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Special REPORT

Expert Consensus on the Benefit-to-Risk Ratio of PPIs:

An Analysis of Recent Observational Studies

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Recent observational studies linking proton pump inhibitors (PPIs) and adverse events (AEs), including osteoporosis, acute interstitial nephritis (AIN), chronic kidney disease, myocardial infarction (MI), and dementia have resulted in greater scrutiny, leading some clinicians and patients to discontinue treatment. In response to the concerns stemming from these studies and the resulting media attention, the PPI Roundtable Summit, moderated by Gastroenterology & Endoscopy News, *was convened in August 2016 to review the articles and put them into context in assessing the implications of using PPIs. Given that recent PPI studies are observational and hypothesis-generating, the panelists agreed that a rational and evidence-based approach is essential to avoid denying PPIs to those who may benefit from them.*

Highlights

- There is no single mechanism of action that explains the occurrence of such varied types of AEs.
- The recent wave of negative media press about PPIs and potential AEs is unwarranted.
- Odds ratios reported in the majority of these observational studies were less than 2—AEs were *associated with* but not *caused by* chronic PPI use.
- The likelihood that a chronic PPI user would develop any of the reported serious AEs is extremely low.
- Consumers who use over-the-counter (OTC) PPIs as indicated are at little to no risk of developing these serious AEs.

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For almost 30 years, proton pump inhibitors (PPIs) have been the most commonly prescribed therapy for managing gastrointestinal (GI) diseases, such as gastroesophageal reflux disease (GERD), peptic ulcer disease, and gastric ulceration caused by nonsteroidal anti-inflammatory drugs (NSAIDs).[1] PPIs are used for long-term management of GERD-related complications such as strictures, erosive esophagitis, and Barrett's esophagus.[2] Additionally, over-the-counter (OTC) PPIs have been available for more than 10 years, and are indicated for short-term use in managing heartburn experienced at least twice weekly.[3-5] Despite extensive clinical evidence of the benefits of using PPIs to treat acid-related disorders, recent observational studies linking PPIs and adverse events (AEs), including osteoporosis, acute interstitial nephritis (AIN), chronic kidney disease, myocardial infarction (MI), and dementia have resulted in greater scrutiny, leading some clinicians and patients to discontinue treatment.[6-9]

In response to the concerns stemming from the publication of these observational studies, the PPI Roundtable Summit, moderated by *Gastroenterology & Endoscopy News*, was convened in August 2016 to review the articles and put them into context in assessing the implications of using PPIs. The expert panel recognized that although risks identified in these hypothesis-generating observational studies deserve to be evaluated in the context of their consistency and plausibility, the potential risks also need to be weighed against treatment goals. The panelists agreed that implementing an evidence-based approach to a benefit–risk assessment would enable clinicians to determine which patients would benefit from using PPIs.

This monograph reviews the efficacy and safety of PPIs in managing acid-related disorders and provides an analysis of recent observational studies, evaluating the benefits and risks of using these therapies.

"AEs have allowed this class to be put under scrutiny. We need to look very carefully at every association, remembering that it's association and not necessarily causality. The real challenge is how to integrate this into our prescribing approach and how we communicate it to the public. We have to be able to put these data into perspective and not simply dismiss them, but rather put PPIs in their most careful and correct usage."

—Philip Katz, MD

PPI Efficacy and Safety

The efficacy of PPIs is consistent with the underlying mechanism for acid control. Acid is secreted into the GI tract from the parietal cell, which can be activated by stimuli such as acetylcholine and histamine.[10] The histamine type 2-receptor antagonists (H_2RAs), which block the histamine receptors, inhibit just one of these triggers.[11,12] In contrast, PPIs inhibit the enzyme that regulates the acid pump, which is the final common pathway for acid secretion.[10,13] PPIs, which bind irreversibly to the acid pumps, are not associated with the tachyphylaxis that occurs with repeat dosing of H_2RAs.[14] PPIs, which concentrate rapidly in the parietal cell after administration, have not been clearly linked to any significant biological activity outside of this target.[10]

Multicenter trial programs with omeprazole across multiple indications have been followed with lansoprazole, pantoprazole, rabeprazole, esomeprazole, and dexlansoprazole.[13] These closely resemble one another in chemical structure, appear to achieve similar rates of efficacy for common indications, and have been uniformly associated with a high degree of tolerability and a low rate of AEs.[4,13]

Clinical evidence regarding both the efficacy and safety of PPIs is extensive. In trials comparing PPIs with H_2RAs, the previous standard for acid control, healing rates and symptom control for acid-related disorders—GERD and peptic ulceration—improved significantly with PPIs. Research has shown in GERD-related esophagitis, about 80% of patients experience heartburn relief compared with 50% of patients on H_2RA therapy.[15] In a meta-analysis that calculated per-week benefit, PPIs nearly doubled the rate of both healing (11.7% vs 5.9%) and complete heartburn relief (11.5% vs 6.4%) compared with H_2RAs.[16] Similar

relative efficacy was demonstrated when PPIs were compared with H_2RAs for duodenal ulcer and gastric ulcers.[17] A meta-analysis of 30 studies found that patients receiving 2 weeks of PPI therapy for duodenal ulcers showed a higher healing rate compared with ranitidine (15.2 percentage units; $P<0.001$); after 4 weeks of treatment, the healing rate for patients with gastric ulcers or reflux esophagitis increased (9.9 percentage units [$P=0.005$] and 23 percentage units [$P<0.001$], respectively).[17] PPI therapy also was associated with a higher healing rate than cimetidine (20.6 percentage units; $P<0.0001$) in patients with duodenal ulcer after 2 weeks of treatment.[17]

Because of their efficacy and safety profile, PPIs are considered as accepted empirical therapy for managing acid-related symptoms of GERD, according to guidelines from the American College of Gastroenterology.[18]

Evaluating PPI Observational Studies

PPIs are prodrugs that are activated when they reach the acid space of the gastric parietal cell.[10] Because of their weak base, PPIs accumulate selectively in the stimulated parietal cell's secretory canaliculus.[10] As a result of the limited opportunity for off-target effects, the focus for potential AEs during long-term therapy has been on the direct or indirect consequences of sustained acid suppression. Concern regarding risks from reducing gastric acid predates the approval of the first PPI, and was an important focus of the preclinical development and initial clinical studies.[19] The potential risks cited recently in observational studies are arising decades after initial safety studies demonstrated that reductions in gastric acid by PPIs are safe over the period of time in which clinical testing was performed.[19]

"In [the panelists'] collective years of doing this, none of us really has seen most of these AEs that are found when you do these large or even do extremely large community-based studies with a lot of patients."

—Donald O. Castell, MD

Hypergastrinemia

There are plausible risks from sustained acid suppression. Early on in the development of PPIs, substantial attention was given to the potential carcinogenic effect of hypergastrinemia, a product of sustained acid suppression in the GI tract.[20] This potential risk has been revisited periodically as the experience with PPIs expanded, but progressive histologic changes have been uncommon in patients on these therapies for up to 15 years and no reports of neoplasia could be identified according to a review of 16 studies.[21-23] Similarly, concern about the development of fundic gland polyps, which are common on long-term acid suppression, also dissipated when no clinically meaningful consequences could be identified when using PPIs over a long period of time.[24]

Mineral and Vitamin Deficiencies

Another focus of PPI safety has been their effect on nutrients, such as iron and vitamin B_{12}, which are dependent on acid for absorption. Studies evaluating this risk suggest that the risk for anemia on PPI therapy is small overall,[25] but the risk for vitamin B_{12} deficiency does appear to be elevated in some populations, such as in patients with Zollinger-Ellison syndrome on high doses of PPIs for prolonged periods and in the elderly.[26] The latter group, however, is already at risk for vitamin B_{12} deficiency, making the relative contribution of PPIs unclear.[27]

Bacterial Overgrowth and Infection Risk

Bacterial overgrowth in the GI tract, another potential consequence of sustained acid suppression, also has been evaluated repeatedly since the introduction of PPIs.[28] According to a meta-analysis of 11 studies comparing risk for small intestinal bacterial overgrowth among PPI users and nonusers, the pooled odds ratio (OR) was 2.282 (95% CI, 1.238-4.205).[28] The

authors noted that the association was statistically significant only when the diagnosis was made using a highly accurate testing modality.[28] Additionally, they noted that since the results were based on testing, studies are needed to assess the correlation with symptoms and malabsorption.[28]

The evidence suggests that the risk for enteric infections, particularly overgrowth of *Clostridium difficile*, is modestly increased with PPI use (OR, 1.95 [95% CI, 1.47-2.85]),[29] but susceptibility factors, particularly a previous *C. difficile* infection, appear to be important mediators of risk.[30] PPIs should be used prudently in patients at elevated risk for enteric infections, such as those hospitalized with susceptibility factors.[30] Similarly, observational studies suggest the risk for lung infection from aspirated bacteria in patients on PPI therapy, if real, is small but likely to be most relevant to patients with risk factors.[31]

Osteoporosis and Fractures

Reports of a potential association between PPI therapy and inhibited bone metabolism date back to the early 1990s.[32] Impaired calcium absorption stemming from low gastric acid is among proposed mechanisms, but efforts to confirm this mechanism have generated inconsistent results.[33,34] The focus on this potential complication intensified with publication of a nested case-control study based on population data in the United Kingdom.[35] In this study, an increased risk for hip fracture was associated with increased duration of PPI exposure (adjusted OR, 1.82 [95% CI, 1.67-2]) compared with H_2RAs (adjusted OR, 1.23 [95% CI, 1.14-1.39]).[35] The researchers noted that there could be potential for confounding: Patients with comorbidities are likely to be on PPI therapy and are likely to suffer a hip fracture due to other factors such as poor nutrition and decreased weight.[35] In a more recent meta-analysis that included this and 17 subsequent analyses, an increased risk for hip and all-site fractures was again associated with PPI exposure, but there was no correlation with duration of PPI use, and the increased risk was characterized as modest.[6] Additionally, the authors noted the absence of association between PPIs and fracture risk in some of the studies, as well as the heterogeneity between studies being statistically significant ($P<0.001$).[6]

AIN and Chronic Kidney Disease

A potential association between PPIs and risk for acute interstitial nephritis (AIN) proposed in the early 1990s gained renewed attention when a study conducted with the Veterans Affairs (VA) National Database associated exposure to PPIs, relative to exposure to H_2RAs, with increased rates of AIN and chronic kidney disease.[36,37] A separate and subsequent population-based study supported this association.[7] The authors of an editorial accompanying the VA study suggested that clinicians should be aware of this potential association when considering the risk-to-benefit ratio of PPI therapy but acknowledged that the absolute risk for these complications, if caused by PPIs, is small.[38]

AIN is an idiosyncratic cell-mediated immunologic reaction with many triggers.[39] In addition to common infectious diseases, the list of pharmacologic agents other than PPIs that have been associated with AIN includes most NSAIDs and antibiotics.[39] An assessment of the

"Many of those who read the titles of these studies misinterpret the meaning of associations, failing to understand the limitations of the analysis and the distinction between association and causation. These are exploratory analyses, so that even when an association is made, it is essential to consider whether there is corroborating evidence as well as biological plausibility for a causative relationship. In large sets of data, there is always the potential for statistically significant associations, but these may not be clinically significant even if confirmed in additional studies."

—Donald O. Castell, MD

pathophysiology suggests that AIN occurs in a small percentage of patients receiving therapy and that there is no dose dependence.[39]

Dementia

Research also has focused on the potential association between PPI therapy and risk for dementia. Gomm and colleagues conducted an observational study of 73,679 elderly patients from a German pharmacoepidemiological claims database to assess the association and found that there was an increased incidence of dementia among patients receiving PPI therapy (hazard ratio, 1.44 [95% CI, 1.36-1.52]).[9] The authors noted that residual confounding was possible and that other potential risk factors for dementia had not been included. The authors concluded that although there is a statistical association, further research is needed to assess the clinical implications using prospective trials.[9]

"We've been using these drugs for many years and it is easy to get cavalier about prescribing PPIs. I do think that these observational studies make us pause and think more carefully before prescribing PPIs."

—Gary W. Falk, MD, MS

Further assessment of this study demonstrated the challenge of diagnosing dementia and the effect of other medications being taken for associated symptoms, such as depression, and cognitive impairment, making the association less likely.[41]

Myocardial Infarction Risk

The potential link between PPI therapy and risk for MI has also been explored. Using a novel pharmacovigilance data-mining algorithm, Shah and colleagues reported that PPI therapy was associated with an adjusted OR of 1.16 (95% CI, 1.09-1.24) of having an MI.[8] The authors noted that although the data-mining approach was validated, there may be potential for a false positive; thus, the findings require additional investigation.[8]

Considerations in Evaluating the Data

Population-based cohort studies have been widely used as an exploratory tool to establish drug safety and identify risks that do not occur in controlled studies of finite size and duration of time.[42] An association between exposure to a pharmaceutical agent, such as a PPI, and an outcome of interest provides the basis for additional studies to explore the likelihood of a causal link which cannot be confirmed in these retrospective analyses due to residual confounding.[42] Moreover, associations—even if strong and consistent—do not confer causality, further obscuring the relevance of these data to clinical practice. In cases where controlled trials are impractical due to needing a large sample size or long duration, the strength of the association, its biological plausibility, and the consistency of the evidence guide risk assessment. Even strong associations based on these assessments may not alter the decision to offer treatment when balanced against a proven expectation of benefit.

"In these observational studies, the goal is to control for confounding factors, but retrospective analyses cannot be definitive because of residual confounding."

—Michael Vaezi, MD, PhD, MSc

It is appropriate to recognize both the strengths and weaknesses of large sets of data. Population-based studies have the potential to magnify weak safety signals, but they can also generate data that fail to differentiate statistical from clinical significance. For example, in the dementia observational study featuring data on 73,679 individuals older than age 75,

the mean age of those taking PPIs was 83.8 years compared with 83.0 years for those not taking PPIs—a difference that was highly significantly different ($P<0.001$) but unlikely to be clinically meaningful.[9]

Observational studies are never definitive even if the consistency and plausibility of the observed associations are sufficient to suggest probability and warrant consideration in a benefit–risk calculation. Further analysis is recommended.

PPI Therapy: Benefit–Risk Calculations

The efficacy and tolerability of PPIs for the control of heartburn and other acid-related complaints have made these medications among the most prescribed worldwide.[1] Although the empirical use of PPIs is consistent with guidelines,[18] the widely held perception that these drugs are safe has led to concerns that these have often been prescribed without documentation of clinical benefit.[27] In the absence of definitive diagnostic tests for nonspecific upper GI complaints, a trial of PPIs is an attractive strategy for both confirming and treating heartburn, but benefit should be confirmed before embarking on a sustained regimen. An incomplete response or recurring symptoms after an initial response should suggest further clinical evaluation.

There are a number of reasons to remain circumspect about the unexpected increase in observational studies linking PPI exposure to an array of clinical risks. Although these studies play a critical role in identifying safety signals that do not emerge in controlled trials, their significance is widely misinterpreted by those unfamiliar with their purpose and design. When the findings of these studies reach patients through conventional news sources, it is commonly concluded that PPIs cause rather than are associated with a given outcome. Such associations are often purposefully sensationalized to draw attention, but they may be a disservice to patients who forgo PPI therapy on the basis of a small and often theoretical risk despite the likelihood of substantial clinical benefits.

> ***"It's important to consider disease severity. Maybe you're on a PPI because you've got diabetes, metabolic syndrome—you've got all of these. And whether you're on it or not, you may end with whatever disease you are going to get. But you're on a PPI because you also may need it, and then that association pops up because of the disease severity. It's hard to control for disease severity."***
>
> *—Michael Vaezi, MD, PhD, MSc*

Patients should not take or be prescribed drugs that they do not need. This is appropriate on the basis of both safety and cost. As such, one of the benefits of the publicity surrounding the studies associating long-term PPI therapy with AEs is more judicious use of PPIs. For most patients with an indication for PPI therapy, benefits are likely to outweigh risks to a degree that meets or exceeds the benefit-to-risk calculations common to any therapy employed in clinical medicine. For patients who do not truly need PPI therapy, however, it is likely that any benefit is small.

OTC PPI Use: Short-Term Use as Indicated

For short-term use, the benefit–risk ratio of PPIs, whether prescribed or OTC, favors treatment for any individual experiencing symptom relief. Although a small proportion of patients prescribed PPIs have reported nausea, diarrhea, and other self-limiting events, the rates are generally similar to those observed on placebo.

In 2003, the FDA approved OTC omeprazole for the treatment of heartburn.[3] Two other OTC PPIs, lansoprazole and esomeprazole, followed.[4,3] For all 3 PPIs, the dosing is once daily for 14 days which may be repeated at intervals of every 4 months.[3] Safety warnings are restricted to potential drug–drug interactions and allergic reactions, which are rare.[4] The labeling is consistent with postmarketing data, which continue to support a high degree of safety. In response to several reports of an association between long-term PPI use and altered bone metabolism, for example, a statement issued by the FDA reconfirmed the safety of OTC PPIs when used as directed.[4,3]

Conclusion

The controlled evidence that PPIs are safe and effective for acute relief of heartburn, healing of esophagitis and peptic ulcers, and other specific treatment goals for which they are indicated is exceptional. For patients who require and benefit from PPIs, the lowest dose needed for symptom control is warranted. Risks, including theoretical ones, are relevant to patients on long-term PPI treatment. For patients who benefit from extended courses of PPI, a periodic recalculation of benefit to risk is appropriate. For individuals taking short courses and low doses of PPIs, such as those outlined in OTC schedules, observational studies evaluating risks over long-term exposure cannot be extrapolated. The consistency of the efficacy and safety in the multicenter trials on which these indications are based provides a strong foundation on which to reassure patients likely to benefit from these therapies, whether taken as directed in OTC formulations or as prescribed in higher doses over a defined period of time for a therapeutic goal.

"All of this discussion regarding the recently published associations is likely not applicable when speaking about a short course of OTC PPIs."

—Gary W. Falk, MD, MS

References

1. Vanderhoff BT, Tahoub RM. Proton pump inhibitors: an update. *Am Fam Physician*. 2003;66(2):274-280.
2. Triadafilopoulos G. Proton pump inhibitors for Barrett's oesophagus. *Gut*. 2000;46(2):144-146.
3. Department of Health and Human Services. Prilosec OTC Approval Letter. NDA 21-229. June 2003. www.accessdata.fda.gov/drugsatfda_docs/appletter/2003/21229ltr_Prilosec.pdf. Accessed October 7, 2016.
4. Centers for Medicare & Medicaid Services. Proton pump inhibitors: use in adults. August 2013. www.cms.gov/Medicare-Medicaid-Coordination/Fraud-Prevention/Medicaid-Integrity-Education/Pharmacy-Education-Materials/Downloads/ppi-adult-factsheet.pdf. Accessed October 7, 2016.
5. Vakil N, van Zanten SV, Kahrilas P, et al. The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. *Am J Gastroenterol*. 2006;101(8):1900-1920; quiz 1943.
6. Zhou B, Huang Y, Li H, et al. Proton-pump inhibitors and risk for fractures: an update meta-analysis. *Osteoporos Int*. 2016;27(1):339-347.
7. Lazarus B, Chen Y, Wilson FP, et al. Proton pump inhibitor use and the risk of chronic kidney disease. *JAMA Intern Med*. 2016;176(2):238-246.
8. Shah NH, LePendu P, Bauer-Mehren A, et al. Proton pump inhibitor usage and the risk of myocardial infarction in the general population. *PLoS One*. 2015;10(6):e0124653.
9. Gomm W, von Holt K, Thome F, et al. Association of proton pump inhibitors with risk of dementia: a pharmacoepidemiological claims data analysis. *JAMA Neurol*. 2016;73(4):410-416.
10. Shin JM, Sachs G. Pharmacology of proton pump inhibitors. *Curr Gastroenterol Rep*. 2008;10(6):528-534.
11. McRorie JW, Kirby JA, Miner PB. Histamine$_2$-receptor antagonists: Rapid development of tachyphylaxis with repeat dosing. *World J Gastrointest Pharmacol Ther*. 2014;5(2):57-62.
12. ZANTAC [prescribing information]. Research Triangle Park, NC: GlaxoSmithKline; 2016.
13. McDonagh MS, Carson S, Thakurta S. Drug class review: proton pump inhibitors: final report update 5. *Drug Class Rev*. Portland, OR: Oregon Health & Science University; 2009.
14. Sachs G, Shin JM, Hunt R. Novel approaches to inhibition of gastric acid secretion. *Curr Gastroenterol Rep*. 2010;12(6):437-447.
15. Bardahan KD. The role of proton pump inhibitors in the treatment of gastro-oesophageal reflux disease. *Aliment Pharmacol Ther*. 1995;9 (suppl 1):15-25.

16. Chiba N, De Gara CJ, Wilkinson JM, et al. Speed of healing and symptom relief in grade II to IV gastroesophageal reflux disease: a meta-analysis. *Gastroenterology*. 1997;112(6):1798-1810.

17. Eriksson S, Langstrom G, Rikner L, et al. Omeprazole and H_2-receptor antagonists in the acute treatment of duodenal ulcer, gastric ulcer and reflux oesophagitis: a meta-analysis. *Eur J Gastroenterol Hepatol*. 1995;7(5):467-475.

18. Katz PO, Gerson LB, Vela MF. Guidelines for the diagnosis and management of gastroesophageal reflux disease. *Am J Gastroenterol*. 2013;108(3):308-328; quiz 29.

19. Arnold R, Koop H. Omeprazole: long-term safety. *Digestion*. 1989; 44 (suppl 1):77-86.

20. Jensen RT. Consequences of long-term proton pump blockade: insights from the studies of patients with gastrinomas. *Basic Clin Pharmacol Toxicol*. 2006;98(1):4-19.

21. Fiocca R, Mastracci L, Attwood SE, et al; LOTUS trial collaborators. Gastric exocrine and endocrine cell morphology under prolonged acid inhibition therapy: results of a 5-year follow-up in the LOTUS trial. *Aliment Pharmacol Ther*. 2012;36(10):959-971.

22. Brunner G, Athmann C, Schneider A. Long-term, open-label trial: safety and efficacy of continuous maintenance treatment with pantoprazole for up to 15 years in severe acid-peptic disease. *Aliment Pharmacol Ther*. 2012;36(1):37-47.

23. Lundell L, Vieth M, Gibson F, et al. Systematic review: the effects of long-term proton pump inhibitor use on serum gastrin levels and gastric histology. *Aliment Pharmacol Ther*. 2015;42(6):649-663.

24. Jalving M, Koornstra JJ, Wesseling J, et al. Increased risk of fundic gland polyps during long-term proton pump inhibitor therapy. *Aliment Pharmacol Ther*. 2006;24(9):1341-1348.

25. Koop H, Bachem MG. Serum iron, ferritin, and vitamin B_{12} during prolonged omeprazole therapy. *J Clin Gastroenterol*. 1992;14(4):288-292.

26. Saltzman JR, Kemp JA, Golner BB, et al. Effect of hypochlorhydria due to omeprazole treatment or atrophic gastritis on protein-bound vitamin B_{12} absorption. *J Am Coll Nutr*. 1994;13(6):584-591.

27. Heidelbaugh JJ. Proton pump inhibitors and risk of vitamin and mineral deficiency: evidence and clinical implications. *Ther Adv Drug Saf*. 2013;4(4):125-133.

28. Lo WK, Chan WW. Proton pump inhibitor use and the rise of small intestinal bacterial overgrowth: a meta-analysis. *Clin Gastroenterol Hepatol*. 2013;11(5):483-490.

29. Leonard J, Marshall JK, Moayyedi P. Systematic review of the risk of enteric infection in patients taking acid suppression. *Am J Gastroenterol*. 2007;102(9):2047-2056; quiz 57.

30. McDonald EG, Milligan J, Frenette C, et al. Continuous proton pump inhibitor therapy and the associated risk of recurrent Clostridium difficile infection. *JAMA Intern Med*. 2015;175(5):784-791.

31. Sultan N, Nazareno J, Gregor J. Association between proton pump inhibitors and respiratory infections: a systematic review and meta-analysis of clinical trials. *Can J Gastroenterol*. 2008;22(9):761-766.

32. Sarges R, Gallagher A, Chambers TJ, et al. Inhibition of bone resorption by H+/K(+)-ATPase inhibitors. *J Med Chem*. 1993;36(19): 2828-2830.

33. O'Connell MB, Madden DM, Murray AM, et al. Effects of proton pump inhibitors on calcium carbonate absorption in women: a randomized crossover trial. *Am J Med*. 2005;118(7):778-781.

34. Wright MJ, Sullivan RR, Gaffney-Stomberg E, et al. Inhibiting gastric acid production does not affect intestinal calcium absorption in young, healthy individuals: a randomized, crossover, controlled clinical trial. *J Bone Miner Res*. 2010;25(10):2205-2211.

35. Yang YX, Lewis JD, Epstein S, et al. Long-term proton pump inhibitor therapy and risk of hip fracture. *JAMA*. 2006;296(24):2947-2953.

36. Ruffenach SJ, Siskind MS, et al. Acute interstitial nephritis due to omeprazole. *Am J Med*. 1992;93(4):472-473.

37. Xie Y, Bowe B, Li T, et al. Proton pump inhibitors and risk of incident CKD and progression to ESRD. *J Am Soc Nephrol*. 2016;27(10):3153-3163.

38. Moledina DG, Perazella MA. Proton pump inhibitors and CKD. *J Am Soc Nephrol*. 2016;27(10):2926-2928.

39. Rossert J. Drug-induced acute interstitial nephritis. *Kidney Int*. 2001: 60(2):804-817.

40. Kodner CM, Kudrimoti A. Diagnosis and management of acute interstitial nephritis. *Am Fam Physician*. 2003;67(12):2527-2534.

41. Atri A, Gerson LB. Continued questions about whether avoidance of proton pump inhibitors can reduce risk of dementia. *Gastroenterology*. 2016;151(3):555-558.

42. Szklo M. Population-based cohort studies. *Epidemiol Rev*. 1998;20(1): 81-90.

43. FDA. FDA Drug Safety Communication: possible increased risk of fractures of the hip, wrist, and spine with the use of proton pump inhibitors. www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm213206.htm. Accessed October 7, 2016.

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