



# Effective Health Care Program

## Management Strategies for Gastroesophageal Reflux Disease: An Update

### Executive Summary

#### Background

Gastroesophageal reflux disease (GERD) is one of the most common health conditions affecting Americans. A study of an employed population in the United States estimated that more than 11,000 of 267,000 employees (4 percent) suffered from GERD, contributing an average incremental cost to the employer of \$3,355 per employee during a 3-year observation period—approximately 65 percent related to prescription drugs.<sup>1</sup> At the same time, it is well recognized that some drugs used to treat GERD (such as proton pump inhibitors) are overprescribed.<sup>2</sup>

A number of patients have frequent severe symptoms requiring long-term regular use of antireflux medications. For these individuals with chronic GERD, most authorities consider the goals of therapy to be an improvement in symptoms and quality of life, healing and maintenance of healed erosive esophagitis, and prevention of complications (such as Barrett's esophagus, esophageal stricture formation, or esophageal adenocarcinoma). However, there remains considerable uncertainty regarding how these objectives should be achieved.

Among patients treated medically, several approaches are used, depending in part on the severity of symptoms and clinical

#### Effective Health Care Program

The Effective Health Care Program was initiated in 2005 to provide valid evidence about the comparative effectiveness of different medical interventions. The object is to help consumers, health care providers, and others in making informed choices among treatment alternatives. Through its Comparative Effectiveness Reviews, the program supports systematic appraisals of existing scientific evidence regarding treatments for high-priority health conditions. It also promotes and generates new scientific evidence by identifying gaps in existing scientific evidence and supporting new research. The program puts special emphasis on translating findings into a variety of useful formats for different stakeholders, including consumers.

The full report and this summary are available at [www.effectivehealthcare.ahrq.gov/reports/final.cfm](http://www.effectivehealthcare.ahrq.gov/reports/final.cfm).

response. These include intermittent, periodic, or continuous use of prescription or over-the-counter medications, especially histamine type 2 receptor antagonists (H2RAs) and proton pump inhibitors (PPIs).



The availability of surgery (fundoplication) and, more recently, endoscopic treatments has further complicated the choice among management strategies.

The first Comparative Effectiveness Review (CER) published by the Agency for Healthcare Research and Quality focused on gastroesophageal reflux disease.<sup>3</sup> The Key Questions addressed in that report concerned the comparative effectiveness of medical, surgical, and endoscopic treatments for improving objective and subjective outcomes in patients with this disease. In addition, the report examined the relative efficacy of these interventions in specific patient subgroups as well as adverse event profiles. A number of developments since the publication of the 2005 review have necessitated an update. Among them are the publication of approximately 3,000 new studies; the introduction of novel drugs; the recognition of new drug safety considerations; and the withdrawal of previously approved endoscopic interventions and introduction of new endoscopic interventions. Also notable was the publication of a new consensus definition of GERD in 2006.<sup>4</sup>

The current report addresses developments in the treatment of GERD in adults and additionally includes sections on treatment of extraesophageal syndromes, including chronic cough, laryngitis, and asthma, which an expert panel considered to be of particular clinical importance.

While additional data have clarified many of the prior review's findings, many limitations and the means by which they were addressed have remained unchanged. As with the previous report, definitions of GERD and disease severity among included subjects varied from study to study. For example, many studies defined GERD based on symptomatology, while others incorporated the results of various objective tests, such as ambulatory esophageal pH, endoscopic, or acid suppression studies. In this update, the populations evaluated were, therefore, made explicit and outlined in detail.

Similar considerations apply to the assessment of outcomes, which included measures of formal or informal evaluation of symptoms, medication use, quality-of-life assessment instruments, healing of esophagitis, and changes in esophageal pH exposure. The methods by which these outcomes were evaluated

varied, and not all studies included outcomes of interest. Again, to aid in interpretation of results, outcomes and their definitions were explicitly reported when making comparisons across studies. The quality of studies was also assessed rigorously and weighed in the formulation of conclusions.

Furthermore, as this report was intended to focus on comparative effectiveness, studies that directly compared treatment options for GERD were prioritized. However, noncomparative studies were also considered to fully address particular elements of the review's Key Questions, such as those pertaining to adverse events.

GERD continues to be an important disease in terms of both cost and public health. The large disease burden, economic impact, and market potential for new drugs and devices explain the continued intense interest in GERD and the development of cost-effective approaches for its diagnosis and management. The purpose of this report is to provide a detailed, rigorous, and up-to-date appraisal of the evidence comparing various management strategies for adult patients with GERD. While no clinical recommendations are made in the report, its conclusions should have clinical applicability because they laid out the safety and effectiveness of various treatment approaches for patients with GERD as well as providing guideline-issuing organizations guidance in the formulation of their recommendations for the management of GERD.

## Objectives

### Key Questions

**Key Question 1:** What is the evidence of the comparative effectiveness of medical, surgical, and other newer forms of treatments for improving objective and subjective outcomes in patients with chronic gastroesophageal reflux disease? Is there evidence that effectiveness varies by specific technique, procedure, or medication? Objective outcomes addressed include esophagitis healing, ambulatory pH, other indicators of reflux, need for medication, health care utilization, and incidence of esophageal stricture, Barrett's esophagus, or esophageal adenocarcinoma. Subjective outcomes include symptom frequency and severity, sleep/productivity, and overall quality of life.

**Key Question 2:** Is there evidence that effectiveness of medical, surgical, and newer forms of treatments varies for specific patient subgroups? What are the characteristics of patients who have undergone these therapies, including the nature of previous medical therapy, severity of symptoms, age, sex, weight, and other demographic and medical factors? What are the provider characteristics for procedures, including provider volume and setting (e.g., academic vs. community)?

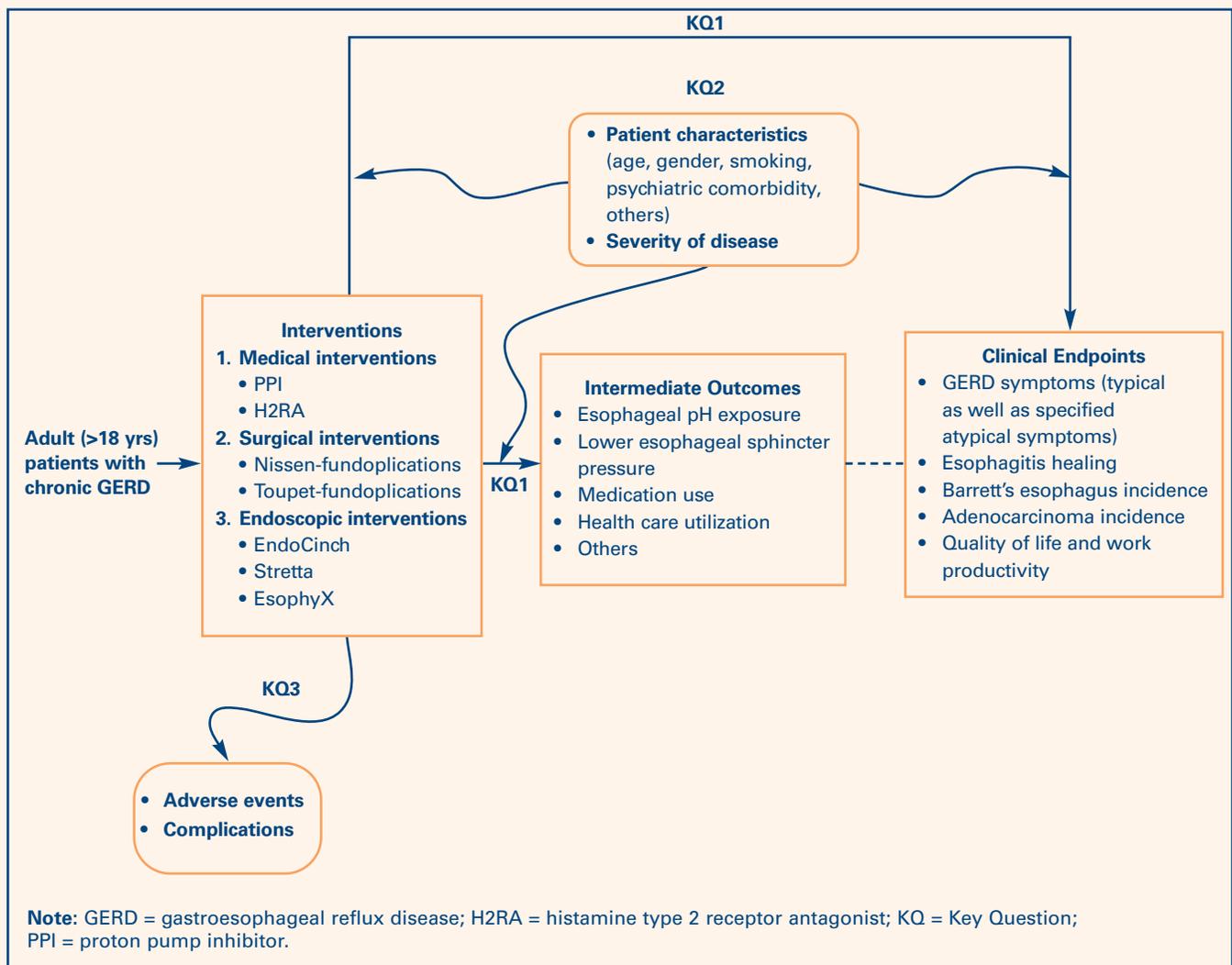
**Key Question 3:** What are the short-term and long-term adverse events associated with specific medical,

surgical, and other newer forms of therapies for GERD? Does the incidence of adverse events vary with duration of followup, specific surgical intervention, or patient characteristics?

**Analytic Framework**

The analytic framework depicted in Figure A was applied to answer the Key Questions in the evaluation of the treatment modalities for GERD. This framework addressed relevant clinical and intermediate outcomes, and also examined clinical factors that affected treatment outcomes.

**Figure A. Analytic framework of the comparative effectiveness of management strategies for GERD**



## Methods

### Search Strategies

To update the 2005 GERD review,<sup>3</sup> we searched MEDLINE® (2004-August 2010) for English language studies of adult humans and for articles pertinent to each Key Question. For the current update, the scope was expanded to include patients with extraesophageal GERD (i.e., patients with chronic cough, laryngitis or hoarseness, or asthma believed to be related to GERD). We also searched for published meta-analyses and systematic reviews for this topic (up to October 2009) in MEDLINE, the Cochrane Database of Systematic Reviews, the American College of Physicians Journal Club, the Database of Abstracts of Reviews of Effects, and the Centre for Reviews and Dissemination's Health Technology Assessments.

The Scientific Resource Center at Oregon Health & Science University conducted the gray literature search that provided information related to GERD from regulatory agencies, trial registries, conference proceedings, and miscellaneous sources. We also searched the Manufacturer and User Facility Device Experience (MAUDE) database of the U.S. Food and Drug Administration (FDA).

### Study Selection

Titles and/or abstracts of citations identified from literature searches were assessed for inclusion using the criteria described below. Full-text articles of potentially relevant abstracts were retrieved, and a second review for inclusion was conducted by applying the same criteria.

For Key Questions related to GERD, eligible studies were comparative, randomized, nonrandomized, and cohort studies of adults (≥18 years) with chronic GERD. Studies that focused exclusively on patients with postsurgical GERD; pregnancy-induced GERD; duodenal or peptic ulcer; gastritis; primary esophageal motility disorder; scleroderma; diabetic gastroparesis; radiation esophagitis; Zollinger-Ellison syndrome; Zenker's diverticulum; previous antireflux surgery; or infectious, pill, or chemical burn esophagitis were excluded.

For Key Questions related to extraesophageal GERD, we included systematic reviews or meta-analyses that aggregated studies focusing exclusively on patients with

extraesophageal GERD symptoms. Systematic reviews had to incorporate the following three elements for inclusion: (1) a statement of the research question, (2) a description of the literature search, and (3) a listing of the study eligibility criteria. If an update of a qualifying systematic review was deemed necessary, we searched for primary studies published after the systematic review using the same inclusion and exclusion criteria.

For studies on medical treatment, we included randomized controlled trials (RCTs) using a PPI or H2RA for the treatment of acute symptoms or as maintenance therapy. For studies with surgical procedures, we accepted only RCTs or cohort studies examining total (Nissen and Nissen-Rossetti) or partial (Toupet) fundoplication, either as an open or as a laparoscopic procedure. For studies with endoscopic procedures, we included only RCTs or cohort studies examining products approved in the United States.

To evaluate the comparative efficacy of different therapies (Key Question 1), we analyzed the subjective and objective outcomes generally considered to represent clinically important endpoints in the management of GERD. Cost-effectiveness and cost-benefit outcomes were excluded. For Key Question 2, we focused on the following baseline patient characteristics that may have influenced treatment efficacy: age, sex, smoking status, obesity status, severity of GERD symptoms, type of and response to previous medication, presence and severity of esophagitis, presence and size of hiatal hernia, presence of esophageal motility abnormality, and (among patients off medication) presence of abnormal esophageal acidification. To evaluate adverse events and complications (Key Question 3), we assessed the rate of each adverse event of medical treatment, the rate of every reported complication, the length of in-hospital stay, and the rate of reoperation after a surgical or endoscopic procedure.

### Data Extraction and Quality Assessment

Study data were extracted into customized forms. They provided information on study design, patient and intervention characteristics, outcome definitions, study results, and the methodological quality of each study, which was rated from A (highest quality, least likely to have significant bias) to C (lowest quality, most likely to have significant bias).<sup>5</sup> Included systematic reviews were evaluated using the AMSTAR checklist.<sup>6</sup>

## Data Synthesis

Evidence tables are provided as a condensed reference of study descriptions arranged by Key Question. The tables contain detailed information concerning design, sample size, intervention and comparison group treatments, patient characteristics, followup, major outcomes, and methodological quality. In addition, for systematic reviews and meta-analyses, we reported the databases searched, time period searched, number and type of primary studies included, and type of comparison addressed. Where a P-value was reported,  $P < 0.05$  was considered statistically significant.

## Grading a Body of Evidence for Each Key Question

An overall rating was assigned to the body of evidence related to each outcome within each Key Question based on the number and quality of the relevant individual studies, duration of followup, and consistency of findings. We determined the strength of evidence as high, moderate, low, or insufficient. The ratings provide a concise summation of the strength of evidence supporting each of the outcomes the major questions addressed. (See AHRQ Methods Reference Guide.<sup>5</sup>)

## Results

### Key Question 1. What is the evidence of the comparative effectiveness of medical, surgical, and other newer forms of treatments for improving objective and subjective outcomes in patients with chronic gastroesophageal reflux disease?

#### Medical Versus Surgical Treatments

The 2005 CER concluded that medical therapy with PPIs and antireflux surgery were similarly effective in improving GERD-related symptoms and decreasing esophageal acid exposure, although some surgical patients required ongoing medical therapy postprocedure. With the addition of long-term followup data (7 to 12 years) from two previously reviewed studies and results from two new RCTs, our updated review found that patients who underwent antireflux surgery experienced a greater improvement in heartburn and regurgitation at followup than patients

who received medical treatment alone. However, some uncertainty remains in the true estimates of the efficacy of surgery vs. medical treatment because of the large proportion of patient dropouts (33 to 58 percent) in studies with long followup. As with the 2005 CER, the studies in this review included patient populations with varying clinical characteristics and response to medical treatments at baseline. One of the previously reviewed studies with long-term followup data enrolled only patients with baseline esophagitis, without restriction on the degree of severity, while the other included patients with no higher than Los Angeles grade B esophagitis at randomization.

Consistent with results from the 2005 CER, fundoplication decreased but did not eliminate the use of antireflux medications at followup. Compared with those who received medical treatment, patients who underwent antireflux surgery also demonstrated improvement (in some cases statistically significant) on reflux symptom scales and quality-of-life measurements. Studies reporting pH results also demonstrated outcomes favoring surgically treated patients. Furthermore, the surgery group in one RCT demonstrated significantly greater sustained remission of GERD symptoms relative to the medication group at followup. The strength of evidence was rated moderate.

The rate of serious adverse events was generally higher in patients who underwent fundoplication than in those who had medical treatment. Fundoplication was also associated with procedural complications such as postoperative infections and incisional hernia, and morbidities such as dysphagia and postprandial bloating, some of which required surgical revisions. Typical adverse events reported with PPI use were generally not serious (e.g., diarrhea, abdominal pain, headache) and tended to self-resolve upon stopping the treatment. Other serious adverse events potentially associated with PPI use are discussed later in this Executive Summary.

#### Medical Versus Endoscopic Treatments

Like the 2005 CER, the present update did not identify any study that compared medical treatment with endoscopic therapy. The strength of evidence was rated insufficient.

## Surgical Versus Endoscopic Treatments

The 2005 CER did not identify any study that compared surgical with endoscopic treatment. The present review identified one small nonrandomized study that compared laparoscopic total fundoplication with EndoCinch™. This study reported that laparoscopic total fundoplication was more effective than EndoCinch in improving GERD symptoms and decreasing acid exposure. The strength of evidence was rated insufficient.

## Medical Treatment Comparisons

**Comparisons Between PPIs and H2RAs.** The addition of four RCTs did not alter the conclusions of the 2005 CER regarding comparisons between PPIs and H2RAs. In both the original CER and the present update, PPIs were found to be superior to H2RAs in the resolution of GERD symptoms at 4 weeks and healing of esophagitis at 8 weeks. The strength of evidence was rated moderate.

In one RCT, lansoprazole 15 mg taken once daily was more effective than ranitidine 150 mg taken twice daily for the healing of esophagitis at 1 year. In another RCT, esomeprazole 20 mg taken once daily or on demand was more effective than ranitidine 150 mg taken twice daily for the prevention of symptom relapse at 6 months. Data from two RCTs indicated that maintenance treatment ( $\geq 6$  months) with PPIs appeared to be more effective than maintenance treatment with H2RAs in symptom remission.

**Comparisons Between Different PPIs.** The 2005 CER did not find significant difference between (1) omeprazole, lansoprazole, pantoprazole, and rabeprazole for relief of symptoms at 8 weeks; (2) esomeprazole 40 mg versus lansoprazole 30 mg or pantoprazole 40 mg for symptom relief at 4 weeks; (3) esomeprazole 20 mg versus omeprazole 20 mg in relief of symptoms at 4 weeks. However, esomeprazole 40 mg was significantly favored for symptom relief at 4 weeks compared with omeprazole 20 mg.

The addition of 10 RCTs to the present update did not alter the conclusions of the original report with respect to these comparisons. Comparisons were made between pantoprazole (20 mg to 40 mg) versus esomeprazole (20 mg to 40 mg), lansoprazole 30 mg versus

esomeprazole 40 mg, and rabeprazole (10 mg to 20 mg) versus esomeprazole (20 mg to 40 mg). The durations of followup ranged from 1 to 6 months. No consistent comparative difference in symptom relief was observed between esomeprazole (20 to 40 mg), lansoprazole (15 to 30 mg), pantoprazole (20 to 40 mg), or rabeprazole (10 to 20 mg) over a period ranging from 4 weeks to 6 months. The strength of evidence was rated moderate.

There is some evidence from individual studies that rabeprazole 10 mg may provide better symptom relief than esomeprazole 40 mg at 4 weeks, and pantoprazole 20 mg better control of heartburn than esomeprazole 20 mg over 24 weeks. Results from three acute treatment trials showed similar esophagitis healing rates for both pantoprazole 40 mg and esomeprazole 40 mg as demonstrated by endoscopy, with the rates increasing with trial duration from 8 to 12 weeks and being equivalent over 6 months.

**Comparisons Between Different Dosages and Dosing Regimens of PPIs.** As opposed to the 2005 CER, which did not evaluate comparisons between different dosages and dosing regimens of commonly used PPIs, the present study reviewed 12 RCTs examining the relative effectiveness of different PPI dosing regimens. Comparisons were made between different dosages of pantoprazole (20 mg to 40 mg), esomeprazole (10 mg to 40 mg), lansoprazole (15 mg to 30 mg), and dexlansoprazole (30 mg to 90 mg). The regimens evaluated included once-daily or on-demand dosing; a regimen of 4-week PPI therapy with relapse of symptoms (intermittent therapy); a regimen of endoscopy-determined dose, where presence of esophagitis on endoscopy necessitated a higher dose of the PPI; and different “step” regimens—stepping down to an H2RA or stepping down to a lower PPI dose. The time periods of followup ranged from 1 to 12 months. There was no consistent difference in the effects of different doses and dosing regimens of PPIs in relation to symptom resolution and esophagitis healing rates. The strength of evidence was rated moderate.

No significant difference in symptom resolution rates was observed at 4 weeks between esomeprazole 20 mg taken once a day and esomeprazole 40 mg taken once a day. A significantly higher rate of esophagitis healing at 4 weeks was observed with esomeprazole 40 mg taken

once a day compared with esomeprazole 20 mg taken once a day. This was corroborated by the observation of a significantly higher percentage of time of exposure to pH > 4 in patients taking esomeprazole 40 mg once a day.

**Comparisons Between Once-Daily and On-Demand Dosing Regimens of PPIs.** Five RCTs compared once-daily with on-demand dosing. Comparisons were made between once-daily and on-demand dosing regimens for rabeprazole 10 mg, rabeprazole 20 mg, and esomeprazole 20 mg. In three RCTs comparing continuous daily intake of esomeprazole 20 mg versus on-demand dosing, continuous intake appeared to provide better symptom control and quality of life than on-demand dosing over a period of 6 months. The strength of evidence was rated moderate.

Continuous daily intake of esomeprazole 20 mg appeared to provide better symptom control and quality of life than on-demand dosing over a period of 6 months. Continuous daily intake of esomeprazole 20 mg also appeared to provide significantly better endoscopic remission than on-demand dosing over a period of 6 months.

**Comparisons Between Prescribed PPIs and Over-the-Counter Dosages of PPIs (Omeprazole 20 mg, Lansoprazole 15 mg).** Eight RCTs compared prescribed PPIs with over-the-counter dosages of PPIs (omeprazole 20 mg and lansoprazole 15 mg, which the FDA has approved for the treatment of frequent heartburn). Frequent heartburn is defined as heartburn that occurs 2 or more days per week. The PPI doses that were compared with omeprazole 20 mg included omeprazole 10 mg, omeprazole 20 mg on demand, esomeprazole (20 mg to 40 mg), rabeprazole 20 mg, lansoprazole 30 mg, and pantoprazole 40 mg. The only PPI that was compared with lansoprazole 15 mg was esomeprazole 20 mg. Followup ranged from 1 to 12 months. No consistent comparative difference in symptom relief or esophagitis healing rates was observed between esomeprazole (20 to 40 mg), lansoprazole 30 mg, pantoprazole 40 mg, or rabeprazole 20 mg versus omeprazole 20 mg or lansoprazole 15 mg over a period ranging from 4 weeks to 1 year. The strength of evidence was rated moderate.

Pantoprazole 40 mg and rabeprazole 20 mg provided significantly better symptom relief and healing of esophagitis at 8 weeks than omeprazole 20 mg in

patients 65 years of age and over. Esomeprazole 20 mg provided higher endoscopic remission rates than over-the-counter dosages of lansoprazole (15 mg) over 6 months.

## **Surgical Treatment Comparisons**

The inclusion of four additional RCTs and seven nonrandomized comparative studies in the present update did not alter the conclusions of the 2005 CER regarding the comparison of surgical treatments. No significant difference was found between laparoscopic total and partial fundoplication, laparoscopic fundoplication with and without division of short gastric vessels, or open total and partial fundoplication in production of symptom relief, quality-of-life improvement, or reduction of antisecretory medication use.

One RCT and five nonrandomized comparative studies examined laparoscopic total versus partial fundoplication. No consistent significant differences in GERD symptoms, diagnostic test results, or quality of life were observed between groups. The strength of evidence was rated moderate.

Two RCTs and two nonrandomized comparative studies examined laparoscopic fundoplication with vs. without division of short gastric vessel. No significant differences in medication use, GERD symptoms, or quality of life were found between groups. The strength of evidence was rated moderate.

Two RCTs and one nonrandomized comparative study examined laparoscopic versus open fundoplication. No significant differences in medication use, GERD symptoms, diagnostic test results, or quality of life were found between groups. The strength of evidence was rated moderate.

The current update also identified five cohort studies that provided data on the long-term effectiveness of surgery. Three of five studies found significant improvement in GERD symptoms at a mean followup of 5 years.

## **Endoscopic Treatment Comparisons**

The 2005 CER evaluated studies on four endoscopic procedures: the EndoCinch™ Suturing System, Stretta®, Enteryx™, and the NDO Plicator™. The

present report excluded Enteryx and the NDO Plicator, as they are no longer available in the United States. Stretta was removed from the market but reintroduced in 2010 by a separate manufacturer. Another device, EsophyX™, was commercialized after the original review.

No study directly comparing endoscopic treatments was identified for this update. However, a number of sham-controlled and cohort studies examining the effectiveness of the individual procedures were reviewed. The strength of evidence was rated insufficient.

Two sham-controlled studies and six cohort studies evaluated the effectiveness of EndoCinch. No consistent differences between EndoCinch and sham were observed. Significant improvements in heartburn, quality of life, and esophagitis healing were found in some, but not all, cohort studies. The strength of evidence was rated low.

Five cohort studies evaluated the effectiveness of EsophyX. The proportion of patients who were off PPIs at the end of followup ranged from 47 to 71 percent. Significant improvement of quality of life as measured by the GERD-HRQL scale was reported by two of the five studies. The strength of evidence was rated insufficient.

One RCT and seven cohort studies evaluated the effectiveness of Stretta. In the RCT, the proportion of patients who stopped or decreased PPI use was significantly greater in the Stretta group than the control group at 6 months, but the difference was no longer significant at 1 year. No significant differences in heartburn score, SF-36 and Global REFLUX-QUAL scores, 24-hour pH study measures, or proportion of patients with esophagitis were observed between the two arms. In contrast, the majority of cohort studies found significant improvements in GERD symptoms, quality of life, and medication use. The strength of evidence was rated insufficient.

### **Medical and Surgical Treatment of Extraesophageal Manifestation of GERD**

The 2005 CER did not address the effect of medical and surgical treatments for GERD with extraesophageal symptoms, including asthma, hoarseness/laryngitis, and chronic cough. Data for this evaluation were extracted

from existing systematic reviews and an updated literature review.

The systematic review and the update RCTs evaluating the effect of medical treatment did not find PPIs or H2RAs to be consistently more effective than placebo in improving asthma symptoms, nocturnal asthma, or use of asthma medications, or in objective indicators such as forced expiratory volume in 1 second (FEV1) and peak expiratory flow. The strength of evidence was rated insufficient.

Two of the six RCTs in the systematic review assessing the effect of PPI treatment on hoarseness found a significantly higher proportion of patients reporting resolution of hoarseness with PPI treatment than with placebo. The strength of evidence was rated low.

A meta-analysis included in the systematic review that evaluated the effect of PPI treatment on nonspecific dry cough of  $\geq 3$  weeks duration did not find a significant difference between PPIs and placebo in complete eradication of cough. A meta-analysis of data from four RCTs reporting mean cough scores at the end of the trial in 109 participants found a borderline significant improvement in the mean cough scores at the end of the trial with PPIs compared with placebo (-0.38 standardized mean difference units; 95-percent confidence interval [CI]: -0.77 to 0.00,  $P = 0.05$ ). However, another meta-analysis within the same systematic review showed a significant improvement in cough scores from baseline favoring PPIs compared with placebo (-0.39 standardized mean difference units; 95-percent CI: -0.71 to -0.08). The strength of evidence was rated low.

One existing systematic review of surgical cohort studies on the treatment of extraesophageal manifestations of GERD found that surgery improved cough and laryngeal symptoms more than it improved asthmatic symptoms: a better range of complete resolution in cough (13 to 96 percent in 11 out of 13 studies reporting outcome) and laryngeal symptoms (64 to 94 percent in 5 out of 8 studies reporting outcome) compared with asthma (0 to 64 percent in 3 out of 7 studies reporting outcome). However, there was a wide range of effect estimates. This is likely due to the considerable heterogeneity in the study populations, interventions, and outcome measures used to estimate the effects. The strength of evidence was rated insufficient.

## **Key Question 2. Is there evidence that effectiveness of medical, surgical, and newer forms of treatments varies for specific patient subgroups?**

The 2005 CER identified a number of patient characteristics and baseline clinical factors that may influence the effectiveness of medical, surgical, or endoscopic treatment. However, the quality and consistency of these primary data were mixed and the strength of the identified associations remained unclear. The studies included in this update were plagued with similar methodological issues.

One study reported that there was no significant difference in the effectiveness of medical vs. surgical treatment between patients with and without Barrett's esophagus. The strength of evidence was rated insufficient.

Six RCTs comparing different PPIs, or dosages and dosing regimens of PPIs, reported mixed findings regarding the impact of esophagitis severity at baseline on healing rates. Ten cohort studies investigated patient characteristics or clinical factors as modifying factors of medical treatment outcomes. Five cohort studies reported that sex was not a significant modifying factor of medical treatment outcomes. Eight cohort studies demonstrated that obesity, presence of baseline typical GERD symptoms, and more severe esophagitis at baseline were significantly associated with worse medical treatment outcomes. Three of five cohort studies on age found that older age was associated with improved symptom control. The strength of evidence was rated moderate.

One RCT found that preoperative esophageal motility did not have a significant impact on the effect of Nissen or Toupet laparoscopic fundoplication on dysphagia, recurrence of reflux, and 24-hour pH-metry and manometry outcomes. Thirty cohort studies showed that the following patient characteristics were inconsistently associated with worse surgical outcome: per-year increase in patient's age, morbid obesity, female sex, presence of baseline symptoms, and esophagitis and hiatal hernia more than 3 centimeters at baseline. The strength of evidence was rated low.

Three cohort studies investigated different modifying factors of endoscopic treatment. One cohort study did not find a significant difference between men and women in symptom improvement. Another study

showed that more patients with less severe esophagitis at baseline than patients with more severe esophagitis stopped PPI use. One study that compared technical procedure parameters observed a learning curve in the performance of a new endoscopic treatment device (EsophyX). The strength of evidence was rated low.

## **Key Question 3. What are the short-term and long-term adverse events associated with specific medical, surgical, and other newer forms of therapies for GERD?**

One RCT reported that the rate of serious adverse events was higher in patients who underwent fundoplication than in those who had medical treatment ( $P = 0.06$ ). Adverse events reported with PPIs included diarrhea, nausea or vomiting, abdominal pain, dyspepsia, and headache. These occurred in fewer than 2 percent of patients. Potential serious complications possibly associated with PPI use that were reported in the 2005 CER included enteric infections (*Campylobacter* and *Clostridium difficile*) and pneumonia. An increased risk of bone fracture is now added to this list, although the strength of association is uncertain. Common adverse events reported in patients who underwent fundoplication included bloating (up to 85 percent) and dysphagia (up to 23 percent). Reoperation rates ranged from 3 to 35 percent. Common adverse events after endoscopic suturing included chest or abdominal pain (up to 24 percent), bleeding (up to 11 percent), dysphagia (up to 50 percent), and bloating (up to 19 percent). None of these quantitative estimates are reliable because of the lack of a standard definition and uniform system of reporting. The strength of evidence was rated low.

## **Discussion**

The findings in this report are summarized in Table A. The present update found that many of the 2005 CER's original conclusions remain valid.

We found that laparoscopic fundoplication in patients whose GERD symptoms were already well controlled by medical treatments is at least as effective as continued medical treatment (and in some cases superior) in controlling GERD-related symptoms for the first 1 to 3 years following surgery. Laparoscopic fundoplication is also effective in helping patients to decrease the use of antireflux medications in the short term ( $\leq 1$  year), but the longer term effect is uncertain.

Predictors of surgical outcomes remain unclear, although a number of predictors have been evaluated.

For patients with GERD symptoms that cannot be adequately managed by standard medical treatments, two cohort studies without a control group found that GERD symptoms had significantly improved after laparoscopic fundoplication in more than 5 years of followup.

We did not identify sufficient evidence to conclude whether medical or surgical treatment was more effective in preventing long-term complications of GERD, such as the development of Barrett's esophagus or esophageal adenocarcinoma.

Our review also evaluated several new studies comparing specific medications. No consistent difference in symptom relief was observed between esomeprazole (20 to 40 mg), lansoprazole (15 to 30 mg), pantoprazole (20 to 40 mg), or rabeprazole (10 to 20 mg). There is some evidence that rabeprazole 10 mg may provide better symptom relief than esomeprazole 40 mg at 4 weeks, and pantoprazole 40 mg better relief than esomeprazole 40 mg over 24 weeks. Continuous daily intake of esomeprazole 20 mg or rabeprazole 20 mg appeared to provide better symptom control and quality of life than on-demand dosing over a period of 6 months. As for comparisons of different PPIs with over-the-counter dosages, pantoprazole 40 mg and rabeprazole 20 mg provided significantly better symptom relief and healing of esophagitis than omeprazole 20 mg at 8 weeks, and esomeprazole 20 mg provided better endoscopic remission rates than over-the-counter dosages of lansoprazole 15 mg at 6 months. While significant, the observed magnitude of these differences was generally small and the clinical relevance remains uncertain. Medical therapy has also been associated with potentially serious complications, which include an increased risk of enteric infections (including *Campylobacter* and *C. difficile*) and pneumonia. There may also be an increased risk of fractures associated with the use of PPIs.

As for the three available endoscopic procedures (EndoCinch™, Stretta™, EsophyX™) for the long-term management of GERD, effectiveness remains substantially uncertain. EndoCinch (suturing) and Stretta (radiofrequency ablation) were examined in the 2005 CER; EsophyX (endoscopic fundoplication) is a new introduction. While some clinical benefits were

observed in patients who had these procedures, the studies were generally small, of variable quality, and of short duration. In addition, all of these procedures have been associated with complications, including dysphagia, infection/fever, and bloating.

For the treatment of patients with extraesophageal manifestations of GERD symptoms, no consistent benefit could be attributed to either medication or surgery. Despite the focus on only those patients with asthma, chronic cough, or laryngeal symptoms, we surmise that the considerable clinical heterogeneity within these subgroups precluded the detection of a reliable effect, if one exists. The impact of GERD treatment may be limited in diseases or symptoms with complex etiologies, such as asthma, cough, and laryngeal complaints, as GERD may not be the cause of symptoms in study participants. The treatment population will include both responders (participants with reflux-triggered symptoms) and nonresponders (participants whose symptoms are not reflux triggered). This will dilute the overall treatment effect. Without any tests and biomarkers to identify GERD-related symptoms, it is not possible to accurately estimate the potential effects from anti-acid treatments.

## Implications for Future Research

- Longer term followup is necessary to determine the efficacy of laparoscopic fundoplication vs. medical treatments. One available study reviewed (the LOTUS trial) reported 3-year interim data; that study remains ongoing.
- Higher quality studies are necessary to determine the role and value of endoscopic procedures in the treatment of patients with GERD.
- Retrospective analyses exploring potential modifiers of treatment outcomes need to carefully consider confounders and perform appropriate adjustments.
- Comparative studies are needed to determine the optimal treatment(s) for patients who did not respond to medication.
- There is a lack of consensus among clinical practitioners around the issue of selecting the best diagnostic method to use, and its timing, in identifying acid and nonacid reflux during symptomatic episodes. The role of newer methods,

such as impedance monitoring, needs to be examined in terms of impact in the areas of diagnosis and treatment.

- There is a need to focus on less frequently reported outcomes of GERD such as refractory esophageal and GERD-related extraesophageal symptoms, as well as different dosing regimens such as twice-daily usage.
- The potential necessity for lifelong medical therapy raises the possibility of unidentified long-term safety issues. Therefore, systematic monitoring of long-term safety data on PPIs should be emphasized, as well as better baseline reporting of patient characteristics and potential confounders. Both could help ferret out any possible association between treatment and adverse events. Administrative databases can provide additional data for addressing long-term safety issues.
- Future studies on extraesophageal manifestations of GERD should target populations with reflux-triggered symptoms to assess the impact of treatment strategies. There is a need to develop tests or biomarkers that can correctly identify individuals with reflux-triggered symptoms.
- Although a systematic review of the literature examining potential drug interactions and adverse events associated with concomitant use of clopidogrel and PPIs was considered outside the scope of this update, we echo recent FDA statements urging health care providers and patients to carefully balance risks with indications for cotherapy.

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## Full Report

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**Table A. Strength of evidence on comparative effectiveness of treatments for GERD**

Key Question	Strength of Evidence	Summary, Conclusion, Comments
<b>Key Question 1. Evidence of comparative effectiveness of medical, surgical, and other newer forms of treatments for improving objective and subjective outcomes in patients with chronic GERD.</b>		
Medical vs. surgical treatments	Moderate	<ul style="list-style-type: none"> <li>• Based on analysis of 4 RCTs and 3 nonrandomized trials with varied:               <ul style="list-style-type: none"> <li>- Medical (PPI and/or H2RA) vs. surgical (open and/or laparoscopic fundoplication) interventions.</li> <li>- Outcomes of study (GERD symptoms, QoL, satisfaction, medication use, pH study results, remission rates).</li> <li>- Followup time period (1 to 12 years).</li> <li>- Study quality: 5 B-level (medium quality, medium likelihood of significant bias), 2 C-level (lowest quality, most likelihood of significant bias).</li> <li>- Dropout rate for studies with 7- to 12-year followup (33 to 58%).</li> </ul> </li> <li>• Patients who underwent antireflux fundoplication surgery experienced a greater improvement in heartburn and regurgitation at followup than patients who received medical treatment alone. Surgery was associated with an increased incidence of dysphagia and postprandial bloating. Surgery decreased, but did not eliminate, the use of antireflux medications at followup.</li> </ul>
Medical vs. endoscopic treatments	Insufficient	<ul style="list-style-type: none"> <li>• No study was identified for this comparison.</li> </ul>
Surgical vs. endoscopic treatments	Insufficient	<ul style="list-style-type: none"> <li>• One small nonrandomized study reported significantly better improvement in heartburn score and 24-hour pH study in the laparoscopic total fundoplication group compared with EndoCinch™. There were no significant differences in other outcomes.</li> </ul>
<b>Medical treatment comparisons:</b>		
Comparisons between PPIs and H2RAs	Moderate	<ul style="list-style-type: none"> <li>• PPIs (esomeprazole 20 mg taken once daily or on demand, lansoprazole 15 mg taken once daily, and omeprazole 20 mg taken once daily) were superior to H2RAs (ranitidine 150 mg and famotidine 20 mg, both taken twice daily) for resolution of GERD symptoms at 6 months.               <ul style="list-style-type: none"> <li>- Data from 1 RCT reported that lansoprazole 15 mg taken once daily was more effective than ranitidine 150 mg taken twice daily for healing of esophagitis at 1 year.</li> <li>- Data from 1 RCT reported that esomeprazole 20 mg taken once daily or on demand was more effective than ranitidine 150 mg taken twice daily for prevention of symptom relapse at 6 months.</li> <li>- Data from 2 RCTs reported that maintenance treatment (≥6 months) with PPIs (esomeprazole 20 mg taken once daily or on demand, lansoprazole 15 mg taken once daily) appears to be more efficacious than maintenance treatment with H2RA (ranitidine 150 mg taken twice daily) in symptom remission.</li> </ul> </li> </ul>

**Table A. Strength of evidence on comparative effectiveness of treatments for GERD (continued)**

Key Question	Strength of Evidence	Summary, Conclusion, Comments
<p><b>Key Question 1. Evidence of comparative effectiveness of medical, surgical, and other newer forms of treatments for improving objective and subjective outcomes in patients with chronic GERD (continued).</b></p>		
<p><b>Medical treatment comparisons (continued):</b></p>		
<p>Comparisons between PPIs and H2RAs (continued)</p>		<ul style="list-style-type: none"> <li>- Data from 1 RCT reported that maintenance-treatment patients taking lansoprazole 15 mg are likely to stay longer on their treatment than those taking ranitidine 150 mg twice daily and thus tend to have a longer median time until relapse of symptoms.</li> <li>• Studies with larger sample sizes suggested PPIs to be more efficacious than H2RAs with respect to GERD symptoms.</li> </ul>
<p>Comparisons between different PPIs</p>	<p>Moderate</p>	<ul style="list-style-type: none"> <li>• Based on analysis of 10 RCTs, no consistent difference in symptom relief and esophagitis healing rates was observed between esomeprazole (20 to 40 mg), lansoprazole (15 to 30 mg), pantoprazole (20 to 40 mg), or rabeprazole (10 to 20 mg) over a period ranging from 4 weeks to 6 months.</li> <li>- There is some evidence from individual studies that rabeprazole 10 mg may provide better symptom relief than esomeprazole 40 mg at 4 weeks, and also that pantoprazole 20 mg provides better control of heartburn than esomeprazole 40 mg over 24 weeks.</li> <li>- Results from 3 acute-treatment trials showed similar esophagitis healing rates for both pantoprazole 40 mg and esomeprazole 40 mg as demonstrated by endoscopy, with the rates increasing with trial duration from 8 to 12 weeks and being equivalent over 6 months.</li> </ul>
<p>Comparisons between different dosages and dosing regimens of PPIs</p>	<p>Moderate</p>	<ul style="list-style-type: none"> <li>• Based on analysis of 12 RCTs, there was no consistent difference in doses and dosing regimens with different PPIs in relation to symptom resolution and esophagitis healing rates.</li> <li>- One RCT reported that there was no significant difference in symptom resolution rates at 4 weeks between esomeprazole 20 mg taken once a day and esomeprazole 40 mg taken once a day.</li> <li>- One RCT reported that a significantly higher rate of healing of esophagitis at 4 weeks was observed with esomeprazole 40 mg once a day than with esomeprazole 20 mg once a day.</li> </ul>
<p>Comparisons between once-daily and on-demand dosing regimens of PPIs</p>	<p>Moderate</p>	<ul style="list-style-type: none"> <li>• Based on 3 RCTs, continuous daily intake of esomeprazole 20 mg appears to provide better symptom control and QoL than on-demand dosing over a period of 6 months.</li> </ul>

**Table A. Strength of evidence on comparative effectiveness of treatments for GERD (continued)**

Key Question	Strength of Evidence	Summary, Conclusion, Comments
<b>Key Question 1. Evidence of comparative effectiveness of medical, surgical, and other newer forms of treatments for improving objective and subjective outcomes in patients with chronic GERD (continued).</b>		
<b>Medical treatment comparisons (continued):</b>		
Comparisons between once-daily and on-demand dosing regimens of PPIs (continued)		<ul style="list-style-type: none"> <li>- One RCT reported that continuous daily intake of esomeprazole 20 mg appears to provide significantly better endoscopic remission compared with on-demand dosing over a period of 6 months.</li> <li>- Two RCTs reported that continuous daily intake of rabeprazole 20 mg appears to provide better symptom control and QoL than on-demand dosing over a period of 6 months.</li> </ul>
Comparisons between PPIs and over-the-counter dosages of PPIs approved for treatment of frequent heartburn (omeprazole 20 mg, lansoprazole 15 mg)	Moderate	<ul style="list-style-type: none"> <li>• Based on analysis of 8 RCTs, no consistent difference in symptom relief and esophagitis healing rates was observed between esomeprazole (20 to 40 mg), lansoprazole 30 mg, pantoprazole 40 mg, or rabeprazole 20 mg vs. omeprazole 20 mg or lansoprazole 15 mg over a period ranging from 4 weeks to 1 year.</li> <li>- One RCT reported that pantoprazole 40 mg and rabeprazole 20 mg provide significantly better symptom relief and healing of esophagitis than omeprazole 20 mg at 8 weeks.</li> <li>- One RCT reported that esomeprazole 20 mg provides higher endoscopic remission rates compared with lansoprazole 15 mg over 6 months.</li> </ul>
<b>Surgical treatment comparisons:</b>		
Total vs. partial fundoplication	Moderate	<ul style="list-style-type: none"> <li>• One RCT and 5 nonrandomized comparative studies compared laparoscopic total vs. partial fundoplication.</li> <li>• No consistent significant differences in GERD symptoms, diagnostic test results, or QoL were observed between groups.</li> </ul>
Fundoplication with vs. without division of short gastric vessel	Moderate	<ul style="list-style-type: none"> <li>• Two RCTs and 2 nonrandomized comparative studies compared laparoscopic fundoplication with vs. without division of short gastric vessel.</li> <li>• No significant differences in medication use, GERD symptoms, or QoL were found between groups.</li> </ul>

**Table A. Strength of evidence on comparative effectiveness of treatments for GERD (continued)**

Key Question	Strength of Evidence	Summary, Conclusion, Comments
<b>Key Question 1. Evidence of comparative effectiveness of medical, surgical, and other newer forms of treatments for improving objective and subjective outcomes in patients with chronic GERD (continued).</b>		
<b>Surgical treatment comparisons (continued):</b>		
Laparoscopic vs. open fundoplication	Moderate	<ul style="list-style-type: none"> <li>Two RCTs and 1 nonrandomized comparative study compared laparoscopic vs. open fundoplication.</li> <li>No significant differences in medication use, GERD symptoms, diagnostic test results, or QoL were found between groups.</li> </ul>
<b>Endoscopic treatments:</b>		
Comparison between endoscopic treatments	Insufficient	<ul style="list-style-type: none"> <li>No direct comparisons between the different endoscopic treatments were identified.</li> </ul>
EndoCinch™	Low	<ul style="list-style-type: none"> <li>Two sham-controlled studies and 6 noncomparative cohort studies evaluated the effectiveness of EndoCinch™.</li> <li>No consistent differences between EndoCinch™ and sham were reported.</li> <li>Significant improvements in heartburn, QoL, and esophagitis healing were found in some but not all cohort studies.</li> </ul>
EsophyX™	Insufficient	<ul style="list-style-type: none"> <li>Five small cohort studies evaluated the effectiveness of EsophyX™.</li> <li>The reported proportion of patients who were off PPIs at the end of the followup period ranged from 47 to 71%.</li> <li>Significant improvement of QoL as measured by the GERD-HRQL scale was reported by 2 of 5 studies.</li> </ul>
Stretta™	Insufficient	<ul style="list-style-type: none"> <li>One sham-controlled study and 7 noncomparative cohort studies evaluated Stretta™.</li> <li>In the RCT, the proportion of patients who stopped or decreased PPI use was significantly greater in the Stretta™ group than the control group at 6 months (but it was not significant at 1 year). No significant differences in heartburn symptoms, QoL, acid exposure, and esophagitis outcomes were found.</li> <li>The majority of cohort studies found significant improvements in GERD symptoms, QoL, and medication use.</li> </ul>

**Table A. Strength of evidence on comparative effectiveness of treatments for GERD (continued)**

Key Question	Strength of Evidence	Summary, Conclusion, Comments
<p><b>Key Question 1. Evidence of comparative effectiveness of medical, surgical, and other newer forms of treatments for improving objective and subjective outcomes in patients with chronic GERD (continued).</b></p>		
<p><b>Medical treatment for extraesophageal symptoms:</b></p>		
Asthma	Insufficient	<ul style="list-style-type: none"> <li>A systematic review did not find consistent effects of PPIs or H2RAs (vs. placebo) in improving asthma symptoms, nocturnal asthma, use of asthma medications, or FEV1.</li> <li>- Eight primary RCTs reviewed in this update also reported inconsistent effects. Omeprazole 20 mg (combined with domperidone 10 mg) or esomeprazole 40 mg showed an improvement in peak expiratory flow rate. Lansoprazole 30 mg or pantoprazole 40 mg did not show an improvement in asthma symptoms or lung function tests. Rabeprazole 20 mg twice a day improved respiratory symptoms during exercise in patients with exercise-induced asthma compared to a placebo, but not QoL or pulmonary function measures.</li> </ul>
Hoarseness	Low	<ul style="list-style-type: none"> <li>Four of 6 RCTs did not find a significant difference in resolution of hoarseness between PPI and placebo.</li> </ul>
Chronic cough	Low	<ul style="list-style-type: none"> <li>Meta-analysis of 4 studies (191 participants) showed no significant difference in total resolution of cough between PPIs and placebo (odds ratio, 0.46; 95% CI: 0.19 to 1.15). A meta-analysis of data from 4 RCTs reporting mean cough scores at the end of the trial in 109 participants found a borderline significant improvement in the mean cough scores at the end of the trial with PPIs compared with placebo (0.38 standardized mean difference units; 95% CI: 0.77 to 0.00, P=0.05). Another meta-analysis examining improvement in cough scores in the same systematic review, however, showed a significant improvement in cough scores from baseline favoring PPIs compared with placebo (0.39 standardized mean difference units; 95% CI: 0.71 to -0.08).</li> </ul>
Surgical treatment for extraesophageal symptoms	Insufficient	<ul style="list-style-type: none"> <li>All of the data on surgical treatment are from cohort studies, with wide variation in population treated, severity of the underlying GERD and its extraesophageal manifestation, outcome measures, surgical interventions, and intensity and duration of followup.</li> <li>The majority of the cohort studies found that surgery may help improve cough and laryngeal symptoms more than asthma, but there is a wide range of effect estimates in these studies.</li> </ul>

**Table A. Strength of evidence on comparative effectiveness of treatments for GERD (continued)**

Key Question	Strength of Evidence	Summary, Conclusion, Comments
<b>Key Question 2. Evidence that the effectiveness of medical, surgical, and newer forms of treatments vary for specific patient subgroups.</b>		
Factors that influenced the comparative effectiveness of surgical vs. medical treatment	Insufficient	<ul style="list-style-type: none"> <li>• One study found that there was no significant difference in the effectiveness of medical vs. surgical treatment between patients with and without Barrett’s esophagus.</li> </ul>
Factors that influenced the outcome of medical therapy	Moderate	<ul style="list-style-type: none"> <li>• Six RCTs comparing different PPIs, or dosages and dosing regimens of PPIs, showed mixed findings regarding the impact of esophagitis severity at baseline on healing rates.</li> <li>• Ten cohort studies examined patient characteristics or clinical factors as modifying factors of medical treatment outcomes.               <ul style="list-style-type: none"> <li>- Sex was not a significant modifying factor of medical treatment outcomes.</li> <li>- Obesity, presence of baseline typical GERD symptoms, and more severe esophagitis were significantly associated with worse medical treatment outcomes.</li> <li>- The associations between age and medical treatment outcomes were inconsistent.</li> </ul> </li> </ul>
Factors that influenced the outcome of surgical treatment	Low	<ul style="list-style-type: none"> <li>• One RCT found that preoperative esophageal motility did not significantly impact the effect of laparoscopic fundoplication on dysphagia, recurrence of reflux, and acid exposure and manometry outcomes.</li> <li>• Thirty cohort studies showed that the following were inconsistently associated with worse surgical outcome: per-year increase in patient’s age, morbid obesity, female sex, presence of baseline symptoms or esophagitis, and hiatal hernia greater than 3 cm at baseline.</li> </ul>
Factors that influenced the outcome of endoscopic treatment	Low	<ul style="list-style-type: none"> <li>• Three cohort studies examined different modifying factors of endoscopic treatment:               <ul style="list-style-type: none"> <li>- One study did not find a significant difference between men and women in symptom improvement.</li> <li>- One study found that more patients with less severe esophagitis at baseline than patients with more severe esophagitis stopped PPI use.</li> <li>- One study that compared technical procedure parameters observed a learning curve in performance of a new endoscopic treatment device (EsophyX).</li> </ul> </li> </ul>

**Table A. Strength of evidence on comparative effectiveness of treatments for GERD (continued)**

Key Question	Strength of Evidence	Summary, Conclusion, Comments
<b>Key Question 3. Short-term and long-term adverse events associated with specific medical, surgical, and newer forms of therapies for GERD.</b>		
Adverse events	Low	<ul style="list-style-type: none"> <li>• None of the quantitative estimates of adverse events are reliable because of a lack of standard definition and uniform system of reporting.</li> <li>• One RCT reported that the rate of serious adverse events was higher with surgery than with medical treatment (P=0.06).</li> <li>• Potential serious complications possibly associated with PPIs included not only enteric infections and pneumonia (reported in 2005 review) but also an increased risk of bone fracture.</li> <li>• Common adverse events reported in patients who underwent fundoplication included bloating and dysphagia.</li> <li>• Common adverse events after endoscopic suturing included chest or abdominal pain, bleeding, dysphagia, and bloating.</li> </ul>

**Notes:** This report is an update to a 2005 Comparative Effectiveness Review: Ip S, Bonis P, Tatsioni A, et al. Comparative Effectiveness of Management Strategies for Gastroesophageal Reflux Disease. Comparative Effectiveness Review No. 1. (Prepared by Tufts-New England Medical Center Evidence-based Practice Center under Contract No. 290-02-0022.) Rockville, MD: Agency for Healthcare Research and Quality. December 2005. Available at: [www.effectivehealthcare.ahrq.gov/reports/final.cfm](http://www.effectivehealthcare.ahrq.gov/reports/final.cfm).

CI = confidence interval; GERD = gastroesophageal reflux disease; H2RA= histamine type 2 receptor antagonist; PPI = proton pump inhibitor; QoL = quality of life; RCT = randomized controlled trial.

**Key Question 1:** What is the evidence of the comparative effectiveness of medical, surgical, and other newer forms of treatments for improving objective and subjective outcomes in patients with chronic gastroesophageal reflux disease? Is there evidence that effectiveness varies by specific technique, procedure, or medication? Objective outcomes addressed include esophagitis healing, ambulatory pH, other indicators of reflux, need for medication, health care utilization, and incidence of esophageal stricture, Barrett's esophagus, or esophageal adenocarcinoma. Subjective outcomes include symptom frequency and severity, sleep/productivity, and overall quality of life.

**Key Question 2:** Is there evidence that effectiveness of medical, surgical, and newer forms of treatments varies for specific patient subgroups? What are the characteristics of patients who have undergone these therapies, including the nature of previous medical therapy, severity of symptoms, age, sex, weight, and other demographic and medical factors? What are the provider characteristics for procedures, including provider volume and setting (e.g., academic vs. community)?

**Key Question 3:** What are the short-term and long-term adverse events associated with specific medical, surgical, and other newer forms of therapies for GERD? Does the incidence of adverse events vary with duration of followup, specific surgical intervention, or patient characteristics?



