Review Article

Use of Proton Pump Inhibitors in the Management of Gastroesophageal Varices: A Systematic Review

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Abstract

Objective: To review the efficacy and safety of proton pump inhibitors (PPIs) in gastroesophageal varices (GEVs). **Data Sources:** MEDLINE (1946 to September 2014), EMBASE (1974 to September 2014), International Pharmaceutical Abstracts (1970 to September 2014), Cochrane Central Register of Controlled Trials (1991 to September 2014), Google, and Google Scholar were searched using the following terms: *esophageal varices, gastroesophageal varices, variceal hemorrhage, variceal bleeding, banding ligation, endoscopic variceal ligation, sclerotherapy, proton pump inhibitor, PPI, omeprazole, pantoprazole, lansoprazole, dexlansoprazole, rabeprazole*, and *esomeprazole*. **Study Selection and Data Extraction:** Published and unpublished studies evaluating the clinical outcomes of PPI use for GEVs were included regardless of study design. Non-English and nonhuman studies were excluded. **Data Synthesis:** Of 1156 studies, 20 were included after assessment. There was wide methodological heterogeneity and moderately high risk of bias among studies. Level I evidence suggests that PPIs reduce esophageal ulcer size post–elective esophageal ligation; the clinical importance of such findings is not known given the self-limiting nature of esophageal ulcer. Available evidence does not support a role of PPIs for long-term prophylaxis of portal hypertension–related bleeding and high-dose infusion for acute management of GEV hemorrhage. Retrospective data demonstrate a potential increase in the incidence of spontaneous bacterial peritonitis in patients with cirrhosis receiving PPIs. **Conclusions:** The best available evidence supports the use of short-course (10 days) PPI post–endoscopic variceal ligation to reduce ulcer size if ulcer healing is a concern. Practices such as high-dose infusion and prolonged use should be discouraged until evidence of benefit becomes available.

Keywords

proton pump inhibitors (PPIs), gastroesophageal varices (GEVs), variceal bleed

Introduction

Gastroesophageal varices (GEVs) are dilated vasculature resulting from portal vein hypertension. Present in 50% of patients at the time of diagnosis,[1] they represent one of the most common pathologies found in cirrhosis. The annual rate of first hemorrhage is 15% with a mortality rate of 7% to 15%.[2-5] After an initial bleed, rebleeding occurs at a median rate of 60%, with a mortality rate of 33% in patients who rebleed.[6]

Few therapeutic interventions have been proven to mitigate the risk of bleeding. Strategies involve the following: (1) acute phase interventions with endoscopic procedures, that is, endoscopic variceal ligation (EVL) or endoscopic injection sclerotherapy (EIS), supplemented with a vasoconstrictor such as octreotide to achieve hemostasis, and (2) prophylaxis with elective EVL or EIS and pharmacotherapies to lower portal vein pressure (eg, propranolol).[1] The quest for effective, safe, and noninvasive therapies is ongoing, and proton pump inhibitors (PPIs), given their safety with short-term use and efficacy in nonvariceal gastrointestinal (GI) bleeding, have been considered a candidate.

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PPIs inhibit H^+K^+-ATPase in the parietal cells, the final step of gastric acid production,[7] and are effective in treating peptic ulcer disease. A Cochrane meta-analysis by Leontiadis et al[8] concluded that acute PPI use reduces rebleeding, surgical intervention, and repeated endoscopic treatment. Proposed mechanisms of PPIs in peptic ulcer bleed include stimulation of platelet aggregation and formation of fibrin clots through maintaining a high gastric pH.[7,9,10] It is not known whether such theoretical benefits extend to varices, where the underlying pathology and location of insult differ significantly.

The use of PPIs in GEV has been mentioned briefly in guidelines[1,11] as a measure to improve the safety and efficacy post-EVL based on a single study by Shaheen et al.[12] Despite the paucity of support from guidelines, PPI use is highly prevalent in patients with GEV. A study revealed that 96.1% of patients given octreotide for variceal hemorrhage were also placed on a parenteral PPI,[13] whereas 45.5% of patients in a retrospective cohort were placed on long-term PPI therapy.[14]

A review article by Lodato[15] in 2008 questioning the overuse of PPIs in cirrhosis suggested that their use may be more a tradition than evidence-based practice. The article stated that the main reason for PPIs in cirrhosis might be to prevent/treat esophageal complications after banding/sclerotherapy. They also concluded that the evidence for protective roles of PPIs was scarce. Since then, new evidence has been published. This systematic review incorporates recent studies to the "scarce evidence" in 2008 and aims to evaluate the clinical outcomes of PPIs in GEV.

Data Sources and Selection

A search of MEDLINE (1946 to September 2014), EMBASE (1974 to September 2014), International Pharmaceutical Abstracts (1970 to September 2014), Cochrane Central Register of Controlled Trials (1991 to September 2014), Google, and Google Scholar was conducted. The following search terms were used and combined: ("esophageal varices" OR "gastroesophageal varices" OR "variceal hemorrhage" OR "variceal bleeding" OR "banding ligation" OR "endoscopic variceal ligation" OR "sclerotherapy") AND ("proton pump inhibitor" OR "PPI" OR "omeprazole" OR "pantoprazole" OR "lansoprazole" OR "dexlansoprazole" OR "rabeprazole" OR "esomeprazole"). Search with both keyword and subject heading (if available) was performed. Reference lists of included articles were manually searched to identify pertinent articles. Studies were included if they assessed clinical outcomes of PPIs in GEV regardless of study design. Non-English and nonhuman studies were excluded. Both published and unpublished studies were included to avoid publication bias. However, given the uncertainty about their quality and lack of reporting details, unpublished studies were only included for reference and not graded for quality of evidence nor assessed for risk of bias.

Information extracted from studies included design, number of participants, baseline characteristics (age, Child-Pugh classification, average variceal size, red wale sign, hepatic venous pressure gradient, type of endoscopic procedure, phase of management, history of variceal bleed, and percentage esophageal and gastric varices), regimen (drug, dose, route, and duration) of intervention, and control group as well as outcomes (ulcer size/ number, rebleeding, hospitalization, mortality, and adverse drug reactions [ADRs]).

The quality of evidence provided by published studies was graded according to the US Preventive Services Task Force 1996 classification system[16]: Level I evidence studies are obtained from at least one properly randomized controlled trial (RCT); level II-1 studies are well-designed controlled trials without randomization; level II-2 studies are well-designed cohort or case-control analytical studies, preferably from more than one center or research group; level II-3 studies are multiple time series or dramatic results in uncontrolled experiments; level III evidence includes expert opinions, descriptive studies, case reports, or reports of expert committees. Published studies were also assessed according to the Cochrane Collaboration's tool for assessing the risk of bias.[17] This tool evaluates studies based on prespecified criteria known to introduce bias into clinical studies.

Data Synthesis and Discussions

Our search resulted in 1156 studies, and manual search of reference lists did not identify additional studies. After screening and assessing for eligibility, 20 studies[12-14,18-34] were included, and the rest were excluded for reasons of irrelevance or language (Figure 1). Among the published trials, there were 5 RCTs,[12,14,18,22,30] 2 retrospective cohort studies,[13,21] 3 single-arm trials,[23-25] 1 case series,[28] and 1 case report.[31] In all, 8 conference abstracts were identified: 4 RCTs[19,29,32,33] and 4 retrospective cohort studies.[20,26,27,34] Study characteristics and results are summarized in Table 1 (published studies)[12-14,21-25,28,30,31] and the appendix (unpublished studies).[19,20,26,27,29,32-34]

Identified studies were categorized according to the focus of study: (1) postendoscopic procedure; (2) long-term prophylaxis; and (3) acute phase management. Risk of bias was assessed for published prospective trials (Table 2).[12,14,22-25,28,30,31]

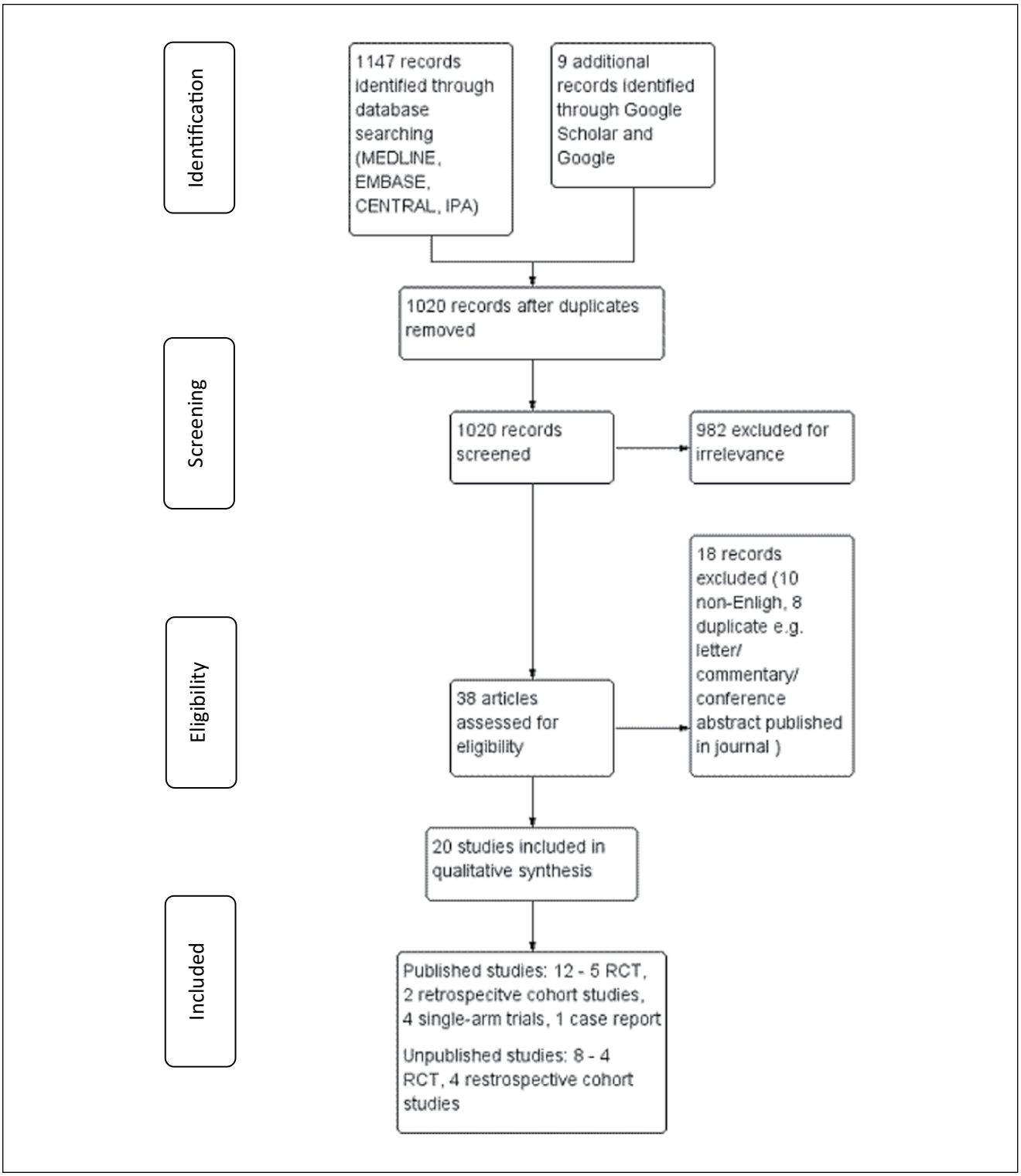

Figure 1. Study flow diagram.
Abbreviations: CENTRAL, Cochrane Central Register of Controlled Trials; IPA, International Pharmaceutical Abstracts; RCT, randomized controlled trial.

Table 1. Summary of Study Characteristics (Published).

Study, Year	Level of Evidence and Study Type	Study Population (Age, Setting, Treatment Phase, Primary/ Secondary Prophylaxis, Procedure)	Special Inclusion/Exclusion Criteria and Study Population Characteristics	Follow-up	Intervention/Control	Primary Outcomes Measures	Intervention Group		Control Group		Effect Size	*P* Value (95% CI)	Outcome Assessment/ Remarks
							n	Results	n	Results			
Postelective endoscopic procedures													
EIS													
Akahoshi et al, 2013[18]	I, RCT	61.6, Hospital, chronic, primary prophylaxis, EIS	• Incl: esophageal varices • Varices: moderate to huge, showed either red wale marking, cherry red spot, or hemotocystic spot • Child-Pugh Class: A, 50%, B, 38.9%, C, 11.1%	NR	I: Rabeprazole 20 mg daily po ×8 weeks C: Famotidine 20 mg bid po ×8 weeks	Mean pH ± SD Time with pH<4 ± SD (min) Heartburn ± SD (days) Dysphagia ± SD (days) Number of ulcer <2/≥2 cm Ulcer healing (weeks)	9	7.02 ± 0.52 0 0.4 ± 0.69 0.71 ± 1.05 6/2 0.78 ± 0.67	9	4.87 ± 0.48 204.5 ± 84.9 1.68 ± 1.3 2 ± 1.5 5/1 1.73 ± 0.66		<0.05 <0.05 <0.05 <0.05 NSS <0.01	Assessment: 24-hour pH monitoring (for pH), bedside questionnaire (for symptoms), endoscopy (for ulcer)
Garg et al, 1995[22]	I, RCT	35.6, NR, chronic, secondary prophylaxis, EIS	Incl: Recurrent EIS-ulcer despite H2RA and sucralfate	NR	I: Omeprazole 20 mg daily po until obliteration of varices C: Placebo	Number of patients with esophageal ulcer (%)	21[a]	16 (76.2)	23[a]	18 (78.3)	-	NSS	Assessment: endoscopy (for ulcer), patient report (for symptoms) NSS for rebleeding, symptoms, healing time, stricture; >90% ulcers healed within 14 days; no sample size calculation
Gimson et al, 1990[23]	II-3, single-arm trial	53, NR, chronic, secondary prophylaxis, EIS	Incl: Persistent nonhealing EIS ulcer despite prolonged treatment with H2RA and sucralfate	NR (up to 56 months)	I: Omeprazole 40 mg daily po ×8 weeks C: –	Complete ulcer healing	10	10	—	—	—	—	Assessment: endoscopy (for ulcer) Recurrent ulcer and bleed in 2 cases
Johlin et al, 1992[25]	II-3, single-arm trial	57, NR, chronic, secondary prophylaxis, EIS	Incl: Persistent nonhealing ulcer with no evidence of healing at 2 consecutive endoscopies 1 month apart on prophylactic H2RA and sucralfate	NR (up to 8 weeks)	I: Omeprazole 20 mg bid po C: –	Complete ulcer healing	9	7 (1 Suicide, 1 refused drug)	—	—	—	—	Assessment: endoscopy (for ulcer) Healing achieved in 3-8 weeks
Jaspersen et al, 1995[24]	II-3, single-arm trial	53, NR, chronic, secondary prophylaxis, EIS	Incl: Persistent nonhealing ulcer despite treatment with H2RA and sucralfate for 1 month	4 Weeks	I: Omeprazole 40 mg bid po ×4 weeks C: –	Complete ulcer healing	14	14	—	—	—	—	Assessment: endoscopy (for ulcer) Healing achieved in 2 weeks
Morgan and Williams, 1989[31]	III, case report	65, NR, chronic, secondary prophylaxis, EIS	Incl: recent (<30 days) variceal hemorrhage	NR	I: Omeprazole 20 mg daily po C: –	Ulcer healing and recurrence	1	Ulcers healed in 3 months compared with 5 months on H2RA and sucralfate; recurrence free since then	—	—			Assessment method not specified
Esophageal transaction													
Kaye et al, 1992[28]	II-3, case series	54.5, NR, chronic, secondary prophylaxis, esophageal transection	Incl: Recurrent bleeding from staple line erosion	NR	I: Omeprazole 40 mg daily po ×1 month C: –	Stable line erosion healing	24	Out of 24, 18 received PPIs and all were healed	—	—	—	—	Assessment: endoscopy (for ulcer) 10 (55.6%) Of patients relapsed when stepped down from omeprazole and required long-term PPI therapy

(continued)

Table 1. (continued)

Study, Year	Level of Evidence and Study Type	Study Population (Age, Setting, Treatment Phase, Primary/ Secondary Prophylaxis, Procedure)	Special Inclusion/Exclusion Criteria and Study Population Characteristics	Follow-up	Intervention/Control	Primary Outcomes Measures	Intervention Group n	Intervention Group Results	Control Group n	Control Group Results	Effect Size	*P* Value (95% CI)	Outcome Assessment/ Remarks
EVL													
Shaheen et al, 2005[12]	I, RCT	50.5, Procedures unit of University of North Carolina Hospital, chronic, secondary prophylaxis, EVL	• Incl: Portal hypertension and varices with prior hemorrhage • Excl: Preexisting esophageal ulcer, ongoing antacid agents • GV: 15.9% • • Varices: Grade 2 68.2%; grade 3, 31.8%; Child-Pugh Class: A, 43.2%; B, 40.9%; C, 15.9% • All patients were on β-blockers	2 Weeks	I: Pantoprazole 40 mg IV 1 day + po 9 days C: Placebo	Number of ulcers ± SE Ulcer size (mm^2) ± SE Number of patients with dysphagia (%) Number of patients with chest pain (%)	22	2.25 ± 0.31 82 ± 22 1 (5) 0 (0)	22	2.18 ± 0.2 37 ± 9 3 (14) 1 (5)	— — — —	0.85 0.01 0.61 1	Assessment: endoscopy (for ulcer), rating by patient (for dysphagia and chest pain) NSS difference in baseline characteristics between groups; NSS for bleeding
Hidaka et al, 2012[14]	I, RCT	63, Procedures unit of University of Kitasato University East Hospital, chronic, primary (60.5%)/ secondary (39.5%), EVL	• Incl: Varices size F2 or above • Excl: Varices 1 month after final EVL, ongoing pharmacological therapy for portal hypertension, Child-Pugh score >10, nonhealing ulcer despite 3 months of PPI therapy • EV: 100%; GV: 37% • HVPG = 16 mm Hg, red sign 100%	Median follow-up: 18.7 months[b]	I: Rabeprazole 10 mg daily po long term C: No treatment	Median time to first variceal bleed, upper GI bleed, serious adverse effects (months)	21	Not reached	22	11.6	HR 0.098	0.029 (0.012-0.79)	Assessment: endoscopy and hemoglobin change on admission (for variceal bleed), assessment method not specified for others NSS for mortality (*P* = 0.072)
Long-term prophylaxis													
Garcia-Saenz-de-Sicilia, 2010 [21]	II-2, retrospective cohort	57, GI and liver clinic, chronic, NR, NR	• Incl: 2 visits to GI and liver clinic in 1 year • Excl: Incomplete record • EV: 78%; GV: 14.3% (86.6% had both) • Child-Pugh Class: A, 47.6%; B, 28.6%; C, 15.2% • Baseline imbalance: more varices in PPI group (with trend of larger and more red sign), more NSAID use	13 Months[c]	I: Omeprazole 20 mg daily or equivalent ×8 weeks C: No PPI exposure	Number of patients with variceal bleeding (%)	48	9 (18.7)	57	8 (14)	OR = 0.83	0.51 (0.5-1.3)	Assessment: medical record
Acute phase management													
Lo et al, 2013[30]	I, non-inferiority RCT	53, Hospital, acute, secondary, EVL	• Incl: Acute EV hemorrhage successfully arrested by EVL • Excl: GV bleed, failure in control of bleeding by EVL, received EIS/EVL within 1 month prior to bleed; Child-Pugh score >13 • EV: 100%; GV: 35.6% • Child-Pugh class: A, 28%, B, 47.5%, C, 24.6% • Varice size: F1, 8.5%; F2, 54.2%; F3, 37.3%	6 Weeks	I: Pantoprazole/ omeprazole 40 mg daily IV 5 days + pantoprazole 40 mg daily po 14 days C: Somatostatin 250 μg/h; terlipressin 1 mg q6h IV 5 days	Treatment failure (%) Failure to control acute bleed (%) Very early rebleeding (%)	60	2 (3.33) 1 (1.67) 1 (1.67)	58	1 (1.72) 0 (0) 1 (1.72)		NSS NSS NSS	Assessment: clinical criteria, eg, hemoglobin drop, vital signs (for treatment failure, acute bleed, early rebleeding) NSS for esophageal ulcer bleeding, amount of blood required, and mortality in 42 days; fewer adverse events in PPI group (3 [5.17%] vs 33 [55%], *P* < 0.001)

(continued)

Table 1. (continued)

Study, Year	Level of Evidence and Study Type	Study Population (Age, Setting, Treatment Phase, Primary/ Secondary Prophylaxis, Procedure)	Special Inclusion/Exclusion Criteria and Study Population Characteristics	Follow-up	Intervention/Control	Primary Outcomes Measures	Intervention Group		Control Group		Effect Size	*P* Value (95% CI)	Outcome Assessment/ Remarks
							n	Results	n	Results			
Alaniz et al, 2009[13]	II-2, retrospective cohort	52, Academic medical center, acute, secondary; EVL, 40.8%; EIS, 32.3%; TIPS, 32.3%	• Incl: Continuous octreotide with variceal hemorrhage confirmed by endoscopy • GV: 28.5% • Child-Pugh score: 9.4 ± 2.1 to 9.9 ± 2.4 • INR = 1.5-1.6 • 39.2% Previous β-blocker • Baseline imbalance: longer octreotide infusion in continuous infusion group; trend of more previous variceal bleed and previous beta blocker therapy in the control group	3.5 Years[c]	I: Pantoprazole 8 mg/h IV for more than 24 hours interval; pantoprazole continuous infusion <24 hours C: Intermittent acid suppression, no PPI	Units of red blood cells transfused ± SD	53	6.4 ± 6.5	77	5.8 ± 6.6		0.66	Assessment: medical record NSS for transfusion of other blood products except more FFP throughout hospital stay in continuous infusion group (6.1 ± 10.6 vs 2.9 ± 6.2 units, *P* = 0.05) NSS for recurrent variceal bleed and mortality

Abbreviations: ALT, alanine aminotransferase; BID, twice daily; C, control; CI, confidence interval; EIS, endoscopic injection sclerotherapy; EV, esophageal varices; EVL, endoscopic variceal ligation; Excl, exclusion criteria; FFP, fresh frozen plasma; GI, gastrointestinal; GV, gastric varices; H2RA, histamine 2 receptor antagonist; HVPG, hepatic venous pressure gradient; I, intervention; Incl, inclusion criteria; IV, intravenous; NR, not reported; NSAID, nonsteroidal anti-inflammatory drug; NSS, not statistically significant; OR, odds ratio; PO, oral; PPI, proton pump inhibitor; RCT, randomized controlled trial; SE, standard error; TIPS, transjugular intrahepatic portosystemic shunt.

[a]47 Patients recruited, 3 lost to follow-up.

[b]Original protocol was to follow for 2 years after enrollment of the last patient but there was early termination.

[c]Study period quoted instead of follow-up duration for retrospective studies.

Table 2. Risk of Bias Assessment (Published Prospective Trials).

Study, Year	Random Sequence Generation	Allocation Concealment	Blinding of Participants and Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data (Attrition Bias)
Postelective endoscopic procedures					
EIS					
Akahoshi et al, 2013[18]	Unclear	Unclear	Unclear	Unclear	Low
Garg et al, 1995[22]	Unclear	Unclear	Low	Low	Low
Gimson et al, 1990[23]	High	High	High	High	Low
Johlin et al, 1992[25]	High	High	High	High	Low
Jaspersen et at, 1995[24]	High	High	High	High	Low
Morgan and Williams, 1989[31]	High	High	High	High	Low
Esophageal transection					
Kaye et al, 1992[28]	High	High	High	High	Low
EVL					
Shaheen et al, 2005[12]	Low	Low	Low	Low	Low
Hidaka et al, 2012[14]	Low	Unclear	High	Partially (radiologists, endoscopists)	Low
Acute phase management					
Lo et al, 2013[30]	Low	Low	High	Partially (endoscopists)	High

Abbreviations: EIS, endoscopic injection sclerotherapy; EVL, endoscopic variceal ligation.

Postendoscopic Procedure

Endoscopic Injection Sclerotherapy

Level I evidence. We identified 2 RCTs evaluating the use of PPI post-EIS.[18,22] Akahoshi et al[18] compared the effect of rabeprazole with famotidine in patients undergoing prophylactic EIS (n = 18). Both groups were similar at baseline and had moderate to severe esophageal varices with clinical markings (eg, red wale marking, cherry red spot, or hematocystic spot) but good Child-Pugh score (Child-Pugh Class A in 50% of patients). Rabeprazole outperformed famotidine in all aspects: higher esophageal pH, less time with pH <4, greater heartburn/dysphagia relief, and less time to ulcer healing. However, the number of ulcers was not significantly different between the 2 groups. Ulcers healed in an average of less than 2 weeks for each group.

The other RCT had 47 patients with recent history of variceal hemorrhage randomized to receive omeprazole or placebo after the first session of EIS until varices were obliterated. Esophageal ulcers developed in 16 patients in the omeprazole group and 18 patients in the placebo group. Statistical significance was not reached for any outcome. Despite the high incidence of ulcer development post-EIS (77%), most of the ulcers (>90%) healed within 2 weeks in both groups.

Level II evidence. Three single-arm trials were identified. All of them involved nonhealing ulcers despite histamine 2 receptor antagonist (H2RA) and sucralfate. The first trial by Gimson et al[23] involved 10 patients with cirrhosis who developed esophageal ulcers despite H2RA and sucralfate. Complete healing of ulcers was achieved in all 10 cases after 8 weeks of omeprazole. Recurrence was observed in 2 cases after treatment discontinuation. The second trial by Johlin et al[25] describes complete ulcer healing in 7 out of 9 cases with omeprazole in an average of 6 weeks. Another similar study, published by Jaspersen et al[24] demonstrated complete ulcer healing in 2 weeks in all 14 patients with H2RA-resistant ulcer when placed on omeprazole. These 3 trials suggest a role of acid in perpetuating post-EIS lesions and the use of omeprazole in patients with nonhealing ulcers despite H2RA and sucralfate therapy.

Level III evidence. Morgan and Williams[31] reported on omeprazole in a patient with recurrent EIS-ulcer despite famotidine and sucralfate. Healing was achieved in 3 months with no recurrence.

Summary and discussion. Esophageal ulcer is a common post-EIS complication and may lead to undesirable sequelae such as chest pain, odynophagia, bleeding, and stricture formation.[35] The toxic nature of EIS sclerosants (eg, ethanolamine oleate) is proposed to be the cause of mucosal and tissue necrosis. Esophageal motility disorders from EIS-induced nerve plexus injury have also been suggested to impair acid clearance and healing. PPIs are

proposed to relieve ulcer through acid suppression. However, the role of motility and acid clearance in the pathogenesis of esophageal ulcer remains controversial, with conflicting evidence regarding changes in esophageal motility and lower esophageal dysfunction.[36,37]

The study by Garg et al[22] failed to show benefit with routine PPI prophylaxis. The lack of power analysis and small sample size gave rise to a potential type II error. Although Akahoshi's study demonstrated benefit with only 18 patients, the results should be interpreted with caution: there was no description about blinding and end points such as symptoms, and endoscopic healing could be subjective. The groups were apparently similar at baseline, but imbalance beyond the described characteristics was still possible with randomization of a small sample. Such findings should be replicated in a well-designed trial with more participants, and a standardized scoring tool for ulcer healing should be used to enhance objectivity of outcome assessment. For instance, in the study by Bonvoisin et al,[19] ulcer severity was assessed by an index of 1 to 5 that took into account the ulcer height and percentage of esophageal circumference.

An important observation from both trials is the self-limiting nature of ulcers. Most ulcers healed within 2 weeks regardless of treatment allocation.[18,22] Endoscopy-confirmed ulcer healing may be the most objective measure in this case but must be balanced with the clinical significance of using such methods if ulcers heal spontaneously. Conversely, PPIs might be an option for H2RA-resistant ulcers with support from the 3 single-arm trials.[23-25] One has to caution against the high risk of bias, given that the trials were not controlled and that ulcer healing was assessed without standardized criteria.

Esophageal Transection

Level II-3 evidence. Esophageal transection is reserved for candidates who are unsuitable for shunting and have failed endoscopic and pharmacological treatment. The rebleeding rate varies from 1.5%[38] to 50%.[28] Kaye et al[28] found most bleeding episodes to be caused by circumferential ulceration at the level of staple transection[39] and proposed a role of omeprazole in mitigating rebleeding risk. A total of 24 patients were followed up prospectively after surgery. Staple line erosion healed in only 6 (25%) patients on ranitidine and sucralfate. The remaining 18 were stepped up to omeprazole, and all healed. More than half of these patients relapsed whenever they were put on maintenance ranitidine and ended up having to take long-term omeprazole. Rebleeding was observed to occur only with staple line erosion. The authors thus concluded that omeprazole is more effective than ranitidine and sucralfate in healing staple line erosion and, thus, in preventing rebleeding.

Summary and discussion. With the low level of evidence, we cannot make strong recommendations for PPI use after esophageal transection. However, in view of the rarity of such procedure, a large RCT is unlikely to be conducted. Although PPIs appear to be a reasonable option to facilitate healing of staple line erosion, their role in preventing rebleeding is unclear.

Endoscopic Variceal Ligation

Level I evidence. Two trials evaluating post-EVL complications were identified.[12,14] The double-blind RCT by Shaheen et al[12] was quoted in guidelines to support PPI use post-EVL.[1,11] Patients undergoing elective EVL with prior variceal hemorrhage were randomized to pantoprazole for 10 days or placebo (n = 44). Endoscopy 10 to 14 days post-banding revealed significantly smaller ulcers in the pantoprazole group. The number of ulcers and symptom score did not differ significantly between the 2 groups, but the study was powered only for ulcer size reduction. Four adverse events (3 postbanding bleed and 1 sepsis) occurred—all in the control group ($P = 0.11$).

The study by Hidaka et al[14] examined the effect of long-term PPI after elective EVL. Both primary (with no previous history of variceal bleed) and secondary prophylactic (with previous history of variceal bleed) patients were randomized to rabeprazole or no treatment on complete healing of postbanding ulcers and followed up for 2 years after recruitment of the last patient. The trial was terminated early, with interim analysis demonstrating a lower risk of bleeding and serious adverse events. The log-rank test showed a significant difference between the groups, with a hazard ratio of 0.098.

Summary and discussion. The proposed role of PPI post-EVL is similar to that suggested for sclerotherapy. Complications following EVL are less severe than with EIS. A study found EVL ulcers to be shallower (0.6 vs 1.8 mm, $P < 0.0001$) and to heal more quickly (14 vs 21 days, $P < 0.0001$).[40] Another study found that 60% of post-EVL ulcers resolved by the end of 2 weeks and 100% by 3 weeks.[41]

Although both published trials yield level I evidence, the trial by Shaheen et al[12] was more rigorously designed and conducted and provides evidence of higher quality. It is not surprising to see positive outcomes for ulcer size reduction but not other end points. However, one should question the value of reducing ulcer size if there is no demonstrated improvement in clinically relevant outcomes such as rebleeding and symptom relief.

The study by Hidaka et al[14] showed increased time to first bleeding and severe complications with long-term PPI. However, it is a small study (n = 43) with internal validity compromised by (1) lack of placebo control and (2) partial blinding (only endoscopists and radiologists were blinded). The characteristics of the studied population also limit the application of evidence. By excluding patients with Child-Pugh score >10, pharmacological treatment for portal hypertension (eg, β blocker), and nonhealing ulcer as well as including a large proportion of primary prophylaxis patients (60%), the bleeding risk was low, as evidenced by the fact that 77% of recruited participants were classified as Child-Pugh class A.

Given that ulcers resolve within weeks and that the role of impaired GI motility remains controversial, better studies should be conducted before routine prolonged use can be recommended. Meanwhile, short-term use (10 days) of PPI postelective EVL is reasonable if ulcer healing is a concern.

Long-term Prophylaxis

Level II-2 Evidence. In the retrospective trial by Garcia-Saenz-de-Sicilia,[21] 105 patients with portal hypertension were analyzed to explore the association between portal hypertension bleed and PPI exposure, which was defined as omeprazole 20 mg daily or equivalent for at least 8 weeks before the episode of portal hypertension bleed or initial evaluation.[21] It was found that 9 out of 48 cases (18.7%) exposed to PPIs versus 8 out of 57 non-PPI cases (14%) experienced portal hypertension-related bleeding (odds ratio [OR] = 0.83; 95% CI = 0.5-1.3; $P = 0.51$). The authors concluded that portal hypertension bleeding was not correlated to PPI use.

Summary and Discussion. As with many retrospective observational trials, the study by Garcia-Saenz-de-Sicilia[21] suffers from confounding. Baseline imbalances included more GEV (92% vs 70%) and a trend of larger varices and more red wale signs in the PPI group. Residual confounding was possible because history of endoscopic procedure and previous bleed was not taken into consideration. The definition of PPI exposure also attributed possible protective effect from PPIs to the non-PPI group. A patient with no bleeding and with PPIs prescribed after initial evaluation might have benefited from PPIs, but this would have been considered a case of nonexposure. This may bias the results toward the null hypothesis and increase the risk of type II error.

PPIs to prevent variceal bleed in the absence of endoscopic procedures should be discouraged until evidence for long-term prophylaxis becomes available.

Acute Phase Management

Level I Evidence. Lo et al[30] proposed that the role of vasoconstrictors diminishes in variceal hemorrhage arrested successfully with EVL because portal pressure is not elevated by EVL[42]; rather, PPIs should be used to prevent ulcers and bleeding. In their study, 118 patients with variceal bleed arrested by EVL were randomized to PPI intravenous (IV) for 5 days and then oral for 14 days, or to a vasoconstrictor (IV for 5 days).[30] No statistically significant difference was detected in any outcome (hemostasis, rebleeding, hospital stay, and mortality). However, there were more esophageal ulcers >1.5 cm and, as expected, more complications (mainly chest pain and abdominal pain) in the vasoconstrictor group. The authors concluded that adjuvant therapy with PPIs was noninferior to vasoconstrictor in terms of initial hemostasis or very early rebleeding rate and was associated with fewer ADRs.

Level II-2 Evidence. Alaniz et al[13] retrospectively reviewed 130 cases receiving octreotide for variceal hemorrhage. The cohort was classified into the continuous infusion group (continuous infusion of pantoprazole for >24 hours) and control group (continuous pantoprazole infusion for <24 hours, intermittent or no acid suppression). Octreotide use was longer in the high-dose PPI group (70.9 ± 33.2 vs 48.4 ± 31.9 hours, $P = 0.0001$). No statistically significant difference was found between the 2 groups for the primary outcome of units of packed red blood cells transfused as well as for mortality, rebleeding rate, and length of hospital stay. However, there was more fresh-frozen plasma use throughout the hospital stay and a trend of more blood product use in the continuous infusion group. The authors concluded that prolonged continuous infusion of pantoprazole does not offer additional benefit in the acute phase management of GEV bleeding.

Summary and Discussion. PPIs are often administered in upper-GI bleed until confirmation of etiology by endoscopy. In the study by Alaniz et al,[13] 97% of patients with variceal hemorrhage were placed on PPIs. Because no additional benefit was evident with PPI infusion from the study, high-dose PPI infusion should be stopped as soon as the diagnosis of variceal bleed is confirmed. Nevertheless, the study might be confounded by baseline imbalance, as suggested by the trend of worse outcomes and prolonged octreotide use in the high-dose PPI group. Treatment assignment was not by randomization but perhaps by patient prognosis and physician preferences. Sicker patients may have been treated more aggressively with

high-dose PPIs, thus biasing results toward the null hypothesis.

The trial by Lo et al[30] is innovative because PPI was compared with vasoconstrictor rather than placebo. The trial showed no difference in rebleeding and fewer ADRs with PPIs versus vasoconstrictors. Of note, this trial applies only to esophageal variceal hemorrhage successfully arrested with EVL. More than one-third of the screened patients were excluded for various reasons, such as failure to arrest variceal bleeding, old age, high Child-Pugh score, and so on. Considering the small sample size and the lack of power to detect differences in mortality and long-term bleeding, one should be conservative in substituting vasoconstrictors with PPIs, especially in those failing to achieve initial hemostasis or at higher risk of rebleeding.

Like Shaheen et al,[12] Lo et al[30] found fewer large esophageal ulcers post-EVL in the PPI group. However, endoscopy was done in only one-third of the participants. The significance of such findings is also questionable, with most rebleeding episodes coming from varices rather than ulcers.

Safety

The safety profile of PPIs is excellent for short-term use and that includes headache, abdominal pain, nausea, and vomiting.[43] However, concerns have been raised about pneumonia, *Clostridium difficile* infection, fractures, low magnesium and vitamin B12 levels, and so on.[44,45]

Many included studies did not incorporate ADR as an end point or were underpowered to detect safety issues of PPIs in GEV.[30] However, there are studies addressing the risk of spontaneous bacterial peritonitis (SBP) with PPIs in patients with cirrhosis. Gastric acid is a nonspecific defense mechanism. Chronic suppression in patients with cirrhosis may increase SBP rates by mechanisms such as intestinal bacterial overgrowth through altered gastric motility, bacterial translocation, and leukocyte function impairment.[46] In the review article by Siple et al,[46] 6 of the included studies found positive association of PPI use and SBP,[47-52] whereas 2 did not.[53,54] A meta-analysis[55] included some of these trials[48,51,53,56] and reported an OR of 2.77 (95% CI = 1.82-4.23).[55] A recent retrospective analysis of SBP in patients with cirrhosis found PPI use (OR = 2.44; 95 % CI = 1.07-5.68; P = 0.03) to be a predictor of SBP.[57] Increased SBP rate was also observed with higher dose[51] and longer duration of PPI use.[49] A study also examined the association of *Clostridium difficile* infection with PPIs in patients with cirrhosis and reported an OR of 37.6 (95% CI = 6.22-227.6).[58] Notably, all these studies are based on retrospective data, and some are conference abstracts.

Risk of Bias Assessment

The risk of bias across studies is moderately high (Table 2). The risk is highest in the literature for PPI use post-EIS[18,22,23,24,25,31] and post–esophageal transection[28] where studies were published in the 1990s. The studies for acute phase management[30] and long-term prophylaxis[14] were fairly well-conducted but suffered from inadequate blinding. This may potentially inflate the benefits of PPIs, especially for subjective outcomes. The study by Shaheen et al[12] for PPI use post-EVL had a low risk of bias and was given most weight in formulating our conclusions.

Limitations

Our ability to draw conclusions was limited by the lack of high-quality studies. The trials are either small or retrospective. Pooling them in a meta-analysis would add power to the assessment. However, the wide methodological heterogeneity and moderately high risk of bias across trials rendered pooling inappropriate. Another limitation is the inability to evaluate unpublished trials because of the lack of reporting details. Efforts were made to contact the authors, but few of them replied. Details of these trials are summarized in the appendix.

Conclusions

Among various trials, the strongest evidence exists for reduction of ulcer size post-EVL.[12] A short course for 10 days post-EVL may be reasonable if ulcer healing is a concern. However, common practices such as high-dose infusion (eg, pantoprazole 8 mg/h) and prolonged use in the absence of endoscopic procedures is not supported by the literature and should be discouraged until evidence of benefit becomes available.

Future, properly conducted multicenter RCTs with good internal and external validity and serial endoscopies over a longer follow-up interval would better inform the use of long-term PPIs as well as their role as an alternative to vasoconstrictors post-EVL. RCTs evaluating high-dose PPI infusion for GEV hemorrhage and those assessing episodes of SBP with PPI use would also be helpful. Although cost, disease, and population considerations may preclude their completion, only such prospective studies can refine the role of PPIs in GEV.

Appendix

Summary of Study Characteristics and Results (Unpublished).

Study, Year	Study Type	Study Population	Follow-up	Intervention	Control	Major Outcomes Measures	Intervention Group		Control Group		Effect Size	*P* Value (95% CI)	Outcome Assessment/ Remarks
							n	Results	n	Results			
Postelective endoscopic procedures													
EIS													
Bonvoisin et al, 1996[19]	Double-blind RCT	Post-EIS	70 Days	Lansoprazole 30 mg daily po ×70 days	Placebo	Patients with at least 1 index 2 ulcer: day 7	50	0/45 (0%)	48	6/41 (14.6%)		0.008	Assessment: endoscopy NSS from Day 14 to70
EVL													
Ooi et al, 2012[32]	Single-blind RCT	Post-EVL n = 64	21 Days	Esomeprazole 40 mg bid po ×21 days	Esomeprazole 40 mg once daily po ×21 days	Ulcer incidence	NR	NR	NR	NR	RR = 0.77[a]	(0.65-0.94)	Assessment: endoscopy No bleeding for both groups
Pisespong sa et al, 2011[33]	RCT	Post-EVL	10 Days	Lansoprazole 15 mg bid po ×10 days	Placebo	Number of ulcers	7	31	9	39		0.012	Assessment: endoscopy
						Partially healed		11		5			
						Completely healed		2		0			
						Mean ulcer size ± SD (mm^2)		126.1 ± 86.7		124.2 ± 77		0.923	
Kang et al, 2013[27]	Retrospective cohort	Post-prophylactic EVL	13.3 Years[b]	PPI	No PPI	Bleeding incidence	359	NR	146	NR	OR = 0.16[a]	<0.001 (0.061-0.4)	Assessment: medical record
Long-term prophylaxis													
Kuwayam a and Nishiki, 2006[29]	RCT	Patients with cirrhosis with EV (41 with history of variceal bleed and endoscopic procedures)	5 Years	Rabeprazole 20 mg daily po, long-term	No treatment	Variceal bleed rate	73	5 (6.8%)	61	16 (26.2%)		0.0034	Assessment: not specified
						Kaplan-Meier analysis for 5-year rate of variceal bleed		14%		29%		0.0019	Subanalysis of secondary prophylaxis showed benefit of greater magnitude
Acute phase management													
Castillo et al, 2012[20]	Retrospective cohort	Acute variceal bleed	NR	High-dose continuous infusion of PPI (80 mg bolus, then 8 mg/h for 72 hours)	Continuous infusion for less than 72 hours, intermittent acid suppression or no PPI	30-Day mortality	39	6 (15.4%)	70	2 (2.9%)		0.024	Assessment: medical record
Shin et al, 2014[34]	Retrospective	Post-EIS for gastric variceal bleed	NR	PPI post-EIS	No PPI post-EIS	Rebleeding interval ± SD (months)	NR	17.8 ± 11.8	NR	8.5 ± 5.5		0.033	Assessment: medical record Total n = 27; significant benefit (*P* = 0.035) also seen in those on PPI >4 weeks than those with ≤4 weeks
Jun, 2014[26]	Retrospective	Post-EIS for gastric variceal bleed		Pantoprazole 40 mg daily po for at least 14 days	No PPI	Rebleeding, bleeding-related death rates, or mucosal ulceration	244	NR	136	NR		NSS	Assessment: medical record

Abbreviations: BID, twice daily; CI, confidence interval; EIS, endoscopic injection sclerotherapy; EV, esophageal varices; EVL, endoscopic variceal ligation; IV, intravenous; NR, not reported NSS, not statistically significant; OR, odds ratio; PPI, proton pump inhibitor; RCT, randomized controlled trial.

[a]Ooi et al: RR = 1.3 for once-daily versus twice-daily dose, quoted in the original study; Kang et al: OR = 6.4 for no PPI versus PPI quoted in the original study.

[b]Study period quoted for retrospective trial.

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