High-dose vs. Low-dose Proton Pump Inhibitors post-endoscopic hemostasis in patients with bleeding peptic ulcer. A meta-analysis and meta-regression analysis

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ABSTRACT

Background/Aims: Present meta-analysis aims to evaluate studies of low- versus high-dose proton pump Inhibitors (PPI) post-endoscopic hemostasis, including the newly published randomized controlled trials (RCTs) and to conclude whether low-dose PPI can generate the comparable results as high-dose PPI.

Materials and Methods: To identify suitable trials, the electronic databases PubMed, Medline, Cochrane Library, and the Embase were used. All RCTs concerning low- versus high-dose PPI administration post-endoscopic hemostasis published until December 2016 were identified. Primary outcomes were rebleeding rates, need for surgical intervention, and mortality.

Results: Studies included a total of 1.651 participants. There were significantly less cases of rebleeding in the low-dose PPI treatment arm (p=0.003). All but one study provided data concerning need for Surgical Intervention and Mortality. The respective effect sizes were [odds ratio (OR), 95% confidence intervals (CI): 1.35, 0.72-2.53] and [OR, 95% CI: 1.20, 0.70-2.05]. Both treatment arms were comparable considering the aforementioned outcomes (p=0.35 and p=0.51, respectively). Meta-regression analysis likewise unveiled comparable outcomes between studies using pantoprazole versus lansoprazole concerning all three outcomes [rebleeding (p=0.944), surgical intervention (p=0.884), and mortality (p=0.961)].

Conclusion: A low-dose PPI treatment is equally effective as a high-dose PPI treatment following endoscopic arresting of bleeding. However, we anticipate the completion of more high-quality RCTs that will embrace distinct ethnicities, standardized endoscopic diagnosis and management, double-blind strategies, and appraisal of results working specific standards over clear-cut follow-up periods.

Keywords: Evidence-based medicine, high-dose PPI, low-dose PPI, meta-analysis, systematic review, ulcer rebleeding

INTRODUCTION

Emergency upper gastrointestinal hemorrhage is a frequent and a substantial situation in clinical practice (1). The fundamental management entails resuscitation and endoscopic therapy, but recurrence still happens following primary control of hemorrhage (2). At present, proton pump inhibitors (PPIs) for endoscopic hemostasis is the customary treatment regimen, and convincing guidelines, consensus-generated, have endorsed the use of a high-dose PPI regimen (80 mg bolus followed by intravenous administration of 8 mg/h for 72 h) after arrest of bleeding for enhanced-risk upper gastrointestinal recurrence of hemorrhage (3,4). The perceived clinical advantage of the high-dose regimen is to progress clot firmness by maintaining the gastric pH more than 6 (5,6). However, when high-dose PPI is contrasted to a low-dose PPI administration after initial control of hemorrhage is accomplished, certain clinical trials (7,8) and two older meta-analyses (9,10) conveyed comparable results in recurrent hemorrhage rate and the demand for surgical management between the high- and low-dose PPI treatments.

Three adequately powered randomized controlled trials (RCTs) have been released (11-13) after the publication

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of the aforementioned meta-analyses. This meta-analysis aims to evaluate RCTs of low- versus high-dose PPI after endoscopic bleeding arrest by additionally including the newly published RCTs and to conclude if low-dose PPI regimen can generate comparable results as the high-dose regimen after initial hemostasis by endoscopists.

MATERIALS AND METHODS

Literature search

All RCTs regarding low- versus high-dose PPI administration post-endoscopic hemostasis were identified (2,7,8, 11-17). In keeping with identification of suitable studies, the electronic databases Medline, Embase, PubMed, and the Cochrane Library were utilized to identify articles from 2000 to 2016 in the English language literature which included the following terms and/or amalgamations in their keyword lists, abstracts, or titles: RCT, double-blind, dexlansoprazole, omeprazole, lansoprazole, rabeprazole, esomeprazole, pantoprazole, high-dose PPI, low-dose PPI, PPI, and bleeding. The last search was done in December 2016.

Where it was appropriate, the aforementioned terms were inserted in "[MESH]" (PubMed and the Cochrane Library) or else the terms were joint with "AND/OR" and asterisks.

The outline for this cyclic search is depicted in Figure 1. Study was approved by the ethics committee.

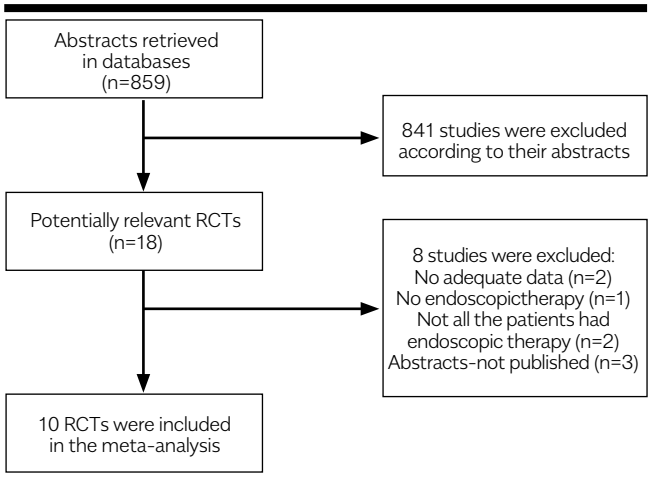

Figure 1. Flow diagram of study selection

Data extraction

Two authors (G.CH and G.S) autonomously chose studies to include and exclude and reached consensus when they did not come to an agreement in the original assignment. The following variables concerning studies were collected: journal and year of publication, country of derivation, authors, duration of trial, participant characteristics and data in regard with rebleeding, need for surgery, and mortality.

Study selection

Trials were encompassed under the subsequent criteria: (a) RCT, (b) contrasting high- versus low-dose PPI for post-endoscopy hemostasis for acute ulcer bleeding, and (c) disposal of satisfactory data (rebleeding, need for surgery, and mortality). Subsequently, studies were excluded if the PPI treatment was commenced before endoscopic engagement and in cases of not being published (conference presentations). Duplicate publications were excluded, and when a study had material overlay with another, the more recent study was integrated to the analysis. High-dose PPI was taken into consideration if at minimum twice the low dose of any of the PPIs administered during the 72-hour post-endoscopic hemostasis.

Interventions and outcome definition

Rebleeding

There was a noteworthy discrepancy in the definition of rebleeding. The difference between failed hemostasis and rebleeding was not distinctly defined. Four studies (2,14,15,17) excluded patients from registration if they did not have spontaneous hemostasis or bleeding was not fostered via endoscopic methods. Consequently, hemorrhage after the primary endoscopic intervention could be considered as rebleeding. Actively bleeding patients were excluded in one study (16). Two studies (7,8) did not explicitly dismiss patients with bleeding ulcer and in whom it could not be ceased by endoscopy. Udd et al. (8) outlined rebleeding as recurrence of bleeding endoscopically documented or continuing hemorrhage requiring an emergency surgical procedure and excluded patients whom endoscopic therapy and operation failed to cure. Bajaj et al. (7) excluded patients with copious bleeding causing unrelenting shock who were incapable of resuscitation without interventional radiology or surgery. Rebleeding was substantiated by endoscopy. Andriulli et al. (14) performed selective sequential endoscopy in high-risk patients presented with ≥6 points graded by the Rockall scoring system.

Surgical Intervention

Indication for surgery was failure to stop bleeding despite repeated endoscopy or radiologic intervention. Only Yüksel et al. (17) stated that surgery was contemplated in cases of failure of the second endoscopic treatment. Whether radiologic intervention was considered as a surgical intervention was not evidently specified in studies.

Mortality

Of the nine studies providing data for mortality, four studies (2,11,12,17) did not declare the timing of assessment. Hsu et al. (13) reported mortality within 14 days. Three studies (7,8,16) reported a 30-day mortality, whereas Andriulli et al. (14) reported only in-hospital mortality.

Statistical analysis

A meta-analysis adhered to the Quality of Reporting of Meta-analyses (QUOROM statement) (18,19) was done for all RCTs comparing low- versus high-dose PPI after post-endoscopic hemostasis. The primary outcomes used for this study were: (a) rebleeding, (b) need for surgery, and (c) mortality.

In order to protect analysis against false-positive conclusions, we prespecified the use of pantoprazole versus lansoprazole and Asian versus non-Asian RCTs as covariates to be investigated by subgroup analysis or meta-regression.

The reviewer level of agreement was assessed by the Maxwell test statistic and the generalized McNemar statistic. A fixed-effects model was used to calculate pooled estimates of outcomes, although a randomized-effects model was used conferring the level of heterogeneity. Binary outcomes from individual studies were gathered to calculate individual odds ratios (OR) with 95% confidence intervals (CI) using the Mantel-Haenszel test. To each total or subtotal the test for overall effect and the test for heterogeneity were provided. Cochrane Q tests and I^2 statistics, correspondingly, were operated to assess statistical heterogeneity and inconsistency of treatment effects across trials (20). For Cochrane Q test, statistical significance was specified at 0.10. To investigate the extent of inconsistency among outcomes of the studies, I^2 statistics were measured. The results were stated as a portion of total variation across studies owed by statistical heterogeneity noticeably by chance. A level of 0% designates that all variability in effect estimates is attributed to chance instead of statistical heterogeneity. A level beyond 50% designates considerable statistical heterogeneity.

Kendall's tau and Spearman rank-order correlation tests were employed to ascertain the symmetry of the funnel plot (effect vs. variance) and detect any publication bias. The standardized effect size was drawn compared with the normal quantile values for visual inspection of possible publication bias in the normal quantile plot.

The magnitude of the publication bias was assessed by the Fail-Safe tests. The effect of covariates on management outcomes was assessed by meta-regression.

Results were significant if $p<0.5$. Analysis of data was done by using the RevMan Version 5.3 (21) Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Center, The Cochrane Collaboration, 2014, the Meta Disk version 1.4 (22) Unidad de Bioestadística Clínica Hospital Ramón y Cajal Planta-2 D Crta. Colmenar km 9.1 28034 Madrid (Spain) and Meta-Win version 2.1 (23) Meta Win: statistical software for meta-analysis, v. 2.0* MS Rosenberg, DC Adams, J Gurevitch-Sunderland, MA: Sinauer Associates, 2000.

Study quality assessment

The Jadad composite scale scored the quality assessment of the methodology of the studies integrated in the meta-analysis (24). Corresponding to this 5-point scale (0 point for "No", 1 point for "Yes" for the succeeding factors: randomized study; randomization designated; double blind trial; double blinding designated; reference to withdrawals and dropouts), low-quality studies are attributed a score of ≤2, whereas the respective scores for high-quality studies are ≥3.

RESULTS

Ten of 859 screened RCTs were finally included (2,7,8,11-17) with a total of 1.651 participants.

Maxwell test statistic was insignificant (p=0.851) demonstrating that reviewers did not differ significantly. The generalized McNemar test (p=0.57) showed that the concordance was spread evenly.

The mean Jadad score of the studies included was 2.6 points. Seven studies had a score of 3 points (8,12-17), two studies of 2 points (2,7), and one study of 1 point (11), respectively.

Table 1. Study design and clinicopathological characteristics

Study	Multicenter trial	Double-blind	Patients	Mean age (y)	Male sex, No. (%)	Forrest classification no. (%)					
						Ia	Ib	IIa	IIb	IIc	III
Udd et al. (8), 2001	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. (15), 2005	No	No	105	64.2	67 (63.8)		98 (93.3)		7 (6.7)	0	
Yilmaz et al. (16), 2006	No	Yes	211	52.7	145 (68.7)	0	0	0	21 (10.0)	46 (21.8)	144 (68.2)
Bajaj et al. (7), 2007	No	No	25	63.0	16 (64.0)	7 (28.0)	7 (28.0)	0	2 (8.0)	9 (36.0)	
Hung et al. (2) 2007	No	No	103	60.9	67 (65.0)	11 (10.7)	52 (50.5)	26 (25.2)	13 (12.6)	0	0
Andriulli et al. (14), 2008	Yes	Yes	474	66.5	307 (64.8)	50 (10.5)	155 (32.7)	166 (35.0)	103 (21.7)	0	0
Yuksel et al. (17), 2008	No	No	97	58.3	74 (76.3)	7 (7.2)	60 (61.9)	30 (30.9)	0	0	0
Hsu et al. (13) 2009	No	No	120	65	82 (68.3)	12 (10)	40 (33.3)	52 (43.3)	16 (13.3)	0	0
Liang et al. (11) 2012	No	No	208	65	145 (69.7)	5 (2.4)	140 (67.3)	12 (5.7)	51 (24.5)	0	0
Masjedizadeh et al. (12) 2014	No	Yes	166	51	114 (69)			N/A			

N/A: not available

The baseline participant characteristics in the analyzed studies are synopsized in Table 1. The results of the included trials are depicted on Table 2. All 10 studies provided data for rebleeding (OR, 95% CI: 1.55, 1.16-2.07]. There were significantly less cases of rebleeding in the low-dose PPI treatment arm (p=0.003) (Table 3, Figure 2). All studies, but the study of Cheng et al. (15), provided data concerning need for surgical intervention and mortality. The respective effect sizes were [OR, 95% CI: 1.35, 0.72-2.53] and [OR, 95% CI: 1.20, 0.70-2.05]. Both treatment arms were comparable considering the aforementioned outcomes (p=0.35 and p=0.51, respectively) (Table 3, Figure 2).

There was no heterogeneity among studies considering all three outcomes. Normal quantile plots did not detect any obvious publication bias concerning all outcomes (Figure 3).

We utilized the fail-safe method (Rosenthal's or Orwin's Method) to calculate the number of future trials with a zero-mean effect size essential to reduce the combined significance to a level (0.05). These tests disclosed that nine studies were needed to change our results concerning rebleeding and five studies concerning the need for surgery. Considering the fact that there have been no more than 10 studies released over the past 14 years, it is extremely unlikely that such a bulky number of relevant trials would have gone unpublished or have been unexploited by our search approach.

Meta-regression analysis also revealed that studies using pantoprazole versus lansoprazole were comparable to all three outcomes [rebleeding (p=0.944), surgical intervention (p=0.884), and mortality (p=0.961) Table 4].

An additional meta-regression analysis considering the episodes of rebleeding did not show significant differences between Asian and Non-Asian populations [coefficient=0.011, standard error=0.4882, p=0.983, relative diagnostic OR (95%CI)=1.01 (0.32-3.21)].

DISCUSSION

High-dose PPIs do not deliver a greater efficiency to non–high-dose PPIs in decreasing the rates of rebleeding, surgical intervention, or mortality after post-endoscopic bleeding arrest. These outcomes did not change with the use of either pantoprazole or lansoprazole.

There may be various reasons for this. (a) One study enrolled patients with not as much of severity of bleeding peptic

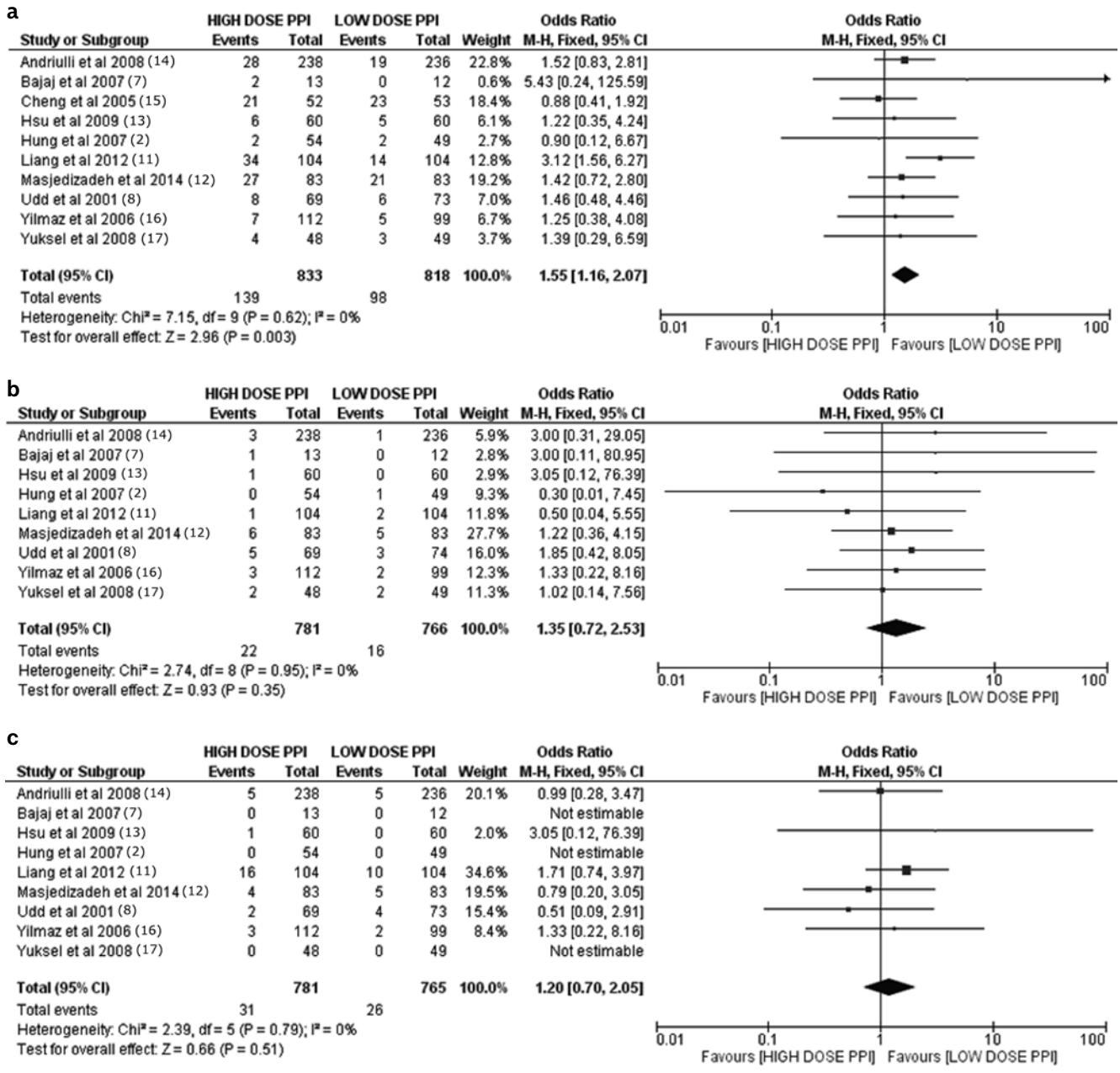

Figure 2. a-c. Meta-analysis of outcomes: (a) rebleeding, (b) need for surgery, and (c) mortality.

ulcer. Yilmaz et al. (16) did not include patients without a history of endoscopic therapy for bleeding ulcer within the past four weeks. They did so to exclude patient categories Ia: Spurting Bleed, Ib: Oozing Bleed, and IIa: Non-Bleeding Visible Vessel. (b) Studies are underpowered, making it problematic to notice significant differences. The episodes of rebleeding did not show significant differences between Asian and Non-Asian populations.

Although some previous meta-analyses state that pharmacogenetic and geographic factors [reduced parietal cell bulk, dissimilar metabolic rates of omeprazole by cytochrome P450s, with Chinese nationals, and greater frequency of *Helicobacter pylori* (HP) infection] contribute to improved efficacy of PPI therapy for bleeding peptic ulcer among Asians. (25) Two of our included trials (2,15) analyzed Asian populations. Our meta-regression analysis

Table 2. Results of the included studies

		Dose		Rebleeding, No. (%)		Surgical Intervention, No. (%)		Mortality, No. (%)	
Author	Patients	High dose PPI	Low dose PPI	High dose PPI	Low dose PPI	High dose PPI	Low dose PPI	High dose PPI	Low dose PPI
Udd et al. (8), 2001	142	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. (15), 2005	105	Omeprazole (IV 80-mg bolus and IF 200 mg/d for3 d)	Omeprazole (IV 80-mg bolus and IF 80 mg/d for 3d)	21/52 (40.4)	23/53 (43.4)	N/A	N/A	N/A	N/A
Yilmaz et al. (16), 2006	211	Omeprazole (IV 80-mg bolus and IF 8 mg/h for 3 d)	Omeprazole (oral 40 mg every 12 h for 3d)	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. (7), 2007	25	Pantoprazole (IV 80-mg bolus and IF 8 mg/h for 3 d)	Pantoprazole (oral 80 mg every 12 h for 3d)	2/13 (15.4)	0/12	1/13 (7.7)	0/12	0/13	0/12
Hung et al. (2), 2007	103	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 3d)	2/54 (3.7)	2/49 (4.1)	0/54	1/49 (2.0)	0/54	0/49
Andriulli et al. (14), 2008	474	Omeprazole or pantoprazole (IV 80-mg bolus and IF 8 mg/h for3 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)
Yuksel et al. (17), 2008	97	Pantoprazole (IV 80-mg bolus and IF 8 mg/h 12 h for 3d) for 3d)	Pantoprazole (IV 40 mg every	4/48 (8.3)	3/49 (6.1)	2/48 (4.2)	2/49 (4.1)	0/48	0/49
Hsu et al. (13), 2009	120	Pantoprazole (IV 80-mg bolus and Pantoprazole 192 mg/day for 3d	Pantoprazole (IV 80-mg bolus and Pantoprazole 160 mg/day for 3d	6/60 (10%)	5/60 (8.3%)	1 /60 (1.7)	0/60	1 /60 (1.7)	0/60
Liang et al. (11), 2012	208	Pantoprazole IV 80-mg bolus and 8 mg/h pantoprazole for 3d, followed by IV 80 mg/d	Pantoprazole (IV 80-mg bolus and IV pantoprazole 80 mg/d until alimentation	34/104 (32.7)	14/104 (13.5)	1/104 (1)	2/104 (1.9)	16/104 (15.4)	10/104 (9.6)
Masjedizadeh et al. (12), 2014	166	Pantoprazole IV 80-mg bolus and 8 mg/h pantoprazole for 3d	Pantoprazole IV 80-mg bolus and 4 mg/h pantoprazole for 3d	27/83 (32.53)	21/83 (25.30)	6/83 (7.2)	5/83 (6)	4/83 (4.8)	5/83 (6)

IF: infusion; IV: intravenous; PPI: proton pump inhibitor; N/A: not available

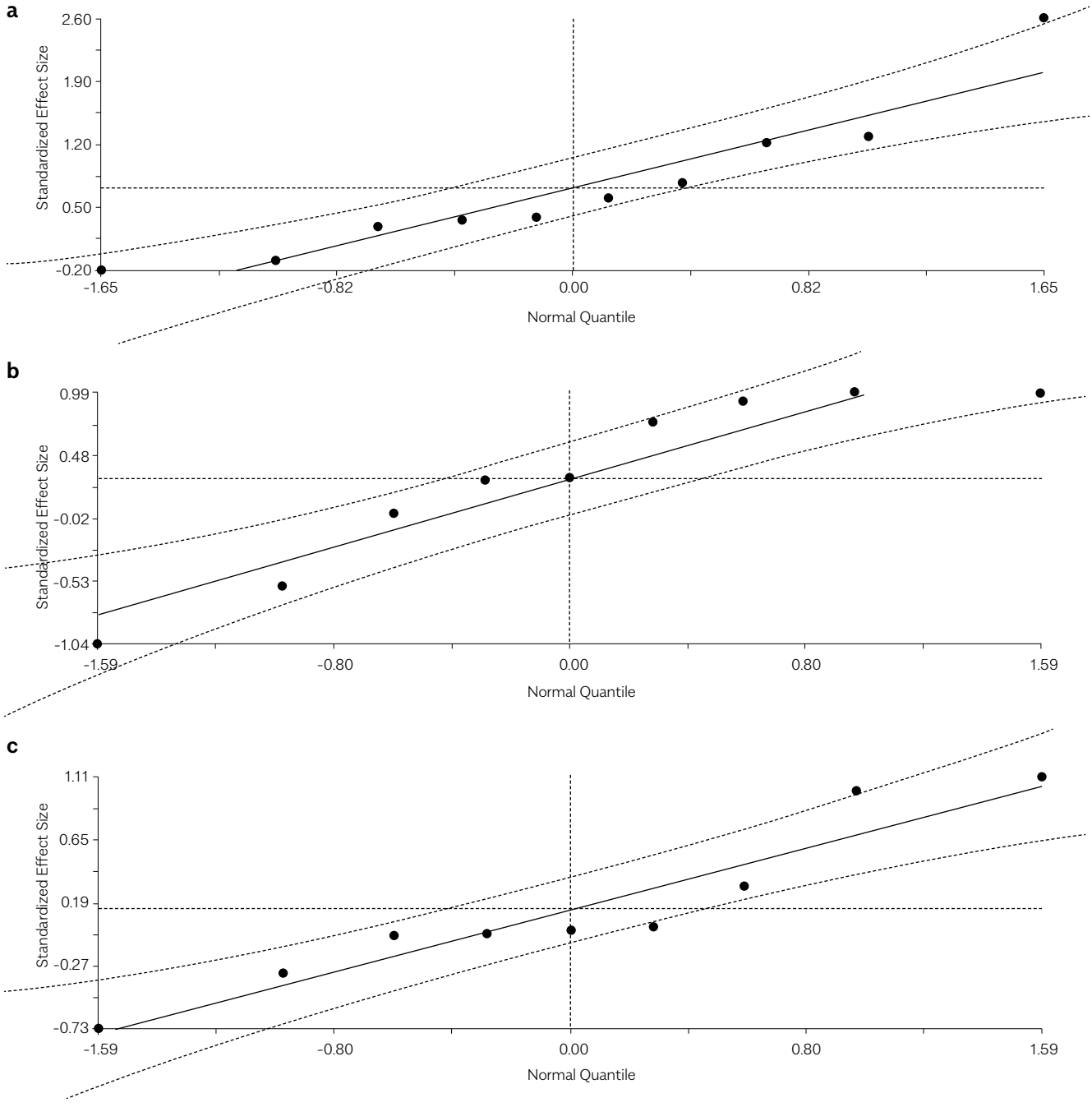

Figure 3. a-c. Normal quantile plot for inspection of publication bias concerning (a) rebleeding, (b) need for surgery, and (c) mortality. The standardized effect size (OR) is plotted against the normal quantile values. The distribution of effect sizes is similar to the distribution of normal quantiles, since data points fall close to the line X=Y.

considering the episodes of rebleeding did not show significant differences between Asian and Non-Asian populations [p=0.983, relative diagnostic OR (95% CI)=1.01 (0.32; 3.21)].

Subsidiary evidence implies that PPI administration outcome may not be straightforwardly associated with intragastric pH. Udd et al. (8) contrasted the influences of high- and low-dose omeprazole on gastric acidity in

Table 3. Meta-analysis of outcomes in rebleeding ulcer

Outcome	Studies	N	Method	Effect size [and 95% CI]	Heterogeneity (Chi2)	Publication bias (Kendall's Tau/ Spearman Rank-Order Correlation)	Test for overall effect
Rebleeding	10	1651	OR-FE	1.55 [1.16, 2.07]	I^2=0% p=0.62	Tau-0.111 p=0.654/ Rs-0.152 p=0.676	Z=2.96 p=0.003 (Favors Low Dose PPI)
Surgical Intervention	9	1546	OR-FE	1.35 [0.72, 2.53]	I^2=0% p=0.95	Tau= 0.000 p=1.00/ Rs= 0.067 p=0.864	Z=0.93 p=0.35
Mortality	9	1546	OR-FE	1.20 [0.70, 2.05]	I^2=0% p=0.79	Tau-0.111 p=0.676/ Rs 0.017 p=0.966	Z 0.66 p=0.51

OR: odds ratio; FE: fixed effect model; CI: confidence interval

Table 4. Meta-regression of omeprazol versus pantoprasol comparison considering outcomes in rebleeding ulcer

Omeprazol vs. Pantoprazol	Coeff.	Std. Err.	RDOR	[95%CI]	p
Rebleeding	-0.027	0.3637	0.97	[0.35, 2.67]	0.944
Surgical Intervention	-0.099	0.6504	0.91	[0.18, 4.45]	0.884
Mortality	-0.028	0.5443	0.97	[0.17, 5.49]	0.961

RDOR: relative diagnostic odds ratio; Coeff: coefficient; Std. Err: standard error; CI: confidence interval

bleeding peptic ulcer managed via endoscopy. Authors discovered a significant difference in gastric pH comparing the two treatment arms on the initial two days of administration. Nevertheless, the difference recurrent hemorrhage rates between the two treatment arms was not statistically significant. Consequently, if gastric pH can operate as a consistent surrogate marker for satisfactory management remains uncertain.

This analysis with fail-safe tests disclosed that nine studies were compulsory to change our results concerning rebleeding and five studies concerning need for Surgery. Bearing in mind the fact that there have been no more than 10 RCTs published over the past 14 years, it is highly unlikely that such a large number of analogous studies would have been missed by our search.

Considering the quality of the evidence, our study encompasses 10 RCTs. Seven of 10 are of high quality (≥3) according to the Jadad classification (24). All studies, but one study (7), was sufficiently powered to validate their results. There was no heterogeneity among studies with regard to each of the three outcomes. Normal quantile plots for inspection of publication bias concerning all three outcomes were normal. The distribution of effect sizes was similar to the distribution of normal quantiles.

In regard with agreements and disagreements with other studies or reviews, a meta-analysis by Leontiadis et al. (25) analyzed 24 RCTs in which participants were provided with high-dose and non–high-dose PPIs. Rebleeding percentages and surgical management were significantly lessened in the high-dose and non–high-dose PPI arms in contrasted to participants who were administered placebo or H_2 receptor antagonists. Nevertheless, meta-regression analysis revealed no association of PPI dose with treatment effects. Two meta-analyses (9,10) have been published comparing low- versus high-dose PPI (administered after endoscopic hemostasis) in terms of rebleeding, need for surgery, and mortality. In the meta-analysis of Wu et al. (10), three of the included nine studies were abstracts enhancing the possibility of selection bias. The meta-analysis by Wang et al. (9) included seven RCTs, but the risk of bias was not provided for visual inspection in

terms of funnel plots. Our results are in accordance with those of the aforementioned meta-analyses given the inclusion of additional three sufficiently powered RCTs. Besides the risk of bias is extensively analyzed both by statistical tests and visual inspection through normal quantile plots. The issue of rebleeding episodes between Asian and non-Asian studies was addressed for first time in our meta-analysis.

Our meta-analysis is not without its limitations. (a) The timeframe for recurrence of hemorrhage rates should be considered, as one study stated rebleeding within the initial 72 h (17), one study stated rebleeding within 7 days (14), one study reported only in-hospital rebleeding (8), one study stated rebleeding within 14 days (13), and six studies stated rebleeding within a month (2,7,11,12,15,16). Results for rebleeding should be unraveled with thoughtfulness, and additional subgroup analyses were not conducted in the present meta-analysis. (b) Studies analyzed in the present meta-analysis were accomplished with diverging doses of PPI, various ethnicities with distinct preponderance of rebleeding, and fluctuating extent of related comorbidities. (c) Analysis in the present meta-analysis was not completed in accordance to the intent-to-treat principle, with violations of this principle in four studies (2,8,14,17). Yet, detailed data were deficient, and postulations were problematic to make.

In conclusion, a low-dose PPI is equally effective as a high-dose PPI administration following endoscopic bleeding arrest in bleeding peptic ulcer patients. We anticipate the completion of more high-quality RCTs that will embrace distinct ethnicities, standardized endoscopic diagnosis and management, double-blind strategies, and appraisal of results working specific standards over clear-cut follow-up periods.

Ethics Committee Approval: Ethics committee approval was received for this study from The Ethics Committee of Korgialenio-Benakio Red Cross Hospital (Decision Date: 04.03.2016).

Informed Consent: Since this study is a meta-analysis of already published trials, there is no need for informed consent.

Peer-review: Externally peer-reviewed.

Author contributions: Concept - G.S., T.S., G. C.; Design - G.S., T.S.; Supervision - T.S.; Resource - A.P., P.M., T.A., G.R., A.V.; Materials - I.K., A.B., H. T.; Data Collection and/or Processing - A.P., P.M., T.A., G.R., A.V., I.K., A.B., H.T.; Analysis and/or Interpretation - G.S.; Literature Search - A.P., P.M., T.A., G.R., A.V., I.K., A.B., H.T.; Writing - G.S.; Critical Reviews - T.S.

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REFERENCES

1. Rockall TA, Logan RF, Devlin HB, Northfield TC. Incidence of and mortality from acute upper gastrointestinal haemorrhage in the United Kingdom. Steering Committee and members of the National Audit of Acute Upper Gastrointestinal Haemorrhage. BMJ 1995; 311: 222-6. [CrossRef]

2. Hung WK, Li VK, Chung CK, et al. Randomized trial comparing pantoprazole infusion, bolus and no treatment on gastric pH and recurrent bleeding in peptic ulcers. ANZ J Surg 2007; 77: 677-81. [CrossRef]

3. Non-variceal upper gastrointestinal haemorrhage: guidelines. Gut 2002; 51 Suppl 4: 1-6.

4. Barkun A, Bardou M, Marshall JK; Nonvariceal Upper GI Bleeding Consensus Conference Group. Consensus recommendations for managing patients with nonvariceal upper gastrointestinal bleeding. Ann Intern Med 2003; 139: 843-57. [CrossRef]

5. Green FW Jr, Kaplan MM, Curtis LE, Levine PH. Effect of acid and pepsin on blood coagulation and platelet aggregation. A possible contributor prolonged gastroduodenal mucosal hemorrhage. Gastroenterology 1978; 74: 38-43.

6. Patchett SE, Enright H, Afdhal N, O'Connell W, O'Donoghue DP. Clot lysis by gastric juice: an in vitro study. Gut 1989; 30: 1704-7. [CrossRef]

7. Bajaj JS, Dua KS, Hanson K, Presberg K. Prospective, randomized trial comparing effect of oral versus intravenous pantoprazole on rebleeding after nonvariceal upper gastrointestinal bleeding: a pilot study. Dig Dis Sci 2007; 52: 2190-4. [CrossRef]

8. 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. [CrossRef]

9. 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. [CrossRef]

10. Wu LC, Cao YF, Huang JH, Liao C, Gao F. High-dose vs low-dose proton pump inhibitors for upper gastrointestinal bleeding: a meta-analysis. World J Gastroenterol 2010; 16: 2558-65. [CrossRef]

11. 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. [CrossRef]

12. Masjedizadeh AR, Hajiani E, Alavinejad P, Hashemi SJ, Shayesteh AA, Jamshidian N. High Dose versus Low Dose Intravenous Pantoprazole in Bleeding Peptic Ulcer: A Randomized Clinical Trial. Middle East J Dig Dis 2014; 6: 137-43.

13. Hsu YC, Perng CL, Yang TH, et al. A randomized controlled trial comparing two different dosages of infusional pantoprazole in peptic ulcer bleeding. Br J Clin Pharmacol 2012; 69: 245-51. [CrossRef]

14. Andriulli A, Loperfido S, Focareta R, et al. High- versus low-dose proton pump inhibitors post-endoscopy haemostasisin patients with peptic ulcer bleeding: a multicentre, randomized study. Am J Gastroenterol 2008; 103: 3011-8. [CrossRef]
15. Cheng HC, Kao AW, Chuang CH, Sheu BS. The efficacy of high- and low-dose intravenous omeprazole in preventing rebleeding for patients with bleeding peptic ulcers and comorbid illnesses. Dig Dis Sci 2005; 50: 1194-201. [CrossRef]
16. Yilmaz S, Bayan K, Tuzun Y, Dursun M, Canoruc F. A head to head comparison of oral vs intravenous omeprazole for patients with bleeding peptic ulcers with a clean base, flat spots and adherent clots. World J Gastroenterol 2006; 12: 7837-43. [CrossRef]
17. Yuksel I, Ataseven H, Koklu S, et al. Intermittent versus continuous pantoprazole infusion in peptic ulcer bleeding: a prospective randomized study. Digestion 2008; 78: 39-43. [CrossRef]
18. Mahid SS, Hornung CA, Minor KS, Turina M, Galandiuk S. Systematic reviews and meta-analysis for the surgeon scientist. Br J Surg 2006; 93: 1315-24. [CrossRef]
19. Moher D, Cook DJ, Eastwood S, Olkin I, Rennie D, Stroup DF. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. Quality of Reporting of Meta-analyses. Lancet 1999; 354: 1896-900. [CrossRef]
20. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003; 327: 557-60. [CrossRef]
21. Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Cochrane Collaboration; 2014.
22. Zamora J, Abraira V, Muriel A, Khan K, Coomarasamy A. Meta-DiSc: a software for meta-analysis of test accuracy data. BMC Med Res Methodol 2006; 6: 31. [CrossRef]
23. Rosenberg MS, Adams DC, Gurevitch J. MetaWin. Statistical software for meta-analysis. Version 2. Massachusetts: Sinauer Associates; 2000.
24. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 1996; 17: 1-12. [CrossRef]
25. Leontiadis GI, Sharma VK, Howden CW. Proton pump inhibitor treatment for acute peptic ulcer bleeding. Cochrane Database Syst Rev 2006: CD002094. [CrossRef]