# Beyond PPIs: New Options for Treating GERD

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### KEY TAKEAWAYS

- Gastroesophageal reflux disease can be classified as nonerosive reflux disease (NERD) and erosive esophagitis (EE).
- Both NERD and EE cause significant health impacts and reduced quality of life and require accurate diagnosis and effective treatment.
- Proton pump inhibitors (PPIs) have been frequently used for treatment of NERD and EE. Although they are often effective, some patients have inadequate symptom relief and—in EE—incomplete healing and subsequent relapse.
- Potassium-competitive acid blockers (PCABs) such as vonoprazan, currently the only approved PCAB in the United States, are alternatives to PPIs. They produce more effective and long-lasting inhibition of gastric acid secretion.

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## INTRODUCTION

Acid-related gastrointestinal disorders encompass a variety of diseases affecting the esophagus, stomach, and duodenum. Of these, gastroesophageal reflux disease (GERD) is one of the most common, with an estimated prevalence of 21% in the United States[1]: approximately 45 million adults have nonerosive reflux disease (NERD), and 20 million have erosive esophagitis (EE).[2] Although NERD is more common, EE has received more attention over the years. EE is estimated to be present in 25% to 50% of individuals with GERD symptoms.[3]

The pathophysiology of GERD includes dysfunction of the lower esophageal sphincter, impaired esophageal clearance, and changes in esophageal mucosal integrity. EE can develop as acidic gastric juice refluxes into the esophagus, where it may activate inflammatory responses. Additional factors that may be involved in some patients with GERD include delayed gastric emptying, decreased or inadequate salivary production, and esophageal hypersensitivity.[4] It can be challenging to establish the diagnosis of GERD accurately. EE and NERD can be classified and distinguished only by endoscopy. The management of GERD is based on patients' symptoms and, for EE, on the extent of esophageal mucosal involvement seen at endoscopy.

In addition to EE and NERD, another manifestation of GERD is Barrett's esophagus, in which the normal squamous mucosa of areas of the distal esophagus is replaced by specialized columnar epithelium (a form of intestinal metaplasia).[5] Barrett's esophagus is a complication of chronic EE and is a major risk factor for the development of esophageal adenocarcinoma.[6]

Although many patients with NERD or EE can be managed with existing treatments, gaps in care still exist. Proton pump inhibitors (PPIs) are frequently used to treat NERD, but up to 40% of patients with NERD continue to be symptomatic even when receiving standard therapy.[7] In some patients with EE, symptom resolution and complete mucosal healing on PPI treatment continue to be inadequate. Up to 15% of patients with EE do not achieve complete mucosal healing after 8 weeks of standard PPI treatment, and approximately 45% exhibit residual symptoms while receiving standard PPI therapy.[8] EE recurrence is almost inevitable if PPI treatment is interrupted, making continuous maintenance treatment essential for most—if not all.[9] Additional challenges with adequate treatment of NERD and EE include suboptimal adherence to treatment regimens and inadequate acid suppression.[4,9,10] The symptoms of GERD

are nonspecific, leading to misdiagnosis in some patients. In such patients, symptoms are related to cause(s) other than acidic gastroesophageal reflux, highlighting the need for accurate diagnosis. "Cycling" of PPIs is a common practice but unlikely to lead to improved outcomes for patients whose symptoms were refractory to a PPI.[4]

PPIs have been the mainstay for the treatment of GERD because they inhibit gastric acid secretion.[4] However, a new class of gastric acid–inhibiting drugs, potassium-competitive acid blockers (PCABs), has recently emerged with the potential to change the treatment landscape of GERD. In November 2023, the US Food and Drug Administration (FDA) approved vonoprazan as the first PCAB in the United States for EE. This marked the first innovation in approximately 30 years of drugs marketed for EE.[11] In July 2024, vonoprazan was subsequently also approved for relief of heartburn associated with NERD.[12]

GERD is one of the most common diseases seen by primary care practitioners (PCPs) and gastroenterologists.[4] PCPs should seek to implement evidence-based, best-practice approaches as recommended by clinical guidelines and recent data, referring patients to a gastroenterologist when appropriate. PCABs were not considered in the most recent clinical guidelines for the treatment of GERD.[4,13] However, this simply reflects the fact that there was no available evidence from US-based clinical trials at the time of guideline generation. Because current guidelines do not discuss where PCABs fit in the GERD treatment paradigm, clinicians need additional information to understand the clinical profile of PCABs and their appropriate place in clinical practice.

### CASE STUDY 1

A 32-year-old woman with a history of irritable bowel syndrome has been self-treating her presumed GERD symptoms with over-the-counter (OTC) histamine-2 (H2)–blockers and OTC PPIs with only minimal improvement.

#### *Clinical assessment/learning*

The clinician should ask the patient to describe her symptoms in detail. The most common symptoms of GERD are heartburn and regurgitation. Heartburn is a retrosternal discomfort that is often worsened by eating. Regurgitation is the effortless return of gastric contents into the esophagus and, possibly, the throat. Both of these symptoms are experienced in the chest. However, many patients often perceive other symptoms—such as upper abdominal discomfort—as "heartburn." Patients with upper abdominal discomfort probably have dyspepsia rather than GERD and are much less likely to have symptom improvement with an acid-suppressing medicine. The clinician should also inquire about the patient's treatment history (eg, medications, dosage, frequency, and delivery mechanism).

## EVALUATION AND DIAGNOSIS OF GERD

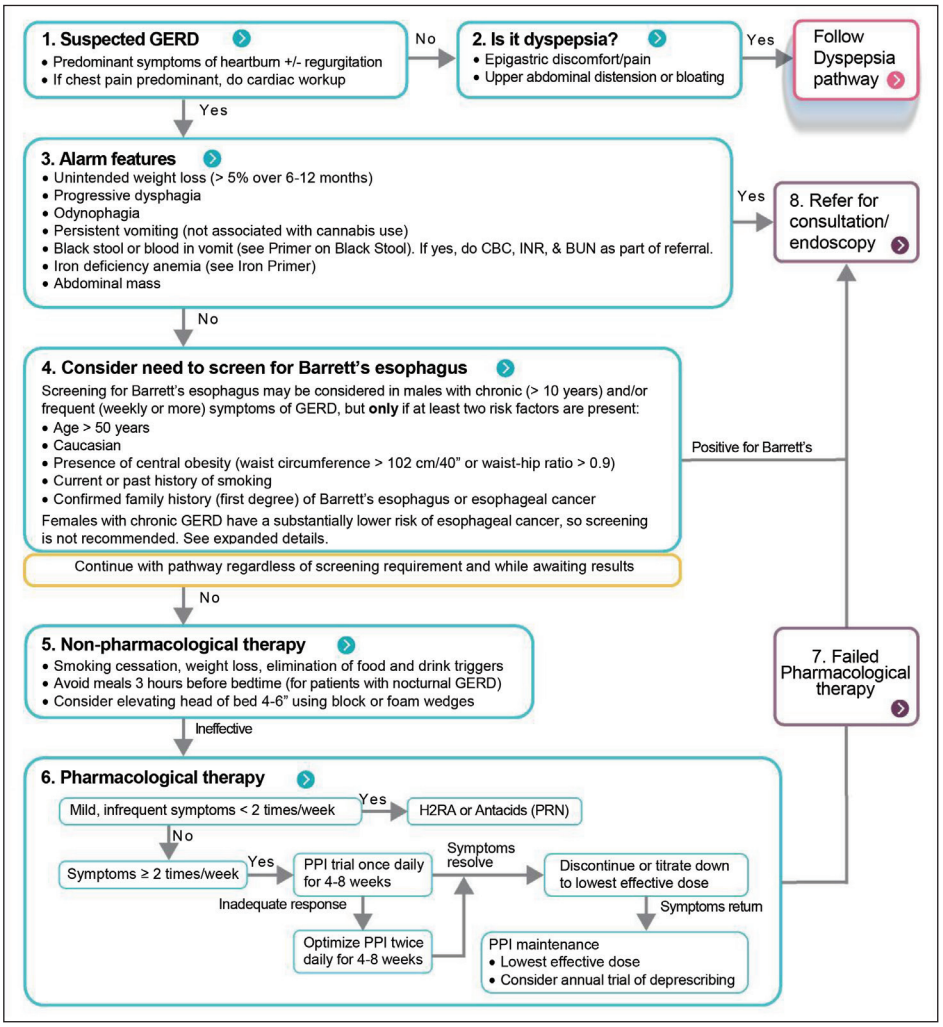
Clinicians sometimes view GERD as synonymous with heartburn (as described previously). However, GERD is more than one symptom; it is a disease that must be accurately diagnosed and effectively managed.[14]

In GERD, the patient journey usually begins with the identification of the typical symptoms of heartburn and regurgitation. Since these are common to both EE and NERD, the diagnosis of EE can be established only by an upper endoscopy that demonstrates mucosal breaks (erosions) in the distal esophagus. For patients with typical GERD symptoms occurring more than twice per week and no "alarm" features (such as dysphagia, unexplained weight loss, or gastrointestinal bleeding), an 8-week trial of empiric PPI therapy is appropriate.[4] A diagnostic algorithm for GERD is available in the 2022 American College of Gastroenterology (ACG) guideline to assist clinicians with diagnosis.[4] Patients with chest pain (and in whom heart disease has been excluded) or alarm symptoms at presentation, as well as those with multiple risk factors for Barrett's esophagus should receive objective testing for GERD via endoscopy and/or reflux monitoring.[4] Upper endoscopy is the only method for identifying EE or Barrett esophagus.[4] Algorithms for the evaluation and management of GERD in primary care have been proposed; an example is shown in **FIGURE**.[4]

EE is graded using the Los Angeles (LA) classification. This has four grades (A-D), with A being the least severe and D the most severe.[15,16] EE that is LA grade A is not considered sufficient for a definitive GERD diagnosis because it is not reliably differentiated from normal mucosa and can occur in healthy individuals without GERD symptoms.[17] EE that is LA grade B is considered diagnostic of GERD when accompanied by typical symptoms and PPI response.[4] EE that is LA grade C is nearly always diagnostic of GERD, and EE that is LA grade D is considered a manifestation of severe GERD. Patients with EE that is LA grades C and D should undergo endoscopy after PPI treatment to ensure healing and to evaluate further for Barrett's esophagus, because it may not be detectable when severe EE is present. Notably, if patients undergo endoscopy while taking a PPI, the diagnosis of EE may be missed due to mucosal healing from PPI therapy.[4]

Patients with EE who do not achieve complete healing with PPI treatment are predisposed to long-term complications.[6] More severe grades of EE (typically LA grades C and D) are more difficult to heal even with PPI therapy. Up to 30% of patients with EE that is LA grade C or D have incomplete healing with a PPI and may be at risk of progression to Barrett's esophagus.[6,18] Even with resolution of esophagitis, many patients continue to experience heartburn or regurgitation.[19]

**FIGURE. Example GERD management pathway for primary care.[4]**




**Abbreviations:** BUN, blood urea nitrogen; CBC, complete blood count; H2RA, histamine 2 receptor agonist; INR, international normalized ratio; PRN, as needed.

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## MANAGEMENT OF GERD IN PRIMARY CARE: NERD AND EE

Although current guidelines recommend PPI treatment for symptomatic relief in NERD, up to 40% of patients with suspected NERD do not respond adequately.[7,20] PPIs are also recommended for control of symptoms and healing in EE.[8] However, despite recommendations for long-term maintenance in EE, PPIs often do not achieve optimal outcomes.[8,9] Additionally, reports suggest that overall management of EE remains suboptimal, often leading to cycling of PPIs, which is frequently ineffective and may delay effective treatment; there has been a long-standing need for better therapies.[6,8,9]

In addition to the need for initial healing of esophageal erosions, patients with EE almost always require long-term maintenance therapy.[9] After stopping maintenance treatment, up to 90% of patients with EE relapse within 6 months—and many relapse sooner than that.[21,22] Relapse rates of up to 41% are seen in patients with EE of LA grade D despite receiving maintenance PPI therapy.[23] Considering the burden of low healing rates, high relapse rates, and persistence of symptoms, alternative therapies are needed.

### *The potential role of PCABs in GERD management*

PCABs are a new class of acid-suppressing agents. Compared to conventional doses of PPIs, they have a faster onset of action and produce more potent inhibition of gastric acid secretion.[24,25] PCABs that are currently available or in development around the world include vonoprazan, tegoprazan, fexuprazan, keverprazan, revaprazan, linaprazan glurate, and zastaprazan.[26] PCABs have been studied for various acid-related disorders including NERD and EE.[24,26]

Although guideline recommendations for PCABs in the United States are limited because they were published prior to the first US approval of a PCAB, practical suggestions for real-world implementation in clinical practice may offer additional insights. For example, experts suggest that PCABs may address unmet needs in patients with GERD, such as those who do not adhere to PPI dosing recommendations with regard to meals, have uncontrolled nocturnal symptoms, or experience moderate-to-severe EE.

#### *PCABs: Mechanism of action*

The mechanism of action of PCABs differs from that of PPIs.[26] As with the PPIs, PCABs inhibit the hydrogen potassium (H+/K+) ATPase on the luminal membrane of parietal cells. Although they share the same target, PCABs produce their effect by a different mechanism. PCABs are absorbed systemically and concentrate in parietal cells. They bind ionically to the potassium channel of H+/K+ ATPase to disrupt

acid secretion. Unlike PPIs, PCABs are not pro-drugs and do not require acid activation or chemical conversion before they are active. Also, unlike PPIs, they do not require any form of enteric coating and do not need to be taken at any particular time with respect to meals. They act rapidly on the proton pump.[27] PCABs demonstrate more rapid and potent acid suppression than conventional (approved) doses of PPIs and have a longer duration of action.[28,29] Additional differences between PCABs and PPIs are noted in **TABLE**.[26]

**TABLE. Comparison of characteristics of PCABs and PPIs.[26]**

| Characteristic | PCABs | PPIs |
|---|---|---|
| Prodrug | No | Yes |
| Acid stability | Yes | No |
| Inhibition and binding | Reversible, ionic | Irreversible, covalent |
| Half-life | 6-9 hours (vonoprazan) | 1 to 2 hours |
| Significantly affected by CYP2C19 polymorphism | No | Yes |
| Optimal administration | Independent of meals | 30 to 60 minutes prior to mealtimes (for most PPIs) |

**Abbreviations:** CYP2C19, cytochrome P450 2C19.

### *Vonoprazan efficacy data for treating NERD and EE*

The approval of vonoprazan for treatment of heartburn associated with NERD is based on results of a phase 3 trial, PHALCON-NERD-301.[30] This trial included patients with NERD who experienced heartburn 4 or more days of the week, with most patients having 6 to 7 days of symptoms per week. Patients were randomized to vonoprazan 10 mg or placebo. Patients receiving vonoprazan had significant improvement of heartburn compared with those taking placebo through week 4 of the trial. The mean percentage of heartburn-free days was 45% for vonoprazan and 28% for placebo ($P$ <.001); median percentages of 24-hour heartburn-free days were 48% (vonoprazan) and 17% (placebo).[30]

A phase 2 study, PHALCON-NERD-201, compared vonoprazan and placebo as episodic treatments for heartburn. It found significant improvement in heartburn relief 1 hour after dosing of vonoprazan. Furthermore, vonoprazan was associated with relief of significantly more heartburn episodes than placebo.[31] In an earlier study of 26 patients with PPI-resistant NERD, 69.2% reported an improvement in symptoms when switching from a PPI to vonoprazan, 23.1% reported no change in symptoms, and 7.7% reported an exacerbation of symptoms.[32] The change to vonoprazan was significantly associated with improved self-reported symptoms (odds ratio 9.0, $P$ <.001).[32]

The phase 3 PHALCON-EE trial assessed EE healing in patients across the United States and in 7 European countries.[3] A total of 1024 patients were randomized to vonoprazan 20 mg once daily or lansoprazole 30 mg once daily for up to 8 weeks. Results demonstrated the noninferiority of vonoprazan to lansoprazole for EE healing at week 8 (93% vs 85%) and higher rates of healing at week 2 (74% vs 68%). For healing of EE of LA grades C and D, vonoprazan was superior to lansoprazole at week 2 (70% vs 53%).[3] Furthermore, a recent analysis reviewed data from trials on various PPIs, H2 blockers, and PCABs, and noted that PCABs provide the longest duration of intragastric pH >4, the highest predicted healing rates for EE, and the greatest probability of achieving healing.[33]

In Asian populations, vonoprazan, tegoprazan, and keverprazan have demonstrated noninferiority to PPIs for treatment of EE in phase 3 trials.[34-36] A smaller study has also identified successful healing with vonoprazan in patients with EE refractory to PPIs.[37] Higher healing rates with vonoprazan than lansoprazole were observed at week 2 (90% vs 79%), week 4 (96% vs 91%), and week 8 (99% vs 95%).[38] Several analyses have shown specific benefits of PCABs compared to PPIs for the healing of severe EE in Asian populations. In patients with LA grade C or D esophagitis, higher rates of mucosal healing with vonoprazan vs PPIs were observed (vonoprazan vs lansoprazole, 84.0% vs 80.6% in 1 study; 98.7% vs 87.5% in another study).[35,38]

### *Vonoprazan safety data*

Most safety data for PCABs relates to vonoprazan, which has demonstrated short- and medium-term safety comparable to placebo or PPIs.[26] In PHALCON-NERD-301, although overall adverse events were somewhat higher in the vonoprazan groups, the drug was generally well tolerated.[30] Nausea was more common in those receiving vonoprazan than those receiving placebo.[30] In PHALCON-EE-301, rates of adverse events were similar between those receiving vonoprazan and those receiving lansoprazole.[3] A dedicated phase 4 trial (VISION) evaluated the safety profile of vonoprazan and lansoprazole over 5 years in 208 Japanese patients (139 taking vonoprazan, 69 taking lansoprazole) with healed EE.[39] After 5 years, significantly more patients taking vonoprazan (97.1%) compared with lansoprazole (86.5%) had parietal cell hyperplasia and foveolar hyperplasia (14.7% vs 1.9%). The clinical significance—if any—of these differences is unknown.

Analyses of multiple trials have indicated the safety profile of vonoprazan is consistent and comparable to PPIs for treatment-emergent adverse events.[40,41] An integrated anal-

ysis of 14 clinical trials of vonoprazan in multiple countries reported similar rates of adverse events for vonoprazan and PPIs. Both vonoprazan and PPIs had higher rates of serious adverse events (serious infections, gastrointestinal disorders, neoplasms, hepatobiliary disorders, cardiac disorders, and others) compared with placebo per 100 person-years (10.39 for vonoprazan, 10.65 for PPIs, and 1.69 for placebo).[41] Additionally, a meta-analysis comparing vonoprazan to PPIs for GERD also found similar safety outcomes, with a nonsignificant risk ratio for adverse events of 1.08 (95% CI, 0.96-1.22) for vonoprazan vs PPIs.[40]

### *Incorporating PCABs into clinical practice*

Incorporating newer interventions in clinical practice is often a slow and challenging process, even when the intervention is evidence based. Slow uptake of novel, effective drugs can delay improvements in patient health outcomes and healthcare efficiency.[42,43]

The ACG and American Gastroenterological Association (AGA) guidelines on GERD were published before any PCABs were approved by the FDA. Both recognized that greater acid suppression might be required for patients who have inadequate response to PPIs.[4,13] With the FDA approval of vonoprazan, the data support the potential role of this agent in certain patients with GERD[44]:

- ***NERD:*** Vonoprazan is approved for the relief of heartburn associated with NERD in adults.[12] In theory, patients with NERD who have partial (but incomplete) response to a PPI may benefit from switching to a PCAB, although this has not been demonstrated in controlled studies.
- ***EE:*** Vonoprazan is approved for the healing and maintenance of all grades of EE, and relief of heartburn associated with EE in adults.[11] Patients with moderate-to-severe EE may derive particular benefit from vonoprazan, as it has higher rates of healing and maintenance of severe EE than PPIs.[3]

In a study evaluating the real-world perspectives of physicians and patients regarding EE, medications that work quickly were most important to patients. Physicians identified that faster healing is important and that better initial symptom relief would help improve adherence to therapy. Additionally, longer-lasting effects and better long-term maintenance for EE were key preferences among patients and physicians.[8]

As with many novel agents, access to and cost of vonoprazan may be challenging for some patients. Clinicians must work with insurance companies by completing prior authorizations and other requirements for coverage, as well as be aware of additional savings opportunities through copay cards that reduce out-of-pocket costs. Engaging clinic staff in helping with access issues can expedite the removal of barriers to implementing PCAB therapy for eligible patients.

## CASE STUDY 2

A 59-year-old overweight White man with a previous diagnosis of EE is currently taking a once-daily PPI with incomplete heartburn relief. He undergoes esophagogastroduodenoscopy (EGD) on the recommendation of his gastroenterologist. The EGD shows that he has EE that is LA grade B and no evidence of Barrett's esophagus. He is switched from a PPI to a PCAB.

### *Clinical assessment/learning*

There were 2 valid reasons for performing endoscopy in this patient. First, he was symptomatic despite taking a PPI once daily. Second, he had risk factors for Barrett's esophagus: male, White, and overweight, and he had a history of heartburn. Endoscopy was appropriate to exclude another cause for his symptoms aside from EE and to help to rule out Barrett's esophagus. (He had a previous diagnosis of EE; although we do not know the grade. Barrett's esophagus could have been missed if severe EE had been present.) Endoscopy showed mild EE (LA grade B). Because this was present despite taking a PPI once daily, switching to a PCAB was appropriate. Studies have shown superiority of PCABs over approved maintenance doses of PPIs in preventing endoscopic relapse of EE during maintenance treatment.

## SUMMARY

Many individuals experience symptoms of GERD. The presentation of "heartburn" does not necessarily point to the diagnosis of GERD, as heartburn may have causes other than acidic reflux. Heartburn may, however, be a feature of either NERD or EE. Both can have a significant impact on patient lives, leading to problems such as loss of productivity and—in EE—the potential for serious long-term consequences. Because we cannot be certain which patients truly have GERD as a cause of their symptoms, adequate assessment is essential in all patients.

Optimal management of patients with NERD or EE in primary care is essential for relieving symptoms, improving quality of life, and reducing the risk of complications. It is important to recognize that not all patients with GERD will achieve adequate symptom control with PPIs. In such cases, clinicians should be aware that a new class of acid-suppressive therapy is now available. PCABs, such as vonoprazan, offer a novel mechanism of action and may provide an effective alternative for patients with suboptimal response to standard PPI therapy. It is important for clinicians to have access to alternatives to PPIs for select patients. PCABs such as vonoprazan may fill a clinical need for improved outcomes through more effective and long-lasting inhibition of gastric acid secretion. ●

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