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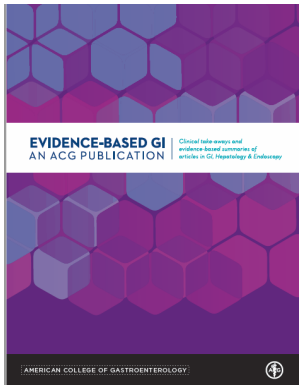

The American College of Gastroenterology (ACG) is an international organization with more than 14,000 physician members representing some 85 countries. The College's vision is to be the pre-eminent professional organization that champions the evolving needs of clinicians in the delivery of high-quality, evidence-based and compassionate health care to advance world-class care for patients with gastrointestinal disorders through excellence, innovation, and advocacy in the areas of scientific investigation, education, prevention, and treatment. *Evidence-Based GI* is a member publication of the American College of Gastroenterology.

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EDITORIAL

Evidence-Based GI: One-Year Review

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Evidence-Based GI: An ACG Publication (EBGI) launched in October 2021. During the past year, we've created multiple initiatives to enhance the educational value to members of the American College of Gastroenterology (ACG) while remaining faithful to our core mission: providing evidence-based summaries of the best GI clinical research. GI research published in top general medicine journals, including *New England Journal of Medicine, JAMA, Annals of Internal Medicine*, and the *Lancet* is highlighted since these journals aren't routinely reviewed by many ACG members. We're dedicated to filtering the "wheat from the chaff" to identify the 1%-2% of published GI research that is relevant to your practice[1] by utilizing evidence-based medicine (EBM) critical appraisal techniques to identify well-designed studies that produce unbiased and clinically important results.[2] This approach was pioneered by the work of Brian Haynes and his colleagues at the American College of Physicians Journal Club for general internists. Of course, the philosophy of EBM recognizes that each individual patient is different and every question may not be answered by a randomized controlled trial (RCT). Therefore, we hope that our expert commentaries provide important context about the application of study results to patient care, as we highlight in the "Caution," "My Practice," and "For Future Research" sections.

Clinical practice guideline development has been greatly enhanced by EBM, and the ACG guidelines rely on high-quality RCTs to make strong recommendations. Therefore, we started the *In Case You*

Missed It (ICYMI) series which summarizes landmark RCTs from the past 3 years that are the basis for recommendations in new ACG clinical practice guidelines. This month's issue adds to this series by summarizing the seminal 2019 VA Cooperative Study[3] comparing laparoscopic Nissen fundoplication to aggressive medical therapy for heartburn, which is the foundation for recommendations about surgical management of GERD in the 2022 ACG Clinical Guideline for the Diagnosis and Management of Gastroesophageal Reflux Disease.[4]

We recognize that ACG members may use multiple different platforms to access educational material. Under the guidance of our Associate Editor for Social Media, Joseph Sleiman, we've created a social media team that produces weekly tweetorials of EBGI summaries. This has led to collaborations with @TuesdayNightIBS and @ScopingSundays that utilize our content as the foundation for their discussions. We look forward to expanding these collaborations with @MondayNightIBD, @GIJournal, and other live Twitter discussions. Podcasts of each summary are now featured on Spotify, Stitcher, Google and iTunes, and the publication is formatted for optimal reading on your smartphone. We encourage you to download the ACG Mobile App, which will facilitate this as well as providing easy access to other ACG educational material.

In 2023, we'll focus on outreach to GI fellows. *EBGI* is a natural resource for journal clubs at fellowship programs, and we hope to become an indispensable resource for this. We will be reaching out to GI fellowship program directors in our new venture of developing *EBGI*-branded slides to facilitate this. We'll also provide new links to other EBM resources, like the EQUATOR network, on our homepage. Also, look for issues devoted to specific themes, including a colorectal cancer (CRC) screening and prevention issue in March 2023.

Finally, this issue of *EBGI* is being released on Friday, November 11—Veteran's Day. As a Navy veteran and a physician at a Veterans Affairs Medical Center, I'm so thankful for the service of our active-duty military and our Veterans. Let's also remember the VA and military gastroenterologists who have conducted groundbreaking research. The implementation of screening colonoscopy is largely due to the results of VA Cooperative Study 380[5-6], and its associated studies guide much of our approach to CRC screening. The CARE study highlighted the frequency of incomplete polyp resection.[7] The VA Cooperative Study program has also produced the RCT[3] comparing laparoscopic Nissen fundoplication versus medical therapy for PPI-unresponsive GERD highlighted in this issue of *EBGI* as well as producing the definitive RCT to determine if screening colonoscopy is superior to annual fecal immunochemical testing for CRC screening[8], which

will report out results in the coming years. We owe a great debt to the Veterans who participate in this research as well as these researchers.

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ESOPHAGUS

In Case You Missed It

Surgery is Superior to Medical Therapy for PPI-refractory Heartburn in the "Right" Patients

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This summary reviews Spechler SJ, Hunter JG, Jones KM, et al. Randomized Trial of Medical versus Surgical Treatment for Refractory Heartburn. N Engl J Med 2019;381:1513-1523. https://pubmed.ncbi.nlm.nih.gov/31618539/

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**In Case You Missed It* is a recurring series about landmark RCTs from the past 3 years which impact new clinical practice guidelines.

STRUCTURED ABSTRACT

Question: Is laparoscopic Nissen fundoplication superior to medical therapy with PPI plus baclofen for patients with proton pump inhibitor (PPI)-unresponsive heartburn secondary to reflux.

Design: Randomized controlled trial (RCT) with 3 arms stratified based on impedance pH testing.

Setting: Veterans Affairs (VA) gastroenterology clinics.

Patients: Three hundred sixty-six patients referred to GI clinic for PPI-refractory heartburn were screened for eligibility by completing the Gastroesophageal Reflux Disease-Health Related Quality of Life (GERD-HRQL) questionnaire followed by a 2-week trial of omeprazole 20 mg twice daily (30 minutes before breakfast and 30 minutes before dinner) for 2 weeks followed by completing the

GERD-HRQL again. The GERD-HRQL is a validated questionnaire that ranges from 0 to 50 with higher scores indicating worse symptoms. Patients whose GERD -HRQL decreased by < 50% underwent diagnostic evaluation including endoscopy with biopsy, esophageal manometry, and esophageal impedance-pH monitoring while continuing omeprazole 20 mg twice daily. Inclusion criteria were: (a) abnormal acid exposure time (pH<4 for ≥4.2% of 24 hours); (b) symptom association probability >95% based on impedance-pH monitoring; or, (c) both. This ensured enrolling patients with abnormal acid reflux despite PPI therapy as well as individuals with reflux hypersensitivity who report GERD symptoms during physiologic reflux episodes although they do not have abnormal esophageal acid exposure time. Exclusion criteria included severe reflux esophagitis, non-GERD endoscopic abnormalities, eosinophilic esophagitis, achalasia, or absent contractility.

Interventions/Exposure: Study patients were randomized to: 1) surgical treatment with laparoscopic Nissen fundoplication; 2) active medical treatment with omeprazole 20 mg twice daily plus baclofen up to 20 mg 3 times daily followed by desipramine up to 100 mg nightly if baclofen was ineffective; and, 3) control medical treatment with omeprazole 20mg twice daily plus placebo.

Outcome: The primary outcome was treatment success, defined as a decrease of 50% of more in the GERD-HRQL score at 1 year. In the surgery group, treatment failure was also defined as resuming medication for heartburn. Secondary outcomes were the frequency of non-GERD disorders, anxiety, and depression, although these outcomes were not reported in this publication.

Data Analysis: Intention-to-treat analysis was performed, and Fisher's exact test was used for pairwise comparison of treatment success across the groups.

Funding: Department of Veterans Affairs Cooperative Studies Program.

Results: Between August 29, 2012 through December 2, 2015, 366 patients were screened for the study, but 288 patients were excluded because of symptom resolution after 2-week PPI twice daily trial (12%), non-GERD disorders (6%), functional heartburn/negative symptom-associated profile with normal acid reflux (27%), incomplete testing and other reasons (34%), 78 patients were randomized to surgery (n = 27), active medical treatment (n = 25), or control medical treatment (n = 26). Treatment success was higher in the surgical group compared to the active medical treatment (67% vs 28%, P=0.007, RR 2.43; 95% CI: 1.20-4.71) or control medical treatment (67% vs 12%, P<0.001, RR 5.78; 95% CI: 1.93-17.31) but there was no significant difference between the active medical group vs control medical group (P=0.17) (**Figure 1**).

There were 5 serious adverse events in the surgery group (among 4 patients), 4 in the active medical group (4 patients), and 5 in the control medical group (3 patients).

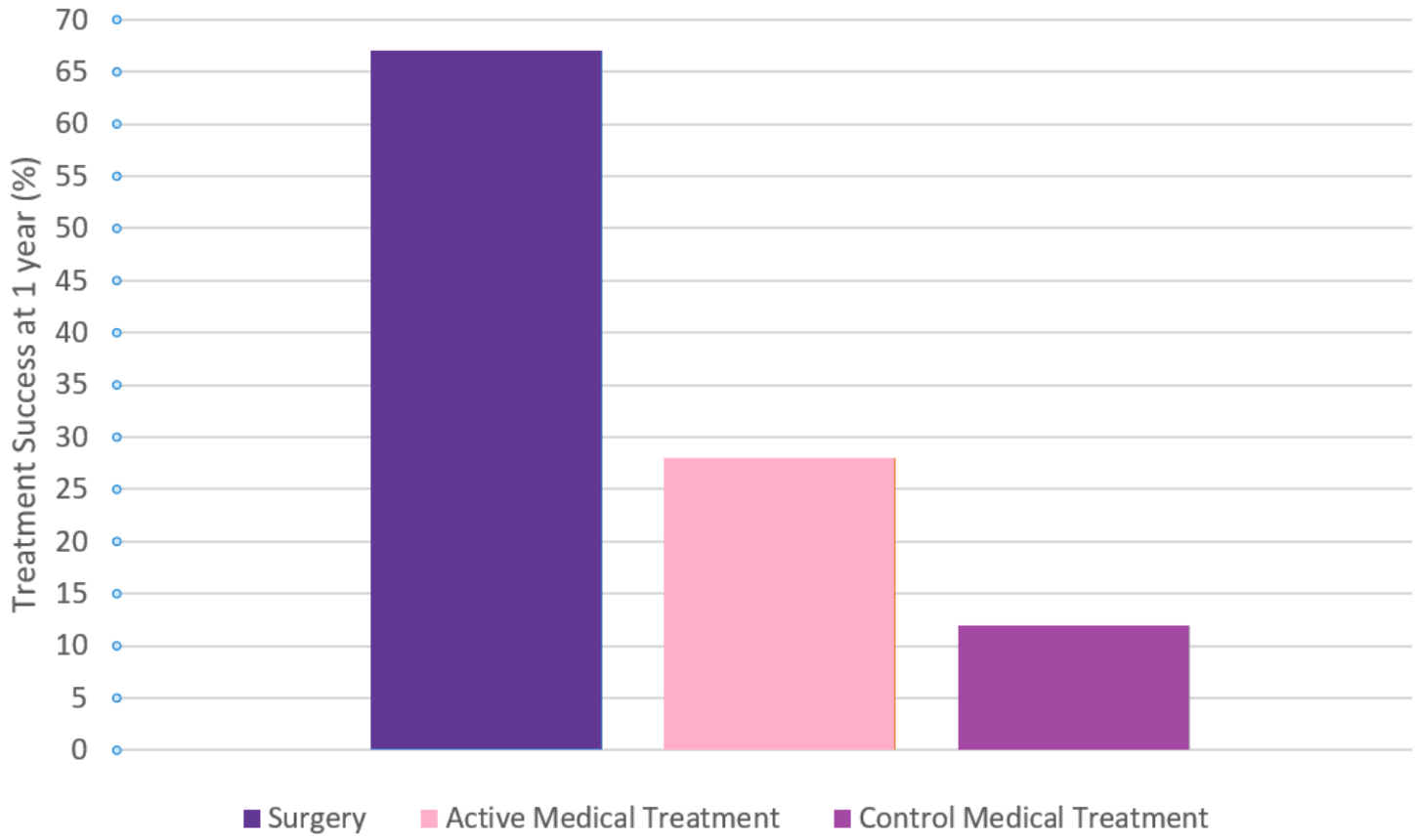

Figure 1: Treatment success at 1 year. Treatment success was defined as a decrease of 50% or more in the GERD-HRQL score from baseline. The incidence of treatment success with surgery was superior to active medical treatment (P = 0.007) or control medical treatment (P <0.001). The incidence of treatment success between the active medical group and the control medical group was 16% (P = 0.17).

COMMENTARY

Why Is This Important?

GERD affects almost 20% of the US population and causes significant burden and cost on the healthcare system. Heartburn is a challenging symptom that can negatively impact a person's quality of life, interfere with everyday activities, and cause psychological distress. PPIs are widely available over the counter so many people self-treat and they are also frequently prescribed by primary care doctors. Often, patients only reach gastroenterologists when their symptoms are not responding to medication. For PPI-unresponsive heartburn, the next steps in the workup should include upper endoscopy to evaluate for erosive esophagitis and/or manometry plus pH monitoring to confirm pathologic acid.[1,2] If true PPI-unresponsive heartburn is confirmed, there is uncertain value in continuing the medication, and question of whether these individu-

als would respond to an anti-reflux procedure. This is the first study that evaluates medical versus surgical therapy in a pure cohort of PPI-unresponsive heartburn due to reflux. The rigorous pre-randomization evaluation was critical to identify those specific individuals.

The appropriate evaluation of PPI-refractory heartburn is particularly important because its common and has multiple etiologies. First, failure to properly take PPI twice daily (30 minutes before breakfast and dinner) is common and an easy fix. However, if patients are adherent, then simply switching PPIs or increasing dosage is frequently insufficient. After ruling out non-GERD disorders, including eosinophilic esophagitis, achalasia, other esophageal motility disorders, atypical chest pain due to cardiovascular disease, costochondritis, and even panic attacks, it's important to rule out functional heartburn with impedance-pH monitoring (i.e., patients complaining of heartburn despite no abnormal esophageal acid exposure nor positive symptom-associated profile in response to physiologic reflux). These are not appropriate candidates for surgery.

Key Study Findings

The first important takeaway is that only 23% of patients referred to GI clinic for PPI-refractory heartburn actually had abnormal acid reflux and/or confirmed reflux symptoms based on pH-impedance monitoring while on twice daily omeprazole. During the pre-randomization phase, 12% of patients had a response to PPI, 6% had non-GERD disorders and 27% had functional heartburn.

In the highly selective group of individuals with heartburn that is PPI-refractory and due to reflux, laparoscopic Nissen fundoplication was more effective than medical therapy with twice daily omeprazole plus baclofen followed by desipramine.

Caution

This study was performed in a Veteran population which was largely White males, which could limit generalizability. More importantly, the updated trial protocol was not adequately powered to detect differences between active medical therapy with omeprazole, baclofen, and desipramine vs control medical treatment limited to omeprazole, although the trend favored active medical therapy.

My Practice

At any opportunity during a clinic visit or endoscopy, I ask patients when they are taking their PPI in relation to food and try to help them find a good schedule based on timing of their symptoms and their meals. Since 12% of study patients referred for PPI-refractory heartburn had an adequate response to twice daily PPI taken 30 minutes before breakfast and dinner, this underscores

the importance of providing clear instructions to the patient on how and when to take their medications to optimize efficacy. Switching to another PPI and/or increasing the dose may be helpful since polymorphisms of the hepatic CYP2C19 or CYP3A4 enzymes may impact the metabolism and duration of action of different PPIs.

Esophageal motility disorders, non-esophageal diseases, and functional disorders can all result in heartburn and GERD-like symptoms, emphasizing the value of a comprehensive diagnostic workup. I typically perform an upper endoscopy with pH testing to confirm the diagnosis then tailor medications. H2 receptor blockers can be added for nocturnal symptoms, alginate antacids can be used for breakthrough symptoms, and baclofen for belching or regurgitation. Simple lifestyle interventions such as avoiding meals at night, elevating the head of the bed, avoiding trigger foods, weight loss if obesity is contributing, and smoking cessation can have a meaningful impact.

If these interventions are inadequate and diagnostic work-up demonstrates abnormal acid reflux and/or confirmed reflux symptoms based on pH-impedance monitoring, then the updated ACG Clinical Guideline on the Diagnosis and Management of Gastroesophageal Reflux Disease recommends surgery for these patients, largely based on this RCT. Per the guideline, surgery is also an option for patients with LA Grade C/D erosive esophagitis despite PPI use and large hiatal hernias. This potential option should be brought up early so that patients can become more comfortable with this idea.

For Future Research

This well designed and supported study encountered numerous obstacles to patient enrollment since so few patients met inclusion criteria after diagnostic work-up, which led to intra-trial protocol amendments. This suggests that future studies may face similar challenges and alternative approaches are needed to evaluate GERD treatments.

Conflict of Interest

The author has no conflicts of interest.

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Vonoprazan, a Potassium-Competitive Acid Blocker, Is Superior to Lansoprazole for Managing Erosive Esophagitis

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Editor-in-Chief

This summary reviews Laine L, DeVault K, Katz P, et al. Vonoprazan versus Lansoprazole for Healing and Maintenance of Healing of Erosive Esophagitis: A Randomized Trial. Gastroenterology 2022; In Press. doi: https://doi.org/10.1053/j.gastro.2022.09.041

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STRUCTURED ABSTRACT

Question: Is vonoprazan, a potassium-channel acid blocker (PCAB), non-inferior to lansoprazole for healing and maintenance of healing of erosive esophagitis?

Design: A phase III, multi-center, double-blind randomized controlled trial (RCT).

Setting: One hundred eleven sites in the US, United Kingdom, Bulgaria, the Czech Republic, Hungary, and Poland.

Patients: Included patients were ≥ 18 years old and had erosive esophagitis on endoscopy, which was confirmed by blinded central reading of endoscopic images. Exclusion criteria included active *Helicobacter pylori* infection and Barrett's esophagus.

Interventions/Exposure: Eligible patients were randomized 1:1 to

vonoprazan 20 mg daily vs lansoprazole 30 mg daily for 8 weeks. Endoscopy to assess healing was performed at 2 weeks and 8 weeks. Study medication was taken 30 minutes before breakfast. Patients who achieved healing were re-randomized 1:1:1 to vonoprazan 20 mg daily, vonoprazan 10mg daily, or lansoprazole 15 mg daily X 24 weeks, followed by repeat upper endoscopy.

Outcome: The primary endpoint was healing of erosive esophagitis after 8 weeks of treatment for the initial treatment phase. Among patients who entered the maintenance phase, the primary endpoint was absence of erosive esophagitis at 24 weeks. Pre-determined sub-group analysis of patients with Los Angeles (LA) Grade C/D esophagitis at baseline was performed for both primary endpoints. During the initial 8-week treatment period, percentage of 24-hour heartburn-free days and proportion of subjects with onset of sustained heartburn resolution by day 3 were also assessed.

Data Analysis: Modified intention-to-treat analysis and per-protocol analysis (defined as patients who were compliant with study treatment, did not take additional PPI or H2 receptor antagonists, and completed all study endoscopies) was performed for the primary and secondary endpoints. Analyses were conducted in a hierarchical order, non-inferiority analyses with 10% margin were first performed for both healing and maintenance. If non-inferiority was demonstrated, then superiority analyses were performed.

Funding: Phathom Pharmaceuticals, manufacturer of vonoprazan.

Results: From November 2019 through December 2019, 1,027 patients were enrolled and randomized for the initial treatment phase (mean age: 51-52 years old; 38% male; 91% White; 63% from US; 34% LA Grade C/D esophagitis); 893 achieved healing and were randomized for the maintenance phase. Non-inferiority was demonstrated for defined primary and secondary endpoints. Vonoprazan 20 mg daily was superior to lansoprazole 30 mg daily for healing of erosive esophagitis (93% vs 85%, $P< 0.0001$) and for the sub-group of patients with LA Grade C/D esophagitis (92% vs 72%, $P< 0.001$) (Figure 1). Similarly, vonoprazan 20 mg daily and vonoprazan 10 mg daily was superior to lansoprazole 15 mg daily for maintenance of healing (81% vs 79% vs 72%, $P< 0.0001$) and in the sub-group of patients who initially had LA Grade C/D esophagitis

(77% vs 75% vs 61%, $P < 0.001$). In the maintenance phase, higher proportions of vonoprazan-treated patients (20 mg and 10 mg daily) had heartburn-free days than with lansoprazole 15 mg daily: median 95.2% vs 94.6% vs 89.3%, $P < 0.03$. No significant difference in adverse events between groups were identified.

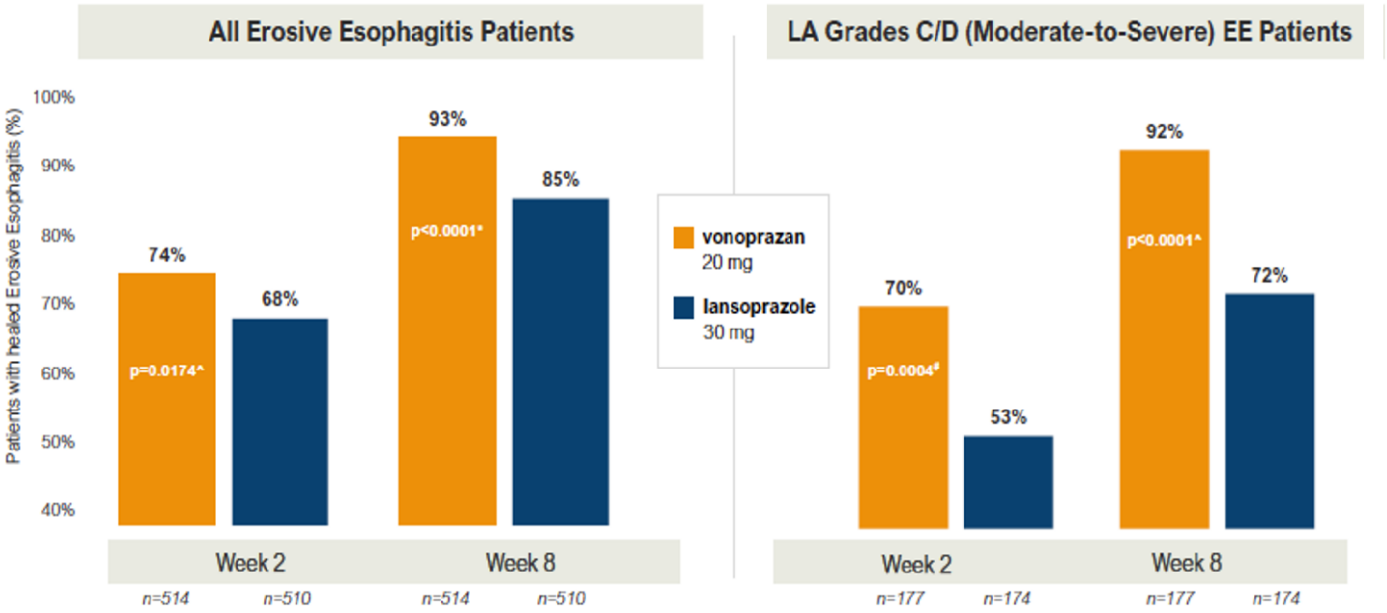

Figure 1. Healing of erosive esophagitis.

LA, Los Angeles

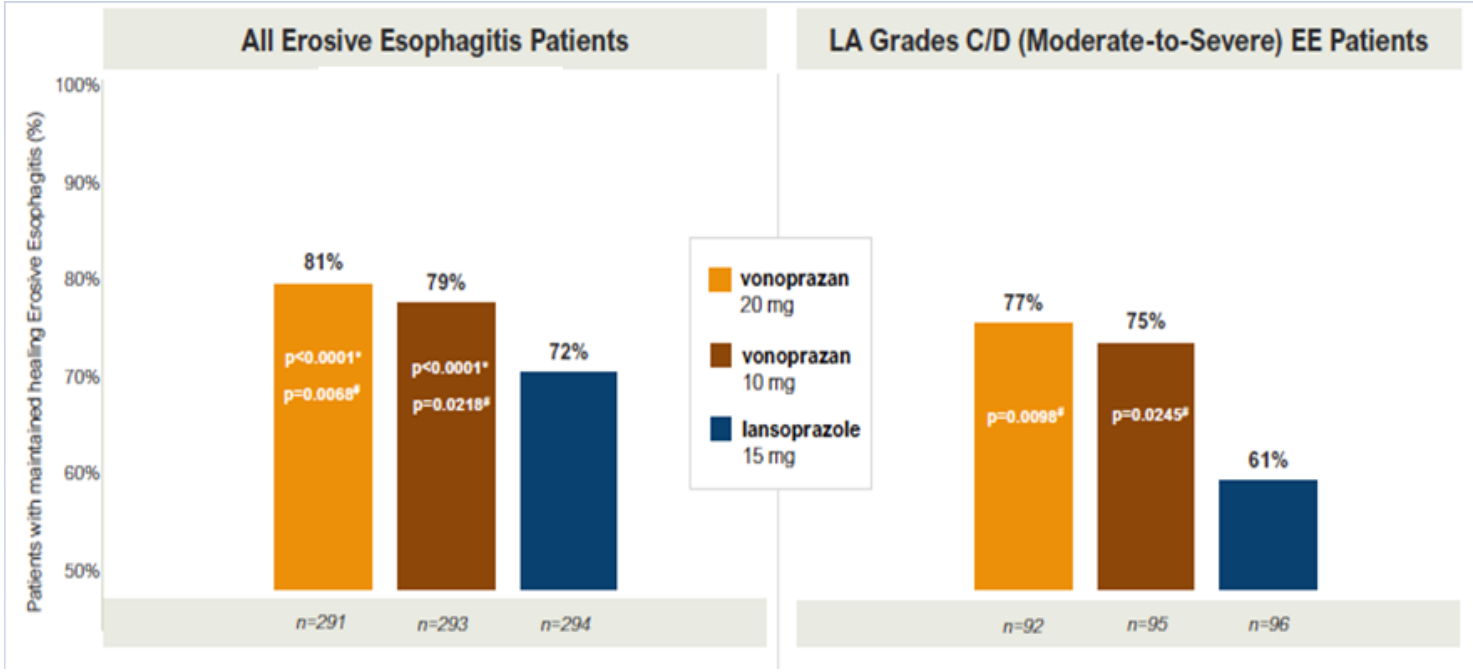

Figure 2. Maintenance of healing erosive esophagitis.

EE, erosive esophagitis

COMMENTARY

Why Is This Important?

Vonoprazan, a potassium-channel acid blocker, offers multiple pharmacologic advantages over proton pump inhibitors (PPIs).[1] Since they are acid stable, they don't need the enteric coating that acid labile PPIs require. This equates to a more rapid onset of action, which is sustained with a t1/2 of about 9 hours as opposed to the relatively short t1/2 of 1-2 hours for PPIs. PPIs bind only to activated proton pumps, which is why optimal dosing is 30 minutes before meals, while vonoprazan reversibly binds to the H, K-ATPase to compete with potassium binding, eliminating the need for pre-prandial dosing. Ultimately, PCABs produce more potent and more prolonged acid suppression with a more rapid onset compared to PPIs. Nevertheless, PPIs are still quite potent, and RCTs are needed to determine if PCABs are superior to PPIs for clinically important outcomes, including management of erosive esophagitis and heartburn.

Key Study Findings

Vonoprazan 20 mg daily was superior to lansoprazole 30 mg daily for healing of erosive esophagitis (93% vs 85%, $P< 0.0001$) and for the sub-group of patients with LA Grade C/D esophagitis (92% vs 72%, $P < 0.001$) (**Figure 1**). Similarly, vonoprazan 20 mg daily and vonoprazan 10 mg daily was superior to lansoprazole 15 mg daily for maintenance of healing (81% vs 79% vs 72%, $P < 0.0001$) and in the sub-group of patients who initially had LA Grade C/D esophagitis (77% vs 75% vs 61%, $P< 0.001$).

Caution

There were no significant differences in adverse events between vonoprazan and lansoprazole in this RCT. Unfortunately, the lay media has publicized retrospective case-control studies that suggest an association between the acid inhibition of PPIs and many different disorders. Similar concerns could be expressed about PCABs, which produce more potent acid inhibition. However, careful review of well-designed epidemiologic studies[2] and placebo-controlled RCTs only demonstrate an increased risk of enteric infection with PPIs, but do not find PPIs associated with other disorders like dementia or fractures. It's possible, but unproven, that PPIs could produce interstitial nephritis leading to decreased renal function. Even if this hypothesis is proven, this would not equate to a similar risk with PCABs. Nevertheless, US safety data is limited to approximately 34 weeks of use and longer-term safety data would be beneficial.

My Practice:

Vonoprazan will not be commercially available in the US until 2023. When it is available, it will be my preferred treatment for healing and maintenance

of LA Grade C/D erosive esophagitis as well as for PPI-resistant heartburn patients with confirmed abnormal esophageal acid exposure while on twice daily PPIs. It may also prove to be helpful for patients with breakthrough nocturnal heartburn despite PPI therapy combined with nightly H2RAs.

For Future Research

Vonoprazan has been available in Japan for several years. Additional safety data from Japanese databases would be welcome. Since vonoprazan has a rapid onset of action, it may be an option for on-demand treatment of heartburn. Finally, additional RCTs comparing vonoprazan with PPIs for improvement in the gastroesophageal reflux disease (GERD)-Health Related Quality of Life Questionnaire and other GERD symptoms would be helpful.

Conflict of Interest

Dr. Schoenfeld reports being an advisory board member and consultant for Phathom Pharmaceuticals.

Note: The authors of this article are active on social media. Tag them to discuss their work and this EBGI summary.

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Reinvestigating the Lack of Association Between Proton Pump Inhibitor Use and Mortality by Accounting for Reverse Causation

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This summary reviews Lo CH, Ni P, Yan Y, et al. Association of Proton Pump Inhibitor Use With All-Cause and Cause-Specific Mortality. *Gastroenterology* 2022; 163:852-61.

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STRUCTURED ABSTRACT

Question: Are proton pump inhibitors (PPIs) associated with increased mortality?

Design: Prospective cohort study.

Setting: Combined data from the Nurses' Health Study and the Health Professionals Follow-up Study.

Patients: The Nurses' Health Study is an ongoing prospective cohort study in the United States that recruited female nurses who were ages 30–55 in 1976. The Health Professionals Follow-up Study recruited male health professionals who were ages 40–75 in 1986. For both stud-

ies, investigators obtained information from medical records and questionnaires every 2 years. The sub-cohort selected for this study was new users of PPIs.

Exposure: Self-reported PPI use.

Outcome: The primary outcome was death from any cause. Secondary outcomes were death from specific causes such as cancer, cardiovascular diseases, respiratory diseases, digestive diseases, renal diseases, neurologic diseases, and infectious diseases.

Data analysis: The association of PPI use and death was estimated using Cox proportional hazards regression to calculate a hazard ratio (HR). To reduce the possibility of protopathic bias (also called reverse causation), the investigators conducted several secondary analyses that incorporated PPI-use lag windows (see ***Why Is This Important*** section below).

Two-year, 4-year, and 6-year lag times were assessed. For example, in a 4-year lag-time analysis, this means exposure to PPI had to be self-reported in the biennial questionnaires at least 4 years before death occurred.

Funding: National Institutes of Health and the Crohn's and Colitis Foundation.

Results: Out of 71,887 study participants, 22,125 died during follow-up, of which 2033 (10.1%) were PPI users at the time of death. In the analysis that did not account for lag time, PPI use was associated with mortality from all-causes, cancer, cardiovascular diseases, respiratory diseases, digestive diseases, and renal diseases. There was no association with neurologic or infectious diseases. By incorporating progressively longer lag-times, the investigators demonstrated that the association of PPI use with each cause of death was nullified, except for the association of PPI use and death from renal causes (HR 2.45, 95% confidence interval (CI) 1.59 – 3.78 in the 6-year lag analysis) (**Figure 1**).

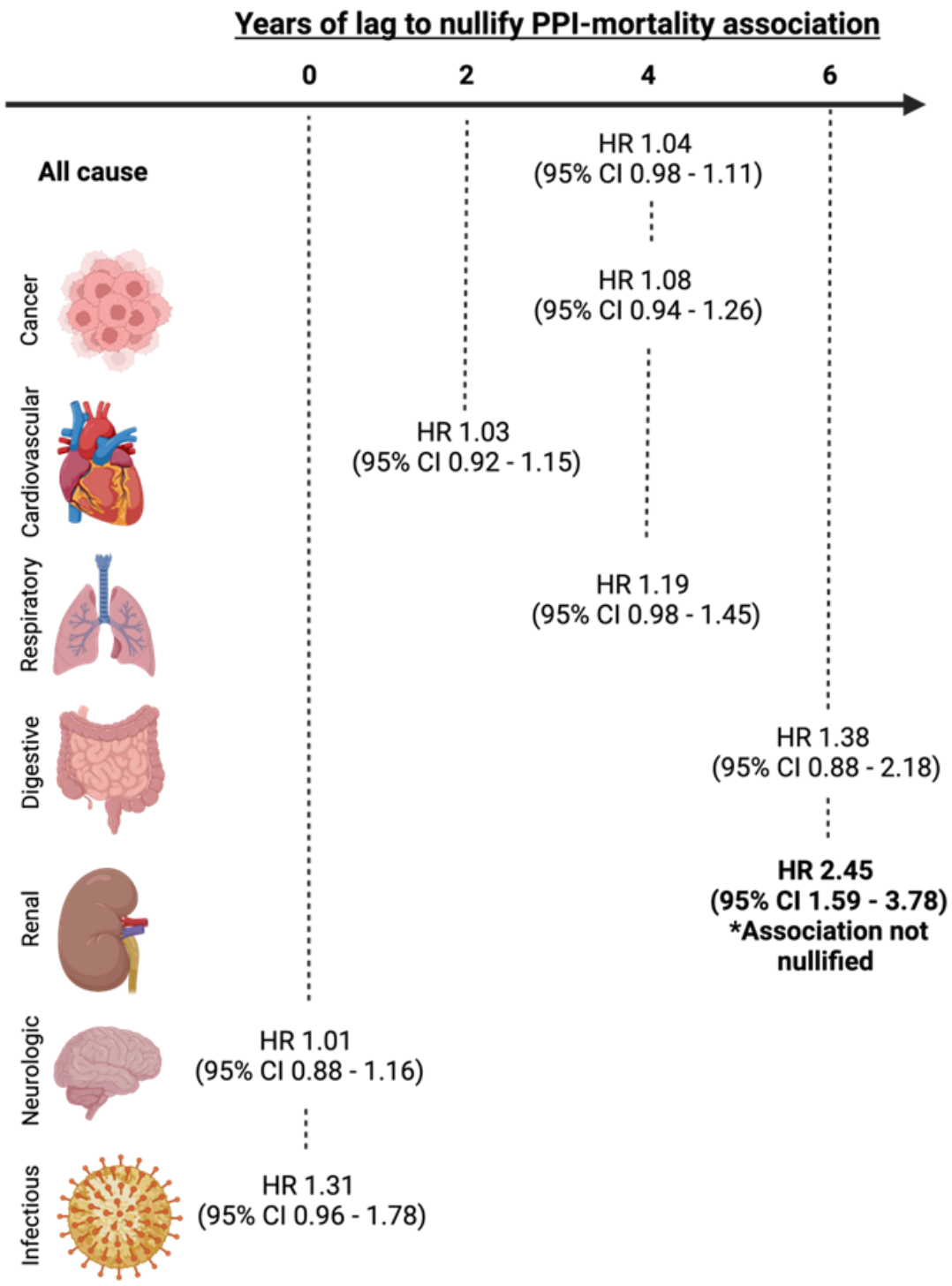

Figure 1. Years of lag time to nullify statistically significant association between proton pump inhibitor (PPI) use and mortality. Nullification of association implies that protopathic bias contributes to spurious associations. Image created with BioRender.com. CI, confidence interval; HR, hazard ratio.

COMMENTARY

Why Is This Important?

PPIs are one of the most frequently used medications in the United States.[2,3] Recently, several retrospective studies have linked PPIs to adverse effects, such as chronic kidney disease, dementia, and death.[4-6] However, there are concerns about the validity of these conclusions due to methodologic limitations of the studies[7-9], including inadequate adjustment for protopathic bias, which occurs when patients receive an exposure of interest to treat prodromal symptoms of an impending outcome.

A common example helps explain protopathic bias, which is also called reverse causation. Imagine a patient who presents to their primary care physician for assessment of atypical chest pain. The patient receives a PPI for presumptive treatment of gastroesophageal reflux disorder (GERD), but the patient later develops a fatal myocardial infarction because the chest pain was truly angina secondary to coronary artery disease. If a retrospective study including this patient does not account for protopathic bias, the PPI would be associated with the death, which was actually caused by coronary artery disease. To reduce the influence of protopathic bias in the current study results, the investigators incorporated lag windows so that PPI use was only considered after sufficient time had passed from initiation.

Randomized controlled trials (RCTs) are the standard for demonstrating causation, and COMPASS, a recent double-blind, placebo-controlled RCT of over 17,000 individuals with chronic cardiovascular disease followed for a mean duration of 3 years, only found an increased risk of enteric infections with PPI use. There are some remaining details to be investigated based on the limitations of the study[10], including the relatively short length of follow-up and limited generalizability of the study population. Reassurance about the safety of PPIs also comes from two recent retrospective cohort studies corroborated the findings of COMPASS by demonstrating no association between PPI use and mortality using data from the U.S. Medicare system and the UK Biobank.[7,11] This study from Lo et al. adds to these reassuring results by incorporating lag times of 2, 4, and 6-years of PPI use to adjust for protopathic bias.

Key Study Findings

After accounting for protopathic bias, PPI use was not associated with death from all-causes, cancer, cardiovascular disease, respiratory disease, digestive disease, neurologic disease, or infectious diseases. There was an association between PPI use and death from renal disease.

Caution

Because PPI use was assessed only every 2-years, the lag-time windows are

long. Excluding events in 2-year increments reduces the statistical power of the analysis to identify conditions that confer small increased risk in mortality. Additionally, the authors did not implement competing-risks approaches for the analysis of the secondary mortality outcomes. This could bias the conclusions of the study. Finally, this study only investigated mortality. The lack of association between cause-specific mortality and PPI use does not necessarily mean that the PPI use is not associated with the condition itself—especially if the condition does not usually lead to death.

My Practice

I prescribe PPIs frequently in my luminal gastroenterology practice at a Veterans Affairs Health System. The most common indications are chronic GERD, chemoprevention of Barrett's esophagus progression, and eosinophilic esophagitis. For patients who will use PPIs longer than eight weeks, I counsel about the state of the PPI adverse effects literature. In particular, I summarize the concerns raised by early retrospective cohort studies and mention that there were methodologic issues with many of them. I then summarize the results of the COMPASS randomized control trial, which did not find any association between PPI and fractures, diabetes, COPD, dementia, cancer, chronic kidney disease, etc., and relay that more recent, high-quality retrospective cohort studies have corroborated it. Finally, I acknowledge that there still may be risks to long-term PPI use, in particular risk of enteric infections as identified by COMPASS and risk of renal disease as demonstrated in this study. As such, I assure patients that we will periodically reassess their need for chronic PPIs and maintain them on the lowest effective dose.

For Future Research

The mechanism of action for the association between PPI use and renal disease is often hypothesized to be secondary to acute interstitial nephritis. Further characterization of this relationship and whether it mediates the association between PPI use and renal mortality is warranted.

Conflicts of Interest

Dr. Vajravelu reports no conflicts of interest. He is an employee of the Department of Veterans Affairs. This commentary does not represent the views of the U.S. Department of Veterans Affairs or the United States Government.

Note: The authors of this article are active on social media. Tag them to discuss their work and this EBGI summary.

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