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

Zhenhua Zhu, MD, PhD[1], Yongkang Lai, MD[1], Liu Ouyang, MD[1], Nonghua Lv, MD[1], Youxiang Chen, MD[1] and Xu Shu, MD, PhD[1]

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.**

Clinical and Translational Gastroenterology 2021;12:e00294. https://doi.org/10.14309/ctg.0000000000000294

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

[1]Department of Gastroenterology, The First Affiliated Hospital of Nanchang University, Nanchang, People's Republic of China.
Correspondence: Xu Shu, MD, PhD. E-mail: shuxu_tg@163.com. Youxiang Chen, MD. E-mail: chenyx102@126.com.
Received July 22, 2020; accepted November 23, 2020; published online January 14, 2021

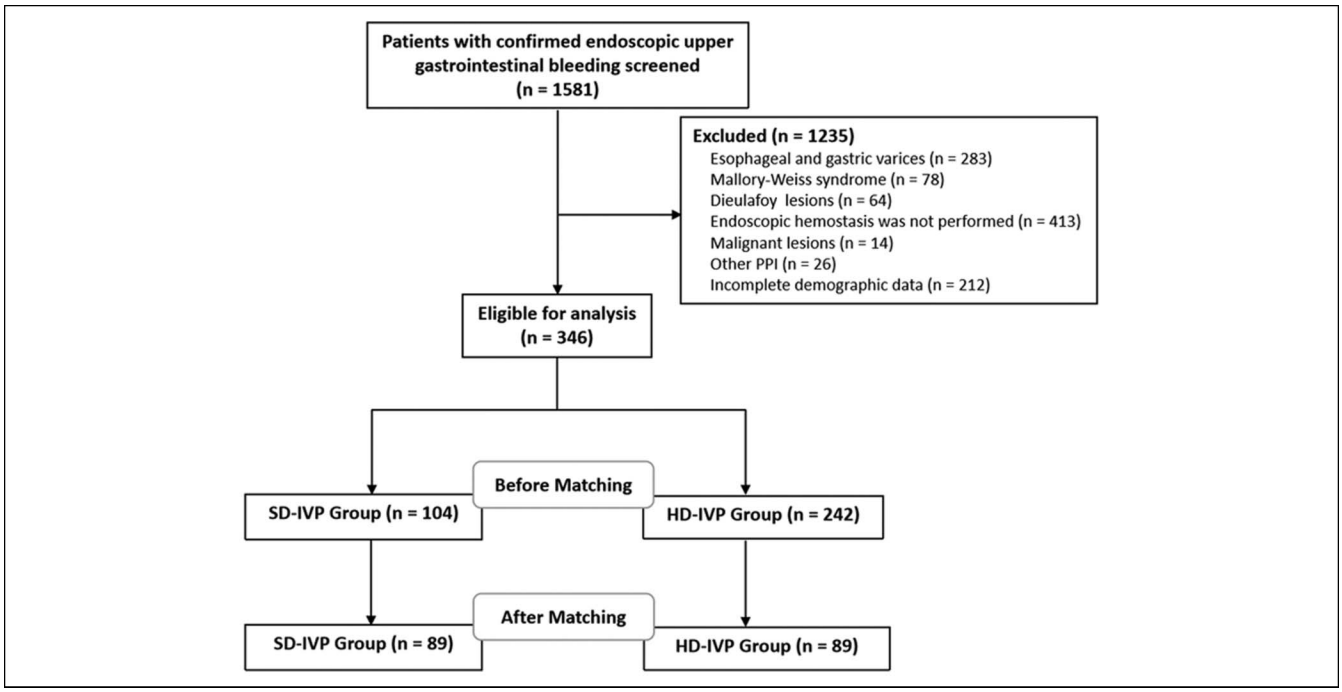

Figure 1. The flowchart of patients included in this study. HD-IVP, high-dose intravenous proton pump inhibitor; PPI, proton pump inhibitor; SD-IVP, standard-dose intravenous proton pump inhibitor.

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 ≥ 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

Table 1. Baseline characteristics before and after propensity score matching

Characteristic	Total	Before matching			After matching		
		SD-IVP group n = 104	HD-IVP group n = 242	*P*	SD-IVP group n = 89	HD-IVP group n = 89	*P*
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 χ^2 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.

Table 2. Laboratory findings before and after propensity score matching

Characteristic	Total	Before matching			After matching		
		SD-IVP group n = 104	HD-IVP group n = 242	*P*	SD-IVP group n = 89	HD-IVP group n = 89	*P*
Hemoglobin level on admission, g/L, mean ± SD	81.7 ± 24.8	84.5 ± 25.1	80.4 ± 24.7	0.149	82.9 ± 24.8	83.6 ± 25	0.86
Low HB level < 100 g/L, no. (%)	268 (77.5)	77 (74)	191 (78.9)	0.319	67 (75.3)	71 (79.8)	0.473
White cell count, $\times 10^9$/L, median (IQR)	7.9 (5.79–11.14)	7 (5.1–10.1)	8.4 (6.2–11.3)	0.006	7.4 (5.3–10.5)	7.5 (5.9–10.5)	0.698
Platelet, $\times 10^9$/L, median (IQR)	167 (116–219)	181 (135–233.5)	163 (107–214)	0.017	174 (130–233)	160 (120–207)	0.101
Blood urea nitrogen, mmol/L, median (IQR)	8.3 (5.7–12.3)	7.5 (5.4–10.7)	9.3 (5.8–13)	0.003	7.5 (5.3–10.8)	8.2 (5.7–11.9)	0.359
Creatinine, μmol/L, median (IQR)	73.4 (61.2–89.3)	73 (61.3–86.4)	75.7 (61.2–91.1)	0.445	72.9 (60.7–85.1)	75.6 (64.4–86.1)	0.39
ALB < 30 g/L, no. (%)	117 (33.8)	22 (21.2)	95 (39.3)	0.001	22 (24.7)	32 (36)	0.103
Prothrombin time, s, median (IQR)	11.8 (11–12.8)	11.7 (11–12.6)	11.8 (11–13.1)	0.307	11.9 (11–12.7)	11.7 (10.9–12.5)	0.375
APTT, median (IQR)	28.4 (24.5–33.2)	28.4 (23.8–32.1)	28.6 (24.6–34.4)	0.049	28.4 (23.8–32.4)	27.8 (23.7–32.6)	0.864
INR > 1.5, no. (%)	14 (4)	1 (1)	13 (5.4)	0.079	1 (1.1)	3 (3.4)	0.621

ALB, albumin; APTT, activated partial thromboplastin time; HB, hemoglobin; 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; INR, international normalized ratio; IQR, interquartile range; SD-IVP, standard-dose intravenous proton pump inhibitor, 40-mg infusion twice daily for a period of 72 hours.

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 the low-risk population, and the χ^2 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 end point 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 end points 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%

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

Characteristic	Total	Before matching			After matching		
		SD-IVP group n = 104	HD-IVP group n = 242	*P*	SD-IVP group n = 89	HD-IVP group n = 89	*P*
Ulcer size, mm, median (IQR)	8 (5–10)	6 (5–10)	8 (5–12)	0.09	6 (5–10)	8 (5–10)	0.759
Ulcer size ≥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
Stomach	121 (35)	33 (31.7)	88 (36.4)		30 (33.7)	29 (32.6)	
Duodenum	176 (50.9)	55 (52.9)	121 (50)		45 (50.6)	40 (44.9)	
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 Ia	21 (6.1)	3 (2.9)	18 (7.4)		3 (3.4)	2 (2.2)	
Forrest Ib	133 (38.4)	34 (32.7)	99 (40.9)		32 (36)	32 (36)	
Forrest IIa	108 (31.2)	33 (31.7)	75 (31)		27 (30.3)	33 (37.1)	
Forrest IIb	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)	

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 h; IQR, interquartile range; PPI, proton pump inhibitor; SD-IVP, standard-dose intravenous proton pump inhibitor, 40-mg infusion twice daily for a period of 72 h.

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%,

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

Characteristic	All patients			Propensity score–matched patients		
	SD-IVP group n = 104	HD-IVP group n = 242	*P*	SD-IVP group n = 89	HD-IVP group n = 89	*P*
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.

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 reduced recurrent bleeding, Bai et al. (22) also reported that high-dose intravenous esomeprazole was a 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

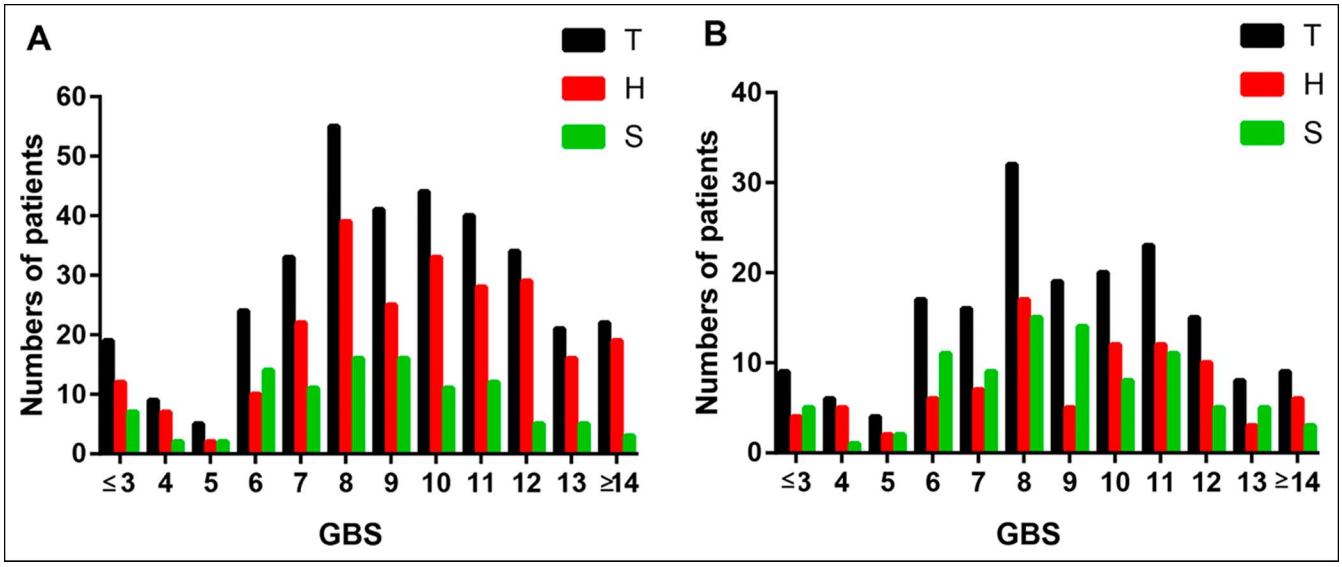

Figure 2. Patient distribution based on the GBS before (**a**) and after (**b**) matching. GBS, Glasgow-Blatchford score; H, patients in high-dose intravenous proton pump inhibitor group; S, patients in standard-dose intravenous proton pump inhibitor group; T, total patients.

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

	High-risk population (high GBS)			Low-risk population (low GBS)		
GBS cutoff	SD-IVP group n/N (%)	HD-IVP group n/N (%)	*P*	SD-IVP group n/N (%)	HD-IVP group n/N (%)	*P*
4	19/84 (22.6)	8/85 (9.4)	0.139	0/5 (0)	1/4 (25)	0.444
5	19/83 (22.9)	8/80 (10)	0.126	0/6 (0)	1/9 (11.1)	0.493
6	19/81 (23.5)	8/78 (10.3)	0.118	0/8 (0)	1/11 (9.1)	0.487
7	17/70 (24.3)	8/72 (11.1)	0.143	2/19 (10.5)	1/17 (5.9)	1
8	17/61 (27.9)	7/65 (10.8)	0.015	2/28 (7.1)	2/24 (8.3)	1
9	11/46 (23.9)	4/48 (8.3)	0.115	8/43 (18.6)	5/41 (12.3)	0.788
10	7/32 (19.3)	4/43 (8.3)	0.433	12/57 (21.1)	5/46 (10.9)	0.377
11	5/24 (20.8)	2/31 (6.5)	0.357	14/65 (21.5)	7/58 (12.1)	0.426
12	2/13 (15.4)	2/19 (10.5)	1	17/76 (22.4)	7/70 (10)	0.207
13	1/8 (12.5)	1/9 (11.1)	1	18/81 (22.2)	8/80 (10)	0.246

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.

rates of rebleeding in these clinical trials, the different degrees of severity might be the main reason. Consequently, we adopted the GBS for stratification of severity after endoscopic hemostasis in this study, which was the most widely used method for predicting the risk of peptic ulcer rebleeding. When we chose GBS = 8 as the cutoff, HD-IVPs showed higher efficacy than SD-IVPs in high-risk rebleeding patients (GBS ≥ 8), with a significant difference (P = 0.015) by day 30, but similar efficacy to SD-IVPs in the low-risk rebleeding patients (GBS < 8), with no difference (P = 1). Therefore, GBS = 8 is the best cutoff for defining high-risk and low-risk rebleeding 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 6. Outcome measures after endoscopic hemostasis according to the GBS = 8

	GBS ≥ 8 after matching			GBS < 8 after matching		
Characteristic	SD-IVP group n = 61	HD-IVP group n = 65	*P*	SD-IVP group n = 28	HD-IVP group n = 24	*P*
Recurrent bleeding, no. (%)						
By day 3	8 (13.1)	6 (9.2)	0.488	2 (7.1)	0	0.493
By day 7	13 (21.3)	7 (10.8)	0.106	2 (7.1)	2 (8.3)	1
By day 14	15 (23)	7 (10.8)	0.041	2 (7.1)	2 (8.3)	1
By day 30	17 (27.9)	7 (10.8)	0.015	2 (7.1)	2 (8.3)	1
Surgery due to rebleeding, no. (%)	1 (1.6)	1 (1.5)	1	0	1 (4.2)	0.462
Mortality, no. (%)	5 (8.2)	0	0.024	0	1 (4.2)	0.462
Median hospital stay > 7 d, no. (%)	22 (36.1)	24 (36.9)	0.92	7 (25)	8 (33.3)	0.553
Hospitalization stay, median (IQR)	7 (5–9)	6 (5–9)	0.623	5 (4–8)	7 (5–10)	0.122
Hospitalization stay, range	2–45	3–51		2–15	3–21	
Units of blood transfused, mean ± SD						
Before endoscopic therapy	1.3 ± 2.75	1.3 ± 2.75	0.983	0.3 ± 0.9	0.2 ± 0.6	0.926
After endoscopic therapy	2.1 ± 5.2	3.1 ± 5	0.29	0.6 ± 1.9	2.8 ± 6.6	0.129

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.

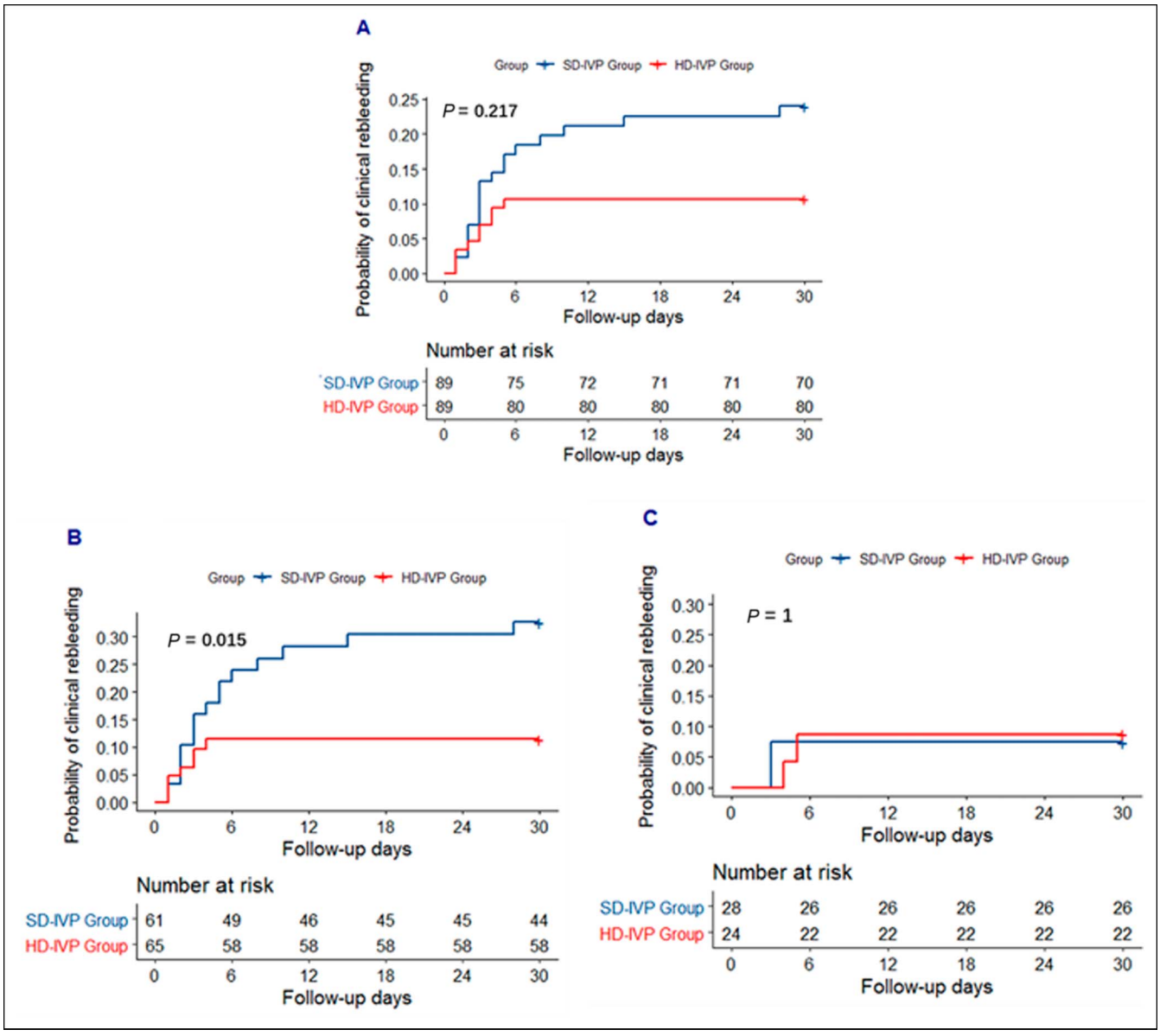

Figure 3. Recurrent bleeding of patients within the 30-day follow-up period. (**a**) After matching; (**b**) after matching and GBS ≥ 8; and (**c**) after matching and GBS < 8. GBS, Glasgow-Blatchford score; HD-IVP, high-dose intravenous proton pump inhibitor; SD-IVP, standard-dose intravenous proton pump inhibitor.

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.

Financial support: Funding was provided by grants from the National Natural Science Foundation of China (No. 81660101).

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.

REFERENCES

1. Longstreth GF. Epidemiology of hospitalization for acute upper gastrointestinal hemorrhage: A population-based study. Am J Gastroenterol 1985;90:206–10.
2. Gralnek IM, Barkun AN, Bardou M. Management of acute bleeding from a peptic ulcer. N Engl J Med 2008;359:928–37.
3. Hearnshaw SA, Logan RF, Lowe D, et al. Acute upper gastrointestinal bleeding in the UK: Patient characteristics, diagnoses and outcomes in the 2007 UK audit. Gut 2011;60:1327–35.
4. Barkun AN, Bardou M, Kuipers EJ, et al. International consensus recommendations on the management of patients with nonvariceal upper gastrointestinal bleeding. Ann Intern Med 2010;152:101–13.
5. Sung JJ, Barkun A, Kuipers EJ, et al. Intravenous esomeprazole for prevention of recurrent peptic ulcer bleeding: A randomized trial. Ann Intern Med 2009;150:455–464.
6. Abougergi MS, Travis AC, Saltzman JR. The in-hospital mortality rate for upper GI hemorrhage has decreased over 2 decades in the Unites States: A nationwide analysis. Gastrointest Endosc 2015;81:882–888.e1.
7. Barkun A, Sabbah S, Enns R, et al. The Canadian Registry on Nonvariceal Upper Gastrointestinal Bleeding and Endoscopy (RUGBE): Endoscopic hemostasis and proton pump inhibition are associated with improved outcomes in a real-life setting. Am J Gastroenterol 2004;99:1238–46.
8. Barkun AN, Almadi M, Kuipers EJ, et al. Management of nonvariceal upper gastrointestinal bleeding: Guideline recommendations from the international consensus group. Ann Intern Med 2019;171(11):805–22.
9. Schonekas H, Ahrens H, Pannewick U, et al. Comparison of two doses of intravenous pantoprazole in peptic ulcer bleeding. Gastroenterology 1999;116:A305.
10. Udd M, Miettinen P, Palmu A, et al. Regular-dose versus high-dose omeprazole in peptic ulcer bleeding: A prospective randomized double-blind study. Scand J Gastroenterol 2001;36:1332–8.
11. Andriulli A, Loperfido S, Focareta R, et al. High- versus low-dose proton pump inhibitors after endoscopic hemostasis in patients with peptic ulcer bleeding: A multicentre, randomized study. Am J Gastroenterol 2008;103(12):3011–8.
12. Andriulli A, Annese V, Caruso N, et al. Proton-pump inhibitors and outcome of endoscopic hemostasis in bleeding peptic ulcer: A series of meta-analysis. Am J Gastroenterol 2005;100:207–19.
13. Sgourakis G, Chatzidakis G, Poulou A, et al. High-dose vs. low-dose proton pump inhibitors post-endoscopic hemostasis in patients with bleeding peptic ulcer: A meta-analysis and meta-regression analysis. Turk J Gastroenterol 2018;29(1):22–31.
14. Liang CM, Lee JH, Kuo YH, et al. Intravenous non-high-dose pantoprazole is equally effective as high-dose pantoprazole in preventing rebleeding among low risk patients with a bleeding peptic ulcer after initial endoscopic hemostasis. BMC Gastroenterol 2012;12:28.
15. Forrest JA, Finlayson ND, Shearman DJ. Endoscopy in gastrointestinal bleeding. Lancet 1974;2:394–7.
16. Sung JJY, Chiu PCY, Chan FKL, et al. Asia-pacific working group consensus on non-variceal upper gastrointestinal bleeding: An update 2018. Gut 2018;67:1757–68.
17. Laine L, Jensen DM. Management of patients with ulcer bleeding. Am J Gastroenterol 2012;107:345–60.
18. Gralnek IM, Dumonceau JM, Kuipers EJ, et al. Diagnosis and management of nonvariceal upper gastrointestinal hemorrhage: European Society of Gastrointestinal Endoscopy (ESGE) guideline. Endoscopy 2015;47(10):a1–46.
19. Masjedizadeh AR, Hajiani E, Alavinejad P, et al. High dose versus low dose intravenous pantoprazole in bleeding peptic ulcer: A randomized clinical trial. Middle East J Dig Dis 2014;6:137–43.
20. Sachar H, Vaidya K, Laine L. Intermittent vs continuous proton pump inhibitor therapy for high-risk bleeding ulcers: A systematic review and meta-analysis. JAMA Intern Med 2014;174(11):1755–62.
21. Wang CH, Ma MH, Chou HC, et al. High-dose vs non-high-dose proton pump inhibitors after endoscopic treatment in patients with bleeding peptic ulcer: A systematic review and meta-analysis of randomized controlled trials. Arch Intern Med 2010;170:751–8.
22. Bai Y, Chen DF, Wang RQ, et al. Intravenous esomeprazole for prevention of peptic ulcer rebleeding: A randomized trial in Chinese patients. Adv Ther 2015;32(11):1160–76.
23. Lam SK, Hasan M, Sircus W, et al. Comparison of maximal acid output and gastrin response to meals in Chinese and Scottish normal and duodenal ulcer subjects. Gut 1980;21:324–8.
24. Caraco Y, Lagerstrom PO, Wood AJ. Ethnic and genetic determinants of omeprazole disposition and effect. Clin Pharmacol Ther 1996;60:157–67.