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Long-term PPI use: safety concerns

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Disclosures: none

GERD and the cost of PPI

- The proton pump inhibitors market was valued at USD 2,750 million in 2020, and it is anticipated to reach USD 3,585 million in 2026. The United States National Library of Medicine (NCBI) published a report in October 2018
- Approximately 8.8–25.9% of the population in Europe, 2.5–7.8% in East Asia, 18.1–27.8% in North America, 11.6% in Australia, and 23.0% in South America had gastroesophageal reflux disease (GERD) in that year. Also, according to the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) 2017, globally, there were 9283 (8189 to 10400) cases per 100,000 population in 2017, and 709 million (626 to 795) people of the world reported GERD in 2017.

https://www.mordorintelligence.com/industry-reports/proton-pump-inhibitors-market

Cost, continued

- Population-based cohort study:
  - Total number of pts with GERD increased: more common in younger and not ≥70 yo. One study demonstrated prevalence of sx higher in ≥50 years as compared with those who were aged < 50 years (OR, 1.32; 95% CI, 1.12–1.54; $P < 0.001$).
  - Another study: Greatest rise in pts 30-39 yo in the last decade, up to 30% reported decreased work productivity
  - General characteristics: obese, older women, Caucasian
  - Limitation: The results are based on the Explorys dataset, which originates from 26 major Healthcare systems and 360 hospitals overall, but may not reveal regional/local hospital trends, possibly lacking in diversity.

Yamasaki et al J Neurogastroenterol Motil. 2018 Oct; 24(4): 559–569.

Published online 2018 Oct 1. doi: 10.5056/jnm18140

FDA indications for PPI

Table 3

Food and Drug Administration Approved Indications for Proton Pump Inhibitors

Indication	Omeprazole	Esomeprazole	Lansoprazole	Dexlansoprazole	Pantoprazole	Rabeprazole
Gastro esophageal reflux disease						
Erosive esophagitis—healing	✓	✓	✓	✓	✓	✓
Erosive esophagitis—maintenance	✓	✓	✓	✓	✓	✓
Nonerosive reflux disease	✓	✓	✓	✓		✓
Peptic ulcer disease						
Duodenal ulcer—healing	✓		✓			✓
Duodenal ulcer—maintenance			✓			
Gastric ulcer—healing	✓		✓			
NSAID induced ulcers—healing			✓			
NSAID induced ulcers—prophylaxis		✓	✓			
Zollinger-Ellison syndrome	✓	✓	✓		✓	✓
Treatment of *Helicobacter pylori*						
Dual therapy	✓		✓			

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NASID, nonsteroidal anti-inflammatory drugs; GI, gastrointestinal; IV, intravenous; NG, nasogastric.

Gut Liver. 2017 Jan; 11(1): 27–37.

Published online 2016 Nov 14.
doi: 10.5009/gnl15502

The trouble with PPI and data

Several body systems are affected:

-dementia

-heart disease

-enteric infections

-renal insufficiency

-fractures

-B12 deficiency

-hypomagnesemia

- Observational
- Meta analyses
- RCT

Table 1 Summary of potential adverse effects and clinical recommendations

Theoretical risk	Evidence summary	Recommendations for clinical practice
Nutritional deficiencies		
B_{12} deficiency	Most patients consuming normal diet will not experience clinically significant B_{12} deficiency. Elderly and malnourished patients at higher risk	Evidence does not justify routine screening Screening may be reasonable for elderly or malnourished patients
Iron deficiency	Little data that long-term PPI use results in clinically significant iron deficiency	Evidence does not justify routine screening Long-term PPI use does not result in clinically significant iron deficiency under normal clinical circumstances Reduced iron absorption secondary to long-term PPI use may only be clinically significant in hemochromatosis and other iron overload states
Hypomagnesemia	<30 case reports published in peer-reviewed literature	Remain vigilant for unexplained hypomagnesemia, hypokalemia, or hypocalcemia in PPI users
Fracture risk	Inconsistent study results	Evidence does not justify routine pharmacologic prophylaxis or bone mineral density screening
	Possible that long-term PPI use in patients with risk factors for fracture may increase risk for certain fractures	Consider risks and benefits of long-term PPI therapy in patients with risk factors such as osteoporosis and steroid use
Infections		
Community acquired pneumonia	No substantial increase in risk of community-acquired pneumonia after controlling for potential confounders	PPIs should not be withheld from patients with pulmonary disease if they have indications for treatment Patients who are immunocompromised, elderly, smokers, and those with COPD or other risk factors for CAP should receive annual influenza vaccination
Enteric infections	Growing evidence that acid suppression increases risk of enteric infections by *C. difficile* and a variety of pathogens	Benefits and risks of long-term PPI therapy for inpatients who are immunocompromised or chronically ill should be weighed PPI discontinuation should be considered in patients with life-threatening enteric infections without urgent indication for acid suppression
Hypergastrinemia and malignancy		
Gastric polyps	Long-term PPI use is likely associated with increased frequency of fundic gland polyps (FGPs) in *H. pylori*-negative patients without familial adenomatous polyposis (FAP)	Majority of FGPs are benign, routine endoscopic surveillance or removal not indicated FAP patients with FGPs may benefit from closer monitoring
Gastric cancer	No controlled human data supporting increased risk of gastric cancer from long-term PPI use	Maastricht consensus panel recommends *H. pylori* eradication before prolonged PPI use, while American College of Gastroenterology currently does not
	Acid suppression alters pattern of gastritis in *H. pylori*; unclear whether this increases gastric cancer risk	
Gastric carcinoids	No formal studies in humans, no studies showing increased risk of carcinoid development in any non-rat species	Risk does not justify altering current PPI prescribing practices or routine screening
Colon cancer	Clinical studies have not supported relationship between hypergastrinemia and increased risk of CRC	Risk does not justify altering current PPI prescribing or CRC screening practices
Drug interactions		
Cytochrome P450 interactions	Rare and usually clinically insignificant	Take note of established drug interactions and polypharmacy, monitor individual responses
Interactions with clopidogrel	Inconsistent study results	Consider risks and benefits of PPI therapy on an individual basis
Safety during pregnancy	Most studies have involved omeprazole; no significant association between omeprazole use and birth defects	Based on existing data, omeprazole appears to be safe during the first trimester of pregnancy

Edward Sheen • George Triadafilopoulos
Dig Dis Sci (2011) 56:931–950
DOI 10.1007/s10620-010-1560-3

What if it isn't a RCT?
Odds Ratio (OR)
Relative Risk (RR)
Absolute Risk

Andrade, P

J Clin Psychiatry 2015;76(7):e857–e861
dx.doi.org/10.4088/JCP.15f10150

Clinical Points

- The absolute risk is the probability of an event in a sample or population of interest. The relative risk (RR) is the risk of the event in an experimental group relative to that in a control group. The odds ratio (OR) is the odds of an event in an experimental group relative to that in a control group.
- An RR or OR of 1.00 indicates that the risk is comparable in the two groups. A value greater than 1.00 indicates increased risk; a value lower than 1.00 indicates decreased risk. The 95% confidence intervals and statistical significance should accompany values for RR and OR.
- RR and OR convey useful information about the effect of a risk factor on the outcome of interest. However, the RR and OR must be interpreted in the context of the absolute risk as well as the clinical importance of the outcome in the individual patient.

Who is saying it? (a few or a lot, consistency)

How is the data presented? (does it make sense and is there a feasible biological explanation)

Association vs causality?

- 2 people walked onto GG bridge. One got hit by a bike and broke his leg
  - 50% of people who walk onto the GG break his leg
  - OR 2
- A traffic light was installed by my house. 4 people have been hit by a car the year prior. In the past 12 mos, only one person has been hit
  - 75% reduction in car accidents
    - Was the driver drunk, the sun in his eyes, and what does my house have to do with this?
    - The source is the manufacturer of the lights

Safety of Proton Pump Inhibitors Based on a Large, Multi-Year, Randomized Trial of Patients Receiving Rivaroxaban or Aspirin (COMPASS) Moayyedi, P et al Gastroenterology 2019;157:682–691

- **Trial Design:** The Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trial is a 3 × 2 partial factorial, multicenter, double-blind, randomized placebo-controlled trial evaluating patients with stable atherosclerotic vascular disease.
- **Methods:** 3 × 2 partial factorial double-blind trial of 17,598 participants with stable cardiovascular disease and peripheral artery disease randomly assigned to: rivaroxaban 2.5 mg twice daily with aspirin 100 mg once daily, rivaroxaban 5 mg twice daily alone, aspirin 100 mg once daily alone. All participants who were not already taking a PPI at baseline (64%) were randomized to receive either pantoprazole 40 mg or matching placebo once daily.
  - Also looked at including pneumonia, *C difficile* infection, other enteric infections, fracture, gastric atrophy, chronic kidney disease, and dementia. We also evaluated diabetes mellitus and chronic obstructive lung disease, as previous observational data had suggested increased rates of these diseases in patients taking PPI therapy, although this was not the primary focus of the analyses
  - Follow up at 1 mo the 6 mos, then q 6 mos following. 580 centers, 33 countries, 17,598 participants recruited between March 2013 and May 2016. 53,152 patient-years of follow-up
- **Results: no difference in composite outcome of CV death, MI, Stroke**

Figure 2. Cumulative incidence of combined cardiovascular death, myocardial infarction, and stroke in the pantoprazole vs placebo arm.

Moayyedi, P et al

Gastroenterology 2019;157:682–691

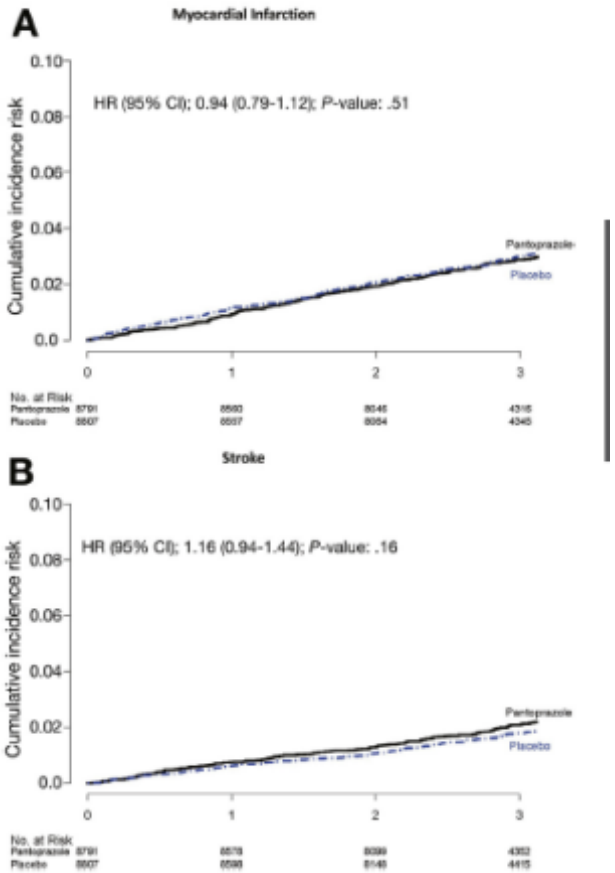

Figure 3. Cumulative incidence of individual cardiovascular events in the pantoprazole vs placebo arm.

Then there’s everything else

C difficile

Trifan A, Stanciu C, Girleanu I, Stoica OC, Singeap AM, Maxim R, Chiriac SA, Ciobica A, Boiculese L. Proton pump inhibitors therapy and risk of Clostridium difficile infection: Systematic review and meta-analysis. World J Gastroenterol. 2017 Sep 21;23(35):6500-6515. doi: 10.3748/wjg.v23.i35.6500.

Hafiz RA, Wong C, Paynter S, David M, Peeters G. The Risk of Community-Acquired Enteric Infection in Proton Pump Inhibitor Therapy: Systematic Review and Meta-analysis. Ann Pharmacother. 2018 Jul;52(7):613-622. doi: 10.1177/1060028018760569. Epub 2018 Feb 18. PMID: 29457492.

- Systematic review and meta-analysis: PPI and risk of C diff infection. Jan 1990 to March 2017
- Results: 56 studies, 356, 683 pts
- Increased risk despite heterogeneity
- Combined OR 1.99, CI 1.73-2.3. statistically significant
- **Conclusion:** This meta-analysis provides further evidence that PPI use is associated with an increased risk for development of CDI. Further high-quality, prospective studies are needed to assess whether this association is causal.
- ----------
- Previous meta-analyses suggest PPI have higher risk for CDI, BUT heterogeneity and is risk the same for different organisms
- electronic databases (all available years until November 2017). PubMed, EMBASE, Cochrane, and Web of Science were searched using specific keywords related to PPI therapy and community-acquired enteric infection.
- Results: pooled OR 4.28, 95% CI 3.01-6.98
- The strength of the association was similar for Salmonella (pooled OR = 4.84; 95% CI = 2.75-8.54; I^2 = 58.7%; P = 0.064) and Campylobacter (pooled OR = 5.09; 95% CI = 3-8.64; I^2 = 81%; P < 0.001) but lower for studies that combined all bacteria (pooled OR = 2.42; 95% CI = 0.96-6.14; I^2 = 94.3%; P < 0.001).
- **Conclusion:** PPI users have an increased risk of developing community-acquired enteric infections compared with nonusers. The heterogeneity was partially explained by type of microorganism; the association is stronger for Salmonella and Campylobacter than for all bacteria combined.

Tseng, HJ., Cheng, CM., Tsai, SJ. *et al.* Proton Pump Inhibitor Exposure and Acute Myocardial Infarction Risk: A Nested Cohort Study. *Cardiovasc Toxicol* **21,** 444–450 (2021). https://doi.org/10.1007/s12012-021-09637-2

Background: association of PPI in Caucasian population remains under debate. Did PPI use lead to increased risk of new onset MI in Asian population.

Data from Taiwanese Health Insurance database: 27, 624 age and sex-matched controls with PPI exposure, but no AMI and no development of ischemic heart dz

Results: AMI risk increased with an increase in PPI exposure

COVID risk

Almario CV, Chey WD, Spiegel BMR. Increased risk of COVID-19 among users of proton pump inhibitors. *Am J Gastroenterol* 2020

- Does the hypochlorhydria associated with PPI use increase risk for COVID in the community
- Online survey May-June 2020:
  - 53, 130 participants: 6.4% had pos COVID test and regression analysis showed aOR 2.15 for qd and 3.67 for bid. Risk remained despite duration
  - Other co-morbidities
  - H2B not increased risk
  - More studies needed, encourage good clinical practice

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The Risk of COVID-19 is Higher in Females Using Proton Pump Inhibitors

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PURPOSE / OBJECTIVES

- The coronavirus disease 2019 (COVID-19) is a global respiratory disease outbreak caused by a novel coronavirus called severe acute respiratory system coronavirus 2 (SARS-CoV-2).
- A slew of adverse events related to chronic proton pump inhibitors (PPIs) treatment have been documented in the past decade.
- However, the risk of infection with the novel coronavirus in patients with gastro-esophageal reflux disease (GERD) using PPI still remains to be elucidated.
- The aim of this study was to determine the incidence of COVID-19 in GERD patients on chronic PPI treatment.

MATERIAL & METHODS

- We reviewed data from a large commercial database (Explorys IBM) that aggregates electronic health records from 26 large nationwide healthcare systems.
- Using systemized nomenclature of clinical medical terms (SNOMED CT), we identified adults with GERD (November 1999- November 2020) and COVID-19 (January 2020 – November 2020).
- Comorbidities known to be associated with GERD and COVID-19 such as obesity, diabetes mellitus (DM), Barrett's esophagus (BE), gender, smoking, advance age were also collected.
- Incidence of COVID-19 was compared among different risk groups. Univariable and multivariable logistic regression analyses were performed to investigate the strongest association.

RESULTS

- Out of 61.4 million active adult patients in the database, 6,173,950 patients (9.85%) had documented GERD.
- In univariate analysis in GERD cohort, there was a higher incidence of COVID-19 in patients who are on PPIs (0.11% vs 0.03 % OR 3.28 [95% CI: 3.03 – 3.55]), females (0.11% vs 0.05%; OR 2.05 [95%CI: 1.94–2.17]), younger than 65 years (0.10% vs 0.07%, OR 1.50 [95%CI: 1.41 - 1.59]) diabetic (0.13% vs 0.07%, OR 1.93 [95%CI: 1.83–2.04]), or have BE (0.32% vs 0.08%, OR 4.00 [95%CI: 3.39–4.72]).
- Incidence of COVID-19 was also higher among smokers (0.09% vs 0.08%, OR 1.12 [95%CI: 1.05–1.20]), those with hiatal hernia (0.11% vs 0.08% OR 1.31 [95%CI: 0.98–1.76]) and obese (0.13% vs 0.07%, OR 1.91; 95%CI: 1.81–2.02]).
- In multivariable model, the incidence of COVID with PPI use was modified with gender after adjusting for other risk factors for COVID -19 from the univariate model.
- Female patients using PPIs had higher risk of COVID-19 (OR 9.94, 95%CI: 8.91-11.09) than their male counterparts using PPI (OR 1.20, 95%CI: 1.04–1.36). This interaction was found to be statistically significant ($P < 0.05$).

The risk of COVID-19 is higher in GERD patients using PPIs

This risk is even higher in females with GERD

RESULTS

Table 1. Baseline characteristics of the study population

Characteristics	Total Cohort	COVID-19	Non-COVID-19	P- value
Age				
Less than 65 yrs	2,839,070 (45.98%)	1,855 (0.07%)	2,837,215 (99.93%)	<0.001
Older than 65 yrs	3,334,880 (54.02%)	3,245 (0.10%)	3,331,635 (99.90%)	
Gender				
Female	3,014,575 (48.83%)	3,375 (0.11%)	3,011,200 (99.89%)	<0.001
Male	3,159,375 (51.171%)	1,725 (0.05%)	3,157,650 (99.95%)	
PPI use				
Yes	4,025,445 (65.20%)	4,385 (0.11%)	4,021,060 (99.89%)	<0.001
No	2,148,505 (34.80%)	715 (0.03%)	2,147,790 (99.97%)	
Smoking				
Yes	1,335,030 (21.62%)	1,200 (0.09%)	1,333,830 (99.91%)	<0.001
No	4,838,920 (78.38%)	3,900 (0.08%)	4,835,020 (99.92%)	
Diabetes Mellitus				
Yes	1,619,630 (26.23 %)	2,075 (0.13%)	1,617,555 (99.87%)	<0.001
No	4,554,320 (73.77 %)	3,025 (0.07%)	4,551,295 (99.93%)	
Obesity				
Yes	1,666,395 (26.99%)	2,110 (0.13%)	1,664,285 (99.87%)	<0.001
No	4,507,555 (73.01%)	2,990 (0.07%)	4,504,565 (99.93%)	
Barrett's Esophagus				
Yes	44,930 (0.73%)	145 (0.32%)	6,124,065 (99.92%)	<0.001
No	6,129,020 (99.27%)	4,955 (0.08%)	4,785 (99.68 %)	
Hiatal Hernia				
Yes	41,670 (0.67%)	45 (0.11%)	41,625 (99.89%)	<0.07
No	6,132,280 (99.33%)	5,055 (0.08%)	6,127,225 (99.92%)	

Table 2. Adjusted odds ratio for COVID-19 in patients with GERD with effect modification

Risk Factors	Adjusted Odds Ratio (95% CI)
Diabetes Mellitus	7.76 (7.13–8.44)
Barrett's Esophagus	**3.37 (2.85–3.98)**
Obesity	1.27 (1.24–1.28)
Hiatal Hernia	1.18 (0.83–1.5)
Smoking	0.97 (0.91–1.03)
Age	0.56 (0.54–0.60)
PPI use	
Female	9.94 (8.91–11.09)
Male	1.19 (1.04–1.36)

SUMMARY / CONCLUSION

PPI use in patients with GERD is associated with higher risk of COVID-19, especially among female patients and those with Barrett's esophagus.

association.

RESULTS

- Out of 61.4 million active adult patients in the database, 6,173,950 patients (9.85%) had documented GERD.
- In univariate analysis in GERD cohort, there was a higher incidence of COVID-19 in patients who are on PPIs (0.11% vs 0.03 % OR 3.28 [95% CI: 3.03 – 3.55]), females (0.11% vs 0.05%; OR 2.05 [95%CI: 1.94–2.17]), younger than 65 years (0.10% vs 0.07%, OR 1.50 [95%CI: 1.41 - 1.59]) diabetic (0.13% vs 0.07%, OR 1.93 [95%CI: 1.83–2.04]), or have BE (0.32% vs 0.08%, OR 4.00 [95%CI: 3.39–4.72]).
- Incidence of COVID-19 was also higher among smokers (0.09% vs 0.08%, OR 1.12 [95%CI: 1.05–1.20]), those with hiatal hernia (0.11% vs 0.08% OR 1.31 [95%CI: 0.98–1.76]) and obese (0.13% vs 0.07%, OR 1.91; 95%CI: 1.81–2.02]).
- In multivariable model, the incidence of COVID with PPI use was modified with gender after adjusting for other risk factors for COVID -19 from the univariate model.
- Female patients using PPIs had higher risk of COVID-19 (OR 9.94, 95%CI: 8.91-11.09) than their male counterparts using PPI (OR 1.20, 95%CI: 1.04–1.36). This interaction was found to be statistically significant ($P < 0.05$).

Renal Disease

Wu, B., Li, D., Xu, T. *et al.* Proton pump inhibitors associated acute kidney injury and chronic kidney disease: data mining of US FDA adverse event reporting system. *Sci Rep* **11,** 3690 (2021). https://doi.org/10.1038/s41598-021-83099-y

Lazarus B, Chen Y, Wilson FP, Sang Y, Chang AR, Coresh J, Grams ME. Proton Pump Inhibitor Use and the Risk of Chronic Kidney Disease. JAMA Intern Med. 2016 Feb;176(2):238-46. doi: 10.1001/jamainternmed.2015.7193. PMID: 26752337; PMCID: PMC4772730.

- Adverse events reporting system: 2004-2009
  - 3187 PPI associated AKI cases, 3457 CVD cases
  - The signal strength was stronger for CKD (ROR = 8.80, 95% CI 8.49–9.13) than AKI (ROR = 3.95, 95% CI 3.81–4.10), w dexlansoprazole showed stronger association for CKD (ROR = 34.94, 95% CI 30.89–39.53) and AKI (ROR = 8.18, 95% CI 7.04–9.51)
- **Population based cohort: 248, 751 pts**
  - PPI use was associated with CKD in all analyses, including a time-varying new-user design (adjusted HR, 1.24; 95% CI, 1.20-1.28).
  - Twice-daily PPI dosing (adjusted HR, 1.46; 95% CI, 1.28-1.67) was associated with a higher risk than once-daily dosing (adjusted HR, 1.15; 95% CI, 1.09-1.21).

What to do?

AGA Guideline, 2017

- Bethesda, MD (April 7, 2017) -- When proton pump inhibitors (PPIs) are appropriately prescribed, their benefits are likely to outweigh their risks, according to an American Gastroenterological Association (AGA) Clinical Practice Update1 published in *Gastroenterology*, the official journal of AGA. Additionally, there is currently insufficient evidence to recommend specific strategies for mitigating PPI adverse effects.
- The long-term use of PPIs by patients for gastroesophageal reflux disease (GERD), Barrett's esophagus and non-steroidal anti-inflammatory drug (NSAID) bleeding prophylaxis doubled in the U.S. from 1999 to 2012. Studies have shown that the number of adverse events doubled during the same period. AGA provides best practice advice for the use of PPIs based on expert opinion and relevant publications:
- 1. Patients with GERD and acid-related complications should take a PPI for short-term healing, maintenance of healing and long-term symptom control.
- 2. Patients with uncomplicated GERD who respond to short-term PPIs should subsequently attempt to stop or reduce them. Patients who cannot reduce PPIs should consider ambulatory esophageal pH/impedance monitoring before committing to lifelong PPIs to help distinguish GERD from a functional syndrome.
- 3. Patients with Barrett's esophagus and symptomatic GERD should take a long-term PPI.
- 4. Asymptomatic patients with Barrett's esophagus should consider a long-term PPI.
- 5. Patients at high risk for ulcer-related bleeding from NSAIDs should take a PPI, if they continue to take NSAIDs.
- 6. The dose of long-term PPIs should be periodically reevaluated so that the lowest effective PPI dose can be prescribed to manage the condition.
- 7. Long-term PPI users should not routinely use probiotics to prevent infection.
- 8. Long-term PPI users should not routinely raise their intake of calcium, vitamin B12 or magnesium beyond the recommended dietary allowance.
- 9. Long-term PPI users should not routinely screen or monitor bone mineral density, serum creatinine, magnesium or vitamin B12.
- 10. Specific PPI formulations should not be selected based on potential risks.

The New York Times

Pop a Pill for Heartburn? Try Diet and Exercise Instead

295

What to do:

-Know what you are treating

-smallest effective dose

-frank discussions with patients

-additional evaluation?