ABSTRACT

Objective To investigate the incidence of gastrointestinal bleeding (GIB) in patients with acute myocardial infarction (AMI), clarify the association between adverse clinical outcomes and GIB, and identify risk factors for in-hospital GIB after AMI.

Design Retrospective cohort study.

Setting 108 hospitals across three levels in China.

Participants From 1 January 2013 to 31 August 2014, after excluding 2639 patients because of incorrect age and missing GIB data, 23,794 patients with AMI from 108 hospitals enrolled in the China Acute Myocardial Infarction Registry were divided into GIB-positive (n=282) and GIB-negative (n=23,512) groups and were compared.

Primary and secondary outcome measures Major adverse cardiovascular and cerebrovascular events (MACCEs) are a composite of all-cause death, reinfarction and stroke. The association between GIB and endpoints was examined using multivariate logistic regression and Cox proportional hazards models. Independent risk factors associated with GIB were identified using multivariate logistic regression analysis.

Results The incidence of in-hospital GIB in patients with AMI was 1.19%. GIB was significantly associated with an increased risk of MACCEs both in-hospital (OR 2.314; p<0.001) and at 2-year follow-up (HR 1.407; p=0.0008). Glycoprotein IIb/IIIa (GPIIb/IIIa) receptor inhibitor, percutaneous coronary intervention (PCI) and thrombolyis were novel independent risk factors for GIB identified in the Chinese AMI population (p<0.05).

Conclusions GIB is associated with both in-hospital and follow-up MACCEs. Gastrointestinal prophylactic treatment should be administered to patients with AMI who receive primary PCI, thrombolytic therapy or GPIIb/IIIa receptor inhibitor.

Trial registration number NCT01874691.

Strengths and limitations of this study

► We carried out a comprehensive study that identified independent risk factors for gastrointestinal bleeding after acute myocardial infarction using nationwide registry data.
► High-quality and complete data were used to examine the association between gastrointestinal bleeding and adverse outcomes and mortality.
► The large sample, broad representation and involvement of both the principal investigator, and clinical and research experts are the main strengths of this study.
► The relatively lower gastrointestinal bleeding rates in our study limit the division of the data into training (80%) and validation (20%) sets, increasing the risk of overfitting in our models.
► Despite some limitations making our findings less convincing, our study allows evaluation of the importance of demographic and geographical variations.

INTRODUCTION

Gastrointestinal bleeding (GIB) is a common cause of haemorrhage in patients with acute myocardial infarction (AMI). The current
the incidence, outcomes and predictors of GIB occurring during hospitalisation.

METHODS

The CAMI Registry has a broad representation of all provinces and different-level hospitals, allowing for the exploration of GIB in patients with AMI across diverse geographic regions and economic circumstances. This study was registered with ClinicalTrials.gov.

We collected, validated and submitted standardised data through a secure, password-protected, web-based electronic data capture system (http://www.CAMIRegistry.org) by the local investigators at each participating site. Data included patient demographics, clinical presentation, medical history, risk factors, triggering factors, physical examination findings, laboratory and imaging results, transfer facility therapies, reperfusion strategies, medications, clinical events and cost. All the information was collected using a standardised set of variables and standard definitions (element dictionary), systematic data entry and transmission procedures, and rigorous data quality control. CDISC (the Clinical Data Interchange Standards Consortium), ICD-10 (International classification of diseases), MedDra, and WHO-DD (World Health Organization-drug dictionary) codes were used to standardise the variables.

Trained research participants called the patients at 30 days, and 6, 12, 18 and 24 months and asked the patient about their lifestyle, medications and reasons for discontinuation, and clinical events (including death, cardiovascular events and bleeding), which were validated using source documents.

Other detailed descriptions about data management and quality control are found in the published methodological article of the CAMI Registry.

Overall, patients with AMI from 108 hospitals were enrolled in the CAMI Registry from 1 January 2013 to 31 August 2014. A total of 2659 patients with incorrectly recorded age or missing GIB data were excluded (figure 1). GIB was defined as clinically evident GIB (gross haematemesis, haeme-positive coffee ground emesis and haeme-positive melena) accompanied by a decrease in haemoglobin level of ≥1g/dL. Significant GIB was defined as clinically evident bleeding with a decrease in haemoglobin level of ≥3g/dL, without an identifiable extraintestinal source. Major adverse cardiovascular and cerebrovascular events (MACCEs) are a composite of all-cause death, reinfarction and stroke. Bleeding Academic Research Consortium types 3 or 5 were defined according to a consensus report.

The study population was separated into GIB-positive and GIB-negative groups, and continuous variables were presented as either means with SD or medians with IQRs, and categorical variables were presented as percentages. Differences in baseline characteristics were assessed using the χ² test or Fisher’s exact test for categorical variables and analysis of variance or Wilcoxon rank test for continuous variables. Multivariate logistic regression analyses were conducted to evaluate independent risk factors for GIB. The association between GIB and clinical endpoints was examined using multivariate logistic regression analysis and Cox proportional hazards models. Clinical characteristics that significantly differed between the two groups, including age, clinical presentation and medicine therapy, were identified and included in the final adjusted model (detailed variables are presented further the relevant tables).

ORs and HRs were presented with 95% CIs. All statistical analyses were performed using SAS V.9.4, and a two-tailed p value of <0.05 was considered statistically significant.

Patient and public involvement

We did not involve patients or the public directly in the design, conduct, reporting or dissemination plans of our research.

RESULTS

GIB after AMI in China

The most frequent bleeding site in our study was gastrointestinal (n=282, 80.6%) (online supplemental table). Patients’ baseline characteristics and clinical presentations are shown in table 1. Among the 23 794 patients with AMI included in the final analysis, the mean age was 62 years, 25% were females and 55% came from prefecture-level hospitals. Patients with GIB were more likely to be female, older, with a lower systolic pressure and haemoglobin but higher Killip class at admission, and had a history of hypertension, dyslipidaemia, congestive heart failure, peptic ulcer, prior bleeding and malignancy. They were often treated with thrombolytic therapy and glycoprotein IIb/IIIa (GPIIb/IIIa) receptor inhibitors during hospitalisation.

Our study reported an overall incidence of in-hospital GIB and SGB (severe gastrointestinal bleeding) in
Table 1  Baseline clinical data in patients with and without GIB

| Variables                        | Total (n=23794) | GIB (n=282) | No GIB (n=23512) | P value |
|----------------------------------|----------------|------------|------------------|---------|
| **Demographics**                 |                |            |                  |         |
| Age                              | 62.34±13.31    | 67.53±12.39| 62.28±13.46      | 0.0000  |
| Female, n (%)                    | 6020 (25.3)    | 86 (30.5)  | 5934 (25.2)      | 0.0000  |
| Hospital level, n (%)            |                |            |                  | 0.0000  |
| Province-level hospital          | 7569 (31.8)    | 71 (25.2)  | 7498 (31.9)      |         |
| Prefecture-level hospital        | 13075 (55.0)   | 162 (57.4) | 12913 (54.9)     |         |
| County-level hospital            | 3150 (13.2)    | 49 (17.4)  | 3101 (13.2)      |         |
| **Medical history, n (%)**       |                |            |                  |         |
| Hypertension                     | 11959 (50.3)   | 161 (57.1) | 11798 (50.3)     | 0.0225  |
| Dyslipidaemia                    | 1598 (6.7)     | 29 (10.3)  | 1569 (6.7)       | 0.0254  |
| Diabetes mellitus                | 4548 (19.1)    | 56 (19.9)  | 4492 (19.2)      | 0.7473  |
| Myocardial infarction            | 1693 (7.1)     | 25 (8.9)   | 1668 (7.1)       | 0.2739  |
| PCI                              | 1110 (4.7)     | 18 (6.4)   | 1092 (4.7)       | 0.1979  |
| CABG                             | 95 (0.4)       | 3 (1.1)    | 92 (0.4)         | 0.1035  |
| Congestive heart failure         | 560 (2.4)      | 24 (8.5)   | 536 (2.3)        | 0.0000  |
| Stroke                           | 2169 (9.1)     | 39 (13.8)  | 2130 (9.1)       | 0.0101  |
| Peripheral arterial disease      | 140 (0.6)      | 4 (1.4)    | 136 (0.6)        | 0.0856  |
| Chronic kidney disease           | 299 (1.3)      | 12 (4.3)   | 287 (1.2)        | 0.0003  |
| PUD/Helicobacter pylori          | 676 (2.8)      | 29 (10.3)  | 647 (2.8)        | 0.0000  |
| GIB                              | 417 (1.8)      | 27 (9.6)   | 390 (1.7)        | 0.0000  |
| Malignancy                       | 298 (1.3)      | 11 (3.9)   | 287 (1.2)        | 0.0010  |
| **Admission features, n (%)**    |                |            |                  |         |
| Diagnosis                        |                |            |                  | 0.9716  |
| NSTEMI                           | 5928 (24.9)    | 70 (24.8)  | 5858 (24.9)      |         |
| STEMI                            | 17866 (75.1)   | 212 (75.2) | 17654 (75.1)     |         |
| Heart rate (beats/min)           | 78.05±18.94    | 78.69±20.90| 78.05±18.81      | 0.6087  |
| Systolic BP (mm Hg)              | 128.95±25.82   | 121.92±27.27| 129.04±25.69     | 0.0000  |
| Killip class IV                  | 980 (4.1)      | 36 (12.8)  | 944 (4.0)        | 0.0000  |
| Ccr (ml/(min·1.73 m²))           | 92.23±607.28   | 84.60±161.04| 92.32±610.15     | 0.5639  |
| Hb (g/L)                         | 135.90±21.69   | 124.34±28.66| 136.03±21.41     | 0.0000  |
| Hct (%) (Q1;Q3)                  | 36.68;44.10    | 31.50;43.30| 36.70;44.10      | 0.4466  |
| LVEF (%)                         | 53.46±11.09    | 51.91±12.45| 53.48±10.93      | 0.0734  |
| CRUSADE score                    | 20.05±15.47    | 28.70±18.21| 19.95±15.24      | 0.0000  |
| **Prehospital medications, n (%)** |            |            |                  |         |
| Aspirin                          | 2611 (11.0)    | 38 (13.5)  | 2573 (11.0)      | 0.1954  |
| P2Y12 receptor inhibitor         | 871 (3.7)      | 11 (3.9)   | 860 (3.7)        | 0.8342  |
| Oral anticoagulants              | 78 (0.3)       | 1 (0.4)    | 77 (0.3)         | 0.6072  |
| Statin                           | 2119 (8.9)     | 33 (11.9)  | 2086 (9.0)       | 0.1137  |
| β-blockers                       | 1376 (5.8)     | 21 (7.5)   | 1355 (5.8)       | 0.2582  |
| ACEI/ARB                         | 1572 (6.6)     | 28 (10.1)  | 1544 (6.6)       | 0.0304  |
| **In-hospital medications, n (%)** |            |            |                  |         |
| Aspirin                          | 22970 (96.5)   | 236 (83.7) | 22734 (96.8)     | 0.0000  |
| P2Y12 receptor inhibitor         | 22933 (96.4)   | 248 (87.9) | 22685 (97.0)     | 0.0000  |
| GPIIb/IIa receptor inhibitor     | 7103 (29.9)    | 101 (36.5) | 7002 (30.8)      | 0.0451  |
| Oral anticoagulants              | 382 (1.6)      | 4 (1.4)    | 378 (1.6)        | 1.0000  |
| Heparin/LMWH                     | 21097 (88.7)   | 219 (78.8) | 20878 (90.6)     | 0.0000  |

Continued
patients with AMI of 1.19% and 0.32%, respectively. The incidence of GIB in provincial, prefecture and county hospitals was 0.94%, 1.24% and 1.50%, respectively. The proportion of haemoglobin decrease caused by GIB in hospitals at different levels is shown in figure 2.

Outcomes of patients with GIB

As shown in table 2, GIB was associated with an increased risk for MACCE (OR 2.314; 95% CI 1.801 to 3.418; p<0.0001) and individual endpoints during hospitalisation. At the 2-year follow-up (table 3 and online supplemental figure 1), GIB-positive patients still had a significantly higher risk for MACCE (adjusted HR 1.4107; 95% CI 1.124 to 1.761; p=0.0008) and death (adjusted HR 1.392; 95% CI 1.105 to 1.764; p=0.0071).

Independent risk factors for GIB

Independent risk factors for GIB after adjusting for covariates were identified (table 4). Significant risk factors in the entire study population included older age (>65 years) (online supplemental figure 2A) higher Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the ACC/AHA Guidelines (CRUSADE) score (online supplemental figure 2B), dyslipidaemia, prior congestive heart failure, peptic ulcer disease (PUD)/ Helicobacter pylori, or GIB, Killip VI class, glycoprotein IIb/IIIa (GPIIb/IIIa) receptor inhibitor, primary percutaneous coronary intervention (PCI) and thrombolytic therapy. In patients with SGIB, risk factors included male sex, higher CRUSADE score and prior GIB. In patients with GIB with a drop of haemoglobin ≥5 g/dL, risk factors included male sex and in-hospital aspirin.

DISCUSSION

In the CAMI Registry, GIB was the most frequent source of AMI-related bleeding in the entire population. Another large registry study involving 3.3 million PCI procedures

Table 1 Continued

| Variables | Total (n=23794) | GIB (n=282) | No GIB (n=23512) | p value |
|-----------|----------------|-------------|------------------|---------|
| Statin    | 21726 (91.3)   | 243 (92.0)  | 21483 (97.4)     | 0.0000  |
| β-blockers| 16719 (70.3)   | 176 (62.4)  | 16543 (70.5)     | 0.0039  |
| ACEI/ARB  | 14354 (60.3)   | 140 (49.6)  | 14214 (60.6)     | 0.0002  |
| Treatment, n (%) | | | | |
| Primary PCI| 8617 (36.2)   | 105 (46.7)  | 8512 (44.5)      | 0.5334  |
| Primary CABG| 38 (0.2)      | 0 (0.0)     | 38 (0.2)         | 1.0000  |
| Thrombolysis| 1759 (7.4)    | 32 (13.7)   | 1737 (8.7)       | 0.0121  |
| Hospitalisation (Q1;Q3) | | | | |
| LOS in ICU | 0.00;6.00  | 1.00;8.00   | 0.00;6.00         | 0.0000  |
| LOS in general wards | 2.00;10.00 | 1.00;14.00  | 2.00;10.00        | 0.5350  |
| Total cost | 10845;48831  | 11269;54128 | 10763;48799       | 0.1733  |

ACEI/ARB, ACE inhibitor/angiotensin receptor blocker; BP, blood pressure; CABG, coronary artery bypass grafting; Ccr, creatinine clearance rate; CRUSADE, Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the ACC/AHA Guidelines; GIB, gastrointestinal bleeding; GPIIb/IIIa, glycoprotein IIb/IIIa; Hb, haemoglobin; Hct, haematocrit; ICU, intensive care unit; LMWH, low molecular weight heparin; LSO, length of stay; LVEF, left ventricular ejection fraction; NSTEMI, non-STEMI; PCI, percutaneous coronary intervention; PUD, peptic ulcer disease; STEMI, ST-elevation myocardial infarction.

Figure 2 Proportion of haemoglobin drop caused by GIB in hospitals at different levels. GIB, gastrointestinal bleeding.
showed that entry-site bleeding was the first common cause of bleeding complications,\(^8\) because of a lower frequency of bleeding avoidance strategies, such as radial artery access and arterial closure devices. In China, transluminal intervention was adopted as a safety entry site for PCI, which may have reduced the entry-site bleeding rate.

Moreover, GIB occurred in 282 (1.19%) patients during hospitalisation, consistent with several studies ranging from 1.1% to 3.0%.\(^3\)\(^,\)\(^9\) It seems that the GIB incidence in our study is lower than that in the ACUITY (acute catheterization and urgent intervention triage strategy) trial (1.3%),\(^3\) which studied acute coronary syndrome (ACS) patients treated with a combination of aspirin, clopidogrel and enoxaparin (2.5%).\(^9\) The population in our study was AMI patients, while the population in the previously mentioned two studies were selected patients with intense antiplatelet or antithrombotic therapy that might have contributed to a higher GIB rate. In addition, a temporal trend study for GIB indicated that the incidence of PCI-associated GIB decreased within a decade, despite aggressive therapies for ACS.\(^3\) Expert consensus recommendations focusing on decreasing bleeding events were discussed in 2010\(^6\) and issued since 2011,\(^11\) which might exert a positive effect on gastrointestinal protection.

Physicians in China tend to follow the guidelines and prescribe proton-pump inhibitors against GIB, which may have alleviated the incidence in our study.

Previous studies have demonstrated an association between in-hospital GIB and adverse clinical outcomes.\(^3\)\(^,\)\(^12\) In our study, AMI patients with GIB had a risk of death and an increased risk of ischaemic events (reinfarction and stroke). In addition, those who suffered GIB in the hospital still had a higher risk of MACCE and all-cause death after 2 years. The mechanism behind the poor outcomes of patients with AMI experiencing GIB is multifactorial. These patients had worse baseline clinical characteristics, such as older age, higher prevalence of peptic ulcer and prior GIB, which are independent risk factors for GIB.\(^3\) In addition, one-fourth of patients had SGIB, which may cause bleeding-related haemodynamic instability and contribute to ischemia, resulting in reinfarction and stroke. Moreover, GIB is also a well-known signal for physicians to stop DAPT prescription (only 71.6% of GIB-positive patients quit DAPT), which may increase the risk for both in-hospital and out-of-hospital adverse clinical outcomes.\(^13\)

Consistent with previous reports, the occurrence of GIB in patients with AMI was strongly associated with older age and prior congestive heart failure, PUD/\textit{Helicobacter pylori} and GIB.\(^3\)\(^,\)\(^5\) Several studies had reported

### Table 2 Comparison of in-hospital outcomes between patients with GIB and without GIB

| Clinical endpoint | GIB (n=282) (%) | No GIB (n=23512) (%) | P value | Adjusted OR (95% CI) | P value |
|-------------------|-----------------|---------------------|---------|----------------------|---------|
| MACCE             | 26.2            | 7.1                 | <0.0001 | 2.314 (1.801 to 3.418) | <0.0001 |
| Death             | 22.0            | 6.3                 | <0.0001 | 2.194 (1.499 to 3.007) | <0.0001 |
| MI                | 3.9             | 0.5                 | <0.0001 | 3.983 (2.012 to 7.741) | <0.0001 |
| Stroke            | 5.7             | 0.7                 | <0.0001 | 5.063 (2.801 to 9.173) | <0.0001 |

Variables included in the model: age; hospital level; hypertension; diabetes mellitus; congestive heart failure; stroke; peripheral arterial disease; PUD/\textit{Helicobacter pylori}; GIB; malignancy; STEMI; systolic BP; Hb; Ccr; aspirin; P2Y12 receptor; GPIIb/IIIa receptor inhibitor; oral anticoagulants; heparin/LMWH; steroids; β-blockers; ACEI/ARB; primary PCI; emergent CABG; and thrombolysis therapy.

### Table 3 Thirty-day, 6-month and 2-year clinical outcomes of patients with and without GIB

| Clinical endpoints | 30 days | 6months | 2years |
|-------------------|---------|---------|--------|
|                   | Adjusted HR (95% CI) | P value | Adjusted HR (95% CI) | P value | Adjusted HR (95% CI) | P value |
| MACCE             | 1.383 (1.031 to 1.802) | 0.0187 | 1.355 (1.026 to 1.763) | 0.0102 | 1.407 (1.124 to 1.761) | 0.0008 |
| Death             | 1.377 (1.053 to 1.796) | 0.0294 | 1.395 (1.081 to 1.792) | 0.0008 | 1.392 (1.105 to 1.764) | 0.0071 |
| MI                | 3.931 (1.301 to 10.292) | 0.0218 | 1.809 (0.703 to 4.614) | 0.1836 | 1.981 (0.968 to 3.931) | 0.0511 |
| Stroke            | –       | –       | –       | 0.477 (0.058 to 3.447) | 0.4641 |
| BARC 3/5          | 9.739 (2.018 to 42.318) | 0.0009 | 4.211 (1.430 to 11.903) | 0.0076 | 2.365 (0.815 to 6.618) | 0.1022 |

Variables included in the model: age; hospital level; hypertension; diabetes mellitus; congestive heart failure; stroke; peripheral arterial disease; PUD/\textit{Helicobacter pylori}; GIB; malignancy; STEMI; systolic BP; Hb; Ccr; aspirin; P2Y12 receptor; GPIIb/IIIa receptor blocker; BP; blood pressure; CABG, coronary artery bypass grafting; Ccr, creatinine clearance rate; GIB, gastrointestinal bleeding; GPIIb/IIIa receptor blocker; BP; blood pressure; CABG, coronary artery bypass grafting; Ccr, creatinine clearance rate; GIB, gastrointestinal bleeding; LMWH, low molecular weight heparin; MACCE, major adverse cardiovascular and cerebrovascular events; MI, myocardial infarction; PCI, percutaneous coronary intervention; PUD, peptic ulcer disease; STEMI, ST-elevation myocardial infarction.
increasing age as an independent risk factor for GIB, and we identified that AMI patients aged >65 years had a high association with GIB risk (online supplemental figure 2), thus GI prophylaxis should be prescribed to them in a timely manner. The CRUSADE bleeding risk score is a quantitative tool used to stratify bleeding risk in patients with non-ST-elevation myocardial infarction (NSTEMI). A small population study demonstrated that the CRUSADE score was the most accurate quantitative tool for NSTEMI and ST-elevation myocardial infarction patients undergoing coronary arteriography among contemporary bleeding risk scores. However, the applicability of CRUSADE bleeding risk scores to predict GIB among patients with AMI remains uncertain. In our study, we found that patients with higher scores had a higher risk of GIB. Therefore, this tool could help physicians in risk stratification during clinical practice.

The latest myocardial revascularisation guidelines recommend GP IIb/IIIa antagonists for bail-out use if there is evidence of no-reflow or thrombotic complications. In our study, 7103 patients received GP IIb/IIIa antagonists during primary PCI and were identified as an independent risk factor for GIB (OR 1.671; 95% CI 1.238 to 2.255; p=0.0008). However, only 66.9% of patients treated with GP IIb/IIIa antagonists were prescribed with GI prophylactic medications. Moreover, patients who received thrombolysis as revascularisation had a higher risk of GIB (OR 3.206; 95% CI 2.095 to 4.907; p<0.0001), and a lower proportion (29.6%) received GI prophylaxis. It might be that GI prophylaxis use for patients treated with GP IIb/IIIa and thrombolysis was not recommended by the guidelines. To reduce the incidence of GIB, GI prophylaxis should be used before revascularisation, which had been verified useful in prospective, randomised studies.

Limitations
Our study has some limitations. First, although a large sample size could ensure a wide representation, the danger of overfitting in our models cannot be ignored. A small GIB population limited the division of data into training and validation sets. Second, the CAMI Registry is the first national study focusing on the management and therapy for AMI in China, and we noticed that the patients’ treatment compliance in the CAMI Registry was worse than that in registries from other developed countries; thus, this might limit the global clinical relevance of the study. We recommend further research to provide more evidence.

CONCLUSION
As shown in our research, GIB is the most common cause of bleeding in the Chinese AMI population and is associated with poor clinical prognosis. After multivariate analysis, we confirmed that the independent risk factors for GIB during hospitalisation, advanced age, heart failure (Killip IV), and history of GIB, PUD or Helicobacter pylori infection were common high-risk groups for GIB. Moreover, GPIIb/IIIa receptor inhibitor or thrombolysis therapy were also independent risk factors for GIB, which were less reported in previous studies. Clinicians should identify the high-risk groups of GIB among the AMI population early based on the clinical characteristics and prescribe gastrointestinal prophylaxis as soon as possible to improve clinical endpoints.

Author affiliations
1Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China
2Department of Cardiology, Langfang People’s Hospital, Hebei Province, Langfang, China
3Department of Cardiology, First Hospital of Qinhuangdao, Qinhuangdao, China
4Department of Cardiology, China-Australia Medical Research and Biometrics Center, State Key Laboratory of Cardiovascular Disease, Wuhan, China
5Department of Cardiology, First Hospital of Qinhuangdao, Qinhuangdao, China
6Department of Cardiology, Xuancheng Central Hospital, Xuancheng, China
7Department of Cardiology, Beijing Union Medical College, Beijing, China
8Department of Cardiology, Fuwai Hospital, National Center for Cardiovascular Diseases, Beijing, China
9Department of Cardiology, China Academy of Medical Sciences & Peking Union Medical College, Beijing, China
10Department of Cardiology, FuWai Hospital, National Center for Cardiovascular Diseases, Beijing, China
11Department of Cardiology, Fuwai Hospital, National Center for Cardiovascular Diseases, Beijing, China
12Department of Cardiology, First Hospital of Qinhuangdao, Qinhuangdao, China
13Department of Cardiology, Fuwai Hospital, National Center for Cardiovascular Diseases, Beijing, China
14Department of Cardiology, China Academy of Medical Sciences & Peking Union Medical College, Beijing, China
15Department of Cardiology, First Hospital of Qinhuangdao, Qinhuangdao, China
16Department of Cardiology, China Academy of Medical Sciences & Peking Union Medical College, Beijing, China

Table 4 Independent risk factors of GIB in the entire CAMI population and in patients with a drop of haemoglobin ≥3 g/dL or ≥5 g/dL

| Multivariable predictors | OR    | 95% CI     | P value   |
|--------------------------|-------|------------|----------|
| All patients             |       |            |          |
| Age                      | 1.17  | 1.07 to 1.28 | 0.0008   |
| Dyslipidaemia            | 1.17  | 1.07 to 1.28 | 0.0008   |
| Congestive heart failure | 1.27  | 1.17 to 1.37 | 0.0008   |
| Prior PUD/ Helicobacter pylori | 1.27  | 1.17 to 1.37 | 0.0008   |
| Prior GIB                | 2.13  | 1.94 to 2.34 | 0.0008   |
| Killip VI                | 1.71  | 1.51 to 1.94 | 0.0008   |
| GP IIb/IIIa receptor inhibitor | 1.71  | 1.51 to 1.94 | 0.0008   |
| Thrombolysis therapy     | 3.21  | 2.10 to 4.70 | 0.0008   |
| Patients with a drop of haemoglobin ≥3 g/dL |       |            |          |
| Male                     | 2.04  | 1.14 to 3.65 | 0.0161   |
| Prior GIB                | 3.12  | 1.51 to 6.58 | 0.0021   |
| Patients with a drop of haemoglobin ≥5 g/dL |       |            |          |
| Male                     | 2.50  | 1.09 to 5.70 | 0.0295   |
| In-hospital aspirin      | 3.25  | 1.24 to 8.56 | 0.0109   |
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Contributors WS was responsible for literature search, study design, data management, data interpretation and writing. XF and LN were responsible for data analysis, data interpretation and writing. JY, SS, MeiY and HY were involved in study design, statistical analysis plan and data interpretation. MenY and YY were involved in data interpretation and writing of the manuscript.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval CAMI registry was approved by the institutional review board central committee at Fuwai Hospital, NCCD of China (No 2012-431). The institutional review board approved protocol describes methods used to protect the privacy of patients and maintain confidentiality of data collected was maintained by the study group. Every eligible patient before registration signed a written informed consent.

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ORCID iDs Mengyue Yu http://orcid.org/0000-0003-3004-8948 Yuejin Yang http://orcid.org/0000-0002-1800-4566

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