

ORIGINAL ARTICLES

Effectiveness of Proton Pump Inhibitors in Nonerosive Reflux Disease

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Background & Aims: Little information is available about the efficacy of proton pump inhibitors (PPIs) in patients with nonerosive reflux disease (NERD). We aimed to synthesize available data and determine the effectiveness of PPIs on symptom resolution in patients with NERD. **Methods:** A systematic review of the literature identified studies reporting the effects of PPIs in patients with NERD. Heartburn resolution data were pooled across studies. The effectiveness of PPI therapy in inducing complete heartburn resolution was compared in patients with NERD vs. erosive esophagitis (EE). **Results:** Seven trials evaluating heartburn resolution in NERD were identified. Higher proportions of patients reported achieving sufficient heartburn resolution compared with complete heartburn resolution. The effect of PPIs on sufficient heartburn resolution was observed sooner than was complete heartburn resolution. Therapeutic gain of PPI therapy over placebo ranged from 30% to 35% for sufficient heartburn control and from 25% to 30% for complete heartburn control. Pooled response rates at 4 weeks were significantly higher for patients with EE compared with NERD (56% vs. 37%, $P < 0.0001$). **Conclusions:** PPIs provide a more modest therapeutic gain in patients with NERD as compared with those with EE. A trend in increased therapeutic gain for NERD patients was shown throughout the 4 weeks, suggesting that 4 weeks of follow-up evaluation may be insufficient to show full therapeutic gain in this patient population.

Gastroesophageal reflux disease (GERD) is a common disorder characterized by heartburn and acid regurgitation, with or without the presence of esophageal mucosal damage.¹ Patients with nonerosive reflux disease (NERD) may experience severe and even debilitating heartburn episodes. In fact, studies have shown that GERD symptom severity, frequency, and intensity are correlated poorly with degree of esophageal mucosal

injury.²⁻⁵ Attention recently has shifted to patient symptoms rather than endoscopically verified esophageal mucosal injury.

In practice, decisions about diagnosis and clinical interventions for GERD often are based on symptomology, with heartburn and acid regurgitation as 2 of the defining characteristics. Diagnostic clinical confirmation with upper endoscopy or 24-hour esophageal pH monitoring is invasive, costly, and may not be readily available for many physicians.

The use of proton pump inhibitors (PPIs) is becoming more common because mounting evidence indicates their superior efficacy in both NERD and erosive esophagitis (EE).⁶ Despite available information pertaining to the efficacy of PPI therapy in NERD, little has been done to synthesize existing data with respect to different PPI therapeutic regimens.⁷ Clinical efficacy measures for EE therapies commonly focus on acute healing and maintenance of healing using upper-gastrointestinal endoscopy. Much less information pertaining to symptomatic resolution in EE patients can be found. Most clinical end points in NERD are based on less-verifiable clinical outcomes such as symptom severity, frequency, and intensity. Furthermore, outcome assessment in NERD is complicated by the lack of clear disease definition and inconsistent definition of symptom relief.⁸

The objective of this study was to perform a systematic review of the literature and to synthesize all available data on the effectiveness of PPI therapy in resolving symptoms in NERD patients. The secondary objective

Abbreviations used in this paper: CI, confidence interval; EE, erosive esophagitis; GERD, gastroesophageal reflux disease; NERD, nonerosive reflux disease; PPI, proton pump inhibitor.

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was to compare the effectiveness of PPI therapy between patients with NERD and those with EE.

Materials and Methods

Systematic Review

A review of the medical literature was conducted to identify trials evaluating the effect of PPIs in patients with classic symptoms of GERD and negative upper endoscopy. Medline and HealthStar databases were searched for English language articles published between 1980 and 2002. Medical subject headings for the search included: proton pump inhibitor (PPI), esophagitis, gastroesophageal reflux, rabeprazole, omeprazole, lansoprazole, esomeprazole, and pantoprazole. We searched the Food and Drug Administration web site for pertinent reports concerning PPI treatment indications for NERD and abstracts presented during the American College of Gastroenterology and the Digestive Disease Week conferences between 1999 and 2001. Additional articles were identified through a hand search of references from relevant articles and from physicians and researchers in the field.

Titles, abstracts, and articles were reviewed serially against explicit exclusion criteria. Two reviewers conducted independent appraisals and resolved disagreements by consensus. Interrater reliability was tested on a 10% sample, with κ values > 0.70 at each review stage.

Articles were rejected at the title stage if they did not pertain to PPI monotherapy or a condition of interest (i.e., esophagitis, acid reflux, heartburn, GERD, NERD, gastric or esophageal acid), or were classified as reviews, case reports, editorials, letters, or meta-analyses. Similar criteria were applied to abstracts, with the additional requirement of data on NERD, on esophagitis grade 0 and/or 1, and on outcomes of interest. The full text of selected articles were reviewed and rejected if they did not report primary results from a randomized trial of symptomatic resolution with acute PPI treatment, or failed to include adults age 18 or older with esophagitis grade 0 and/or 1.

Data Abstraction

Abstracted study data included: location, design, description, multi- or single-center setting, endoscopic grade and definition of included patients, classification system, treatment goal, and symptom severity. Data pertaining to reported symptom occurrence, frequency, and severity also were collected. Symptom measures included heartburn, acid regurgi-

Table 2. Classification of Esophageal Mucosal Involvement Used in the Analysis

Group	Patient definition
Group 1	a) Endoscopically negative
Group 2	a) Endoscopically negative and erythema and friability b) Erythema and friability
Group 3—all studies	a) Endoscopically negative b) Endoscopically negative and erythema and friability c) Erythema and friability

tation, daytime heartburn, nighttime heartburn, and measures of symptom severity. Information on available outcome measures was abstracted for all available periods.

Applying the definitions of complete and sufficient heartburn resolution as described later (see the Complete Versus Sufficient Resolution Over Time section), we abstracted the proportions of patients meeting these definitions from the selected articles based on intent-to-treat results. Data were available on the following combinations: complete heartburn resolution, sufficient heartburn resolution, complete heartburn maintenance, and sufficient heartburn maintenance.

Grading and Classification

In accepted manuscripts, the study population was identified as having NERD or mild nonerosive GERD based on endoscopic results. A majority of investigators classified patients based on the grade of EE. A few investigators did not use a standard esophageal grading scheme but provided enough information to determine if patients were endoscopy negative, had erythema or friability, and/or had erosions. The most common classification schemes were the Savary–Miller, the Hetzel–Dent, and the Los Angeles, along with their modifications.

Criteria varied across the classification systems (Table 1). For example, although patients without erythema or friability would receive no grade using the Savary–Miller or Los Angeles systems, they would be assigned a grade 0 using the Hetzel–Dent system. Likewise, patients with erythema or friability are assigned a grade I using the Savary–Miller, a grade 1 using the Hetzel–Dent, and no grade using the Los Angeles system. Another issue in comparing patient populations was that some studies included only patients with negative endoscopy, others with erythema or friability only, and still others included patients with negative endoscopy, erythema, or friability, but no erosions.

Because of the different definitions of endoscopic findings and study populations, we developed a system for classifying studies based on reported grades from various classification systems (Table 2). Treatment comparisons were separated into 3 groups. Group 1 included only endoscopically negative patients. Group 2 was more flexible, allowing for erythema and friability but without erosions; this group included mixed patient populations, some with no endoscopic findings and others with erythema and friability. Group 3 combined all

Table 1. Classification of Esophageal Mucosal Involvement

Definition	Classification system		
	Savary–Miller	Hetzel–Dent	Los Angeles
Negative	No grade	Grade 0	No grade
Erythema and friability	Grade I	Grade 1	No grade
Erosions	Grade II–IV	Grade 2–4	Grade A–D

studies of patients with negative endoscopy, negative endoscopy or erythema and friability, or erythema and friability alone.

Complete Versus Sufficient Heartburn Resolution

Acute heartburn resolution was defined as either complete or sufficient. Complete resolution was defined as no heartburn during the preceding 7 days. Studies also measured sufficient (or satisfactory) heartburn resolution, defined as less than 1 day of moderate heartburn during the preceding 7 days of treatment.

Statistical Analysis

We focused our analysis on placebo-controlled trials. Estimates of the pooled treatment effect were calculated for the risk difference (the proportion with heartburn resolution in the treated group minus the proportion with heartburn resolution in the placebo group) using Bayesian modeling. The risk difference captures the therapeutic gain or effect of treatment over placebo.

We stratified available treatment arms by the following parameters: endoscopic grade of study population (Table 2), duration of PPI administration, and complete or sufficient control of heartburn. Differences across grades, time periods, and definitions of heartburn control were evaluated.

Comparison of PPI Therapy in NERD and EE

We compared the effectiveness of PPI treatment on complete heartburn resolution in patients with NERD vs. EE. We conducted a systematic review of the published literature and Food and Drug Administration reports pertaining to the effectiveness of PPI therapy in patients with endoscopically confirmed EE (Hetzel–Dent, grades 2–4).⁹ Strict criteria were used to identify relevant placebo-controlled articles of PPI therapy in EE. Results were pooled in a similar manner to the NERD estimates.

Results

Systematic Review

The search identified 1169 references published between January 1980 and January 2002. Figure 1 shows the inclusion and exclusion of articles at different points during the review process. We accepted 363 titles for further screening and reviewed their abstracts, and reviewed the full text of 107 articles.

Three published articles met inclusion criteria, presenting results from randomized placebo-controlled trials with sufficient information for estimating the effects of acute treatment on symptomatic GERD or NERD. Our search of the Food and Drug Administration web site yielded 4 additional reports concerning PPI treatment

indications for symptomatic GERD or NERD. Our search of the American College of Gastroenterology and Digestive Disease Week databases resulted in 59 abstracts for review. None presented data that were not also available in the published literature or Food and Drug Administration reports. Seven trials^{10–16} were included in our final sample (Table 3).

Of the 7 clinical trials evaluating heartburn resolution, there were 2 rabeprazole studies,^{15,16} 2 esomeprazole studies,^{13,14} and 3 omeprazole studies.^{10–12} All 7 studies evaluated PPI therapy vs. placebo in patients with NERD. A total of 1854 patients were evaluated, with the smallest study including 123 patients¹⁶ and the remaining studies including over 200 patients each. Although all studies allowed for a run-in period without PPI or histamine-2 receptor antagonists, only one study¹⁰ excluded patients with any previous use. Five^{10,12–15} of the 7 studies presented data with multiple treatment arms. A total of 12 treatment arms and 7 placebo arms were identified. The most frequent drug-dose combination examined was omeprazole 20 mg (3 treatment arms). Two treatment arms were available for omeprazole 10 mg, esomeprazole 20 mg, esomeprazole 40 mg, and rabeprazole 20 mg, with only one treatment arm for rabeprazole 10 mg.

Table 4 shows all sufficient and complete heartburn resolution outcomes at all time periods across all 7 studies. The majority of studies reported heartburn resolution rates for 2 time periods. Thus, our analysis explored the risk difference (therapeutic gain) for the 2-week and 4-week assessments.

Complete Versus Sufficient Resolution Over Time

Group 1: endoscopically negative subjects. Two studies^{10,11} provided data on heartburn resolution for endoscopically negative patients (Figure 2). The therapeutic gain of PPI treatment over placebo for sufficient resolution at the 2-week assessment was 0.29 (95% confidence interval [CI], 0.21–0.37). At 4 weeks, the therapeutic gain increased to 0.34 (95% CI, 0.28–0.41). No significant difference was observed between the therapeutic gains at 2 and 4 weeks ($P = 0.42$). No measurements of complete resolution were available at 2 weeks. At the 4-week assessment, the therapeutic gain of PPI treatment over placebo was 0.25 (95% CI, 0.18–0.31).

In comparing therapeutic gains at 4 weeks, a higher proportion of treated vs. placebo patients achieved sufficient resolution compared with achieving complete resolution. This difference between therapeutic gains was not statistically significant ($P = 0.14$).

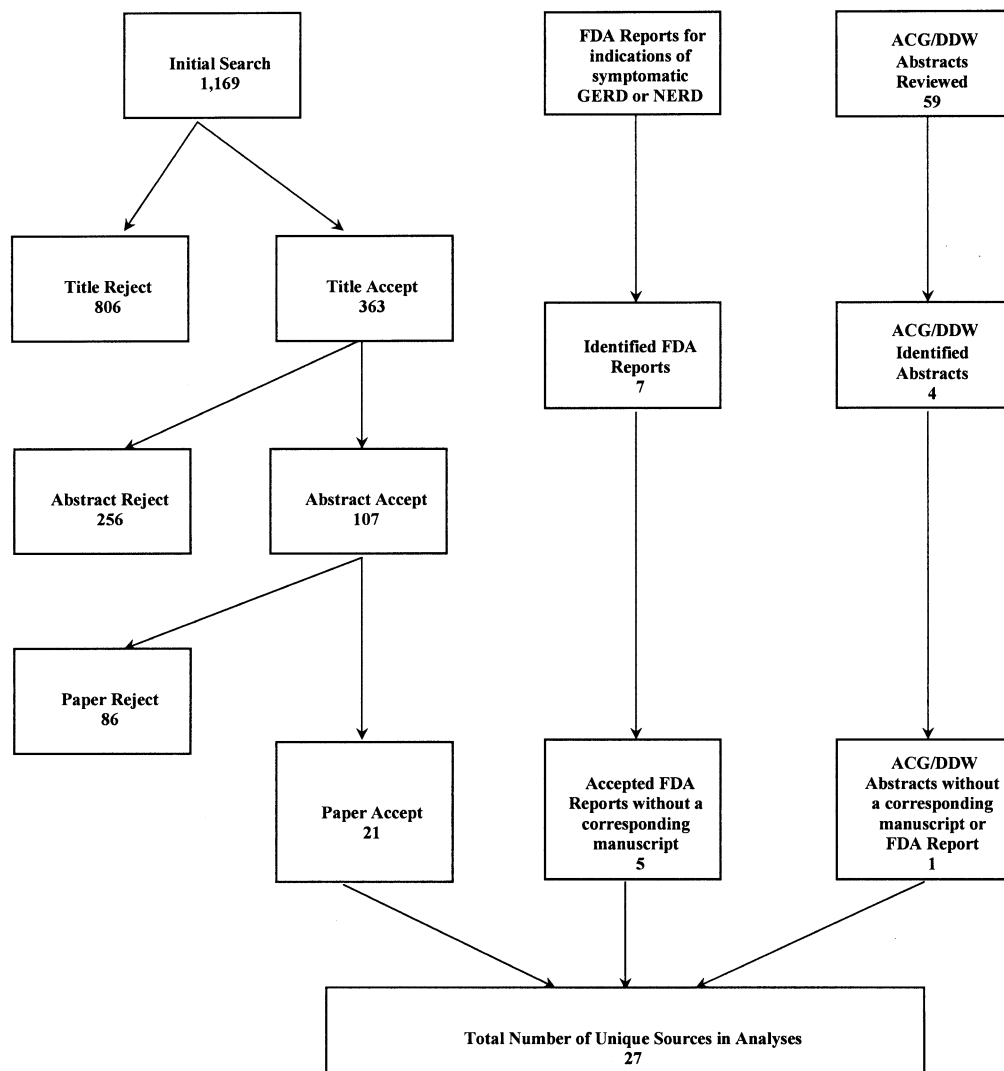


Figure 1. Flowchart of the systematic review for NERD and symptomatic GERD.

Group 2: patients with negative endoscopy and erythema and friability, or erythema and friability alone. Five studies^{12–16} contributed data on heartburn resolution for our group 2 patient population (Figure 3). For sufficient resolution, the therapeutic gain of PPI treatment over placebo at the 2-week measurement was 0.35 (95% CI, 0.26–0.44). At the 4-week measurement, the therapeutic gain decreased to 0.29 (95% CI, 0.19–0.39). The difference between the therapeutic gains at the 2- and 4-week measurements was nonsignificant ($P = 0.52$).

For complete resolution, therapeutic gains were calculated for the 1-, 2-, and 4-week time periods. The therapeutic gain of PPI treatment over placebo at 1 week was 0.14 (95% CI, 0.10–0.17). An increase in therapeutic gain was observed between the 1- and 2-week assessments, with the therapeutic gain at 2 weeks calculated as 0.22 (95% CI, 0.19–0.25). For the 4-week assessment,

the therapeutic gain of PPI treatment was 0.26 (95% CI, 0.23–0.30). Although therapeutic gains increased over time, no significant difference was observed between the assessments (1-week vs. 2-week, $P = 0.58$; 2-week vs. 4-week, $P = 0.23$).

When therapeutic gains were compared within time periods, a higher proportion of group 2 patients reported achieving sufficient resolution compared with achieving complete resolution. The therapeutic gain for sufficient resolution was significantly different from the therapeutic gain for complete resolution at 2 weeks ($P = 0.04$). At 4 weeks, the gap between the therapeutic gains decreased, resulting in a nonsignificant difference between the 2 measurements ($P = 0.69$).

Group 3: patients with negative endoscopy, negative endoscopy and erythema and friability, or erythema and friability alone. Results are consistent when data for patients in both groups 1 and 2 are combined

Table 3. Identified Placebo-Controlled Trials of NERD Patients

Study	Year	Treatment arms	Study location	Source	Center type	Study support	Study population	Jadad score ^a	Measure of heartburn resolution
Lind et al. ¹⁰	1997	OME10, OME20, placebo	Europe	Published report	Multiple	Astra Hassle	Group 1	4	Yes
Hatlebakk ¹¹	1999	OME20, placebo	Europe: Norway	Published report	Multiple	Astra Norge	Group 1	4	Yes
Richter et al. ¹²	2000	OME10, OME20, placebo	United States/Canada	Published report	Multiple	Astra Merck	Group 2	4	Yes
AstraZeneca ¹³	1999	ESO20, ESO40, placebo	United States/Canada	FDA report	Multiple	AstraZeneca	Group 2	5	Yes
AstraZeneca ¹⁴	1999	ESO20, ESO40, placebo	United States/Canada	FDA report	Multiple	AstraZeneca	Group 2	5	Yes
Zheng et al. ¹⁵	2002	RAB10, RAB20, placebo	United States/Canada	FDA report	Multiple	Janssen Pharmaceutica	Group 2	5	Yes
Mozeika et al. ¹⁶	2001	RAB20, placebo	United States/Canada	FDA report	Multiple	Janssen Pharmaceutica	Group 2	5	Yes

OME10, omeprazole 10 mg; OME20, omeprazole 20 mg; ESO20, esomeprazole 10 mg; ESO40, esomeprazole 20 mg; FDA, Food and Drug Administration; RAB10, rabeprazole 10 mg; RAB20, rabeprazole 20 mg.

^aThe JADAD score is a way of assessing the quality of reports involving randomized controlled clinical trials.³⁰

(Figure 4). For sufficient resolution, the therapeutic gain of PPI treatment over placebo at 2 weeks was 0.32 (95% CI, 0.26–0.38). At the 4-week measurement, the therapeutic gain was 0.33 (95% CI, 0.27–0.38). No significant difference was detected between the therapeutic gains ($P = 0.80$).

Results for complete resolution mirrored the results for group 2 patients at the 1-week (therapeutic gain = 0.14; 95% CI, 0.10–0.17) and 2-week (therapeutic gain = 0.22; 95% CI, 0.19–0.25) assessments. The therapeutic gain of PPI treatment for complete heartburn resolution at 4 weeks was 0.26 (95% CI, 0.23–0.29).

Again, no significant difference was observed between the therapeutic gains at 2 and 4 weeks ($P = 0.25$).

Within time periods, higher proportions of patients achieved sufficient resolution as opposed to complete resolution. At the 2-week measurements, the difference between therapeutic gains was significant ($P < 0.05$). The difference between therapeutic gains decreased at the 4-week measurement, and was not significant ($P = 0.12$).

Summary. In general, the therapeutic gain of PPI treatment over placebo ranged from 30%–35% for sufficient heartburn control and 25%–30% for complete

Table 4. Heartburn Measures Available for All Studies

Study	Comparison	1 week sufficient	1 week complete	2 week sufficient	2 week complete	4 week sufficient	4 week complete
Richter et al. ¹²	OME20 vs. placebo				X		X
Richter et al. ¹²	OME10 vs. placebo				X		X
Lind et al. ¹⁰	OME20 vs. placebo			X		X	X
Lind et al. ¹⁰	OME10 vs. placebo			X		X	X
Hatlebakk ¹¹	OME20 vs. placebo					X	
AstraZeneca ¹³	ESO40 vs. placebo		X		X		X
AstraZeneca ¹³	ESO20 vs. placebo		X		X		X
AstraZeneca ¹⁴	ESO40 vs. placebo		X		X		X
AstraZeneca ¹⁴	ESO20 vs. placebo		X		X		X
Zheng et al. ¹⁵	RAB20 vs. placebo			X	X	X	X
Zheng et al. ¹⁵	RAB10 vs. placebo			X	X	X	X
Mozeika et al. ¹⁶	RAB20 vs. placebo			X	X	X	X

OME20, omeprazole 20 mg; OME10, omeprazole 10 mg; ESO40, esomeprazole 20 mg; ESO20, esomeprazole 10 mg; RAB20, rabeprazole 20 mg; RAB10, rabeprazole 10 mg.

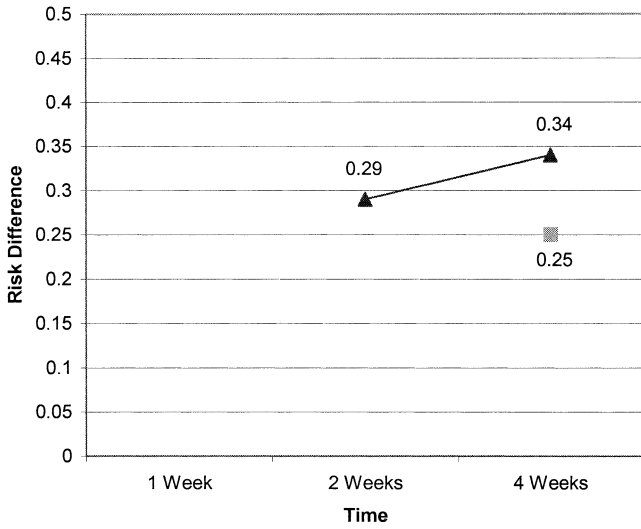


Figure 2. Treatment comparison with placebo for group 1 (endoscopy negative) patients: pooled difference (treatment – placebo) in proportion with heartburn resolution by time. ▲, Sufficient; ■, complete.

heartburn control. In other words, PPIs successfully treated between one quarter and one third of the population. This held true for pooled estimates across all treatments. Among all grades and time periods, PPIs resulted in higher proportions of patients achieving sufficient resolution compared with complete resolution. The effects of PPIs for sufficient resolution appeared sooner (approximately 2 weeks) compared with complete resolution (4 weeks). At 2 weeks, the therapeutic gain for sufficient resolution was significantly different from the

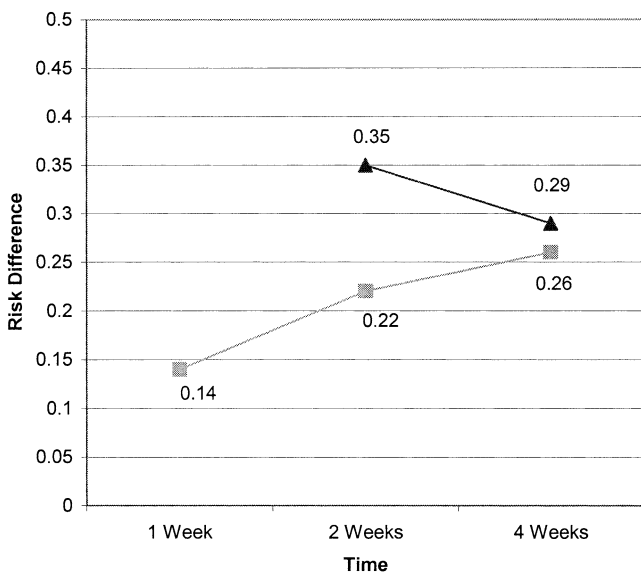


Figure 3. Treatment comparison with placebo for group 2 (negative endoscopy and erythema and friability) patients: pooled difference (treatment – placebo) in proportion with heartburn resolution by time. ▲, Sufficient; ■, complete.

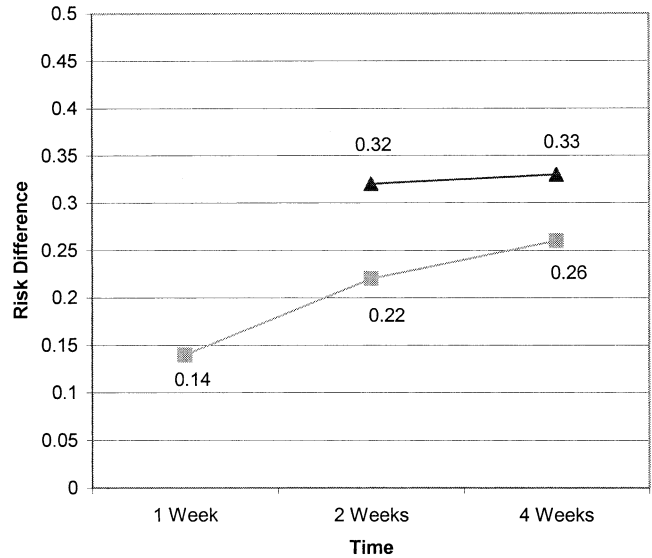


Figure 4. Treatment comparison with placebo for all studies (group 3): pooled difference (treatment – placebo) in proportion with heartburn resolution by time. ▲, Sufficient; ■, complete.

therapeutic gain for complete resolution for both group 2 patients (endoscopically negative and erythema and friability) and for all patients combined (group 3) ($P = 0.04$ and $P = 0.05$, respectively). Over time, the therapeutic gain for complete resolution increased. However, the difference between sufficient and complete resolution at 4 weeks was not significant ($P = 0.14$, $P = 0.69$, and $P = 0.12$ for groups 1, 2, and 3, respectively).

Comparison of Heartburn Resolution in NERD and EE

We compared the symptomatic response rates of patients with NERD with those diagnosed with EE. Although endoscopic healing rates are reported commonly in EE studies, symptomatic response to PPI therapy is not reported commonly. When reported, 4- and 8-week data usually are presented. Thus, across the NERD and EE literature, only 4-week symptomatic response rates were reported for each population. As was performed for NERD, the combined effect of PPI therapy on the symptomatic response rate at 4 weeks was pooled across treatment strategies and dosages for EE patients.

A systematic literature review of symptomatic healing rates associated with PPI therapy in patients with EE identified 2 randomized controlled trials.^{17,18} Both were placebo-controlled and contributed multiple treatment arms of rabeprazole and pantoprazole, respectively. Complete resolution of heartburn was the outcome measure for comparison.

Table 5. Symptomatic Response Rates and Therapeutic Gains at 4 Weeks Among Patients With NERD and EE

Study population	PPI symptomatic response pooled rate (95% CI)	Placebo symptomatic response pooled rate (95% CI)	Therapeutic gain – difference (95% CI)
NERD (n = 1854)	36.7 (34.1–39.3)	9.5 (7.1–11.9)	27.2 (20.9–35.3)
EE (n = 705)	55.5 (51.5–59.5)	7.5 (2.5–12.5)	48.0 (24.6–93.8)

Table 5 displays the pooled 4-week symptomatic response rates and therapeutic gains for patients with NERD and EE. The 4-week symptomatic response rate was significantly higher for patients with EE compared with NERD (56% vs. 37%, respectively; $P < 0.0001$), whereas the placebo symptomatic response rates were similar between the 2 groups (9.5% vs. 7.5%, respectively; $P > 0.05$). Thus, the therapeutic gain of PPI therapy over placebo was more than 75% higher among EE patients (48% for EE vs. 27% for NERD).

Discussion

NERD is the most common type of GERD that community-based physicians encounter. Because of the lack of esophageal mucosal injury, treatment of NERD is based commonly on a step-up approach. However, therapeutic studies in NERD have shown that PPIs are superior to histamine-2 receptor antagonists or pro-motility compounds.^{19–21} In this study, we compared the effectiveness of PPI therapy with that of placebo for symptom resolution at different time periods in NERD patients, using published literature. Because of the lack of esophageal mucosal injury, almost all NERD studies limited the treatment period to 4 weeks.^{12,22–25} Last, symptom response to PPI was compared between patients with NERD and those with EE.

Several important points stand out. First, higher proportions of NERD patients reported attaining sufficient heartburn resolution as compared with attaining complete heartburn resolution. This was apparent across all grades of NERD and across all time periods. In addition, PPI treatment led to sufficient heartburn resolution, with the effects observed at the 2-week time period; the effects of complete heartburn resolution were observed at the 4-week period. Finally, symptomatic response rate at 4 weeks was significantly higher for patients with EE compared with NERD patients.

Our analysis suggests that to improve the outcome of therapeutic studies in NERD, more modest clinical end points should be considered. For many NERD patients, sufficient heartburn control may be a satisfactory therapeutic outcome. Because NERD patients rarely develop EE, physicians can accept sufficient heartburn control as a reasonable therapeutic outcome.^{26,27}

The lower symptom response rate to PPI treatment in NERD patients as compared with patients with EE likely is owing to the different subgroups of patients identified as having NERD. A recent study by Martinez et al.²⁸ showed that 50% of the patients with NERD have normal esophageal acid exposure. Of these patients with functional heartburn, 37% showed a close correlation between GERD symptoms and acid reflux events, and the rest (63%) were likely to experience heartburn caused by non-acid-related stimuli. These findings are consistent with the view that patients with NERD are a heterogeneous group with different symptom causes and thus different therapeutic responses to PPIs.

The analysis also suggests that owing to the significantly lower symptom response rates to PPIs in patients with NERD compared with those with EE, the step-up approach has little merit in NERD patients. Adding the studies that showed a very limited (30%) symptom response rate of NERD patients to histamine-2 receptor antagonists, a step-in approach with a PPI should be the appropriate therapeutic intervention for NERD.^{19,23}

An important finding of our study is that the pooled therapeutic gain of PPI treatment for complete heartburn resolution increased from the 1-week to 2-week assessment and again at the 4-week time period (0.14 → 0.22 → 0.26). Our study showed the need to reconsider the 4-week study design in NERD patients undergoing therapeutic intervention because some patients with NERD may have a longer lag time to symptom response.

This study systematically assessed and synthesized the literature on the effectiveness of PPI therapy in the NERD population and compared symptomatic response rates on PPI therapy in both NERD and EE populations in the same time frame. Therapeutic gain (response to treatment minus response to placebo) allows for the combination of data across a variety of studies and provides clinicians with a clinically meaningful range of responses they should expect with therapy.

A few limitations were inherent to this study. One was the lack of a standard definition for NERD and the use of different classifications for GERD. Another limitation was the lack of data points included in this analysis. This may have resulted from the selected parameters used in the systematic review or the definitions of NERD used

by the researchers. A third limitation was the lack of comparable end points among included studies. Some studies reported complete daytime and/or nighttime heartburn resolution, whereas others reported complete resolution of global symptoms. A hierarchy was created a priori to account for the choice of end points used in the analysis when a study reported more than one end point. Last, we found low placebo symptom response rates for PPI therapy in patients with NERD and with EE. Low placebo response rates may be the result of assessing the rigorous outcome of complete symptom resolution. In addition, the low placebo response rates could be the result of the time period assessed because patient expectations of treatment response may vary by time.

In summary, as expected, NERD patients are likely to report sufficient heartburn resolution more often than complete heartburn resolution and achieve sufficient resolution sooner than complete resolution. Symptom response rate was significantly lower in NERD patients compared with those with EE receiving standard-dose PPI. Most importantly, during the first 4 weeks of treatment, patients with NERD showed increased therapeutic gain for complete heartburn resolution (from 0.14 to 0.26), suggesting that the trend of symptom improvement may well continue into the second month of therapy. Future study designs in NERD patients should not be limited to 4 weeks, and randomized placebo-controlled studies comparing various PPI therapies for sufficient and complete heartburn resolution in patients with NERD should be conducted.

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