that it takes several days for the INR to reach therapeutic anticoagulation\[26\], during which time a hypercoagulable state may occur due to the procedure itself or drug interruption\[27\], leading to thromboembolism risk.

No data are available on the role of heparin bridge in acute GIB, and endoscopic guidelines do not mention this topic\[2,3\]. In our study, heparin bridge did not significantly increase or decrease the risk of rebleeding, or thromboembolism. In a recent randomized controlled trial, the heparin bridge group experienced more major bleeding than the non-bridged group, with no difference in thromboembolism in the peri procedural period\[28\]. Therefore, heparin bridge might be ineffective in the acute GIB setting. We also had only one rebleeding event and no thromboembolic events in patients who had no reversal agent use, heparin bridge, or

### Table 7. (Continued)

|                          | Rebleeding | Thromboembolism |
|--------------------------|------------|-----------------|
|                          | 9 (12.5)   | 6 (8.3)         |
|                          | 12 (14.1)  | 3 (3.5)         |

Values in parentheses are percentages. Values presented with a plus/minus sign are means ± SD. Bold values mean statistical significance at $P < 0.05$.\footnote{Shock was defined as decrease in systolic blood pressure to $< 90$ mmHg, paleness, cold sweats, dizziness, syncope, or unconsciousness.}

\footnote{Metabolic syndrome was a clustering of $\geq 2$ of the 4 following medical conditions: abdominal (central) obesity, hypertension, diabetes mellitus, and dyslipidemia.}

\footnote{History of thromboembolism was defined as the presence of acute coronary syndrome, stroke, transient ischemic attack, pulmonary embolism, deep vein thrombosis, or arterial thromboembolism.}

\footnote{Other antiplatelets were cilostazol, dipyridamole, sarpogrelate hydrochloride, ethylicosapentate, dilazep, limaprost, and beraprost.}

Abbreviations: BMI, body mass index; PT-INR, prothrombin time-international normalized ratio; CHA2DS2-VASc, Congestive heart failure, Hypertension, Age $\geq 75$, Diabetes mellitus, Stroke, Vascular disease, Sex female; HAS-BLED, Hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratios [INR], elderly, drugs/alcohol concomitantly; BUN, blood urea nitrogen; NSAIDs, non-steroidal anti-inflammatory drugs; LDA, low-dose aspirin; PPIs, Proton-pump inhibitors.

https://doi.org/10.1371/journal.pone.0183423.t007
anticoagulant interruption. To summarize these points and the results of safe endoscopy in anticoagulant users, early endoscopy without INR correction, reversal agent use, heparin bridge, or anticoagulant interruption may be warranted for acute GI bleeders.

In our sub-analysis, DOAC users had a significantly higher rate of lower GIB and fewer received transfusions than warfarin users, and no significant differences were found between the groups in the rate of endoscopic therapy need, rebleeding, or thromboembolism. With respect to GIB outcomes, only one study (involving 13 dabigatran users and 26 warfarin users) has reported that dabigatran users had a lower rate of hypotension at baseline and a lower rate of transfusion need[13], similar to our findings. The reason for this remains to be elucidated, but warfarin users had a lower hemoglobin level and higher INR level at baseline, which affect blood loss, and this resulted in transfusion requirement.

Our study showed outcomes differences in anticoagulated patients between those with upper and lower GIB. Although 44% of patients used PPIs before the onset of upper GIB and all patients were administered them during their hospital stay, upper GI bleeders were associated with a higher rate of transfusion need and endoscopy therapy need than were lower GI bleeders. This finding suggests that anticoagulated GI bleeders may need to be managed differently, with upper GI bleeders handled more cautiously. Yamaguchi et al[29] showed that patients taking antithrombotics exhibited more severe clinical signs in upper GIB, which supports our findings.

One of the strengths of our study was the analysis of detailed clinical and endoscopic data that was collected from 314 GI bleeders. Another was that we identified a difference in the endoscopic results and clinical outcomes of the subgroup analyses of DOAC and warfarin users and of upper and lower GI bleeders. We also recognize several limitations. First, the 90-day outcome rate in anticoagulant users was 13.4% for rebleeding and 5.7% for thromboembolism in our study—similar to that of a Western study of 14%, and 4%, respectively[9]—but obtained with a relatively small number of subjects in this study. Second, INR correction, reversal agent use, and heparin bridging were at the discretion of the treating physicians, so further randomized controlled trials are needed to examine the role of these practices in managing acute GIB. Third, this was a single-center retrospective cohort investigation, and a prospective multicenter study is needed to generalize the results of this study.

In conclusion, endoscopy appears to be safe for anticoagulant users with acute GIB compared with non-users. Patient background factors were associated with rebleeding, whereas anticoagulant management factors (e.g. INR correction, reversal agent use, and drug interruption) were associated with thromboembolism. Early intervention without reversal agent use, heparin bridge, or anticoagulant interruption may be warranted for acute GIB.

Acknowledgments

We wish to thank Ms. Kuniko Miki, Ms. Eiko Izawa, Ms. Kenko Yosida, Ms. Akiko Shimizu, Ms. Chie Watanabe, and Ms. Haisa Kawashiro for assistance with data collection. None received financial compensation.

Author Contributions

Conceptualization: Takuro Shimbo.

Data curation: Naoyoshi Nagata, Toshiyuki Sakurai, Shiori Moriyasu, Takuro Shimbo, Hidetaka Okubo, Kazuhiro Watanabe, Chizu Yokoi.

Formal analysis: Takuro Shimbo.
Funding acquisition: Naoyoshi Nagata.
Methodology: Naoyoshi Nagata, Toshiyuki Sakurai, Takuro Shimbo, Kazuhiro Watanabe.
Resources: Naoyoshi Nagata.
Supervision: Takuro Shimbo, Mikio Yanase, Junichi Akiyama, Naomi Uemura.
Writing – original draft: Naoyoshi Nagata.
Writing – review & editing: Naoyoshi Nagata, Naomi Uemura.

References
1. Yamaguchi D, Sakata Y, Tsuruoka N, Shimoda R, Higuchi T, Sakata H, et al. Upper Gastrointestinal Bleeding in Japanese Patients Prescribed Antithrombotic Drugs: Differences in Trends over Time. Hepatogastroenterology. 2014; 61: 1055–1062. PMID: 26158165
2. ASGE Standards of Practice Committee, Acosta RD, Abraham NS, Chandrasekhara V, Chathadi KV, Early DS, et al. The management of antithrombotic agents for patients undergoing GI endoscopy. Gastrointest Endosc. 2016; 83: 3–16. https://doi.org/10.1016/j.gie.2015.09.035 PMID: 26621548
3. Veitch AM, Vanbiervliet G, Gershlick AH, Boustiere C, Baglin TP, Smith LA, et al. Endoscopy in patients on antithrombotic therapy, including direct oral anticoagulants: British Society of Gastroenterology (BSG) and European Society of Gastrointestinal Endoscopy (ESGE) guidelines. Gut. 2016; 65: 374–389. https://doi.org/10.1136/gutjnl-2015-311110 PMID: 26673868
4. Fujishiro M, Iguchi M, Kakushima N, Kato M, Sakata Y, Hoteya S, et al. Guidelines for endoscopic management of non-variceal upper gastrointestinal bleeding. Dig Endosc. 2016; 28: 363–378. https://doi.org/10.1111/den.12639 PMID: 28980005
5. Choudhari CP, Rajgopal C, Palmer KR. Acute gastrointestinal haemorrhage in anticoagulated patients: diagnoses and response to endoscopic treatment. Gut. 1994; 35: 464–466. PMID: 8174982
6. Thomopoulos KC, Mimidis KP, Theocharis GJ, Gatopoulou AG, Kartalis GN, Nikolopoulou VN. Acute upper gastrointestinal bleeding in patients on long-term oral anticoagulation therapy: endoscopic findings, clinical management and outcome. World J Gastroenterol. 2005; 11: 1365–1368. https://doi.org/10.3748/wjg.v11.i10.1365 PMID: 15761977
7. Radaelli F, Dentali F, Repici A, Amato A, Paggi S, Rondonotti E, et al. Management of anticoagulation in patients with acute gastrointestinal bleeding. Dig Liver Dis. 2015; 47: 621–627. https://doi.org/10.1016/j.dld.2015.03.029 PMID: 25935464
8. Wolf AT, Wasan SK, Saltzman JR. Impact of anticoagulation on rebleeding following endoscopic therapy for nonvariceal upper gastrointestinal hemorrhage. Am J Gastroenterol. 2007; 102: 290–296.
9. Sengupta N, Feuerstein JD, Patwardhan VR, Tapper EB, Keturwar GA, Thaker AM, et al. The risks of thromboembolism vs. recurrent gastrointestinal bleeding after interruption of systemic anticoagulation in hospitalized inpatients with gastrointestinal bleeding: a prospective study. Am J Gastroenterol. 2015; 110: 328–335. https://doi.org/10.1038/ajg.2014.398 PMID: 25512338
10. Fujimoto K, Fujishiro M, Kato M, Higuchi K, Iwakiri R, Sakamoto C, et al. Guidelines for gastroenterological endoscopy in patients undergoing antithrombotic treatment. Dig Endosc. 2014; 26: 1–14.
11. Connerota AJ, Ramacciotto E. A Comprehensive Overview of Direct Oral Anticoagulants for the Management of Venous Thromboembolism. Am J Med Sci. 2016; 352: 92–106. https://doi.org/10.1016/j.amjms.2016.03.018 PMID: 27432042
12. Hernandez I, Baik SH, Pinera A, Zhang Y. Risk of bleeding with dabigatran in atrial fibrillation. JAMA Intern Med. 2015; 175: 18–24.
13. Holster IL, Valkhoff VE, Kuipers EJ, Tijwa ET. New oral anticoagulants increase risk for gastrointestinal bleeding: a systematic review and meta-analysis. Gastroenterology. 2013; 145: 105–112.e15. https://doi.org/10.1053/j.gastro.2013.02.041 PMID: 23476018
14. Manatsathit W, Al-Hamid H, Leelasinnaroen P, Hashmi U, McCullough PA. Management of gastrointestinal bleeding in patients anticoagulated with dabigatran compared with warfarin: a retrospective, comparative case review. Cardiovasc Diagn Ther. 2014; 4: 224–231. https://doi.org/10.3978/j.issn.2223-3652.2014.03.07 PMID: 25009791
15. Nagata N, Sakurai T, Shimbo T, Moriyasu S, Okubo H, Watanabe K, et al. Acute Severe Gastrointestinal Tract Bleeding is Associated with an Increased Risk of Thromboembolism and Death. Clin Gastroenterol Hepatol. 2017 Jun 17. https://doi.org/10.1016/j.cgh.2017.06.028 PMID: 28634133
16. Nagata N, Nikura R, Sekine K, Sakurai T, Shimbo T, Kishida Y, et al. Risk of peptic ulcer bleeding associated with Helicobacter pylori infection, nonsteroidal anti-inflammatory drugs, low-dose aspirin, and
Antihypertensive drugs: a case-control study. J Gastroenterol Hepatol. 2015; 30: 292–298. https://doi.org/10.1111/j.1440-1746.2010.06610.x PMID: 21198829

17. Nagata N, Niikura R, Aoki T, Shimbo T, Kishida Y, Sekine K, et al. Lower GI bleeding risk of nonsteroidal anti-inflammatory drugs and antiplatelet drug use alone and the effect of combined therapy. Gastrointest Endosc. 2014; 80: 1124–31. https://doi.org/10.1016/j.gie.2014.06.039 PMID: 25088922

18. Tsuruoka N, Iwakiri R, Hara M, Shihara N, Sakata Y, Miyahara K, et al. NSAIDs are a significant risk factor for colonic diverticular hemorrhage in elderly patients: evaluation by a case-control study. J Gastroenterol Hepatol. 2011; 26: 1047–1052. https://doi.org/10.1111/j.1440-1746.2010.06610.x PMID: 21198829

19. Aoki T, Nagata N, Shimbo T, Niikura R, Sakura T, Moriyasu S, et al. Development and Validation of a Risk Scoring System for Severe Acute Lower Gastrointestinal Bleeding. Clin Gastroenterol Hepatol. 2016; 14: 1562–1570. https://doi.org/10.1016/j.cgh.2016.05.042 PMID: 27311620

20. Nagata N, Niikura R, Sakurai T, Shimbo T, Aoki T, Moriyasu S, et al. Safety and Effectiveness of Early Colonoscopy in Management of Acute Lower Gastrointestinal Bleeding on the Basis of Propensity Score Matching Analysis. Clin Gastroenterol Hepatol. 2016; 14: 558–564. https://doi.org/10.1016/j.cgh.2015.10.011 PMID: 26492844

21. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987; 40: 373–383. PMID: 3558716

22. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. Chest, 2010; 137: 263–272. https://doi.org/10.1378/chest.10-1584 PMID: 19762550

23. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the EuroHeart Survey. Chest, 2010; 138: 1093–1100. https://doi.org/10.1378/chest.10-134 PMID: 20299623

24. Ono K, Hidaka H, Koyama Y, Ishii K, Taguchi S, Kosaka M, et al. Effects of heparin bridging anticoagulation on perioperative bleeding and thromboembolic risks in patients undergoing abdominal malignancy surgery. J Anesth. 2016; 30: 723–726. https://doi.org/10.1007/s00540-016-2187-0 PMID: 27206420

25. Rubin TA, Murdoch M, Nelson DB. Acute GI bleeding in the setting of supratherapeutic international normalized ratio in patients taking warfarin: endoscopic diagnosis, clinical management, and outcomes. Gastrointest Endosc. 2003; 58: 369–373. PMID: 14528210

26. Harrison L, Johnston M, Massicotte MP, Crowther M, Moffat K, Hirsh J. Comparison of 5-mg and 10-mg loading doses in initiation of warfarin therapy. Ann Intern Med. 1997; 126: 133–136. PMID: 9005747

27. Kearon C, Hirsh J. Management of anticoagulation before and after elective surgery. N Engl J Med. 1997; 336: 1506–1511. https://doi.org/10.1056/NEJM199705223362107 PMID: 9154771

28. Douketis JD, Spyropoulos AC, Kaatz S, Becker RC, Caprini JA, Dunn AS, et al. Perioperative Bridging Anticoagulation in Patients with Atrial Fibrillation. N Engl J Med. 2015; 373: 823–833. https://doi.org/10.1056/NEJMoa1501035 PMID: 26095867

29. Yamaguchi D, Sakata Y, Tsuruoka N, Shimoda R, Higuchi T, Sakata H, et al. Characteristics of patients with non-variceal upper gastrointestinal bleeding taking antithrombotic agents. Dig Endosc. 2015; 27: 30–36.