Comparative Effectiveness Review
Number 1

Comparative Effectiveness of Management Strategies For Gastroesophageal Reflux Disease

U.S. Department of Health and Human Services
Agency for Healthcare Research and Quality
www.ahrq.gov

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Prepared for:
Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
540 Gaither Road
Rockville, MD 20850
www.ahrq.gov

Contract No. 290-02-0022

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AHRQ Publication No. 06-EHC003-EF
December 2005

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Suggested citation:
Ip S, Bonis P, Tatsioni A, Raman G, Chew P, Kupelnick B, Fu L, DeVine D, Lau J. Comparative Effectiveness of Management Strategies for Gastroesophageal Reflux Disease. Evidence Report/Technology Assessment 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.

Preface

The Agency for Healthcare Research and Quality (AHRQ) conducts the Effective Health Care Program as part of its mission to organize knowledge and make it available to inform decisions about health care. As part of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Congress directed AHRQ to conduct and support research on the comparative outcomes, clinical effectiveness, and appropriateness of pharmaceuticals, devices, and health care services to meet the needs of Medicare, Medicaid, and the State Children's Health Insurance Program (SCHIP).

AHRQ has an already-established network of Evidence-based Practice Centers (EPCs) that produce Evidence Reports/Technology Assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care. The EPCs now lend their expertise to the Effective Health Care Program by conducting Comparative Effectiveness Reviews of medications, devices, and other relevant interventions, including strategies for how these items and services can best be organized, managed, and delivered.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews are useful because they define the strengths and limits of the evidence, clarifying whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about systematic reviews, see www.effectivehealthcare.ahrq.gov/purpose.

AHRQ expects that Comparative Effectiveness Reviews will be helpful not only to government programs but also to individual health plans, providers, and purchasers, and to the health care system as a whole. In addition, AHRQ is committed to presenting information in different formats so that the greatest range of decisionmakers possible (and that includes consumers who make decisions about their own and their family's health) can benefit from the evidence.

Work under this program is transparent and user driven. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an e-mail list to learn about new program products and opportunities for input.

Acknowledgments

We would like to acknowledge with appreciation the following members of the Technical Expert Panel for their advice and consultation to the Evidence-based Practice Center during preparation of this report.

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Executive Summary

Background

Gastroesophageal reflux disease (GERD), defined as weekly heartburn and/or acid regurgitation, is one of the most common health conditions affecting older Americans. Direct costs attributable to GERD were estimated to be $10 billion in the United States in 2000.

Some patients have frequent, severe symptoms requiring long-term regular use of antireflux medications. For these patients, who have chronic GERD, most authorities consider the goals of therapy to be improvement in symptoms and quality of life, healing of 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 upon the severity of symptoms and clinical 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 management strategies. While surgery has been considered to provide an alternative to permanent use of antisecretory medications, long-term followup of a landmark randomized controlled trial comparing medications with surgery found that approximately two-thirds of surgically treated patients still required regular antireflux medications. Furthermore, while advocates of surgery continue to suggest that it might be more effective than medical therapy for prevention of Barrett's esophagus and esophageal cancer, evidence supporting this assertion has been inconclusive.

A challenge in treating GERD is that neither improvement in symptoms nor reduction in the need for antisecretory medications has consistently correlated with objective measures such as normalization of esophageal pH exposure or healing of esophagitis. The endoscopic approaches, in particular, have drawn into focus the disparities that can exist among various objectives in treating GERD.

This report examines alternatives for managing the chronic symptoms of uncomplicated GERD in patients who may require long-term treatment. It summarizes the available evidence comparing the efficacy and safety of medical, surgical, and endoscopic interventions in the treatment of chronic GERD, particularly after long-term followup. Questions addressed in this report are:

1. What is the evidence of the comparative effectiveness of medical, surgical, and endoscopic treatments for improving objective and subjective outcomes in patients with chronic GERD?

2. Is there evidence that effectiveness of medical, surgical, and endoscopic treatments varies for specific patient subgroups?

3. What are the short- and long-term adverse effects associated with specific medical, surgical, and endoscopic therapies for GERD?

A summary of the findings is shown in Table A.

Conclusions

Comparison of medical treatments with surgery

- Medical therapy with PPIs and surgery (fundoplication) appeared to be similarly effective for improving symptoms and decreasing esophageal acid exposure. However, only a few studies directly compared these approaches and the total number of patients studied was small.

- In the studies reviewed for this report, from 10 percent to 65 percent of surgical patients still required medications.

- The body of evidence supporting the above conclusion was based on three head-to-head comparative trials. The studies had methodological flaws making them susceptible to some bias, but not sufficient to invalidate the results (Grade B).

- The limited data available did not support a significant benefit of fundoplication compared with medical therapy for preventing Barrett's esophagus or esophageal adenocarcinoma.

Comparison of surgery with endoscopic procedures

- Of the three nonrandomized studies that compared an endoscopic procedure with laparoscopic fundoplication in patients with GERD documented by pH or endoscopy, the longest followup was 8 months, and all three studies had significant bias that may invalidate the results (Grade C).

- Two studies reported that more patients treated with laparoscopic fundoplication were satisfied with their results compared with those who had EndoCinch™. One of these studies and a study of Stretta® also found less need for PPIs in patients who had fundoplication.

Comparison of medical treatments with endoscopic procedures

- There was no head-to-head comparison of medical treatments with endoscopic treatments.

Comparison of medical treatments (between classes and within class)

- PPIs were superior to H2RAs in resolution of GERD symptoms at 4 weeks and healing of esophagitis at 8 weeks.

- The above conclusion was based on three recent meta-analyses of randomized controlled trials comparing one medication to another. These analyses had minimal bias and their results are considered valid (Grade A).

- There was no difference between omeprazole, lansoprazole, pantoprazole, and rabeprazole for relief of symptoms at 8 weeks.

- No significant difference was found in the comparisons of esomeprazole 40 mg with lansoprazole 30 mg or pantoprazole 40 mg for relief of symptoms at 4 weeks. Similarly, there was no difference in the comparison of esomeprazole 20 mg with omeprazole 20 mg in relief of symptoms at 4 weeks. When esomeprazole 40 mg was compared with omeprazole 20 mg, there was a significant difference in favor of esomeprazole for relief of symptoms at 4 weeks.

- For maintenance medical treatment of 6 months to 1 year, PPIs taken at a standard dose (as suggested by the manufacturers' prescribing information) were more effective than those taken at a lower dose (usually one-half of the standard dose) in preventing relapse of symptoms.

Comparison of surgical techniques

- Laparoscopic fundoplication was as effective as open fundoplication for relieving heartburn and regurgitation, improving quality of life, and decreasing use of antisecretory medications. Almost 90 percent of patients who were followed for 5 or more years in both surgical arms reported improvement in symptoms.

- The above conclusion was based on one fair-quality (Grade B) randomized controlled trial and one poor-quality (Grade C) nonrandomized study.

Comparison of endoscopic treatment with sham

- Compared to sham, Stretta™ was more effective in improving symptoms of reflux and improving quality of life at 6 months and was associated with a decrease in the need for antisecretory medications. Improvement of esophageal pH exposure compared with sham could not be demonstrated for Stretta™.

- This one study on Stretta™ versus sham had a small number of patients and short duration of followup (Grade B).

Patient characteristics associated with outcomes of medical, surgical, and endoscopic treatments

- Patients on maintenance antireflux medications may have higher rates of esophagitis if they have any of the following factors: increased severity of esophagitis at baseline (pretreatment), younger age, and moderate to severe regurgitation.

- There is no substantial evidence to support a difference in surgical outcome based on age, preoperative presence or severity of esophagitis, lower esophageal sphincter incompetence, or esophageal body hypomotility.

- Patients treated surgically who have a history of psychiatric disorders may have worse symptom and satisfaction outcomes than those without a significant psychiatric history.

Adverse events associated with medical, surgical, and endoscopic treatments

- The quality of reporting of adverse events and complications was inconsistent across studies. None of the studies used an acceptable standard or scale for defining severity.

- Higher adverse event rates were described for PPIs than for H2RAs or placebo. The most commonly cited events for PPIs and H2RAs were headache, diarrhea, and abdominal pain.

- The most commonly reported complications occurring intraoperatively or within 30 days after open fundoplication were the need for splenectomy, dysphagia, inability to belch, and inability to vomit. The most commonly reported complications for laparoscopic procedures were gastric or esophageal injury or perforation, splenic injury or splenectomy, pneumothorax, bleeding, pneumonia, fever, wound infections, bloating, and dysphagia. Major complications were generally reported at very low rates.

- Frequently reported complications for endoscopic treatments–intraoperatively or within 30 days after the procedure–included chest or retrosternal pain, gastrointestinal injury, bleeding, and short-term dysphagia. The frequency and types of complications varied with the different procedures. Serious complications, including fatalities, have also been described.

Remaining Issues

- More studies are needed to inform how patients with GERD should be managed based upon patient characteristics or response to previous therapy. Additional information is needed to select patients for specific testing for GERD and to determine how treatment should be guided by the results of testing.

- Randomized controlled trials of laparoscopic fundoplication versus PPIs with long-term followup are needed to ascertain the relative benefits and harms of each approach and whether certain subgroups are better served with one or the other alternative.

- Data on comparative endoscopic treatments with continued (or intensified) use of PPIs are needed to better understand their efficacy compared to an established standard.

- More efficacy and safety data on new endoscopic approaches tested against a sham procedure with adequate followup are needed.

To minimize patients' exposure to life-long medications, methods need to be developed to identify patients who do not need long-term antisecretory medications. Long-term studies are needed to assess the risks associated with acid suppression on the development of pneumonia and enteric infections, and to assess the consequences of long-term hypergastrinemia.

Table A. Summary of Comparative Data on Treatments of GERD

Key Question 1: comparisons	Quality of evidence	Summary/conclusion/comments
Medical vs. surgical	Acceptable	• There were 3 head-to-head comparisons. Baseline characteristics of populations varied across studies. None of the trials enrolled patients whose symptoms were poorly controlled with medical therapy. • Open fundoplication vs. non-PPIs in patients with complicated GERD: At 10-year followup (PPIs were used by most patients in a nonstandardized fashion during the followup period), surgical patients had better symptom score when taken off antireflux medications compared to medical patients; less bodily pain; no difference in esophagitis grade; 2/3 of surgical patients were on medications. (*Comment: observational and comparative surgical studies reported 90% of patients were off antireflux medications at ≥ 5 years followup.*) • Open fundoplication vs. omeprazole in patients with GERD but without complications: At 5-year followup, there was less treatment failure in surgical group, but no significant difference if dose of omeprazole was adjusted in cases of relapse. • Laparoscopic fundoplication vs. PPIs in patients who were dependent on PPIs: At 1-year followup, mean GI symptom score was better in the surgical group; no objective findings reported for 1-year followup. (*Comment: observational data reported 80-90% improvement in symptoms at ≥ 5 years followup.*) • Conclusion: Fundoplication was as effective as medical treatments for relief of GERD symptoms and decreasing esophageal acid exposure, at least for up to 2 years of followup. There was no difference in the outcome of esophagitis. The proportion of patients freed from long-term antireflux medications is unclear.
Surgical vs. endoscopic	Weak	• There was no head-to-head comparison for the 2 treatments. • In nonrandomized studies, more patients treated with laparoscopic fundoplication were satisfied with their results compared with those who had endoscopic therapies.
Medical vs. endoscopic	Not applicable	• No comparative data were available.

Key Question 2: modifying factors	Quality of evidence	Summary/conclusion/comments
	Weak	• Data largely were from observational studies. • Higher rate of esophagitis relapse while on maintenance medical treatment was associated with: increased pretreatment severity of esophagitis, younger age; moderate/severe regurgitation (1 meta-analysis). • Decreased lower esophageal sphincter pressure was associated with less likelihood of stopping all medications (2 studies). • Preop good response to medications was associated with good symptom outcomes in 3 surgical studies. • Psychiatric history was associated with worse outcomes (3 studies: increased symptoms, increased dysphagia, or increased surgical failure). • In endoscopic studies, age <48-50 years was associated with decreased PPI dosage (1 study) and decreased acid exposure (1 study).

Table A. Summary of Comparative Data on Treatments of GERD

Key Question 3: adverse events	Quality of evidence	Summary/conclusion/comments
	Weak	• Open fundoplication vs. non-PPI treatment at 10-year followup (1 RCT): more gas-bloat syndrome in surgical group; no difference in abdominal girth, fullness, inability to belch and to vomit • Open fundoplication vs. omeprazole at 3-year followup (1 RCT): in surgical group, more complaints of rectal flatus, inability to belch and to vomit • Laparoscopic fundoplication vs. PPIs (1 RCT): no direct comparative adverse event data reported in this study; in surgical group, 3.7% intraoperative complications (splenic, esophageal, and liver injury), 5.5% early postoperative complications (wrap migrations related to forceful vomiting, respiratory tract infections, inclusion of nasogastric tube by a wrap suture, gastric necrosis); there were no deaths in the surgical group; 4.5% developed dysphagia that persisted for > 3 months after surgery; adverse event data for PPIs not presented in this study. • There are no direct comparative adverse event data for endoscopic vs. laparoscopic procedures. • Laparoscopic fundoplication vs. open fundoplication at 5-year followup (1 RCT): difficulty with belching and increased flatulence were still dominant side effects; no differences between the 2 groups. • From 2 meta-analyses, PPIs reported more adverse events compared with H2RA or placebo; headache, diarrhea, and abdominal pain were the most common.

Abbreviations: GERD = gastroesophageal reflux disease, GI = gastrointestinal, H2RA = histamine type 2 receptor antagonist, PPI = proton pump inhibitor, RCT = randomized controlled trial.

Chapter 1. Introduction

Gastroesophageal reflux disease (GERD) has been defined as symptoms or mucosal damage caused by the abnormal reflux of gastric contents into the esophagus.[1] A systematic review of 15 epidemiologic studies estimated an overall prevalence of 10 to 20 percent in the Western world when GERD was defined as at least weekly heartburn and/or acid regurgitation.[2] Direct costs attributable to GERD were estimated to be $10 billion in the United States in 2000.[3]

Optimal strategies for evaluating patients suspected of having GERD remain unclear. National guidelines endorse an initial trial of empirical therapy in patients with symptoms suggesting uncomplicated GERD, reserving endoscopy for those with risk factors for Barrett's esophagus or certain alarm features such as dysphagia.[1] However, a variety of upper digestive symptoms have features that may resemble GERD while several disorders (such as asthma, laryngitis, and chronic cough) have been attributed to GERD even in patients who do not have heartburn or regurgitation. Furthermore, a clinical response to an empiric trial with proton pump inhibitors (PPIs) does not confidently establish the diagnosis of GERD when GERD is defined using objective reference standards.[4]

Most authorities consider the goals of therapy to be improvement in symptoms and quality of life, healing of 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.[5] Among patients treated medically, there are several approaches that are used depending in part upon the severity of symptoms and clinical response including lifestyle modifications, intermittent, periodic, or continuous use of prescription or over-the-counter histamine type 2 receptor antagonists (H2RAs) and PPIs. Objective criteria for how these approaches should be used (and their cost-effectiveness) have not been defined clearly.

The availability of endoscopic and surgical treatments for GERD has further complicated management strategies. The endoscopic approaches in particular have drawn into focus the disparities that can exist among various objectives in treating GERD. The endpoints of endoscopic therapies have included changes in symptoms, quality of life, healing of esophagitis, improvement in esophageal pH studies, and reduction in the need for maintenance antisecretory treatment (particularly PPIs). While ideally these endpoints would occur concordantly, improvement in symptoms or a reduction in the need for antisecretory medications have not consistently correlated with objective measures such as normalization of esophageal pH[6] exposure or healing of esophagitis.[7] Furthermore, while a reduction in the required daily dose of a PPI may have favorable economic consequences, the benefit (from the perspective of a patient who continues to require daily antisecretory therapy) is uncertain. The durability of benefit is also unclear.

Similarly, while surgery has been considered to provide an alternative to permanent use of antisecretory medications, long-term follow-up of a landmark randomized controlled trial (RCT) comparing medical with surgical approaches found that approximately two-thirds of surgically treated patients required regular antireflux medications.[8] In addition, while advocates of surgery continue to suggest that it might be more effective than medical therapy for prevention of Barrett's esophagus and esophageal cancer, evidence supporting this assertion has been inconclusive. Whether surgery has a role in patients whose symptoms are refractory to medical

therapy continues to be controversial, particularly since consensus has not been achieved on the definition of “refractory” GERD.

Treatment with PPIs is considered to be the standard against which other approaches to GERD can be compared. However, while PPIs have proven to be generally safe, there continues to be lingering concerns related to safety with life-long use. Adverse effects reported with PPIs include a possible increase in the risk of enteric infections[9,10] and community acquired pneumonia.[11] Also unsettled are concerns related to prolonged hypergastrinemia[12] and atrophic gastritis in the setting of Helicobacter pylori infection.[13,14]

Scope and Key Questions

This report summarizes the available evidence comparing the efficacy and safety of medical, surgical, and endoscopic approaches in the treatment of chronic GERD, particularly after long-term follow-up. Key questions addressed in this report are:

1. What is the evidence of the comparative effectiveness of medical, surgical, and endoscopic, treatments for improving objective and subjective outcomes in patients with chronic GERD? Is there evidence that effectiveness varies by specific techniques/procedures or medications? Objective outcomes include esophagitis healing, ambulatory pH, other indicators of reflux, need for medication, healthcare 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.

2. Is there evidence that effectiveness of medical, surgical, and endoscopic treatments vary 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, other demographic and medical factors, or by specific patient subgroups, and provider characteristics for procedures including provider volume and setting (eg, academic versus community)?

3. What are the short- and long-term adverse effects associated with specific medical, surgical, and endoscopic therapies for GERD? Does the incidence of adverse effects vary with duration of follow-up, specific surgical intervention, or patient characteristics?

The following is a brief description of the participants, interventions, outcome measures, and the types of studies reviewed in this report. A detailed discussion of the study selection criteria is provided in the Methods section.

Types of participants

The population of interest for this report is adults with chronic GERD. Because of the variability in definitions of GERD, this report includes population with a diagnosis of GERD

based on any commonly used criteria including an abnormal ambulatory pH study, endoscopic esophagitis, typical symptoms of GERD (heartburn or regurgitation), a response to a therapeutic trial of a proton pump inhibitor, and other definitions.

Types of interventions

The interventions of interest are medical, surgical, and endoscopic treatments. Medical treatments include PPIs or H2RAs. Surgical treatments include total or partial fundoplication, either as an open or as a laparoscopic procedure. Endoscopic treatments include endoscopic suturing, radiofrequency energy delivery to the gastroesophageal junction, or implantation of inert polymers.

Types of outcome measures

Subjective outcomes of interest are GERD-related symptoms and patient's quality of life (QOL). Objective outcomes include esophageal acid exposure, status of esophagitis, lower esophageal sphincter competence, use of antireflux medications, incidence of Barrett's esophagus and esophageal adenocarcinoma.

Types of studies

For comparing efficacy between a medical treatment and a surgical procedure, we retrieved all randomized and non-randomized comparative studies. For interclass and intraclass comparison of medical treatments, we used information from recent meta-analyses. For comparison of surgical techniques, we included randomized and non-randomized comparative studies. To supplement data on long-term efficacy of surgery, we also included surgical cohort studies. For endoscopic procedures, we used both comparative and cohort studies.

Chapter 2. Methods

Technical Expert Panel

This report on the management strategies for GERD is based on a systematic review of the literature. The Tufts-NEMC EPC held teleconferences with a Technical Expert Panel (TEP) formed for this project. The TEP served in an advisory capacity for this report, helping to refine key questions, identify important issues, and define parameters for the review of evidence.

Analytic Framework

We applied the analytic framework depicted in Figure 1 to answer the key questions in the evaluation of the treatment modalities for GERD. This framework addressed relevant subjective and objective outcomes. It also examined clinical factors that affected treatment outcomes. While evidence from high quality randomized controlled trials was preferred, when there was a paucity of data or when they were unavailable, non-randomized and uncontrolled studies were used to augment the evidence.

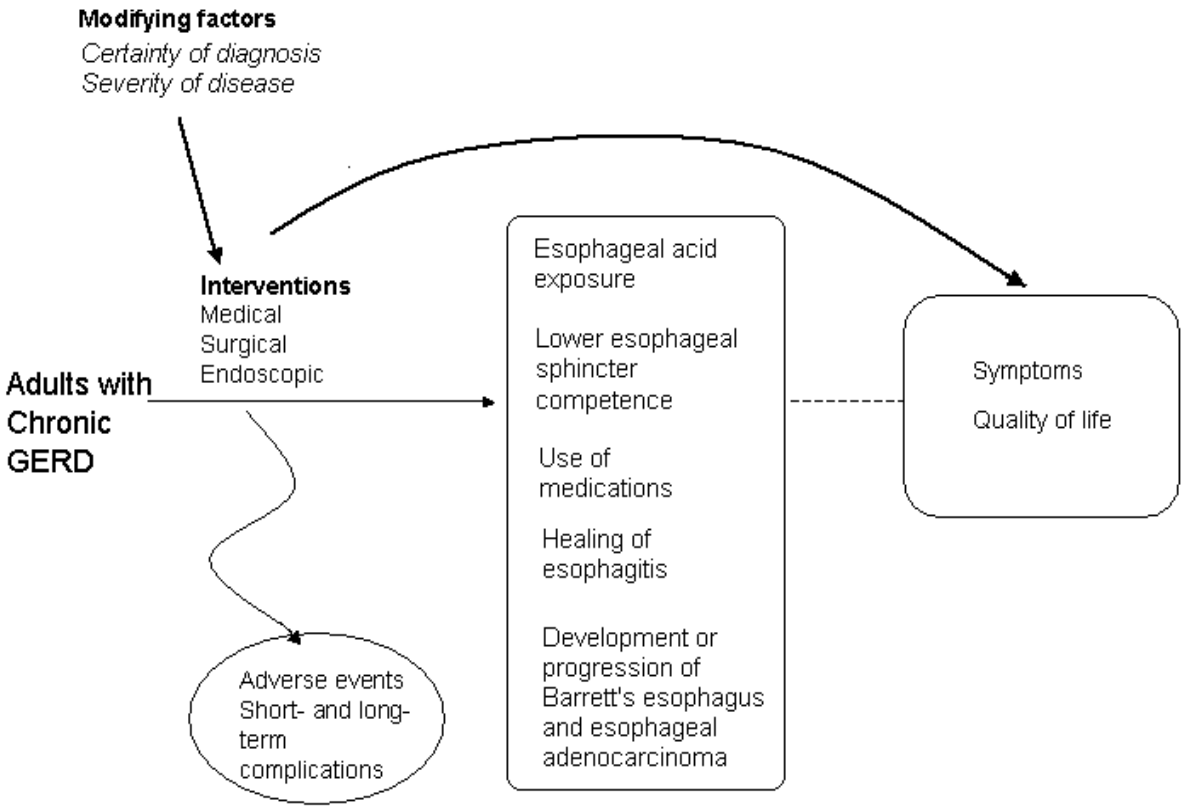

Figure 1. Analytic framework for evaluating the effectiveness and safety of treatments for chronic GERD. Arrows depict studies sought to address key questions formulated in this report.

Search Strategy

A comprehensive search of the scientific literature was conducted to identify relevant studies addressing the key questions. Results from previously conducted meta-analyses and systematic reviews on these topics were sought and used where appropriate and updated when necessary. When this evidence was not adequate, systematic reviews on the specific topics were conducted. Evidence tables of study characteristics and results were compiled, and the methodological quality of the studies was appraised.

We searched MEDLINE (1966-February 15, 2005) for English language studies of adult humans to identify articles relevant to each key question. We conducted a supplemental search of the Cochrane Database of Systematic Reviews on March 29, 2005. We also searched reference lists of all review articles. In electronic searches, we combined terms for gastroesophageal reflux and relevant research designs (see Appendix A for complete search strategy). We invited TEP members to provide additional citations. Because the literature on endoscopic therapies was evolving rapidly, we supplemented our data on endoscopic therapy with the latest information on additional and ongoing studies provided by technical experts. Additional studies recommended by our technical experts were included if they were relevant and were published prior to June 30th, 2005. We included one study that reported five-year comparative data of different doses of rabeprazole and placebo that was published after our literature review. We also asked peer reviewers to provide relevant unpublished data that could be made publicly available. We did not search systematically for unpublished data.

We compared lists of authors and study centers and contacted authors as needed to identify reports that included patients who we suspected had been described elsewhere. When such reports were identified, they were considered together to identify study features as completely as possible but patients were analyzed only once. Such reports are identified in the evidence tables.

Study Selection

We assessed titles and/or abstracts of citations identified from literature searches 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 reapplying the inclusion criteria. Results published only in abstract form are generally not included in our reviews because adequate information is not available to assess the validity of the data.

Population and condition of interest

According to a national consensus statement, GERD has been defined as symptoms or mucosal damage produced by the abnormal reflux of gastric contents into the esophagus.[1] GERD is considered a chronic and recurrent disease. There are several potential complications related to GERD including esophageal strictures, Barrett's esophagus, and esophageal adenocarcinoma, which together are considered to represent "complicated" GERD.

There is substantial variability how GERD has been defined in different reports. To be as inclusive as possible, we considered studies that based the diagnosis of GERD on any commonly used criteria including an abnormal ambulatory pH study while off medications, endoscopy showing esophagitis* in patients with symptoms suggestive of GERD, typical symptoms of GERD (heartburn or regurgitation), a response to a therapeutic trial of a proton pump inhibitor, and other definitions, such as ICD-9 codes. The stringency of the diagnosis was recorded for each study.

We included comparative, randomized and non-randomized, and cohort studies of adults (≥18 years) with chronic GERD using the above definitions. Some studies did not explicitly state that they had recruited only adult patients; they were accepted provided that the median age for the population was at least 40. We also included comparative and cohort studies that specifically examined the incidence of Barrett's esophagus or esophageal adenocarcinoma in patients with complicated GERD.

We excluded studies that focused exclusively on patients with extra-esophageal manifestations of GERD (eg, reflux laryngitis, asthma), those with post-surgical 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, infectious, pill, or chemical burn esophagitis.

Intervention of interest

For studies on medical treatment, we included meta-analyses of RCTs, in which a PPI was used for treatment of acute symptoms or for maintenance therapy. Acute treatment is considered the short-term therapy – usually up to 8 weeks or, in some trials, 12 weeks – until symptom resolution or esophagitis healing. Maintenance treatment is considered the long-term treatment – at least 6 months – for preventing symptoms or esophagitis relapse. We included studies using any type of PPI given at any dose. We excluded reports that combined a PPI with antibiotic treatment for H. pylori.

For studies with surgical procedures, we accepted only studies examining total (Nissen and Nissen-Rossetti) or partial (Toupet) fundoplication either as an open or as a laparoscopic procedure. These techniques represent the most commonly used surgical approaches for treatment of GERD. We excluded studies on surgical treatment of achalasia, esophageal strictures or rings, esophageal adenocarcinoma, hiatal hernia repair (unless the indication was for reflux), and colon interposition. We also excluded procedures that are no longer in use, such as the Angelchik prosthesis.

We included all endoscopic procedures, such as endoscopic suturing, radiofrequency energy delivery to the gastroesophageal junction, or implantation of inert polymers; but we limited these articles to products approved in the United States (eg, Stretta™, EndoCinch™ Suturing System, NDO Plicator™, and Enteryx™) (see Appendix F). One of the procedures, Enteryx™, was voluntarily recalled from the market due to safety concerns during final preparation of this report (*Boston Scientific recalls Enteryx Products*, <http://www.bostonscientific.com/common_templates/procedureOverview.jsp?task=tskProcedur

* Several grading systems have been proposed to evaluate the severity of GERD; the most common of which are the Savary-Miller Classification and the Los Angeles Grade. Patients were considered to have mild to moderate esophagitis if they were categorized as Savary-Miller class I-II or Los Angeles grade A-B, while they were considered to have severe esophagitis if it was categorized as Savary-Miller class III-IV or Los Angeles grade C-D (see Appendix E).

eOverview.jsp&sectionId=4&relId=7,323,324&procedureId=7004&uniqueId=MPPO1216>, accessed on 9/28/2005). However, we elected to include the data pertaining to Enteryx™ since it was the method used in one of the only two sham-controlled trials and because of the relatively large number of reports, which allowed for a better understanding of how various endpoints in the endoscopic studies correlated with one another.

Comparators of interest

For studies comparing one medical treatment with another, we included only those comparing a PPI versus another PPI or a H2RA irrespective of type or dose. Trials including other medical treatments (eg, prokinetic agents, antacids, sucralfate), combinations of other medical treatment with a PPI or an H2RA, or placebo as the only comparative group to a PPI group were excluded. These options are not considered to represent a typical medical approach for patients with GERD in the United States.

For studies comparing a surgical or endoscopic procedure with a medical treatment, we set no restrictions as to the medication used in the control arm. We also accepted sham procedure as potential control group.

For studies comparing one surgical procedure with another, the control arm was considered to be eligible if it included a total (Nissen) or partial (Toupet) fundoplication, either as an open or as a laparoscopic procedure.

No restrictions were set for control groups in studies that compared different endoscopic procedures.

Outcomes of interest

To evaluate the comparative efficacy of different therapies (question 1), we analyzed subjective and objective outcomes that are generally considered to represent clinically important endpoints in the management of GERD.

Subjective outcomes included:

- change in symptoms based on the clinical methods and scales that were described in each study;
- quality of life (QOL) when it was based on a validated quality of life-instrument such as the Medical Outcomes Study Short-Form-36 or the GERD-Health Related Quality of Life Instrument (see Appendix G); in addition, we recorded any outcome related to a systematic assessment of patient satisfaction.

Objective outcomes included:

- esophageal pH exposure either as a change from baseline exposure or as the proportion of patients achieved "normal" acid exposure whenever it was provided; since there is variability in the techniques for performing and interpreting esophageal pH studies, we accepted each study's definition of "normal" (for details see Streets 2003[15]);

- lower esophageal sphincter (LES) competence as described in each study;

- esophagitis healing rate based on the proportion of patients without esophagitis after treatment as assessed visually by endoscopy; to evaluate the medical maintenance treatment we used esophagitis relapse rate as the proportion of patients who developed esophagitis again after healing as assessed visually by endoscopy;

- continued need for antisecretory medications, as the proportion of patients who continued to require medications after treatment; we sought reporting of the proportion of patients who no longer required any antisecretory medications but also recorded the proportion who were freed from requiring PPIs or in whom the daily requirement for PPIs was reduced;

- development of Barrett's esophagus or esophageal carcinoma.

We focused on the results with the longest follow-up when an endpoint was measured more than once and the trial reported results from different time points. We excluded cost-effectiveness or cost-benefit outcomes. We also excluded outcomes on extra-esophageal GERD symptoms.

For question 2, we focused on the following baseline patient characteristics that may influence treatment efficacy of GERD: age, sex, smoking status, presence of obesity or not, severity of GERD symptoms (as described in each study), type and response to previous medication, presence and severity of esophagitis, presence and size of hiatal hernia, presence of esophageal motility abnormality or not (as assessed in each study), and presence of abnormal esophageal acidification (abnormal pH study) or not among patients off medication.

To evaluate adverse events and complications (question 3), we extracted from each study the rate for each adverse event of medical treatments and the rate for every reported complication of surgical and endoscopic procedures. In addition, we looked at the length of in-hospital stay and assessed the rate for re-operation after a surgical procedure and, specifically for laparoscopic operations, the conversion rate to an open procedure. We attempted to differentiate complications for surgical and endoscopic procedures that happened intra-operatively, or resolved within 30 days from the procedure and long-term complications presenting, or persisting after the first 30 days, whenever possible.

Study designs of interest

To address question 1, we used information from recent meta-analyses of RCTs comparing efficacy between medical therapies for acute and maintenance treatment of GERD. Among the recent meta-analyses of good quality, we chose the most comprehensive in terms of included comparisons and number of primary studies. For comparing efficacy between a medical and a surgical treatment, we retrieved all the comparative studies – randomized and non-randomized – between medical and surgical treatments. For comparing efficacy between different surgical techniques, we retrieved all RCTs that recruited at least 50 participants and had a mean or median follow-up duration of at least 5 years; we also included non-randomized comparative studies that had at least 100 participants and a mean or median follow-up of at least 5 years. To supplement data on long-term efficacy of surgery, we also included surgical cohort studies –

prospective and retrospective – that recruited at least 100 participants and had a mean or median follow-up of at least 5 years. To assess the efficacy of endoscopic procedures, we collected all endoscopic papers, including comparative and cohort studies.

To address question 2, we included data on specific patient characteristics of interest from the studies collected to address question 1. In addition, we retrieved comparative studies and cohorts that specifically investigated the relationship between certain patient characteristics with the efficacy of a treatment modality for GERD. To assess whether hospital setting influences the efficacy of surgical therapy for GERD, we included all studies that directly compared the surgical efficacy in an academic versus a community setting.

To address question 3, we examined all the studies already included in addressing questions 1 and 2. We also collected all studies, including case reports, cohorts, comparative studies, and reviews in which the specific focus was on adverse events and complications after medical, surgical, or endoscopic interventions for GERD. For surgical procedures, we also retrieved papers that were designed to compare the complication rate at different institutions with different volumes of patients. In addition, we used the Food and Drug Administration's MAUDE (Manufacturer and User Facility Device Experience) database (accessed May 31, 2005) to identify adverse events, complications, and interactions.[16]

Data Extraction

Items extracted included first author, year, country, setting, funding source, study design, inclusion,and exclusion criteria. For RCTs, we recorded the method of randomization, allocation concealment, blinding, and whether results were reported on an intention-to-treat basis. Specific population characteristics included demographics such as age and sex, presence of obesity (as assessed by BMI), and smoking status. For studies that reported short-term and long-term data in separate publications, we used the short-term publication to extract baseline data if the baseline data were not reported in the long-term publication.

To help interpret the results, we also extracted the following factors that are related to the diagnosis of GERD and disease severity (if they were reported at study entry): presenting symptoms and quality of life for patients on medication (as described in the paper); whether patients underwent endoscopy; whether patients with a hiatal hernia, esophagitis, esophageal stricture, or Barrett's esophagus were included. For hiatal hernia, we also extracted the size of hiatal hernia that the study used to exclude patients from participation. We also recorded whether pH or esophageal motility tests were performed as well as their results (as described in the study). For pH studies, we clarified, if possible, whether patients were receiving or abstaining from PPIs during the study. Finally, we recorded whether patients had tried any medical treatment, or lifestyle modifications previously, the type of medication, and their response to these therapies. For all population-related factors that were extracted, we investigated whether their baseline values differed significantly among the comparison groups.

We extracted information on treatment modality and the comparator. Primary and secondary outcomes were also extracted. For each outcome of interest, we reported the number of patients enrolled and analyzed, and the results (including baseline value, final value, within-treatment change, or between-treatment difference, with their variability estimate) as provided by the study. Duration of in-hospital stay after a surgical or an endoscopic procedure was also recorded.

We collected the duration of follow-up, as well as the number and the reasons for the dropouts during the follow-up period.

Quality Assessment

We assessed the methodological quality of studies based on predefined criteria. For the assessment of meta-analyses, the criteria for methodological quality were based on the QUOROM Guidelines for Meta-analyses and Systematic Reviews of RCTs.[17] For the assessment of RCTs, the criteria were based on the CONSORT statement for reporting RCTs.[18,19] We mainly considered the methods used for randomization, allocation concealment, and blinding as well as the use of intention-to-treat analysis, the report of dropout rate and the extent to which valid primary outcomes were described. For non-randomized trials, we used the report of eligibility criteria, and the similarity of the comparative groups in terms of baseline characteristics and prognostic factors. We also considered the report of intention-to-treat analysis, and the crossovers, as well as important differential loss to follow-up between the comparative groups or overall high loss to follow-up. The validity and the adequacy of the description of outcomes and results were also assessed. For the assessment of prospective and retrospective cohorts, as well as case-control studies, we used the Newcastle-Ottawa Quality Assessment scales for cohort and case-control studies. Items assessed included selection of cases or cohorts and controls, comparability, and exposure or outcome.

We applied a three-category quality grading system (A, B, C) to studies within each of the study designs. This grading scheme applies to meta-analyses, RCTs, cohorts, and case-control studies. An assigned grade to a study of one design is not equivalent to the same grade in a study of a different design. This grading system does not attempt to assess the comparative validity of studies across different design strata. For example, a “B” rated RCT is not judged to have the same methodological quality as a "B” rated case-control study. Thus, both study design and quality grade should be noted when interpreting the methodological of a study.

A (good)

Category A studies have the least bias and results are considered valid. A study that adheres mostly to the commonly held concepts of high quality including the following: a rigorously conducted meta-analysis; a formal randomized study; clear description of the population, setting, interventions, and comparison groups; appropriate measurement of outcomes; appropriate statistical and analytic methods and reporting; no reporting errors; less than 20% dropout; clear reporting of dropouts; and no obvious bias.

B (fair/moderate)

Category B studies are susceptible to some bias, but not sufficient to invalidate the results. They do not meet all the criteria in category A because they have some deficiencies, but none likely to cause major bias. The study may be missing information, making it difficult to assess limitations and potential problems.

C (poor)

Category C studies have significant bias that may invalidate the results. These studies have serious errors in design, analysis, or reporting; have large amounts of missing information, or discrepancies in reporting.

Data Synthesis

Review of meta-analyses

We used the results reported in meta-analyses on comparative efficacy of medical treatment. We considered the outcomes on acute and maintenance medical treatment as combined by the meta-analyses. Meta-analyses reported dichotomous outcomes, which included, for acute treatment: esophagitis healing and complete heartburn resolution, and for maintenance treatment: esophagitis relapse and symptom relapse. To combine these outcomes, meta-analyses applied the random effects model to estimate risk difference or relative risk with 95% confidence interval. Compared with the fixed effects model, the random effects model is more conservative in that it results in broader confidence intervals when between-study heterogeneity is present. We used the estimates as reported by the meta-analyses. We also used any attempt reported by the meta-analyses to explore heterogeneity using sub-group analyses or meta-regression.

Evidence and summary tables

The evidence tables offer a detailed description of the studies that addressed each of the key questions. The tables (see Appendix C) provide detailed information about the study design, the sample size, the intervention and comparison group treatments, the patient characteristics, the follow-up, the major outcomes, and the quality. In addition, for systematic reviews and meta-analyses, we reported the databases searched and for which time period, the number and the type of primary studies included, and the type of comparison addressed (medical versus medical; medical versus surgery; or endoscopic versus sham procedure).

Summary tables succinctly report summary measures of the main outcomes evaluated. They include information regarding study design, intervention and comparison group, therapeutic modality, study duration or follow-up, whether patients with severe esophagitis were also recruited, sample size (subjects enrolled and analyzed in each arm), results of major outcomes, and methodological quality. These tables were developed by condensing information from the evidence tables. They are designed to facilitate comparisons and synthesis across studies. A methodological quality was assigned to each study as described previously.

We reported medication usage data as described by the study authors without attempting to standardize the definitions. Some authors reported medication usage as the proportion of patients off PPIs while others reported the proportion of patients on PPIs or the number of days that patients regularly used antisecretory medications.

We also included an overall synthesis table in the results section to succinctly report the findings. The table included information on the data sources, populations studied, limitations of the included studies, a summary on major outcomes (symptoms, quality of life, esophagitis

healing, esophageal acid exposure, medication use), treatment-related factors with or without an association on outcomes, the type and frequency of major adverse events, and complications for the three treatment modalities.

Adverse events reporting

We reported the main adverse events of medical treatments in a summary table. We grouped studies according to the type of comparison (PPI versus H2RA or placebo; PPI maintenance dose versus healing dose), and the adverse event reported. For adverse events in each comparison, we reported the total number of patients included in the studies, the number of studies, and the total percent adverse event rate for each of the comparative arms, whenever the data are available.

We summarized complications of surgical and endoscopic procedures in evidence and summary tables. We considered studies with Nissen and Nissen-Rossetti fundoplication within the same category. In evidence tables, we grouped studies reporting complications according to the type of procedure and the complication reported. In these tables, for each study we report the data on the absolute number and the percentage of subjects with the complication. In summary tables, we reported the number of studies and the event rate for each complication and for each procedure. The mean event rate was calculated for two or more studies. Separate evidence and summary tables were created for studies that reported complications occurred within 30 days from the procedure, for studies with complications after 30 days from the procedure and for studies that were unclear for the time period between the procedure and a complication. We did not include case reports in the evidence or the summary tables.

Overall comparative synthesis table

To aid discussion, we summarized the comparative data across treatment modalities (medical, surgical, and endoscopic) in one table in the section on conclusions/discussion/future research. Separate cells were constructed for each key question. Important comparative findings for each key question were summarized whenever the data were available.

Grading a body of evidence for each key question

We assigned an overall grade describing the body of evidence for each key question that was based on the number and quality of individual studies, duration of follow-up and the consistency across studies. To assess the evidence for the first key question on comparative efficacy, we relied on direct and indirect comparative data between treatment modalities. We provided separate grades that assessed the body of evidence on medical versus surgical treatments and surgical versus endoscopic treatments. No studies compared medical with endoscopic treatments, and we did not assign a grade to this comparison. For the second key question on factors influencing outcomes, we relied mainly on observational studies. For the third question on adverse events, we relied on direct and indirect comparative studies, cohort studies, and various databases that reported adverse events. The grades corresponded to the following definitions:

Robust – There is a high level of assurance with validity of the results for the key question based on at least two high quality studies with long-term follow-up of a relevant population. There is no important scientific disagreement across studies in the results for the key question.

Acceptable – There is a good to moderate level of assurance with validity of the results for the key question based on fewer than two high quality studies or in high quality studies that lack long-term outcomes of relevant populations. There is little disagreement across studies in the results for the key question.

Weak – There is a low level of assurance with validity of results for the key question based on either moderate to poor quality studies or on studies of a population that may have little direct relevance to the key question. There could be disagreement across studies in the results for the key question.

The grades provide a shorthand description of the strength of evidence supporting the major questions we addressed. However, they may oversimplify the many complex issues involved in appraising a body of evidence. The individual studies involved in formulating the composite grade differed in their design, reporting, and quality. As a result, the strengths and weaknesses of the individual reports addressing each key question should also be considered, as described in detail in the text and tables.

Peer Review

A draft version of this report was reviewed by a panel of expert reviewers, including representatives from professional organizations, pharmaceutical companies, and manufacturers of endoscopic devices used in the management of GERD. Revisions of the draft were made, where appropriate, based on their comments. (See Appendix D[**]) The draft and final reports were also reviewed by staff from the Scientific Resource Center at Oregon Health and Science University. However, the findings and conclusions are those of the authors, who are responsible for the contents of the report.

[**] Appendix D (Peer Reviewers) is available electronically at www.ahrq.gov/clinic/epcindex.htm.

Chapter 3. Results

The MEDLINE search yielded 6,163 citations. We identified 327 of these as potentially relevant and retrieved them for further evaluation. A total of 98 primary studies were included in this report. In addition, the MEDLINE search yielded 75 meta-analyses and a search of the Cochrane Database of Systematic Reviews produced 140 titles. We retrieved 37 of these systematic reviews and meta-analyses for consideration and used seven in our report.

Key Question 1A. What is the evidence of the comparative effectiveness of medical, surgical, and endoscopic treatments in improving objective and subjective outcomes in patients with chronic GERD?

Key points for comparisons of medical, surgical and endoscopic treatments

- There were three head to head comparative trials of medical versus surgical treatments. The studies had methodological flaws making them susceptible to some bias, but not sufficient to invalidate the results (Grade B).

- There were differences in the population and approach to fundoplication among the studies: the 10-year study of open fundoplication (Spechler) included mostly patients with complicated GERD (Barrett's esophagus, dysplasia, esophageal ulcer, and stricture) who received non-PPI based medical interventions at enrollment, the 5-year study of open fundoplication (Lundell) included patients whose symptoms and esophagitis responded to PPI treatment, and the 1-year study of laparoscopic fundoplication (Mahon) included mostly patients with GERD symptoms but without complications who had been treated with PPIs for at least 3 months. The three trials did not enroll patients whose symptoms were poorly controlled with medical therapy.

- Despite these differences, the two studies of open fundoplication (Spechler and Lundell) reported similar degree of improvement in symptoms compared with baseline in the medical and surgical groups with no significant differences in between-group comparisons.

- Reduction in esophageal acid exposure was significantly better in the surgical group compared to medical therapy at three months in the study by Mahon and one year in the study by Spechler. However, no significant difference was found at two years in the Spechler study while later follow-up was not reported in the study by Mahon. Lundell reported complete normalization of esophageal acid exposure at 1-year in the surgical group, but not in the medical group (statistical comparison was not reported).

- No study comparing medical therapy with fundoplication reported that either was superior to the other for maintaining healing of esophagitis. All three trials included

patients with erosive esophagitis. Of the two trials involving open fundoplicaton: the Spechler study reported no difference in the endoscopic grade of esophagitis between treatment groups at 10 years; the Lundell study reported worsening esophagitis in both treatment groups at 3 years. The Mahon study with laparoscopic surgery did not report the status of esophagitis at follow-up.

- The proportion of patients who will be freed from the need for anti-secretory medications after fundoplication was unclear. In the Spechler study (the major strengths of which were its long observation period and relatively complete follow-up), up to two-thirds of patients who underwent open fundoplication continued to require some form of anti-secretory medications regularly. Lundell and Mahon did not report explicitly the proportion of patients who were on regular anti-secretory medications. Different conclusions were reached in the non-randomized surgical studies (see surgical studies described below) in which only approximately 10 percent of patients required regular anti-secretory medications. The reasons for these differences are unclear. (*Comment: Possible explanations include the relatively severe disease in patients included in the Spechler report and relatively large proportion of patients who were lost to follow-up in the other studies (making the proportion of patients who were off all medications uncertain from an intention-to-treat perspective). Some patients who resume anti-secretory medications following fundoplication do not in fact have objective evidence of GERD; thus there may have been differences in use of these medications across studies that do not truly reflect whether surgery was unsuccessful.)*

- There were insufficient data to determine whether fundoplication or medical therapy was more effective in reducing the incidence of Barrett's esophagus or esophageal adenocarcinoma. The limited data that were available did not support a significant benefit of fundoplication versus medical therapy for preventing these endpoints.

- There was no head to head comparison of medical treatments with endoscopic treatments.

- There was no head to head comparison of endoscopic treatments with laparoscopic treatments.

- There were three non-randomized studies that compared an endoscopic procedure to laparoscopic fundoplication in patients with GERD documented by pH or endoscopy. All three studies had significant bias that may invalidate the results (Grade C). The longest follow-up was 8 months. Two studies reported more patients treated with laparoscopic fundoplication were satisfied with their results compared with those who had EndoCinch™. Two studies – one on Stretta™ and the other on EndoCinch™ – found less of a need for PPIs in patients who had fundoplication. Other outcomes were not sufficiently reported to understand comparative efficacy.

- There was no long-term head to head comparison of laparoscopic surgery versus PPIs.

- No studies focused exclusively on patients with endoscopy negative reflux disease (non-erosive GERD).

Detailed analysis

A total of six publications reported results on four RCTs comparing medical with surgical treatments.[8,20-24] One RCT was excluded because the surgical techniques did not meet our inclusion criteria of reviewing only Nissen or Toupet methods.[20] Lundell et al. reported 3-year[21] and 5-year[22] follow-up data. Spechler et al. reported 2-year[24] and 10-year[8] follow-up data (N.B., For Lundell and Spechler, unless otherwise noted, the longer follow-up data are presented here). Mahon et al. reported data for 1-year follow-up.[23] The three RCTs enrolled a total of 762 patients, 666 of whom had follow-up information. The studies differed in the severity of esophagitis in patients at baseline and in the procedure performed. Spechler[24] and Mahon[23] included patients with erosive esophagitis. Lundell included patients with no higher than grade one esophagitis at baseline.[21] Lundell[21] and Spechler[24] used open fundoplication while Mahon[23] used laparoscopic fundoplication. All three studies were graded as methodological quality B.

The three studies included patients with different medical treatments and different response to medical treatments at baseline. None of the trials enrolled patients whose symptoms were poorly controlled with medical therapy. Spechler included patients whose reflux disorder responded to non-PPI based medical treatments at enrollment.[24] Lundell included patients whose symptoms and esophagitis responded to omeprazole.[21] Mahon[23] reported that the enrolled patients were "dependent" on PPIs for at least 3 months (although the definition of "dependent" was not stated). Lundell[21] and Mahon[23] used regular intake of a PPI for the medical intervention; Spechler[24] used a combination of H2RAs, antacids and pro-motility agents either on a regular or as needed basis for the medical intervention (However, most of the patients used PPIs during the follow-up period, but in a nonstandardized fashion.[8]). In all three RCTs, more than 80% of the patients who actually received the interventions provided follow-up data.

A total of seven non-randomized studies compared medical with surgical treatments in patients with GERD.[25-32] The average follow-up duration ranged from 6 months to more than 10 years. All were graded as methodological quality C.

Four provided data on baseline response to medical therapy.[25,27,28,31] A prospective study compared patients whose GERD symptoms or esophagitis responded to PPIs and were maintained on them with a group that underwent laparoscopic fundoplication because they either had recurrent symptoms of GERD or esophagitis, did not respond to PPIs, or were unwilling to continue PPIs.[31] A retrospective study compared all patients with GERD who were "managed nonoperatively" and were not referred for operation with all patients who underwent laparoscopic fundoplication over a 1-year period.[25] Another retrospective study compared patients whose GERD symptoms and esophagitis responded to H2RAs and lifestyle modification and were kept on medical management with patients whose GERD symptoms did not respond to the same therapy and therefore, underwent open fundoplication.[27] One open label study compared ranitidine with open fundoplication in patients with symptomatic GERD. [28] Patients were selected for fundoplication or ranitidine based on the patient's and surgeon's preference. Three of the studies included patients with severe esophagitis.[27,28,31]

A 1-year[26] and 4-year[29] retrospective analysis of administrative data and computerized health care records from the Tennessee Medicaid program compared the usage of prescription antireflux medications in patients with GERD treated medically with those treated surgically.

Two retrospective cohort analyses specifically examined the incidence of esophageal adenocarcinoma in medically versus surgically treated patients.[30,32]

The findings from both the RCTs and non-randomized comparisons have been organized by the following outcomes of interest: change in symptoms, quality-of-life (QOL), and patient satisfaction; change in esophagitis status; change in pH study results; change in lower esophageal sphincter (LES) pressure; change in medication usage status; change and follow-up information regarding Barrett's esophagus, and the incidence of esophageal adenocarcinoma. Details of these outcomes are presented in the Evidence Tables while the key points are summarized here. Adverse effects are presented under key question 3.

Change in symptoms, quality-of-life and patient satisfaction (Table 1)

Three RCTs and three non-randomized studies reported outcomes in symptoms, quality-of-life, and patient satisfaction.[8,22,23,25,27,28] The various studies used different methods of measuring symptom improvement and patient satisfaction. They ranged from patients' descriptions of heartburn, regurgitation, and satisfaction to structured scales like GERD-Health Related Quality of Life (GERD-HRQL), Visick Scale, and SF-36. The Spechler RCT reported significantly better Gastroesophageal Reflux Disease Activity Index (GRACI) score in the surgical (open fundoplication) arm than in the medical group after both groups discontinued all antireflux medications during the week of assessment; the medically treated patients went from having mild reflux symptoms to having mild to moderate symptoms.[8] The difference between groups was not significant when both groups were on their usual antireflux medications. The Lundell RCT did not demonstrate a difference between omeprazole and open fundoplication in the prevalence of patients with moderate to severe heartburn at defined time points during the follow-up.[22] The Mahon RCT reported that Gastrointestinal and General Well-Being Score improved more in the laparoscopic group compared with the PPI group at 1 year follow-up.[23] The Gastrointestinal well-being score went from a baseline of 31.7 to 37 in the surgical group and from 34.3 to 35.0 in the medical group (between group $P<0.001$). The clinical implication of the two-point difference between groups was not described.

Lundell and Spechler also examined quality-of-life outcomes. Lundell used the Psychological General Well-Being Index (PGWB) and Gastrointestinal Symptom Rating Scale (GSRS); Spechler used Medical Outcome Short Form Health Survey (SF-36). There were no differences in quality-of-life assessment.

The one retrospective study comparing laparoscopic surgery with medical treatment reported better quality-of-life score in the surgical group.[25] The one retrospective study comparing open Nissen with medical treatment with more than 10 years follow-up reported more symptom improvement in the surgical than the medical group.[27]

Table 1. Medical vs. surgical treatments of GERD: Change in symptoms, QOL and satisfaction

Study Intervention Design	N enrolled N with follow-up data Excluded ≥ grade 3 esophagitis	Follow-up duration	Quality	Results
Randomized controlled trials				
Lundell, 2001 OME vs. OAS	298 255 Yes	5 yr	B	Similar results in the 2 groups in % of pts with moderate to severe heartburn at defined time points. No difference in QOL assessment between 2 groups
Spechler, 2001 MED vs. ONF	247 208 (129 survivors; 79 deaths) No	10 yr	B	Symptom score better in ONF than MED (off-med in both groups during the week of comparison), *P*=0.003; difference was not significant when both groups were on their usual antireflux meds. SF-36-P & SF-36-M, difference between groups: NS
Mahon, 2005 PPI vs. LNF	217 203 No	1 yr	B	GI well being score & General well-being score improved more in LNF (*P*=0.003)
Non-randomized studies				
Johansson, 1986 RAN vs. OPA Open label comparison	31 No	6 mos	C	All OPA pts symptom free except for 2 (mild dysphagia & chest pain) All OPA pts were satisfied. 5 pts in RAN dissatisfied with treatment.
Isolauri, 1997 MED vs. ONF Retrospective Cohort	120 105 No	10.9 yr	C	No or mild heartburn: MED 53% ONF 84%
Fernando, 2002 MED vs. LAS Retrospective Cohort	171 138 ND	23 mos (MED) 18 mos (LAS)	C	Better SF-36 & HRQOL in LAS (*P*<0.05)

OME: omeprazole; OAS: open antireflux surgery; MED: medical treatments; ONF: open Nissen fundoplication; SF-36-P: short form 36 – physical; SF-36-M: short form 36 – mental; PPI: proton pump inhibitor; LNF: laparoscopic Nissen fundoplication; RAN: ranitidine; OPA: open partial fundoplication; LAS: laparoscopic antireflux surgery; HRQOL: health related quality of life

Change in esophagitis status (Table 2)

Two RCTs, one non-randomized comparison, and one retrospective cohort study reported on changes in esophagitis status.[8,21,24,27,28] Spechler RCT, with a 10-year follow-up, reported no difference in the endoscopic grade of esophagitis between open fundoplication and medical treatment,[8] although there were lower grades of esophagitis in the surgical group at 2-year follow-up.[24] Lundell RCT reported an increase in percentage of esophagitis in both open fundoplication and medically treated groups at 3-year follow-up.[21] Isolauri et al. – the retrospective study reporting on change in esophagitis status – reported improvement in both open fundoplication and medically treated groups, although there was more improvement in the open fundoplication than in the medical group. At 10-year follow-up, 86% of the open fundoplication group had grade 0 compared with 46% of the medical group. Similar differences were found for the other grades.[27] Johansson and Tibbling – the open label comparison of ranitidine with open fundoplication, where 90% of the patients in both groups had esophagitis at

baseline – reported that there was a significant improvement in the ranitidine group but not in the open fundoplication group after 8 weeks of ranitidine. Six months later, there was no further improvement in the ranitidine maintenance group, however, all the patients in the open fundoplication group had a normal endoscopic mucosa.[28]

Table 2. Medical vs. surgical treatments of GERD: Change in esophagitis status

Study Intervention Design	N enrolled N with follow-up data Excluded ≥ grade 3 esophagitis	Follow-up duration	Quality	Results
Randomized controlled trials				
Lundell, 2000 OME vs. OAS	298 252 Yes	3 yr	B	+ esophagitis Baseline → Follow-up OME 6/154(4%) 22/133 (17%) OAS 10/144(7%) 16/119 (13%)
Spechler, 2001, 1992 MED vs. ONF	247 208 (129 survivors; 79 deaths) No	10 yr 1992 paper: 1 & 2 yr f/u	B	Long-term: no significant difference between the 2 groups in endoscopic grade. At 1 & 2 yr, grade of esophagitis improved in all 3 groups compared to baseline (*P*<0.03). Grades of esophagitis lower in ONF than MED during the 2 yr f/u (*P*<0.003)
Non-randomized studies				
Johansson, 1986 RAN vs. OPA Open label comparison	31 No	6 mos	C	Baseline esophagitis: RAN 15/16 OPA 13/15 After 8 wks of ranitidine, significant improvement in RAN (*P*<0.05), not in OPA. 6 mos later, no further improvement in RAN; all OPA pts had normal mucosa (*P*<0.01)
Isolauri, 1997 MED vs. ONF Retrospective Cohort	120 105 No	10.9 yr	C	Baseline → Follow-up Grade 3 MED 12% 4% ONF 16% 0 Grade 2 MED 34% 22% ONF 57% 0 Grade 1 MED 54% 28% ONF 27% 14%

OME: omeprazole; OAS: open antireflux surgery; MED: medical treatments; ONF: open Nissen fundoplication; RAN: ranitidine; OPA: open partial fundoplication

Change in pH study results (Table 3)

Three RCTs and one non-randomized comparison reported changes in pH study results.[8,21,24,28]. Spechler RCT, in the 10-year follow-up, reported a non-significant lower percent-time with pH<4 in the open fundoplication group compared with the medical group, although only 10 surgical patients were evaluated (versus 38 in the medical arm).[8] The same RCT, in the 1-year follow-up, reported that the percent-time pH<4 improved more in open fundoplication group compared to the group on symptomatic medical therapy (*P*<0.03).[24] Lundell RCT, in the 1-year follow-up, reported lower percent-time with pH<4 in both open fundoplication and medical groups compared to their baseline values.[21] Mahon RCT, in the 3-

month follow-up of laparoscopic surgery versus PPI study, reported lower percent-time with pH<4 in both groups and there was greater improvement in surgical than medical group.[23]

Table 3. Medical vs. surgical treatments of GERD: Change in pH study results

Study Intervention Design	N enrolled N with follow-up data Excluded ≥ grade 3 esophagitis	Follow-up evaluation	Quality	Results
Randomized controlled trials				
Lundell, 2000 OME vs. ARS	298 252 Yes	12 mos	B	% time pH<4 Baseline → Follow-up OME 20% 10% OAS 19% 4% (estimated from fig.1 in original paper; no statistical comparison was reported)
Spechler, 2001, 1992 MED vs. ONF	247 208 (129 survivors; 79 deaths) No	10 yr 1992 paper: 1 & 2 yr f/u	B	At 10 yr, % time pH<4 MED (n=38) 31% (62SD) ONF (n=10) 17% (41SD) NS At 1 & 2 yr, % time pH<4 improved in all groups compared to baseline (*P*<0.03) At 1 yr, %time pH<4 improved more in ONF compared to symptomatic MED therapy (*P*<0.03).
Mahon, 2005 PPI vs. LNF	217 203 No	3 mos	B	% time pH<4 (Mean ± SD) Baseline → Follow-up PPI 9.5% ± 7.3 3.8% ± 7.8 LNF 12.9% ± 10.9 1.4% ± 3.6 (Between groups, *P*=0.002 by ANCOVA) DeMeester (Mean ± SD) Baseline → Follow-up PPI 36.9 ± 26.5 17.7 ± 21.4 LNF 42.7± 33.1 8.6 ± 16.3 (Between groups, *P*<0.001 by ANCOVA)
Non-randomized studies				
Johansson, 1986 RAN vs. OPA Open label comparison	31 No	6 mos	C	After 8 wks of ranitidine (n=19), no significant change in total reflux time for RAN. After OPA (n=15), total reflux time =0.04±0.09%, which is lower than during RAN (*P*<0.01)

OME: omeprazole; ARS: antireflux surgery; OAS: open antireflux surgery; MED: medical treatments; ONF: open Nissen fundoplication; PPI: proton pump inhibitor; LNF: laparoscopic Nissen fundoplication; RAN: ranitidine; OPA: open partial fundoplication

Change in lower esophageal sphincter pressure (Table 4)

Two RCTs and two non-randomized studies provided information on lower esophageal sphincter (LES) pressure.[23,24,28,31] Spechler RCT reported a significant increase in LES pressure in the open fundoplication group compared with the medical group 1 year after surgery (*P* value, not stated).[24] Mahon RCT reported an increase in LES pressure in the laparoscopic surgery group compared with the PPI group 3 months after surgery (*P*<0.001 between groups).[23] One retrospective study reported that patients who developed Barrett's esophagus at follow-up had

more defective LES pressure and more impaired esophageal peristalsis before treatment ($P<0.05$).[31] Johansson and Tibbling – the open label comparison of ranitidine with open fundoplication – reported that the LES pressure had a significant increase in the open fundoplication group compared to baseline ($P<0.05$).[28]

Table 4. Medical vs. surgical treatments of GERD: Change in LES pressure

Study Intervention Design	N enrolled N with follow-up data Excluded ≥ grade 3 esophagitis	Follow-up evaluation	Quality	Results
Randomized controlled trials				
Spechler,1992 MED vs. ONF	247 176 No	1 yr	B	LES pressure in mm Hg Baseline → Follow-up MED continuous 25 ± 18 (SD) 23 ± 1 MED as needed 27 ± 19 26 ± 1 ONF 23 ± 18 31 ± 1 Surgical group was significantly higher than baseline and the two medical groups (*P* values not stated).
Mahon, 2005 PPI vs. LNF	216 170 No	3 mos	B	Baseline → Follow-up PPI 8.1 ± 7.6 7.9 ± 7.7 LNF 6.3 ± 5.8 17.2 ± 7.0 Difference between group, $P<0.001$ by ANCOVA
Non-randomized studies				
Johansson, 1986 RAN vs. OPA Open label comparison	31 No	6 mos	C	Baseline → Follow-up RAN 5.6 (0-20) ND OPA 6.0 ± 6.7 10.0 ± 4.6 $P<0.05$
Wetscher, 2001 MED vs. LAS Prospective cohort compared to a retrospective surgical group	125 Yes in MED No in LAS	MED 2 yr LAS 3.5 yr	C	Baseline → Follow-up MED 6 (2.5-8.0) ND LAS 4.7 (2.9-9.2) Normal Pts enrolled in LAS arm only if they had normal LES, pH study, no symptom and no esophagitis after antireflux surgery. Pts with Barrett's at baseline were excluded from study. Pts who developed Barrett's at follow-up had more defective LES & more impaired esophageal peristalsis before treatment ($P<0.05$).

MED: medical treatments; ONF: open Nissen fundoplication; PPI: proton pump inhibitor; LNF: laparoscopic Nissen fundoplication; RAN: ranitidine; OPA: open partial fundoplication; LAS: laparoscopic antireflux surgery;

Change in medication usage status (Table 5)

One RCT[8] and two retrospective analyses[26,27] (one[26] with a subsequent follow-up publication[29]) reported on changes in medication usage. Spechler RCT,[8] with the 10-year follow-up, reported that proportionately fewer patients were on PPIs after open fundoplication compared with the medically treated patients, but almost two-thirds of the surgically treated patients with available follow-up information were still on some form of antireflux medications regularly (By contrast, data from comparative studies of surgical techniques and surgical cohort studies reported that approximately 90% of the patients were off antireflux medications at 5-years

follow-up.). In a retrospective cohort analysis, Isolauri et al. reported that 5% of the surgically treated patients were on H2RAs occasionally compared with 33% of the medically treated patients at more than 10 years follow-up.[27]

In a 4-year follow-up study using administrative data and computerized health care records from the Tennessee Medicaid program, Khaitan et al. determined that the proportion of persons using prescription medications (H2RAs, PPIs, or prokinetic agents) for acid suppression was lower in the surgical group than the medical group during each year of follow-up.[29] Using the same database, Holzman et al. reported a marked decrease in use of GERD-related prescription pharmaceuticals in the surgical cohort the first year after surgery.[26]

Table 5. Medical vs. surgical treatments of GERD: Change in medication usage status

Study Intervention Design	N enrolled N with follow-up data	Follow-up / duration	Quality	Results
Randomized controlled trials				
Spechler, 2001, 1992 MED vs. ONF	247 127	10 yr	B	Off PPI: MED (n=89) 36% ONF (n=37) 68% *P*=0.002 Off any antireflux meds: MED (n=90) 8% ONF (n=37) 38% *P*<0.001
Non-randomized studies				
Holzman, 2001 MED vs. ARS Retrospective matched cohort from Tennessee Medicaid research database	MED n=250 ARS n=135	1 yr	C	Use of GERD drugs first year after ARS: MED 339 days ARS 123 days *P*<0.001
Khaitan, 2003 MED vs. ARS Follow up of Holzman, 2001 study	MED n=200 ARS n=111	4 yr	C	Proportion of pts using GERD drugs was less in ARS than MED for each year of follow-up; In year 4: MED 90% ARS 74% *P*<0.001
Isolauri, 1997 MED vs. ONF Retrospective Cohort	120 105	10.9 yr	C	MED: 14/68 (21%) on omeprazole or H2RA regularly; 22/68 (33%) occasionally ONF: 2/37 (5%) on H2RA occasionally

MED: medical treatments; ONF: open Nissen fundoplication; PPI: proton pump inhibitor; ARS: antireflux surgery; H2RA: H2 receptor antagonists

Changes and follow-up information regarding Barrett's esophagus (Table 6)

Two RCTs and three non-randomized studies provided follow-up information on Barrett's esophagus.[8,22,24,27,28,31]. Lundell RCT reported that there was no difference in the point prevalence of Barrett's esophagus between the two study arms at 5-year follow-up.[22] Spechler RCT reported an almost six-fold increase in the incidence of esophageal adenocarcinoma in patients with Barrett's esophagus at baseline compared to patients without Barrett's esophagus[8] (see additional details in the next section). The retrospective study by Wetscher et al. reported that 14% of medically treated patients developed Barrett's esophagus at 2-year follow-up while

none of the surgically treated patients developed Barrett's at 3.5 year follow-up.[31] Isolauri et al. reported increase in Barrett's in both study arms at follow-up of 9 to 13 years.[27] Johansson and Tibbling reported one patient with Barrett's at baseline was found to have only "mild basal cell hyperplasia" 6 months after open fundoplication.[28]

Table 6. Medical vs. surgical treatments of GERD: Status of Barrett's esophagus

Study Intervention Design	N enrolled N with follow-up data	Follow-up / duration	Quality	Results
Randomized controlled trials				
Lundell, 2001 OME vs. ARS	298 252	5 yr	B	Baseline → Follow-up OME 17% 18% ARS 15% 15% (estimated from Fig. 4A in original paper)
Spechler, 2001, 1992 MED vs. ONF	247 208 (129 survivors; 79 deaths)	10 yr	B	Baseline → Follow-up cases of Barrett's MED 74 3 developed esophageal adeno-CA ONF 34 1 developed esophageal adenocarcinoma 1 case of esophageal adeno-CA without Barrett's in MED. Esophageal adenocarcinoma rate in pts with Barrett's 0.4% per year without Barrett's 0.07% per year
Non-randomized studies				
Johansson, 1986 RAN vs. OPA Open label comparison	31	6 mos	C	Baseline → Follow-up RAN 1/16 (6%) ND OPA 1/15 (7%) only mild basal cell hyperplasia was found after surgery
Wetscher, 2001 MED vs. LAS Prospective cohort compared to a retrospective surgical group	125	MED 2 yr LAS 3.5 yr	C	Baseline → Follow-up MED 0 12/83 (14%) LAS 0 0 Pts with Barrett's at baseline were excluded from study. Pts who developed Barrett's had more defective LES & more impaired esophageal peristalsis before treatment (P<0.05).
Isolauri, 1997 MED vs. ONF Retrospective Cohort	120 105	10.9 yr	C	Baseline → Follow-up MED 0 8/68(12%) ONF 5/39 (13%) 12/37(32%) 1 case of esophageal adenocarcinoma without Barrett's.

OME: omeprazole; ARS: antireflux surgery; MED: medical treatments; ONF: open Nissen fundoplication; RAN: ranitidine; OPA: open partial fundoplication; LAS: laparoscopic antireflux surgery;

Incidence of esophageal adenocarcinoma (Table 7)

One RCT and two retrospective analyses provided information on the comparative incidence of esophageal adenocarcinoma.[8,30,32] Spechler RCT reported no difference in the incidence of esophageal adenocarcinoma between the medical arm and the surgical arm at follow-up ranged

from 4 to 12 years (this study also reported a six-fold increase in the incidence of esophageal adenocarcinoma in patients with Barrett's at baseline compared to patients without Barrett's).[8] However, the authors acknowledged that the study lacked sufficient statistical power to detect important differences between groups in the rate of cancer development.

Tran et al. – a retrospective study based on data from national computerized Veterans Administration databases (1986-1990) – examined the incidence of esophageal adenocarcinoma in patients with GERD who had medical treatment, patients with GERD who had surgical treatment, and in patients without GERD.[30] They did not ascertain prevalence of Barrett's esophagus. The mean duration of follow-up in this study was greater than 10 years. There were 1,892 patients in the GERD medical group, 946 in the surgical group, and 5,676 in the non-GERD group. During a follow-up period of 59,439 person-years and a mean duration of 10.5 years, no patients in the non-GERD group were diagnosed with esophageal cancer. During a follow-up period of 20,115 patient-years and a mean duration of 10.6 years, there were eight cases of esophageal cancer in the GERD medical group (40/100,000 person-years). During a follow-up period of 211,156 patient-years and a mean duration of 11.8 years, there were eight cases of esophageal cancer in the GERD fundoplication group (72/100,000 person-years). The difference in incidence rates between the two GERD groups was not statistically significant. Kaplan-Meier analysis showed that there was no statistically significant difference between the cumulative rates of esophageal cancer in the surgical group versus the medical group.

Ye et al. specifically examined the question of incidence of esophageal adenocarcinoma in patients with GERD who had surgical treatment and in patients who did not have surgical treatment.[32] There were no data specifically concerning Barrett's in these studies. This retrospective cohort analysis was based on data obtained from a Swedish Inpatient Registry (1965 to 1997). The unoperated GERD group had 66,965 patients and the antireflux surgery group had 11,077 patients. The incidence rate of esophageal adenocarcinoma in males in the antireflux surgery group was 37/100,000 person-years. The incidence of esophageal adenocarcinoma in males in the unoperated group was 22.4/100,000 person-years. There were no cases of esophageal adenocarcinoma in females in the antireflux surgery group. The incidence of esophageal adenocarcinoma in females in the unoperated group was 6.6/100,000 person-years. Statistical comparisons between these groups were not reported.

Table 7. Medical vs. surgical treatments of GERD: Incidence of esophageal adenocarcinoma

Study Intervention Design	N enrolled N with follow-up data	Follow-up duration	Quality	Results
Randomized controlled trials				
Spechler, 2001 MED vs. ONF	247 208 (129 survivors; 79 deaths)	7.1 yr (4-12)	B	Esophageal adenocarcinoma: MED 4/137 ONF 1/71 Difference NS
Non-randomized studies				
Tran, 2005 MED vs. ARS vs. non-GERD Retrospective comparison of 3 distinct cohorts from computerized national VA databases	MED 1892 ARS 946 Non-GERD 5676	MED 10.6yr ARS 11.8yr Non-GERD 10.5yr	C	Esophageal CA: MED 8/20,115 PY 40/100,000 PY ARS 8/11,156 PY 72/100,000 PY (MED vs. ARS, NS) Non-GERD 0/59,439 PY
Ye, 2001 Unoperated GERD vs. ARS Retrospective cohort analysis from Swedish Inpatient Register	NoSurgGERD 66,965 ARS 11,077	NoSurgGERD M 5.6 yr F 5.7 yr ARS M 7.7 yr F 8.0 yr	C	Esophageal adeno-CA Standardized Incidence Ratio (SIR): NoSurgGERD M 6.3 (CI 4.5-8.7) F 6.1 (CI 2.9-11.2) ARS M 14.1(CI 8.0-22.8) F 0 SIR increased with f/u time (*P*=0.03)

MED: medical treatments; ONF: open Nissen fundoplication; ARS: antireflux surgery; PY: person-years; NoSurgGERD: Patients with GERD who did not have antireflux surgery, database did not provide information on medical treatments.

Comparative effectiveness of medical treatments

Key points for interclass and intraclass comparisons of medical treatments

- We focused on comparisons between PPIs and H_2 receptor antagonists (H2RAs) and on PPI intraclass differences. Three recent, good-quality meta-analyses of RCTs comparing one medication versus another provided the data on the efficacy of medical treatments. The primary studies included in the meta-analyses had a follow-up duration of no more than 1 year with the exception of one study that reported a follow-up of 5 years.

- For medical treatments, results are applicable to adults with heartburn and/or regurgitation and some degree of esophagitis, corresponding to the characteristics of patients who were enrolled in the primary RCTs included in the meta-analyses.

- PPIs were superior to ranitidine for resolution of GERD symptoms at 4 weeks. PPIs were significantly more effective than ranitidine for healing of esophagitis at 8 weeks. PPIs at a standard dose (as suggested by the manufacturers' prescribing information) or a lower

dose (usually one-half of the standard dose) were better than H2RAs in maintaining healing.

- There was no comparative difference between omeprazole, lansoprazole, pantoprazole, and rabeprazole for relief of symptoms at 8 weeks.

- No significant difference was found in the comparisons of esomeprazole 40 mg with lansoprazole 30 mg or pantoprazole 40 mg for relief of symptoms at 4 weeks. There was a significant difference in favor of esomeprazole when esomeprazole 40 mg was compared to omeprazole 20 mg for symptom relief at 4 weeks. The combined risk difference in three trials was 10% (95% CI 6%, 14%); for 10 patients treated with esomeprazole 40 mg versus omeprazole 20 mg, one additional patient would be symptom-free at 4 weeks in the esomeprazole group (NNT=10).

- For maintenance medical treatment of 6 months to 1 year, PPIs at a standard dose were more effective than at a lower dose in preventing relapse of symptoms.

- For healing of esophagitis at 8 weeks, there was no comparative difference between omeprazole, lansoprazole, pantoprazole, and rabeprazole.

- Esomeprazole 40 mg and lansoprazole 30 mg were equally effective in healing of esophagitis at 8 weeks in an analysis that combined the results of three RCTs. Two trials compared esomeprazole 40 mg to pantoprazole 40 mg for esophagitis healing at 8 weeks. One reported that healing rate was higher in the esomeprazole group; the risk difference was 3% (95% CI 1%, 5%) (NNT=33). In the other, esomeprazole and pantoprazole were equally effective. Two trials compared esomeprazole 40 mg with omeprazole 20 mg, and both found a higher 8-week healing rate in the esomeprazole group, risk difference was 8%, (95% CI 5%, 11%) (NNT=13). (*Comment: The clinical importance of these differences is unclear since the magnitude of difference was small and the exact dosage equivalence between various PPIs has not been established. Furthermore, whether healing of esophagitis at 8 weeks predicts maintenance of healing is uncertain.)*
- For maintenance medical treatment of 6 months to 1 year, PPIs at a standard dose were more effective than at a lower dose in preventing relapse of esophagitis.

Detailed analysis

We relied on three rigorously conducted systematic reviews of PPIs and H2RAs published in 2001, and 2005 for this section of the report. McDonagh and Carson from the Oregon Health and Science University Evidence-based Practice Center (OHSU EPC) assessed the comparative efficacy of different PPIs in healing esophagitis, and reducing symptoms of GERD, among adults presenting with GERD symptoms.[33] The methodological quality of this review was grade A. Caro et al. assessed the comparative efficacy of PPIs and ranitidine in healing esophagitis, and reducing symptoms of GERD, among adult outpatients with an endoscopically confirmed diagnosis of gastroesophageal reflux.[34] The methodological quality of this review was grade B. Donnellan et al. assessed the efficacy of PPIs (at different doses) compared to H2RAs in preventing the relapse of mucosal inflammation in adults with esophagitis as well as in

preventing relapse of symptoms in adults with endoscopy negative reflux disease and esophagitis.[35] The methodological quality of this review was grade A.

PPIs included esomeprazole, lansoprazole, omeprazole, pantoprazole, and rabeprazole. Donnellan et al.[35] defined healing or standard dose as 20 mg once daily for esomeprazole, omeprazole, and rabeprazole; 30 mg once daily for lansoprazole; and 40 mg once daily for pantoprazole. A lower, maintenance dose was defined 10 mg once daily for esomeprazole, omeprazole, and rabeprazole; 15 mg once daily for lansoprazole; and 20 mg once daily for pantoprazole. Double dose was defined as double the standard (healing) dose. These definitions were not adopted by the other two meta-analyses.[33,34] H2RAs included cimetidine, famotidine, nizatidine or ranitidine. Acute treatment ranged in duration from 4 to 8 weeks while maintenance treatment was administered continuously for at least 6 months.

Acute treatment of symptoms

McDonagh and Carson[33] reported four RCTs with comparisons between PPIs that measured symptom relief as a primary outcome, and 13 that reported symptom relief as a secondary outcome. Symptom relief in these studies was assessed through patient diaries, investigator-elicited reports, or both. The definition of "symptom relief" varied. Evaluated symptoms included day and nighttime heartburn, dysphagia, odynophagia, pain on swallowing, or acid regurgitation. Complete resolution of heartburn was usually defined as seven consecutive days without heartburn. Quality of life and patient satisfaction were also evaluated in one study.

Fourteen trials reported the proportion of patients with complete resolution of symptoms at 4 weeks. McDonagh and Carson performed a random effects meta-analysis of data from these studies to determine an estimate of the proportion of patients who were symptom free at 4 weeks for each drug. Proportions ranged from 65% to 77%; and 95% confidence intervals overlapped, indicating the drugs are similarly efficacious for complete resolution of symptoms at 4 weeks. Risk differences in rates of complete symptom resolution at 4 weeks were also calculated in these trials. With the exception of esomeprazole 40 mg versus omeprazole 20 mg, risk differences were non-significant in rest of the comparisons. The combined data significantly favored esomeprazole 40 mg; for every 10 persons treated with esomeprazole 40 mg versus omeprazole 20 mg, one additional patient would be symptom-free at 4 weeks in the esomeprazole group. The combined data for esomeprazole 40 mg versus either lansoprazole 30 mg (risk difference 5%; 95%CI 0%, 9%) or pantoprazole 40 mg (risk difference 2%; 95%CI –11%, 7%) did not indicate a significant difference between the drugs.

Eleven studies reported the time to resolution of symptoms (defined as the absence of heartburn) either as the percentage of patients with the outcome after a given time point (1 day, 7 days, etc.) or the median number of days to resolution, or both. In one study this outcome was reported as the number of days needed for 50% and 75% of patients to achieve relief of symptoms. Another measure used was "the time to sustained resolution of heartburn", defined as the time to the first series of 7 consecutive days without heartburn. This outcome was used only in studies on esomeprazole, so it is not possible to compare this outcome with studies of other PPIs. However, time-to-relief of heartburn was similar for all PPIs.

Caro et al.[34] analyzed 11 RCTs that compared a PPI with ranitidine. These RCTs reported resolution of symptoms as an outcome. Omeprazole was used in eight RCTs, lansoprazole in one, pantoprazole in one, and rabeprazole in another. Symptoms in these studies were assessed through patient diary cards, interviews, and visual analogue scales. Evaluated symptoms

included day and nighttime heartburn, dysphagia, odynophagia, acid eructation, or regurgitation. PPIs were generally superior to ranitidine for resolution of GERD symptoms at 4 weeks. Because the studies used different methods of collecting and recording various symptoms at different time points, only the data on complete heartburn resolution were combined. The rate of heartburn resolution was 1.53-fold higher with PPIs compared with ranitidine (95% CI 1.37, 1.72).

Acute treatment of esophagitis (Tables 8, 9)

McDonagh and Carson[33] retrieved 13 published RCTs that compared a PPI versus a second PPI. All of the PPIs were effective at healing esophagitis. Healing rates at 4 weeks ranged from 49% to 91%, and at 8 weeks ranged from 71 % to 99%. To determine an estimate of healing rates for each drug, they combined data from the trials, using a random effects model to control for the effect of the study. Healing rates were similar and confidence intervals overlapped, indicating no significant differences among PPIs.

McDonagh and Carson also calculated the percent risk difference for healing in the comparisons. Table 8 shows the differences in healing rates at 4 and/or 8 weeks for the 18 trials that provided the number healed and the total number of patients in each arm of the studies. With the exception of esomeprazole 40 mg versus omeprazole 20 mg, risk differences at 4 and 8 weeks were non-significant in rest of the comparisons. Two trials compared esomeprazole 40 mg to omeprazole 20 mg, and both found a higher healing rate in the esomeprazole group. Two studies compared esomeprazole 20 mg to omeprazole 20 mg, and found no significant difference in healing rate at 4 or 8 weeks.

Three studies compared esomeprazole 40 mg to lansoprazole 30 mg. In a large trial with 5,241 patients at multiple centers in the US, healing rates were higher in the esomeprazole group at 4 weeks (risk difference 4%; 95% CI 2%, 6%) and at 8 weeks (risk difference 3%; 95% CI 1%, 5%). A second, smaller trial of lansoprazole 30 mg versus esomeprazole 40 mg in patients with mostly mild to moderate esophagitis found the two to have equivalent healing rates at 8 weeks. Results at 4 weeks were not reported. The third study was conducted in patients with moderate to severe esophagitis (Los Angeles Grade C and D). At 4 weeks, the esomeprazole group had a higher healing rate, but at 8 weeks the difference was not significant. Combined estimates showed a 5% higher healing rate at 4 weeks and 3% at 8 weeks for esomeprazole 40 mg. The difference at 8 weeks was not significant using a random effects model (risk difference 3%; 95% CI 0%, 5%). Two trials compared esomeprazole 40 mg to pantoprazole 40 mg. In one trial that was rated as fair to poor quality in the McDonagh and Carson report, healing at 4 weeks was 6% greater in the esomeprazole group (95% CI 3%, 9%). At 8 weeks, the difference was smaller but statistically significant (risk difference 3%; 95% CI 1%, 5%). In the other comparison of esomeprazole 40 mg to pantoprazole 40 mg, healing rates were reported at “early” (4 to 6 weeks) and “late” (8 to10 weeks) time points. Healing rates were equivalent at early and late time points. It was not possible to pool these two studies because of differences in how results were reported. In addition, one of the studies included only patients with grade B (84%) and C (16%) esophagitis, whereas the other study enrolled patients with grade A through D.

In the systematic review by Caro et al.,[34] seven RCTs compared omeprazole 20 mg with ranitidine in 1,575 participants. The omeprazole group achieved a significantly higher healing rate (relative risk 1.81; 95% CI 1.54, 2.13) at 4 weeks. In the same systematic review, lansoprazole was associated with a significantly higher healing rate than ranitidine (relative risk

1.83; 95% CI 1.63, 2.08) at 4 weeks, as shown by three RCTs including 948 patients. Two RCTs compared pantoprazole versus ranitidine and rabeprazole versus ranitidine, recruiting 249 and 338 subjects, respectively. The pantoprazole and rabeprazole groups achieved significantly higher healing rates than ranitidine at 4 weeks. At 8 weeks, a similar pattern was observed in all the comparisons between PPIs and ranitidine.

Table 8. Medical Treatment for GERD: Esophagitis healing rates in trials of PPIs (Risk difference, 95% CI)

Comparison	Studies[a]	Risk difference (95% CI) after 4-week treatment	Risk difference (95% CI) after 8-week treatment
esomeprazole 20 mg vs. omeprazole 20 mg	Kahrilas 2000	0.05 (0.00, 0.10)	0.02 (-0.02, 0.07)
esomeprazole 40 mg vs. omeprazole 20 mg	Kahrilas 2000 Richter 2001	0.10 (0.05, 0.15) 0.12 (0.09, 0.16)	0.06 (0.02, 0.10) 0.09 (0.06, 0.12)
esomeprazole 40 mg vs. lansoprazole 30 mg	Castell 2002 Fennerty 2005 Howden 2002	0.04 (0.02, 0.06) 0.08 (0.02, 0.14) no data	0.03 (0.01, 0.05) 0.04 (-0.01, 0.10) -0.02 (-0.09, 0.05)
esomeprazole 40 mg vs. pantoprazole 40 mg	Gilleson 2004 Labenz 2005	0.11 (-0.02, 0.24) 0.06 (0.03, 0.09)	-0.02 (-0.12, 0.08) 0.03 (0.01, 0.05)
lansoprazole 15 mg vs. omeprazole 20 mg	Castell 1996	-0.08 (-0.15, 0.00)	-0.12 (-0.19, -0.05)
lansoprazole 30 mg vs. omeprazole 20 mg	Castell 1996 Hatlebakk 1993 Mee 1996	0.00 (-0.05, 0.05) -0.02 (-0.15, 0.10) 0.05 (-0.02, 0.13)	0.00 (-0.05, 0.04) -0.02 (-0.11, 0.08) 0.04 (-0.03, 0.11)
lansoprazole 30 mg vs. omeprazole 40 mg	Mulder 1996	0.07 (-0.03, 0.17)	0.03 (-0.03, 0.09)
pantoprazole 20 mg vs. omeprazole 20 mg	Bardhan 2001	-0.04 (-0.12, 0.05)	-0.07 (-0.15, 0.00)
pantoprazole 40 mg vs. omeprazole 20 mg	Corinaldesi 1995	-0.01 (-0.13, 0.11)	0.03 (-0.03, 0.10)
pantoprazole 40 mg vs. omeprazole 40 mg	Korner 2003	0.03 (-0.04 0.09)	no data
pantoprazole 40 mg vs. lansoprazole 30 mg	Dupas 2001	0.01 (-0.06, 0.08)	0.04 (-0.02, 0.10)
rabeprazole 10 mg vs. omeprazole 20 mg	Delchier 2000	-0.06 (-0.15, 0.03)	-0.03 (-0.10, 0.04)
rabeprazole 20 mg vs. omeprazole 20 mg	Delchier 2000	-0.03 (-0.11, 0.05)	-0.03 (-0.10, 0.04)

[a] Complete references of the published studies are included in the systematic review by McDonagh and Carson[33]

Table 9. Medical treatment for GERD: Esophagitis healing after 4-weeks of medical treatment

	Omeprazole 20 mg vs. H2RA	Lansoprazole 30 mg vs. H2RA	Pantoprazole 20 mg vs. H2RA	Rabeprazole 40 mg vs. H2RA
RCTs	7	6	1	1
Participants, total	1575	948	249	338
Relative risk (95%CI)	1.81 (1.54-2.13)	1.83 (1.63-2.08)	1.31 (1.03-1.73)	1.61 (1.27-2.05)

H2RA: H2 receptor antagonists

Maintenance of symptom relief (Table 10)

Donnellan et al.[35] included 18 RCTs in a meta-analysis that compared healing versus maintenance dose of a PPI in 5,116 participants. At the end of follow-up, which ranged from 26 to 52 weeks among the RCTs, the percentage of patients experiencing relapse of symptoms was significantly lower for those treated with a healing dose of a PPI (relative risk 0.78; 95%CI 0.68, 0.88).

In the same meta-analysis, there were five RCTs comparing a healing dose of a PPI versus H2RA in about 800 participants. At the end of follow-up, which again ranged from 26 to 52 weeks, the percentage of patients experiencing relapse of symptoms was significantly lower for those treated with a healing dose of PPI (relative risk 0.48; 95%CI 0.39, 0.60).

Four RCTs compared a maintenance dose of a PPI with H2RA in 831 participants. At the end of follow-up, which ranged from 24 to 52 weeks, the percentage of patients experiencing relapse of symptoms was significantly lower for those treated with a maintenance dose of a PPI (relative risk 0.55; 95%CI 0.47, 0.65).

There were three more comparisons addressed by the systematic review: a healing dose of PPI versus a second healing dose of a PPI, which included two RCTs with 1,001 participants; lansoprazole maintenance dose versus lansoprazole 30 mg alternate days, including two RCTs with 187 subjects; and double dose of PPI versus healing dose of a PPI that used two RCTs with 347 patients. None of the three comparisons showed any significant benefit for any of the treatment modalities examined.

Meta-regression was also used to assess the effect of follow-up duration, country in which the trial was conducted, type of drug, and method of randomization on the outcomes. No significant association between any of the factors and relapse of symptoms was reported.

Table 10. Medical Treatment for GERD: Relapse of symptoms on treatments

	PPI healing dose vs. PPI maintenance dose	PPI healing dose vs. H2RA	PPI maintenance dose vs. H2RA
RCTs	18	5	4
Participants, total	5116	797	831
Follow-up (wk)	26 to 52	26 to 52	24 to 52
Relapse of symptoms, %	30.7 vs. 35.8	21.6 vs. 44.3	31.4 vs. 57

Maintenance of healed esophagitis (Table 11)

Twenty-two RCTs were included in a meta-analysis comparing a healing versus maintenance dose of a PPI in about 6,000 participants.[35] Less than one third of the participants presented initially with severe esophagitis. At the end of follow-up, which ranged from 24 to 52 weeks, the percentage of patients experiencing relapse of esophagitis was significantly lower for those treated with a healing dose of PPI (relative risk 0.63; 95%CI 0.55, 0.73).

Ten RCTs compared healing dose of a PPI with an H2RA in about 1,600 participants. Almost one third of the participants presented initially with severe esophagitis. At the end of follow-up, again from 24 to 52 weeks, the percentage of participants experiencing relapse of

esophagitis was significantly lower for those treated with a healing dose of a PPI (relative risk 0.36; 95%CI 0.28, 0.46).

Six RCTs compared a maintenance dose of a PPI with an H2RA in 1,156 participants. About 30% of the participants presented initially with severe esophagitis. At the end of 24 to 52 weeks of follow-up, the percentage of patients experiencing relapse of esophagitis was significantly lower for those treated with a maintenance dose of PPI (relative risk 0.57; 95%CI 0.47, 0.69).

There were three more comparisons of interest addressed by the systematic review: a healing dose of PPI versus a second healing dose of a PPI, which included three RCTs with 1,020 participants; lansoprazole maintenance dose versus lansoprazole 30 mg alternate days, including two RCTs with 189 subjects; and esomeprazole 40 mg versus esomeprazole 20 mg that used two RCTs with 693 patients. None of the three comparisons showed any significant benefit for any of the treatment modalities examined.

Meta-regression was also used to assess the effect of follow-up duration, country in which the trial was conducted, type of drug and method of randomization on the outcomes. No significant association between any of the factors and relapse of esophagitis was reported.

Table 11. Medical treatments for GERD: Relapse of esophagitis on maintenance therapy

	PPI healing dose vs. PPI maintenance dose	PPI healing dose vs. H2RA	PPI maintenance dose vs. H2RA
RCTs	22	10	6
Sample size, mean (range)	348 (97-1224)	258 (63-721)	324 (97-721)
Participants, total	5964	1583	1156
Patients with originally severe esophagitis, n (%)	1527 (28.9)	471 (32)	318 (24.6)
Follow-up (wk)	24 to 52	24 to 52	24 to 52
Relapse esophagitis, %	17.5 vs. 29.1	22.5 vs. 58.4	38.9 vs. 66.1

Comparative effectiveness of surgical treatments (Tables 12, 13) and long-term effectiveness of surgical treatments (Tables 12, 13, 14)

Key points for comparisons of surgical techniques

- Four RCTs and four non-randomized studies compared different approaches to fundoplication. All the RCTs were graded methodological quality B. The grade of the non-randomized comparative studies ranged from B to C.

- Studies differed in their inclusion criteria, particularly in the extent to which the prior response to medical therapy was described. Only non-randomized trials explicitly included patients with an unsatisfactory response to medical treatment. However, even in such studies the definitions of “unsatisfactory” varied and were not always defined clearly.

- One RCT and one non-randomized study compared laparoscopic with open approach. Efficacy was similar for the two approaches. There was no difference in outcomes of

heartburn, regurgitation, QOL, and usage of antisecretory medications. Almost 90% of patients who were followed for 5 or more years in both surgical arms reported improvement in symptoms.

- There was no difference in the efficacy for symptom relief, QOL improvement and decrease usage of antisecretory medications in the two study arms of laparoscopic total fundoplication versus partial fundoplication, laparoscopic fundoplication with division of short gastric vessels versus without, and open total fundoplication versus partial fundoplication. Notably, fewer than 50 percent of patients who had undergone surgery had follow-up at 5 or more years.

Key points for long-term effectiveness of surgery

- In addition to the long-term data from comparative studies, nine observational studies also provided data on long-term effectiveness of surgery. These focused on patients with GERD that had been well documented by objective measures. The methodological quality of the studies ranged from grade B to C.

- All of the studies reported improvement in symptoms in 80-90% of patients at 5 or more years of follow-up.

- Only one-third of the studies provided data on QOL at 5 or more years. These suggested that QOL had either improved compared to the preoperative period or had normalized.

- None of the observational studies reported esophagitis status at follow-up.

- About one-third of the surgical studies reported data on pH status. The mean pH score had normalized; however they did not report the proportion of patients in whom esophageal pH exposure improved or normalized.

- The proportion of patients requiring regular antisecretory medications after surgery was described in about two-thirds of the studies. Approximately 80 to 90 percent of patients were off all such medications. However, fewer than 50 percent of patients who had undergone surgery were available for long-term follow-up and there was no information regarding medication use in patients who were lost to follow-up.

Detailed analysis of technique comparisons

We identified four RCTs (a total of 406 patients)[36-39] and four non-randomized comparative studies (a total of 1,141 patients in five publications)[40-44] of fundoplication for the treatment of GERD. One RCT[38] and one non-randomized comparative study[44] examined open fundoplication versus laparoscopic fundoplication. Two RCTs[37,39] and three non-randomized comparative studies[40-43] compared two different approaches to laparoscopic fundoplication techniques: laparoscopic total versus partial, laparoscopic with versus without division of short gastric vessels. One non-randomized comparative study compared open total fundoplication versus open partial fundoplication.[36] More than 80% of the subjects had follow-up data from 5 to 11 years in

the RCTs. All the RCTs were graded methodological quality B. Approximately 60%[41] and 20%[40] of subjects had follow-up of 5 to 6 years, respectively, in two prospective non-randomized comparative studies. The methodological grades in non-randomized comparative studies ranged from B to C.

All studies were conducted in an academic setting. All patients had symptoms of chronic GERD, and all had at least one GERD-related diagnostic test performed in the preoperative period. The studies differed in their inclusion criteria, particularly in the extent to which patients' prior response to medical therapy was described. Only one RCT[38] stated clearly patients were treated with a PPI but the specific definition of response or the dose used was not reported. Two RCTs[36,38] reported consecutive patient enrollment. Two RCTs excluded patients with severe esophageal motility disorders.[37,39]

Among non-randomized comparative studies, three reported recurrent GERD symptoms in the patients despite 15 to 24 months of treatment with PPIs.[40,41,44] One study reported consecutive patient enrollment.[44] One study reported symptom recurrence shortly after medication withdrawal as an indication for surgery.[44] Three studies of laparoscopic partial fundoplication included patients with poor esophageal motility.[40,41,43] One study excluded 47% of patients from analysis for multiple reasons.[43]

Symptoms and quality of life

Symptoms and quality of life were assessed using a structured interview or validated quality-of-life scale instrument. Among RCTs, almost 90% of patients who were followed for 5 or more years in both surgical arms reported improvement in heartburn or regurgitation. Three RCTs[37-39] reported improved quality-of-life in both treatment arms. One RCT reported significant improvement in quality of life compared to pre-operative period but no significant differences between surgical treatments.[38]

One non-randomized study reported a significantly higher proportion of patients with improved GERD symptoms in the total fundoplication group, compared with the patients in the partial fundoplication group.[43] In the rest of the non-randomized studies, 80 to 90% of patients with follow-up data reported improvement in heartburn or regurgitation in both arms at 5 or more years. Two non-randomized comparative studies provided data on improved quality of life with mean score comparable to that of healthy individuals, but provided no information on the proportion of patients with improvement.[40,41]

Need for antisecretory medications

Two RCTs[37,39] reported that approximately 90% of patients were off PPIs or off all antisecretory medications in both treatment arms at 5-year follow-up. One RCT reported more subjects were off PPIs in the laparoscopic fundoplication arm compared with the open fundoplication arm.[38] Approximately 90% of patients were off PPIs or off all antisecretory medications in both treatment arms of two non-randomized comparative studies[41,44]at 5-year follow-up.

Esophageal acid exposure and manometry findings

One RCT reported the mean pH score returned to normal and the mean LES pressure improved in both treatment arms but provided no information on the proportion of patients with improvement.[38] Other RCTs did not provide data on esophageal acid exposure at long-term follow-up. Three non-randomized comparative studies reported long-term data on pH status and esophageal manometric studies,[40,41,43] and one reported a significantly higher proportion of patients who had normalized pH status with laparoscopic total fundoplication compared to patients with partial fundoplication (72% versus 44%).[43]

Healing of esophagitis

No studies provided long-term endoscopic data.

Barrett's esophagus and adenocarcinoma

Two RCTs included patients with Barrett's esophagus (6%[36] and 13%[38]). None of these patients developed dysplasia and/or adenocarcinoma in the columnar-lined esophagus at 5 or more years of follow-up. No long-term follow-up data were provided in a non-randomized comparative study where 52% of the patients had Barrett's esophagus in the preoperative period.[41]

Table 12. Comparative studies evaluating the long-term outcomes of Laparoscopic Total fundoplication versus Open fundoplication

Author Year	Study Design	Enroll/ Final	Objective Outcomes			Subjective Outcomes		Study quality[d]
	Follow-up Duration		Off PPI	Off all med	Diagnostic tests	Symptom improved	Quality of life	
Nilsson 2004[a]	RCT 5 yr	30/17	94%	ND	pH status Normal level [b]	100%	PGWB Improved [b] *P*<0.001	B
		30/24	74%		EMS Increased and stable NS	92%		
Pelgrims 2001	nRCT[c] 6 yr	149	ND	85%	ND	94%	ND	C
		61		88%		92%		

RCT: randomized controlled trial; nRCT: non-randomized comparisons; EMS: esophageal manometric studies; PGWB: Psychological General Well-Being Index

[a] Primarily compared patients in a per-protocol analysis; intention to treat analysis did not differ from the per-protocol analysis

[b] Significant differences compared to pre-operative values, but no significant differences between two types of surgery

[c] Retrospective study

[d] RCT and nRCT were graded using different quality grading scheme

Table 13. Comparative studies evaluating the long-term outcomes of technique variation of laparoscopic fundoplication and open fundoplication

Author Year	Study design / Follow-up Duration	Enroll/ Final	Objective Outcomes: Off PPI	Objective Outcomes: Off All Meds	Objective Outcomes: Diagnostic tests	Subjective Outcomes: Symptom improved	Subjective Outcomes: Quality of life	Study quality[d]
Laparoscopic Total vs. Laparoscopic Partial								
Ludemann 2005	RCT 5 yr	53/51	88%	ND	ND	Heartburn 95%	88% Normal	B
		54/50	96%			Heartburn 90%	98% Normal	
Kamolz 2002 UI12430078	nRCT 5 yr	104/69	100%	ND	pH status Normal mean score EMS 94% Normal	100%	GIQLI Mean score normal	B
		65/33	97%	ND	EMS Normal mean score EMS 94% Normal	93%	GIQLI Mean score normal	
Granderath 2002[a] UI1997816 Kamolz 2002 UI12236479	nRCT 5 yr	345/64	ND	ND	pH status Normal mean score EMS Normal mean score	Heartburn 97% Regurgitation 91%	Improved to normative healthy data	C
		155/39	ND	ND				
Patti 2004[b]	nRCT Retros-pective ~6 yr	94	ND	ND	pH status 72% Normal EMS Normal mean score	85%	ND	C
		141	ND	ND	pH status 44% normal EMS Normal mean score	67%	ND	
Laparoscopic (with vs. without) division of short gastric vessels								
O'Boyle 2002	RCT 5 yr	52/50	ND	91%	ND	Heartburn 88% Regurgitation 90%	70% good	B
		50/49				Heartburn 82% Regurgitation 96%	76% good	
Open Total vs. Open Partial								
Hagedorn 2002	RCT 11.5 yr	65/ND [c]	ND	ND	ND	Heartburn 90% Regurgitation 91%	ND	B
		72/ND [c]						

EMS: esophageal manometric studies; GIQLI: gastrointestinal quality of life index comparative trials; nRCT: non-randomized comparisons; PGWB: Psychological General Well-Being Index; RCT: randomized controlled trial

[a] Data presented for the whole group

[b] 20% and 34% follow-up, respectively, for EMS in the laparoscopic total vs. partial fundoplication

[c]. Data presented for the whole group at follow-up: at 11.5 yr n=110 followed up for both groups and data obtained from administrative files

[d] RCT and nRCT were graded using different quality grading scheme

Detailed analysis of long-term effectiveness of surgery

In addition to the comparative studies, five cohort studies[45-49] of laparoscopic fundoplication and four cohort studies[50-53] of open fundoplication provided data on long-term efficacy of surgical treatment of GERD. These nine cohort studies enrolled a total of 1,752 patients. Except for two studies that reported close to 100% follow-up for 6 years[49] and 20 years[51], the rest of the observational studies had fewer than 50% of patients at follow-up of 5 to 6 years. The methodological grades in these studies ranged from B to C.

All studies were conducted in an academic setting. All patients had symptoms of chronic GERD, and all had at least one GERD-related diagnostic test performed in the preoperative period. The studies differed in their inclusion criteria, particularly in the extent to which patients' prior response to medical therapy was described.

Three studies reported recurrent GERD symptoms despite 6 to 18 months of treatment with PPIs or antisecretory medications.[45,48,50] One study included patients whose symptoms were controlled adequately on PPIs, but chose to undergo surgery in preference to long-term medical therapy.[45] Four studies[47,49,50,52] enrolled consecutively operated patients and one[52] included patients who underwent primary antireflux procedures.

Symptoms and quality of life

All cohort studies reported improvement in reflux symptoms. One study reported that preoperative response to PPI correlated significantly with response to surgery.[45]

Need for antisecretory medications

All cohort studies (except for two studies[52,53] which did not provide data) reported that 80 to 90% of the subjects were off PPIs or off all antisecretory medications.

Esophageal acid exposure and manometry findings

Four cohort studies[45,48,50,53] reported data on pH status, and in two,[50,53] the proportion of patients who had normalized was also mentioned. One study reported significant improvement in mean esophageal acid exposure score and manometric score compared to preoperative period.[45]

Healing of esophagitis

No cohort studies provided long-term endoscopic data.

Barrett's esophagus and adenocarcinoma

Thirteen percent of patients in one cohort study had Barrett's esophagus and none developed dysplasia or adenocarcinoma at 6-year follow-up.[46]

Table 14. Cohort studies evaluating the long-term outcomes of fundoplication

Author year	Follow-up Duration	Enroll/ Final	Objective outcomes			Subjective symptoms		Study quality[c]
			Off PPI	Off All meds	Diagnostic Tests	Reflux Symptom improved	Quality of life	
Laparoscopic Fundoplication								
Laffullarde 2001	6 yr	178/176	ND	89%	ND	No reflux symptoms	ND	B
Anvari 2000	5 yr	332/181	88%	ND	pH status; EMS improved mean score *P*<0.0001	GERD symptom score *P*<0.0001	ND	C
Booth 2002	8 yr	179/48	ND	86%	ND	Heartburn 93% Regurgitation 91%	ND	C
Granderath 2002 11918872	5 yr	153/39	97%	ND	pH status Normal mean score	Heartburn 97% Regurgitation 97%	Improved to normative healthy data	C
Bammer 2001[b]	6.4 yr	171/171	86%	ND	ND	Heartburn 94% Regurgitation 94%		C
Open Fundoplication								
Grande 1994	20 yr	160/157	ND	85%	ND	81%	ND	B
Franzen 1999[a]	10 yr	101/87	ND	94%	pH status 53% improved	92%	ND	B
Luostarinen 1993	~6 yr	127/109	ND	ND	pH status 71% improved	70%	ND	B
Henderson 1985	6.5 yr	351/335	ND	ND	ND	93.1%	ND	C

EMS: esophageal manometric studies
[a] Posterior partial fundoplication
[b] Retrospective follow-up
[c] Cohort studies were graded using different quality grading scheme

Comparative endoscopic studies (comparison with sham) and cohort studies (Tables 15, 16)

Key points for comparative endoscopic studies (comparison with sham) and cohort studies

- Three endoscopic procedures are available in the US: EndoCinch™ Suturing System, NDOplicator™, and Stretta™. A fourth (Enteryx™) was voluntarily removed from the market due to safety concerns during final preparation of this report. We elected to include the data pertaining to Enteryx™ since it was the method used in one of the only two sham-controlled trials and because of the relatively large number of reports, which

allowed for a better understanding of how various endpoints in the endoscopic studies correlated with one another.

- There were only two sham-controlled trials: one using Enteryx™ and the other Stretta™. There were 14 cohort studies. The longest mean follow-up was one year for the sham-controlled trials and 27 months for the cohort studies. Both sham-controlled trials were given a methodological grade of B. The methodological grade of the cohort studies ranged from B to C. No studies directly compared one endoscopic procedure with another.

- The inclusion and exclusion criteria in most of the studies limited applicability to patients with well-defined GERD who have a small hiatal hernia and either mild to moderate or no esophagitis.

- Stretta™ was more effective than sham in improving symptoms of reflux and QOL at 6 months. Enteryx™ was more effective than sham in improving symptoms of reflux at 3 months. QOL at 6 months improved in both the Enteryx™ and sham groups. Between group comparison was not described.

- Enteryx™ and sham both reported improvement in QOL at 6 months.

- Healing of esophagitis has not been consistently demonstrated in endoscopically treated patients. Esophagitis improved in some patients and worsened in others in the various reports.

- Improvement of esophageal pH exposure compared with sham could not be demonstrated for either Enteryx™ or Stretta™. Uncontrolled studies of all the endoscopic procedures suggest improvement or normalization in pH in some patients, but there were insufficient data to determine the magnitude of improvement relative to one another or the correlation of pH changes with other outcome measures.

- Significantly more patients treated with Enteryx™ were able to discontinue PPIs compared with sham while there was no significant difference in patients treated with Stretta™. The proportion of patients who were freed from regular use of any antisecretory agents (PPIs, H2RAs, or antacids) was no different between sham and Stretta™.

Detailed analysis

Three endoscopic therapies are currently available in the United States while a fourth (Enteryx™) was voluntarily recalled in September 2005:

1. The Stretta™ procedure (Curon Medical, Freemont, CA), which involves application of radiofrequency energy to the lower esophageal sphincter

2. EndoCinch™ Suturing System (EndoCinch™) (Bard, Murray Hill, NJ), which involves creation of a submucosal plication in the region of the gastric cardia using a device that allows for sutures to be placed endoscopically.

3. NDO Plicator™ (NDO Plicator ™, NDO Surgical, Mansfield, MA), which involves creation of a transmural plication in the region of the gastric cardia.

4. Enteryx™ (Boston Scientific, Natick, MA), which involves injection of a biopolymer into the lower esophageal sphincter.

Our literature search identified a total of 30 studies on endoscopic procedures (see Evidence Table 2 for details). Five studies[54-58] included data from patients already reported in 10 other studies[57,59-67] from this group of 30. As a result, data from these 10 studies were not included in this review unless they provided unique information (two studies[57,65]) that was not included in the five studies, but each patient was analyzed only once. In final tabulation, data from 22 studies on endoscopic procedures are summarized below. Three of them were RCTs.[6,7,68] Three of them were non-randomized comparisons.[65,69,70] Fourteen were cohort studies. One was a survey[71] and one was a *post hoc* analysis[58] of data from two other studies.[57,67] Additional data from unpublished studies that have been presented in preliminary form were not included in the primary analysis but are discussed in Appendix F.

Two sham-controlled studies have been published in final form: one for Stretta™ [7] and the other for Enteryx™.[6] Four other comparative trials were identified. One RCT[68] compared two different configurations of EndoCinch™ sutures. Two other non-randomized studies[69,70] compared EndoCinch™ with laparoscopic fundoplication. A fourth non-randomized study[65] compared the Stretta™ procedure with laparoscopic fundoplication. We did not identify a RCT comparing any of the endoscopic techniques directly with fundoplication or continued (or intensified) medical therapy. No studies directly compared the endoscopic procedures to one another.

Studies were generally of short duration, reporting outcomes at three, six and 12 months with only a few reports describing follow-up as long as 24 to 27 months.[54,55,72] The largest studies (other than a survey study of 558 respondents[71]) included fewer than 150 subjects,[54] while the two sham-controlled trials included only 64 subjects each.[6,7].

Both of the sham-controlled studies were rated methodologic quality B. Their main deficiencies were small size and short duration. Effectiveness of blinding was not assessed in either study. Many of the uncontrolled studies and non-randomized comparative studies were rated methodologic quality C. They had important limitations in their design, analysis (such as lack of an intention-to-treat analysis), and/or reporting. The corresponding device manufacturer provided direct funding for almost all the reports or supported the investigators.

Patient characteristics were similar in all of the endoscopic trials. In general, all the studies defined GERD by symptoms, findings at endoscopy, pH studies, and response to medications. Approximately half of the studies excluded patients who had severe esophagitis (Savary Miller grade >2 or Los Angeles grade >C). All of the studies excluded patients with a hiatal hernia exceeding a certain size. Studies of Stretta™, EndoCinch™, and NDO Plicator™ generally excluded patients with a hiatal hernia >2cm while two of the Enteryx™ studies permitted inclusion of patients with a hiatal hernia as large as 5 cm.[6,54] Patients with severe esophageal motility disturbances were excluded from all of the studies.

As noted in the methods section, we focused on the five major important outcomes in treating GERD: symptoms, change in esophagitis grade, improvement in esophageal pH exposure, reduction in the need for antisecretory medications, and improvement in quality of life. Details of these outcomes are presented in the evidence tables while the key points are summarized here. Adverse effects are presented separately. Because of the short-term follow-up, there are no data from which to assess other important objectives such as prevention of esophageal stricture, development of Barrett's esophagus or esophageal adenocarcinoma, or possible long-term adverse effects from therapy.

Patients in the two sham studies had PPI-responsive GERD who had no more than a small hiatal hernia and only mild to moderate esophagitis. Stretta™ was more effective than sham in improving symptoms of reflux and QOL at 6 months.[7] Symptoms at follow-up were assessed while patients were off their medications. Information on symptoms while on medications was not described. Enteryx™ was more effective than sham in improving symptoms of reflux at 3 months.[6] Enteryx™ and sham both reported improvement in QOL at 6 months compared with baseline. Between group comparison was not described. Significantly more patients treated with Enteryx™ were able to discontinue PPIs compared with sham while there was no significant difference in patients treated with Stretta™. The proportion of patients who were freed from regular use of any antisecretory agents (PPIs, H2RAs or antacids) was no different between Stretta™ and sham, and was not reported in the Enteryx™ study. An improvement in esophageal pH exposure could not be demonstrated when compared to sham for either Enteryx™ or Stretta™. Both studies had small number of patients and short duration of follow-up.

Table 15. Endoscopic treatments: Sham controlled trials

Author Year Intervention	N enrolled/ follow-up Duration ≥ grade 3 esophagitis	Quality	Follow-up status				
			Change in symptoms	Quality of Life	pH status	Medication	Esophagitis status Others
Deviere 2005 Enteryx™ (ERX) vs. Sham	64 61 3 mos & 6 mos No	B	Heartburn score & regurg score improved ≥ 50% more in ERX vs. Sham at 3 mos (Ratio 3.05, CI 1.55-6.33; Ratio 2.03, CI 1.14-3)	At 3 mos, SF-36-P & SF-36-M improved in ERX, % change between groups=NS; GERD-HRQOL improved by ≥50% more in ERX (*P*<0.001)	Difference in pH exposure between groups=NS (incomplete data)	At 3 mos, 68% ERX vs. 41% Sham off PPI (ratio 1.67, CI 1.03-2.80); ≥ 50%↓ in PPI use is 81% ERX vs. 53% Sham (ratio 1.52, CI 1.06-2.28)	ND 6 of 9 re-treated in ERX; 20 of 23 Sham proceeded to ERX (ratio 0.42, CI 0.22-0.73) at 3 mos
Corley 2003 Stretta™ (STR) vs. Sham with	64 56 6 mos & 12 mos	B	At 6 mos, mean heartburn score improved in STR compared to	At 6 mos, SF-36-P & HRQOL improved in STR compared to Sham (*P*=0.05,	At 6 mos, no difference in median acid exposure between groups	At 6 mos, 58% STR vs. 57% Sham off PPI (NS); daily PPI use ↓46% in STR vs. ↓29% in	At 6 mos, no difference between groups No significant change in LES

X-over at 6 mos	No		Sham (*P*=0.01)	*P*=0.003)		Sham (NS)	

SF-36-P: Short form 36 – physical; SF-36-M: Short form 36 – mental; HRQOL: health related quality of life;

Almost all of the uncontrolled and non-randomized endoscopic studies reported symptom improvement compared to baseline (see Table 16). Normalization of esophageal pH exposure was observed in 25 to 50% of patients. Except for one study on the Stretta™ procedure,[58] which found that responders (defined by improvement in quality of life) had improved distal esophageal exposure time compared with nonresponders, none of the other studies showed data on correlation of pH changes with other outcome measures.

Almost all the uncontrolled studies showed a reduction in the need for PPIs. The proportion of patients who did not require any antisecretory medications was reported infrequently but was in the range of only 25 to 40% in studies in which it was described.

The effect of the endoscopic procedures on healing of esophagitis was unclear. Two uncontrolled studies of Enteryx™ showed a worsening of esophagitis in approximately one-third of patients;[54,73] the same studies also reported improvement in approximately 10% of the patients.

The durability of benefits for any of the procedures is unclear because most of the studies had short-term follow-up. One study on EndoCinch™ reported improvement in symptoms relative to baseline at 24 months.[72] However, two studies on EndoCinch™ with follow-up of 12 and 18 months, respectively, reported loss of plications in the majority of patients.[74,75]

Only three studies compared an endoscopic procedure with laparoscopic fundoplication: two with EndoCinch™,[69,70] and one with Stretta™.[65] The two studies of EndoCinch™[69,70] concluded that patients who had fundoplication were more satisfied with their results. One of them reported that significantly fewer patients in the fundoplication group used PPIs or motility drug compared with patients in the EndoCinch™ group at follow-up of 8 months.[69] The study on Stretta™[65] reported that fewer patients in the fundoplication group required PPIs, but both procedures improved symptoms and quality of life. No studies directly compared the endoscopic procedures to one another.

Table 16. Endoscopic treatments: Uncontrolled and non-randomized studies

Intervention	Quality	Longest follow-up duration	Follow-up status			
		Excluded ≥ grade 3 esophagitis	Change in symptom Quality of Life	Esophagitis status	Medication status	pH study
Enteryx™ Cohen 2005[54] Deviere 2002[76] Schumacher 2005[73]	B C B	24 months [Cohen 2005]	Symptoms improved relative to baseline (3 studies);	ND (1 study) Improved 12-13% (2 studies) No change 55% (2 studies) Worsen 32-33% (2 studies)	ND (1 study); Reduced need for PPIs (2 studies); 65 -67% off PPIs (2 studies); % not requiring any antisecretory medication ND	pH exposure improved (2 studies) pH normalized 37-52% (2 studies) pH status not described (1 study)
		2 studies Yes	ND (1 study); Improved (2 studies)			
Stretta™ Go 2004[77] Lutfi 2005[55] Tam 2003[78] Triadafilopoulos, 2002[57]	C C C C	26 months [Lutfi 2005]	Symptoms improved relative to baseline (4 studies)	ND (2 studies); 2/20 baseline→ 10/19 at 6 mos had LA grade A [Tam 2003]; No change (1 study)	29-70% off PPI (4 studies) 40% off all meds (1 study)	ND (1 study); 42% of patients in group not requiring or requiring reduced dose of PPI normalized (1 study); 25% normal acid exposure (1 study); DeMeester improved significantly (1 study)
		2 studies Yes	Improved (4 studies)			
EndoCinch™ Filipi 2001[68] Chadalavada 2004[69] Velanovich 2002[70] Arts 2005[79] Chen 2005[72][Mahmood 2003[80] Schiefke 2005[75] Tam 2004[81] Abou-Rebyeh,2005[74]	C C C C C C C C C	24 mos [Chen 2005]	Symptoms improved relative to baseline (9 studies); ND (1 study);	No change (2 studies); ND (3 studies); [1 healed, 3 of 4 same grade] (1study); [No Change:57%; Improved: 29%; Worsened:14%] (1 study); [3 of 5 had same grade; 2 resolved; 2 new cases of grade A] (1 study); [Esophagitis present in 41% at baseline; 31% at 2 mos; 56% at 12 mos] (1 study)	6-64% off PPI (6 studies); 62% taking fewer PPIs or H2RAs (1 study); 25% off an antisecretory med (1 study); ND (1 study)	pH improved (2 studies) ND (2 studies) 14-40% normalized (5 studies)
		4 studies Yes	Improved or Satisfied (5 studies); 14/70 considered non-responders (1 study); ND (3 studies)			
NDO Plicator™ Pleskow 2005[56]	B	12 mos	Median symptom scale improved from baseline off med (no change compared to baseline on med)	ND	68% off PPI 23% off all antisecretory meds	pH normalized 30%
		No	Improved			

Key Question 1B. In patients with Barrett's esophagus, what is the result of medical versus surgical management in terms of the incidence of adenocarcinoma of the esophagus?

Key point for outcome of adenocarcinoma of the esophagus in patients with Barrett's who had medical versus surgical treatment

- There were limited direct comparative data concerning the incidence of esophageal adenocarcinoma in patients diagnosed with Barrett's esophagus who received medical treatment versus those who underwent fundoplication. The available evidence suggests that surgical management offers no significant advantage over medical therapy in patients with Barrett's esophagus in reducing the incidence of adenocarcinoma. However, more studies are needed to fully understand the relative efficacy of the two approaches.

Detailed analysis

We reviewed studies comparing fundoplication with medical treatment in patients with Barrett's esophagus that reported the incidence of adenocarcinoma as an outcome. Only one RCT addressed this question. Parrilla et al. reported data from 113 patients with Barrett's esophagus from 1982 to 2000.[82] (Ortiz et al.[83] reported earlier data on 59 patients from 1982-1993 apparently based on the same trial). The authors reported that multiple biopsies were taken systematically during endoscopy: "the first immediately above the squamo-columnar junction, the next immediately below, and the rest every 1-2 cm in a caudal direction in the various quadrants of the circumference."[83] Both macroscopic and histological data were presented. In the medical treatment arm, the median follow-up was 5 years (range 1-18), two patients developed adenocarcinoma of the esophagus. In the surgical treatment arm, the median follow-up was 6 years (range 1-18), also two patients developed adenocarcinoma. The rate of malignancy was 1/129 patient-years (0.8% per year) for the medical group and 1/203 patient-years (0.5% per year) for the surgical group. The difference was not significant.

There were two pooled analyses that compared the reported rates of esophageal adenocarcinoma in patients managed medically with patients who underwent surgery[84,85]. A review by Corey et al. included cohorts and trials published from 1966 through October 2001.[85] Sixteen publications had at least 12 months of follow-up. Medical patient-years totaled 4906. Surgical patient-years totaled 4678. The incidence rate of esophageal adenocarcinoma in patients with Barrett's esophagus who received medical treatment was 5.3 (95%CI, 3.6-7.8)/1000 patient-years. The incidence rate of esophageal adenocarcinoma in patients with Barrett's esophagus who received surgical treatment was 3.8 (95%CI, 2.4-6.1)/1000 patient-years. The incidence rate of esophageal adenocarcinoma in the subgroup of patients with Barrett's esophagus who received medical treatment in the most recent 5 year analyzed (1996-2001) was 4.3 (95%CI, 2.6-5.8)/1000 patient-years. This subanalysis was done because of the advances in medical therapy in recent years with the addition of proton pump inhibitors to GERD treatment. There was no significant difference in rate of esophageal adenocarcinoma per patient-year between the surgical and medical groups or between the surgical groups and the medical therapy group in the last 5 years.

The study by Bammer et al.[84] included a retrospective review of 21 articles regarding the cancer risk for patients with Barrett's treated medically; it was 1 in 144.7 patient-years. A review

of 19 articles including unpublished data showed the cancer risk in patients after antireflux surgery was 1 in 294.4 patient-years. The mean follow-up for medical surveillance was 2.7 years; the mean follow-up for antireflux surgical surveillance was 4.0 years. The authors stated that patient groups were not homogeneous in terms of age, length of symptom duration, presence of Barrett esophagus and dysplasia at baseline, and other possible risk factors for Barrett cancer. Statistical comparative data were not presented in this study. The authors concluded that the data do not prove that surgery is superior to medical treatment in the prevention of Barrett cancer, but they show a strong tendency for surgery to be the better treatment to prevent progression and the development of Barrett carcinoma.

Key Question 2A. What are the characteristics of patients who have undergone these therapies, including the nature of previous medical therapy, severity of symptoms, age, sex, weight, other demographic and medical factors or by specific patient subgroups, and provider characteristics for procedures including provider volume and setting (eg, academic versus community)?

Key points for characteristics of patients who have undergone medical, surgical and endoscopic surgery

- Half of the surgical patients were 40-60 years of age.
- Sex distribution was equal.
- Patients' BMI ranged from 19 to >35.
- Objective testing for GERD varied among studies.
- Endoscopic studies included patients with less severe esophagitis and a smaller hiatal hernia compared to patients from surgical studies.

Detailed analysis

We did not find any epidemiologic studies describing the setting in which most surgical and endoscopic antireflux procedures are performed. Most of the published literature of surgical and endoscopic therapies were written by authors affiliated with academic institutions.

Judging by the characteristics of patients who were included in the treatment studies, the vast majority of patients who eventually underwent surgical therapies exhibited the typical symptoms of GERD, including heartburn and regurgitation. Primary complaints of dysphagia, water brash, chest pain, respiratory symptoms, and bloating were much less frequent.[86-89] Patients usually were symptomatic for several years before undergoing surgery.[87,90-92] The majority of patients who underwent laparoscopic therapy reported a moderate level of symptoms as measured by Visick, DeMeester, or other symptom scale.[90,91,93,94]

In terms of patient demographic data, approximately half of the surgical patients were in the 40 to 60 years age bracket.[92,95,96] The sex distribution was approximately equal. The range of the

weight data for the few studies that provided these data include BMI 19 to ≥35 and weight 86-87 Kg with one study[92] reporting less than 70 kg to more than 90 kg. Race or smoking status were rarely reported.

Objective testing for GERD in the observational surgical studies varied widely. In some studies, pH studies were undertaken only in the subset of patients presenting with atypical symptoms or those unresponsive to PPI therapy, but without evidence of esophagitis on endoscopy or reflux on barium swallow.[91-93] More than 40 percent of patients had at least the equivalent of Savary-Miller grade 1 esophagitis in studies for which it was reported.[86,89,90,92,93,96-98] Preoperative hiatal hernias were common in both patients who underwent open or laparoscopic treatment with more than 40 percent of all patients with evidence of a hiatal hernia in studies for which it was reported.[86,87,89,91,92,96-98]

Endoscopic studies had strict entry criteria. Most patients did not have severe esophagitis (Savary Miller grade >2 or Los Angeles grade >C). All but two studies excluded patients with hiatal hernia > 2 to 3 cm; the two exceptions permitted inclusion of patients with hiatal hernia up to 3 to 5 cm.[6,54] Patients with severe esophageal motility disturbances were excluded from all the studies.

Key Question 2B. Is there evidence that effectiveness of medication, surgical and endoscopic therapies vary for specific patient subgroups?

Key points for specific patient subgroups

- Medically treated patients who have a low LES resting pressure or LES incompetence may have a worse symptomatic response and may be less likely to discontinue medical therapy compared to those with a normal LES.

- Patients on maintenance antireflux medications may have higher rates of esophagitis if they have any of the following factors: increased severity of esophagitis pretreatment, younger age, and moderate to severe regurgitation.

- Virtually all data concerning patient or treatment-related factors that influenced outcomes for open and laparoscopic surgery were derived from observational studies.

- There is no substantial evidence to support a difference in surgical outcome based on age, preoperative presence or severity of esophagitis, LES incompetence/low LES resting pressure, or esophageal body hypomotility.

- Patients treated surgically who have a history of psychiatric disorders may have worse outcomes in the dimensions of symptom and satisfaction compared to those without a significant psychiatric history.

- Patients treated surgically who respond to antisecretory medications preoperatively may have better symptomatic and global surgical outcomes, as well as GERD-HRQL and Visick scores as compared to those who did not respond.

- All studies concerning factors that influenced the outcomes of endoscopic therapy were small and likely underpowered to find differences. Although age was a modifying factor in some reports, the strength of the association was unclear.

- There was no substantial evidence to support a difference in endoscopic outcome based on characteristics of the pretreatment response to antisecretory medications, symptoms, BMI, sex, injection volume, baseline esophageal acid exposure, presence of esophagitis, or a hiatal hernia. However, most of the studied patients did not have severe esophagitis or hiatal hernia >2-3 cm.

Detailed analysis

There were two studies that examined whether factors that influenced treatment outcome differed for those treated medically versus surgically.[82,99] In an observational study of 28 patients with low LES resting pressure, those who declined surgery for medical therapy (H2RAs or omeprazole) had worse symptoms and were less likely to have discontinued all antireflux medications than those who opted for open Nissen fundoplication after an average of 31 months post therapy.[99] In one RCT involving 101 patients with Barrett's esophagus, rates of esophagitis were greater in patients treated medically (H2RAs and/or omeprazole) than in patients treated with Nissen fundoplication after a median of 5 years. There was no significant difference between the two groups in rates of Barrett's esophagus, length of Barrett's segment, progression to dysplasia, or adenocarcinoma at follow-up.[82]

Factors that influenced the outcome of medical therapy

A meta-analysis of five RCTs involving a total of 1,154 patients found an increased risk of esophagitis during maintenance therapy on omeprazole, ranitidine, or placebo in patients with the following associations: 1) increased pretreatment severity of esophagitis; 2) younger age; 3) non-smoking status; and 4) moderate/severe regurgitation. Body mass index, sex, alcohol consumption, concomitant NSAID therapy, disease duration, pretreatment severity of heartburn, and residual symptoms at healing were non-significant factors for relapse.[100].

Four studies evaluated specific patient characteristics on outcomes of medical therapy.[99,101-103] Two evaluated the risk of medical therapy failure based on esophageal manometry.[99,103] One of these (a cohort study with 55 patients) reported that the likelihood of stopping all antireflux medicines was reduced in patients with low LES pressure.[99] The likelihood of stopping all medical therapy was not influenced by esophageal body motility or esophageal pH pattern. A single arm, open trial of omeprazole involving 128 patients with mild esophagitis reported that the likelihood of relapse/persistence was higher in patients with a structurally incompetent LES.[103] The risk was highest in patients with LES incompetence and poor esophageal peristalsis. An RCT conducted at 19 centers examined the effects of ranitidine versus placebo on 232 patients.[101] Smoking status had no effect on esophageal healing between or within treatment groups. Although there was no difference in symptomatic improvement regardless of the intervention group, antacid use was reduced significantly among smokers on ranitidine versus smokers on placebo ($P<0.05$). One cohort study found no difference between elderly and non-elderly for esophageal healing and heartburn resolution after ranitidine therapy.[102]

Factors that influenced the outcome of fundoplication (Table 17)

There were 10 case-control and 15 cohort studies of laparoscopic antireflux surgery studies that analyzed the influence of specific patient characteristics on outcomes after surgery. There were no randomized controlled or direct comparison trials. Variables examined included study setting, race, sex, obesity, aerophagia, weight, symptoms, preoperative response to antisecretory medications, severity of acid reflux, preoperative LES incompetence and pressure, esophagitis severity, presence of hiatal hernia, and psychological traits. Outcomes assessed included symptoms; pH status; whether the patients were off PPIs or all medications; quality of life or patient satisfaction, which included response of whether patient would undergo surgery again; and global success or failure. Evidence for effectiveness of therapies based on patient characteristics was limited, and almost all studies that we identified were graded as methodologic quality B or C. Results are summarized below.

One study examined the rates of laparoscopic antireflux surgery failure in 445 patients identified through a nationwide registry in Sweden who were treated at low- or high-volume hospitals.[95] There was no significant increase in the rates of laparoscopic antireflux surgery failure in patients between these two settings. Nevertheless, the learning curve for surgeons performing laparoscopic fundoplication has been documented in several studies.[104-108] Two studies found that outcomes of laparoscopic fundoplication performed by a relatively inexperienced surgeon could be improved by assistance from a more experienced surgeon.[106,107]

Patient characteristics

Age

Eleven studies (with a total of 2,125 patients) examined the influence of the patient's age on surgical outcomes.[86,87,89,92,93,95,109-113] Sample sizes ranged from 48 to 408 patients and ages ranged from 15 to 82 years. Follow-up ranged from a median of 14 to 71 months.

Eight studies reported that age was unrelated to symptomatic outcomes.[86,92,95,109-113] One study reported better outcomes in patients younger than 50.[86] Five reported that there was no effect of age on the quality of life/satisfaction and the ability to return to work.[92,95,110-112] One found no effect of age on the likelihood of abnormal esophageal pH exposure[87] while another reported no effect of age on global success or failure.[93] Two cohort studies[114,115] examined the outcomes for elderly patients only. However, they were not included in the analysis since neither provided a direct comparison with a non-elderly group.

Sex

Eight studies (with a total of 1,681 patients) examined the influence of sex on surgical outcomes.[86,87,89,92,94,95,109,113] Four reported that sex had no effect on symptomatic outcomes.[86,89,95,109] O'Boyle et al.[92] reported that men had better heartburn scores (P=0.018) as well as higher patient satisfaction scores (P=0.015), while Stewart et al.[113] reported that women had worse abdominal pain, diarrhea, indigestion and constipation (P=0.043 to 0.001). Stewart et al. also showed that women more frequently reported bloating (P=0.001) and inability to vomit (P=0.021). Sex was not a factor for abnormal postoperative DeMeester score[87] or patient satisfaction.[95] A study by Khajanchee et al.[94] reported a multivariate analysis in which sex was a statistically significant predictor of a poor symptomatic outcome, but did not specify which sex was at increased risk.

BMI

Nine studies (with a total of 2,219 patients) analyzed the association of body mass index (BMI) or weight on surgical outcomes.[86,92,94-96,109,116-118] One reported aggregate BMI data stratified by low- versus high-volume hospitals.[95] Three studies did not report the data for the weight of the patients. Five studies reported no effect of weight or BMI on symptomatic outcomes.[86,92,94,96,109] One reported worse heartburn scores for the normal weight group compared with the overweight or obese groups (P=0.001).[117] By contrast, another study reported obese patients had more recurrences of symptoms than the normal or overweight patients (P=0.03).[118] Three studies reported no effect of BMI on patient satisfaction or the ability to return to work.[92,96,117] Increasing BMI correlated with patient satisfaction in one Swedish study regardless of the hospital's volume of laparoscopic procedures.[95] Two studies reported that BMI was not associated with global success or failure of surgery.[96,116]

Psychological profile

Four studies (with a total of 388 patients) evaluated an association between a history of psychological disorders or certain psychological traits at outcomes of laparoscopic fundoplication. Psychological conditions reported in three studies included major depression, anxiety disorders, sexual abuse, and functional gastrointestinal dysfunction.[93,119,120]

Absence of psychiatric disorders was associated with greater improvement in GERD-HRQL symptom and total score, and patient satisfaction.[119,120] Another study reported psychiatric history was significantly associated with surgical failure.[93] The study by Kamolz et al.[121] examined the impact of a patient's personality traits on temporary dysphagia and found that a correlation between dysphagia and a patient's "internal locus of control." For patients with strong internal control (ie, high expectations that they can control their health-related outcomes), there was less dysphagia. This was compared to patients with a predominantly fatalistic external control (a belief that their health outcomes were beyond their control), which was highly correlated with dysphagia.[121] It is unclear if there was overlap of patients for the two studies by Kamolz et al.[120,121]

Clinical data

Baseline symptoms

The association of patients' baseline symptoms and the outcomes of laparoscopic fundoplication was analyzed in eight studies (with a total of 984 patients).[45,86-89,93,109,116] Three found that typical symptoms of heartburn, regurgitation, dysphagia were associated with better symptomatic outcomes.[86,88,89] By contrast, heartburn, reflux, and dysphagia had no effect on global success or failure.[86,88,89] Preoperative symptoms were not associated with postoperative dysphagia in one study.[109] Another study reported that severe preoperative symptom scores correlated positively with a symptomatic response.[45]

Preoperative response to acid-suppression therapy

Four studies (with a total of 592 patients) examined the effect of the patient's preoperative response to antisecretory medications on outcomes of laparoscopic fundoplication, as measured by patient satisfaction, QOL, and global success or failure.[45,86,89,93] Two studies reported that patients with a complete or partial response to PPI therapy at baseline had a better symptomatic response.[45,86] One study in which 79% of patients had a complete symptomatic response to PPI therapy also reported good outcomes by Visick score.[89] Similarly, another study reported that non-response to a PPI was predictive of surgical failure.[93]

Esophagitis

Seven studies (with a total of 1,413 patients) evaluated the relationship between baseline esophagitis and surgical outcomes.[86,89,91-94,109] Six of the seven found no difference in the rates of treatment failure between those who had esophagitis and those who did not, as measured by differences between groups in GERD symptoms, medication use, or satisfaction. One found slightly higher rates of dysphagia postoperatively in patients with esophagitis preoperatively, but not of other symptoms or outcomes measured.[91]

Five studies (with a total of 553 patients) examined the association between the presence of severe esophagitis (defined as circumferential erosions, strictures and Barrett's esophagus) and the outcomes of laparoscopic fundoplication.[86,87,89,93,109] Outcomes were considered to be poor in patients who had symptomatic relapse/persistence, acid reflux, or reliance on medical therapy. Four of five studies found no difference in the likelihood of poor outcomes in patients with and without severe esophagitis.[86,89,93,109] Only one small study found an increased risk of acid reflux in patients with baseline severe esophagitis.[87]

Esophageal pH

Nine studies (with a total of 1,307 patients) analyzed the influence of preoperative esophageal pH exposure on the outcomes of laparoscopic fundoplication.[45,86,87,89,92-94,97,109] Outcomes considered included relapse/persistence of symptoms, acid reflux, reliance on medical therapy, satisfaction, or a combination of factors. Four studies explicitly reported that pH testing was performed while the patient was off all acid-modifying medications.[45,86,87,94] Of these, two reported better results in patients with increased preoperative acid reflux;[86,94] while one study reported no outcome differences based on preoperative 24-hour pH study results;[45] and another reported an increased risk of an abnormal postoperative DeMeester score with increasing preoperative DeMeester scores.[87]

LES competence/pressure

Nine studies (with a total of 1,279 patients) examined the risk of surgical failure, including relapse/persistence of symptoms, acid reflux, reliance on medications and a combination of factors, based on LES incompetence (abnormally low pressure and short length at rest) or low LES resting pressure.[45,86-88,93,94,97,116,122] Eight did not find an increased risk of surgical failure with preoperative LES incompetence or a low resting pressure.[45,86,88,93,94,97,116,122] One found that low preoperative LES pressure was a risk factor for increased postoperative acid reflux.[87]

Another study found that preoperative increased LES pressure was associated with increased risk of new-onset postoperative dysphagia.[109] The same study found that LES competence was also a risk factor for postoperative dysphagia.

Esophageal motility

Four studies (with a total of 361 patients) examined various esophageal motility parameters on outcomes of laparoscopic fundoplication.[87,89,90,96] Two studies (with a total of 156 patients) did not find an increased risk of laparoscopic fundoplication failure with preoperative esophageal body hypomotililty/low amplitude contractions as assessed by symptomatic relapse/persistence or 24-hour pH studies.[87,90] Three studies of distal esophageal segment dysmotility (either hyper- or hypomotility) involving 244 patients found no effect on laparoscopic treatment outcomes, including symptomatic relapse/persistence and acid reflux.[87,89,96] One study involving 124 patients found that nonspecific spastic disorders of the esophagus increased the risk of postoperative heartburn, regurgitation, and antireflux medication requirement after laparoscopic fundoplication.[96] Nonetheless, patients in this study with spastic esophagus still reported improvement equal to those without spastic disorder.

Hiatal hernia

Seven studies (with a total of 1,038 patients) analyzed the influence of a hiatal hernia on surgical outcomes.[86,87,89,92-94,109] Six studies examined the effect of hernias >2cm.[86,87,89,92,94,109] None found differences in surgical failure rates. The one study that examined the effect of large hiatal hernias >3 cm reported a significant increase in risk of symptomatic relapse and persistence of symptoms.[93]

Table 17. Summary of studies that evaluated patient characteristics as modifying factors of fundoplication outcome

Potential modifying factor (references)	Number of Studies Total patients (range)	Outcomes					
		Symptoms[a]	pH	Medications		Quality of life/ Satisfaction	Global Success/ Failure[b]
				Off PPIs	Off all meds		
Age[86,87,89,92,93,95,109-113]	11 2,125 (48-408)	No effect (8 studies) <50 years old associated with better outcomes (1 study)	No effect (1 study)	ND	ND	No effect (5 studies)	No effect (1 study)
Sex[86,87,89,92,94,95,109,113]	8 1,681 (48-408)	No effect (4 studies) Females have more symptoms (1 study) Males have fewer heartburn (1 study)	No effect (1 study)	ND	ND	No effect (1 study) Males had higher satisfaction (1 study)	ND
BMI/weight[86,92,94-96,109,116-118]	9 2,219 (103-505)	No effect (4 studies) Normal weight patients have higher heartburn (worse) scores (1 study) Obese patients had more recurrent symptoms (1 study)	ND	ND	ND	No effect (3 studies) Increasing BMI correlated with satisfaction (1 study)	No effect (2 studies)

Potential modifying factor (references)	Number of Studies Total patients (range)	Outcomes					
		Symptoms[a]	pH	Medications		Quality of life/ Satisfaction	Global Success/ Failure[b]
				Off PPIs	Off all meds		
Psychosocial[93,119-121]	4[d] 388 (76-131)	Major depression associated with more symptoms (2 studies) Personality traits correlated with subjective swallowing difficulties (1 study)	No effect (1 study)	ND	No effect (1 study)	Greater satisfaction associated with patients without psychiatric disorders (2 studies)	Psychiatric history associated with failure (1 study)
Symptoms[45,86-89,93,109,116]	8 984 (48-199)	Typical symptoms associated with better outcomes than atypical symptoms (3 studies) No effect for dysphagia outcome (1 study) Severe symptom score correlated with symptomatic response (1 study)	ND	ND	ND	ND	No effect (3 studies)
Preoperative response to acid-suppression therapy[c45,86,89,93]	4 592 (81-199)	Responders associated with better symptomatic outcomes (2 studies)	ND	ND	ND	No effect on satisfaction (1 study)	Responders associated with better outcomes (1 study) Non-response to PPI associated with failure (1 study)
Esophagitis (any severity)[86,89,91-94,109]	7 1413 (81-414)	No effect (5 studies) Esophagitis associated with increased risk of dysphagia (1 study)	ND	No effect (1 study)	No effect (2 studies)	No effect on satisfaction (2 studies)	ND

Potential modifying factor (references)	Number of Studies Total patients (range)	Outcomes					
		Symptoms[a]	pH	Medications		Quality of life/ Satisfaction	Global Success/ Failure[b]
				Off PPIs	Off all meds		
Esophagitis (grade 3 or 4)[86,87,89,93,109]	5 553 (39-199)	No effect (2 studies)	Grade 3 & 4 esophagitis associated with increased risk of abnormal DeMeester score (1 study)	ND	No effect (1 study)	ND	ND
Severity of acid reflux[45,86,87,89,92-94,97,109]	9 1307 (39-262)	No effect (3 studies) Increased time with acid reflux while upright associated with more symptoms (1 study) Increased acid reflux associated with less symptom severity (2 studies)	Increased pre-op DeMeester score associated with increased post-op DeMeester score (1 study)	ND	Increased DeMeester score associated with increased likelihood of being off all meds (1 study)	Increased time with acid reflux associated with increased satisfaction (1 study)	No effect (1 study)
LES competence[e86,88,109,116]	4 543 (103-199)	No effect (2 studies) LES competence associated with new-onset dysphagia (1 study)	ND	ND	No effect (1 study)	ND	ND
LES pressure[45,87,93,94,97,109,122]	7 1045 (39-280)	No effect (4 studies) Increased LES pressure associated with increased risk of dysphagia (1 study)	Low LES pressure associated with increased risk of abnormal DeMeester score (1 study)	ND	ND	ND	No effect (1 study)

Potential modifying factor (references)	Number of Studies Total patients (range)	Outcomes					
		Symptoms[a]	pH	Medications		Quality of life/ Satisfaction	Global Success/ Failure[b]
				Off PPIs	Off all meds		
Esophageal motility[87,89,90,96]	4 361 (39-124)	No effect (2 studies) Nonspecific spastic disorder associated with increased risk of symptoms (1 study)	No effect (2 studies)	ND	Nonspecific spastic disorder associated with decreased likelihood of being off all meds (1 study)	No effect (1 study)	ND
Hiatal hernia[86,87,89,92-94,109]	7 1038 (39-262)	No effect (4 studies) Hernia >3cm associated with increased risk of symptoms (1 study)	No effect (1 study)	ND	No effect (1study)	No effect on satisfaction (1 study)	ND

[a] Symptoms include dysphagia.
[b] Individual study's definition of success or failure defined by multiple variables.
[c] Responders may be complete or partial.
[d] Possible overlap of Nissen patients for studies Kamolz 2000 and Kamolz 2003. Open surgery conducted for 17 (18%) patients for Velanovich 2001.
[e] Incompetent LES is defined by: LES length< 2cm, intra-abdominal length< 1cm and/or maximum LES resting pressure criteria (of 6 or 10 mmHg according to study authors[86,88,116] Cut-off criteria are not defined by Blom 2002.

Factors that influenced the outcomes of endoscopic treatments

Four cohort studies examined the association of various patient characteristics with the outcomes of the endoscopic procedures.[54,57,73,76] No consistent associations were observed.

The study on Enteryx™ by Schumacher et al.[73] analyzed age as a predictor for outcomes in 76 patients and reported that age less than 48 years was predictive of a treatment response (defined as a decrease in the PPI dosage) but not for symptom score improvement. Other variables examined included study center, BMI, sex, PPI dose at baseline, baseline esophagitis, investigator experience, and injection volume. None of these factors were associated with any of the outcomes examined.

Another study on Enteryx™ by Cohen et al. found a non-significant trend toward improved response among patients with greater residual implant volume.[54] No significant associations were found for other variables examined including sex, BMI, baseline hiatal hernia, baseline esophagitis, symptoms while off PPIs, baseline esophageal acid exposure, baseline PPI dose, duration of prior therapy, study center, investigator prior experience, implant volume, and residual implant.

The third study on Enteryx™ had just 15 patients and found no relationship with the primary outcome (PPI dose reduction ≥50% at 3 month) and baseline PPI, duration of prior PPI therapy, baseline GERD-HRQL score, baseline esophageal acid exposure, Savary-Miller grade of esophagitis, or presence of hiatal hernia.[76]

One study on Stretta™ found that age less than 50 was significantly associated with improved esophageal acid exposure, but there was no difference in medication use or GERD symptoms after treatment.[57] No significant associations were found for sex, GERD symptoms, years of GERD, medication use, baseline esophageal acid exposure, baseline lower esophageal sphincter pressure, esophageal peristaltic amplitude, baseline acid exposure, or baseline esophagitis.

Miscellaneous factors

Four studies examined miscellaneous factors influencing outcomes of laparoscopic surgery.[98,123-125] At 1-year follow-up, Kamolz et al. reported that patients with aerophagia at baseline had less improvement in quality of life compared with patients who did not have aerophagia at baseline.[124] The retrospective review by Haithcock et al. reported higher rate of conversion from a laparoscopic to an open approach in African-American women compared with Caucasian women.[123] One study of laparoscopic antireflux surgery performed on 26 patients in a rural county hospital setting reported that 95% of the patients had symptomatic relief from heartburn and required no medication at follow-up ranged from 2 to 21 months (mean, 10 months). Complication and conversion rates were both 7%. The authors suggested that their results were not different from those at large urban hospitals, at least for the length of the follow-up period.[125] Yau et al. reported that the overall rate of reoperation (for paraesophageal hiatus hernia, tight esophageal hiatus, recurrent reflux, tight or slipped Nissen fundoplication) after laparoscopic fundoplication was not associated with esophageal length. There was a non-significant increased rate of reoperation for a postoperative paraesophageal hernia in patients with the shortest esophageal length index (esophageal length divided by the patient height multiplied by 100) compared with patients who had the longest esophageal length index (8% vs. 2%, P=0.36).[98] The authors concluded that the increased risk of this problem was small and

therefore, a case could not be made for patients with a manometrically short esophagus to routinely undergo an esophageal lengthening procedure. Because of the paucity of studies, no meaningful conclusions can be derived for each of these factors.

Key Question 3. What are the short- and long-term adverse effects associated with specific medical, surgical and endoscopic therapies for GERD? Does the incidence of adverse effects vary with duration of follow-up, specific surgical intervention, or patient characteristics?

Key points for adverse events

- The quality of reporting of adverse events and complications was inconsistent across studies. Some did not report specific adverse events (even though they were likely to have occurred). Furthermore, whether complications were temporary or persistent was frequently unclear. None of the studies used an acceptable standard or scale for defining their severity.

- Higher adverse event rates were described with PPIs compared with H2RAs or placebo. The most commonly cited events for PPIs and H2RAs were headache, diarrhea, and abdominal pain.

- Few studies included patients with a follow-up of more than 1 year. The longest follow-up was 5 years (for omeprazole and rabeprazole). PPIs examined in these studies included omeprazole, rabeprazole, and lansoprazole. No significant differences in adverse events were found in direct comparison between omeprazole and rabeprazole after 5 years of follow-up. None of the events reported was considered clinically significant.

- The most commonly reported complications occurring intraoperatively or within 30 days after open fundoplication were the need for splenectomy, dysphagia, inability to belch, and inability to vomit; while the most commonly reported complications for laparoscopic procedures were gastric or esophageal injury or perforation, splenic injury or splenectomy, pneumothorax, bleeding, pneumonia, fever, wound infections, bloating, and dysphagia. Major complications were generally reported rarely and at very low rates. No deaths were reported in the few studies of open-fundoplication in our report. (*Comment: previously reported mortality ranged from 0 to <1%*[126-128]) The mortality rate for laparoscopic fundoplication ranged from 0 to 1.3%. Conversion rates from laparoscopic to open fundoplication ranged from 3.1% to 7.3%. Re-operation rates ranged from <1% to 5.6%. Frequently reported long-term complications (>1 month post surgery) included dysphagia (17% to 100%) and bloating (22% to 46%).

- The most frequently reported complications in endoscopic treatments – intra-operatively or within 30 days after the procedure – included chest or retrosternal pain, gastrointestinal injury, bleeding, and short-term dysphagia. The frequency and types of complications varied with the different procedures. Serious complications including fatalities have also been described.

Medical treatments (Table 18)

The Cochrane Systematic Review by Donnellan et al. identified 51 RCTs (6,242 participants) that reported adverse events associated with medical treatments for GERD.[35] The drugs used were PPIs and H2RAs. PPIs included omeprazole, lansoprazole, pantoprazole, rabeprazole, and esomeprazole. The duration of the trials ranged from 12 to 52 weeks. Table 18 summarizes the adverse events of headache, diarrhea, and abdominal pain reported in this systematic review. This review found that PPIs had more overall adverse events in comparison with H2RAs (cimetidine, famotidine, nizatidine, ranitidine) and with placebo. Only one trial in this review showed a significant difference in headache occurrence between PPIs and H2RAs (Relative Risk 2.27, 95% CI 1.04, 4.97).[129]

Table 18. Adverse events in RCTs comparing PPI to H2RA or placebo, and PPI healing vs. maintenance dose

	Overall		Headache		Diarrhea		Abdominal Pain	
	Patients (RCTs)	event rate%	Patients (RCTs)	event rate%	Patients (RCTs)	event rate%	Patients (RCTs)	event rate%
PPI healing dose vs. placebo	806 (5)	54.1 vs. 41.6[a]	348 (2)	3.4 vs. 3.0	305 (2)	5.2 vs. 2.0	190 (1)	3.1 vs. 2.2
PPI healing dose vs. H2RA	469 (3)	18.9 vs. 15	189 (1)	19.1 vs. 8.4*	ND	ND	259 (1)	9.2 vs.10.2
PPI healing dose vs. PPI maintenance dose	2812 (10)	41.5 vs. 41.4	1764 (4)	5.6 vs. 4.3	2441 (4)	5.8 vs. 5.2	2590 (4)	4.1vs. 3.7
PPI maintenance dose vs. placebo	1057 (6)	42.4 vs. 33.9*	336 (2)	4.2 vs. 3.0	183 (1)	1.1 vs. 3.3	183 (1)	1.1 vs. 2.2
PPI maintenance dose vs. H2RA	574 (3)	43.6 vs. 31.3*	188 (1)	9.7 vs. 8.4	ND	ND	261 (1)	11.3 vs.10.2

[a] statistically significant difference

Table 18 from the Cochrane Database of Systematic Reviews, Vol (2): "Medical treatments for the maintenance therapy of reflux esophagitis and endoscopic negative reflux disease" © 2005 The Cochrane Collaboration

The OHSU EPC report identified 26 head-to-head comparisons of PPIs for acute treatment of GERD that reported adverse events.[33] The number of participants was 23,466, and the medications tested were omeprazole, esomeprazole, rabeprazole, and lansoprazole. The rate of adverse events ranged from 1.5 to 55.7%, and the proportion of patient withdrawal secondary to adverse events ranged from 0.9 to 13%. The most common adverse events were headache, diarrhea, nausea, and abdominal pain. These events were reported similarly between drugs. Other events reported were respiratory infection, eructation, flatulence, dizziness, paresthesia, somnolence, and gastritis. Serum gastrin levels were found to be elevated compared to baseline although the magnitude of increase was small and not considered clinically significant.

There were only two RCTs of maintenance treatment of GERD that included participants who completed 5 years of follow-up.[130,131] Thjodleiffson et al. reported adverse event data for omeprazole 20 mg, rabeprazole 10 mg and 20 mg.[131] The study recorded 1,086 adverse events. The most commonly reported event was diarrhea: 6.4% in rabeprazole 20 mg, 3.7% in rabeprazole 10 mg, and 4.8% in omeprazole 20 mg. There were 177 treatment-related adverse events. The majority of them were mild in intensity, and only 13% were considered to be severe (details not provided). There was no significant difference in the number of adverse events

reported or the number of withdrawals due to adverse events in different PPI groups. Caos et al. compared rabeprazole 10 mg and 20 mg with placebo and reported that 8% of the patients experienced adverse events.[130] The most common adverse events were rhinitis, diarrhea, flu syndrome, headache, pharyngitis, back pain, and abdominal pain. The proportion of these adverse events was significantly higher in the two treatment arms compared to placebo ($P<0.018$).

The OHSU EPC report also identified a nested case-control study of 10,008 lansoprazole users who were followed for 4 years. The authors found a trend for diarrhea to be dose related; it was reported in 5%, 3.7%, and 1.5% of patients using 60 mg or more, 30 mg, and 15 mg or less, respectively. The dose of lansoprazole was reduced or discontinued in 42.1% of patients who reported diarrhea.[132] There were no studies with a follow-up longer than one year for pantoprazole and esomeprazole.

Several studies assessed the association of acid suppression therapies (PPIs and H2RAs) with the development of pneumonia, hypergastrinemia, atrophic gastritis, and vitamin B12 malabsorption. A population-based cohort study comprised 364,683 individuals who subsequently developed 5,551 first occurrences of pneumonia during follow-up.[11] Incidence rates of pneumonia in acid-suppressive drug users and non acid-suppressive drug users were 2.45 and 0.6 per 100 person years, respectively. The relative risk of pneumonia among persons currently using PPIs compared with those who stopped was 1.89 (95% CI 1.36-2.62), after adjusting for matching factors, respiratory illness, long-term heart failure, diabetes mellitus, use of antibiotics, and use of immunosuppressants.

Another report included 230 patients whose severe reflux esophagitis had healed after up to 12 weeks of treatment and were followed for up to 11 years.[133] Patients older than 65 years of age had twice as many adverse events (including deaths) compared with younger patients. The annual incidence of gastric corpus mucosal atrophy was 4.6% and 0.7% in H. pylori-positive and -negative patients, respectively. It was observed mainly in elderly patients who had moderate/severe gastritis at baseline. Corpus intestinal metaplasia was rare, but no dysplasia or neoplastic changes were observed.

Two studies addressed the effect of acid suppression therapy on gastric atrophy.[13,14] Kuipers et al. compared two groups of H. pylori infected patients with chronic GERD.[13] One group was treated with omeprazole for 5 years, the other underwent antireflux surgery and had follow up for more than 5 years. None of the surgically treated patients developed atrophic gastritis, but 31% of the medically treated patients showed evidence of some degree of atrophic gastritis. However, a subsequent RCT comparing omeprazole to antireflux surgery after 3 years showed no significant differences between the two groups in the development of gastric glandular atrophy or the occurrence of intestinal metaplasia.[14]

One case-control study revealed that omeprazole treatment was associated with a 10-fold increased risk of campylobacter infection.[10] Risk for current users (1 month before infection) but not former users suggests that the relation was causal. No relation was seen with H2RA. Another cohort study was identified from a pharmacy database of 1,187 inpatients who received antibiotics for more than 9 months at a Canadian teaching hospital.[9] *C. difficile* diarrhea was significantly associated with use of a PPI (adjusted OR 2.1, 95% CI 1.3-3.4). From the same report, but in a case-control design, *C. difficile* diarrhea also was associated with use of PPI (adjusted OR 2.7, 95% CI 1.4-5.2). A retrospective case-control study showed that PPI use within the preceding 8 weeks was associated with increased risk of *C. difficile* diarrhea (OR 2.5, 95% CI 1.5-4.2).[134]

Drug Interactions

Table 10 of the OHSU EPC report lists the clinically significant drug interactions with PPIs.[33] All PPIs reduce the absorption of drugs that require an acidic gastric pH for maximal absorption, such as ketoconazole, iron, digoxin, delaviridine, indinivir, and enteric-coated salicylates. Omeprazole interacts with several drugs, specifically carbamazepine, phenytoin, diazepam, methotrexate, and trovafloxacin. So far, no clinically significant drug interactions have been reported, with the exception that there is decreased clearance of theophylline with lansoprazole. Esomeprazole has the potential to interact with cytochrome 2C19 and thereby may cause interactions with diazepam, phenytoin, and warfarin.[135]

Drug interactions with cimetidine were not reported in the aforementioned meta-analyses. However, a literature search showed that cimetidine interacts with many drugs: when added to warfarin it increases INR and may be dose dependent.[136] Cimetidine inhibits cytochrome P-450 and other isoenzymes involved in the metabolism of theophylline, phenytoin, diazepam, caffeine, and other drugs. Interaction with beta-blockers results in significant sinus bradycardia and hypotension.

Surgical treatments (Tables 19, 20, 21)

We identified two recently published systematic reviews that reported on perioperative mortality and morbidity and adverse events associated with specific surgical treatments for GERD.[137,138] We also identified one database analysis of major adverse outcomes in antireflux surgery from the Nationwide Inpatient Sample of the Health Care Utilization Project.[139] In addition, from 106 articles identified through MEDLINE search that met our study inclusion criteria, we identified three RCTs, five prospective cohorts, nine retrospective cohorts and two case-control surgical studies of various fundoplication techniques for GERD in 24 publications that reported adverse event data which were not included in the two systematic reviews (except for one study[24] that provided subsequent long-term[8] follow-up data).[8,23-25,45,46,65,69,82,93,95,103,109,140-150] The first systematic review examined outcomes for 41 papers published between 1974 and 2002;[138] the second review examined outcomes for another 41 papers published between 1993 and 2003.[137] Because of the overlap between the two reviews, primary studies common to both reviews were labeled clearly in the evidence tables.

One RCT[24] and one subsequent long-term follow-up report[8] compared medical with surgical therapy for GERD and provided data for operative and postoperative complications (Spechler 1992[24] [included in Carlson 2001[137]]). The RCT from the VA Cooperative Study[24] compared Nissen fundoplication to continuous medical therapy or to stepwise medications such as Maalox®, ranitidine, metoclopramide, and sucralfate in 247 patients for up to 2 years. Ten of 82 surgical patients had one or more operative complications including six with splenic injury and four with a gastrointestinal perforation; 12 of 82 had one or more postoperative complications including wound infection, pulmonary embolism, two with ileus lasting more than 5 days, two with bleeding requiring transfusion, and two with abscesses. No complications were fatal, and all resolved without apparent sequelae. “Side effects” occurred in 84% of surgical patients, 88% in those receiving continuous medical therapy, and in 88% of those given stepwise medication for symptoms. Early satiety, inability to belch, and inability to vomit were increased for surgical therapy compared to either medical therapy ($P<0.05$). A follow-up to this study was published in 2001 – mean duration of follow-up for surgical patients was 9.1 years and, 10.6 years for

medically treated patients.[8] There were no significant differences between groups in the frequency of any symptoms described in the earlier paper: increased abdominal girth (34% surgical versus 36% medical), inability to belch (29% surgical versus 20% medical), and inability to vomit (32% surgical versus 20% medical).

Another RCT compared laparoscopic total fundoplication with anterior partial fundoplication.[37] There were 107 patients with available follow-up for 5 years. The two groups did not differ significantly in the rate of adverse events such as dysphagia (27% for total and 18% for partial fundoplication) or diarrhea (27% for total and 24% for partial fundoplication). However, abdominal bloating at 5 years was significantly higher among the total fundoplication patients when compared to partial fundoplication group (75% versus 44%, respectively, P=0.002). Inability to belch at 5 years was also significantly higher among the total fundoplication patients when compared with the partial fundoplication group (43% versus 20%, respectively, P=0.018).

The numbers and rates of adverse events or complications extracted from the reviews and the primary papers are tabulated in the summary tables below.

Table 19. Intraoperative complications (and those occurring within 30 days) for surgical and endoscopic procedures

	Surgical				Endoscopic			
	Open Nissen Fundo-plication	**Laparoscopic Nissen Fundoplication**	**Open Nissen Fundoplication / Laparoscopic Nissen Fundoplication**	**Laparoscopic Nissen Fundoplication /Laparoscopic Toupet Fundoplication**	**Endocinch™**	**Enteryx™**	**NDO Plication™**	**Stretta™**
Mortality event rate	1 review 0 / 429 (0%) 1 study 0 / 58 (0%)	1 review 0 / 233 (0%) 4 studies 1 / 521 (<1%) range 0 -1.3%	1 study 0 / 93,864 (0%)	1 review 8 / 8,742 (<1%)	1 study 0 / 51 (0%)	ND	ND	2 studies 0 / 151 (0%)
Re-operation event rate	ND	2 studies 5 / 1231 (<1%) range <1% – <1%	ND	ND	ND	ND	ND	1 study 2 / 61 (3.3%)
Conversion event rate	ND	1 review 17 /233 (7.3%) 4 studies 7 / 430 (1.6%) range 0 – 4%	ND	1 review 271 / 8,742 (3.1%)	ND	ND	ND	ND
Gastrointestinal injury /perforation event rate	ND	2 studies Injury 5 / 227 (2.2%) range <1% – 3.4% 1 study Perforation 1 / 120 (<1%)	1 study Injury 1,283 / 91,643 (1.4%)	1 study Enterotomy 1 / 59 (1.7%) 1 study Perforation 3 / 250 (1.2%) 1 review Injury 62 / 8,742 (<1%)	2 studies Injury 4 / 143 (2.8%) range 2% – 3.8% 2 studies Perforation 1 / 117 (<1%) range 0 –2%	1 study Injury 0 / 144 (0%)	1 study Injury 1 / 63 (1.6%) Perforation 1 / 63 (1.6%)	2 studies Injury 8 / 482 (1.7%) range 0 – 6.8% 1 study Perforation 0 / 118 (0%)

Pneumothorax event rate	ND	4 studies 7 / 378 (1.9%) range 1.4% – 3%	ND	1 review 67 / 8,742 (<1%)	ND	ND	1 study 1 / 64 (1.6%)	ND
Splenic injury event rate	1 study Splenectomy 1 / 59 (1.7%)	3 studies Injury 4 / 355 (1.1%) range <1% – 1.8%	1 study Splenectomy 2065 / 93,864 (2.2%)	1 review Injury 16 / 8,742 (<1%) Splenectomy 4 / 8,742 (<1%) 1 study Injury 1 / 268 (<1%)	ND	ND	ND	ND
Bleeding event rate	ND	3 studies 10 / 337 (3%) range 1% – 5%	ND	1 review 49 / 8,742 (<1%) 1 study 2 / 268 (<1%)	6 studies 16 / 299 (5.4%) range 0 – 11%	ND	ND	2 studies 2 / 51 (3.9%) range 3% – 5.6%
Pulmonary event rate	ND	1 study Embolism 3 / 120 (2.5%)	ND	1 study Aspiration 1 / 268 (<1%) 1 review Embolism 11 / 8,742 (<1%) Effusion 12 / 8,742 (<1%) Atelectasis 10 / 8,742 (<1%)	1 study Aspiration 2 / 87 (4%) 1 study Bronchospasm 1 / 85 (1.2%)	ND	1 study Dyspnea 2 / 64 (3.1%)	ND
Gastrointestinal event rate	1 study Inability to belch, vomit 13 / 59 (22%)	1 study gastric outlet obstruction 1 / 120 (<1%) gastric dilation 1 / 120 (<1%) 1 study esophageal leak 1 / 578 (<1%)	ND	1 review wrap herniation 85 / 6,538 (1.3%) ulcer 10 / 8,742 (<1%) 1 study acute recurrence hiatal hernia 1 / 268 (<1%) pancreatitis 1 / 268 (<1%)	ND	ND	1 study Not specified 11 / 64 (17%) Eructation 9 / 64 (14%)	1 study gastroparesis /esophagitis 1/ 25 (4%)

Infection/ Fever event rate	ND	1 study Pneumonia 1 / 120 (<1%) Wound infection 1 / 120 (<1%) 1 study Umbilical port site infection 1 / 133 (<1%)	ND	1 review Wound infection 7 / 8,742 (<1%) Abscess 18 / 8,742 (<1%) Pneumonia 37 / 8,742 (<1%) 1 study Fever 1 / 268 (<1%) Pneumonia 1 (<1%)	1 study Fever 2 / 38 (5.3%) 1 study Sepsis 0 / 15 (0%)	ND	ND	1 study Mediastinitis 1 / 26 (3.8%) 1 study Fever 2 /118 (1.7%)
Dysphagia event rate	1 study 17 / 59 (29%)	1 study 2 / 77 (2.6%)	ND	1 study 6 / 167 (3.6%)	3 studies 4 / 129 (3.1%) range 1.2% – 7.7%	3 studies 48 / 253 (19%) range 6.7% – 24%	1 study 7 / 64 (11%)	1 study 1 / 118 (<1%)
Bloating event rate	ND	1 study 1 / 133 (<1%)	ND	ND	1 study 2 / 26 (7.7%)	ND	ND	1 study 1 / 33 (3%)
Nausea /vomiting event rate	ND	1 study 3 / 38 (8%)	ND	ND	5 studies 26 / 226 (11.5%) range 2.6% – 17%	ND	1 study 4 / 64 (6%)	ND

Pain /discomfort event rate	ND	ND	ND	ND	4 studies Chest /retrosternal 16 / 171 (9.3%) range 0 – 19.2% 3 studies Abdominal 11/ 105 (10.5%) range 0 – 14% 2 studies Sore throat 11 / 41 (26.8%) range 26.7% –26.9% 1 study Retrosternal /pharyngeal 58 / 70 (83%)	1 study Retrosternal 8 / 15 (53.3%)	1 study Abdominal 13 / 64 (20%) Chest 11 / 64 (17%) Epigastric 1 / 64 (1.6%)	2 studies Chest /retrosternal 6 / 482 (1.2%) Range 1.7% - 11% 1 study Discomfort with RF energy delivery 68 / 118 (58%) Discomfort with catheter passage 22 / 118 (19%)

Other event rate	ND	3 studies Acute urinary retention 3 / 248 (1.2%) range <1% – 3% 2 studies Atrial fibrillation 2 / 251 (<1%) 1 study Acute delirium 1 / 77 (1.3%) Acute lower extremity ischemia 1 / 77 (1.3%) 1 study Liver injury 1 /109 (<1%) 1 study Dehydration 1 / 120 (<1%) 1 study Port site hematoma 1 / 131 (<1%)	ND	1 study Stroke 1 / 268 (<1%) Deep venous thrombosis 1 / 268 (<1%) Arrhythmia 1 / 268 (<1%) Myocardial infarction 1 / 268 (<1%) 1 review Myocardial infarction 5 / 8,742 (<1%) Trocar hernia 12 / 8,742 (<1%)	3 studies Hypoxia 12 / 196 (6.1%) range 2.4% –13% 2 studies Pharyngitis 22 / 98 (22.4%) range 31% – 57%	ND	1 study Pharyngitis 26 / 64 (41%)	1 study Submental swelling 1 / 118 (<1%) Hypotension 1 / 118 (<1%)

Table 20. Complications occurring more than 30 days after surgical or endoscopic procedures

	Surgical					Endoscopic	
	Open Nissen Fundoplication	**Laparoscopic Nissen Fundoplication**	**Open Toupet Fundoplication**	**Laparoscopic Toupet Fundoplication**	**Laparoscopic Nissen Fundoplication /Laparoscopic Toupet Fundoplication**	**Enteryx™**	**Stretta™**
Re-operation event rate	1 review 9 / 265 (3.4%)	1 review 19 / 339 (5.6%) 3 studies 16 / 1,398 (1.1%) range <1% - 6 (4.3%)	1 review 2 / 409 (2.2%)	1 review 1 / 100 (1%) 1 study 3 / 50 (6%)	ND	ND	ND
Bleeding event rate	ND	ND	ND	ND	ND	ND	1 study 0 / 118 (0%)
Gastrointestinal event rate	ND	3 studies Ulcer 2 / 77 (2.6%) Penetration of Teflon pledgets 7 / 1,175 (<1%) Inability to belch normally 22 / 51 (43%) Diarrhea 14 / 51 (27%) Increased flatulence 41 / 51 (80%)	ND	1 study Inability to belch normally 10 / 50 (20%) Diarrhea 12 / 50 (24%) Increased flatulence 31 / 50 (62%)	1 study Diarrhea 15 / 84 (17.9%) 1 review Reflux 206 / 5886 (3.5%)	1 study Injury 0 /144 (0%)	2 studies Pancreatitis 1/ 25 (4%) Ulceration 0 /85 (0%) Ulcer 0 /118 (0%) Stricture 0 /118 (0%)
Dysphagia event rate	1 review 42 / 321 (13.1%)	1 review 55 / 364 (15.1%) 3 studies 28 / 298 (9.4%) range 4.6% - 27%	1 review 14 / 106 (13.2%)	1 review 6 / 152 (5.2%) 1 study 9 / 50 (18%)	1 review 188 / 7,520 (2.5%) 1 study 0 / 25 (0%)	3 studies 21 / 314 (6.7%) range <1% – 13%	2 studies 0 / 203 (0%)
Bloating event rate	1 review 24 / 188 (12.8%)	1 review 23 / 189 (12.2%) 3 studies 80 / 269 (29.7%) range 7.8% - 75%	ND	1 study 22 / 50 (44%)	1 review 239 / 7,543 (9.4%) 2 studies 16 / 99 (16.2%) range 0 - 19%	ND	1 study 0 / 85 (0%)
Pain event rate	ND	ND	ND	ND	ND	ND	1 study Chest 0 / 118 (0%)

Table 21. Complications occurring after surgical and endoscopic procedures (time period, uncertain)

	Surgical		Endoscopic
	Laparoscopic Nissen Fundoplication	**Laparoscopic Nissen Fundoplication /Laparoscopic Toupet Fundoplication**	**Enteryx™**
Mortality event rate	ND	1 study 1/ 268 (<1%)	ND
Re-operation event rate range	5 studies 18 / 832 (2.2%) 1.5% - 3.7%	1 review 162 / 6000 (2.7%) 2 studies 26 / 676 (3.8%) 3% - 4.4%	ND
Pulmonary event rate	1 study Atelectasis 4 / 250 (1.6%)	ND	1 study Effusion 1 / 91 (1.1%)
Gastrointestinal event rate	2 studies Diarrhea 21 / 171 (12.3%) Ileus: 1 / 101 (~ 1%)	2 studies Difficulty to vomit 193 / 408 (47.3%) Difficulty or unable to belch 154 / 408 (37.7%) Constipation 3 / 107 (2.8%)	2 studies Nausea /vomiting 12 /85 (14.1%) Regurgitation 1 / 91 (1.1%) 2 studies Belching 7 / 117 (6%) range 3.1% - 7.1%
Infection/ fever event rate	2 studies Respiratory tract infection 2 / 111 (1.8%) Pneumonia 1 / 101 (~1%) Mediastinitis 1 / 101 (~1%)	1 study Gastrostomy tube site infection 1 / 33 (3%)	3 studies Fever 41 / 209 (19.6%) range 11.8% - 26%
Dysphagia event rate range	6 studies 216 / 793 (27.2%) 2.6% - 100%	3 studies 119 / 715 (16.6%) 7.8% - 51%	2 studies 21 / 124 (16.9%) 13% - 28.1%
Bloating event rate range	2 studies 89 / 288 (30.9%) 20.5% - 46%	2 studies 147 / 676 (21.7%) <1% - 35.5%	3 studies 7 / 253 (2.8%) 1.1% - 5.9%
Pain /discomfort event rate	ND	2 studies Chest 12 / 40 (30%) Abdominal 6 / 109 (5.5%)	1 study Retrosternal 122 / 144 (85%) 1 study Chest 72 / 94 (77%) 1 study Retrosternal /epigastric 22 / 32 (68.8%) 1 study Shoulder 3 / 83 (3.6%) Rib 1 / 83 (1.2%) Breast 1 / 83 (1.2%)
Other event rate	2 studies Trocar wound problems /scars 10 / 167 (6%) Atrial fibrillation 1 / 101 (~1%) Biloma 1 / 101 (~1%)	2 studies Recurrent hiatal hernia 9 / 265 (3.4%) Incisional hernia 2 / 61 (3.3%)	2 studies Flu syndrome 2/174 (1.1%) range 1.1% –1.2% 1 study Pharyngitis 9 / 85 (10.6%) Body odor /bad taste 4 / 83 (4.7%) Dry mouth 2 / 83 (2.4%) Anxiety 2 / 83 (2.4%) Bradycardia 1 / 91 (1.1%)

The meta-analysis of nine RCTs comparing partial versus total wrap and six RCTs comparing open versus laparoscopic fundoplication reported overall morbidity in the trials from 9.4 to 13.1%. The need for conversion arose in 17 cases (7.3%).[138] The mortality rate for 10,489 laparoscopic procedures (ie, Nissen, Toupet, Nissen-Rossetti) was 0.08%. The causes of death were myocardial infarction, duodenal or gastric perforation, and unspecified. The rate of open conversion as reported in 34 of 41 papers (8,620 cases) was 3.1%.[137] Four studies of laparoscopic Nissen fundoplication reported a mean conversion rate of 1.6%.[93,137,138,146]

The most commonly reported complications occurring intraoperatively or within 30 days after open fundoplication were splenectomy, dysphagia, inability to belch, and inability to vomit; while the most commonly reported complications for laparoscopic procedures were gastric or esophageal injury or perforation, splenic injury or splenectomy, pneumothorax, bleeding, pneumonia, fever, wound infections, bloating, and dysphagia. Gastrointestinal injury was reported in six surgical studies and one review, the rate of event ranged from <1% to 3.4%. Pneumothorax was reported in four studies and one review. Bleeding was reported in four studies and one review. Splenic injury was reported in six studies and one review.[23,25,65,137,139,146,150]

Dysphagia 30 days after the procedure ranging in frequency from 2.5 to 27% was reported in many surgical studies.[23,37,65,137,138,148] Nine other surgical studies also reported high postsurgical dysphagia rates, but the data were not reported with sufficient detail to determine when these adverse events occurred relative to the procedure.[25,46,69,93,95,109,144,148,150] One study reported that 45 out of 142 patients (32%) with either mild or absent bloating preoperatively had an increase in bloating 6 months after surgery (However, patients in whom bloating was moderate preoperatively showed little change and patients with severe bloating preoperatively showed the greatest improvement in bloating at 6 months follow-up.).[143] One RCT reported 27% dysphagia and 75% bloating 5 years after the procedure.[37]

Length of stay

Length of stay (LOS) after a primary minimally invasive antireflux procedure often offers a convenient and objective measure of overall morbidity associated with operating technique. Eight papers reported this information and LOS varied greatly from paper to paper and from procedure to procedure.[45,93,103,137-139,144,146]. The meta-analysis by Carlson et al.[137] reviewed 28 papers from 1993 to 2000 and reported average LOS of 2.8 days and stated that there was no real trend to a decreased length of stay with later publication, as might be expected. The meta-analysis by Catarci et al.[138] combined the results of six RCTs from 1997 to 2002 and reported a LOS of 3.1 days for laparoscopic Nissen surgery and 5.2 days for open Nissen. Leggett et al.[146] reported 2.7 days for Nissen and 2.3 days for Nissen-Rossetti. In 2003, Anvari et al.[45] reported 2.8 days for Nissen, but Klaus et al.[103] in the same year reported 1.5 days for laparoscopic Nissen or Toupet procedures combined.

Learning curve

Seven papers (two prospective and five retrospective studies) explicitly discussed the implications of the learning curve in antireflux procedures.[46,104-108,139] A prospective study from Australia of 280 cases undertaken by 11 surgeons over 46 months demonstrated that the complication, reoperation, and conversion rates (laparoscopic to open surgery) were all higher in

the first 50 cases performed by the group of surgeons, and in the first 20 cases by each individual surgeon.[108] Rates were higher in the initial 20 cases and in the initial five individual cases. The early experience was associated with prolonged operating times and technical difficulties because of the need to adjust to new instruments and an altered method of vision. A prospective study from Canada of 100 consecutive cases undertaken by four general surgeons reported a laparoscopic failure rate of 26% (18/68) during a surgeon's first 20 operations and 11% (3/28) thereafter ($P<0.09$); corresponding conversion rates were 22% and 4% ($P<0.05$).[106] During a surgeon's first 20 operations, the failure rate rose from 21% (12/67) to 55% 6/11 ($P<0.04$) if a second surgeon did not assist. The authors concluded that the individual learning curve requires about 20 operations to surmount.

A retrospective chart review of the first 100 laparoscopic fundoplications in Canada was analyzed.[104] Two surgeons performed the majority of the procedures and routinely assisted each other. Patients were grouped chronologically with the first 50 cases defined as early institutional experience and a surgeon's first 20 cases defined as early personal experience. Operative time was longer in both the early institutional and personal experience. The rate of dysphagia requiring intervention was significantly higher during the early institutional experience (22% versus 4%, $P=0.017$). The rate of dysphagia requiring intervention was also higher with early personal experience than with late personal experience, but the difference did not reach statistical significance (19% versus 8%, P=NS). The conversion rate was 0%, reoperation rate was 1% and the length of stay was 2.5 days. These outcomes were unaffected by a learning curve.

A retrospective study by case-note analysis of 61 patients undergoing laparoscopic fundoplication in England was analyzed.[105] The authors reported a significant decline in conversion rate with time ($P=0.002$). In the first set of 12 patients, there were seven conversions; in the last subset of 13, there was only one. A review of 241 consecutive patients undergoing laparoscopic fundoplication in a US hospital over 6 years was evaluated.[107] Comparing the first 25 attempts with the second 25 attempts, there were 14 conversions (56%) versus four (16%) ($P<0.01$), respectively. Operative times decreased significantly and intraoperative complication rates were five (20%) and one (4%), respectively. The authors described their learning curve as very steep.

Endoscopic treatments (Tables 19, 20, 21,)

For endoscopic studies, we identified only three comparative studies: one non-randomized parallel group comparison of laparoscopic fundoplication and the EndoCinch™ device,[69] one RCT that compared two different configurations of stitching using Endocinch™, [68] and another RCT that compared Enteryx™ injection versus sham.[6] There were a total of 20 studies in 25 publications of various techniques and devices for endoscopic surgery.[6,7,54-57,59,60,62-69,72-76,79-81,151] Finally there were 47 individual adverse events reports submitted by the manufacturers since 2000 to the FDA.

The frequency and rate of adverse events varied widely. The major intraoperative complications reported in the endoscopic studies were pain/discomfort (eg, chest/retrosternal, pharyngeal, gastric, and abdominal) and major bleeding episodes. Ten endoscopic studies in 12 publications reported on postsurgical pain.[7,56,57,63,67-69,74-76,80,81] Bleeding was reported in eight studies.[7,59,68,69,72,75,80,81] One study of Enteryx™ reported 85% of patients developed retrosternal pain.[54] A second study of Enteryx™ reported 77%[73] of patients developed chest pain and a third study reported 69%[6] of patients developed retrosternal and epigastric pain. One study on

Stretta™ reported chest pain in 1.7% of patients.[57]In addition, short-term dysphagia occurred in eight studies reported in 10 publications.[54,56,57,63,67,72,73,76,79,80] Five studies in seven publications reported dysphagia persisting more than 30 days after endoscopic procedure (ranged from <1% to 13%).[54,55,57,62,66,67,73]

A case report published in 2005 described a pneumomediastinum following Enteryx™ injection procedure.[152] Other complications involving the mediastinum after the Enteryx™ procedure had also been described.[153] A 2004 report described development of an abscess at the gastroesophageal junction in continuity with the esophagus following Enteryx™ injection; the patient in this case died but the actual cause of death could not be determined because this patient had multiple co-morbidities and the family refused an autopsy.[154] A search of the FDA/MAUDE database (Manufacturer and User Facility Device Experience)[16] on May 31, 2005, revealed the following: the manufacturers of Enteryx™ reported 26 adverse events from 2002-2005 including five deaths, six incidents of chest pain, five polymer exudation, three pneumonia, and three dysphagia. The manufacturers of Stretta™ reported 26 adverse events from 2000-2005; 18 occurred in 2000-2001. These included three deaths, four chest pain, three nausea/vomiting, two bouts of abdominal pain, gas, or bloating, two burns, and two pleural effusion.

Summary of results

The following table included information on the data source, population studied, limitations of the included studies, as well as a result summary on symptoms and quality of life, esophagitis healing, esophageal acid exposure, medication use, variables that either do or do not affect outcomes, and adverse event data.

Table 22. Summary of medical, surgical and endoscopic treatments

	Medical	Surgical	Endoscopic
Data source	• 3 recent meta-analyses (MAs) • Medical arm from one RCT of medical therapy vs. antireflux surgery • Additional studies including a MA of individual patient data, RCTs, cohort and case-control studies	• 3 head to head RCTs with medical therapy • 7 non-randomized comparisons with medical therapy • 4 RCTs on surgical techniques • 10 non-randomized studies	• 3 non-randomized comparisons with laparoscopic surgery • 2 sham RCTs • 16 cohorts
Population studied	• Pts with GERD and some degree of esophagitis.	• Pts with GERD documented by objective testing, a wide range of esophagitis and response to medications, do not have severe esophageal dysmotility, or comorbidities preventing surgery • Pts whose symptoms were poorly controlled with medical therapy were not enrolled in RCTs	• Pts with GERD well-documented by objective testing, who responded to medical therapy and do not have severe esophagitis, a large hiatal hernia or severe esophageal dysmotility
Limitations	• Incomplete data from primary studies • Heterogeneity in	• High dropout at f/u • RCT on laparoscopic surgery vs. medical therapy has short f/u	• Small N • Short f/u • No head to head

	Medical	Surgical	Endoscopic
	classification schemes for symptoms and esophagitis • Most studies with long-term data from MAs reported follow-up ≤ 1year		comparison with medical therapy
Symptom Improvement QOL	Acute Rx[a] • PPIs are superior to ranitidine • No difference among omeprazole, lansoprazole, pantoprazole, and rabeprazole • No difference between esomeprazole 40 mg and lansoprazole 30 mg or pantoprazole 40 mg • Esomeprazole 40 mg more effective than omeprazole 20 mg (*Comment: Clinical importance is uncertain.*) Maintenance Rx[b] • PPI (healing-dose[c]) better than PPI (maintenance-dose[c]) in preventing Sx relapse	• Symptom similarly improved in antireflux surgery compared with medical therapy • Laparoscopic fundoplication as good as open fundoplication	• Symptoms improved in 2 sham RCTs (Enteryx™ and Stretta™) • Improved or satisfied in most non-randomized studies • More pts satisfied or improved QOL in laparoscopic fundoplication than endoscopic treatments

	Medical	Surgical	Endoscopic
Healing of esophagitis	Acute Rx • PPIs are superior to ranitidine • No difference among omeprazole, lansoprazole, pantoprazole, and rabeprazole • No difference between esomeprazole 40 mg and lansoprazole 30 mg or pantoprazole 40 mg • Esomeprazole 40 mg more effective than omeprazole 20 mg (*Comment: Clinical importance is uncertain.*) Maintenance Rx • PP I (healing-dose[c]) better than PPI (maintenance-dose[c]) in preventing relapse	• Antireflux surgery vs. medical therapy: no difference (1 study)	• Healing of esophagitis has not been consistently demonstrated
Esophageal acid exposure	• No data from MAs	• % time pH<4 improved in all antireflux surgery compared to medical therapy in 3 RCTs	• No difference in sham RCTs • 14-52% normalized in non-randomized studies
Medication Use	• At 10 yr follow-up, 92% of medical therapy group still use antireflux meds regularly (from 1 RCT)	• More pts on PPI in medical therapy group compared to antireflux surgery group in 1 RCT • ~2/3 of the surgically treated patients w/ follow-up information were still on antireflux medications in 1 RCT after 10 yr • 90% of pts in 2 RCT's of surgical techniques and most surgical cohort studies were off meds at 5-year follow-up • Use of GERD drugs less in ARS in non-randomized studies	• 1 RCT reported significant % off PPI compared to Sham • 1 RCT reported non-significant % off PPI • 6-70% off PPIs in non-randomized studies • More pts off PPI in LAS than endoscopic treatments
Factors that influence outcomes	• Higher rate of esophagitis relapse on maintenance therapy was associated with: increased severity of pretreatment esophagitis; younger age; moderate/severe regurgitation (1 MA of 5 studies) • Low LES resting pressure/ LES incompetence was	• Response to antisecretory meds was associated with improved symptomatic outcomes (3 studies) • Psychiatric history is associated with worse outcomes (3 studies: ↑Symptoms, ↑dysphagia, or ↑surgical failure)	• Age <48-50 yrs was associated with improved outcomes (2 studies: ↓PPI dosage in one and ↓ acid exposure in the other)

	Medical	Surgical	Endoscopic
	associated with worse symptomatic outcome (2 studies)		
Factors with no effect	• No data	• Age (9/10 studies) • Esophagitis (any severity) (6/7 studies) • Grade 3 & 4 Esophagitis (4/5 studies) • Incompetent LES/ low LES resting pressure (6/7 studies) • Esophageal hypomotility (3 studies) • Hiatal hernia (4 studies)	• Response to antisecretory meds (2 studies) • Preop symptoms (3 studies) • Acid reflux (3 studies) • Esophagitis (4 studies) • Hiatal hernia (2 studies) • BMI (2 studies) • Sex (3 studies) • Polymer Injection volume (2 studies)
Factors with an inconclusive effect	• Smoking (6 studies) • Esophageal motility (1 cohort study) • Acid reflux (1 cohort study)	• Preop symptoms (8 studies) • Sex (8 studies) • BMI (9 studies) • Increased preop LES pressure (1 study) • Nonspecific spastic esophagus (1 study) • Large hiatal hernias >3 cm (1 study)	• LES pressure (1 study) • Esophageal motility (1study)
Adverse Events and Complications	• 2 MAs of 51 RCTs found more overall adverse events with PPIs compared to H2RAs or placebo • Headache, diarrhea, and abdominal pain were the most commonly cited events • One trial showed higher frequency of headache among patients using acid-suppression therapies • Isolated studies reported PPI use associated with pneumonia, hypergastrinemia and atrophic gastritis	• 3 RCTs (medical therapy vs. antireflux surgery) and 14 cohorts reported complications • Most frequently reported complications within 30 days after the procedure included: splenic injury or splenectomy (<1%-2.2%), gastrointestinal injury or perforation (<1%-3.4%), and infection or fever (<1%) • Pneumothorax (<1%-5%) and bleeding (<1%-5%) were reported in 5 studies and 1 review • Major complications such as pulmonary embolism, liver injury, myocardial infarction, or acute lower extremity ischemia were reported rarely and in very low rates • Mortality for laparoscopic fundoplication ranged from 0-1.3% • Conversion of a laparoscopic to an open procedure ranged between 3.1% and 7.3% • Re-operation rate 1 mo after antireflux surgery ranged from <1% to 5.6% • Long-term complications included bloating (0-32%) and dysphagia (0-15.1%)	• 3 RCTs and 20 cohorts reported complications • Most frequently reported complications within 30 days after the procedure included: pain (0-83%), gastrointestinal injury (0-6.8%), bleeding (0-11%), and short-term dysphagia (<1%-24%) • Dysphagia 1 mo after the procedure ranged from 0 to 13% • Complications involving mediastinum and esophageal abscess following Enteryx™ injection have been described. • FDA/MAUDE reveals 26 adverse events from Enteryx™ (2002-2005) and 26 adverse events from Stretta™ (2000-2005)

	Medical	Surgical	Endoscopic
Overall Summary	• Effective for treatment and maintenance of healed esophagitis in GERD with some degree of esophagitis • 5-year comparative safety data are available for omeprazole and rabeprazole; 4-year comparative safety data are available for lansoprazole	• Open and laparoscopic fundoplication are effective for symptom control and improvement of quality-of-life in pts with GERD who have mild to severe esophagitis • Long-term comparative data with medical treatments are lacking for laparoscopic fundoplication • One must weigh the risk of short- and long-term adverse events in medical versus surgical treatments in making the optimal treatment decision.	• The technologies are new, widely varied and rapidly evolving • More sham-controlled trials and head to head comparisons with PPIs with long-term follow-up are needed before their effectiveness can be understood.

PPI: proton pump inhibitor; H2RA: H2 receptor antagonists
[a] Acute Rx: medical treatment of 4-8 wk
[b] Maintenance Rx: medical treatment ~6 or more mos
[c] Based on the Cochrane systematic review (Donnellan et al 2005) definitions: healing or standard dose for esomeprazole, omeprazole, and rabeprazole 20 mg once daily; for lansoprazole 30 mg once daily, and for pantoprazole 40 mg once daily; maintenance dose is defined as half the healing dose.

Chapter 4. Summary and Discussion

The following table summarizes the main comparative findings for the three treatment modalities. Discussion regarding the findings of our report follows.

Table 23. Summary of Comparative Data in Treatments of GERD

Key Question 1: comparisons	Quality of evidence	Summary/Conclusion/Comments
Medical vs. Surgical	acceptable	• There were 3 head to head comparisons. Baseline characteristics of populations varied across studies. None of the trials enrolled patients whose symptoms were poorly controlled with medical therapy. • Open fundoplication vs. non-PPIs in patients with complicated GERD: At 10-year follow-up (PPIs were used by most patients in a nonstandardized fashion during the follow-up period), surgical patients had better symptom score when taken off antireflux medications compared to medical patients; less bodily pain; no difference in esophagitis grade; 2/3 of surgical patients were on medications (*Comment: observational and comparative surgical studies reported 90% of patients were off antireflux medications at ≥ 5 years follow-up*). • Open fundoplication vs. omeprazole in patients with GERD but without complications: At 5-year follow-up, there was less treatment failure in surgical group, but no significant difference if dose of omeprazole was adjusted in cases of relapse. • Laparoscopic fundoplication vs. PPIs in patients who were dependent on PPIs: At 1-year follow-up, mean GI symptom score was better in the surgical group, no objective findings reported for 1-year follow-up (*Comment: observational data reported 80-90% improvement in symptoms at ≥ 5 years follow-up*). • Conclusion: Fundoplication was as effective as medical treatments for relief of GERD symptoms and decreasing esophageal acid exposure, at least for up to 2 years of follow-up. There was no difference in the outcome of esophagitis. The proportion of patients freed from long-term antireflux medications is unclear.
Surgical vs. Endoscopic	Weak	• There was no head to head comparison for the two treatments. • In non-randomized studies, more patients treated with laparoscopic fundoplication were satisfied with their results compared with those who had endoscopic therapies.
Medical vs. Endoscopic	Not applicable	• No comparative data were available.

Key Question 2: modifying factors	Quality of evidence	Summary/Conclusion/Comments
	weak	• Data largely were from observational studies. • Higher rate of esophagitis relapse while on maintenance medical treatment was associated with: increased pretreatment severity of esophagitis, younger age; moderate/severe regurgitation (1 meta-analysis). • Decreased lower esophageal sphincter pressure was associated with less likelihood of stopping all medications (2 studies). • Pre-op good response to medications was associated with good symptom outcomes in 3 surgical studies. • Psychiatric history was associated with worse outcomes (3 studies: increased symptoms, increased dysphagia, or increased surgical failure). • In endoscopic studies, age <48-50 years was associated with decreased PPI dosage (1 study) and decreased acid exposure (1 study).

Key Question 3: adverse events	Quality of evidence	Summary/Conclusion/Comments
	weak	• Open fundoplication vs. non-PPI treatment at 10 year follow-up (1 RCT): more gas-bloat syndrome in surgical group, no difference in abdominal girth, fullness, inability to belch and to vomit • Open fundoplication vs. omeprazole at 3-year follow-up (1 RCT): in surgical group, more complaints of rectal flatus, inability to belch and to vomit
		Summary/Conclusion/Comments
		• Laparoscopic fundoplication vs. PPIs (1 RCT): no direct comparative adverse event data reported in this study; in surgical group, 3.7% intraoperative complications (splenic, esophageal, and liver injury), 5.5% early post-operative complications (wrap migrations related to forceful vomiting, respiratory tract infections, inclusion of nasogastric tube by a wrap suture, gastric necrosis); there were no deaths in the surgical group; 4.5% developed dysphagia that persisted for > 3 months after surgery; adverse event data for PPIs not presented in this study. • There are no direct comparative adverse event data for endoscopic vs. laparoscopic procedures. • Laparoscopic fundoplication vs. open fundoplication at 5-year follow-up (1 RCT): difficulty with belching and increased flatulence were still dominant side-effects; no differences between the 2 groups. • From 2 meta-analyses, PPIs reported more adverse events compared with H2RA or placebo; headache, diarrhea, and abdominal pain were the most common.

The seemingly straightforward definition of GERD proposed in a guideline from the American College of Gastroenterology (ie, "symptoms or mucosal damage caused by the abnormal reflux of gastric contents into the esophagus.[1]) belies the complex issues related to its diagnosis and management. Patients with GERD have a wide spectrum of disease severity while caregivers have to choose from many options for evaluating such patients, embarking upon specific therapy and assessing the response, and considering the options for long-term treatment. This report cannot address all of these issues but does shed light upon the comparative efficacy and safety of the available treatment options.

GERD is generally considered a chronic condition that requires long-term treatment. Thus, we emphasized comparisons of the long-term efficacy and safety of medical, surgical, and endoscopic approaches. As a general rule, the surgical and endoscopic approaches are applicable only to patients who are seeking a long-term strategy for avoidance of symptoms and medication dependency.

It is important to stress that the populations evaluated in all of the studies included in this report focused on patients who had GERD that was well established based upon a formal evaluation that included objective testing (albeit the rigor with which the diagnosis was established varied across studies). By contrast, the majority of patients with symptoms suggestive of GERD are treated clinically without such an evaluation. Many such patients may have symptoms that are caused by other upper digestive disorders such as nonulcer dyspepsia.

Thus, the results are directly applicable only to patients in whom there is a relatively high-degree of certainty regarding the underlying diagnosis.

Furthermore, the studies of medical therapy used in this report were based mainly upon previously published meta-analyses. The primary controlled trials included in the meta-analyses enrolled almost exclusively patients who had some degree of esophagitis, thus excluding a population of patients with symptoms compatible with GERD but without visible esophagitis (a population sometimes referred to as having "non-erosive reflux disease"). The pathogenesis, natural history and response to therapy in such patients may be different than patients with GERD and esophagitis.[155,156] Similarly, the studies of surgical and endoscopic therapy typically enrolled patients with esophagitis or those who were already on antisecretory medications thus making it unclear whether the patients had non-erosive reflux disease at baseline. Thus, the summary of medical therapy described in this report is not directly applicable to patients with non-erosive reflux disease while the surgical and endoscopic literature has not addressed this population explicitly.

There were differences in the spectrum of disease severity in patients included in the various studies. As a general rule, studies of fundoplication included patients with the widest spectrum of disease severity, at least as assessed by the degree of esophagitis, since they included patients with esophagitis ranging in severity from none to Barrett's esophagus and esophageal strictures. Differences in baseline characteristics of patients may influence the results of some of the comparative trials, particularly those comparing surgery to medical therapy since patients undergoing surgery had relatively more severe disease at baseline in some of the comparative trials. Further complicating comparisons were the different classification systems used across studies for describing symptoms, the degree of esophagitis, and variation in how esophageal pH testing was performed and interpreted.

In addition, there are multiple subtle variations in surgical techniques that may influence the outcomes of surgery. The surgical reports did not provide sufficient detail on these technical nuances to understand their implications on clinical endpoints. We considered all of these factors in deriving our conclusions; nevertheless, accounting for all of these differences is sometimes not attainable.

Treatment outcomes were not defined uniformly across studies. Studies described a variety of subjective outcomes (such as changes in symptoms and quality of life) and more objective outcomes (such as healing of esophagitis, use of medications, and changes in esophageal pH exposure) and did not always use the same definitions to describe these endpoints. There was variability in the rigor with which some of these endpoints were defined, particularly those that were relatively subjective. For example, while some studies used a validated measure of quality of life, others used symptoms scales whose measurement properties have not been well studied. Similar differences were notable for more objective endpoints such as esophageal pH exposure and grading of esophagitis. Some studies used 12-hour while others 24-hour pH measurements and defined normalization differently. Some studies defined "normal" as a DeMeester score of less than <14.7 while others used a criterion of esophageal pH less than 4, less than 4.7 percent of the time. Still others did not define normal and simply used pre-treatment and post-treatment difference to report improvement or worsening. Studies reporting the grade of esophagitis also used varied definitions; some used the Savary-Miller grade while others the Los Angeles Classification or provided only macroscopic descriptions without using any classification system.

The maximal duration of follow-up also differed across the three interventions. Most of the primary studies included in the meta-analyses of medical therapy had follow-up duration of approximately one year. By contrast, for surgical therapy, we focused on cohort studies with at least five-years of follow-up while the follow-up on the studies comparing surgical and medical approaches ranged from 1 to 10 years. The endoscopic studies generally had follow-up of 1 year or less with the longest reported follow-up of 27 months.

All studies that were included had important limitations. Many of the surgical studies reported more than 50% of the patients were lost to follow-up at 5 or more years. Some of the uncontrolled studies and non-randomized comparative studies presented data only on evaluable patients (without an intention-to-treat analysis). Because many of the studies were non-randomized or lacked a suitable control group and focused on endpoints that can be subjective or vulnerable to a placebo effect, it was particularly difficult to confidently attribute benefits to the intervention. This was illustrated in a prospective cohort study by Cohen et al.,[54] which evaluated one of the endoscopic approaches. The authors reported that 67% of patients were off PPIs at 24 months. The clinical impact of this important endpoint is diminished when considering that 41% of the patients in the sham group in the controlled trial by Deviere et al.[6] were also off PPIs at the end of the study.

We summarized the various objective and subjective outcomes that are considered to be important in the care of patients with GERD, without attempting to define treatment success or failure. We relied on the definitions of endpoints used in the individual studies and did not attempt to adjust results in any way to increase comparability. Thus, whether variations in definitions of endpoints could account for differences in results across studies is unclear.

Two long-term RCTs that directly compared medical with surgical treatments qualified for inclusion in this report. One reported that there was no difference in heartburn symptoms between the medical and surgical patients at pre-defined time points through 5 years. The other reported significantly improved GERD symptoms in the surgical arm compared to the medical arm, after both groups discontinued all antireflux medications during the week of assessment. However, the difference was no longer significant when the assessment was made while both groups were kept on their usual antireflux medications.

Neither of the two long-term RCTs on medical versus surgical treatments demonstrated superiority of one treatment modality over the other in healing of esophagitis. Whether any of the endoscopic procedures has a favorable impact on patients who have esophagitis is also unclear. Two uncontrolled studies of Enteryx™ showed a worsening of esophagitis in approximately one-third of patients. Whether this represents chance, ineffectiveness of the procedure, or an adverse effect of treatment is uncertain.

Esophageal acid exposure improved to a greater extent in surgical arms compared to medical arms in two RCTs, at least for up to 1-year of follow-up. Uncontrolled studies of all the endoscopic procedures suggested improvement or normalization in pH in some patients, but there are insufficient data to determine the magnitude of improvement relative to one another, or correlation of pH changes with other outcome measures. Normalization of esophageal pH exposure was observed in 30 to 50% of patients in uncontrolled endoscopic studies, which is similar to what has been reported with medical therapy and inferior to what has been described with fundoplication (at least with short-term follow-up).

In most surgical cohort studies, 90% of patients were off antireflux medications at 5-year follow-up. However, in one of the medical versus surgical RCTs, approximately two-thirds of the surgical patients were still dependent on some form of antireflux medications at 10 years

follow-up.[8] The reasons for these different outcomes are unclear. But, it is important to note that some patients who continued to take antisecretory medications following surgery do not have objective evidence of GERD.[157-159] Another possible contributing factor may have been that the patients in the study by Spechler et al.[8] had relatively more severe disease at baseline. However, the Spechler study had the longest follow-up, and the high dropout rates in many of the surgical cohort studies did not permit a confident appraisal of the actual proportion of patients who were off all antisecretory medications on an intention-to-treat basis. The proportion of patients who did not require any antisecretory medications was reported infrequently in endoscopic studies but was in the range of only 25 to 40% in studies in which it was described, a proportion similar to the control rate observed in one of the sham-controlled studies.

Improvement in outcomes relevant to patients (such as symptoms, quality of life, and need for medications) would ideally correlate well with objective measures such as normalization of esophageal pH exposure and healing of esophagitis. The various studies included in this report underscore that these objectives do not always occur concordantly. Furthermore, the degree to which certain objectives should be achieved (such as normalization of pH or complete healing of esophagitis) has not been established.

Proponents of surgery and endoscopic approaches have pointed to a population of patients with “medically refractory” GERD who might benefit from an alternate approach. However, consensus has not been achieved on the definition of “medically refractory” and thus there was corresponding variability in the surgical and endoscopic studies that enrolled patients who “failed” medical treatment. Thus, we could not clearly identify criteria that defined a population of patients with an inadequate response to medical therapy who are likely to respond to surgery or endoscopic therapy. By contrast, we did find evidence that surgical outcomes were better in patients who had responded symptomatically to medical therapy. Thus, there is need for further clarification of the population with medically refractory GERD that might benefit from fundoplication or endoscopic therapy.

Multiple studies have compared one PPI to another. While some differences have been reported, the magnitude of differences has been small and of uncertain clinical importance. Furthermore, most of the comparative trials evaluated doses of the various PPIs that have been approved by the United States Food and Drug Administration (FDA). The doses of various PPIs that would be considered pharmacologically equivalent have not been well established and thus it is possible that all the various PPIs could be equivalent when administered at certain doses. Clinicians often increase the dose of a PPI in patients who do not have an adequate clinical response and do not necessarily rely upon FDA-approved doses and dosing intervals.

We sought and critically evaluated studies that attempted to correlate the outcomes of treatment with baseline patient or treatment-related characteristics. Such associations could be important for guiding patients toward specific options. However, comparison of these studies was difficult because of the heterogeneous study designs and because the reporting of data was often incomplete. Most of the data concerning open and laparoscopic surgery were derived from observational studies of single-center convenience samples. The studies were generally few in number and did not have many subjects. Some studies reported qualitative results without giving actual baseline or post-surgical data. In addition, a diverse range of factors and outcomes were analyzed. Often there was no study or only one study reporting on the association of a specific factor with a specific outcome. Several baseline patient-characteristics were associated with treatment outcomes but the strength of these associations was unclear. Relapse with maintenance

medical therapy appears to be more likely in patients with severe esophagitis, younger age, regurgitation, and LES incompetence at baseline.

The quality of reporting of adverse events was incomplete and inconsistent across studies. Some studies did not report specific adverse events (even though they were likely to have occurred) and the definitions of adverse events differed across studies. Furthermore, studies differed in how they classified adverse events as being temporary or persistent or even when they had occurred and none used an acceptable standard or scale for defining their severity. We also restricted our review of adverse events to treatments of GERD and we did not examine adverse event data from studies of PPI use in a non-GERD setting.

Despite a large body of evidence (and an even larger clinical experience) with medical therapy, there are relatively few studies that have systematically sought side effects of long-term medical therapy with PPIs. While this class of drugs has proven to be generally safe in the short-term, concerns have been identified with regard to long-term safety. Also, the potential need for life-long therapy raises the possibility that additional concerns might arise with longer experience with these drugs.

Published experience with all of the approved endoscopic procedures has been outpaced by clinical experience. The manufacturer of the Stretta™ procedure, for example, reports in their marketing media that more than 7000 procedures have been performed worldwide. There is little information regarding patients treated outside of the studies described in this report. An exception is post-marketing adverse events, which are reported voluntarily by manufacturers to the Food and Drug Administration. It should be noted that one of the devices (Enteryx™) was voluntarily removed from the market due to safety concerns that were not fully appreciated during studies that led to its approval.

In conclusion, PPIs and fundoplication are similarly effective in relieving symptoms and improving quality of life in patients with GERD that has been established based on objective testing. Whether medical therapy or surgery is more effective in preventing long-term complications from GERD remains unclear, however. The benefits of surgery must be balanced against its short- and long-term risks, particularly since some of the long-term side effects may be permanent. Experience of the surgeon may also weigh into the decision regarding surgery, although there were limited data from which to explicitly understand the relationship between the surgeon's experience and long-term outcomes or some of the technical nuances of the surgical approach that might have a bearing on surgical outcomes.

The quality, quantity, and consistency of studies on the endoscopic approaches to treatment of GERD are inferior to those of medical or surgical therapy, which can be expected since endoscopic approaches are new developments and data are evolving. At present, their efficacy compared with continued (or intensified) medical therapy is unclear. Sham controlled trials have demonstrated that some of the benefits of these procedures observed in the uncontrolled trials may not be directly attributable to the interventions, thus underscoring the need for additional sham-controlled trials. Although these devices are already commercially available, their long-term efficacy and safety have not yet been established.

Chapter 5. Future Research

- More studies are needed to clarify how patients with GERD should be managed based upon patient characteristics or response to previous therapy. Additional information is needed to select patients for specific testing for GERD and to determine how treatment should be guided by the results of testing.

- Methods need to be developed to identify patients who do not need long-term antisecretory medications to minimize their exposure to life-long medications.

- Empiric acid-suppression therapy in patients with GERD symptoms to confirm the diagnosis of GERD is imperfect. Data are needed to determine the cost-effectiveness of such an approach.

- Long-term studies are needed to assess the risks associated with acid suppression on the development of pneumonia and enteric infections and to assess the consequences of long-term hypergastrinemia.

- Randomized controlled trials of laparoscopic fundoplication versus PPIs with long-term follow-up are needed to ascertain the relative benefits and harms of each approach and whether certain subgroups are better served with one of the other alternative.

- Unmeasured differences in the surgical procedures (for example, the size of the bougie and length of the wrap) may have accounted for some differences among surgical series. Additional research might clarify which technical aspects of the surgical procedures are important for optimizing surgical outcomes.

- Studies to assess the efficacy and safety of antireflux surgery performed in a community setting compared with an academic setting are needed.

- Studies to address the annual number of operations per surgeon or center to maintain skills are also needed.

- Data on comparative endoscopic treatments with continued (or intensified) use of PPIs are needed to better understand their efficacy against an established standard.

- More efficacy and safety data on new endoscopic approaches tested against a sham procedure with adequate follow-up are needed.

- Future studies should use rigorous and validated standards for comparing all relevant clinical outcomes. Similarly, future studies should define as clearly as possible the certainty of the diagnosis of GERD and use measures that help define its severity.

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AHRQ Publication No. 06-EHC003-EF
December 2005