High-Dose Proton Pump Inhibitors Are Superior to Standard-Dose Proton Pump Inhibitors in High-Risk Patients With Bleeding Ulcers and High-Risk Stigmata After Endoscopic Hemostasis

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INTRODUCTION: To define the best cutoff of the Glasgow-Blatchford score (GBS) for identifying high- and low-risk rebleeding patients with bleeding ulcers and high-risk stigmata after endoscopic hemostasis and compare the efficacy of high-dose and standard-dose intravenous proton pump inhibitors (HD-IVPs and SD-IVPs, respectively) in this patient population.

METHODS: We retrospectively reviewed the data of 346 patients with bleeding ulcers and high-risk stigmata who underwent endoscopic hemostasis between March 2014 and September 2018 in our center and were divided into an HD-IVP group and an SD-IVP group. Propensity score–matching analysis was performed to control for selection bias and other potential confounders. Recurrent bleeding rates were calculated according to the GBS.

RESULTS: Overall, 346 patients meeting the inclusion criteria were enrolled, with 89 patients in the SD-IVP group and 89 patients in the HD-IVP group after matching with all baseline characteristics balanced (P > 0.05). GBS ≥ 8 was the best cutoff for identifying high-risk rebleeding patients (GBS ≥ 8) with a significant difference (P = 0.015) in recurrence rate between the SD-IVP (17/61, 27.9%) and HD-IVP (7/65, 10.8%) groups and low-risk rebleeding patients (GBS < 8) with no difference (P = 1) in recurrence rate between the SD-IVP (2/28, 7.1%) and HD-IVP (2/24, 8.3%) groups.

DISCUSSION: The best cutoff for identifying high-risk and low-risk rebleeding patients with bleeding ulcers and high-risk stigmata after endoscopic hemostasis was GBS ≥ 8. Although HD-IVP is more effective than SD-IVP in high-risk patients, they are equally effective in low-risk patients.

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INTRODUCTION
Peptic ulcer bleeding (PUB), which accounts for the majority of acute nonvariceal upper gastrointestinal bleeding, remains a common medical emergency with significant morbidity and mortality (1–4). With the development of endoscopic hemostasis and proton pump inhibitors (PPIs), the prognosis of PUB has changed over the past few decades (5–7). Previous studies have shown that successful endoscopic hemostasis and high-dose PPIs can reduce peptic ulcer rebleeding, the need for surgery, and mortality in patients at high risk of rebleeding. Therefore, the latest guidelines from the international consensus group recommended high-dose PPI therapy with an intravenous bolus followed by continuous infusion (80 mg then 8 mg/hr) for 72 hours for patients who undergo endoscopic hemostasis (8). However, several clinical trials and meta-analyses reported different or even contradictory conclusions in the rebleeding rate between high-dose PPIs and standard-dose PPIs (40-mg infusion twice daily for a period of 72 hours) (9–13). Consequently, Andriulli et al. (11) did not endorse the recommendation by consensus statements on the routine use of high-dose PPIs for PUB. Thus, the optimal dose of PPIs after endoscopic hemostasis remains controversial. Because of the small sample size, selection bias of disease severity, and low rates of rebleeding in these clinical trials, it is hard to conclude that the 2 treatments are equivalent. In addition, stratification of the proportion of disease severity after endoscopic hemostasis may be another important confounding factor (14).

A previous retrospective study showed that rebleeding rates in low-risk patients with Rockall scores < 6 were similar

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between the standard- and high-dose groups \( P = 1.000 \); however, that study had serious statistical deficiencies, leading to inconsistencies between the results and the actual clinical situation. The study tried to minimize the selection bias with use of the greedy matching method to control the baseline conditions of the patients; nevertheless, selection bias definitely still existed and was serious because of the clinicians’ tendency to use high-dose PPIs in severe patients and insufficient statistical matching, which resulted in a higher rebleeding rate in the high-dose group after matching (standard-dose group vs high-dose group = 13.5% [14/104] vs 32.7% [34/104], \( P = 0.001 \)) and a much higher rebleeding rate in the high-risk patients with Rockall score \( \geq 6 \) (standard-dose group vs high-dose group = 14.3% vs 40.2%, \( P = 0.001 \)) in the high-dose group. The results of the aforementioned study indicated that high-dose PPIs will lead to a significantly higher rebleeding rate in the high-risk population than in the low-risk population, which seems very inconsistent with clinical practice. In addition, many scoring tools have been developed for predicting outcomes, and among these, the Glasgow-Blatchford score (GBS) is the most widely used for predicting the risk of peptic ulcer rebleeding, while the Rockall score is mainly used for predicting mortality (8). Therefore, the GBS was adopted for stratification of severity after endoscopic hemostasis in our study. We hypothesized that high-dose PPIs are superior to standard-dose PPIs in preventing rebleeding after endoscopic hemostasis in a high-risk population but not in a low-risk population. The aim of our study was to define the best cutoff of the GBS for identifying high-risk rebleeding patients and low-risk rebleeding patients with bleeding ulcers and high-risk stigmata after endoscopic hemostasis and to compare the efficacy of high- and standard-dose PPIs in high- or low-risk populations after endoscopic hemostasis.

METHODS

Patients and study design
This was a single-center, retrospective, propensity-matched study. An endoscopy database and clinical records from the First Affiliated Hospital of Nanchang University, Nanchang, China, were used to screen for patients with clinical manifestations of gastrointestinal bleeding, such as hematemesis, coffee ground vomiting, melena, or hematochezia, and who underwent endoscopy retrospectively between March 2014 and September 2018. If endoscopic findings revealed peptic ulcers with high-risk stigmata and endoscopic hemostasis was performed, the patients were eligible for enrollment. Patients with other possible reasons for bleeding were excluded, such as esophageal and gastric varices, hemorrhagic erosive gastritis, Mallory-Weiss syndrome, Dieulafoy lesions, vascular ectasia, malignant lesions, esophageal foreign-body injury, esophageal diverticulitis, portal hypertensive gastropathy, esophageal diverticulitis, and gastric stromal tumor. Patients with Forrest IIc and III peptic ulcers, which did not require endoscopic therapy, were also excluded. A total of 346 consecutive PUB patients with high-risk stigmata and endoscopic hemostasis were enrolled. We checked the electronic medical records of the patients for information including demographic information, clinical characteristics, physical examinations, laboratory findings, endoscopic findings, the GBS, the Rockall score, the AMIS65 score, pharmacological therapy after endoscopic hemostasis, and clinical outcomes. This study was approved by the Ethics Committee of the First Affiliated Hospital of Nanchang University.

Endoscopic evaluation and pharmacologic therapy
Experienced gastroenterologists in our department performed all the endoscopic therapies for these enrolled patients within 12
followed for at least 30 days. 

meprazole was given once daily for 30 days. All patients were including esomeprazole or pantoprazole; thereafter, 40-mg eso-

an 80-mg bolus injection followed by a continuous infusion of 8 mg per hour for a period of 72 hours; IQR, interquartile range; NSAID, nonsteroidal anti-inflammatory drug; PUB, peptic ulcer bleeding; SD-IVP, standard-dose intravenous proton pump inhibitor, 40-mg infusion twice daily for a period of 72 hours.

Median age, median (IQR) 56 (43–65) 54 (38–64) 56 (44–66) 0.135 55 (41–64) 56 (46–61) 0.705 

Sex: male, no. (%) 286 (82.7) 92 (88.5) 194 (80.2) 0.062 79 (88.8) 77 (86.5) 0.649 

Alcohol use, no. (%) 56 (16.2) 21 (20.2) 35 (14.5) 0.185 20 (22.5) 13 (14.6) 0.177 

Smokers, no. (%) 107 (30.9) 30 (28.8) 77 (31.8) 0.583 27 (30.3) 32 (36) 0.426 

Medication history 

Use of NSAIDs, no. (%) 21 (6.1) 4 (3.8) 17 (7) 0.256 4 (4.5) 6 (6.7) 0.515 

Use of anticoagulants, no. (%) 4 (1.2) 1 (1) 3 (1.2) 1 1 (1.1) 2 (2.2) 1 

Use of antiplatelets, no. (%) 4 (1.2) 1 (1) 3 (1.2) 1 1 (1.1) 0 1 

PUB history, no. (%) 66 (19.1) 26 (25) 40 (16.5) 0.066 20 (22.5) 21 (23.6) 0.859 

Coexisting diseases, no. (%) 

Ischemic heart disease 15 (4.3) 3 (2.9) 12 (5) 0.567 3 (3.4) 4 (4.5) 1 

Cancer 42 (12.1) 11 (10.6) 31 (12.8) 0.56 11 (12.4) 9 (10.1) 0.635 

Renal disease 4 (1.2) 1 (1) 3 (1.2) 1 1 (1.1) 0 1 

Liver cirrhosis 21 (6.1) 5 (4.8) 16 (6.6) 0.519 5 (5.6) 6 (6.7) 0.756 

Hypertension 85 (24.6) 20 (19.2) 65 (26.9) 0.131 18 (20.2) 24 (27) 0.29 

Diabetes mellitus 33 (9.5) 7 (6.7) 26 (10.7) 0.244 7 (7.9) 8 (9) 0.787 

Systolic blood pressure, mm Hg, mean ± SD 116.1 ± 17.6 117.6 ± 16.2 115.5 ± 18.1 0.328 117.2 ± 16.2 117.7 ± 17.0 0.836 

Systolic blood pressure < 90, no. (%) 13 (3.8) 2 (1.9) 11 (4.5) 0.358 2 (2.2) 2 (2.2) 1 

Heart rate > 100 beats/min, no. (%) 73 (21.1) 11 (10.6) 62 (25.6) 0.002 11 (12.4) 13 (14.6) 0.661 

Bleeding to shock, no. (%) 41 (11.8) 7 (6.7) 34 (14) 0.053 7 (7.9) 6 (6.7) 0.773 

GBS, median (IQR) 9 (7–11) 8.5 (7–10) 10 (8–12) 0.002 9 (7–11) 9 (7–11) 0.346 

Rockall score, median (IQR) 3 (3–4) 3 (3–4) 4 (3–5) <0.001 3 (3–4) 3 (3–4) 0.896 

AIMS65 score, median (IQR) 1 (0–1) 0 (0–1) 1 (0–1) 0.001 0 (0–1) 1 (0–1) 0.349 

GBS, Glasgow-Blatchford score; HD-IVP, high-dose intravenous proton pump inhibitor, an 80-mg bolus injection followed by a continuous infusion of 8 mg per hour for a period of 72 hours; IQR, interquartile range; NSAID, nonsteroidal anti-inflammatory drug; PUB, peptic ulcer bleeding; SD-IVP, standard-dose intravenous proton pump inhibitor, 40-mg infusion twice daily for a period of 72 hours.

hours of hospital admission, including thermal coagulation, mechanical therapy, injection therapy, or combination therapy by endoscopy (GIF-XQ260; Olympus Optical, Tokyo, Japan). Bleeding activity was classified based on the modified Forrest classification (15). For patients with more than 1 ulcer, the most severe ulcer was used for classification. After ulcer bleeding was successfully controlled by endoscopic hemostasis, patients subsequently received high-dose intravenous PPIs (HD-IVP group, an 80-mg bolus injection followed by a continuous infusion of 8 mg per hour for 72 hours) or standard-dose intravenous PPIs (SD-IVP group, 40-mg infusion twice daily for 72 hours), including esomeprazole or pantoprazole; thereafter, 40-mg esomeprazole was given once daily for 30 days. All patients were followed for at least 30 days.

Outcomes and statistical analysis

Statistical analyses were performed using R statistical software 3.6.1 (www.r-project.org). For abnormally distributed data, continuous variables were expressed as the median and interquartile range and were analyzed utilizing the Mann-Whitney rank-sum test when 2 medians were compared. For normally distributed data, continuous variables were expressed as the mean ± SD and were analyzed using the Student t test. Categorical variables were presented as proportions, and the χ² test or Fisher exact test was used as appropriate.

To control and reduce the selection bias and other potential confounders in retrospective studies, propensity score (PS) analysis was performed as a nonrandomized sensitivity analysis. PS was estimated by using a multivariable logistic regression model with the following covariates: sex, age, ulcer type, ulcer size, ulcer location, Forrest classification, endoscopic hemostasis, medication history (use of nonsteroidal anti-inflammatory drugs, use of anticoagulants, and use of antiplatelets), PUB history, coexisting diseases (hypertension, ischemic heart disease, cancer, renal disease, liver cirrhosis, and diabetes mellitus), the Rockall score, the AIMS65 score, the GBS, PPI use, and heart rate. The SD-IVP group was matched to the HD-IVP group in a 1:1 ratio using the nearest neighbor method with a caliper width of 0.1. After matching, all baseline characteristics were balanced (P > 0.05) between the 2 groups.
The high-risk population and low-risk population were defined based on the different GBSs (4–13) after matching. The recurrence rates were calculated in the SD-IVP group and HD-IVP group of the high-risk population or low-risk population, and the χ² test or Fisher exact test was used between the SD-IVP group and HD-IVP group as appropriate. The best cutoff of the GBS was defined as a score with a significant difference (P < 0.05) in the recurrence rate between the SD-IVP group and HD-IVP group in the high-risk population with a high GBS; meanwhile, this value should show no difference (P = 1 or close to 1) in the recurrence rate between the SD-IVP group and HD-IVP group in the low-risk population with a low GBS.

The primary endpoint of this study was to define the best cutoff of the GBS for identifying high-risk rebleeding patients who need HD-IVPs and low-risk rebleeding patients who simply need SD-IVPs, the efficacy of which was similar to that of HD-IVPs. The secondary endpoints included recurrent bleeding rates within 3 days, 7 days, 14 days, and 30 days of endoscopic hemostasis, mortality, length of hospital stay, and surgery.

**RESULTS**

**Baseline characteristics of patients**

Between March 2014 and September 2018, a total of 1,581 consecutive patients with confirmed endoscopic upper gastrointestinal bleeding were screened; of these patients, 346 PUB patients who met the inclusion criteria were enrolled with 104 patients in the SD-IVP group and 242 patients in the HD-IVP group (Figure 1). Tables 1–3 show the baseline characteristics of the enrolled patients. There were differences (P < 0.05) between the 2 groups in many baseline variables before PS matching (PSM). After PSM, 89 patients who received SD-IVP were matched with 89 patients who received HD-IVP. No significant difference occurred in baseline variables between the 2 groups after PSM (Tables 1–3).

**Outcome measures after endoscopic hemostasis**

Table 4 shows that the recurrent bleeding rates by days 3, 7, 14, and 30 after PSM were 11.2%, 16.9%, 19.1%, and 21.3% in the SD-IVP group, respectively, which seems higher than those in the HD-IVP group (6.7%, 10.1%, 10.1%, and 10.1%), but there was no significant difference between the 2 groups. The surgery, mortality, hospitalization stay, and units of blood transfusion were similar between the SD-IVP group and HD-IVP group after PSM.

**Recurrent bleeding rates according to different GBSs and the best cutoff of the GBS for high-risk and low-risk rebleeding patients after endoscopic hemostasis**

Figure 2 shows the patient distribution based on the GBS before and after PSM. Because of the small sample size, we chose the GBS (4–13) as the cutoff for stratification of severity after PSM. Table 5 shows the recurrent bleeding rates in the SD-IVP group and HD-IVP group of the high-risk population or low-risk population according to the GBS after PSM. GBS = 8 was the best cutoff for identifying the high-risk rebleeding patients (GBS ≥ 8) with a significant difference (P = 0.015) in recurrence rate between the SD-IVP group (17/61, 27.9%) and HD-IVP group (7/65, 10.8%); using this cutoff, the low-risk rebleeding patients (GBS < 8) showed no difference (P = 1) in recurrence rate between the SD-IVP group (2/28, 7.1%) and HD-IVP group (2/24, 8.3%).

**Outcome measures after endoscopic hemostasis according to GBS = 8**

Table 6 shows that the recurrent bleeding rates by days 3, 7, 14, and 30 after PSM were similar between the SD-IVP group and the HD-IVP group in the low-risk population (GBS < 8) with no significant difference. The surgery, mortality, hospitalization stay, and units of blood transfusion were also similar. However, in the high-risk population (GBS ≥ 8), the recurrent bleeding rates by days 3, 7, 14, and 30 after PSM were 13.1%, 21.3%, 23%, and 27.9% respectively, which were significantly higher than those in the low-risk group. In the high-risk population, the surgery, mortality, hospitalization stay, and units of blood transfusion were also similar between the SD-IVP group and HD-IVP group after PSM.
in the SD-IVP group and 9.2%, 10.8%, 10.8%, and 10.8% in the HD-IVP group, respectively, with significant differences between the 2 groups by days 14 and 30 (P = 0.041 and P = 0.015); the surgery, hospitalization stay, and units of blood transfused were similar between the SD-IVP group and HD-IVP group, although mortality was significantly different (P = 0.024). Figure 3 shows the cumulative recurrent bleeding rates of patients within 30 days.

**DISCUSSION**

Forrest classification can provide prognostic information regarding the risk of rebleeding, need for therapeutic intervention, and death. Therefore, the Forrest classification is recommended for stratifying patients with ulcer bleeding and guiding management decisions, including endoscopic and pharmacological therapy (8,16-18). Peptic ulcers with stigmata of recent hemorrhage (such as active bleeding, visible vessels, and adherent clots) are at high risk of rebleeding and are recommended for endoscopic hemostasis. In most previous clinical trials, the Forrest classification was adopted to stratify patients to guide endoscopic therapy. However, stratification of severity after endoscopic hemostasis was not performed in those clinical trials, which might have resulted in different degrees of severity in different clinical trials. Theoretically, more low-risk patients in clinical trials are more likely to lead to no significant difference in efficacy between high-dose and standard-dose treatments, which means that high-dose therapy and standard-dose therapy have the same efficacy in low-risk patients after endoscopic hemostasis. By contrast, more high-risk patients are more likely to lead to significant differences, meaning that high-dose therapy may have better efficacy in high-risk patients after endoscopic hemostasis. Therefore, stratification of severity after endoscopic hemostasis seems important. If this turns out to be true, dose selection for future treatments should be based on risk stratification. In this study, we focused on whether high-dose and standard-dose PPI therapies have different efficacies in high-risk populations and low-risk populations after endoscopic hemostasis. In addition, we defined the best cutoff value of the GBS for stratifying high-risk patients and low-risk patients after endoscopic hemostasis. The results of our study showed that the best cutoff is GBS = 8 for identifying high-risk rebleeding patients (GBS ≥ 8) who need HD-IVPs with higher efficacy than SD-IVPs and low-risk rebleeding patients (GBS < 8) who need only SD-IVPs, which could achieve similar efficacy to that of HD-IVPs.

Because of the tendency of clinicians to use high-dose PPIs in severe patients, we could see more high-risk patients in the high-dose PPI group than in the standard-dose PPI group before PSM in our study, which is similar to a previous study (14). After using the strict matching method for PSM, which included all possible risk-related baseline variables for matching, high-risk patients in the 2 treatment groups were similar, with no significant difference in baseline variables, including the GBS, Rockall score, AIMS65 score, etc., which made the 2 treatment groups suitable for comparing the efficacy of the 2 treatments. Our study showed that recurrent bleeding rates by days 3, 7, 14, and 30 after PSM were 11.2%, 16.9%, 20 mm, no. (%) 29 (8.4) 2 (1.9) 27 (11.2) 0.004 2 (2.2) 1 (1.1) 1
 Ulcer location, no. (%) 0.697 0.504
 Stoma 49 (14.2) 16 (15.4) 33 (13.6) 14 (15.7) 20 (22.5)
 Stigmata of hemorrhage, no. (%) 0.044 0.738
 Forrest la 21 (6.1) 3 (2.9) 18 (7.4) 3 (3.4) 2 (2.2)
 Forrest lb 133 (38.4) 34 (32.7) 99 (40.9) 32 (36) 32 (36)
 Forrest Ila 108 (31.2) 33 (31.7) 75 (31) 27 (30.3) 33 (37.1)
 Forrest llb 84 (24.3) 34 (32.7) 50 (20.7) 27 (30.3) 22 (24.7)
 Methods of endoscopic hemostasis, no. (%) 0.073 0.76
 Thermal coagulation 12 (3.5) 2 (2) 10 (4.1) 2 (2.2) 4 (4.5)
 Mechanical therapy 60 (17.3) 25 (24) 35 (14.5) 21 (23.6) 18 (20.2)
 Injection therapy 197 (56.9) 60 (57.7) 137 (56.6) 51 (57.3) 49 (55.1)
 Combination therapy 77 (22.3) 17 (16.3) 60 (24.8) 15 (16.9) 18 (20.2)
 Intravenous PPI infusion after endoscopic hemostasis, no. (%) 0.008 0.876
 Esomeprazole 235 (67.9) 60 (57.7) 175 (72.3) 56 (62.9) 57 (64)
 Pantoprazole 111 (32.1) 44 (42.3) 67 (27.7) 33 (37.1) 32 (36)

**Table 3.** Endoscopic findings and pharmacologic therapy before and after propensity score matching

| Characteristic | Total | Before matching | After matching |
|---------------|-------|----------------|--------------|
| Ulcer size, mm, median (IQR) | | | |
| n = 104 | n = 242 | | | |
| SD-IVP group | HD-IVP group | P | SD-IVP group | HD-IVP group | P |
| Ulcer size ≤ 20 mm, no. (%) | 29 (8.4) | 2 (1.9) | 27 (11.2) | 0.004 | 2 (2.2) | 1 (1.1) |
| Ulcer location, no. (%) | 0.697 | 0.504 |
| Stoma | 49 (14.2) | 16 (15.4) | 33 (13.6) | 14 (15.7) | 20 (22.5) |
| Stigmata of hemorrhage, no. (%) | 0.044 | 0.738 |
| Forrest la | 21 (6.1) | 3 (2.9) | 18 (7.4) | 3 (3.4) | 2 (2.2) |
| Forrest lb | 133 (38.4) | 34 (32.7) | 99 (40.9) | 32 (36) | 32 (36) |
| Forrest Ila | 108 (31.2) | 33 (31.7) | 75 (31) | 27 (30.3) | 33 (37.1) |
| Forrest llb | 84 (24.3) | 34 (32.7) | 50 (20.7) | 27 (30.3) | 22 (24.7) |
| Methods of endoscopic hemostasis, no. (%) | 0.073 | 0.76 |
| Thermal coagulation | 12 (3.5) | 2 (2) | 10 (4.1) | 2 (2.2) | 4 (4.5) |
| Mechanical therapy | 60 (17.3) | 25 (24) | 35 (14.5) | 21 (23.6) | 18 (20.2) |
| Injection therapy | 197 (56.9) | 60 (57.7) | 137 (56.6) | 51 (57.3) | 49 (55.1) |
| Combination therapy | 77 (22.3) | 17 (16.3) | 60 (24.8) | 15 (16.9) | 18 (20.2) |
| Intravenous PPI infusion after endoscopic hemostasis, no. (%) | 0.008 | 0.876 |
| Esomeprazole | 235 (67.9) | 60 (57.7) | 175 (72.3) | 56 (62.9) | 57 (64) |
| Pantoprazole | 111 (32.1) | 44 (42.3) | 67 (27.7) | 33 (37.1) | 32 (36) |
19.1%, and 21.3% in the SD-IVP group and 6.7%, 10.1%, 10.1%, and 10.1% in the HD-IVP group, respectively. These results seem more consistent with the actual clinical situation than those in a previous study after matching (standard-dose group vs high-dose group 13.5% [14/104] vs 32.7% [34/104], P = 0.001) (14). Although recurrent bleeding rates in the SD-IVP group seem higher than those in the HD-IVP group, there was no significant difference between the 2 groups, which is similar to many previous clinical studies and meta-analyses (9–13,19–21). However, Sung et al. (5) found that high-dose intravenous esomeprazole could reduce recurrent bleeding, Bai et al. (22) also reported that high-dose intravenous esomeprazole was an effective way to prevent peptic ulcer rebleeding. And, some consensus support and recommend the routine use of high-dose PPIs for PUB after endoscopic hemostasis. Although limitations were noted in these previous studies, e.g., some studies included patients with low rebleeding risk (10,21), some studies did not compare the efficacy between high-dose PPIs and low-dose PPIs (5,22). Moreover, the endoscopic intervention were not standardized in some studies (11–13,20). Nonetheless, the optimal dose of PPIs after endoscopic hemostasis remains controversial. How did this discrepancy emerge? In addition to the small sample size, selection bias, and low

Table 4. Outcome measures after endoscopic hemostasis before and after propensity score matching

| Characteristic                        | All patients | Propensity score–matched patients |
|--------------------------------------|--------------|-----------------------------------|
|                                      | SD-IVP group | HD-IVP group | P      | SD-IVP group | HD-IVP group | P      |
|                                      | n = 104      | n = 242      |       | n = 89      | n = 89      |       |
| Recurrent bleeding, no. (%)          |              |              |       |              |              |       |
| By day 3                             | 10 (9.6)     | 28 (11.6)    | 0.594 | 10 (11.2)   | 6 (6.7)     | 0.444  |
| By day 7                             | 15 (14.4)    | 38 (15.7)    | 0.762 | 15 (16.9)   | 9 (10.1)    | 0.296  |
| By day 14                            | 18 (17.3)    | 40 (16.5)    | 0.859 | 17 (19.1)   | 9 (10.1)    | 0.423  |
| By day 30                            | 20 (19.2)    | 40 (16.5)    | 1     | 19 (21.3)   | 9 (10.1)    | 0.217  |
| Surgery due to rebleeding, no. (%)   | 1 (1)        | 9 (3.7)      | 0.293 | 1 (1.1)     | 1 (1.1)     | 1       |
| Mortality, no. (%)                   | 5 (4.8)      | 10 (4.1)     | 0.778 | 5 (5.6)     | 1 (1.1)     | 0.211  |
| Median hospital stay > 7 d, no. (%)  | 33 (31.7)    | 39 (16.1)    | 0.001 | 29 (32.6)   | 32 (36)     | 0.636  |
| Hospitalization stay, median (IQR)   | 6 (4–8)      | 7 (5–11)     | <0.001| 6 (4–8)     | 6 (5–9)     | 0.189  |
| Hospitalization stay, range          | 2–45         | 1–83         |       | 2–45        | 3–51        |       |
| Units of blood transfused, mean ± SD |              |              |       |              |              |       |
| Before endoscopic therapy            | 0.9 ± 2.2    | 1.5 ± 2.8    | 0.048 | 1 ± 2.4     | 1 ± 2.3     | 0.886  |
| After endoscopic therapy             | 1.4 ± 4.2    | 3.3 ± 5.6    | 0.001 | 1.6 ± 4.5   | 3 ± 5.5     | 0.07   |

HD-IVP, high-dose intravenous proton pump inhibitor, an 80-mg bolus injection followed by a continuous infusion of 8 mg per hour for a period of 72 hours; IQR, interquartile range; SD-IVP, standard-dose intravenous proton pump inhibitor, 40-mg infusion twice daily for a period of 72 hours.

Figure 2. Patient distribution based on the GBS before (a) and after (b) matching. GBS, Glasgow-Blatchford score; H, patients in high-dose intravenous proton pump inhibitor group; S, patients in standard-dose intravenous proton pump inhibitor group; T, total patients.
In the high-risk population (GBS ≥ 8), the recurrent bleeding rates by days 3, 7, 14, and 30 after PSM were 13.1%, 21.3%, 23%, and 27.9% in the SD-IVP group and 9.2%, 10.8%, 10.8%, and 10.8% in the HD-IVP group, respectively, with a significant difference between the 2 groups by days 14 and 30 (P = 0.041 and P = 0.015). From the aforementioned data about the recurrent bleeding rate in our study, we can see that the first 3 days of high-dose PPI treatment can greatly reduce the recurrent bleeding rate 3 days after endoscopic therapy with a stable recurrent bleeding rate in the HD-IVP group but increase it in the SD-IVP group, especially by days 14 and 30, which indicates that the first 3 days

Table 5. Recurrent bleeding rates according to the GBS after propensity score matching

| GBS cutoff | SD-IVP group (n/N) (%) | HD-IVP group (n/N) (%) | P  |
|------------|------------------------|------------------------|----|
| 4          | 19/84 (22.6)           | 8/85 (9.4)             | 0.139 |
| 5          | 19/83 (22.9)           | 8/80 (10)              | 0.126 |
| 6          | 19/81 (23.5)           | 8/78 (10.3)            | 0.118 |
| 7          | 17/70 (24.3)           | 8/72 (11.1)            | 0.143 |
| 8          | 17/61 (27.9)           | 7/65 (10.8)            | 0.015 |
| 9          | 11/46 (23.9)           | 4/48 (8.3)             | 0.115 |
| 10         | 7/32 (19.3)            | 4/43 (8.3)             | 0.433 |
| 11         | 5/24 (20.8)            | 2/31 (6.5)             | 0.357 |
| 12         | 2/13 (15.4)            | 2/19 (10.5)            | 1   |
| 13         | 1/8 (12.5)             | 1/9 (11.1)             | 1   |

GBS, Glasgow-Blatchford score; HD-IVP, high-dose intravenous proton pump inhibitor, an 80-mg bolus injection followed by a continuous infusion of 8 mg per hour for a period of 72 hours; SD-IVP, standard-dose intravenous proton pump inhibitor, 40-mg infusion twice daily for a period of 72 hours.

Table 6. Outcome measures after endoscopic hemostasis according to the GBS = 8

| Characteristic                        | GBS ≥ 8 after matching | GBS < 8 after matching |
|---------------------------------------|------------------------|------------------------|
|                                       | SD-IVP group n = 61    | HD-IVP group n = 65    | P  |
| Recurrent bleeding, no. (%)           |                        |                        |    |
| By day 3                              | 8 (13.1)               | 6 (9.2)                | 0.488 |
| By day 7                              | 13 (21.3)              | 7 (10.8)               | 0.106 |
| By day 14                             | 15 (23)                | 7 (10.8)               | 0.041 |
| By day 30                             | 17 (27.9)              | 7 (10.8)               | 0.015 |
| Surgery due to rebleeding, no. (%)    | 1 (1.6)                | 1 (1.5)                | 1   |
| Mortality, no. (%)                    | 5 (8.2)                | 0                      | 0.024 |
| Median hospital stay > 7 d, no. (%)   | 22 (36.1)              | 24 (36.9)              | 0.92 |
| Hospitalization stay, median (IQR)    | 7 (5–9)                | 6 (5–9)                | 0.623 |
| Hospitalization stay, range           | 2–45                   | 3–51                   | 2–15 |

GBS, Glasgow-Blatchford score; HD-IVP, high-dose intravenous proton pump inhibitor, an 80-mg bolus injection followed by a continuous infusion of 8 mg per hour for a period of 72 hours; IQR, interquartile range; SD-IVP, standard-dose intravenous proton pump inhibitor, 40-mg infusion twice daily for a period of 72 hours.
of high-dose PPIs are very important for controlling recurrent bleeding in high-risk patients. In addition, high-dose PPIs can decrease mortality (SD-IVP group vs HD-IVP group: 8.2% [5/61] vs 0 [0/65], \( P = 0.024 \)) in the high-risk population. However, the recurrent bleeding rates were low and stable in the SD-IVP group and HD-IVP group with no significant difference from day 3 through day 30, which indicated that the first 3 days of standard-dose PPIs is enough to control recurrent bleeding in low-risk patients. Standard-dose PPIs have the obvious advantage of reduced cost and have not been shown to increase the risk of transfusion requirement, need for surgery, length of hospital stay, or mortality in the low-risk population.

This study has several advantages. First, the strict matching method, PSM, was used with all possible risk-related baseline variables included for matching, such as the GBS, Rockall score, AIMS65 score, etc., which made the 2 groups suitable for comparing the efficacy of the 2 treatments. Second, the GBS was adopted for stratification of severity after endoscopic hemostasis in this study, and the best cutoff was determined for identifying high-risk patients and low-risk patients. However, there are several limitations in this study. First, this was a single-center, retrospective study. Second, the sample size is small after PSM. Third, because of the different genetic polymorphisms of CYP2C19 between Asian and Western populations (23,24), whether the results of this study can be used in Western populations remains unknown.

In conclusion, the best cutoff is GBS = 8 for identifying high-risk rebleeding patients (GBS ≥ 8) and low-risk rebleeding patients (GBS < 8) with bleeding ulcers and high-risk stigmata after endoscopic hemostasis. Intravenous high-dose PPIs have higher efficacy than standard-dose PPIs in high-risk patients. However,
intravenous standard-dose PPIs are equally as effective as high-dose PPIs in low-risk patients.

CONFLICTS OF INTEREST
Guarantor of the article: Xu Shu, MD, PhD.
Specific author contributions: Zhenhua Zhu, MD, PhD, Yongkang Lai, MD, and Liu Ouyang, MD, contributed equally to this work. Y.C. and X.S. contributed to the study concept and design. Y.L. and L.O. collected the data. Y.L. analyzed and interpreted the data. Z.Z. drafted the manuscript and all authors critically revised the manuscript for important intellectual content. N.L. and Z.Z. obtained the funding to conduct the study.

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Potential competing interests: None to report.

Study Highlights

WHAT IS KNOWN

✓ PUB remains a common medical emergency with significant morbidity and mortality.
✓ Intravenous infusion of PPIs after endoscopic hemostasis can effectively prevent PUB rebleeding.
✓ The optimal dose of PPIs after endoscopic hemostasis remains controversial.

WHAT IS NEW HERE

✓ Use PSM to control and reduce the selection bias and other potential confounders.
✓ The GBS was adopted for stratification of severity after endoscopic hemostasis in this study, and the best cutoff was determined for identifying high-risk patients and low-risk patients.
✓ Intravenous high-dose PPIs have higher efficacy than standard-dose PPIs in high-risk patients. However, intravenous standard-dose PPIs are equally as effective as high-dose PPIs in low-risk patients.

TRANSLATIONAL IMPACT

✓ Glasgow-Blatchford Score ≥ 8 has the potential ability to identify the high-risk rebleeding patients with bleeding ulcers and high-risk stigmata who need high-dose PPI after endoscopic hemostasis.

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