Clinical Roundtable Monograph

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Safety of Proton Pump Inhibitors

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Abstract

Proton pump inhibitors (PPIs) are commonly prescribed for the management of upper gastrointestinal tract disorders, and over 2 decades of use have demonstrated that these drugs provide significant clinical benefits with very few serious acute adverse events. However, several recent reports have suggested that short-term and long-term PPI treatment may be associated with certain risks. Specifically, studies have demonstrated a modest magnitude of association (odds ratio <2) between PPI therapy and osteoporotic fractures, micronutrient deficiencies, inhibition of antiplatelet therapy, enteric infections, and pneumonia. In response to some of these studies, the US Food and Drug Administration recently required labeling changes that reflect several of these potential risks. While available studies suggest a possible association between various risks and PPI use, demonstrating a causal link is difficult due to the absence of randomized controlled studies, heterogeneity among available studies, inconsistency of findings, and presence of confounding factors. As with all drug therapies, therefore, clinicians need to weigh the benefit of the therapy against any potential risks. Overall, the absolute risk for the majority of patients is small, and the benefits of these drugs often outweigh their potential risks.

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Target Audience: This activity has been designed to meet the educational needs of gastroenterologists, pediatric gastroenterologists, colon/rectal surgeons, and high-prescribing primary care physicians.

Statement of Need/Program Overview: The management of gastroesophageal reflux disease (GERD) is a considerable therapeutic challenge for clinicians. Advances in diagnosis, evaluation, treatment, predictors of response, and emerging data regarding current and novel therapies for the treatment of GERD continue to evolve. The overall safety of long-term proton pump inhibitor (PPI) use has also recently come into question, prompting the US Food and Drug Administration to send out a special alert to practicing physicians and patients. Physicians therefore need to be aware of all the variables that can influence treatment choices and outcomes.

Educational Objectives: After completing this activity, the participant should be better able to:

1. Discuss the risk of nutrient malabsorption and/or fracture associated with long-term PPI use.
2. Describe the issues involved in treating patients with concomitant antiplatelet therapy and PPIs.
3. Review current evidence regarding the risk of infection associated with PPI use.

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Introduction

Since the introduction of omeprazole in 1989, proton pump inhibitors (PPIs) have had a long history of safety and efficacy for relieving symptoms and preventing complications associated with acid-related conditions. In terms of sales, PPIs were the third largest class of drugs in 2009, with more than 110 million prescriptions, and the number of dispensed prescriptions in 2009 was 5% higher than the previous year.[1]

PPIs are often prescribed to treat peptic ulcer disease and associated complications, such as bleeding, as well as conditions associated with excessive acid production, including nonulcer dyspepsia, gastroesophogeal reflux disease (GERD), erosive esophagitis, and Zollinger-Ellison syndrome.[2-7] PPIs are also used in combination with antibiotics to combat *Helicobacter pylori*, as *H. pylori* infection may play a role in recurring stomach ulcers.[2]

Seven PPIs are currently available in the United States, several of which are now sold in over-the-counter formulations (Table 1).[8] PPIs are prodrugs that suppress the release of gastric acid by blocking the final step in acid production through inhibition of the H^+/K^+-ATPase (the proton pump).[2,9] This selective suppression of gastric acid effectively relieves acid-related symptoms and allows for esophageal healing in many patients. Compared to other acid-suppressing agents, PPIs yield greater acid suppression, faster healing, and more complete symptom relief.[10,11]

Over 2 decades of clinical use have demonstrated that treatment with PPIs is associated with a low risk of minor adverse events (1–3%).[12] The most commonly reported adverse events associated with PPIs include headache (1.3–2.9%), diarrhea (1.5–4.1%), dizziness (0.7%), rash (0.4–1.1%), and nausea (0.015–2.6%); the rates of these side effects vary slightly among the different drugs in this class.[12] Overall, these adverse event rates are comparable to the rates observed with placebo or histamine-2 receptor antagonists (H2RAs).[12] However, recent data from epidemiologic studies suggest that additional risks may be associated with PPIs, and the US Food and Drug Administration (FDA) has issued alerts warning physicians about these risks.[13,14]

As with all drug therapies, safety information continuously changes as more data become available. This roundtable was developed to review the current evidence regarding potential safety issues associated with chronic PPI therapy, to raise awareness about these risks, and to discuss how they might affect clinical management of specific cases. In the following pages, 3 expert clinicians provide cases that illustrate major concerns regarding the use of PPIs, present clinical data relevant to each of these cases, and explain how they would manage these patients.

Table 1. Currently Available Proton Pump Inhibitors

- Dexlansoprazole
- Esomeprazole
- Lansoprazole*
- Omeprazole*
- Immediate-release omeprazole plus sodium bicarbonate*
- Pantoprazole
- Rabeprazole

*Available in over-the-counter formulations
Adapted from Madanick RD.[8]

References

1. Gatyas G. IMS Health reports U.S. prescription sales grew 5.1 percent in 2009, to $300.3 billion. Available online at http://www.imshealth.com/portal/site/imshealth/menuitem.a46c6d4df3db4b3d88f611019418c22a/?vgnextoid=d690a27e9d5b7210VgnVCM100000ed152ca2RCRD&vgnextfmt=default.
2. Leontiadis G, Sharma V, Howden C. Proton pump inhibitor treatment for acute peptic ulcer bleeding. *Cochrane Database Syst Rev*. 2006:CD002094.
3. Moayyedi P, Deeks JJ, Delaney B, Innes M, Forman D. Pharmacological interventions for non-ulcer dyspepsia. *Cochrane Database Syst Rev*. 2006:CD001960.
4. van Pinxteren B, Numans M, Bonis P, Lau J. Short-term treatment with proton pump inhibitors, H2-receptor antagonists and prokinetics for gastro-oesophageal reflux disease-like symptoms and endoscopy negative reflux disease. *Cochrane Database Syst Rev*. 2006:CD002095.
5. Moayyedi P, Santana J, Khan M, Preston C, Donnellan C. Medical short term management of reflux oesophagitis. *Cochrane Database Syst Rev*. 2007:CD003244.
6. Donnellan C, Preston C, Moayyedi P, Sharma N. Medical treatments for the maintenance therapy of reflux oesophagitis and endoscopic negative reflux disease. *Cochrane Database Syst Rev*. 2004:CD003245.
7. Shi S, Klotz U. Proton pump inhibitors: an update of their clinical use and pharmacokinetics. *Eur J Clin Pharmacol*. 2008;64:935-951.
8. Madanick RD. Proton pump inhibitor side effects and drug interactions: much ado about nothing? *Cleve Clin J Med*. 2011;78:39-49.
9. Yang YX, Metz DC. Safety of proton pump inhibitor exposure. *Gastroenterology*. 2010;139:1115-1127.
10. Chiba N, De Gara CJ, Wilkinson JM, Hunt RH. Speed of healing and symptom relief in grade II to IV gastroesophageal reflux disease: a meta-analysis. *Gastroenterology*. 1997;112:1798-1810.
11. Fendrick AM. Management of patients with symptomatic gastroesophageal reflux disease: a primary care perspective. *Am J Gastroenterol*. 2001;96(8 suppl):S29-S33.
12. Thomson AB, Sauve MD, Kassam N, Kamitakahara H. Safety of the long-term use of proton pump inhibitors. *World J Gastroenterol*. 2010;16:2323-2330.
13. United States Food and Drug Administration. FDA Drug Safety Communication: possible increased risk of fractures of the hip, wrist, and spine with the use of proton pump inhibitors. Available online at http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm213206.htm.
14. United States Food and Drug Administration. FDA drug safety communication: information on clopidogrel bisulfate (marketed as Plavix). Available online at http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm190836.htm.

Nutrient Malabsorption and Fracture Risk

David A. Peura, MD

Case Report

An active, retired, 67-year-old woman with long-standing GERD presented with questions regarding her current treatment. Five years ago, she had presented with symptoms of heartburn and occasional regurgitation that led to a diagnosis of GERD. She was initially treated with lifestyle changes and an H2RA, but this treatment yielded only partial symptom relief. The patient then started taking a full-dose PPI once daily before breakfast, which resulted in complete symptom relief. An endoscopy performed 4 years ago was normal, with no evidence of erosive esophagitis or Barrett esophagus; because this endoscopy was performed while she was taking a PPI, the native state of her esophagus is unknown. Numerous attempts over the past 4 years to discontinue the PPI or switch back to an H2RA have led to a relatively rapid return of symptoms.

The patient's history included a hysterectomy that was performed when she was 55 years old (with no subsequent hormone replacement therapy) and a wrist fracture that occurred 5 years ago while skiing. At the time of her wrist fracture, the patient underwent a bone density scan that revealed a normal bone density. At the suggestion of her gynecologist, she began taking supplemental calcium at this time. Current medications include the PPI, 25 mg hydrochlorothiazide daily, and a multivitamin. At the patient's most recent visit, her vital signs were normal and her general examination was unremarkable.

While researching PPIs prior to this visit, the patient read the new FDA warning about fracture risks associated with these medications, and she was therefore concerned about her current treatment plan. She wanted to know if she should be taking a PPI given her fracture history; if not, she wanted to know what treatment alternatives were available. In addition, she wanted to know how long she could safely continue taking a PPI. She also asked whether she could take specific measures to prevent subsequent fractures.

Risk of Fractures Associated with PPI Use

For years, clinicians have known that fractures—especially hip fractures—are a major cause of morbidity and mortality, especially in people of advanced age. However, the association between acid suppression and fracture risk is controversial. In 2006, a paper by Yang and associates illuminated the potential association between PPI use and increased fracture risk.[1] In this large, nested, case-control study of individuals in the United Kingdom, patients who had received PPI therapy for more than 1 year were found to have a significant risk of hip fracture (odds ratio [OR], 1.44; 95% confidence interval [CI], 1.30–1.59). This study also found that the risk of hip fracture increased with higher daily doses of PPIs (OR, 2.65; 95% CI, 1.80–3.90). A similar risk of hip fractures was observed in a large, case-control study of Danish patients.[2] This study found that patients treated with a PPI within the previous year had increased risks for any fracture (OR, 1.18; 95% CI, 1.12–1.43), hip fracture (OR, 1.45; 95% CI, 1.28–1.65), and/or spine fracture (OR, 1.60; 95% CI, 1.25–2.04).

Subsequently, a number of studies attempted to confirm this association. Recently, Kwok and associates published a meta-analysis of 12 studies that included over 1.5 million patients.[3] In the 4 studies in this meta-analysis that had information on spine fractures, PPI use was associated with an increased risk of fracture (OR, 1.50; 95% CI, 1.32–1.72); analysis of the 10 studies with hip fracture data also showed an increased risk of fracture associated with PPI use (OR, 1.23; 95% CI, 1.11–1.36). Despite the variety of study designs included in this meta-analysis (eg, case control, cohort), the meta-analysis still found that PPI therapy had a moderate effect on overall fracture risk (OR, 1.20; 95% CI, 1.11–1.30). This finding suggests that PPI therapy does impact fracture risk, but the magnitude of this effect and its clinical relevance remain in question.

Some studies have suggested that the risk of fractures in PPI-treated patients may depend on the drug's dose or duration of use.[1,4,5] To address this question, a retrospective, matched, cohort study involving Canadian patients looked at the association between continuous PPI use and osteoporotic fractures.[4] No statistically significant association was found during Years 1–4 of treatment; however, the risk of hip fractures increased after 5 years of PPI therapy (OR, 1.62; 95% CI, 1.02–2.58), and an even greater risk of hip fractures was observed after 7 years of treatment (OR, 4.55; 95% CI, 1.68–12.29). In contrast, a case-control study by Corley and associates did not observe a consistent increase in fracture risk over time (up to 10 years of cumulative duration). However, the Corley study did find an increase in fracture risk with higher drug doses (≥1.5 pills/day: OR, 1.41 [95% CI, 1.21–1.64]; <0.74 pills/day: OR, 1.12

[95% CI, 0.94–1.33]).[5] Clinicians should note that this latter finding may represent a case of confounding by indication, as sicker patients would presumably be treated with higher doses of a drug for longer periods. In fact, the Corley study found that the excess fracture risk associated with PPI use occurred only in patients who had at least 1 other risk factor for fracture. Given the current state of the evidence, clinicians should follow the suggestion of the recent American Gastroenterological Association guideline and reduce drug dose and duration whenever possible.[6]

Despite PPI use being associated with only a modest increase in fracture risk, the FDA nonetheless changed the required labeling for PPIs in May 2010 to include information about this association.[7] While the FDA noted the absence of data from randomized controlled trials, it indicated that the available observational data provided sufficient grounds to issue the warning. The FDA also indicated that fracture risk may be linked to prolonged or high-dose PPI use, even though the evidence remains inconclusive as to whether PPI use is causing the increased fracture risk observed in some studies.

In light of these labeling changes, clinicians must address the question of whether PPI use is appropriate in a patient with a history of fracture. While the data show an increased fracture risk for patients on PPI therapy, this increase is likely modest, and it may have minimal impact on the majority of patients who are otherwise at low risk for fracture. When extrapolating from data derived from a large cohort study of women, it appears that the number needed to treat for harm (NNTH) with a PPI would be 234 per year (range, 156–424) in nondiabetic postmenopausal women (mean age=63.5 years).[3] In nondiabetic postmenopausal women, the spine fracture risk NNTH associated with PPIs would be 915 per year (range, 634–1,425). In a low-risk population, such as younger women or men with healthy bones, the NNTH for PPIs is estimated to be in the thousands.

In light of these findings, the modestly increased risk of fracture associated with PPI use is not a significant issue for most patients. Overall, the fracture risk associated with PPI use has been consistently demonstrated and appears to increase with longer durations of use and/or higher PPI doses, but the magnitude of this effect remains low (OR, <2.0).[3,8] Thus, this risk may not be clinically significant for the majority of patients. Indeed, the FDA recently announced that over-the-counter PPIs no longer need to carry a warning about the risk of osteoporosis and fractures, as a review of new data found that these risks were primarily associated with prescription-strength PPIs and/or use of PPIs for a duration of 1 year or longer.[9]

In addition to determining the clinical significance of fracture risk, there are several other outstanding issues that still need to be addressed. First, much of the data on this subject comes from observational studies, as no randomized controlled trials assessing PPI use and fracture risk have been performed.[3] Also, researchers studying PPI use and fracture risk often have difficulty controlling for potential confounding variables such as diet, medications, and comorbid conditions.[8] Finally, available data have not yet provided a plausible mechanism for how PPIs affect bone. One possible mechanism is that PPIs affect calcium absorption, although the data examining this mechanism are inconsistent. Other studies suggest that PPIs may affect osteoclast activity, which may influence bone remodeling, but this effect has yet to be demonstrated in humans.[10,11] Finally, studies have postulated that treatment with PPIs could cause hyperparathyroidism and hypergastrinemia, resulting in decreased bone mineral density, but this theory cannot explain the short-term effects of PPIs on bone metabolism and thus remains controversial.[12] Overall, researchers have yet to find strong evidence to support a role for PPIs in accelerated osteoporosis, dietary calcium or vitamin D malabsorption, or direct effect on human bone.

Nutrient Malabsorption

In addition to potentially increasing the risk of fracture, long-term use of PPIs may also be associated with micronutrient deficiencies in vitamin B_{12}, iron, and/or magnesium. As with the association between PPI use and fracture risk, however, the data linking PPI use and micronutrient deficiencies are sometimes conflicting, and their clinical significance are unclear.

Gastric acid facilitates the absorption of vitamin B_{12}. Thus, PPI-induced hypochlorhydria may interfere with the proteolysis and release of B_{12} from dietary protein, or it may promote small bowel bacterial overgrowth that could cause low B_{12} levels.[12] Whether long-term PPI use actually lowers B_{12} levels remains in debate, however, as available reports are conflicting.[12] Fortunately, true deficiencies of B_{12} are rare and typically occur only in elderly patients. Also, if a patient's B_{12} levels are a cause for concern, oral supplemental B_{12} can be administered. As PPIs do not cause true malabsorption but only impair the release of B_{12} from dietary protein, absorption of oral supplemental B_{12} should be unimpaired.

Iron deficiency may also be associated with PPI use, since gastric acid is required for nonheme iron absorption.[12] Whether PPI use affects iron levels is unclear, however, as data on this association are conflicting. One study examining long-term PPI therapy in patients with Zollinger-Ellison syndrome did not find a connection with iron deficiency.[13] On the other hand, a study of patients with hemochromatosis found that short-term PPI therapy resulted in a significant reduction in the absorption of nonheme iron, and long-term PPI therapy reduced phlebotomy requirements.[14] Overall, the impact of PPI therapy on iron

absorption in patients with normal iron levels and normal iron absorption is unclear. While approximately 60% of dietary iron is nonheme iron, most individuals' diets will provide patients with sufficient iron even if they do not have adequate acid levels to reduce nonheme iron. In addition, gastric acid is unnecessary for the absorption of medicinal iron supplements, as this iron is already in a reduced form. Therefore, iron malabsorption should not be a critical issue as long as patients receive sufficient dietary iron or take iron supplements.

Finally, another nutrient that may be affected by PPI therapy is magnesium; hypomagnesemia is a very rare, but serious, risk of PPI therapy.[12] While the mechanism for PPI-induced hypomagnesemia is unknown, it does not appear to involve gastrointestinal malabsorption or renal magnesium wasting.[12] If hypomagnesemia occurs, discontinuing PPI therapy will allow magnesium levels to return to normal. However, if patients are rechallenged with a PPI after correction of the magnesium deficiency and hypomagnesemia quickly recurs, then PPI therapy may be contraindicated in such individuals. Despite the rarity of this finding, the FDA issued a warning to healthcare professionals and the public in March 2011 indicating that prescription PPIs may cause low serum magnesium levels if taken for prolonged periods (in most cases, longer than 1 year).[15] This warning suggested periodic monitoring of magnesium levels in patients taking medications such as digoxin, diuretics, or other drugs that may carry an increased risk of, or by themselves cause, hypomagnesemia.

Conclusion

In summary, PPI therapy is associated with a low absolute risk for fractures or nutrient malabsorption. Nonetheless, patients who require PPIs should be counseled regarding these potential risks, and it is always good practice to use PPIs at the lowest dose and for the shortest time necessary to control symptoms.

For the patient presented in the aforementioned case, the risk-benefit analysis supports continued PPI therapy, as the patient's symptoms recur if she stops the PPI. The patient had never tried intermittent or lower-dose use of the PPI, but these options might be suitable treatment alternatives, particularly in the absence of erosive esophagitis. To address the patient's concerns about preventing subsequent fractures or decreasing her risk of fractures, she should talk to her primary care physician about routine bone density scanning, and she should be managed appropriately based on these results. Calcium supplements may be warranted, but they should be administered in a soluble form, since insoluble calcium may be more difficult to absorb in the setting of concomitant PPI therapy.

Financial Disclosure

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References

1. Yang YX, Lewis JD, Epstein S, Metz DC. Long-term proton pump inhibitor therapy and risk of hip fracture. *JAMA.* 2006;296:2947-2953.
2. Vestergaard P, Rejnmark L, Mosekilde L. Proton pump inhibitors, histamine H2 receptor antagonists, and other antacid medications and the risk of fracture. *Calcif Tissue Int.* 2006;79:76-83.
3. Kwok CS, Yeong JK, Loke YK. Meta-analysis: risk of fractures with acid-suppressing medication. *Bone.* 2010 Dec 23. Epub ahead of print.
4. Targownik LE, Lix LM, Metge CJ, Prior HJ, Leung S, Leslie WD. Use of proton pump inhibitors and risk of osteoporosis-related fractures. *CMAJ.* 2008;179:319-326.
5. Corley DA, Kubo A, Zhao W, Quesenberry C. Proton pump inhibitors and histamine-2 receptor antagonists are associated with hip fractures among at-risk patients. *Gastroenterology.* 2010;139:93-101.
6. Kahrilas PJ, Shaheen NJ, Vaezi MF. American Gastroenterological Association Institute technical review on the management of gastroesophageal reflux disease. *Gastroenterology.* 2008;135:1392-1413, 1413.e1-5.
7. United States Food and Drug Administration. FDA drug safety communication: possible increased risk of fractures of the hip, wrist, and spine with the use of proton pump inhibitors. Available online at http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm213206.htm.
8. Laine L. Proton pump inhibitors and bone fractures? *Am J Gastroenterol.* 2009;104 (suppl 2):S21-S26.
9. United States Food and Drug Administration. Proton pump inhibitors (PPI): class labeling change. Available online at http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm213321.htm.
10. Ito T, Jensen RT. Association of long-term proton pump inhibitor therapy with bone fractures and effects on absorption of calcium, vitamin B12, iron, and magnesium. *Curr Gastroenterol Rep.* 2010;12:448-457.
11. Yang YX. Proton pump inhibitor therapy and osteoporosis. *Curr Drug Saf.* 2008;3:204-209.
12. Yang YX, Metz DC. Safety of proton pump inhibitor exposure. *Gastroenterology.* 2010;139:1115-1127.
13. Stewart CA, Termanini B, Sutliff VE, et al. Iron absorption in patients with Zollinger-Ellison syndrome treated with long-term gastric acid antisecretory therapy. *Aliment Pharmacol Ther.* 1998;12:83-98.
14. Hutchinson C, Geissler CA, Powell JJ, Bomford A. Proton pump inhibitors suppress absorption of dietary non-haem iron in hereditary haemochromatosis. *Gut.* 2007;56:1291-1295.
15. United States Food and Drug Administration. Proton pump inhibitor drugs (PPIs): drug safety communication—low magnesium levels can be associated with long-term use. Available online at http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm245275.htm.

Concomitant Use of PPIs and Antiplatelet Therapy

David A. Johnson, MD

Case Report

A 65-year-old man presented to the emergency room with dizziness and melena. The patient's medical history included hypertension and hyperlipidemia, for which he was taking a statin, an angiotensin-converting enzyme inhibitor, aspirin, and clopidogrel. At the time of his presentation to the emergency room, the patient reported that he was also taking over-the-counter naproxen for a back strain that had occurred while performing yard work. Approximately 4 months prior to this emergency room visit, the patient had received a percutaneous drug-eluting cardiac stent for significant left main coronary artery stenosis and related angina due to cardiac ischemia.

Upon arrival in the emergency room, the patient's blood pressure was 110/70 mmHg, with an orthostatic decline in systolic pressure of 10 mmHg. The patient had an emergency endoscopy that revealed an 8-mm anterior wall gastric antral ulcer with active oozing. Endoscopic injection of 1/10,000 epinephrine followed by mechanical hemoclip therapy was applied to attain hemostasis.

This case brings into focus several key questions: Is clopidogrel itself a source of potential risk for this patient? If so, what antiplatelet therapy would be recommended in this case? Also, what are the recommendations for peptic therapy in this patient? Finally, what are the potential implications of combining peptic therapy with clopidogrel?

PPIs and Antiplatelet Therapy

While combination antiplatelet therapy (clopidogrel plus aspirin) effectively reduces the risk of recurrent cardiovascular events in patients who have been previously treated for acute coronary syndrome, this therapy is not without side effects.[1,2] Because these side effects include an increased risk for gastrointestinal bleeding, antiplatelet therapy can potentially place the gastroenterologist and the cardiologist at odds: the gastroenterologist may be focused on withdrawing the antiplatelet agents (given the risk of gastrointestinal bleeding), while the cardiologist is primarily concerned with the integrity of the stent patency. Slowly, however, a mutual understanding has developed between cardiologists and gastroenterologists, with both groups acknowledging that although clopidogrel may be helpful from a cardiovascular perspective, it is also clearly potentially harmful from a gastrointestinal perspective. In fact, evidence from a prospective, randomized trial indicates that clopidogrel is associated with recurrent ulcer-related bleeding.[3] In an effort to guide good clinical practice, the American College of Gastroenterology (ACG), American College of Cardiology Foundation (ACCF), and American Heart Association (AHA) published a consensus document in 2008 in which they recommended combination antiplatelet therapy and a PPI for patients with a defined risk of ulcer complications such as bleeding.[4] A recent report further highlighted the risk of gastrointestinal bleeding in patients treated with dual antiplatelet therapy.[5]

However, recent pharmacodynamic studies suggest that concomitant use of a PPI and antiplatelet therapy may reduce the effectiveness of clopidogrel. Because clopidogrel is a prodrug, it must be biotransformed through the cytochrome P450 system in order to become active. Clopidogrel may therefore face possible competitive interaction from PPIs for the hepatic enzymes CYP2C19 or CYP3A4, both of which are necessary for conversion of clopidogrel to its active metabolite. This competitive interaction has the potential to impede the biotransformation of clopidogrel and, in turn, decrease clopidogrel activity and reduce its antiplatelet effect.[6,7]

This interaction was first investigated for the PPI omeprazole. One randomized, double-blind, placebo-controlled trial found a higher platelet reactivity index when patients received omeprazole, clopidogrel, and aspirin together versus clopidogrel and aspirin alone.[7] As a result of this study, a number of data mining analyses were performed, 2 of which are of particular importance: the Veterans Affairs database analysis by Ho and colleagues and the Merck-Medco database analysis by Kreutz and colleagues.[8,9] The results of these studies suggest that the combined use of a PPI and clopidogrel leads to an increased risk of all-cause mortality and recurrent coronary syndrome. Given these data, the FDA issued a warning in 2009 regarding the potential interaction between clopidogrel and omeprazole.[10] The FDA further recommended that neither omeprazole nor esomeprazole be used concomitantly with clopidogrel. However, only retrospective data were available at the time these recommendations were made; there was no risk stratification, no adjustment for confounding variables, and no overall global assessment of the implied risk of cardiovascular and gastrointestinal harm.

Subsequently, evidence began to emerge that genetic polymorphisms are an important factor in clopidogrel activity. The biotransformation of clopidogrel requires a certain allelic phenotype that dictates whether patients metabolize clopidogrel at a normal, relatively rapid rate or a slow rate. If a patient has a reduced-function allele that makes them a slow biotransformer, then clopidogrel would be expected to have less of an effect, due to delays in converting the prodrug to its active form. The presence of reduced-function polymorphisms would thus diminish clopidogrel's ability to prevent recurrent coronary syndrome. While these polymorphisms exhibit interethnic differences, they are quite prevalent, affecting 30% of whites, 40% of blacks, and 55% of East Asians.[11]

A meta-analysis of 9 studies including more than 9,000 patients was conducted to evaluate variants of the reduced-function CYP2C19 alleles.[12] Clopidogrel-treated patients with reduced-function alleles were found to have a more-than-50% increased risk of adverse cardiovascular events and a 2.76-fold increased risk of stent thrombosis compared to patients without reduced-function alleles. In 2009, a French registry study that looked at genetic determinants of response to clopidogrel following myocardial infarction found that patients carrying any 2 CYP2C19 loss-of-function alleles had higher rates of adverse events (21.5% vs 13.3%; adjusted hazard ratio [HR], 1.98; 95% CI, 1.10–3.58).[13] However, there was no significant risk associated with concomitant use of PPIs. The most recent data in this area suggest that even patients with the loss-of-function genotype do not have a significant increase in adverse cardiovascular outcomes when the analysis coadjusts for PPI exposure.[14] Overall, these studies demonstrate that reduced-function and loss-of-function alleles consistently predict lesser cardiac benefit for patients receiving clopidogrel, independent of whether or not these patients receive a PPI.

Other studies have also looked at cardiac outcomes in patients receiving PPIs and clopidogrel. In a post-hoc analysis, O'Donoghue and associates evaluated the risk of cardiovascular death, myocardial infarction, or stroke in patients with acute coronary syndrome who were receiving clopidogrel.[15] Of the 6,795 patients receiving clopidogrel, 4,529 patients were also taking a PPI at the time of randomization. This study found no association between PPI use and risk of cardiac harm in patients treated with clopidogrel (PPI vs no PPI adjusted HR, 0.94; 95% CI, 0.80–1.11).

Researchers further investigated this issue in the COGENT trial, the first randomized, multicenter study to prospectively evaluate the effect of antiplatelet therapy in combination with omeprazole in patients with cardiac risk.[16] Patients in this study received 75 mg clopidogrel plus 75–325 mg aspirin in combination with 20 mg omeprazole or placebo. The primary endpoints of the study included composite gastrointestinal events (overt or occult bleeding, symptomatic gastroduodenal ulcers or erosions, obstruction, or perforation) as well as composite cardiovascular events (death from cardiovascular causes, nonfatal myocardial infarction, revascularization, or stroke). The study intended to enroll 5,000 patients, but it was only able to enroll 3,873 patients (3,761 of whom were analyzed) before the study sponsor declared bankruptcy. Nonetheless, after a median follow-up period of 133 days, no significant difference was found in the rates of cardiovascular events for patients receiving omeprazole versus those randomized to placebo (4.9% vs 5.7%, respectively [HR with omeprazole, 0.99; 95% CI, 0.68–1.44; P=.96]). This study found no significant heterogeneity among high-risk subgroups. However, a significant reduction in the rate of gastrointestinal events was observed at 180 days among patients receiving the PPI (1.1% with omeprazole vs 2.9% with placebo [HR with omeprazole, 0.34; 95% CI, 0.18–0.63; P<.001]).

Given that previous studies found an increased risk of all-cause mortality and recurrent coronary syndrome in patients treated with a PPI and clopidogrel, I find it interesting that the first prospective, randomized trial to evaluate the effects of cotherapy with clopidogrel, aspirin, and a PPI found no evidence of cardiovascular harm, even though this study used the PPI that has most often been implicated as having negative effects on antiplatelet activity. Importantly, this study found a 47% risk reduction in composite gastrointestinal events in patients who received clopidogrel, aspirin, and omeprazole. A recent study by Hsu and colleagues also demonstrated a risk reduction with PPIs for prevention of peptic ulcers in patients taking concomitant clopidogrel.[17] Together, these results highlight an important factor that has been missed in composite studies to date: global risk assessment.

Despite the lack of global risk assessment data, the FDA released a statement on October 27, 2010 in which it reiterated its warning that combining omeprazole with clopidogrel can reduce active levels of clopidogrel and reduce antiplatelet activity.[18] (The FDA rescinded this warning as it relates to other PPIs.) However, data from the COGENT trial indicate that adding a PPI to antiplatelet therapy to control adverse gastrointestinal events does not cause significant cardiovascular harm.[16] Therefore, in a 2010 update to their 2008 consensus document on the concomitant use of PPIs and thienopyridines, the ACCF, ACG, and AHA continued to suggest that patients on antiplatelet therapy can benefit from PPIs if they have multiple risk factors for gastrointestinal bleeding.[4,19] While available data indicate that patients with the reduced-function allele can safely receive a PPI combined with antiplatelet therapy, we do not yet have enough data to make a completely definitive statement regarding use of PPIs in these patients.

Interestingly, the most recent retrospective analyses to assess cardiovascular risk in patients taking both clopidogrel and a PPI suggest that the adverse cardiovascular risk

previously reported in this population was most likely due to "channeling bias"—the tendency among physicians to prescribe certain medications for certain patient populations.[20,21] A recent analysis of the Veterans Administration Pharmacy Benefits Management database evaluated patient outcomes following cardiac stent placement, with specific evaluation of postdischarge medication exposure; gaps in the use of clopidogrel and/or the PPI were noted, and a daily reconciliation of medication exposure was performed for each patient. A cohort of 23,200 patients who had been discharged following an uncomplicated coronary stent intervention had complete demographic and prescription refill information. Omeprazole was the most commonly prescribed PPI (88.1%), with esomeprazole, lansoprazole, rabeprazole, and pantoprazole accounting for the remainder of PPI prescriptions.

Overall, the HRs found in this study confirmed prior studies' findings that the risk of adverse cardiovascular outcomes is increased in patients treated with concomitant clopidogrel and PPIs. However, the authors of this study meticulously corrected for covariate cardiovascular risks using propensity-matched evaluations for major cardiovascular events and use of PPIs, and this adjusted analysis found no significant association between cardiovascular risk and use (or patterns of use) of PPIs—continuous, switched, or discontinued.

This study also found significantly more comorbid conditions among patients on PPIs, which provides evidence for the possibility that channeling bias may have affected prior evaluations. The increased use of rescue nitroglycerin prescriptions in patients receiving clopidogrel and PPIs likely indicates a greater angina symptom burden in these patients and suggests that many of these patients may have been receiving PPIs for nonacid-related disease. This study also illustrates the importance of carefully analyzing drug prescription patterns before finalizing any recommendations. Overall, previously identified cardiovascular risk with combined use of clopidogrel and PPIs is most likely a reflection of channeling bias.

Conclusion

Overall, data on the potential interaction between PPIs and clopidogrel are inconsistent and contradictory. The most definitive evidence is derived from the COGENT trial, but its findings conflict with other studies.[16] Even the most recent pharmacokinetic studies seem to refute the original concerns about impaired antiplatelet effect when PPIs and clopidogrel are combined.[17,22] Therefore, all risks and benefits—both cardiovascular and gastrointestinal—must be weighed when deciding on a therapeutic course. Clearly, intermediate endpoints should never be a substitute for randomized trial data with appropriate clinical outcomes.

For the patient presented in the aforementioned case, antiplatelet therapy should not be stopped, especially given the recent placement of a drug-eluting stent. Without antiplatelet therapy, the patient would face a 20% risk of death and 50% risk of myocardial infarction with possible restenosis of the acute stent. The patient has had definitive hemostatic therapy and the data support PPI use, so normal interventions for gastric ulcer should be conducted, including evaluation for *H. pylori* (with eradication if necessary). The patient should remain on a PPI for as long as he continues aspirin and clopidogrel antiplatelet therapy.

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References

1. Anderson JL, Adams CD, Antman EM, et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-Elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction) developed in collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine. *J Am Coll Cardiol.* 2007;50:e1-e157.

2. Steinhubl SR, Berger PB, Mann JT 3rd, et al. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. *JAMA.* 2002;288:2411-2420.

3. Lai KC, Chu KM, Hui WM, et al. Esomeprazole with aspirin versus clopidogrel for prevention of recurrent gastrointestinal ulcer complications. *Clin Gastroenterol Hepatol.* 2006;4:860-865.

4. Bhatt DL, Scheiman J, Abraham NS, et al. ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents. *Circulation.* 2008;118:1894-1909.

5. Shehab N, Sperling LS, Kegler SR, Budnitz DS. National estimates of emergency department visits for hemorrhage-related adverse events from clopidogrel plus aspirin and from warfarin. *Arch Intern Med.* 2010;170:1926-1933.

6. Gilard M, Arnaud B, Le Gal G, Abgrall JF, Boschat J. Influence of omeprazol on the antiplatelet action of clopidogrel associated to aspirin. *J Thromb Haemost.* 2006;4:2508-2509.

7. Gilard M, Arnaud B, Cornily JC, et al. Influence of omeprazole on the antiplatelet action of clopidogrel associated with aspirin: the randomized, double-blind OCLA (Omeprazole CLopidogrel Aspirin) study. *J Am Coll Cardiol.* 2008;51:256-260.

8. Ho PM, Maddox TM, Wang L, et al. Risk of adverse outcomes associated with concomitant use of clopidogrel and proton pump inhibitors following acute coronary syndrome. *JAMA.* 2009;301:937-944.

9. Kreutz RP, Stanek EJ, Aubert R, et al. Impact of proton pump inhibitors on the effectiveness of clopidogrel after coronary stent placement: the clopidogrel medco outcomes study. *Pharmacotherapy.* 2010;30:787-796.

10. United States Food and Drug Administration. FDA drug safety communication: early communication about an ongoing safety review of clopidogrel bisulfate (marketed as Plavix). Available online at http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm079520.htm.

11. Desta Z, Zhao X, Shin JG, Flockhart DA. Clinical significance of the cytochrome P450 2C19 genetic polymorphism. *Clin Pharmacokinet.* 2002;41:913-958.

12. Mega JL, Simon T, Anderson JL, et al. CYP2C19 genetic variants and clinical outcomes with clopidogrel: a collaborative meta-analysis. *Circulation.* 2009;120:S598-S599.
13. Simon T, Verstuyft C, Mary-Krause M, et al. Genetic determinants of response to clopidogrel and cardiovascular events. *N Engl J Med.* 2009;360:363-375.
14. Simon T, Steg PG, Gilard M, et al. Clinical events as a function of proton pump inhibitor use, clopidogrel use, and cytochrome P450 2C19 genotype in a large nationwide cohort of acute myocardial infarction results. *Circulation*. 2011;123:474-482.
15. O'Donoghue ML, Braunwald E, Antman EM, et al. Pharmacodynamic effect and clinical efficacy of clopidogrel and prasugrel with or without a proton-pump inhibitor: an analysis of two randomised trials. *Lancet.* 2009;374:989-997.
16. Bhatt DL, Cryer BL, Contant CF, et al. Clopidogrel with or without omeprazole in coronary artery disease. *N Engl J Med.* 2010;363:1909-1917.
17. Hsu PI, Lai KH, Liu CP. Esomeprazole with clopidogrel reduces peptic ulcer recurrence, compared with clopidogrel alone, in patients with atherosclerosis. *Gastroenterology*. 2011;140:791-798.
18. United States Food and Drug Administration. FDA drug safety communication: information on clopidogrel bisulfate (marketed as Plavix). Available online at http://www.fda.gov/Drugs/DrugSafety/ucm190836.htm.
19. Abraham NS, Hlatky MA, Antman EM, et al. ACCF/ACG/AHA 2010 expert consensus document on the concomitant use of proton pump inhibitors and thienopyridines: a focused update of the ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use. *Am J Gastroenterol.* 2010;105:2533-2549.
20. Banerjee S, Weideman RA, Weideman MW, et al. Effect of concomitant use of clopidogrel and proton pump inhibitors after percutaneous coronary intervention. *Am J Cardiol*. 2011;107:871-878.
21. van Boxel OS, van Oijen MG, Hagenaars MP, Smout AJ, Siersema PD. Cardiovascular and gastrointestinal outcomes in clopidogrel users on proton pump inhibitors: results of a large Dutch cohort study. *Am J Gastroenterol*. 2010;105:2430-2436; quiz 2437.
22. Gremmel T, Steiner S, Seidinger D, Koppensteiner R, Panzer S, Kopp CW. The influence of proton pump inhibitors on the antiplatelet potency of clopidogrel evaluated by 5 different platelet function tests. *J Cardiovasc Pharmacol*. 2010;56:532-539.

Risk of Infection with PPI Therapy

Michael F. Vaezi, MD

Case Report

A 68-year-old female patient had previously presented with classic symptoms of GERD, including heartburn and regurgitation. She was treated with omeprazole (40 mg twice daily) and achieved excellent relief of symptoms, but she was concerned that use of this drug might increase her risk of pneumonia and other infections. At her most recent clinic visit, she inquired whether she should discontinue her use of omeprazole. She also wanted to know if there were alternative treatments for her condition, since her symptoms returned whenever she discontinued omeprazole.

Effects of Acid Suppression

Recently, concerns have been raised regarding the effect of acid suppression on the host defenses, with some data suggesting that patients who are taking a PPI may be more susceptible to pneumonia and/or infection with *Salmonella*, *Campylobacter*, and *Clostridium difficile*. From a pathophysiologic standpoint, why would PPI-induced acid suppression increase the risk for *C. difficile* colitis, enteric infections, and/or pneumonia?

Several theories have been proposed to answer this question. While a reduction in gastric acid relieves reflux and reflux-related symptoms, some studies suggest that acid-suppressing agents may cause several other effects on the gastrointestinal tract, including a reduction in the gastric microbicidal barrier, delayed gastric emptying, delayed gastric mucosal viscosity, microbial modifications, and increased bacterial translocation. Acid suppression may also affect the immune system by decreasing leukocyte adhesions to endothelial cells and inhibiting neutrophil phagocytosis, thus reducing bactericidal killing of microbes.[1,2] Combined with patient risk factors such as advanced age, immune suppression, chronic disease, hospitalization, and current antibiotic use, these mechanisms might increase the risk of infections such as *C. difficile* or pneumonia.

Enteric Infections

One possible way in which PPIs may affect the gastrointestinal tract is by causing small intestinal bacterial overgrowth. In a study of 200 patients with GERD, small intestinal bacterial overgrowth was detected in 50% of patients taking PPIs compared to only 6% of control patients.[3] While this finding is intriguing, its implications are not yet clear.

PPI use may also increase the risk of infection with acid-sensitive microbes such as *Salmonella* or *Campylobacter.* The risk for *Salmonella*, especially, is elevated in patients who have low gastric acid levels due to gastric hypochlorhydria or pernicious anemia.[4] Several case-control studies have therefore evaluated whether use of acid-suppressing therapy increases the risk of enteric infections. In a review of case-control studies, 4 of 5 studies evaluating the risk of *Salmonella* infection found some association with acid suppression, with ORs of 2.6–11.2.[5] Similarly, 5 case-control studies found an association between *Campylobacter*

infection and acid suppression, with ORs of 1.7–11.7. However, 3 other studies found no association between infection and acid suppression.[5] Interestingly, 2 studies on *Campylobacter* that were published by the same authors using the same database arrived at different conclusions: an association was found in 1 of these studies but not in the other.[6,7] This discrepancy highlights the difficulty clinicians face when evaluating the literature on this subject, and it suggests that an inability to control for confounding factors may result in false associations.

In 2007, results were reported from a meta-analysis of 6 studies that included over 11,000 patients with *Salmonella*, *Campylobacter*, and other enteric infections.[8] This meta-analysis found a significant association between PPI use and enteric infections, with an OR of 3.33 (95% CI, 1.84–6.02). Unless all confounders can be controlled, such findings do not definitively demonstrate a causal link, but they do suggest an association. As with most of the studies on this subject, the CI varied due to significant heterogeneity among the studies that could not be explained by subgroup analysis.

In addition to a possible association with *Salmonella* or *Campylobacter* infection, PPI use may also be associated with *C. difficile* infection. A Gram-positive, anaerobic bacterium, *C. difficile* is a primary cause of infectious diarrhea in hospitalized patients, and the use of antibiotics—particularly clindamycin, cephalosporins, fluoroquinolones, and penicillins—is a significant risk factor for acquiring *C. difficile* infection.[9,10] Despite an overall decrease in the use of antibiotics over the past 2 decades, patients have continued to become infected with *C. difficile*. In fact, a more severe form of *C. difficile* colitis is gaining prevalence among patients who are not hospitalized or on antibiotics.[11]

Again, clinicians must address the question of how acid suppression might increase the risk of *C. difficile*-associated diarrhea. Since gastric acid inhibits germination and survival of *C. difficile*, PPI use may place patients at an increased risk for infection simply by reducing levels of gastric acid. In addition, other effects of acid-suppressing therapy—such as delayed gastric emptying, bile salt conversion to unconjugated bile acids, and bacterial overgrowth—may favor the acid-sensitive vegetative growth phase and contribute to an increased risk for *C. difficile* infection.[5] This hypothesis has led to several studies investigating the association between acid suppression and *C. difficile* infection.

In 2005, Dial and associates conducted 2 population-based, case-control studies to determine if the use of acid-suppressing agents increased the risk of *C. difficile* infection.[12] Using the United Kingdom General Practice Research Database, over 1,000 cases of *C. difficile* infection were compared to more than 10,000 control patients. This study found that the adjusted rate ratio of *C. difficile*-associated disease with PPI use was 2.9 (95% CI, 2.4–3.4). H2RAs were associated with a lower risk of infection than PPIs (rate ratio=2.0; 95% CI, 1.6–2.7), while antibiotic use was associated with a greater risk (rate ratio=3.1; 95% CI, 2.7–3.6).

Since the release of this study, various other reports have also suggested an association between PPI use and *C. difficile*-associated disease. In 2007, a large meta-analysis published by Leonard and associates pooled the various study data on *C. difficile* infection and acid-suppressing therapy.[8] This analysis included 12 studies evaluating 2,948 patients with *C. difficile* infection, and it found an OR for PPI use of 2.05 (95% CI, 1.47–2.85) compared to an OR for H2RA use of 1.48 (95% CI, 1.06–2.06). As with the previously mentioned meta-analyses of other enteric infections, the various studies in this analysis were heterogeneous. In addition, clinicians should keep in mind that a true causal link cannot be reliably established without controlling for possible confounding factors, which is difficult to do in most case-control studies.

Pneumonia

Finally, numerous publications have investigated the link between the use of acid-suppressing therapy, specifically PPIs, and community-acquired pneumonia (CAP) or hospital-acquired pneumonia. The initial study that examined the potential link between acid-suppressing therapy and CAP was published by Laheij and colleagues in 2004.[13] In this case-control study involving the Netherlands Integrated Primary Care Database, 5,551 cases of first-time CAP were identified from a study population of 364,683 people. The incidence rate of CAP was found to be 0.6 per 100 person-years among patients who were not taking acid-suppressing drugs, 2.5 per 100 person-years among patients taking PPIs, and 2.3 per 100 person-years among patients taking H2RAs. The adjusted relative risk for CAP was 1.89 (95% CI, 1.36–2.62). A significant positive dose-response association was observed for PPI use, with more than 1 daily dose associated with a greater risk for CAP. No significant dose-response was found for H2RAs. Interestingly, this study found a difference among various PPIs; an increased risk of CAP was associated with omeprazole and pantoprazole but not with lansoprazole. This confusing result again highlights the importance of controlling for confounding factors.

A 2008 study by Sarkar and colleagues examined the United Kingdom General Practice Research Database to look for an association between PPI use and CAP.[14] This nested case-control study included over 80,000 case patients and more than 700,000 control patients. While this study found an increased risk of CAP among patients who began PPI therapy within the previous 30 days, it did not find an association between increased risk and long-term or chronic PPI use; in fact, such use was found to be protective against CAP, which is contradictory to a causal association between

PPI use and CAP. The likely reason for this confusing result is the presence of confounding factors; after fully adjusting for gender, age, hospital, office visit, opiate use, and other confounding factors, this study found no association between current PPI use and increased risk of CAP (adjusted OR, 1.02; 95% CI, 0.97–1.08). If the authors controlled for only gender and age, an association was found, but it disappeared as they incrementally controlled for all other factors.

To determine whether a clearer association between PPI use and infection exists with hospital-acquired pneumonia, Herzig and associates conducted a prospective cohort study in 2009 in which they evaluated the association between acid-suppressing medication and hospital-acquired pneumonia among patients who were not in the intensive care unit.[15] The adjusted OR of hospital-acquired pneumonia in patients on any type of acid-suppressing therapy was 1.3 (95% CI, 1.1–1.4). A subset analysis found a significant risk for hospital-acquired pneumonia in patients who were taking PPIs (OR, 1.3; 95% CI, 1.1–1.4) but not in patients who were taking H2RAs (OR, 1.2; 95% CI, 0.98–1.4). Again, it should be noted that the magnitude of this association was small and the potential contribution from uncontrolled confounding factors cannot be excluded.

Conclusion

When considering the various reports that have linked PPI therapy and risk of infection, clinicians should keep in mind that these are epidemiologic studies. Thus, while many of these studies indicate an association, it may not be a true association, depending on how well the study controlled for confounding factors. An increased risk of infection in patients taking PPIs is biologically plausible, but the majority of the aforementioned studies show only a weak magnitude of association, with OR of 1–2. Overall, the inconsistent findings, heterogeneity among studies, high potential for confounding, and lack of randomized controlled studies hinder our attempts to arrive at a definitive conclusion regarding the relationship between PPI use and risk of infection.

For the patient presented in the previously discussed case, I would recommend continuing on acid suppression therapy, since it improves the patient's reflux symptoms, and I would educate her about the potential risk of infection. Also, as much as acid suppression is beneficial for patients with acid reflux disease, we must be vigilant about reducing the dose to the minimum effective level.

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References

1. Zedtwitz-Liebenstein K, Wenisch C, Patruta S, Parschalk B, Daxbock F, Graninger W. Omeprazole treatment diminishes intra- and extracellular neutrophil reactive oxygen production and bactericidal activity. *Crit Care Med.* 2002;30:1118-1122.
2. Yoshida N, Yoshikawa T, Tanaka Y, et al. A new mechanism for anti-inflammatory actions of proton pump inhibitors—inhibitory effects on neutrophil-endothelial cell interactions. *Aliment Pharmacol Ther.* 2000;14(suppl 1):74-81.
3. Lombardo L, Foti M, Ruggia O, Chiecchio A. Increased incidence of small intestinal bacterial overgrowth during proton pump inhibitor therapy. *Clin Gastroenterol Hepatol.* 2010;8:504-508.
4. Gray JA, Trueman AM. Severe salmonella gastroenteritis associated with hypochlorhydria. *Scott Med J.* 1971;16:255-258.
5. Dial MS. Proton pump inhibitor use and enteric infections. *Am J Gastroenterol.* 2009;104(suppl 2):S10-S16.
6. Health Protection Agency. Reports of *Clostridium difficile* isolated from faecal specimens under the voluntary reporting scheme: England, Wales, and Northern Ireland 1990-2004. Available online at http://www.hpa.org.uk/infections/topics_az/clostridium_difficile/vol_data.htm.
7. Barrett S. *Clostridium difficile*—the next step in mandatory reporting. *J Hosp Infect.* 2004;56:83.
8. Leonard J, Marshall JK, Moayyedi P. Systematic review of the risk of enteric infection in patients taking acid suppression. *Am J Gastroenterol.* 2007;102:2047-2056.
9. Mylonakis E, Ryan ET, Calderwood SB. *Clostridium difficile*—associated diarrhea: a review. *Arch Intern Med.* 2001;161:525-533.
10. Thomas C, Stevenson M, Riley TV. Antibiotics and hospital-acquired *Clostridium difficile*-associated diarrhoea: a systematic review. *J Antimicrob Chemother.* 2003;51:1339-1350.
11. Pepin J, Valiquette L, Alary ME, et al. *Clostridium difficile*-associated diarrhea in a region of Quebec from 1991 to 2003: a changing pattern of disease severity. *CMAJ.* 2004;171:466-472.
12. Dial S, Delaney JA, Barkun AN, Suissa S. Use of gastric acid-suppressive agents and the risk of community-acquired *Clostridium difficile*-associated disease. *JAMA.* 2005;294:2989-2995.
13. Laheij RJ, Sturkenboom MC, Hassing RJ, Dieleman J, Stricker BH, Jansen JB. Risk of community-acquired pneumonia and use of gastric acid-suppressive drugs. *JAMA.* 2004;292:1955-1960.
14. Sarkar M, Hennessy S, Yang YX. Proton-pump inhibitor use and the risk for community-acquired pneumonia. *Ann Intern Med.* 2008;149:391-398.
15. Herzig SJ, Howell MD, Ngo LH, Marcantonio ER. Acid-suppressive medication use and the risk for hospital-acquired pneumonia. *JAMA.* 2009;301:2120-2128.

Question-and-Answer Forum

In which patients is PPI use contraindicated?

Michael F. Vaezi, MD PPIs are very effective for reducing the pH of gastric acid, and these drugs can effectively treat both GERD and peptic ulcer disease. From my perspective, PPIs are generally very safe. However, PPIs should be discontinued in any patient who does not need this medication—for example, a patient who was misdiagnosed with reflux but actually has nonulcer dyspepsia or another nonreflux-related symptom. If the patient truly has reflux disease and benefits from PPI therapy, then I would only discontinue the PPI if the patient experiences acute side effects of treatment.

David A. Peura, MD Clinicians should keep in mind that the absolute risk of most side effects is still very, very small, even if the relative risk may be doubled for a particular factor. From the perspective of nutrient absorption, the potential risks are also preventable and treatable, with the exception of hypomagnesemia, which may be more difficult to manage. Therefore, the only situation where I might discontinue a PPI is if the patient develops persistent hypomagnesemia for which no other cause is found.

David A. Johnson, MD In general, the relative assessment of risk is fairly de minimis. ORs less than 2 are challengeable, particularly in retrospective studies, as these studies are frequently criticized for their potential channeling bias toward sicker patients—ie, these patients may be more complicated and already at risk for a complication related to nonsteroidal anti-inflammatory drugs (NSAIDs). Also, any perceived harm, even be it extremely small, needs to be weighed against the potential benefit. For example, if a patient is on aspirin or NSAID therapy, their risk of gastrointestinal bleeding may be far greater than their perceived risk of fracture. If the patient discontinues the PPI because they are concerned about fracture risk, a dangerous situation may be created, especially when the odds of this harm are minimal, or potentially even confounded by channeling bias.

If a patient must discontinue PPI therapy, what alternative treatments could you consider?

DP There are very few instances in which I would recommend stopping PPI therapy in patients with documented GERD. H2RAs may be an effective alternative in some patients, but there are robust data demonstrating that PPIs are better at controlling symptoms and mucosal damage than H2RAs. Surgery is another alternative option, but it is invasive.

MV Weighing various treatment alternatives should involve looking at their effectiveness for a given diagnosis and the potential risk for each therapy. I would argue that PPIs and surgical fundoplication may be equally effective in the short term; from a long-term perspective, however, both risk and cost issues tip the balance in favor of PPIs. If patients are unwilling or unable to take PPIs, then either surgical intervention or less effective therapies, such as H2RAs, might be alternative strategies.

DJ Some patients may require surgical intervention, particularly if they develop a change in their composite gastrointestinal GERD profile (ie, more regurgitation and/or increased volume of regurgitation), but such cases are extremely rare. In this situation, the selection of the surgeon would be critical; a high-volume, experienced surgeon should be identified before a patient is considered for an antireflux surgical intervention.

If a patient is receiving long-term PPI therapy, do you advise them to take extra precautions when traveling to parts of the world where they may be at increased risk for infection?

MV I do not. Some studies have examined the risk of cholera or *Escherichia coli* infection in patients taking PPIs, but none have conclusively shown a higher association between risk of infection and PPI use.

DP Yes, I do. For patients who do a lot of travelling to less-developed countries, I tell them to be a little bit more careful, but I do not recommend changing their medical therapy.

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Postulated Explanations for an Association Between Fractures and PPI Use

- PPIs may affect calcium absorption
  - Data inconsistent: both positive and negative studies
  - May be an issue with insoluble calcium such as carbonate
- PPIs may cause hyperparathyroidism and hypergastrinemia leading to decreased bone mineral density
  - Cannot explain short-term effects of PPIs on bone metabolism
- PPIs may inhibit osteoclast activity and negatively affect bone remodeling and repair of microfractures
  - Has not been shown in humans

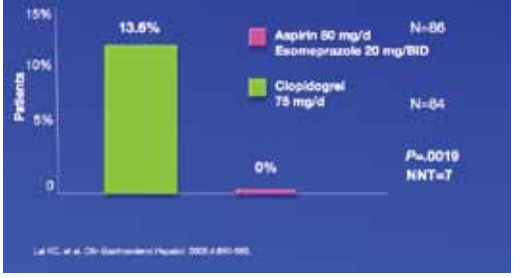
Strengths and Weaknesses of Data Relating to PPIs and Fractures

- Strengths
  - Consistent risk demonstrated, albeit of low magnitude (odds ratio <2.0)
  - Risk appears greater with higher doses and durations of use
- Weaknesses
  - Data come from observational studies: no randomized controlled trials
  - Unable to control for all potentially confounding variables (diet, medications, comorbid illness, etc.)
  - Absolute risk of fractures is low and of questionable clinical significance
  - No definite mechanism to explain effect has been demonstrated

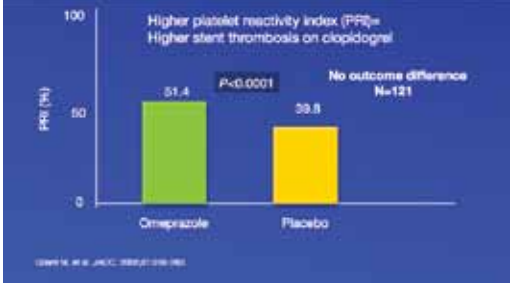
Effects on Vitamin B_{12}, Iron, and Magnesium Absorption

- Vitamin B_{12}
  - PPIs may interfere with proteolysis and release of B_{12} from dietary protein and/or gastric IFBG that could cause low B_{12} levels
  - Conflicting reports of lower B_{12} levels in long-term PPI users, but true deficiency or symptoms are rare and confined to the elderly
  - Absorption of oral supplemental B_{12} should be normal
- Iron
  - PPIs may affect absorption of nonheme iron (~80% of dietary iron)
  - No effect of PPIs on heme iron or medicinal iron
  - Reduction in phlebotomy requirement reported in patients with hemochromatosis receiving PPIs
- Magnesium
  - PPI-associated hypomagnesemia is a rare but potentially serious problem with an unknown mechanism
  - Can recur with PPI re-challenge

Risks of Clopidogrel Ulcer Rebleeding (12 months)

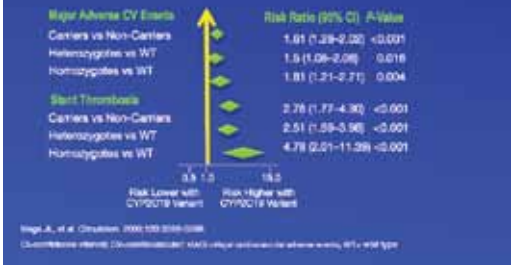


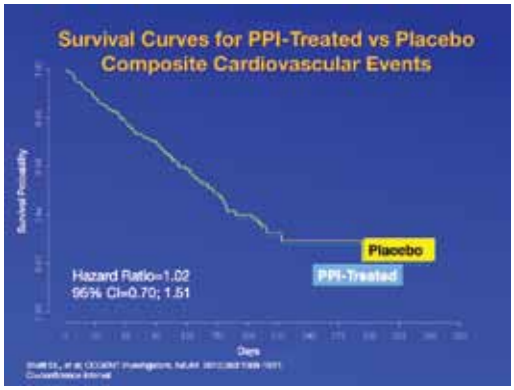
Clopidogrel-Related Mean PRI at Day 7

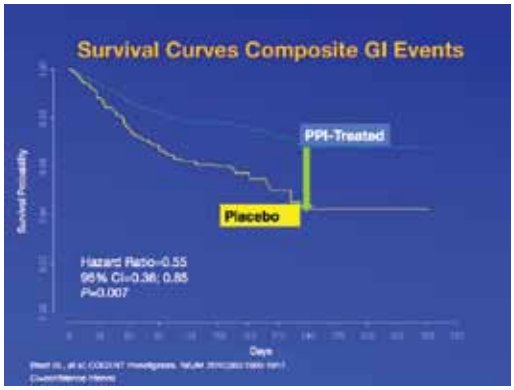


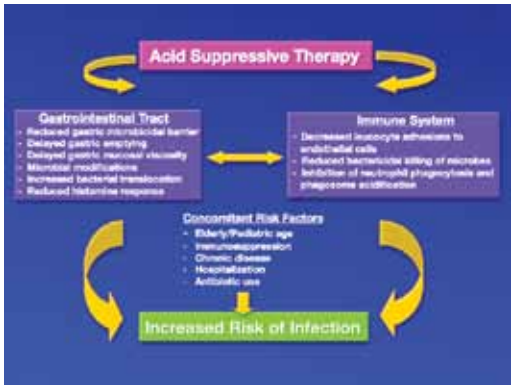
CYP2C19 Variants Affect Outcome on Clopidogrel

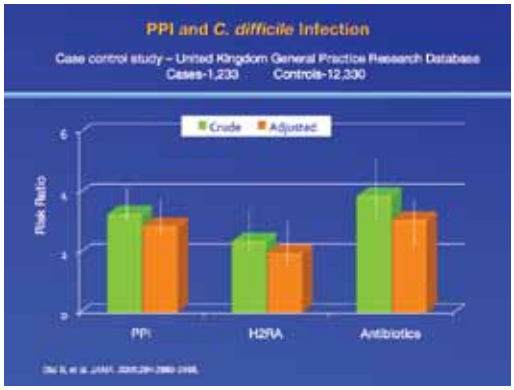
Nine studies of association of CYP2C19 reduced-function genetic variants with MACE in pts treated with clopidogrel (N=9,554 subjects)

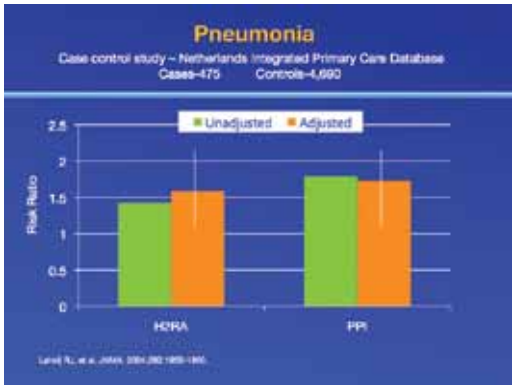












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