The Role of Proton Pump Inhibitors in the Management of Upper Gastrointestinal Disorders

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Abstract: Proton pump inhibitors (PPIs) have been in use since the early 1990s and play a crucial role in the management of a number of conditions affecting the upper gastrointestinal tract, including gastroesophageal reflux disease, Barrett esophagus, eosinophilic esophagitis, and dyspepsia. PPIs also play an important role in the treatment of *Helicobacter pylori* infection and in the prevention of upper gastrointestinal tract ulcers and bleeding among patients taking antiplatelet therapy and/or nonsteroidal anti-inflammatory drugs. Despite recent concerns regarding the long-term safety of PPIs, their risk-benefit profiles strongly favor their appropriate use in patients who have genuine indications for them. As with all drugs, PPIs should be administered in the lowest effective dose and only for as long as clinically indicated. However, for at least some of their approved indications, PPIs are likely to be required indefinitely. This article outlines the current indications for PPIs for the management of upper gastrointestinal disorders and reviews safety concerns.

Keywords
Proton pump inhibitors, gastroesophageal reflux disease, *Helicobacter pylori* infection, peptic ulcer disease, nonsteroidal anti-inflammatory drugs, eosinophilic esophagitis

Since the approval of omeprazole by the US Food and Drug Administration (FDA) in 1991, proton pump inhibitors (PPIs) have been extensively used to treat a variety of conditions in the upper gastrointestinal (GI) tract, commonly referred to as acid-related disorders. This article summarizes the current indications and safety concerns of PPIs for the management of such disorders.

The Role of Proton Pump Inhibitors in the Management of Gastroesophageal Reflux Disease

Gastroesophageal reflux disease (GERD) was defined by the Montreal Consensus Group as a condition that develops when the reflux of stomach contents causes troublesome symptoms and/or complications.[1] The American College of Gastroenterology (ACG) defines GERD as symptoms or complications resulting from the reflux of gastric contents into the esophagus or the oral cavity, larynx, or even lungs.[2] GERD can be further classified according to the

presence or absence of erosions (erosive esophagitis vs nonerosive reflux disease, respectively). Pharmacologic options for the management of GERD include antacids, histamine-2 receptor antagonists (H_2RAs), and PPIs. PPI therapy has consistently demonstrated higher healing rates and lower relapse rates in erosive esophagitis than H_2RAs or placebo.[3] Chiba and colleagues[4] also reported faster healing rates in erosive esophagitis with PPIs than with H_2RAs or placebo (12% per week vs 6% per week and 3% per week, respectively). Additionally, the cumulative healing rate irrespective of treatment duration was highest with PPIs (84%) as compared to H_2RAs (52%) and placebo (28%).[4] PPIs alleviate symptoms in 80% of patients with erosive esophagitis and in approximately 60% of patients with nonerosive reflux disease.[5,6]

The ACG treatment guidelines[2] gave a strong recommendation for an 8-week course of PPI therapy for the initial management of erosive esophagitis in terms of healing and symptom control. The guidelines also reported no difference in symptom relief and erosive esophagitis healing among various PPIs. A meta-analysis of 10 studies including more than 15,000 patients had reported an 8% relative increase in GERD symptom relief at 4 weeks and a 5% relative increase in the probability of erosive esophagitis healing after 8 weeks with esomeprazole over other PPIs[7]; however, the clinical relevance of this finding is unclear. Except for dexlansoprazole (Dexilant, Takeda Pharmaceuticals) and immediate-release omeprazole with sodium bicarbonate, PPIs should be administered approximately 1 hour before meals to ensure maximal efficacy. Immediate-release omeprazole with sodium bicarbonate can be taken at bedtime and is highly effective in controlling nocturnal acidity.[8] Dexlansoprazole is a dual delayed-release formulation of R-lansoprazole and can be taken at any time regardless of food intake.[9]

A Cochrane systematic review[10] comparing the use of PPIs, H_2RAs, and prokinetics in patients with nonerosive reflux disease reported that PPIs were more effective than H_2RAs (relative risk, 0.66; 95% CI, 0.60-0.73) and prokinetics (relative risk, 0.53; 95% CI, 0.32-0.87).

Continuous maintenance therapy with a PPI is appropriate for GERD patients who develop symptomatic relapse when therapy is discontinued, as well as in patients with erosive esophagitis or Barrett esophagus. Because approximately 60% of patients with nonerosive reflux disease experience relapse of GERD symptoms over time,[11] intermittent or on-demand PPI therapy may be beneficial in this patient population. A systematic review comparing on-demand PPI therapy to continuous PPI therapy reported that patient satisfaction was noninferior to on-demand PPI therapy in patients with nonerosive reflux disease.[12] However, on-demand PPI therapy is not FDA-approved for this patient population. Risk factors for incomplete control of GERD symptoms include the presence of a hiatal hernia, lack of compliance, longer duration of disease, suboptimal dosing, and presence of extraesophageal symptoms.[13] Options for patients with incompletely controlled GERD are limited. Although switching to another PPI is common clinical practice, it is not supported by evidence. The addition of a nocturnal dose of a H_2RA may temporarily produce better control of overnight pH, although this effect is limited due to the development of tachyphylaxis to the H_2RA.

The Role of Proton Pump Inhibitors in the Management of Barrett Esophagus

Known risk factors for the development of Barrett esophagus are chronic GERD (>5 years), age older than 50 years, male sex, smoking, central obesity, and white race.[14-16] In practice, PPI therapy is given to virtually all patients with Barrett esophagus, as this treatment effectively controls reflux symptoms and maintains healing of esophagitis in these patients. Studies have shown that continuous maintenance PPI therapy might slow the progression of Barrett esophagus.[17-20] The ACG guidelines for the management of Barrett esophagus[21] recommend routine once-daily PPI treatment; twice-daily dosing is not recommended unless there is insufficient control of reflux symptoms.

The Role of Proton Pump Inhibitors in the Management of *Helicobacter pylori* Infection

Helicobacter pylori is a major cause of peptic ulcer disease and gastric cancer. The updated ACG clinical guidelines for the management of *H pylori* infection[22] recommend that all patients who test positive for the infection should receive treatment. The guidelines list several treatment regimens for the management of *H pylori* infection, all of which include a PPI; these treatments are listed in the Table. Monotherapy with a PPI is ineffective in eradicating *H pylori* infection. However, the addition of a PPI to a combination of antibiotics improves eradication rates compared to those achieved with antibiotics alone.[23] PPIs elevate intragastric pH levels and optimize the antibacterial action of concomitantly administered antibiotics. Furthermore, because PPIs decrease gastric secretory volume, they increase the concentration of antibiotics within the stomach.

The Role of Proton Pump Inhibitors in the Management of Peptic Ulcer Bleeding

GI bleeding was the most common hospital admission diagnosis in 2012 among all GI-related disorders.[24]

Table. Treatment Regimens for *Helicobacter pylori* Infection

Regimen	Duration
Clarithromycin triple therapy • PPI + clarithromycin (500 mg) + amoxicillin (1 g) or metronidazole (500 mg)	14 days
Bismuth quadruple therapy • PPI + bismuth subsalicylate (300 mg) + tetracycline (500 mg) + metronidazole (500 mg)	10-14 days
Concomitant therapy • PPI + clarithromycin (500 mg) + amoxicillin (1 g) + metronidazole (500 mg)	10-14 days
Sequential therapy • PPI + amoxicillin (1 g) • PPI + clarithromycin (500 mg) + metronidazole (500 mg)	5-7 days 5-7 days
Hybrid therapy • PPI + amoxicillin (1 g) • PPI + amoxicillin + clarithromycin (500 mg) + metronidazole (500 mg)	7 days 7 days
Levofloxacin triple therapy • PPI + levofloxacin (500 mg) + amoxicillin (1 g)	10-14 days
LOAD therapy • Omeprazole (20 mg) + levofloxacin (250 mg) + nitazoxanide (500 mg) + doxycycline (100 mg)	7-10 days

LOAD, levofloxacin, omeprazole, nitazoxanide, and doxycycline; PPI, proton pump inhibitor.

Peptic ulcer disease remains the most common cause of upper GI bleeding. For upper GI bleeding, it is now common practice to initiate intravenous PPI therapy once the hemodynamic status has been assessed and any necessary resuscitative measures have been implemented. Lau and colleagues[25] reported in a randomized trial the benefit of a high-dose bolus followed by continuous infusion of omeprazole before patients underwent endoscopy. Endoscopic treatment was required in 19.1% of patients who received omeprazole compared to 28.4% of patients who received placebo (P=.007). Likewise, among patients with peptic ulcer disease, active bleeding was significantly less common in patients who received omeprazole (6.4% vs 14.7%; P=.01), and clean-based ulcers were found more often (64.2% vs 47.4%; P=.001). A systematic review of 6 randomized trials with 2223 patients[26] evaluating the use of a PPI before endoscopic evaluation found that PPI therapy prior to endoscopy did not significantly reduce mortality (odds ratio [OR], 1.12; 95% CI, 0.72-1.73), rebleeding (OR, 0.81; 95% CI, 0.61-1.09), or the requirement for surgery (OR, 0.96; 95% CI, 0.68-1.35). However, there was a significantly lower proportion of peptic ulcers with high-risk stigmata at endoscopy (OR, 0.67; 95% CI, 0.54-0.84) and significantly lower rates of endoscopic treatment (OR, 0.68; 95% CI, 0.50-0.93). The ACG guidelines for peptic ulcer bleeding[27] recommend the use of a bolus PPI and continuous infusion to decrease the proportion of patients with ulcers with high-risk stigmata and the requirement for endoscopic treatment. PPI therapy can be discontinued after endoscopy if the patient is found to have an etiology for bleeding other than peptic ulcer. However, if endoscopic evaluation has to be delayed or cannot be performed, intravenous PPI therapy should be continued to reduce the risk of further bleeding.

The ACG guidelines from 2012 recommend the use of intravenous PPI therapy (high-dose bolus and continuous infusion) for 72 hours after successful endoscopic treatment of high-risk peptic ulcers.[27] A subsequent Cochrane meta-analysis of 22 randomized trials[28] compared the use of a high-dose bolus PPI with continuous infusion vs intermittent PPI therapy after an endoscopic evaluation of peptic ulcer bleeding. There was no significant difference in mortality (risk ratio [RR], 0.85; 95% CI, 0.47-1.54), risk of rebleeding (RR, 1.27; 95% CI, 0.96-1.67), surgery (RR, 1.33; 95% CI, 0.63-2.77), length of hospital stay (mean difference, 0.26; 95% CI, -0.08 to 0.6), or requirement for blood transfusion (mean difference, 0.05; 95% CI, -0.21 to 0.3). Likewise, a 2014 systematic review[29] comparing high-dose PPI therapy to intermittent PPI therapy after successful endoscopic treatment of high-risk peptic ulcers reported that intermittent PPI therapy was noninferior to high-dose PPI plus continuous infusion therapy in terms of rebleeding within 7 or 30 days, mortality, and requirement for blood transfusion. However, intermittent PPI therapy is not currently recommended after endoscopic treatment of peptic ulcers with high-risk stigmata, as most evidence supports the use of a continuous infusion. Finally, patients who have peptic ulcers with flat, pigmented spots or clean bases require only oral PPI therapy because rates of serious rebleeding are very low.[27,30]

The Role of Proton Pump Inhibitors in Reducing Gastrointestinal Bleeding Associated With Antiplatelet Therapy and NSAIDs

Antiplatelet therapy forms a pivotal part of preventive management for patients at risk for secondary cardiovascular events. In a meta-analysis of secondary prevention trials, aspirin therapy was associated with a decrease in all

major cardiovascular events but was also linked to a significantly higher risk of extracranial bleeds.[31] Even low-dose aspirin was associated with increased risks for upper and lower GI bleeds (RR, 2.3 and 1.8, respectively).[32,33] Clopidogrel is frequently used with aspirin in patients with acute coronary syndrome. In one study, this dual antiplatelet therapy (DAPT) reduced the risk of cardiac death, myocardial infarction, and stroke compared to aspirin alone; however, it also increased the bleeding risk from 2.7% to 3.7%.[34] DAPT increases the risk of GI bleeding 2- to 3-fold; data from a large randomized trial found a RR of 1.78 (95% CI, 1.25-2.54) with a number needed to harm of 130.[34] The strongest risk factors for GI bleeding in patients on DAPT are a history of GI bleeding and complications of peptic ulcer disease. Other factors include advanced age, concomitant use of anticoagulant drugs or nonsteroidal anti-inflammatory drugs (NSAIDs), and *H pylori* infection.[35-39] Aspirin can cause direct mucosal damage to the gastric lining, but its major effect is due to its systemic inhibition of cyclooxygenase resulting in decreased production of prostaglandins.[33] Clopidogrel is not ulcerogenic but may promote bleeding at sites of preexisting ulcers due to its antiplatelet effects.[40]

PPIs reduce gastric acid secretion for up to 36 hours,[41] thereby promoting healing of ulcers and erosions as well as stabilizing thrombi and decreasing rates of GI bleeding in patients on DAPT. Ray and colleagues[42] reported that PPIs decreased the risk of upper GI bleeding in patients on clopidogrel by 50% and decreased the risk of GI bleeding by 2.8% per year in patients with more than 3 risk factors. In an observational study of 8311 patients,[43] PPI use along with clopidogrel resulted in less GI bleeding compared to clopidogrel alone (RR, 0.19; 95% CI, 0.07-0.49). A randomized trial[44] evaluating patients on DAPT in combination with PPI vs patients taking clopidogrel alone reported fewer GI events in the DAPT plus PPI arm (hazard ratio [HR], 0.34; 95% CI, 0.18-0.63). Therefore, evidence supports a role for PPI therapy in preventing upper GI bleeding in patients on DAPT. However, some studies reported that PPIs may decrease the efficacy of clopidogrel and may subsequently result in an increased rate of cardiovascular events. In the CREDO (Clopidogrel for Reduction of Events During Observation) study, PPI use was associated with an increase in cardiovascular events in patients on clopidogrel.[45] In a retrospective evaluation of a randomized trial of 13,608 patients receiving clopidogrel or prasugrel (Effient, Eli Lilly) after percutaneous coronary intervention, the use of PPIs was not associated with any increased rate of major cardiovascular events.[46] Only 1 randomized, controlled trial has evaluated the efficacy of clopidogrel with the use of a PPI.[44] In this trial, 3761 patients with acute coronary syndrome or percutaneous coronary intervention were randomized to receive a fixed-dose combination of clopidogrel and omeprazole or clopidogrel alone. All patients also received low-dose aspirin. There was no difference in the incidence of major cardiovascular events between the 2 arms (HR, 0.99; 95% CI, 0.68-1.44), but there were fewer GI events in the patients who received omeprazole in combination with clopidogrel (HR, 0.34; 95% CI, 0.18-0.63). The joint consensus statement from the ACG, the American College of Cardiology Foundation, and the American Heart Association[47] recommends the use of PPIs in patients receiving DAPT who have a history of or multiple risk factors for GI bleeding. Routine use of PPIs is not recommended in patients who do not have risk factors for GI bleeding. The FDA currently recommends against the use of omeprazole or esomeprazole in patients on clopidogrel.[48]

The ACG guidelines for the prevention of NSAID-related ulcer complications[49] recommend the use of daily PPIs to reduce the risk of gastric and duodenal ulcers and complications caused by NSAIDs. A multicenter, randomized trial of 844 patients compared 2 doses of esomeprazole (20 and 40 mg) with placebo in patients taking NSAIDs or cyclooxygenase-2 inhibitors.[50] Patients were considered to be at high risk for ulcers based on age older than 60 years or a history of gastric or duodenal ulcers. After 8 weeks, ulcers were documented in 5.3%, 4.7%, and 20.4% of patients taking 20 mg of esomeprazole, 40 mg of esomeprazole, and placebo, respectively.

A propensity-matched cohort of 2777 patients with endoscopic evidence of upper GI bleeding was compared with 5532 controls.[43] Among patients taking NSAIDs, PPI use was associated with a significant risk reduction for bleeding (RR, 0.30; 95% CI, 0.17-0.53). Thus, evidence from observational studies and randomized, controlled trials supports PPI use in at-risk patients taking NSAIDs to decrease ulcer formation and the risk of upper GI bleeding.

The Role of Proton Pump Inhibitors in the Management of Dyspepsia

Dyspepsia affects approximately 20% of the world's population and is more commonly seen in women, people who smoke, and people who take NSAIDs.[51] Although patients in these populations have a normal life expectancy, dyspepsia significantly affects the quality of life and is estimated to cost the US health care system approximately $18 billion annually.[52,53] The ACG guidelines for dyspepsia[54] recommend an empiric trial of PPI therapy in patients younger than 60 years who

are *H pylori*–negative or in whom *H pylori* has been eradicated. Data pooled from 6 trials found a RR of 0.75 (95% CI, 0.64-0.88) in favor of PPI therapy over placebo and antacid therapy in dyspeptic patients.[54] Pooled data from trials comparing PPIs and H_2RAs in dyspeptic patients younger than 60 years found an advantage to PPIs (pooled RR, 0.81; 95% CI, 0.72-0.91).[54] In all of these trials, PPI treatment was given once daily. PPI therapy for dyspepsia was given a strong recommendation based on high-quality evidence from randomized trials. Once-daily PPI therapy is also recommended for 8 weeks in patients with functional dyspepsia who are *H pylori*–negative or in whom *H pylori* has been eradicated. Pooled data from 15 trials including 5853 patients comparing PPI use to placebo in patients with functional dyspepsia revealed a RR of 0.87 (95% CI, 0.82-0.94) in favor of PPI therapy (number needed to treat=10).[54]

The Role of Proton Pump Inhibitors in the Management of Eosinophilic Esophagitis

The ACG guidelines for the management of eosinophilic esophagitis (EoE)[54] define the condition as a distinct clinicopathologic disorder that fulfills the following criteria: (1) symptoms related to esophageal dysfunction, (2) eosinophil-predominant inflammation on esophageal biopsy characterized by a peak value of at least 15 eosinophils per high-power field, (3) mucosal eosinophilia that is isolated to the esophagus and persists after a PPI trial, (4) exclusion of secondary causes of esophageal eosinophilia, and (5) response to treatment (eg, dietary elimination, topical corticosteroids). PPI–responsive esophageal eosinophilia (PPI-REE) may represent a different clinical entity. Patients with PPI-REE have symptoms suggestive of EoE and may have endoscopic features of EoE, but have resolution of symptoms and esophageal eosinophilia after a course of PPI therapy. Therefore, the ACG guidelines[55] recommend that all patients who have symptoms of EoE and are found to have isolated esophageal eosinophilia should be given an 8-week trial of a PPI and should then undergo repeat endoscopy with biopsies. Resolution of esophageal eosinophilia is classified as PPI-REE rather than EoE. More than one-third of patients diagnosed with esophageal eosinophilia will respond to PPI treatment.[56] The mechanisms of action of PPIs in this regard are incompletely understood. One hypothesis is that acid exposure in patients with GERD damages esophageal epithelial tight junctions, allowing allergen penetration and eosinophil recruitment.[57] Alternatively, PPIs may have a direct anti-inflammatory effect on the esophageal epithelium by blocking the secretion of eotaxin, which recruits eosinophils.[58]

Safety Concerns Associated With Long-Term Proton Pump Inhibitor Use

Based on several reported associations, there has been recent widespread media attention given to the safety of PPIs. This has resulted in considerable patient anxiety and, in some cases, the inappropriate discontinuation of treatment for conditions for which it is strongly recommended. Vaezi and colleagues[59] have comprehensively reviewed the evidence for the various proposed complications of PPI therapy using the Hill criteria.[60] The authors found moderate strength of evidence to suggest that PPI use may be associated with bacterial enteric infections, including *Clostridium difficile*. However, the remaining associations, including fracture, hypomagnesemia, renal failure, dementia, myocardial infarction, hepatic encephalopathy, and spontaneous bacterial peritonitis, were weak and were most likely explained by residual confounding due to study design issues. The overextrapolation of quantitatively small effect sizes has led to disproportionate safety concerns. As with all other drugs, PPIs should be prescribed in the lowest effective doses and only continued for as long as necessary. However, for some indications (eg, erosive esophagitis, the prevention of NSAID-related ulcers or bleeding), treatment may be needed indefinitely.

Conclusion

Although PPIs were initially approved only for the treatment of erosive esophagitis, they have subsequently been used in the treatment of a number of other conditions of the upper GI tract. PPIs contribute to the management of diverse states, including *H pylori* infection, Barrett esophagus, and the prevention of NSAID-related ulcers. However, PPIs have only limited value for the management of uninvestigated and functional dyspepsia, and they should not be continued if they are not providing symptom relief. Conversely, PPIs play an important role in the prevention of upper GI bleeding in high-risk patients taking NSAIDs, aspirin, or DAPT. Such patients are often elderly and with comorbidity; however, PPI treatment should be continued for as long as is appropriate even though patients may not experience any upper GI symptoms. Despite the multiple recent reports alleging a range of harms associated with PPI use, these drugs are generally safe for continuous use assuming they are being given for an appropriate indication.

Dr Howden has been a consultant, investigator, and/or speaker for all proton pump inhibitor manufacturers at one time. He is currently a consultant for Pfizer Consumer Healthcare, Aralez Pharmaceuticals, Ironwood Pharmaceuticals, US

WorldMeds, and SynteractHCR. Dr Khan has no relevant conflicts of interest to disclose.

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