LESS IS MORE

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

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Background: High-dose proton pump inhibitors (PPIs) (80-mg bolus, followed by 8-mg/h continuous infusion for 72 hours) have been widely studied and used. However, to date no concrete evidence has shown that high-dose PPIs are more effective than non–high-dose PPIs.

Methods: We performed a literature search for randomized controlled trials that compared the use of high-dose PPIs vs non–high-dose PPIs in patients with bleeding peptic ulcer and determined their effects on rebleeding, surgical intervention, and mortality. Outcomes data were combined in a meta-analysis and were reported as odds ratios (ORs) with 95% confidence intervals (CIs).

Results: A total of 1157 patients from 7 high-quality randomized studies were included in this meta-analysis. High-dose PPIs and non–high-dose PPIs did not differ in their effects on the rates of rebleeding (7 studies and 1157 patients; OR, 1.30; 95% CI, 0.88-1.91), surgical intervention (6 studies and 1052 patients; 1.49; 0.66-3.37), or mortality (6 studies and 1052 patients; 0.89; 0.37-2.13). Post hoc subgroup analyses revealed that summary outcomes measures were unaffected by severity of signs of recent hemorrhage at initial endoscopy, route of PPI administration, or PPI dose.

Conclusion: Compared with non–high-dose PPIs, high-dose PPIs do not further reduce the rates of rebleeding, surgical intervention, or mortality after endoscopic treatment in patients with bleeding peptic ulcer.

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BLEEDING PEPTIC ULCER IS A common cause of emergency admissions to hospitals. It is associated with high morbidity, mortality, and health care costs.[1-3] Primary management of bleeding peptic ulcer includes prompt fluid replacement, treatment of comorbidities, administration of acid-suppressing agents, endoscopic therapy, and surgery. Despite advances in pharmacologic options and endoscopic techniques, morbidity and mortality have remained around 5% to 10% over the past decade.[2,3] Endoscopic intervention has significantly reduced the rates of rebleeding, surgical intervention, and mortality.[4] However, about 10% to 20% of patients undergoing endoscopic intervention experience rebleeding and have almost a 4% mortality rate.[5] Medical treatment is useful to stabilize clots after endoscopic treatment.

See also pages 747, 749, 765, 772, 779, and 784

In vitro studies[6-8] have shown that coagulation and stable platelet aggregation do not occur at pH levels below 6. Moreover, when pH is elevated above 5, clot lysis by pepsin is largely reduced.[9] Histamine$_2$ receptor antagonists (H_2RAs) and proton pump inhibitors (PPIs) are widely used to suppress gastric acid secretion. Several studies[10-13] have shown that PPIs are superior to H_2RAs in gastric acid suppression and in control of rebleeding episodes. However, no consensus exists about the optimal dose of intravenous PPIs.

One study[14] revealed that intragastric pH can be maintained above 6 using high-dose PPIs. Several randomized controlled studies[15-18] compared high-dose PPIs vs placebo. Those investigators concluded that high-dose PPIs were effective in reducing rebleeding rates. Nevertheless, a meta-analysis[19] demonstrated that non–high-dose PPIs were also superior to placebo or H_2RAs in terms of rebleeding rates. In other words, there was little solid evidence demonstrating that high-dose PPIs were more effective than non–high-

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dose PPIs in stopping bleeding peptic ulcer. Because high-dose PPIs are significantly more expensive, we systematically reviewed the literature and performed a meta-analysis to determine whether high-dose PPIs were superior to non–high-dose PPIs in treating bleeding peptic ulcer.

METHODS

DATA SOURCES AND SEARCH STRATEGY

Two of us (C.-H.W. and Z.-S.Y.) performed a comprehensive literature search of several databases, including BioMedCentral, CINAHL, MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials. We searched Micromedex for available PPIs and found 5 agents (omeprazole, sodium/magnesium, pantoprazole sodium, lansoprazole, rabeprazole sodium, and esomeprazole sodium/magnesium). The following strategy keywords were *proton pump inhibitor*, *omeprazole*, *pantoprazole*, *lansoprazole*, *rabeprazole*, *eosmeprazole*, *hemorrhage*, and *bleeding*. The full search strategies are available in the Appendix (available on request from the corresponding author). No language limits were imposed. The search was performed independently by two of us (C.-H.W. and Z.-S.Y.) in August 2009. We used backward snowballing (ie, scanning of references of retrieved articles and pertinent reviews) for further studies.

STUDY SELECTION

References acquired from databases and the literature search were first examined at the title and abstract level. High-dose PPIs were defined as a dose equivalent to an 80-mg bolus of omeprazole or pantoprazole, followed by a continuous intravenous infusion of drug at 8 mg/h for 72 hours.[5,19-21] Continuous infusion doses exceeding 192 mg/d were also considered high-dose PPIs. Other doses were considered non–high-dose PPIs.

We used the following inclusion criteria to select pertinent studies: (1) randomized controlled trials, (2) comparison of high-dose vs non–high-dose PPIs, (3) endoscopically confirmed bleeding peptic ulcer, (4) administration of PPIs after endoscopic intervention, and (5) outcomes reported as rates of rebleeding, surgical intervention, or mortality.

DATA EXTRACTION

Baseline and outcomes data were independently abstracted by two of us (C.-H.W. and Z.-S.Y.), with divergences resolved by consensus. Specifically, we extracted study design, patient characteristics (age, sex, and endoscopic findings), population, number of randomized patients, and interventions (route, dose, and frequency of administration of PPIs). On the basis of endoscopic appearance of ulcers, patients were categorized as being at high risk for further bleeding (spurting, oozing, nonbleeding visible vessel, or adherent clot) or at low risk for further bleeding (flat pigmented spot or clean ulcer base). Our primary outcome was recurrent ulcer bleeding within 30 days of randomization. Rebleeding should be confirmed by endoscopy. Secondary outcomes included surgical intervention and mortality from any cause (30-day mortality or "in-hospital" mortality).

DEFINITIONS OF OUTCOMES

Rebleeding

Rebleeding rate was difficult to define because there was significant variation in the definition of rebleeding among the studies. The distinction between continuing bleeding (active bleeding with failed endoscopic intervention) and rebleeding (recurrent bleeding after endoscopically confirmed hemostasis spontaneously or due to endoscopic intervention) was not clearly made. Four studies[22-25] excluded patients from study enrollment if their ulcer bleeding did not stop spontaneously or was promoted by endoscopy. Therefore, bleeding after the index endoscopy could be deemed recurrent bleeding. Another study[26] excluded patients with peptic ulcers that were actively bleeding. Two other studies[27,28] did not specifically exclude patients whose ulcer was bleeding and in whom it could not be terminated by endoscopic intervention. Udd et al[27] defined rebleeding as rebleeding found on endoscopy or persistent bleeding necessitating an emergency operation. Udd et al excluded patients with immediate failure of endoscopic therapy and operation from analysis. Bajaj et al[28] excluded patients with profuse hemorrhage leading to persistent shock who were unable to be resuscitated without interventional radiology or surgery.

All studies set some clinical criteria for suspicion of rebleeding, including hemodynamic changes (hypotension or tachycardia), decline in hemoglobin level, or overt bleeding (hematemesis or melena). Suspected rebleeding was subsequently confirmed by endoscopy. The time from suspicion to confirmation was not stated. Udd et al[27] performed routine control endoscopy 72 hours after the index endoscopy. In their study, 14 patients had rebleeding, 3 of whom were found to have signs of rebleeding or ongoing bleeding on routine endoscopic examination, without any clinically detectable bleeding signs or symptoms. Andriulli et al[24] performed selective successive endoscopy in high-risk patients (≥6 points at admission according to the scoring system by Rockall et al[29]). Timing of assessment for rebleeding varied across studies. Udd et al[27] and Yüksel et al[25] did not clearly specify the timing. Andriulli et al[24] recorded rebleeding within 7 days and did not record rebleeding episodes after patients were discharged. Cheng,[22] Yılmaz,[26] Bajaj,[28] and Hung[23] and colleagues assessed episodes of rebleeding within 30 days. In the present meta-analysis, the pooled rebleeding analysis referred to rebleeding reported from the time the patient was randomized up to 30 days later.

Surgical Intervention

There were no clearly stated surgical indications in most studies except for that by Yüksel et al.[25] The most common indication for surgery was unsuccessful endoscopic treatment. However, it was not mentioned how many times endoscopic treatment could be performed before endoscopic intervention was deemed a failure and radiologic or surgical intervention began. Only Yüksel et al specified that, if rebleeding occurred after the second endoscopic treatment, surgery was indicated. It was not clearly stated in all studies whether radiologic intervention was counted as a surgical intervention. In our meta-analysis, the pooled surgical intervention analysis referred to surgical intervention indicated at the discretion of the primary care physicians when medical treatment was deemed a failure.

Mortality

Of 6 studies reporting mortality, Hung et al[23] and Yüksel et al[25] did not state the timing of assessment of mortality. Udd,[27] Yılmaz,[26] and Bajaj[28] and colleagues reported mortality within 30 days. Andriulli et al[24] reported only in-hospital mortality. Regarding the causes of mortality, all studies described them in the text. Causes included unsuccessful hemostasis, pneumonia, myocardial infarction, and unrelated operations. Only Andriulli et al specifically reported mortality rates according to the cause of death. In this meta-analysis, the pooled mortality analysis referred to all-cause mortality.

VALIDITY ASSESSMENT

Two of us (C.-H.W. and Z.-S.Y.) assessed the methods quality of each in-

cluded study using the system described by Jadad et al.[30] Each study was evaluated using a 5-point scale, with 1 point being awarded for each of the following criteria: randomized controlled trial, details of randomization methods provided, double-blind study, details of blinding method provided, and information on study withdrawals provided. Studies scoring 3 points or higher were included. Discrepancies in ratings were resolved by discussion between the 2 of us.

DATA SYNTHESIS AND ANALYSIS

All data were entered and analyzed using available software (Review Manager [RevMan], version 5.0; Copenhagen, Denmark The Nordic Cochrane Centre, The Cochrane Collaboration, 2008). Binary outcomes from individual studies were collected to compute individual odds ratios with 95% confidence intervals by the Mantel-Haenszel method. A fixed-effects model was used to calculate the pooled summary effect. A random-effects model was used if we detected moderate (50%) or higher statistical inconsistency.[31]

To evaluate statistical heterogeneity and inconsistency of treatment effects across studies, Cochrane Q tests and I^2 statistics, respectively, were used.[32] Statistical significance was set at 0.10 for Cochrane Q tests. I^2 statistics measured the extent of inconsistency among results of the studies. The outcome is expressed as a percentage of total variation across studies that is due to statistical heterogeneity rather than chance. A value of 0% indicates that all variability in effect estimates is due to chance rather than statistical heterogeneity. A value exceeding 50% indicates substantial statistical heterogeneity.

Post hoc subgroup analyses were performed to examine the effect of severity of signs of recent hemorrhage at initial endoscopy, route of PPI administration, and PPI dose. This study was performed in compliance with The Cochrane Collaboration and the Quality of Reporting of Meta-analyses statement.[33]

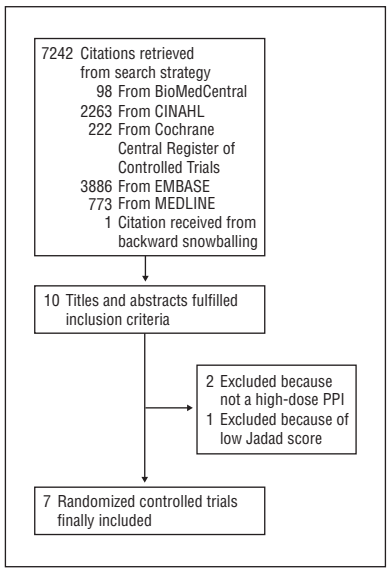

Figure 1. Literature search performed herein. PPI indicates proton pump inhibitor.

RESULTS

SEARCH FINDINGS

Using our search strategy, we initially found 7243 citations (**Figure 1**). These included heterogeneous studies. The treatment groups differed in the dose, route, and frequency of administration of PPIs. The control groups also varied, with the use of placebo, H_2RAs, somatostatin, or the same PPI via different doses, routes, and frequencies of administration. After examining these studies at the title and abstract level, we found 9 citations through database searches that might compare high-dose with non–high-dose PPIs. Backward snowballing identified another relevant study. We retrieved the full texts of these 10 articles and assessed them using our inclusion criteria. Two studies[34,35] were excluded because the PPI doses in the treatment groups were slightly lower than our predetermined high-dose PPI level. One study[34] used omeprazole, 80-mg bolus injection, followed by 160-mg continuous infusion for 24 hours; the other study[35] used pantoprazole, 40-mg bolus injection, followed by 8-mg/h continuous infusion for 72 hours. Thereafter, we evaluated the quality of the remaining 8 studies. A third study[36] was excluded because it achieved only 1 point using the scoring system by Jadad et al.[30] The remaining 7 studies[22-28] were consistent with the inclusion criteria and achieved at least 3 points using the scoring system (**Table 1** and **Table 2**). These 7 studies included 1157 patients. The study by Hung et al[23] compared treatment effects among high-dose, non–high-dose, and placebo groups. We extracted only the results of the high-dose and non–high-dose groups for analysis.

QUANTITATIVE DATA SYNTHESIS

The odds ratios (95% confidence intervals) for rebleeding, surgical intervention, and mortality were 1.30

Table 1. Study Design and Patient Characteristics

Source	Multicenter Enrollment	Double-Blind	No. of Patients	Age, Mean, y	Male Sex, No. (%)	Forrest Classification by Endoscopy, No. (%)					
						F1A	F1B	F2A	F2B	F2C	F3
Udd et al,[27] 2001[a]	Yes	Yes	142	64.7	85 (59.9)	16 (11.3)	47 (33.1)	19 (13.4)	22 (15.5)	38 (26.8)	0
Cheng et al,[22] 2005	No	No	105	64.2	67 (63.8)	98 (93.3)[b]				7 (6.7)	0
Yilmaz et al,[26] 2006	No	Yes	211	52.7	145 (68.7)	0	0	0	21 (10.0)	46 (21.8)	144 (68.2)
Bajaj et al,[28] 2007	No	No	25	63.0	16 (64.0)	7 (28.0)		7 (28.0)	0[c]	2 (8.0)	9 (36.0)
Hung et al,[23] 2007	No	No	103	60.9	67 (65.0)	11 (10.7)	52 (50.5)	26 (25.2)	13[d] (12.6)	0	0
Andriulli et al,[24] 2008[a]	Yes	Yes	474	66.5	307 (64.8)	50 (10.5)	155 (32.7)	166 (35.0)	103 (21.7)	0	0
Yüksel et al,[25] 2008	No	No	97	58.3	74 (76.3)	7 (7.2)	60 (61.9)	30 (30.9)	0	0	0

Abbreviations: F1A, spurting blood; F1B, oozing blood; F2A, nonbleeding visible vessel; F2B, adherent clot; F2C, flat pigmented spot; F3, clean ulcer base.
[a] The percentages of 2 studies[24,27] do not total 100 owing to rounding.
[b] This study used a different classification system for endoscopic findings, which were converted to corresponding Forrest classifications.
[c] There was a discrepancy between the text and table in the original article. The data in the table are given here.
[d] The original article missed 1 patient in this classification, but the correct data cannot be retrieved from the text. This mistake does not influence the outcomes analysis.

Table 2. Outcomes Data in the Meta-analysis

Source	No. of Patients	Analysis	High-Dose PPI	Non–High-Dose PPI	Rebleeding, No. (%)		Surgical Intervention, No. (%)		Mortality, No. (%)	
					High-Dose PPI	Non–High-Dose PPI	High-Dose PPI	Non–High-Dose PPI	High-Dose PPI	Non–High-Dose PPI
Udd et al,[27] 2001	142	PP	Omeprazole (IV 80-mg bolus and IF 8 mg/h for 3 d)	Omeprazole (IV 20 mg/d for 3 d)	8/69 (11.6)	6/73 (8.2)	5/69 (7.2)	3/73 (4.1)	2/69 (2.9)	4/73 (5.5)
Cheng et al,[22] 2005	105	ITT	Omeprazole (IV 80-mg bolus and IF 200 mg/d for 3 d)	Omeprazole (IV 80-mg bolus and IF 80 mg/d for 3 d)	21/52 (40.4)	23/53 (43.4)	Unavailable	Unavailable	Unavailable	Unavailable
Yılmaz et al,[26] 2006	211	ITT	Omeprazole (IV 80-mg bolus and IF 8 mg/h for 3 d)	Omeprazole (oral 40 mg every 12 h for 3 d)	7/112 (6.2)	5/99 (5.1)	3/112 (2.7)	2/99 (2.0)	3/112 (2.7)	2/99 (2.0)
Bajaj et al,[28] 2007	25	ITT	Pantoprazole (IV 80-mg bolus and IF 8 mg/h for 3 d)	Pantoprazole (oral 80 mg every 12 h for 3 d)	2/13 (15.4)	0/12	1/13 (7.7)	0/12	0/13	0/12
Hung et al,[23] 2007	103	PP	Pantoprazole (IV 80-mg bolus and IF 8 mg/h for 3 d)	Pantoprazole (IV 80-mg bolus and IV 40 mg every 12 h for 3 d)	2/54 (3.7)	2/49 (4.1)	0/54	1/49 (2.0)	0/54	0/49
Andriulli et al,[24] 2008	474	PP	Omeprazole or pantoprazole (IV 80-mg bolus and IF 8 mg/h for 3 d)	Omeprazole or pantoprazole (IV 40 mg/d for 3 d)	28/238 (11.8)	19/236 (8.1)	3/238 (1.3)	1/236 (0.4)	5/238 (2.1)	5/236 (2.1)
Yüksel et al,[25] 2008	97	PP	Pantoprazole (IV 80-mg bolus and IF 8 mg/h for 3 d)	Pantoprazole (IV 40 mg every 12 h for 3 d)	4/48 (8.3)	3/49 (6.1)	2/48 (4.2)	2/49 (4.1)	0/48	0/49

Abbreviations: IF, infusion; ITT, intent to treat; IV, intravenous; PP, per protocol; PPI, proton pump inhibitor.

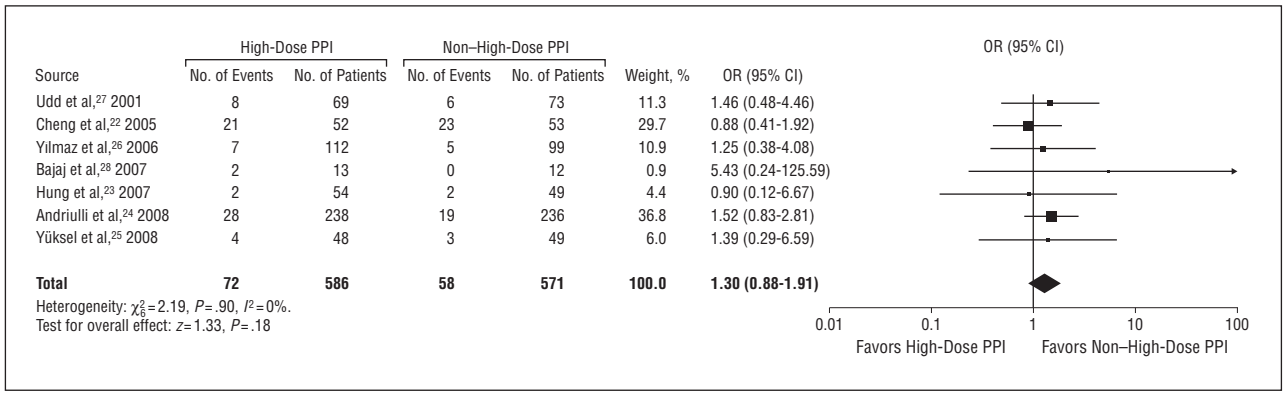

Figure 2. Effect of high-dose vs non–high-dose proton pump inhibitors (PPIs) on rebleeding. Odds ratios (ORs) and 95% confidence intervals (CIs) were computed by the Mantel-Haenszel method.

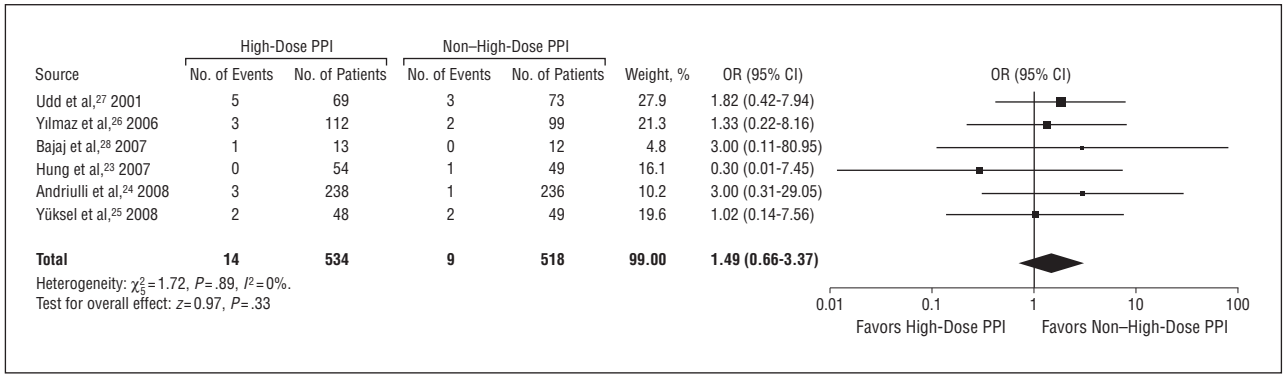

Figure 3. Effect of high-dose vs non–high-dose proton pump inhibitors (PPIs) on surgical intervention. Odds ratios (ORs) and 95% confidence intervals (CIs) were computed by the Mantel-Haenszel method.

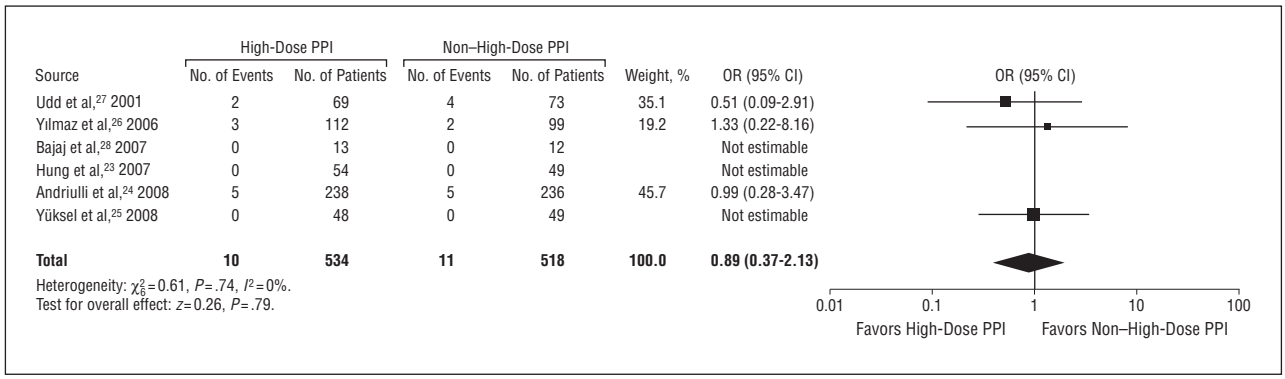

Figure 4. Effect of high-dose vs non–high-dose proton pump inhibitors (PPIs) on mortality. Odds ratios (ORs) and 95% confidence intervals (CIs) were computed by the Mantel-Haenszel method.

Table 3. Results of Post Hoc Subgroup Analyses of Summary Outcomes Measures

Variable	Pooled Rate, %		Heterogeneity	Odds Ratio (95% Confidence Interval)	Trials Included
	High-Dose PPI	Non–High-Dose PPI			
Severity of Signs of Recent Hemorrhage at Initial Endoscopy Among High-Risk Patients					
Rebleeding	10.2	6.9	No, P=.94	1.53 (0.92-2.54)	5 Studies[23-25,27,28]
Surgical intervention	1.7	1.2	No, P=.67	1.34 (0.42-4.32)	4 Studies[23-25,28]
Mortality	1.4	1.5	NA	0.99 (0.28-3.47)	4 Studies[23-25,28]
Route of PPI Administration					
Oral PPI as control treatment					
Rebleeding	7.2	4.5	No, P=.39	1.58 (0.54-4.66)	2 Studies[26,28]
Surgical intervention	3.2	1.8	No, P=.67	1.64 (0.34-7.87)	2 Studies[26,28]
Mortality	2.4	1.8	NA	1.33 (0.22-8.16)	2 Studies[26,28]
Intravenous PPI as control treatment					
Rebleeding	13.7	11.5	No, P=.85	1.26 (0.83-1.90)	5 Studies[22-25,27]
Surgical intervention	2.4	1.7	No, P=.67	1.44 (0.56-3.74)	4 Studies[23-25,27]
Mortality	1.7	2.2	No, P=.55	0.78 (0.29-2.14)	4 Studies[23-25,27]
PPI Dose					
Low-dose PPI as control treatment					
Rebleeding	11.7	8.1	No, P=.95	1.51 (0.88-2.58)	2 Studies[24,27]
Surgical intervention	2.6	1.3	No, P=.72	2.14 (0.63-7.29)	2 Studies[24,27]
Mortality	2.3	2.9	No, P=.55	0.78 (0.29-2.14)	2 Studies[24,27]
Intermediate-dose PPI as control treatment					
Rebleeding	12.9	12.6	No, P=.83	1.10 (0.63-1.92)	5 Studies[22,23,25,26,28]
Surgical intervention	2.6	2.4	No, P=.79	1.09 (0.36-3.32)	4 Studies[23,25,26,28]
Mortality	1.3	1.0	NA	1.33 (0.22-8.16)	4 Studies[23,25,26,28]

Abbreviations: NA, not applicable; PPI, proton pump inhibitor.

(0.88-1.91), 1.49 (0.66-3.37), and 0.89 (0.37-2.13), respectively (**Figures 2**, **3**, and **4**). Statistical heterogeneity values for rebleeding, surgical intervention, and mortality were P=.90, P=.89, and P=.74, respectively. I^2 statistic was 0% for all 3 effect measures. Therefore, there was no significant statistical heterogeneity or inconsistency across included studies.

Results of post hoc subgroup analyses are summarized in **Table 3**. No significant difference was noted in rebleeding, surgical intervention, or mortality between high-dose and non–high-dose groups among subgroups categorized by severity of signs of recent hemorrhage at initial endoscopy, route of PPI administration, or PPI dose. Outcomes data among high-risk patients were retrieved from 5 articles.[23-25,27,28] Among those studies, Udd et al[27] did not classify adherent clots as high-risk lesions. Therefore, in that study we used outcomes data from patients with F1A, F1B, and F2A lesions (based on the Forrest classification[37]). Low-dose PPIs were defined as 40 mg/d or less of intravenous or oral omeprazole or pantoprazole.[24] Intermediate-dose PPIs were defined as those between high and low doses of intravenous or oral omeprazole or pantoprazole.

COMMENT

The most important result of this meta-analysis is the finding among patients with bleeding peptic ulcer that high-dose PPIs are not superior to non–high-dose PPIs in reducing the rates of rebleeding, surgical intervention, or mortality after endoscopic treatment. While a plethora of studies have compared high-dose PPI treatment with placebo or H_2RAs, few studies have compared different doses of PPIs. A meta-analysis by Leontiadis et al[5] included 24 randomized controlled studies in which patients received

high-dose and non–high-dose PPIs. Rates of rebleeding and surgical intervention were significantly reduced in the high-dose and non–high-dose PPI groups compared with patients who received placebo or H_2RAs. However, meta-regression analysis revealed no association of PPI dose with treatment effects. Our meta-analysis further focused on head to head randomized controlled studies and surprisingly identified only 7 such studies. The results of this meta-analysis might be considered counterintuitive in that higher doses of PPIs had no advantage over lower doses of PPIs.

There may be several explanations for this. The first is related to pharmacogenetic and geographic factors. Enhanced efficacy of PPI therapy for bleeding peptic ulcer has been noted among Asians.[5] Two of our 7 reviewed trials studied Asians. One was performed in Taiwan[22] and the other in Hong Kong.[23] Other investigators have suggested that Chinese populations may have smaller parietal cell mass compared with populations of white race/ethnicity.[38] High-dose and non–high-dose PPIs may have similar ability to saturate parietal cells. Other studies[39,40] identified different metabolic rates of omeprazole by cytochrome P450s, with Chinese populations metabolizing omeprazole more slowly than persons of white race/ethnicity.[39,40] The higher prevalence of *Helicobacter pylori* infection among Asian populations would also be consistent with a greater acid-suppressive effect of a given PPI dose.[41] In the meta-analysis by Leontiadis et al,[5] including 8 studies in Asia and 16 studies mainly in Europe, treatment effects of PPIs were consistently higher among Asians than non-Asians in rates of rebleeding, surgical intervention, and mortality. Therefore, it would be less likely that high-dose PPI treatment would exhibit significant benefit over non–high-dose PPI treatment in head to head studies among Asians.

A second explanation for our findings may be that some studies enrolled patients with less severity of bleeding peptic ulcer. The studies by Udd,[27] Cheng,[22] Yılmaz,[26] and Bajaj[28] and colleagues included patients having ulcers with lower potential for rebleeding (ie, Forrest classification types IIC and III).[37] The study by Bajaj et al excluded patients who could not take oral medications, which might exclude seriously ill patients from study enrollment. Inclusion of patients with lower potential for rebleeding or exclusion of seriously ill patients might dilute the effect of high-dose PPI treatment. Post hoc subgroup analyses performed herein among high-risk patients demonstrated that high-dose PPIs were no more effective than non–high-dose PPIs. However, only 5 studies were included in the subgroup analysis, with one of them (by Andriulli et al[24]) providing most of the patients, which might have affected the pooled results. More studies were needed to have adequate power in such an analysis.

Third, these studies each recruited a small population, rendering it difficult to detect significant differences in head to head studies. In the study by Andriulli et al,[24] an estimated 8% difference in rebleeding rates between high-dose and non–high-dose PPIs was used to calculate the required sample size. However, the actual difference might be even smaller, if a difference existed. Larger populations are needed to assess any benefit of high-dose over non–high-dose PPIs.

Theoretically, maintenance of intragastric pH above 6 in patients with bleeding peptic ulcer should result in better clinical outcomes, including reduced rates of rebleeding, surgical intervention, and mortality. This was indirectly corroborated in the retrospective study by Simon-Rudler et al,[42] who reviewed patients with high-risk bleeding peptic ulcer (ie, spurting and oozing hemorrhage or nonbleeding visible vessels) from 1997 to 2004. Compared with non–high-dose omeprazole (40 mg/d intravenously), high-dose omeprazole reduced the occurrence of rebleeding, need for surgery, and mortality due to hemorrhagic shock in this patient group. Other studies[11,18,23] recorded the fraction of time during which the intragastric pH was above 6 using 24-hour pH monitors in patients with bleeding peptic ulcer receiving PPIs. The reported fractions of time differed among these studies, ranging from 50% to 85%. However, the rebleeding rate was similar or lower in the study[23] with a short period during which intragastric pH was kept above 6. Such indirect evidence suggests that PPI treatment effect may not be directly related to intragastric pH. Another study by Udd et al[43] further compared the effects of high-dose and non–high-dose omeprazole on intragastric acidity among patients with bleeding peptic ulcer treated endoscopically. They found a significant difference in intragastric pH between the 2 groups on the first and second days of treatment. However, the difference in rebleeding rates between the 2 groups was not significant. Therefore, whether intragastric pH can serve as a reliable proxy for adequate treatment is questionable.

Since publication of a 2000 article by Lau et al,[17] the use of high-dose PPIs has been widely studied. Two consensus documents in 2002 and 2003 endorsed the use of high-dose PPI treatment.[44,45] However, because of the cost of high-dose PPIs, more evidence is needed to recommend this therapy. A 2008 review article by Gralnek et al[37] recommended the use of high-dose PPIs in high-risk patients. However, the authors questioned the goal of "intragastric pH above 6" as a reliable proxy for adequate treatment. Our meta-analysis provides insufficient evidence to support the use of high-dose over non–high-dose PPIs. Only 7 randomized controlled studies compared high-dose with non–high-dose PPIs. No study showed any significant difference in the associated rates of rebleeding, surgical intervention, or mortality. Despite the absence of statistical heterogeneity, there was much clinical heterogeneity across these 7 trials in study design, patient inclusion, endoscopic treatment, route and dose of PPI administration in control groups, and outcomes assessment. We anticipate the performance of more high-quality randomized controlled trials (such as the recent study by Sung et al[20]) that will include diverse racial/ethnic groups, standardized endoscopic diagnosis and treatment, double-blind treatment design, and outcomes assessment using specific criteria over set periods. In this way,

the issue of high-dose PPIs can be explored, and the effect of H_2RAs can be reexamined.[21]

There were 2 limitations to our study. First, data synthesis in this meta-analysis was not performed according to the intent-to-treat principle, with violations of this principle in the studies by Udd,[27] Hung,[23] Andriulli,[24] and Yüksel[25] and colleagues. We strove to reconstruct the results using the intent-to-treat principle. However, detailed data were lacking, and assumptions were difficult to make. Per-protocol analysis tended to overestimate the treatment effect. In studies analyzed using per-protocol analysis, high-dose PPIs showed no benefit. Therefore, we conservatively assumed that, even if these studies had been performed using the intent-to-treat principle, they would not have shown better treatment effects, and the results of this meta-analysis would not have changed. Second, we did not perform funnel plots to detect publication biases. Our study included only 7 studies, most of which enrolled few patients. It had limited power to detect publication bias by visual inspection of funnel plots. Instead, we tried to avoid such biases by adhering to the most stringent guidelines of The Cochrane Collaboration and the Quality of Reporting of Meta-analyses statement. The results of our meta-analysis indicate that, compared with non–high-dose PPIs, high-dose PPIs do not further reduce the rates of rebleeding, surgical intervention, or mortality after endoscopic treatment in patients with bleeding peptic ulcer.

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