

Draft Comparative Effectiveness Review

Number XX

Comparative Effectiveness of Management Strategies for Gastroesophageal Reflux Disease – an Update to the 2005 Report

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

This information is distributed solely for the purposes of pre-dissemination peer review under applicable information quality guidelines. It has not been formally disseminated by the Agency for Healthcare Research and Quality. It does not represent and should not be construed to represent an Agency for Healthcare Research and Quality or Department of Health and Human Services determination or policy.

Contract No.

Prepared by:

Investigators:

This document is in the public domain and may be used and reprinted without permission except those copyrighted materials noted, for which further reproduction is prohibited without the specific permission of copyright holders.

Suggested Citation:

None of the investigators has any affiliations or financial involvement that conflicts with the material presented in this report.

Financial disclosure: None noted.

This report is based on research conducted by the XXX (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. XXX). The findings and conclusions in this document are those of the author(s), who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ. Therefore, no statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

This report is intended as a reference and not as a substitute for clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information.

This report may be used, in whole or in part, as the basis for development of clinical practice guidelines and other quality enhancement tools, or as a basis for reimbursement and coverage policies. AHRQ or U.S. Department of Health and Human Services endorsement of such derivative products may not be stated or implied.

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 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 (CERs) 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 <http://effectivehealthcare.ahrq.gov/reference/purpose.cfm>.

AHRQ expects that CERs will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. In addition, AHRQ is committed to presenting information in different formats so that consumers who make decisions about their own and their family's health can benefit from the evidence.

Transparency and stakeholder input from are essential to the Effective Health Care Program. 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. Comparative Effectiveness Reviews will be updated regularly.

Acknowledgments

Technical Expert Panel

EPC Program Director

AHRQ Contacts

This report is based on research conducted by the XXX (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. XXX). The findings and conclusions in this document are those of the author(s), who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ. Therefore, no statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

The information in this report is intended to help health care decision-makers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

This report may be used, in whole or in part, as the basis for development of clinical practice guidelines and other quality enhancement tools, or as a basis for reimbursement and coverage policies. AHRQ or U.S. Department of Health and Human Services endorsement of such derivative products may not be stated or implied.

Table of Contents

Executive Summary	ES-1
Background and Key Questions.....	ES-1
Conclusions.....	ES-2
Remaining Issues	ES-7
Introduction.....	1
Methods.....	3
Analytic Framework and Key Questions.....	3
Search Strategy	4
Study Selection	5
Data Extraction	9
Quality Assessment.....	10
Critical appraisal of systematic reviews	11
Data Synthesis.....	11
Peer Review	13
Results	15
Key Question 1: What is the evidence of the comparative effectiveness of medical, surgical and other newer forms of treatments for improving objective and subjective outcomes in patients with chronic Gastroesophageal Reflux Disease (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.....	17
Key Question 1A. Medical versus surgical treatments.....	17
Key Question 1B. Surgical versus endoscopic treatments.....	20
Key Question 1C. Medical versus endoscopic treatments.....	20
Key Question 1D. Medical treatment	27
Key Question 1E. Surgical treatments	60
Key Question 1F. Endoscopic treatments.....	67
Key Question 1G. Comparative effectiveness of treatment for extra-esophageal Manifestation of Gastroesophageal Reflux Disease	75

Key Question 2: Is there evidence that effectiveness of medical, surgical and newer forms of treatment 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, and other demographic and medical factors? What are the provider characteristics for procedures including provider volume and setting (e.g., academic versus community)? 93

Key Question 3: What are the short-term and long-term adverse events associated with specific medical, surgical and newer forms of therapies for GERD? Does the incidence of adverse events vary with duration of followup, specific surgical intervention, or patient characteristics? 113

Discussion.....145

Abbreviation168

Tables

Table A. Summary of evidence 8

Table 1. Medical vs. surgical treatments for GERD: Change in symptoms, QOL and satisfaction 21

Table 2. Medical vs. surgical treatments for GERD: Change in medication usage status 23

Table 3. Medical vs. surgical treatments for GERD: Change in pH study results 24

Table 4. Medical vs. surgical treatments for GERD: Remission rates 25

Table 5. Comparative studies evaluating surgical versus endoscopic treatments for GERD..... 26

Table 6. Comparison of PPI w/ H2 Receptor Antagonist - Symptom Assessment 41

Table 7. Comparison of PPI w/ H2 Receptor Antagonist or Different H2 Receptor Antagonists - Quality of Life..... 42

Table 8. Comparison of PPI w/ H2 Receptor Antagonist - Esophagitis Healing 43

Table 9. Comparison of PPI w/ H2 Receptor Antagonist - Relapse rate, patient satisfaction, time to recurrence and medication use..... 43

Table 10. Comparison of different PPIs – Symptom Assessment 44

Table 11. Comparison of different PPIs – Quality of Life 46

Table 12. Comparison of different PPIs - Endoscopic Esophagitis Healing 47

Table 13. Comparison of different PPIs – Antacid Medication Use 48

Table 14. Comparison of different dosages as well as different dosing regimens of the same PPIs – Symptom Assessment 49

Table 15. Comparison of different dosages as well as different dosing regimens of the same PPIs – Quality of Life..... 51

Table 16. Comparison of different dosages as well as different dosing regimens of the same PPIs – Esophagitis healing 52

Table 17. Comparison of different dosages as well as different dosing regimens of the same PPIs – Acid Control..... 53

Table 18. Comparison of different dosages as well as different dosing regimens of the same PPIs - Antacid Medication Use and Treatment Satisfaction 54

Table 19. Comparisons between once daily and on-demand dosing regimens of commonly used PPIs – Symptom Assessment.....	55
Table 20. Comparisons between once daily and on-demand dosing regimens of commonly used PPIs – Quality of Life	56
Table 21. Comparisons between once daily and on-demand dosing regimens of commonly used PPIs – Esophagitis healing.....	57
Table 22. Comparison of PPI w/ Over the Counter Doses of approved PPIs (OME 20 mg, LAN 15 mg) – Symptom Assessment.....	57
Table 23. Comparison of PPI w/ Over the Counter Doses of approved PPIs (OME 20 mg, LAN 15 mg) – Quality of Life	58
Table 24. Comparison of PPI w/ Over the Counter Doses of approved PPIs (OME 20 mg, LAN 15 mg) - Esophagitis Healing	59
Table 25. Comparative studies evaluating the long-term outcomes of different types of fundoplication	62
Table 26. Cohort studies evaluating the long term outcomes of surgical procedures	65
Table 27. Comparative studies evaluating endoscopic treatment for GERD	69
Table 28. Cohort studies evaluating endoscopic treatment	71
Table 29. Treatment of GERD and its effect on Asthma – Data from Systematic reviews	84
Table 30. Treatment of GERD and its effect on Asthma: RCTs published between 2002 - 2010	86
Table 31. Treatment of GERD and its effect on extra-esophageal symptoms: Hoarseness and laryngitis	89
Table 32. Treatment of GERD and its effect on extra-esophageal symptoms: Chronic Cough...	91
Table 33. Summary of studies that evaluated patient characteristics as modifying factors in randomized, controlled trials comparing effects of different proton pump inhibitors.	102
Table 34. Summary of studies that evaluated patient characteristics as modifying factors in randomized, controlled trials comparing different dosages and dosing regimens of commonly used proton pump inhibitors	103
Table 35. Summary of studies that evaluated patient characteristics as modifying factors of medical treatment outcome	104
Table 36. Summary of studies that evaluated patient characteristics as modifying factors of fundoplication outcome	107
Table 37. Adverse events in RCTs comparing medical to surgical treatments	118
Table 38. Adverse events reported in randomized, controlled trials of PPIs or H2RA	120
Table 39. Observational studies that examined the relationships between the use of PPIs or H2RAs and fracture risk	125
Table 40: Intraoperative complications (and those occurring within 30 days) for surgical procedures.....	127
Table 41: Complications occurring more than 30 days after surgical procedures.....	131
Table 42: Intraoperative complications (and those occurring within 30 days) for endoscopic procedures.....	142
Table 43: Complications occurring more than 30 days after endoscopic procedures	143
Table 44: Devices and Adverse events from the MAUDE database	144
Table 45: List of Adverse events from the MAUDE database	144
Table 46. Summary of evidence	148

Figures

Figure 1. Analytic framework of the comparative effectiveness of management strategies for
GERD..... 3
Figure 2. Study selection flow 15

Appendix A. Search Strategies

Appendix B. Excluded Studies

Appendix C. Evidence Tables

Appendix D. Peer Reviewers

Executive Summary

Background and Key Questions

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

A number of patients have frequent, severe symptoms requiring long-term regular use of antireflux medications. For these individuals with chronic GERD, most authorities consider the goals of therapy to be an improvement in symptoms and quality of life, healing 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 the choice of management strategy.

The initial Comparative Effectiveness Review (CER) published by the Agency of Healthcare Quality and Research (AHRQ) focused on gastroesophageal reflux disease (GERD); the Key Questions addressed within concerned the comparative effectiveness of medical, surgical and endoscopic treatments for improving objective and subjective outcomes in patients with this disease. In addition, the report examined the relative efficacy of these interventions in specific patient subgroups as well as their adverse event profiles. A number of developments since the final publication of the 2005 review have necessitated an update. Among them: the publication of approximately 3000 new studies, the introduction of novel drugs, the recognition of new drug safety considerations, and the withdrawal of previously approved, and introduction of new, endoscopic interventions. Also notable was the publication of a new consensus definition of GERD in 2006.

The current report addresses these developments and has additionally been expanded to include sections on extra-esophageal syndromes, including chronic cough, laryngitis, and asthma, which were considered to be of particular clinical importance by an expert panel.

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

Similar considerations were made for the assessment of outcomes, which included measures of formal or informal evaluation of symptoms, medication use, quality of life instruments, healing of esophagitis, and changes in esophageal pH exposure. The methods by which these outcomes were evaluated varied and not all studies included outcomes of interest.

Again, to aid in interpretation of results, outcomes and their definitions were explicitly reported when making comparisons across studies. The quality of studies was also assessed rigorously and weighed in the formulation of conclusions.

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

GERD continues to be an important disease both in terms of cost and public health. The large disease burden, economic impact, and market potential for new drugs and devices explain the continued intense interest in GERD and the development of cost-effective approaches for its diagnosis and management. The purpose of the current report is to provide a detailed, rigorous, and up-to-date appraisal of the evidence comparing various management strategies for patients with GERD. While not intended to make clinical recommendations, its conclusions should have immediate clinical applicability by elucidating the safety and effectiveness of various treatment approaches for subgroups of patients with GERD as well as providing guideline-issuing organizations guidance in the formulation of their recommendations for the management of GERD.

Conclusions

The findings in this report are summarized in Table A.

Key Question 1. What is the evidence of the comparative effectiveness of medical, surgical and other newer forms of treatments for improving objective and subjective outcomes in patients with chronic Gastroesophageal Reflux Disease (GERD)? Is there evidence that effectiveness varies by specific technique, procedure, or medication? Objective outcomes addressed include esophagitis healing, ambulatory pH, other indicators of reflux, need for medication, 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.

Medical versus surgical treatments

The 2005 CER concluded that medical therapy with PPIs and antireflux surgery were similarly effective in improving GERD-related symptoms and decreasing esophageal acid exposure, although some surgical patients required ongoing medical therapy post-procedure. With the addition of long-term followup data (7 to 12 years) from two previously reviewed studies and results from two new RCTs, our updated review found that patients who underwent antireflux surgery experienced a greater improvement in heartburn and regurgitation at followup compared with patients who received medical treatment alone. However, the true estimates of the efficacy of surgery versus medical treatment are highly uncertain because of the large proportion of patient dropouts (33 to 58 percent) in studies with long followup.

Consistent with results from the 2005 review, fundoplication decreased, but did not eliminate, the use of antireflux medications at followup. Compared with those who received medical treatment, patients who underwent antireflux surgery also demonstrated improvement (in some cases statistically significant) on reflux symptoms scales and quality of life measurements. Studies reporting data from pH study results also demonstrated outcomes favoring surgically treated patients. Furthermore, the surgery group in one RCT demonstrated

significantly greater sustained remission of GERD symptoms relative to the medication group at followup. However, the rate of serious adverse events was in general higher in patients who underwent fundoplication compared with those who had medical treatment. Fundoplication was also associated with procedural complications like postoperative infections and incisional hernia, and morbidities like dysphagia and postprandial bloating, some of which required surgical revisions. On the other hand, typical adverse events reported with PPI use were generally not serious (e.g., diarrhea, abdominal pain, headache) and tend to self-resolve upon stopping the treatment (see section below for other serious adverse events potentially associated with PPI use).

Medical versus endoscopic treatments

Similar to the 2005 CER, the present update did not identify any study that compared medical treatment with endoscopic therapy.

Surgical versus endoscopic treatments

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

Medical treatment comparisons

Comparisons between PPIs and H2RAs

The addition of four RCTs did not alter the conclusions of the 2005 CER. In both the original CER and the present update, PPIs were found to be superior to H2RAs in the resolution of GERD symptoms at 4 weeks and healing of esophagitis at 8 weeks.

Lansoprazole 15 mg, taken once daily, was found to be more effective than ranitidine 150 mg taken twice daily for the healing of esophagitis at 1 year. Esomeprazole 20 mg, taken once daily or on-demand, was more effective than ranitidine 150 mg taken twice daily for the prevention of symptom relapse at 6 months. Maintenance treatment (≥ 6 months) with PPIs appeared to be more effective than maintenance treatment with H2RA in symptom remission.

Comparisons between different PPIs

The 2005 CER report did not find significant difference between omeprazole, lansoprazole, pantoprazole, and rabeprazole for relief of symptoms at 8 weeks and no significant difference between esomeprazole 40 mg with lansoprazole 30 mg and pantoprazole 40 mg for symptom relief at 4 weeks. Similarly, no difference was observed in the comparison of esomeprazole 20 mg with omeprazole 20 mg in relief of symptoms at 4 weeks. However, esomeprazole 40 mg was significantly favored for symptom relief at 4 weeks compared with omeprazole 20 mg.

In the present update, eleven additional RCTs did not alter the conclusions of the original report with respect to these comparisons. Comparisons were made between pantoprazole (20 mg to 40 mg) with esomeprazole (20 mg to 40 mg), lansoprazole 30 mg with esomeprazole 40 mg, and rabeprazole (10 mg to 20 mg) with esomeprazole (20 mg to 40 mg) and dexrabeprazole 10 mg. The durations of followup ranged from 1 to 6 months. No consistent comparative difference in symptom relief was observed between esomeprazole (20 to 40 mg), lansoprazole (15 to 30

mg), pantoprazole (20 to 40 mg), dexlansoprazole (10 mg) or rabeprazole (10 to 20 mg) over a period ranging from 4 weeks to 6 months. There is some evidence that rabeprazole 10 mg may provide better symptom relief than esomeprazole 40 mg at 4 weeks, and pantoprazole 20 mg better control of heartburn than esomeprazole 20 mg over 24 weeks.

Comparisons between different dosages and dosing regimens of PPIs

As opposed to the 2005 CER, which did not evaluate comparisons between different dosages and dosing regimens of commonly used PPIs, the present report reviewed eleven RCTs examining the relative effectiveness of different PPI dosing regimens. Comparisons were made between different dosages of pantoprazole (20 mg to 40 mg), esomeprazole (10 mg to 40 mg), lansoprazole (15 mg to 30 mg), and dexrabeprazole (30 mg to 90 mg). The regimens evaluated included once daily or on-demand dosing, a regimen of 4-wk PPI therapy with relapse of symptoms (intermittent therapy), a regimen of endoscopy-determined dose, where presence of esophagitis on endoscopy necessitated a higher dose of the PPI, and different “step” regimens – “step down” to H2RA or “step down” to lower PPI dose. The time periods of followup ranged from 1 to 12 months.

No significant difference in symptom resolution rates was observed at 4 weeks between esomeprazole 20 mg taken once a day and esomeprazole 40 mg taken once a day. A significantly higher rate of esophagitis healing at 4 weeks was observed with esomeprazole 40 mg taken once a day compared with esomeprazole 20 mg taken once a day. This was corroborated by the observation of a significantly higher percentage of time of exposure to pH >4 in patients taking esomeprazole 40 mg once a day.

Comparisons between once daily and on-demand dosing regimens of PPIs

Five RCTs compared once daily with on-demand dosing. Comparisons were made between the once daily and on-demand dosing regimens for rabeprazole 10 mg, rabeprazole 20 mg and esomeprazole 20 mg. Followup ranged from 6 months to 6.5 months.

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

Comparisons between PPIs and over-the-counter dosages of PPIs (omeprazole 20 mg, lansoprazole 15 mg)

Seven RCTs compared prescribed PPIs with over-the-counter dosages of PPIs (omeprazole 20 mg and lansoprazole 15 mg, as approved by the US Food and Drug Administration (FDA)). The PPI doses that were compared with omeprazole 20 mg included omeprazole 10 mg, omeprazole 20 mg on-demand, esomeprazole (20 mg to 40 mg), rabeprazole 20 mg, lansoprazole 30 mg and pantoprazole 40 mg. The only PPI that was compared with lansoprazole 15 mg was esomeprazole 20 mg. Followup ranged from 1 to 12 months.

Pantoprazole 40 mg and rabeprazole 20 mg provided significantly better symptom relief and healing of esophagitis at 8 weeks compared with omeprazole 20 mg. Esomeprazole 20 mg provided higher endoscopic remission rates as compared to over-the-counter dosages of lansoprazole (15 mg) over 6 months.

Surgical treatment comparisons

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

One RCT and five non-randomized comparative studies examined laparoscopic total versus partial fundoplication. No consistent significant differences in GERD symptoms, diagnostic test results, or quality of life were observed between groups.

Two RCTs and two non-randomized comparative studies examined laparoscopic fundoplication with versus without division of short gastric vessel. No significant differences in medication use, GERD symptoms, or quality of life were found between groups.

Two RCTs and one non-randomized comparative study examined laparoscopic versus open fundoplication. No significant differences in medication use, GERD symptoms, diagnostic test results, or quality of life were found between groups.

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

Endoscopic treatment comparisons

The 2005 CER evaluated studies on four endoscopic procedures: the EndoCinch™ Suturing System, Stretta®, Enteryx™, and the NDO Plicator™. The present report excluded Enteryx and the NDO Plicator as they are no longer available in the US. Stretta was removed from the market but reintroduced in 2010 by a separate manufacturer. Another device, EsophyX™, was commercialized after the original review.

No study directly comparing endoscopic treatments were identified for this update; however, a number of sham-controlled and cohort studies examining the effectiveness of the individual procedures were reviewed.

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

Five cohort studies evaluated the effectiveness of EsophyX. The reported proportion of patients who were off PPIs at the end of the followup period ranged from 47 to 71 percent. Significant improvement of GERD-HRQL was reported by two of the five studies.

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

Medical and surgical treatment of extra-esophageal manifestation of GERD

The 2005 CER did not address the effect of medical and surgical treatments for GERD with extra-esophageal symptoms including asthma, hoarseness/laryngitis, or chronic cough. Data for this evaluation were extracted from existing systematic reviews and update studies.

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

Two of the six RCTs in the systematic review assessing the effect of PPI treatment on hoarseness found a significantly higher proportion of patients reporting resolution of hoarseness symptom with PPI treatment compared with placebo.

A meta-analysis included in the systematic review did not find a significant difference between PPIs and placebo in complete eradication of cough. A second meta-analysis reported within the same systematic review however, showed a significant improvement in cough scores from baseline favoring PPIs compared to placebo (-0.39 standardized mean difference units; 95 percent CI -0.71 to -0.08).

One existing systematic review of surgical cohort studies on the treatment of extra-esophageal manifestations of GERD found that surgery may help improve cough and laryngeal symptoms more so than asthmatic symptoms - a better range of complete resolution in cough (13 to 96 percent in 11 out of 13 studies reporting outcome) and laryngeal symptoms (64 to 94 percent in 5 out of 8 studies reporting outcome) compared to asthma (0 to 64 percent in 3 out of 7 studies reporting outcome). However, there is a wide range of effect estimates. This is likely due to the considerable heterogeneity in the study populations, interventions, and the outcome measures used to estimate the effects.

Key Question 2. Is there evidence that effectiveness of medical, surgical and newer forms of 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, and other demographic and medical factors? What are the provider characteristics for procedures including provider volume and setting (e.g., academic versus community)?

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

One study reported that there was no significant difference in the effectiveness of medical versus surgical treatment between patients with and without Barrett's esophagus.

Six RCTs comparing different PPIs, or dosages and dosing regimens of PPIs, reported mixed findings regarding the impacts of esophagitis severity at baseline on healing rates.

Ten cohort studies investigated patient characteristics or clinical factors as modifying factors of medical treatment outcomes. Five cohort studies reported that sex was not a significant modifying factor of medical treatment outcomes. Eight cohort studies demonstrated that obesity, presence of baseline typical GERD symptoms, or more severe esophagitis at baseline were significantly associated with worse medical treatment outcomes. Three of five cohort studies on age found that older age was associated with improved symptom control.

One RCT found that preoperative esophageal motility did not significantly impact the effect of Nissen or Toupet laparoscopic fundoplication on dysphagia, recurrence of reflux, and 24-hour pH-metry and manometry outcomes.

Thirty cohort studies showed the following patient characteristics were inconsistently associated with worse surgical outcome: per year increase in patient's age, morbid obesity, female sex, presence of baseline symptoms, and esophagitis and hiatal hernia more than 3 centimeter at baseline.

Three cohort studies investigated different modifying factors of endoscopic treatment. One cohort study did not find a significant difference between men and women in symptom improvement. Another study showed more patients with less severe esophagitis at baseline stopped PPI use than patients with more severe esophagitis. One study observed a learning curve in performance of a new endoscopic treatment device (EsophyX) comparing the technical procedure parameters.

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

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

Remaining Issues

- Longer term followup is necessary to determine the efficacy of laparoscopic fundoplication versus medical treatments. One available study reviewed reported 3-year interim data; however, that study remains ongoing.¹
- Higher quality studies are necessary to determine the role and value of endoscopic procedures in the treatment of patients with GERD.
- Retrospective analyses exploring potential modifiers of treatment outcomes need to carefully consider confounders and perform appropriate adjustments.
- Comparative studies are needed to determine the optimal treatment(s) for patients who did not respond to medication.
- The potential necessity for life-long medical therapy raises the possibility of unidentified long-term safety issues. Therefore, a systematic monitoring of long-term safety data on PPIs should be emphasized, as well as better baseline reporting of patient characteristics and potential confounders. Both could help ferret out any possible association between treatment and adverse events.

Table A. Summary of evidence

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

		<ul style="list-style-type: none"> - symptom remission. - In maintenance treatment, patients taking lansoprazole 15 mg are likely to stay longer on their treatment as compared to ranitidine 150 mg taken twice daily and thus tend to have a longer median time to relapse of symptoms. - Studies with larger sample sizes suggested PPIs to be more efficacious than H2RAs with respect to GERD symptoms.
Comparisons between different PPIs	Moderate	<ul style="list-style-type: none"> - No consistent comparative difference in symptom relief was observed between esomeprazole (20 to 40 mg), lansoprazole (15 to 30 mg), pantoprazole (20 to 40 mg), dexlansoprazole (10 mg) or rabeprazole (10 to 20 mg) over a period ranging from 4 weeks to 6 months. - There is some evidence that rabeprazole 10 mg may provide better symptom relief than esomeprazole 40 mg at 4 weeks, and also that pantoprazole 20 mg provides better control of heartburn than esomeprazole 40 mg over 24 weeks.
Comparisons between different dosages and dosing regimens of PPIs	Moderate	<ul style="list-style-type: none"> - There was no significant difference in symptom resolution rates at 4 weeks between esomeprazole 20 mg taken once a day and esomeprazole 40 mg taken once a day. - A significantly higher rate of healing of esophagitis at 4 weeks was observed with esomeprazole 40 mg once a day compared with esomeprazole 20 mg once a day.
Comparisons between once daily and on-demand dosing regimens of PPIs	Moderate	<ul style="list-style-type: none"> - Continuous daily intake of esomeprazole 20 mg appears to provide better symptom control and quality of life relative to on-demand dosing over a period of 6 months. - Continuous daily intake of esomeprazole 20 mg appears to provide significantly better endoscopic remission compared with on-demand dosing over a period of 6 months. - Continuous daily intake of rabeprazole 20 mg appears to provide better symptom control and quality of life relative to on-demand dosing over a period of 6 months.
Comparisons between PPIs and over-the-counter dosages of PPIs (omeprazole 20 mg, lansoprazole 15 mg)	Moderate	<ul style="list-style-type: none"> - Pantoprazole 40 mg and rabeprazole 20 mg provide significantly better symptom relief and healing of esophagitis than omeprazole 20 mg at 8 weeks. - Esomeprazole 20 mg provides higher endoscopic remission rates compared with lansoprazole 15 mg over 6 months.
Surgical treatment comparisons Total versus partial fundoplication	Moderate	<ul style="list-style-type: none"> - One RCT and five non-randomized comparative studies compared laparoscopic total versus partial fundoplication. - No consistent significant differences in GERD symptoms, diagnostic test results, or quality of life were observed between groups.
Fundoplication with versus without division of short gastric vessel	Moderate	<ul style="list-style-type: none"> - Two RCTs and two non-randomized comparative studies compared laparoscopic fundoplication with versus without division of short gastric vessel. - No significant differences in medication use, GERD symptoms, or quality of life were found between groups.
Laparoscopic versus open fundoplication	Moderate	<ul style="list-style-type: none"> - Two RCTs and one non-randomized comparative study compared laparoscopic versus open fundoplication. - No significant differences in medication use, GERD

		symptoms, diagnostic test results, or quality of life were found between groups.
Endoscopic treatments		
Comparison between endoscopic treatments	insufficient	- No direct comparisons between the different endoscopic treatments were identified.
EndoCinch™	Low	- Two sham-controlled studies and six non-comparative cohort studies evaluated the effectiveness of EndoCinch™. - No consistent differences between EndoCinch™ and sham were reported. - Significant improvements in heartburn, quality of life, and esophagitis healing were found in some but not all cohort studies.
EsophyX™	Insufficient	- Five small cohort studies evaluated the effectiveness of EsophyX™. - The reported proportion of patients who were off PPI at the end of the followup period ranged from 47 to 71 percent. - Significant improvement of GERD-HRQL was reported by two of five studies.
Stretta™	Insufficient	- One sham-controlled study and seven non-comparative cohort studies evaluated Stretta™. - In the RCT, the proportion of patients who stopped or decreased PPI use was significantly greater in the Stretta™ group compared with the control group at 6 months (but it was not significant at 1 year). No significant differences in heartburn symptoms, QoL, acid exposure and esophagitis outcomes were found. - The majority of cohort studies found significant improvements in GERD symptoms, QoL, and medication use.
Medical treatment for extra-esophageal symptoms		
Asthma	Insufficient	- A systematic review did not find consistent effects of PPI or H2RA (versus placebo) in improving asthma symptoms, nocturnal asthma, use of asthma medications or FEV1. - 8 primary RCTs in the update to the systematic review also reported inconsistent effects. Omeprazole 20 mg (combined with domperidone 10 mg) or esomeprazole 40 mg showed an improvement in peak expiratory flow rate. Lansoprazole 30 mg or pantoprazole 40 mg did not show an improvement in asthma symptoms or lung function tests. Rabeprazole 20 mg twice a day improved respiratory symptoms during exercise in patients with exercise induced asthma, as compared to a placebo, but not QoL or pulmonary function measures.
Hoarseness	Low	- Four of six RCTs did not find a significant difference in resolution of hoarseness between PPI and placebo.
Chronic cough	Low	- Meta-analysis of 6 studies (191 participants) showed no significant difference in total resolution of cough between PPIs and placebo, odds ratio 0.46 (95% CI: 0.19 to 1.15). A second meta-analysis of 6 studies (161 participants) showed a significant difference in the change in cough scores from baseline comparing PPI with placebo: -0.39 standardized mean difference (SMD) units (95% CI -0.71 to -0.08).
Surgical Treatment for extra-esophageal symptoms	Insufficient	- All of the data on surgical treatment are from cohort studies, with a wide variation in the population treated, the severity of the underlying GERD and its extra-esophageal manifestation, the outcome measures, the

		<p>surgical interventions, the intensity and duration of followup.</p> <ul style="list-style-type: none"> - The majority of the cohort studies found that surgery may help improve cough and laryngeal symptoms more so than asthma, but there is a wide range of effect estimates in these studies.
<p>Key Question 2: Is there evidence that the effectiveness of medical, surgical and newer forms of 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 (e.g., academic versus community)?</p>		
Factors that influenced the comparative effectiveness of surgical versus medical treatment	Insufficient	<ul style="list-style-type: none"> - One study found that there was no significant difference in the effectiveness of medical vs. surgical treatment between patients with and without Barrett's esophagus.
Factors that influenced the outcome of medical therapy	Moderate	<ul style="list-style-type: none"> - Six RCTs comparing different PPIs, or dosages and dosing regimens of PPIs showed mixed findings regarding the impacts of esophagitis severity at baseline on healing rates. - Ten cohort studies examined patient characteristics or clinical factors as modifying factors of medical treatment outcomes. <ul style="list-style-type: none"> • Sex was not a significant modifying factor of medical treatment outcomes. • Obesity, presence of baseline typical GERD symptoms, and more severe esophagitis were significantly associated with worse medical treatment outcomes • The associations between age and medical treatment outcomes were inconsistent.
Factors that influenced the outcome of surgical treatment	Low	<ul style="list-style-type: none"> - One RCT found that preoperative esophageal motility did not significantly impact the effect of laparoscopic fundoplication on dysphagia, recurrence of reflux, and acid exposure and manometry outcomes. - Thirty cohort studies showed the following were inconsistently associated with worse surgical outcome: per year increase in patient's age, morbid obesity, female sex, presence of baseline symptoms or esophagitis, and hiatal hernia greater than 3 cm at baseline.
Factors that influenced the outcome of endoscopic treatment	Low	<ul style="list-style-type: none"> - Three cohort studies examined different modifying factors of endoscopic treatment: <ul style="list-style-type: none"> • One study did not find a significant difference between men and women in symptom improvement. • One study found more patients with less severe esophagitis at baseline stopped PPI use than patients with more severe esophagitis. • One study observed a learning curve in performance of a new endoscopic treatment device (EsophyX) comparing the technical procedure parameters.
<p>Key Question 3: What are the short-term and long-term adverse events associated with specific medical, surgical and newer forms of therapies for</p>		

GERD? Does the incidence of adverse events vary with duration of follow-up, specific surgical intervention, or patient characteristics?

Adverse events	Low	<ul style="list-style-type: none">- None of the adverse event quantitative estimates are reliable because of a lack of standard definition and uniform system of reporting.- One RCT reported that the rate of serious adverse events was higher with surgery than with medical treatment (P=0.06).- Potential serious complications possibly associated with PPIs included an increased risk of bone fracture, as well as enteric infections and pneumonia previously reported in our 2005 CER.- Common adverse events reported in patients who underwent fundoplication included bloating and dysphagia.- Common adverse events after endoscopic suturing included chest or abdominal pain, bleeding, dysphagia, and bloating.
----------------	-----	--

Introduction

The first Comparative Effectiveness Report published by the Agency of Healthcare Quality and Research (AHRQ) focused on gastroesophageal reflux disease (GERD).² The Key Questions addressed concerned the comparative effectiveness of medical, surgical and endoscopic treatments for improving objective and subjective outcomes in patients with GERD. In addition, the report examined the relative efficacy of these interventions in specific patient subgroups as well as their adverse event profiles.

A number of developments since the final publication of the report in 2005 have necessitated an update. Among them: the publication of approximately 3000 new studies, the introduction of new drugs, the recognition of new drug safety considerations, and the market withdrawal and introduction of new endoscopic interventions. Also notable was the publication of a new consensus definition of GERD in 2006.³

The current report addresses these developments. In addition, it has been expanded to include sections on extra-esophageal syndromes, including chronic cough, laryngitis, and asthma, which were considered to be of particular clinical importance by an expert panel.

Despite these developments, many considerations remained unchanged. As with the previous report, definitions of GERD and disease severity among included subjects varied from study to study. For example, many studies defined GERD based on symptomatology, while others incorporated the results of various objective tests such as ambulatory esophageal pH, endoscopic, or acid suppression studies. The populations evaluated were, therefore, made explicit and outlined in detail.

Similar considerations were made for assessment of outcomes, which included measures of formal or informal assessment of symptoms, use of medications, quality of life instruments, healing of esophagitis, and changes in esophageal pH exposure. The methods by which these outcomes were evaluated varied and not all studies included outcomes of interest. Again, outcomes and their definitions were explicitly reported when making comparisons across studies. The quality of studies was also assessed rigorously and weighed in the formulation of conclusions.

Furthermore, as this report was intended to focus on comparative effectiveness, studies that directly compared treatment options for GERD were prioritized. However, non-comparison studies were also considered in order to fully address particular of the Key Questions, such as those pertaining to adverse events.

GERD continues to be an important disease both in terms of cost and public health. One study of an employed population in the United States estimated that more than 11,000 of 267,000 employees (4%) suffered from GERD, contributing an average incremental cost of \$3,355 per employee during a three year observation period—approximately 65% related to prescription drugs.⁴ At the same time, it is well recognized that some drugs used to treat GERD (such as proton pump inhibitors) are overprescribed.⁵ The large disease burden, economic impact, and market potential for new drugs and devices explain the continued intense interest in GERD and the development of cost-effective approaches for its diagnosis and management.

The purpose of the current report is to provide a detailed, rigorous, and up-to-date appraisal of the evidence comparing various management strategies for patients with GERD. While not intended to make clinical recommendations, its conclusions should have immediate clinical applicability by elucidating the safety and effectiveness of various treatment approaches

for subgroups of patients with GERD as well as providing guideline-issuing organizations guidance in the formulation of their recommendations for the management of GERD.

Methods

The present report is an update of the 2005 AHRQ Comparative Effectiveness Review (CER) of management strategies for GERD.² The Tufts EPC held teleconferences with a Technical Expert Panel (TEP) formed for this project. The TEP served in an advisory capacity, helping to refine key questions, identify important issues, and define parameters for the review.

Analytic Framework and Key Questions

The analytic framework depicted in Figure 1 was applied to answer the Key Questions in the evaluation of the treatment modalities for GERD. This framework addressed relevant clinical and intermediate outcomes, as well as examined clinical factors that affected treatment outcomes. While evidence from high quality randomized controlled trials (RCTs) was preferred, where there was a paucity of data or such studies were unavailable, non-randomized and uncontrolled studies were also included.

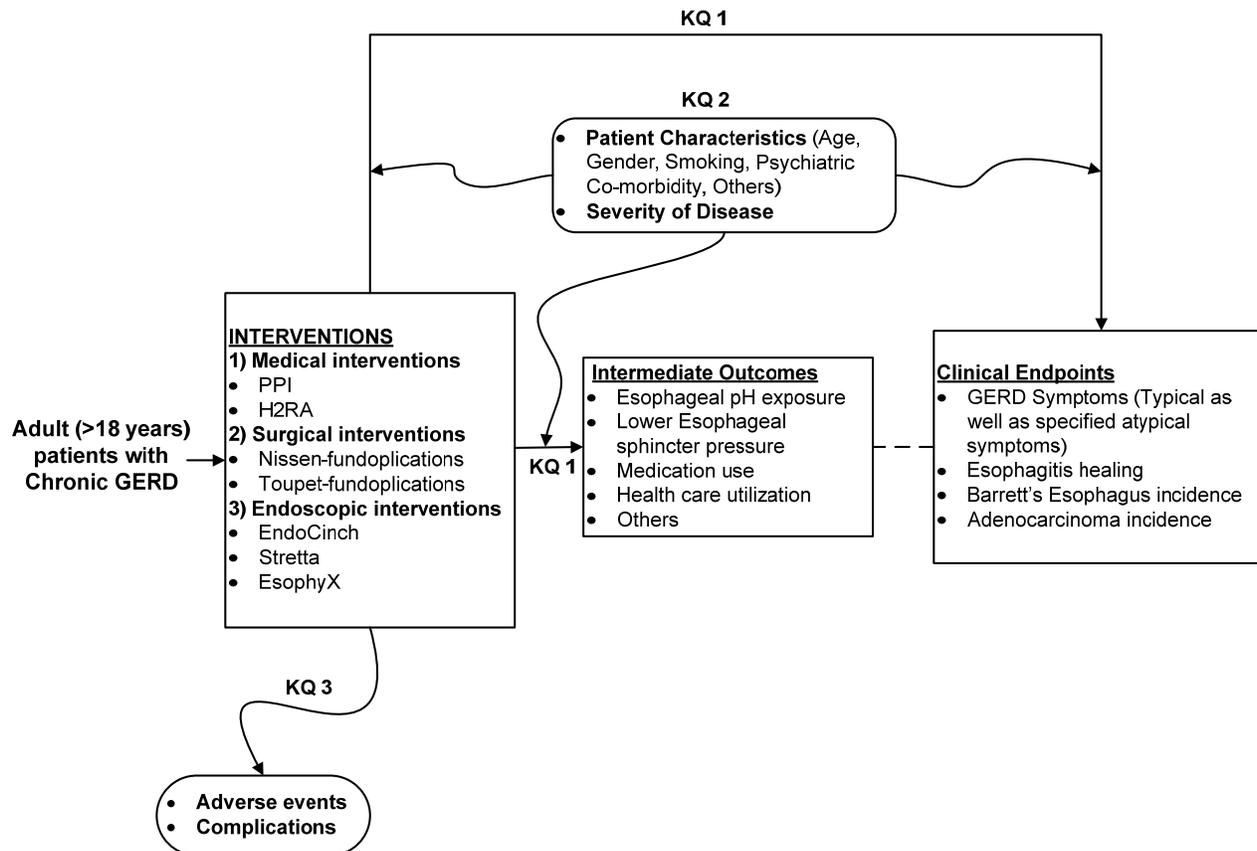


Figure 1. Analytic framework of the comparative effectiveness of management strategies for GERD

Key Question 1: What is the evidence of the comparative effectiveness of medical, surgical and other newer forms of treatments for improving objective and subjective outcomes in patients with chronic Gastroesophageal Reflux Disease (GERD)? Is there evidence that effectiveness varies by specific technique, procedure, or medication? Objective outcomes

addressed include esophagitis healing, ambulatory pH, other indicators of reflux, need for medication, 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.

Key Question 2: Is there evidence that effectiveness of medical, surgical and newer forms of 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, and other demographic and medical factors? What are the provider characteristics for procedures including provider volume and setting (e.g., academic versus community)?

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

Search Strategy

A comprehensive search of the literature was conducted to identify relevant studies published since the compilation of the 2005 CER concerning GERD.² In this update, the scope was expanded to include patients with extra-esophageal GERD (i.e., patients with chronic cough, laryngitis or hoarseness, or asthma believed to be related to GERD). For extra-esophageal GERD topics, results from previously conducted meta-analyses and systematic reviews were sought and included where appropriate and updated when necessary. Evidence tables of study characteristics and results were compiled, and the methodological quality of the studies was appraised.

In order to update the previous CER, MEDLINE was searched (2004- April Week 2 2010) for English language studies of adult humans and articles relevant to each key question identified. Reference lists of all review articles were also inspected. The search was also expanded to include previously conducted meta-analyses and systematic reviews of management strategies for patients with extra-esophageal GERD listed in Medline, the Cochrane Database of Systematic Reviews, the American College of Physicians Journal Club, the Database of Abstracts of Reviews of Effects, and the Centre for Reviews and Dissemination's Health Technology Assessments (up to October, 2009). In the electronic searches, terms for gastroesophageal reflux disease and relevant research designs were combined. For the search of meta-analyses and systematic reviews, the same terms for gastroesophageal reflux disease were combined with those for systematic reviews or meta-analyses and major extra-esophageal GERD symptoms such as chronic cough, reflux laryngitis, and asthma (see Appendix A for complete search strategy). TEP members were also invited to provide additional references. The Scientific Resource Center at Oregon Health & Science University conducted the grey literature search that provided information related to GERD from regulatory agencies, trial registries, conference proceedings, and miscellaneous sources. This was supplemented with an internal search of the FDA MAUDE database. We did not search systematically for unpublished data.

As the adverse events related to PPI use (GERD and non-GERD indications) are of particular interest, the decision was made to further explore this topic by searching for the latest

systematic review on this subject. A Medline targeted search (up to July, 2010) related specifically to fracture risk associated with the use of PPIs was also conducted upon recommendation of a domain expert. (see Appendix A for complete search strategy)

Study Selection

Titles and/or abstracts of citations identified from literature searches were assessed for inclusion using the criteria described below. Full-text articles of potentially relevant abstracts were retrieved and a second review for inclusion was conducted by applying the same criteria. Results published only in abstract form were generally not included in the review due to lack of adequate information with which to assess the validity of data.

Population and condition of interest

Patients with chronic GERD

GERD is considered a chronic and recurrent disease. The coincidence of one or more of several potential complications related to GERD including esophageal strictures, Barrett's esophagus and esophageal adenocarcinoma, is considered "complicated" GERD.

GERD has been variously defined throughout the literature. To be as inclusive as possible, studies that based the diagnosis of GERD on any commonly used criteria were considered. Such criteria included 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 (e.g., ICD-9 codes). The stringency of the diagnosis was recorded for each study.

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

Studies that focused exclusively on patients 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 were excluded.

Patients with extra-esophageal manifestations of GERD

In addition to heartburn and regurgitation, multiple studies have suggested that GERD may have extra-esophageal manifestations like chronic cough, laryngitis or hoarseness, asthma, or other non-gastrointestinal symptoms. Diagnosis of extra-esophageal GERD is difficult as patients may not have concomitant complaints of heartburn or regurgitation. Studies that focused exclusively on patients with extra-esophageal manifestations of GERD were excluded in the

* 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.

previous CER;² however, the topic is considered in the present update upon recommendation of the TEP.

In the interests of efficiency, for the review of extra-esophageal GERD, rather than relying on data from primary studies, we instead capitalized on synthesized data from existing systematic reviews. We included systematic reviews or meta-analyses that aggregated studies focusing exclusively on patients with extra-esophageal GERD symptoms (e.g., chronic cough, laryngitis or hoarseness, asthma). At minimum, systematic reviews had to incorporate the following three elements for inclusion: 1) a statement of the research question (aims or objectives), 2) a description of the literature search; and 3) a listing of the study eligibility criteria (methods used for evaluating published systematic reviews are listed in the “Study designs of interest” section). If an update of a qualifying systematic review was deemed necessary, we searched for primary studies published after the systematic review using the same inclusion and exclusion criteria.

Intervention of interest

For studies on medical treatment, we included RCTs using a proton pump inhibitor (PPI) or histamine-2 receptor antagonist (H2RA) for the treatment of acute symptoms or as maintenance therapy. Acute treatment was defined as short-term therapy—up to 8 or, in some trials, 12 weeks—until symptom resolution or esophagitis healing. Maintenance treatment was defined as long-term treatment—at least 6 months—for the prevention of symptoms or esophagitis relapse. Studies using any type of PPI or H2RA given at any dose were included. We excluded reports that combined a PPI or H2RA 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 the treatment of GERD. Studies on surgical treatment of achalasia, esophageal strictures or rings, esophageal adenocarcinoma, hiatal hernia repair (unless the indication was for reflux), and colon interposition were excluded.

In the previous CER, all endoscopic procedures, such as endoscopic suturing, radiofrequency energy delivery to the gastroesophageal junction, or implantation of inert polymers were included; however, reviewed studies were limited to those examining products approved in the United States (eg, Stretta™, EndoCinch™ Suturing System, NDO Plicator™, and Enteryx™).² In the present update, Enteryx and NDO Plicator were excluded as they are no longer being marketed in the United States. Another device, EsophyX™, commercialized since the 2005 CER, was also included in the present update.

Comparators of interest

For studies comparing one medical treatment with another, we included only those comparing a PPI with another PPI or an H2RA, irrespective of type or dose. Trials including other medical treatments (e.g., prokinetic agents, antacids, sucralfate), combinations of an alternate medical treatment with a PPI or an H2RA, or placebo as the only comparative group were excluded. Trials comparing different doses of H2RAs or different H2RA drugs were also excluded. These options are not considered to represent major current research interest.

For studies comparing a surgical or endoscopic procedure with a medical treatment, no restrictions were set as to the medication used in the control arm. Sham procedures were also considered as an acceptable 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 (Key Question 1), we analyzed the subjective and objective outcomes 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.
- Any systematic assessment of patient satisfaction.

Objective outcomes included:

- Esophageal pH exposure, either as change from baseline exposure or, when provided, as the proportion of patients achieving "normal" acid exposure (as techniques for performing and interpreting esophageal pH studies, we accepted each study's definition of "normal").
- 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 by endoscopy (to evaluate the medical maintenance treatment, we used esophagitis relapse rate, which was defined as the proportion of patients who developed esophagitis again after healing as assessed by endoscopy).
- Continued need for antisecretory medications, reported as the proportion of patients who continued to require medication after treatment (we sought reporting of the proportion of patients who no longer required any antisecretory medications and also recorded the proportion in whom the daily requirement for PPIs or H2RAs had been reduced).
- Development of Barrett's esophagus or esophageal carcinoma.

We focused on the results with the longest followup when an endpoint was measured more than once and the trial in question reported results from different time points. Cost-effectiveness and cost-benefit outcomes were excluded.

For Key Question 2, we focused on the following baseline patient characteristics that may have influenced treatment efficacy: age, sex, smoking status, obesity status, severity of GERD symptoms (as gauged 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 (as determined in each study), and presence of abnormal esophageal acidification (abnormal pH study) among patients off medication.

To evaluate adverse events and complications (Key Question 3), the rate for each adverse event of medical treatment and the rate for every reported complication of surgical and endoscopic procedures were extracted. 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

Primary studies

To address Key Question 1, we focused on evidence from randomized controlled trials. Where there was a paucity of data or RCTs were unavailable, non-randomized and uncontrolled studies were also included. For the comparisons of efficacy between medical and a surgical treatments, we retrieved all comparative studies, randomized and non-randomized. For the comparisons of surgical techniques, we retrieved all RCTs that recruited at least 50 participants and had a mean or median followup duration of at least 5 years, as well as 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 the 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 followup of at least 5 years. To assess the efficacy of endoscopic procedures, we collected all endoscopic publications, including comparative and cohort studies that recruited at least 10 participants and had a mean or median followup of 3 months or more. For comparisons of medical treatments, we included all RCTs in adult outpatients with symptoms of gastroesophageal reflux, peptic ulcer, or NSAID induced ulcer, with at least a 4-week treatment duration.

To address Key Question 2, we compiled data on patient characteristics of interest from the studies collected to address Key Question 1. In addition, we retrieved comparative and cohort studies that expressly investigated the relationship between selected patient characteristics and the efficacy of treatment modality. We also supplemented our review with data previously extracted for a manuscript on patient characteristics as modifiers of surgical outcomes in patients with GERD.⁶

To address Key Question 3, we examined all the studies already marked for inclusion in addressing Key Questions 1 and 2. We also collected all studies, including cohorts, comparative studies, and reviews, in which the focus was adverse events and complications after medical, surgical, or endoscopic interventions for GERD, with a minimum sample size of 100. For surgical procedures, we also retrieved papers that were designed to compare the complication rates at institutions with varying volumes of patients. In addition, data on adverse events related to endoscopic procedures (EndoCinch®, EsophyX®, and Stretta®) were collected from the Manufacturer and User Facility Device Experience (MAUDE) database of the U.S. Food and Drug Administration’s (FDA) Center for Devices and Radiological Health Web site.⁷ The search was performed on July 12, 2010 using the search terms “Endocinch”, “Stretta”, and “Esophyx” individually (N.B., search terms like company names and types of procedure like Bard, Curon, Davol, Endogastric, endoluminal, suture, radio frequency, etc. were also tried; the results were

sensitive but not very specific). Given that the data were reported voluntarily, no judgment was made on the causal link between devices and adverse events.

Systematic reviews of management for extra-esophageal manifestations of GERD

To warrant inclusion, systematic reviews were required, at minimum, to incorporate the following three elements: 1) a statement of the research question (aims or objectives), 2) a description of the literature search; 3) a listing of the study eligibility criteria. Only systematic reviews or meta-analyses that synthesized studies focusing exclusively on patients with extra-esophageal GERD symptoms (e.g., chronic cough, laryngitis, asthma) were included. Definitions and diagnoses of these symptoms and diseases varied across studies. All definitions and diagnoses of chronic cough, laryngitis, and asthma were accepted as reported. As the present review is concerned with the management of GERD in adults, selected systematic reviews were required to include primary studies in adults or provide separate analyses in adults.

If a qualifying systematic review was deemed to be out of date (e.g., search years earlier than 2005), we updated the systematic review by searching for primary studies published after the original review using the same inclusion and exclusion criteria. MEDLINE (2002- November Week 3 2009) and the Cochrane database of Controlled trials (Till 4th Qtr 2009) were searched for English language studies of adult humans to identify articles relevant to the treatment of asthma in patients with GERD and asthma (see Appendix A for complete search strategy).

Data Extraction

Data extracted included first author, year, country, setting, funding source, study design, and 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 noted included age, sex, and smoking and obesity status (as assessed by BMI). 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 related to the diagnosis of GERD and disease severity (if reported at study entry): presenting symptoms and quality of life for patients on medication; whether patients had undergone endoscopy; whether patients with a hiatal hernia, esophagitis, esophageal stricture, or Barrett's esophagus were included. For hiatal hernia, the size used to exclude patients from participation was also noted. We also recorded whether pH or esophageal motility tests were performed as well as their results as described in the study. For pH studies, if possible, it was noted whether patients were receiving or abstaining from PPIs during the study. Finally, we recorded whether patients had tried any medical treatment (and what type) or lifestyle modifications prior to the study, and their response to these therapies. For all population-related factors that were extracted, baseline values were analyzed for significant differences among comparison groups.

Data on treatment modality, comparators, and 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, final value, and within-treatment or between-treatment change with variability estimate) as provided by the study. Duration of in-hospital stay after a surgical or an endoscopic procedure was also recorded. The duration of followup, as well as the number and reasons for dropouts during the followup period were also noted.

For systematic reviews, items extracted were: design, population, intervention (exposure), comparator, and results.

Quality Assessment

The methodological quality of primary studies was assessed based on predefined criteria. For the assessment of RCTs, the criteria were based on the CONSORT statement for reporting RCTs.^{8,9} We primarily 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. We also considered the presence (or absence) of washout periods in crossover studies, as well as any significant differential loss to follow-up between the comparative groups. 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.

The validity and 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. Items assessed included selection of cases or cohorts and controls, comparability, and exposure or outcome.

Based on the aforementioned criteria, each study was assigned one of three grades (A, B, or C). This grading scheme was applied to all included RCTs, cohorts, and case-control studies; however, it should be noted that our grading system did not attempt to assess the comparative validity of studies across different design strata and studies of different design receiving similar grades should not be considered of equivalent rigor (e.g., an RCT rated “B” is not necessarily of the same methodological strength as a “B” case-control study). Thus, both design and quality should be weighed when interpreting the methodological rigor of a study.

A

Category A studies have the least bias and their 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

Category B studies are susceptible to some bias and do not meet all the criteria of category A. While deficient in some respects, they are not sufficiently such so as to invalidate results.

C

Category C studies have significant bias that may invalidate results. These studies have serious errors in design, analysis, or reporting, and may be missing substantial portions of critical information.

Critical appraisal of systematic reviews

The systematic reviews utilized in this report were also critically appraised; however, a summary quality grade was not assigned due to possible ambiguities in interpretation. While it may be straightforward to assign an A to a rigorously carried out systematic review of high quality primary studies, a rigorously conducted systematic review finding only poor quality primary studies to summarize has uncertain value. Similarly, a poorly conducted systematic review of high quality studies may also result in misleading conclusions.

Rather, to help readers appreciate the methodological quality of a systematic review, we applied the AMSTAR checklist.¹⁰ Instead of assigning a composite grade, the AMSTAR checklist evaluates individual elements explicitly for the reader. In addition to using AMSTAR, we made comments on special considerations, issues, or limitations concerning design, conduct, and analyses of the systematic review.

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.¹¹

Data Synthesis

Evidence and summary tables

Evidence tables are provided as a condensed reference of study descriptions arranged by Key Question. The tables (see Appendix C) contain detailed information concerning design, sample size, intervention and comparison group treatments, patient characteristics, followup, major outcomes, and methodological quality. In addition, for systematic reviews and meta-analyses, we reported the databases searched and for which time period, the number and the type of primary studies included, and the category of comparison addressed (medical versus medical, medical versus surgery, or endoscopic versus sham procedure).

Summary tables succinctly report measures of the main outcomes evaluated. They include information regarding study design, intervention and comparison group, therapeutic modality, study or followup duration, whether patients with severe esophagitis were also recruited, sample size (subjects enrolled and analyzed in each arm), results of major outcomes, and methodological quality. Medication usage data were reported 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. These tables were developed by condensing information from the previously compiled evidence tables and were designed to facilitate comparisons and synthesis across studies.

A comprehensive synthesis table was also included in the results section to succinctly summarize all findings. This table includes information on data sources, populations, study limitations, major outcomes (symptoms, quality of life, esophagitis healing, esophageal acid exposure, and medication use), treatment-related factors with or without an association to outcomes, the type and frequency of major adverse events, and complications for all three treatment modalities.

Adverse events reporting

We reported the main adverse events associated with medical, surgical, and endoscopic treatments in both evidence and summary table. For medical treatment, studies were grouped according to the type of comparison (PPI versus H2RA or placebo, and PPI maintenance dose versus healing dose). For the adverse events in each comparison, the total number of patients included, the number of studies, and the total percent adverse event rate for each of the comparative arms were reported when the data were available.

For surgical treatment, we considered studies examining Nissen and Nissen-Rossetti fundoplication within the same category. In the evidence tables, studies reporting complications according to the type of procedure and the complication reported were grouped together. For each study, we reported the absolute number and percentage of subjects with the complication. In the summary tables, we reported the number of studies and event rate for each complication and procedure. The mean event rate was calculated for two or more studies. Separate evidence and summary tables were created for studies that reported complications occurring within 30 days from the procedure, after 30 days, and for studies that were unclear on the time period between the procedure and a complication. Case reports were not included in the evidence or summary tables.

Results from the Manufacturer and User Facility Device Experience (MAUDE) database were summarized in narrative form.

Overall comparative synthesis table

To aid discussion, comparative data were summarized across treatment modalities (medical, surgical, and endoscopic) in one table and grouped according to Key Question (see the section on conclusions/discussion/future research). Important comparative findings for each Key Question were summarized whenever data were available.

Grading a body of evidence for each key question

An overall quality rating was assigned to the body of evidence related to each Key Question based on the number and quality of the relevant individual studies, duration of followup, and consistency of findings. Ratings were defined as follows:

High – There is a high level of assurance that the findings of the literature are valid with respect to the relevant Key Question. No important scientific disagreement exists across studies. At least two A-quality studies are required for this rating.

Moderate – There is a moderate level of assurance that the findings of the literature are valid with respect to the relevant Key Question. Little disagreement exists across studies. Moderately rated bodies of evidence contain fewer than two A quality studies or A quality studies that lack long-term outcomes of relevant populations.

Low – There is a low level of assurance that the findings of the literature are valid with respect to the relevant Key Question. Underlying studies may report conflicting results. Low rated bodies of evidence contain either B or C quality studies or examinations of populations that may have little direct relevance to the key question.

Insufficient – Evidence is either unavailable or does not permit estimation of an effect due to a lack of data.

The ratings provide a concise summation of the strength of evidence supporting the major questions we addressed. However, a number of complex issues involved in appraising a body of evidence are necessarily left unexplored. The studies incorporated in the formulation of the composite rating differed in their design, reporting, and quality; the strengths and weaknesses of these reports ought to be considered individually and in-depth.

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 based on their comments where appropriate (see Appendix D^{**}). However, the findings and conclusions are those of the authors, who are solely responsible for the contents of this report.

^{**} Appendix D (Peer Reviewers) is available electronically at www.ahrq.gov/clinic/epcindex.htm.

Results

Our literature search yielded 3320 citations of primary studies on GERD published from 2004 to April 2010, 107 citations of systematic reviews on extra-esophageal GERD, and 250 citations of primary studies on PPI use (GERD and non-GERD indications) and fracture risk. We identified 538 of these (493 primary studies, 23 systematic reviews, 14 primary studies on PPI use and fracture risk, and 8 RCTs on GERD therapy in patients with asthma) as potentially relevant and retrieved them for further evaluation. A total of 136 publications on GERD, five systematic reviews on extra-esophageal GERD, and nine primary studies on PPI use and fracture risk were finally included in the present review. In addition, we performed a Medline search (from 2002 to 2009) for all RCTs of GERD therapy in patients with asthma to update a previously published systematic review that examined the effect of PPI treatment on asthma in RCTs.¹² This search yielded 277 abstracts, and eight RCTs qualified for inclusion. Figure 2 summarizes the study selection flow.

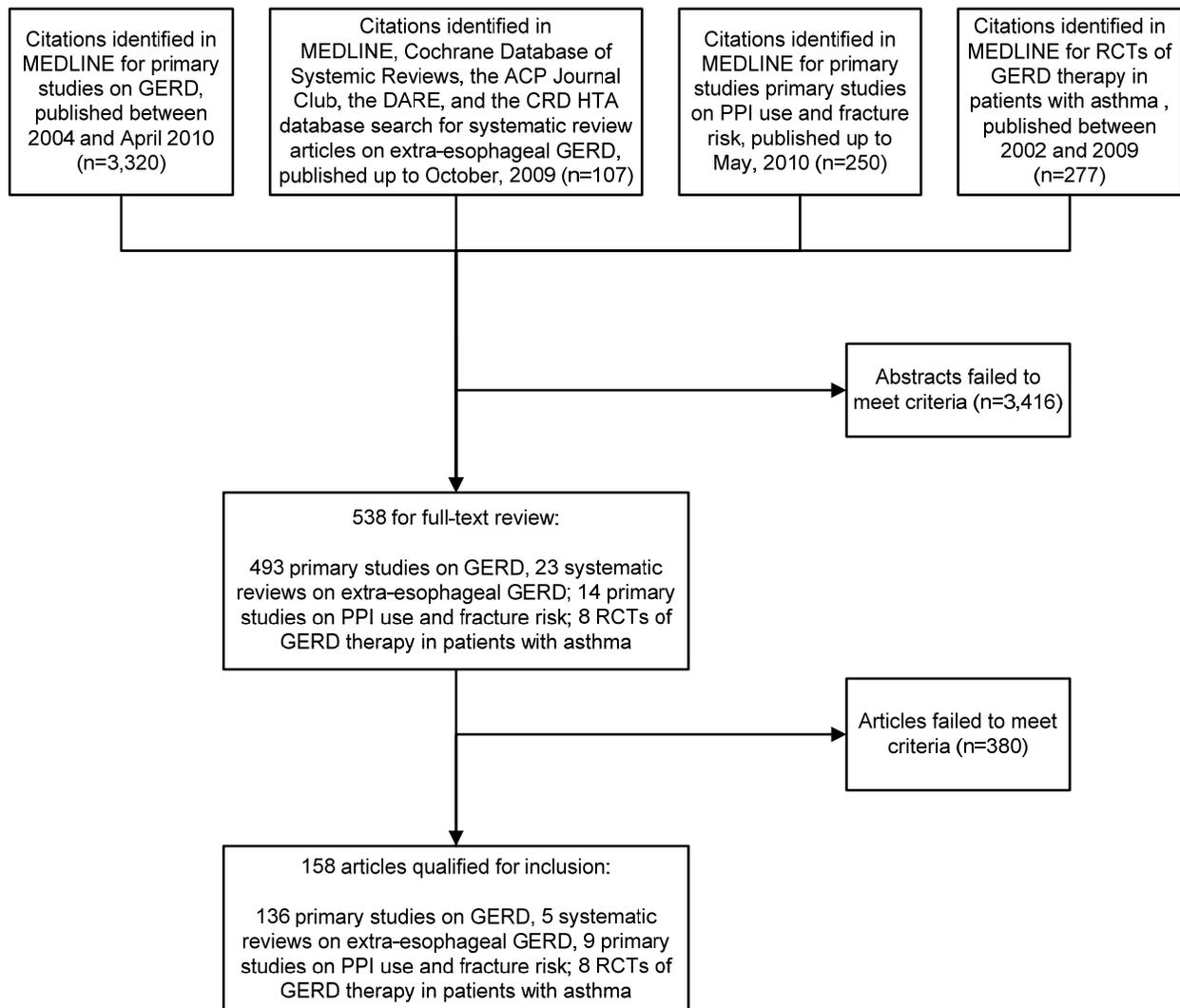


Figure 2. Study selection flow

Key Question 1: What is the evidence of the comparative effectiveness of medical, surgical and other newer forms of treatments for improving objective and subjective outcomes in patients with chronic Gastroesophageal Reflux Disease (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.

Key Question 1A. Medical versus surgical treatments

Synopsis

The 2005 AHRQ Comparative Effectiveness Review (CER), based on findings from 3 RCTs, indicated medical therapy with PPIs and antireflux surgery to be similarly effective in improving GERD-related symptoms and decreasing esophageal acid exposure, with 10 to 65 percent of surgical patients requiring ongoing medical therapy post-procedure. In the present update, the addition of long-term followup data in two of the previously reviewed studies and data from two new RCTs indicate that patients who underwent antireflux surgery experienced a greater improvement in heartburn and regurgitation at followup compared with patients who received medical treatment alone. The patients who had antireflux surgery had increased incidence of dysphagia and postprandial bloating. It was also found that fundoplication decreased, but did not eliminate, the use of antireflux medications at followup. These findings should be interpreted with caution as the reviewed studies with long followup (7 to 12 years) had high proportions of patient dropouts (33 to 58 percent).

Detailed analysis

Four RCTs and three nonrandomized trials (Grant 2008¹³ utilized both randomized and non-randomized study designs) produced 8 publications comparing medical with surgical treatments for GERD.^{1,13-19} Two of these publications, Lundell's 2007¹⁵ and 2009¹⁶ papers, present 7- and 12-year followup data for the SOPRAN study originally reported in the 2005 CER (note: for studies presenting data from multiple time intervals, we present results from the most recent followup, e.g., 12-year followup from the SOPRAN study). Lundell's¹ and Atwood's¹⁴ 2008 analyses report 3-year followup data on outcomes from the LOTUS trial. Mehta 2006¹⁷ reports 6.9 year (median) followup data from the Mahon study,²⁰ while Grant 2008¹³ and Anvari 2006 report 1-year followup data.¹⁹ The four RCTs—the SOPRAN,^{15,16} LOTUS,^{1,14} Grant 2008,¹³ and Anvari 2006¹⁹ studies—enrolled a total of 1325 patients, of which, 944 reported information at the final followup period. Mehta 2006¹⁷ included 67% (145/217) of the patients from the Mahon study²⁰ at long-term followup. Olberg 2005, the only pure non-randomized

study, enrolled 746 patients, 358 of whom reported followup data at a mean of 75 months.¹⁸ All RCTs identified in the present review had methodological limitations including issues concerning possible selection bias,¹³ small sample size,¹⁹ and a large proportion of patient dropouts.^{15,16}

As in the 2005 CER, the studies in this review included patient populations with varying clinical characteristics. SOPRAN enrolled only patients with baseline esophagitis, without restriction on the degree of severity, while patients included in the LOTUS trial had no higher than grade B (Los Angeles classification) esophagitis at randomization (although some patients with Barrett's esophagus were included).

Treatments across studies also varied. SOPRAN patients underwent open fundoplication; LOTUS patients laparoscopic fundoplication; and the Olberg 2005 study included patients who had open or laparoscopic fundoplication procedures.¹⁸ Patients in the Mehta 2006 study were given the option of laparoscopic surgery if unsatisfied with initial PPI treatment.¹⁷ Patients in the medical treatment groups received esomeprazole in the LOTUS trial, or omeprazole in the SOPRAN study, while patients in the Grant 2008 study¹³ and Anvari 2006 study received individualized medical management based on symptom response.¹⁹ The Olberg 2005 study used nonoperated matched controls with some receiving PPI and/or H2RA treatment. Overall, four studies assessed laparoscopic fundoplication versus PPI,^{1,13,14,17,19} one study examined open fundoplication versus PPI^{15,16}, and one study assessed a sample of patients receiving surgery (laparoscopic and open) versus matched control.¹⁸ The strength of evidence for this body of data was rated moderate due to large dropout rates for studies with long followup as well as varied individual study quality, followup time periods, interventions used and outcomes assessed.

Findings from both the RCTs and non-randomized comparisons have been organized by the following outcomes of interest: 1) Change in symptoms, quality of life (QOL) and patient satisfaction; 2) Change in medication usage status; 3) Change in pH study results; and 4) Remission rates. Details of these outcomes are presented in the summary tables that follow.

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

The six included studies (Table 1) utilized a variety of methods to capture outcomes, including patient report of heartburn, regurgitation and satisfaction, and structured scales such as the Gastrointestinal Symptom Rating Scale (GSRS), Quality of Life in Reflux and Dyspepsia, SF-36, EQ-5D, REFLUX Quality of Life (QOL), gastroesophageal reflux score (GERSS), DeMeester Symptom Score, and the Psychological General Well-Being Index (PGWB). Lundell 2008 (LOTUS trial) reported decreases in both heartburn and regurgitation in the surgery group (approximately 30 percent with these symptoms at randomization compared to less than 10 percent at followup) while the medical group reported that the proportion of patients with complaints of heartburn largely stayed the same (approximately 30 percent at both randomization and followup) and the proportion of patients with regurgitation decreased from approximately 25 percent at randomization to 15 percent at followup, but no significance testing was reported (N.B., these proportions were estimated from Figure 4 in the paper).¹ Additionally, more medically treated patients reported mild heartburn, compared to those receiving surgery, at 3-year followup ($P<0.001$).¹ Patients in surgical groups demonstrated significantly greater improvement in mean QOLRAD and GSRS reflux domain scores ($P<0.001$ for both scores); however, they also experienced some mild dysphagia post-surgery—very few (<10%) medically treated patients had dysphagia ($P<0.001$).¹ In contrast, Attwood 2008, also reporting results from the LOTUS trial but with analysis stratified into patients with and without Barrett's

esophagus, did not find a significant difference in GSRS or QOLRAD between surgery or medical treatments in those subgroups.¹⁴

Grant 2008 reported improvements in SF-36, EQ-5D and REFLUX QOL mean scores for the surgical group, with the latter score attaining significance ($P < 0.001$).¹³ No significant differences were detected between groups for “difficulty swallowing” at 12-month followup.¹³ Anvari 2006 similarly reported greater improvements in GERSS ($P = 0.002$) and the SF-36 General Health subscore ($P = 0.005$) in the surgical group compared with the medical group at 1 year.¹⁹ Twelve year followup data from the SOPRAN study demonstrated more heartburn and regurgitation in the medical treatment group, with mean GSRS and PGWB scores remaining similar (in normal range) across followup.^{15,16} These data also indicated that dysphagia was significantly more common after surgery compared with medical treatments (estimated HR 1.7, 95%CI 1.5, 1.9). Mehta 2006,¹⁷ in a non-randomized long-term followup (patients in the medical treatment arm were offered surgery after the original trial ended at 12 months) of the Mahon RCT,²⁰ reported similar significant ($P < 0.01$) DeMeester Symptom Score improvements in all treatment groups; patients opting for surgery after medical treatment demonstrated continued significant ($P < 0.01$) improvement. Additionally, a greater proportion of surgical patients reported being “very satisfied” with symptom control compared to medically treated patients, with a significant ($P < 0.01$) association between treatment group and symptom score. In the Grant 2008 study, the non-randomized patient-preference cohort demonstrated similar, though less marked, results to the randomized cohort, with improvements in QOL scores favoring the surgical groups.¹³ The Olberg 2005 publication also reported symptom scores significantly ($P < 0.001$) favoring surgery with fewer reflux symptoms noted on the GSRS at followup.¹⁸ No significant differences between treatment groups were evident using the PGWB scale.¹⁸

Change in medication usage status (Table 2)

Four studies (Table 2) reported a change in medication usage outcomes.^{13,15,16,18} Grant 2008 reports similar trends, for both randomized and non-randomized cohorts, with the RCT demonstrating a lower percentage of patients on antireflux medication at 12-month followup in the surgery groups versus patients being treated medically (38% vs. 90%, no P value).¹³ Anvari 2006 reported that none of the surgically treated patients were taking PPIs or other anti-secretory medications at 1-year followup.¹⁹ Long-term follow up in the SOPRAN study demonstrated slow but constant increase in treatment with omeprazole or other PPIs for patients in the surgery group (29% were treated for 1 year or longer).^{15,16} Olberg reported a significant decrease in antireflux medication use at followup favoring the surgery group (PPI use the previous week: 9.4% vs. 49.4%, $P < 0.001$).¹⁸

Change in pH study results (Table 3)

Two studies (Table 3) reported a difference in pH study results.^{14,19} Attwood 2008 noted a significant improvement ($P = 0.002$) in total acid exposure for non-Barrett’s esophagus LOTUS trial patients undergoing laparoscopic fundoplication versus patients treated with esomeprazole.¹⁴ Anvari 2006 reported that surgically treated patients (off PPIs) had a significantly lower mean time of pH < 4 compared with medically treated patients (on PPIs) at 1-year followup (mean difference 3.63%, $P = 0.0042$).¹⁹

Remission rates (Table 4)

Both the LOTUS trial^{1,14} and SOPRAN study^{15,16} (Table 4) reported on remission rates of patients undergoing surgery versus those treated medically. In the LOTUS trial, no significant

differences in remission were observed between treatment groups at 3-year followup.^{1,14} It should be noted, however, that the criteria for remission differed between the surgical and medical groups. The SOPRAN study, in contrast, defined remission consistently between surgical and medical groups.^{15,16} In this study, the open fundoplication surgery group demonstrated significantly greater sustained remission of GERD symptoms relative to the medication group at 12-year followup (53% vs. 40%, P=0.022).

Key Question 1B. Surgical versus endoscopic treatments

Synopsis

The 2005 CER did not find any studies that compared surgical treatment and endoscopic treatment. The present report identified one small study of laparoscopic total fundoplication versus EndoCinch™. This study found that laparoscopic total fundoplication was more effective than EndoCinch™ in improving GERD symptoms and 24-hour pH study.

Detailed analysis (Table 5)

One C-rated non-randomized comparative study (Table 5) followed 41 patients who had either EndoCinch™ or laparoscopic total fundoplication (LNF).²¹ Although both EndoCinch™ and LNF groups had significant improvement in GERD symptoms and 24-hour pH study measures over the follow-up period, patients in the LNF had significantly better improvement in heartburn score (P = 0.04), DeMeester score (P < 0.01), and the percentage of time of pH < 4 (P < 0.01). No significant difference in regurgitation score and QOLRAD was observed. At 1 year, the proportions of PPI users in the EndoCinch™ and LNF groups were 37 percent and 13 percent, respectively (P value not reported).

Key Question 1C. Medical versus endoscopic treatments

The 2005 CER did not find any studies that compared medical treatment and endoscopic treatment; neither did this update.

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

Author Year Study Intervention	N enrolled N with f/u data	Follow-up duration	Quality	Results
RCTs				
Lundell 2008 ¹ [18469091] LOTUS Trial LAS vs. EsOME	554 412	3 y	B	<p>Heartburn LAS: Decrease across 3 yr study period EsOME: Similar levels across 3 yr study period</p> <p>More pts reported mild heartburn in EsOME group at f/u (p<0.001; inversely related to dose)</p> <p>Regurg LAS: Decrease across 3 yr study period EsOME: Similar levels across 3 yr study period</p> <p>GSRS reflux: Greater improvement in mean scores for LAS (p<0.001)</p> <p>QOLRAD: Greater improvement in mean scores for LAS (p<0.001 for all dimensions)</p>
Attwood 2008 ¹⁴ [18709511] LOTUS Trial <i>Non-BE Cohort</i> LAS vs. EsOME	554 412	3 y	B	<p>GSRS: mean scores similar for all dimensions for both groups across 3 yr study period (normal values, differences NS)</p> <p>QOLRAD: mean scores similar for all dimensions for both groups across 3 yr study period (normal values, differences NS)</p>
Grant 2008 ¹³ [19074946] <i>Randomized Cohort</i> LAS vs. Medical treatment ^a	357 299	12 mo	B	<p>SF-36: Improvements in mean f/u scores for LAS group—largest difference observed in general health and bodily pain dimensions</p> <p>EQ-5D: Improvements in mean f/u scores for LAS group—some evidence of attenuation at 12 mo f/u</p> <p>REFLUX QoL: Significant improvements in mean f/u scores for LAS group (p<0.001)</p> <p>GERSS: better in LAS (P=0.002)</p>
Anvari 2006 ¹⁹ [17227922] RCT LAS vs. Medical	104 96	12 mo	B	<p>SF-36: similar in PCS and MCS SF-36 Gen Health subscore: better in LAS (P=0.005)</p> <p>EQ-5D: similar in both</p>
Lundell 2007/2009 ^{15,16} [17256807/ 19490952] SOPRAN study <i>12-year f/u Cohort</i> OAS vs. OME	310 218, 7-yr f/u 137, 12-yr f/u	12 y	C Large drop-out	<p>Heartburn: More common in OME (HR=1.73, 95%CI 1.6-1.9)</p> <p>Regurg: More common in OME (HR=2.38, 95% CI 2.1-2.7)</p> <p>GSRS: mean total scores similar—troubled to a minor extent by GI sx—w/ normal values across f/u</p> <p>PGWB: mean total scores similar w/ normal values across f/u</p>
Non-randomized studies				

Author Year Study Intervention	N enrolled N with f/u data	Follow- up duration	Quality	Results
Mehta 2006 ¹⁷ [17114017] LAS vs. PPI vs. PPI / LAS ^b	217 145	Median: 6.9 y (range, 4.3-8.3 y)	C Large drop- out	DeMeester Symptom Score: Significant improvements in mean 12 mo f/u scores for all groups (p<0.01) Pts opting for LAS after 12 mo PPI demonstrated further significant score improvement at long-term f/u (p<0.01) Satisfaction Scores** LAS, PPI/LAS: >80% very satisfied w/ symptom control; 88% would undergo surgery if they had it to do over again PPI: 59% very satisfied, 41% moderately satisfied Significant association b/w tx group and scores (x ² = 15.7; p<0.01)
Grant 2008 ¹³ [19074946] <i>Non-randomized Cohort</i> LAS vs. Medical treatment ^a	453 299	12 mo	B	REFLUX QoL: Improvements in mean f/u scores favored LAS group vs. Med Tx group EQ-5D: Improvements in mean f/u scores favored LAS group vs. Med Tx group
Olberg 2005 ¹⁸ [15932167] OAS/LAS vs. Matched non- operated pt with GERD Matched-pair f/u study	746 358	Mean: 75.25 mo	B	GSRS reflux domain: OAS/LAS Mean scores demonstrate significantly fewer reflux symptoms at f/u (p<0.001) PGWB: No consistent significant differences b/w groups at f/u

EsOME: Esomeprazole; OME: Omeprazole; PPI: Proton pump inhibitor; LAS: Laparoscopic antireflux surgery; OAS: Open Anti-Reflux Surgery; QoL: Quality of Life; GSRS: Gastrointestinal Symptom Rating Scale; QOLRAD: Quality of Life in Reflux & Dyspepsia; gastroesophageal reflux score (GERSS); PGWB: Psychological General Well-Being Index

^a Patients allocated to medical treatment had their treatment reviewed and adjusted as needed by local gastroenterologist to be "best medical management" based on the Genval workshop report

^b Long-term (median 6.9 yr f/u) satisfaction rating: 1 (not at all) – 3 (very much)

Table 2. Medical vs. surgical treatments for GERD: Change in medication usage status

Author Year Study Intervention	N enrolled N with f/u data	Follow-up duration	Quality	Results
RCTs				
Grant 2008 ¹³ [19074946] <i>Randomized Cohort</i> LAS vs. Medical treatment ^a	357 299	12 mo	B	At 12 mo f/u, 38% (59/154) of randomized LAS pts were on antireflux medication compared to 90% (147/164) of randomized med tx pts For those randomized to LAS pts who had surgery, use of antireflux medication dropped to 14% (14/104) at 12 mo f/u
Anvari 2006 ¹⁹ [17227922] RCT LAS vs. Medical	104 96	12 mo	B	0% of LAS on PPIs 100% of medical treatment on PPIs
Lundell 2007/2009 ^{15,16} [17256807/ 19490952] SOPRAN study 12-year f/u Cohort OAS vs. OME	310 218, 7-yr f/u 137, 12-yr f/u	12 y	C Large drop-out	Across f/u, 14% (12/155) OME pts referred for fundoplication; 36% (52/144) OAS pts treated w/ OME or other PPI for > 8 weeks w/ slow but steady increase over time
Non-randomized studies				
Grant 2008 ¹³ [19074946] <i>Non-randomized Cohort</i> LAS vs. Medical treatment ^a	453 299	12 mo	B	At 12 mo f/u, 20% (46/230) of preference LAS pts were on antireflux medication compared to 93% (165/178) of preference med tx pts
Olberg 2005 ¹⁸ [15932167] OAS/LAS vs. Matched non-operated pt with GERD Matched-pair f/u study	746 358	Mean: 75.25 mo	B	Significant difference in antireflux drug use at f/u w/ less use by OAS/LAS group (p<0.001)

EsOME: Esomeprazole; OME: Omeprazole; PPI: Proton pump inhibitor; LAS: Laparoscopic antireflux surgery; OAS: Open Anti-Reflux Surgery

^a Patients allocated to medical treatment had their treatment reviewed and adjusted as needed by local gastroenterologist to be “best medical management” based on the GenvaL workshop report

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

Author Year Study Intervention	N enrolled N with f/u data	Follow- up duration	Quality	Results
RCTs				
Attwood 2008 ¹⁴ [18709511] LOTUS Trial Non-BE Cohort LAS vs. EsOME	554 412	3 y	B	Δ total acid exposure time from baseline favoring LAS: LAS- 13.2%, to a median of 0.4% EsOME-7.4%, to a median of 4.9% (p=0.002)
Anvari 2006 ¹⁹ [17227922] RCT LAS vs. Medical	104 96	12 mo	B	%time pH<4: diff between groups: 3.63 (in favor of LAS), P=0.004

EsOME: Esomeprazole; LAS: Laparoscopic antireflux surgery

Table 4. Medical vs. surgical treatments for GERD: Remission rates

Author Year Study Intervention	N enrolled N with f/u data	Follow-up duration	Quality	Results
RCTs				
Lundell 2008 ¹ [18469091] LOTUS Trial LAS vs. EsOME	554 412	3 y	B	Remission^a rate: No significant difference b/w groups at 3 yr follow up
Lundell, 2007/2009 ^{15,16} [17256807/ 19490952] SOPRAN study 12-year f/u Cohort OAS vs. OME	310 218, 7-yr f/u 137, 12-yr f/u	12 y	C Large drop-out	Remission^b rate: Greater sustained remission in OAS group (p = 0.002; For dose adjustment of OME: p = .022)

EsOME: Esomeprazole; OME: Omeprazole; LAS: Laparoscopic antireflux surgery; OAS: Open Anti-Reflux Surgery

^a *EsOME arm*: relapse (failed remission) defined as need for escalation in treatment, despite dosage adjustment, for control of reflux; *LAS arm*: relapse (failed remission) defined as need for escalation in treatment for control of reflux; post-op complaints requiring medical action, peri-op death, post-op death within 30-days post surgery, dysphagia requiring further treatment, or any other requirement to reoperate for sx control.

^b Relapse (failed remission) defined as presence of at least one of the following criteria: i) moderate or severe heartburn or acid regurgitation during the previous 7 days before a hospital visit; ii) oesophagitis of at least grade 2; iii) moderate or severe dysphagia or symptoms of odynophagia in combination with mild heartburn or acid regurgitation; iv) requirement for OME treatment for more than 8 weeks after antireflux surgery to control reflux symptoms, or need for reoperation; v) after randomization to OME, being considered by the physician to require antireflux surgery to control symptoms; vi) patient opting for antireflux surgery during the course of the study for any reason, despite randomization to OME. Outcome was also analyzed after a dose adjustment to either 40 or 60 mg OME in patients who had a relapse of symptoms with 20 mg daily.

Table 5. Comparative studies evaluating surgical versus endoscopic treatments for GERD

Author Year	Study design	Intervention	Enroll/ Final	Objective Outcomes			Subjective Outcomes		Quality Comments
	Follow-up Duration			Off PPI	Off All Meds	Diagnostic tests	Symptom improved	Quality of life	
Mahmood 2006 ²¹ [16542276] ^a	nRCT 1 y	EndoCinch	27/27	63%	nd	LES pressure 9.7 ± 0.9 % time pH<4 8.5 ± 1.1% Both groups had significant improvement in DeMeester score, but was sig better in LNF group (p<0.01)	Both groups had significant improvement in heartburn symptom score, but was sig better in LNF group (p=0.04) Regurg frequency significantly improved in both groups and there was no difference between group (p=0.21)	QOLRAD significantly improved in both groups and there was no difference between group (p=0.11)	C Small sample size
		Laparoscopic total fundoplication (LNF)	24/24	87%	nd	LES pressure 16.0 ± 1.3 % time pH<4 0.9 ± 0.3%			

LES: lower esophageal sphincter, QOLRAD: GERD-specific quality-of-life questionnaire
 Quality of Life in Reflux and Dyspepsia (QOLRAD) questionnaire: Disease-specific questionnaire covering 5 dimensions: emotional distress, sleep disturbance, problems with food/drink, limitations in physical and social functioning and lack of vitality. Responses are rated on a 7-grade Likert scale (lower score indicating a more severe impact on daily functioning) Scores of the 5 dimensions were calculated by taking the mean of single items: emotion (five items), sleep (five items), food (six items), physical (five items) and vitality (three items).

^a mean± SEM

Key Question 1D. Medical treatment

Synopsis

In the 2005 CER,² comparisons of PPIs to H2RAs found PPIs to be superior to H2RAs in resolution of GERD symptoms at 4 weeks and healing of esophagitis at 8 weeks. There were no significant differences between omeprazole, lansoprazole, pantoprazole, and rabeprazole for relief of symptoms at 8 weeks and no significant difference between esomeprazole 40 mg with lansoprazole 30 mg and pantoprazole 40 mg for symptoms relief at 4 weeks. Similarly, no difference was observed in the comparison of esomeprazole 20 mg with omeprazole 20 mg in relief of symptoms at 4 weeks. However, esomeprazole 40 mg was significantly favored for symptom relief at 4 weeks compared to omeprazole 20 mg. The previous report relied on three unbiased and valid meta-analyses of randomized controlled trials comparing different medications.

In the present, updated review, results from 38 additional primary studies—all relevant RCTs reported since the publication of the 2005 CER—were included. The data from these studies does not alter the conclusions drawn about the comparison between different medical treatment in the previous report. In addition to the PPIs mentioned in the previous report, the present report also includes studies that examined dexrabeprazole and dexlansoprazole. A majority (25/38 trials, 66 percent) of the studies identified in this update were rated B.

Key points for comparisons of medical treatment

We focused on four main comparisons:

- 1) Comparisons between PPIs and H2RAs
- 2) Comparisons between different PPIs
- 3) Comparisons between different dosages and dosing regimens of commonly used PPIs
- 4) Comparisons between once daily and on-demand dosing regimens of commonly used PPIs
- 5) Comparisons between PPIs and over-the-counter dosages of PPIs (omeprazole 20 mg, lansoprazole 15 mg)

Key findings within the four comparison groups are summarized as follows:

- 1) Comparisons between PPIs and H2RAs
 - PPIs (esomeprazole 20 mg taken once daily or on-demand, lansoprazole 15 mg taken once daily and omeprazole 20 mg taken once daily) were superior to H2RAs (ranitidine 150 mg and famotidine 20 mg, both taken twice daily) for resolution of GERD symptoms at 6 months.
 - Lansoprazole 15 mg, taken once daily, was more effective than ranitidine 150 mg taken twice daily for healing of esophagitis at 1 year.
 - Esomeprazole 20 mg, taken once daily or on-demand, was more effective than ranitidine 150 mg taken twice daily for prevention of symptom relapse at 6 months.
 - Maintenance treatment (≥ 6 months) with PPIs (esomeprazole 20 mg taken once daily or on-demand, lansoprazole 15 mg taken once daily) appears to be more efficacious

than maintenance treatment with H2RA (ranitidine 150 mg taken twice daily) in symptom remission.

- Patients on esomeprazole 20 mg taken once daily were more likely to be satisfied with their study medication than patients on ranitidine 150 mg taken twice daily.
- In maintenance treatment, patients taking lansoprazole 15 mg are likely to stay longer on their treatment as compared to ranitidine 150 mg taken twice daily and thus tend to have a longer median time to relapse of symptoms.
- Studies with larger sample sizes suggested PPIs to be more efficacious than H2RAs with respect to GERD symptoms, while smaller studies tend to show them to have equivalent effects.

2) Comparisons between different PPIs

- No consistent comparative difference in symptom relief was observed between esomeprazole (20 to 40 mg), lansoprazole (15 to 30 mg), pantoprazole (20 to 40 mg), dexlansoprazole (10 mg) or rabeprazole (10 to 20 mg) over a period ranging from 4 weeks to 6 months.
- There is some evidence that rabeprazole 10 mg may provide better symptom relief than esomeprazole 40 mg at 4 weeks, and also that pantoprazole 20 mg provides better control of heartburn than esomeprazole 20 mg over 24 weeks.

3) Comparisons between different dosages and dosing regimens of commonly used PPIs

- There was no significant difference in symptom resolution rates at 4 weeks between esomeprazole 20 mg taken once a day and esomeprazole 40 mg taken once a day.
- There was no significant difference in sleep quality at 4 weeks, in patients with GERD and sleep disturbances, between esomeprazole 20 mg and 40 mg, both taken once a day.
- In two studies of 4 weeks and 6 months duration, dexlansoprazole 30 mg showed better heartburn control than dexlansoprazole 60 mg doses, although this effect was not statistically significant.
- A significantly higher rate of healing of esophagitis at 4 weeks was observed with esomeprazole 40 mg taken once a day as compared to esomeprazole 20 mg taken once a day. This was supported by finding a significantly higher percentage of time being exposed to $\text{pH} > 4$ (which indicates better acid control) in subjects taking esomeprazole 40 mg once a day as compared to esomeprazole 20 mg taken once a day.

4) Comparisons between once daily and on-demand dosing regimens of commonly used PPIs

- Continuous daily intake of esomeprazole 20 mg appears to provide better symptom control and quality of life relative to on-demand dosing over a period of 6 months.
- Continuous daily intake of esomeprazole 20 mg appears to provide significantly better endoscopic remission as compared to on-demand dosing over a period of 6 months.
- Continuous daily intake of rabeprazole 20 mg appears to provide better symptom control and quality of life relative to on-demand dosing over a period of 6 months.

- 5) Comparisons between PPIs and over-the-counter dosages of PPIs (omeprazole 20 mg, lansoprazole 15 mg)
 - When comparing different PPIs with over-the-counter dosages of omeprazole (20 mg), it was observed that pantoprazole 40 mg and rabeprazole 20 mg provide significantly better symptom relief and healing of esophagitis at 8 weeks.
 - Esomeprazole 20 mg provides better endoscopic remission rates as compared to over-the-counter dosages of lansoprazole (15 mg) over 6 months.

Detailed analysis

Data from 38 primary studies were analyzed. All were randomized control trials published between 2005 and 2009. The results are applicable to adults diagnosed with GERD and some degree of esophagitis

Overall, 30,241 subjects were enrolled, with data from 27,001 subjects available for follow up. Of the 38 studies, 4 (11 percent) were of Grade A, 24 (63 percent) of Grade B, and 10 (26 percent) were of Grade C quality. The sample size ranged from 43 to 6,017 subjects. Followup duration ranged from 28 days to 1 year. All subjects were adult patients with GERD.

Comparisons were stratified into 5 categories: a) Comparisons between different PPIs and H2RAs - 4 studies from five published articles²²⁻²⁶ b) Comparisons between different PPIs – 11 studies²⁷⁻³⁷. c) Comparisons between different dosages and dosing regimens of commonly used PPIs – 11 studies³⁸⁻⁴⁷. d) Comparisons between once daily and on-demand dosing regimens of commonly used PPIs – 5 studies⁴⁸⁻⁵³ e) Comparisons between PPIs and over-the-counter dosages of omeprazole – 7 studies⁵⁴⁻⁶⁰.

PPIs included esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole, dexrabeprazole, and dexlansoprazole. No standard dose was defined, with the exception of the category for comparison of various PPIs with the over the counter dose of omeprazole (20 mg) and lansoprazole (15 mg). The dosages used in the trials in this category are approved for over-the-counter use by the US Food and Drug Administration (FDA). H2RAs included famotidine and ranitidine.

Comparison of Proton Pump Inhibitors with H₂ Receptor Antagonists

Four RCTs²²⁻²⁶ enrolled a total of 2,268 GERD patients with followup information available from 2,141 subjects. One trial reported outcome data in 2 published articles.^{22,23} One of the articles mainly reported effectiveness and costs outcomes²² while the other reported quality of life and patient satisfaction outcomes.²³ Patients took various proton pump inhibitors (PPI) – esomeprazole 20 mg taken once daily or on-demand, lansoprazole 15 mg taken once daily and omeprazole 20 mg taken once daily, and also two H2RAs – famotidine 20 mg and ranitidine 150 mg, both twice daily. Sample sizes, based on availability of followup data, ranged from 51 to 1797. Three quarters (3 of 4 trials; 75 percent) of the studies in this category of comparisons were graded B. The remaining trial²⁵ was graded C.

The findings from these studies have been organized by the following outcomes of interest: symptom assessment; quality of life (QOL); esophagitis healing; and relapse rates and medication use, time to recurrence and patient satisfaction, which are more general measures of treatment efficacy. The details of these outcomes are presented in the Evidence Tables while key points are summarized below. Adverse effects are presented under Key Question 3.

Symptom Assessment (Table 6)

Out of four trials assessing efficacy, two compared omeprazole with famotidine, one compared esomeprazole with ranitidine and one compared lansoprazole with ranitidine. All but one trial²⁶ included symptomatic treatment-naïve patients.

One large study with 1902 enrolled participants compared esomeprazole 20 mg taken on demand and 20 mg taken once a day with ranitidine 150 mg taken twice a day for a period of 6 months.^{22,23} The study found that esomeprazole 20 mg taken once a day significantly improved all symptoms in 80.2 percent of subjects (as compared to 77.8 percent of subjects taking esomeprazole 20 mg on-demand or 47% of subjects taking ranitidine 150 mg twice a day, $P < 0.001$). Hansen, 2006 510 /id It also found that 72.2 percent of the subjects had no heartburn (significantly higher than 45.1 percent of subjects taking esomeprazole 20 mg on-demand or 32.5% of subjects taking ranitidine 150 mg twice a day, $P < 0.01$). Norman, 2005 1586 /id In addition, the study reported that a higher proportion of patients experienced relief from acid regurgitation when taking esomeprazole 20 mg once a day (78 percent) than when taking esomeprazole 20 mg on demand (62 percent) or ranitidine 150 mg twice a day (46 percent), although this effect was not statistically significant. Norman, 2005 1586 /id In a 1 year trial on 206 patients with erosive esophagitis, Peura et al., reported that a significantly higher proportion (56 percent) of participants remained asymptomatic on lansoprazole 15 mg taken once a day compared to ranitidine 150 mg twice a day (15 percent) over 1 year ($P < 0.001$).²⁶ In other findings, omeprazole and famotidine were shown to be comparative in efficacy in two trials,^{24,25} where similar rates of complete relief were seen in 54 patients over a 4 week treatment period²⁵ and no significant differences were observed in GSRs total score in 106 patients randomized to both treatments over an 8 week treatment period.²⁴

In summary, analysis of these trials indicates that the larger studies suggested PPIs to be more efficacious than H2RAs in resolution of symptoms, while smaller studies tended to show them to have equivalent effects on GERD symptoms. In addition, all the maintenance treatment studies^{22,23,26} showed PPIs to be more efficacious than H2RAs while the acute treatment studies^{24,25} showed no difference between the two classes of drugs.

Quality of Life (Table 7)

Three of the four included trials also reported quality of life outcomes.²³⁻²⁵ In two of these trials,^{24,25} the efficacies of omeprazole 20 mg once a day and ranitidine 20 mg twice a day were compared using the SF-36 quality of life scale. Both the studies reported significant improvement in SF-36 in each of the two treatment arms, in the absence of reported raw scores. However, neither study reported a significant difference in the change in scores from baseline between the two treatment arms. A large trial comparing different dosing regimens of esomeprazole (20 mg once a day or on demand) with ranitidine 150 mg twice a day²³ noted significant improvements in Quality of Life in Reflux and Dyspepsia (QOLRAD) scores in all dimensions (emotional, sleep, food, physical and vitality) in both of the esomeprazole arms versus ranitidine ($P < 0.005$). As for the esomeprazole arms, esomeprazole once a day significantly increased quality of life scores in the domains of emotion, sleep, food, and vitality ($P < 0.005$) compared to the on-demand regimen, while on-demand dosing significantly improved physical activity compared to esomeprazole once a day ($P < 0.005$).

Esophagitis Healing (Table 8)

Only one trial²⁶ assessed esophagitis healing rates. This study, graded B, enrolled 206 adult subjects with GERD and endoscopically proven erosive esophagitis and randomized them

to either lansoprazole 15 mg once a day or ranitidine 150 mg twice a day. At the end of 1 year of therapy, a significantly higher proportion of patients on lansoprazole (67 percent) were confirmed as healed as compared to ranitidine (13 percent), $P < 0.001$.

Relapse rate and medication use, time to recurrence and patient satisfaction (Table 9)

One trial analyzed the number of relapses (resulting in change of medication) and satisfaction with study medication^{22,23} with different dosing regimens of esomeprazole 20 mg (once a day and on-demand) versus ranitidine 150 mg (twice a day). Over a period of 6 months, a significantly higher proportion of subjects with a relapse in symptoms, and hence needing a change in their medication, were observed in the ranitidine group (34.4 percent) as compared to the once a day (7 percent) and on-demand groups (10.9 percent) of esomeprazole ($P < 0.0001$). This is also reflected in the increased level of satisfaction as measured on a Likert scale, with esomeprazole 20 mg once a day (82.2 percent) rated significantly higher than on-demand dosing (75.4 percent), and both in turn significantly higher than ranitidine (33.5 percent). With a 1 year followup, PPIs were also observed to have a longer median time to recurrence of symptoms, as seen with lansoprazole 15 mg (92 days) vs. ranitidine (36 days).²⁶ However, this effect may be due to subjects on lansoprazole remaining on therapy significantly longer (236.9 days) than patients treated with ranitidine (88.7 days), $P < 0.05$. Both these trials were for maintenance treatment of GERD.

Comparison of different Proton Pump Inhibitors

Eleven RCTs²⁷⁻³⁷ enrolled a total of 11,105 GERD patients, with followup information available from 10,236 subjects. Although two of the studies^{28,33} present results from two phases of the same multi-center RCT (EXPO study), they are considered separately, as the drug dosages differed between the two phases. Patients took various PPIs—esomeprazole (20 to 40 mg), lansoprazole (15 to 30 mg), pantoprazole (20 to 40 mg), dexlansoprazole (10 mg) and rabeprazole (10 to 20 mg). Sample sizes, based on availability of followup data, ranged from 50 to 3,151. Most of the studies (9 of 11 trials, 82 percent) in this category of comparisons were graded B.

The findings from these studies have been organized by the following outcomes of interest: symptom assessment; quality of life (QOL); endoscopic esophagitis healing; and antacid medication use. The details of these outcomes are presented in the Evidence Tables while key points are summarized below. Adverse effects are presented under Key Question 3.

Symptom Assessment (Table 10)

All trials were conducted on adult GERD patients. Seven out of eleven trials (64 percent) compared varying dosages of pantoprazole and esomeprazole.²⁷⁻³³ Other comparisons included rabeprazole vs. esomeprazole,^{35,36} lansoprazole vs. esomeprazole,³⁴ and dexrabeprazole vs. rabeprazole.³⁷ Three trials included participants based on clinical symptoms alone, without assessing the presence of esophagitis.^{34,35,37} In the other eight trials, participants had esophagitis at presentation²⁷⁻³³ or it had been ruled out by an endoscopic examination.³⁶

The results from the acute phase of the EXPO study showed similar heartburn resolution rates for both pantoprazole 40 mg (67 percent) and esomeprazole 40 mg (73 percent) at 4 weeks.²⁸ Maintenance therapy with 20 mg doses of the same drugs over 6 months did not significantly alter the results, with pantoprazole (17.4 percent) showing a slightly higher heartburn resolution rate as compared to esomeprazole (9.8 percent). Both studies did not report tests of significance. One non-inferiority trial²⁹ demonstrated that pantoprazole 40 mg and

esomeprazole 40 mg both had similar median post treatment ReQuest GI subscale scores (PAN0.24, EsOME 0.31) after 4 weeks. The same study also reported that esomeprazole had significantly higher rates of symptom relapse post treatment (61 percent) as compared to pantoprazole (51.1 percent), $P=0.0216$. Two additional studies reported results with 8 week³² and 12 week³⁰ followup. At 8 weeks, the proportion of patients with heartburn free days was similar for esomeprazole (70.2 percent) and for pantoprazole (69.8 percent).³² At 12 weeks, the endoscopic and symptomatic relapse rates were the same for both the arms (76 percent).³⁰ However, in another study with a followup of 24 weeks, patients on pantoprazole 20 mg showed a significantly lower mean intensity of heartburn (1.12) as compared to esomeprazole 20 mg (1.32), $P=0.012$.³¹

Results from a non-inferiority trial comparing lansoprazole 30 mg twice a day to esomeprazole 40 mg once a day showed similar percentages of patients who experienced days without symptoms of heartburn (EsOME: 54.4 percent, LAN: 57.5 percent), epigastric pain, (EsOME: 65 percent, LAN: 66.9 percent) and acid regurgitation (EsOME: 60.3 percent, LAN: 65.3 percent).³⁴

Two 4-week studies compared the efficacy of rabeprazole and esomeprazole.^{35,36} One, a three-arm study comparing two doses of esomeprazole (20 and 40 mg) with 20 mg of rabeprazole, showed similar rates of complete resolution of heartburn (rabeprazole = 58.4 percent, esomeprazole 40 mg = 64.4 percent, esomeprazole 20 mg = 60.6 percent, $P=0.184$) and acid regurgitation (rabeprazole = 60.6 percent, esomeprazole 40 mg = 60.3 percent, esomeprazole 20 mg = 60.1 percent, $P=0.363$) in all three arms.³⁵ The second evaluated rabeprazole 10 mg vs. esomeprazole 20 mg and found that rabeprazole led to a more rapid resolution of heartburn (8.5 days versus 9 days for esomeprazole, $P=0.265$) and acid regurgitation (6 days versus 7.5 days for esomeprazole, $P=0.405$), though this finding was not significant.³⁶

A small study, graded C, evaluated the effect of dexrabeprazole 10 mg versus rabeprazole 20 mg on symptoms and found that 96 percent of patients on dexrabeprazole 10 mg had ≥ 50 percent improvement in acid regurgitation scores compared to 60 percent on rabeprazole 20 mg ($P<0.05$) while no significant differences were found between the groups in the change in heartburn and acid regurgitation scores from baseline.³⁷

Quality of Life (Table 11)

Of the 11 reviewed trials, only one reported quality of life outcomes.³⁵ In this study, graded B, 1,392 patients were randomized to esomeprazole 20 mg, esomeprazole 40 mg, or rabeprazole 20 mg, once daily. An increase in the SF-36 quality of life was observed for all domains in all 3 arms ($P<0.05$), although the mean change was not significantly different between groups. Across all groups, the greatest improvements were seen in the bodily pain, role physical, and role emotional domains.

Endoscopic Esophagitis Healing (Table 12)

Four of 11 trials^{27,30,32,37} reported endoscopic healing results. Of these four, three^{27,30,32} compared the efficacy of pantoprazole and esomeprazole in endoscopic healing. Results from two acute treatment trials showed similar esophagitis healing rates for both pantoprazole 40 mg (91.1 to 98 percent of participants) and esomeprazole 40 mg (92.2 to 94 percent of participants) as demonstrated by endoscopy, with the rates increasing with trial duration from 8 to 12 weeks.^{30,32} In a third trial with six months followup, the rates of endoscopic and symptomatic

remission were equivalent (93 percent of participants) for both treatment groups.²⁷ In the fourth, graded C, a greater decrease, from baseline, was observed in the percentage of participants with esophagitis receiving dexrabeprazole 10 mg (a decline of 52 percentage points) as compared to rabeprazole (a decline of 32 percentage points) over a 4-week period.³⁷

Antacid medication use (Table 13)

One trial compared the efficacy of pantoprazole 20 mg with esomeprazole 20 mg, both taken on-demand (i.e. as and when necessary), on the use of antacids as a rescue medication among symptomatic GERD patients over 24 weeks.³¹ The average daily antacid use was found to be higher among participants taking pantoprazole (0.31 tablets/day) than esomeprazole (0.23 tablets/day), though the statistical significance was not reported.

Comparison of different dosages as well as different dosing regimens of the same Proton Pump Inhibitors

Eleven RCTs^{38-47,53} enrolled a total of 4,399 GERD patients with followup data available from 3,630 subjects. Dosages and dosing regimens were compared among a number of PPIs including esomeprazole, pantoprazole, lansoprazole, dexpanoprazole, and dextansoprazole. Sample sizes, based on availability of followup data, ranged from 43 to 873. Three trials compared esomeprazole at different dosages,³⁸⁻⁴⁰ one trial compared different dosing regimens of esomeprazole,⁴¹ two trials compared different dosing regimens of lansoprazole,^{42,53} three trials compared different dosing regimens of dextansoprazole,⁴³⁻⁴⁵ and two trials compared different dosages of pantoprazole.^{46,47} The dosing regimens used were a once daily regimen or an intermittent course therapy (a four week course only when symptomatic). One 4-week trial compared empirical treatment with a specified dose of esomeprazole (40 mg) to a treatment dose based on results of a screening endoscopy (20 or 40 mg).³⁸ 1 out of 11 trials (9.1 percent) was graded A, 4 out of 11 trials (36.4 percent) were graded B, and 6 out of 11 trials (54.5 percent) were graded C.

The findings from these studies have been organized by the following outcomes of interest: symptom assessment; quality of life (QOL); esophagitis healing; acid control, and antacid medication use and treatment satisfaction. Comparisons of dosages and dosing regimens of the same PPI are assessed separately within each outcome. Details of these outcomes are presented in the Evidence Tables while key points are summarized below. Adverse effects are presented under Key Question 3.

Symptom Assessment (Table 14)

Esomeprazole – comparison of dosages:

Two trials compared esomeprazole 20 mg with esomeprazole 40 mg, enrolling 1,287 subjects with followup data available on 1,213 subjects.^{38,39} The trials included patients who either had a history of erosive esophagitis³⁹ or who had undergone a period of treatment with PPIs before entering the trial.³⁸ One, a three-arm trial conducted over 4 weeks, indicated significantly better relief of nighttime heartburn symptoms in subjects taking either 20 mg (50.5 percent) or 40 mg (53.1 percent) esomeprazole as compared to placebo (12.7 percent), $P < 0.0001$.³⁹ In the other, a 24 week trial, treatment response (a patient was considered a responder if the sum of symptom scores over the previous 7 days was either 0 or 1) was observed in 71.8 percent of the group treated empirically and in 68.3 percent of the group whose treatment was determined by endoscopy ($P = 0.389$).³⁸

Lansoprazole – comparison of different dosing regimens:

Two separate trials evaluated different dosing regimens of lansoprazole for its effect on GERD symptoms. In one three-arm trial of 65 participants conducted over 1 year, lansoprazole 15 mg once a day was compared to on-demand lansoprazole 30 mg as well as a 30 mg intermittent therapy course (where recurrence of any symptoms was followed by a full 4-week course of lansoprazole 30 mg).⁵³ In this trial, both the daily and on-demand regimens were shown to significantly decrease the intensity of symptoms as compared to the intermittent therapy ($P<0.05$), though no statistical difference was observed between these two arms.⁵³ In another trial, a three-arm comparison employed 43 participants over 16 weeks to evaluate three different treatment strategies: a once a day dose of lansoprazole 15 mg for the duration of the study (no step group), 30 mg a day stepped down to 15 mg a day halfway through the study (step down to lansoprazole group), and 30 mg a day with a substitution with famotidine 20 mg twice a day halfway through the study (step down to famotidine group).⁴² Heartburn, acid regurgitation and dysphagia symptoms disappeared in the no step and step down to lansoprazole groups, with the exception of one patient in each group (one patient in the no step group had residual heartburn and one person in the step down to lansoprazole group had residual regurgitation). The step down to famotidine group continued to experience residual symptoms.

Dexlansoprazole – comparison of dosages:

Two three-arm trials compared dexlansoprazole 30 mg and dexlansoprazole 60 mg doses with a placebo.^{43,44} In the first, a Grade A study with 947 enrolled subjects, the median proportion of participants with 24-hour heartburn free days after a 4-week treatment period was found to be significantly higher in the dexlansoprazole 30 mg (54.9 percent) and dexlansoprazole 60 mg (50 percent) groups as compared to placebo (18.5 percent).⁴³ Although the 30 mg dosage showed somewhat better results than the higher dosage, these differences were not statistically significant. Similar findings were reported by the second, smaller study of 445 subjects over 6 months; the proportion of participants with no heartburn was significantly higher with dexlansoprazole 30 mg (67 percent) and dexlansoprazole 60 mg (63 percent), as compared to placebo (17 percent, $P<0.0025$).⁴⁴

A third study, comparing dexlansoprazole 60 mg and dexlansoprazole 90 mg doses with a placebo in 451 subjects, reported a significantly higher proportion of patients without heartburn in the 60 mg (95.8 percent) and 90 mg (94.4 percent) groups, as compared to placebo (19.2 percent, $P<0.0001$).⁴⁵

Pantoprazole – comparison of dosages:

One study compared the pure S-isomer of pantoprazole 20 mg with a racemic mixture of S- and R-isomers of pantoprazole 40 mg over a 4-week treatment period.⁴⁶ In the s-isomer, lower dosage group, a significantly higher proportion of patients experienced relief from heartburn (85.5 percent) as compared to the racemic mixture (74.4 percent, $P=0.01$). Similarly, a significantly higher proportion of patients experienced relief from acid regurgitation in the s-isomer group (92.2 percent) as compared to the racemic mixture (82.4 percent, $P=0.004$). Another study, enrolling 548 participants, compared 20 and 40 mg doses of pantoprazole on an on-demand regimen with placebo.⁴⁷ The perceived average daily symptom load (comprising heartburn, epigastric pain and acid regurgitation) was significantly lower for the 40 mg (2.71) and 20 mg on-demand groups (2.91) as compared to placebo (3.93), $P<0.001$.

Quality of Life (Table 15)

Esomeprazole – comparison of dosages:

Two trials compared quality of life with esomeprazole 20 mg versus esomeprazole 40 mg, enrolling a total of 1,287 subjects, with followup data on 1,193 subjects.^{38,39} One was a placebo-controlled three-arm trial lasting for 4 weeks, with treatment administered once daily, and included subjects with GERD as well as sleep disturbances.³⁹ The effect of different dosages of esomeprazole was evaluated on sleep outcomes measured subjectively as well as with the Pittsburgh sleep quality index (PSQI). Using a PSQI score of 5 or less as an indicator of good sleep quality, a significantly higher proportion of participants using esomeprazole 20 mg (57 percent) and 40 mg (46 percent) reported good sleep quality as compared to placebo (36 percent), $P < 0.01$ for EsOME groups versus placebo. A significantly higher fall in PSQI score was also observed in the 20 mg group (-4.00) and the 40 mg groups (-3.64) as compared to the placebo (-2.19), $P < 0.0001$. A fall in the PSQI global score is indicative of better sleep. In the other trial, lasting 24 weeks, no significant difference in the QOLRAD quality of life score was observed between the group treated empirically with esomeprazole 40 mg and the group whose treatment dosage (20 or 40 mg) was determined by endoscopy.³⁸

Rabeprazole – comparison of different dosing regimens:

A trial comparing rabeprazole 20 mg on-demand with rabeprazole 20 mg taken once a day for 6 months assessed quality of life in 268 enrolled subjects and reported that self-reported quality of life significantly improved in the group taking rabeprazole 20 mg once a day and significantly decreased in the rabeprazole 20 mg on-demand group ($P < 0.05$). The difference in change from baseline between the groups was also significant ($P < 0.05$).⁵¹

Dexlansoprazole – comparison of dosages:

A three-arm trial of 445 subjects compared Patient Assessment of Upper Gastrointestinal Disorders Quality-of-Life (PAGI-QoL) scores for groups receiving dexlansoprazole 30 mg or dexlansoprazole 60 mg doses with a placebo.⁴⁴ This study showed that there was a significant improvement in PAGI-QoL in both the 30 mg as well as the 60 mg group as compared to placebo, $P < 0.0025$. In another three-arm trial (451 subjects) comparing PAGI-QoL in groups taking dexlansoprazole 60 mg, dexlansoprazole 90 mg, or a placebo, over 6 months, a higher mean change for PAGI-QoL scores from baseline was observed in both the 60 mg and 90 mg groups when compared to placebo, $P < 0.0025$.⁴⁵

Esophagitis Healing (Table 16)

Esomeprazole – comparison of dosages:

One trial compared a once daily dose of esomeprazole 10 mg with esomeprazole 40 mg in 106 patients over a period of 4 weeks.⁴⁰ A higher proportion of subjects in the 40 mg group (86 percent) had their esophagitis healed as compared to the 10 mg group (55 percent). This trial was graded C.

Lansoprazole – comparison of different dosing regimens:

In a trial of 43 participants, graded C, lasting 16 weeks, three different treatment strategies were evaluated: a once a day dose of lansoprazole 15 mg for the duration of the study (no step group), 30 mg a day stepped down to 15 mg a day halfway through the study (step down to lansoprazole group), and 30 mg a day with a substitution with famotidine 20 mg twice a day halfway through the study (step down to famotidine group).⁴² Esophagitis healing was seen in all arms, with no significant difference between the three groups.

Dexlansoprazole – comparison of dosages

In one three-arm 6-month trial of 445 subjects comparing esophagitis healing rates in patients taking dexlansoprazole 30 mg, dexlansoprazole 60 mg doses, or a placebo, significantly higher rates of esophagitis healing were observed in the 60 mg (82.5 percent) and 30 mg groups (74.9 percent) as compared to the placebo group (27.2 percent), $P < 0.00001$.⁴⁴ Similarly, in another three-arm 6-month trial of 451 subjects comparing esophagitis healing rates in patients taking dexlansoprazole 60 mg, dexlansoprazole 90 mg, or a placebo, higher rates of esophagitis healing were seen in the 60 mg group (86.6 percent) and the 90 mg group (82.1 percent) as compared to the placebo group (25.7 percent), $P < 0.00001$.⁴⁵

Pantoprazole – comparison of dosages:

One study, graded C, compared pure s-isomer of pantoprazole 20 mg with a racemic mixture of S- and R-isomers of pantoprazole 40 mg over a 4 week treatment period and found no difference in the healing of esophagitis and esophageal erosions between the groups.⁴⁶

Acid control (Table 17)

Esomeprazole – comparison of dosages:

One trial in 106 patients over a period of 4 weeks compared acid control in a parallel trial, with one arm taking a once a day dosage of esomeprazole 10 mg and the other arm taking a dose of once a day esomeprazole 40 mg.⁴⁰ Acid control was reported as the percentage time with $\text{pH} > 4$ after 5 days of treatment, with higher values indicating better control. Subjects in the 40 mg group spent a higher proportion of time being exposed to $\text{pH} > 4$ (72 percent) as compared to the 10 mg group (41 percent), indicating that the 40 mg dose gives better acid control. This trial was graded C.

Esomeprazole – comparison of different dosing regimens:

A three-arm trial assessed acid control over 1 month in 75 people taking esomeprazole 40 mg once a day, esomeprazole 40 mg twice a day and esomeprazole 40 mg once every other day.⁴¹ Acid control was evaluated via two indicators: abnormal acid exposure (defined as ≥ 4 percent of total time with $\text{pH} < 4$) and abnormal DeMeester score (≥ 14.7). Abnormal acid exposure was observed in the esomeprazole 40 mg once every other day group (> 7 percent of total time with $\text{pH} < 4$) but not in the esomeprazole 40 mg once a day (> 1.5 percent of total time with $\text{pH} < 4$) or esomeprazole 40 mg twice a day (> 0.7 percent of total time with $\text{pH} < 4$) groups. An abnormal DeMeester score was also observed in the group receiving esomeprazole 40 mg once every other day (29.4) but not in the esomeprazole 40 mg once a day (6.4) or esomeprazole 40 mg twice a day (3.9) groups. This trial was graded B.

Antacid medication use and treatment satisfaction (Table 18)

Esomeprazole – comparison of dosages:

A three-arm trial for 4 weeks evaluated consumption of rescue antacid medication in 675 participants taking either esomeprazole 20 mg or 40 mg once a day, or placebo.³⁹ The average daily use of antacids was observed to be significantly lower in the esomeprazole 40 mg (1.0 tablets/day) and 20 mg groups (0.9 tablets/day) as compared to placebo (1.7 tablets/day), $P < 0.001$.

Lansoprazole – comparison of different dosing regimens:

In a three-arm trial of 65 participants conducted over 1 year, lansoprazole 15 mg once a day was compared to on-demand lansoprazole 30 mg as well as a 30 mg intermittent therapy

course (where recurrence of any symptoms was followed by a full 4-week course of lansoprazole 30 mg).⁵³ Patient satisfaction with treatment was recorded at the end of the trial as a measure of efficacy. A significantly higher level of satisfaction was observed in the lansoprazole 30 mg on-demand group (90 percent) and the lansoprazole 15 mg once a day group (95 percent) when compared to the intermittent treatment group (85 percent), $P < 0.05$.

Dexlansoprazole – comparison of different dosages:

A Grade A study with 947 subjects evaluated rescue medication use with respect to 3 treatment arms: dexlansoprazole 30 mg, dexlansoprazole 60 mg, and a placebo.⁴³ Both treatment groups reported a higher percentage of days without rescue medication (63 percent for both 30 mg and 60 mg groups) versus placebo (37.3 percent), $P < 0.00001$.

Pantoprazole – comparison of dosages:

A study of 548 participants compared 20 and 40 mg doses of pantoprazole on an on-demand regimen with a placebo.⁴⁷ A significantly lower average of daily antacids intake was observed with pantoprazole 40 mg on-demand (0.33 tablets/day) and pantoprazole 20 mg on-demand (0.45 tablets/day) vs. placebo (0.68 tablets/day), $P = 0.0034$.

Comparison of once daily and on-demand dosing regimens of commonly used PPIs

Five RCTs⁴⁸⁻⁵² enrolled a total of 8,849 GERD patients with followup data available from 7,905 subjects. Sample sizes, based on availability of followup data, ranged from 132 to 5,265. Three studies compared esomeprazole 20 mg taken once a day with esomeprazole 20 mg taken on demand,⁴⁸⁻⁵⁰ one study compared rabeprazole 20 mg taken once a day with rabeprazole 20 mg taken on demand⁵¹ and one study compared rabeprazole 10 mg taken once a day with rabeprazole 10 mg taken on demand.⁵²

The findings from these studies have been organized by the following outcomes of interest: symptom assessment; quality of life (QOL) and esophagitis healing. Details of these outcomes are presented in the Evidence Tables while key points are summarized below. Adverse effects are presented under Key Question 3.

Symptom Assessment (Table 19)

Esomeprazole – comparison of on-demand with once daily dosing regimens:

Two trials, 6 months in duration and with 2,412 enrolled subjects (2274 in followup), compared esomeprazole 20 mg on-demand with esomeprazole 20 mg taken once daily.^{48,49} The larger study, with 1,935 enrolled participants, reported a significantly higher proportion of patients experiencing complete relief from symptoms with the once a day dose (86 percent) as compared to the on-demand dose (80 percent, $P < 0.01$).⁴⁹ The other, smaller study with 477 participants revealed no significant differences in the proportion of symptom-free patients assigned to the on-demand (94.3 percent) or once a day regimens (95 percent, $P = 0.77$).⁴⁸

Rabeprazole – comparison of on-demand with once daily dosing regimens:

Two trials, 6 months in duration, were reviewed. One compared rabeprazole 20 mg on-demand with rabeprazole 20 mg taken once a day⁵¹ and another compared rabeprazole 10 mg on-demand with rabeprazole 10 mg taken once a day.⁵² These two studies enrolled 420 subjects, with followup data available on 366 subjects. Results indicated that, in the 20 mg comparison, a significantly higher proportion of patients experienced heartburn free days when rabeprazole was taken once a day (90.3 percent) as compared to on-demand (64.6 percent, $P < 0.0001$).⁵¹ Similar results were observed with a 10 mg dose, with a higher proportion of patients observed as

symptom free when rabeprazole was taken once a day (86.4 percent) as compared to on-demand (74.6 percent).⁵² However, this finding was not statistically significant (P=0.065).

Quality of Life (Table 20)

Esomeprazole – comparison of on-demand with once daily dosing regimens:

A large trial, enrolling 6017 participants, with data available from 5,265 participants after a 26 week followup, assessed the quality of life between two groups taking either a once daily 20 mg dose of esomeprazole or esomeprazole 20 mg on demand.⁵⁰ Using the QOLRAD score, the groups taking a once daily dose were shown to be significantly improved across all dimensions in comparison to those in the on-demand group, P<0.0001.

Rabeprazole – comparison of on-demand with once daily dosing regimens:

A trial comparing rabeprazole 20 mg on-demand with rabeprazole 20 mg taken once a day for 6 months assessed quality of life in 268 enrolled subjects and reported that self-reported quality of life significantly improved in the group taking rabeprazole 20 mg once a day and significantly decreased in the rabeprazole 20 mg on-demand group (P<0.05). The difference in change from baseline between the groups was also significant (P<0.05)⁵¹.

Esophagitis Healing (Table 21)

Esomeprazole – comparison of on-demand with once daily dosing regimens:

One trial evaluated endoscopic remission rates over 6 months in subjects taking esomeprazole 20 mg on-demand with esomeprazole 20 mg once a day.⁴⁸ The study found a significantly higher proportion of patients with endoscopic remission with the once daily dose (81 percent) as compared to the on-demand dose (58 percent), P<0.0001. This trial was graded B.

Comparison of PPIs with Over the Counter Doses of approved PPIs (omeprazole 20 mg, lansoprazole 15 mg)

Six RCTs⁵⁴⁻⁵⁹ enrolled a total of 2,594 GERD patients, with followup data available from 2,343 subjects. The patients took various PPIs including omeprazole, esomeprazole, rabeprazole, pantoprazole, and lansoprazole. Sample sizes, based on availability of followup data, ranged from 44 to 1,106. Half of the studies (3 of 6 trials; 50 percent) in this category of comparisons were graded B.

The findings from these studies have been organized by the following outcomes of interest: symptom assessment, quality of life, and esophagitis healing. Details of these outcomes are presented in the Evidence Tables while key points are summarized below. Adverse effects are presented under Key Question 3.

Symptom Assessment (Table 22)

All six trials were conducted on adult GERD patients. Two out of the four compared esomeprazole with omeprazole,^{54,59} one compared rabeprazole with omeprazole,⁵⁷ and one, a four arm trial, compared lansoprazole, pantoprazole, and rabeprazole with omeprazole.⁵⁵ The remaining two compared esomeprazole 20 mg⁵⁴ and esomeprazole 40 mg⁵⁹ with omeprazole 20 mg over 8 weeks.

In the esomeprazole 20 mg versus omeprazole 20 mg 8-week trial, no significant differences in the resolution of heartburn (60.6 percent esomeprazole vs 60.5 percent

omeprazole, $P=0.995$), proportion of patients with heartburn-free days (72.6 percent esomeprazole vs 70.9 percent omeprazole, $P=0.354$), or proportion of patients with heartburn free nights (85.7 percent esomeprazole vs 83.2 percent omeprazole, $P=0.062$) were observed at 4 weeks.⁵⁴ Similarly, in the other 8-week trial, comparing esomeprazole 40 mg versus omeprazole 20 mg, there were no significant differences in the change in heartburn score from baseline between the esomeprazole 40 mg group (-22.3) and the omeprazole 20 mg group (-21.4).⁵⁹

In the 8-week, 560 participant trial comparing rabeprazole 20 mg with omeprazole 20 mg, the time to first day of satisfactory heartburn relief was significantly lower with rabeprazole (2.8 days) compared to omeprazole (4.7 days).⁵⁷

In the four-arm, 320 participant trial comparing lansoprazole 30 mg, pantoprazole 40 mg, and rabeprazole 20 mg with omeprazole 20 mg,⁵⁵ 100 percent of all participants of the pantoprazole and rabeprazole groups had a complete resolution of heartburn at 2 months, a significantly different result as compared to the omeprazole (87 percent) and lansoprazole (82 percent) groups, $P<0.05$.

In a large study comparing esomeprazole 20 mg with lansoprazole 15 mg, higher endoscopic and symptomatic remission rates were seen with esomeprazole (84.8 percent) than lansoprazole (75.9 percent), $P=0.0007$.⁶⁰

Quality of Life (Table 23)

Two trials reported quality of life and general well-being outcomes.^{57,58} In one trial, 560 participants randomized to rabeprazole 20 mg or omeprazole 20 mg reported a similar change in proportion of patients with self reported “good” general well-being (47.6 percent of the rabeprazole group and 42.8 percent of the omeprazole group).⁵⁷

In the other, comparing omeprazole 20 mg on-demand with omeprazole 10 mg once a day and omeprazole 20 mg once a day in 216 participants, all groups reported similar mean health related quality of life scores at the end of the 12-month treatment period (omeprazole 20 mg on-demand: 9.4, omeprazole 10 mg once a day: 9.7, omeprazole 20 mg once a day: 9.8).⁵⁸

Esophagitis Healing (Table 24)

Seven RCTs⁵⁴⁻⁵⁹ reported endoscopic healing results.

Two were 4-arm trials.^{55,56} One, enrolling 320 participants for a treatment duration of 8 weeks, compared lansoprazole 30 mg, pantoprazole 40 mg, and rabeprazole 20 mg with omeprazole 20 mg and found that pantoprazole and rabeprazole had significantly higher esophagitis healing rates as compared to omeprazole (90 and 89 percent versus 75 percent, respectively), $P<0.05$.⁵⁵ Lansoprazole also had a higher esophagitis healing rate (85 percent) but did not attain significance. The other, which used esomeprazole 40 mg instead of rabeprazole as an arm, enrolled 274 participants and reported similar healing rates for omeprazole (87.7 percent), lansoprazole (89.6 percent), pantoprazole (91.1 percent) and esomeprazole (95.4 percent), NS.⁵⁶

Another, larger study, enrolling 1,176 participants and comparing esomeprazole 20 mg with omeprazole 20 mg over 8 weeks, found similar esophagitis healing rates for esomeprazole (90.6 percent) and omeprazole (88.3 percent), $P=0.621$ ⁵⁴, while a smaller study, enrolling 44 participants, compared esomeprazole 40 mg with omeprazole 20 mg over 8 weeks and found that a higher proportion of participants taking esomeprazole showed esophagitis healing (72.5 percent) as compared to those taking omeprazole (50 percent).⁵⁹

In another trial, with 560 participants randomized to rabeprazole 20 mg or omeprazole 20 mg, a similar proportion of patients with esophagitis healing among groups was observed (97.5 percent of the rabeprazole group and 97.5 percent of the omeprazole group).⁵⁷

A trial enrolling 216 subjects and comparing omeprazole 20 mg on demand and omeprazole 10 mg once a day with omeprazole 20 mg once a day, results were stratified by baseline esophagitis status.⁵⁸ In those subjects with no esophagitis at baseline, a significantly higher proportion of patients with healing of esophagitis in the omeprazole 10 mg once a day group (90.5 percent) was seen as compared to the 20 mg on-demand group (57.7 percent), $P < 0.05$. In those subjects with Grade A esophagitis at baseline, a significantly higher proportion of patients with healing of esophagitis was observed in the omeprazole 10 mg once a day group (90.3 percent) as compared to the 20 mg on-demand group (65.1 percent), $P < 0.01$. In those subjects with Grade B esophagitis at baseline, no significant difference was seen between the groups at one year.

A large trial of 1026 participants graded B, comparing esomeprazole 20 mg versus lansoprazole 15 mg, showed significantly higher endoscopic remission with esomeprazole (86.9 percent) than with lansoprazole (77.8 percent, $P = 0.0003$).⁶⁰

Table 6. Comparison of PPI w/ H2 Receptor Antagonist - Symptom Assessment

Study Year [UI]	Comparisons: Drug Name Dose (Frequency)	N _E (N _{FU})	Results	Quality
		F/U duration		
Norman 2005 ²² [15924594] / Hansen 2006 ²³ [16409423]	EsOME 20 mg (O-D) vs EsOME 20 mg (QD) vs RAN 150 mg (BD)	1902 (1648 / 1797 ^a) 6 mo	↑ % of patients w/o heartburn for EsOME 20 mg QD (72.2%) vs EsOME 20 mg O-D (45.1%) and RAN (32.5%), P<0.01. ²² ↑ % of patients w/o acid regurg for EsOME 20 mg QD (78%) vs EsOME 20 mg O-D (62%) & RAN (45.7%), NS. ²² ↑ improvement in symptoms ^b for both EsOME 20 mg QD (80.2%) & EsOME 20 mg O-D (77.8%) vs RAN (47%), P<0.001. ²³	B
Peura 2009 ²⁶ [18726153]	LAN 15 mg (QD) vs RAN 150 mg (BD)	206 (195) 1 y	↑ % asymptomatic at 1 y for LAN (56%) vs RAN (15%), P<0.001	B
Wada 2005 ²⁴ [15943840]	OME 20 mg (QD) vs FAM 20 mg (BD)	54 (51) 8 wk	Improvement in GSRS ^c total score for OME (2.04 to 1.80), NS; Significant improvement in GSRS total score for FAM (2.56 to 2.13, P<0.05); ↑ % total nighttime heart- burn free rate for OME (75%) vs FAM (43.8%), NS.	B
Fujiwara 2005 ²⁵ [15943841]	OME 20 mg (QD) vs FAM 20 mg (BD)	106 (98) 4 wk	No differences in efficacy between FAM (23/48 (47.9%) w/ complete remission) and OME (28/50 (56%) w/ complete remission), P=0.385 Similar complete relief for OME (56%) & FAM (47.9%), P=0.423.	C Study methods not reported

^a Hansen 2006²³ was a separate publication from the same trial that primarily reported on quality of life, but included data on symptoms

^b Measured by Overall Treatment Evaluation (OTE) questionnaire which asks about change in symptoms and rates the reported change (better/worse) on a 7-point Likert scale.

^c Interview-based rating scale consisting of 15 items for assessment of gastrointestinal symptoms, combined to give scores for the symptoms of reflux, indigestion, pain, diarrhea, and constipation. The GSRS has a scale from 1-7, with 1 indicating no symptoms and 7 indicating severe symptoms. The scores are averages out for the total score⁶¹

Table 7. Comparison of PPI w/ H2 Receptor Antagonist or Different H2 Receptor Antagonists - Quality of Life

Study Year [UI]	Comparisons: Drug Name Dose (Frequency)	N _E (N _{FU}) F/U duration	Results	Quality
Wada 2005 ²⁴ [15943840]	OME 20 mg (QD) vs FAM 20 mg (BD)	54 (51) 8 wk	SF-36: Significant improvement from baseline for OME in domains of general health, vitality and mental health (P<0.05) & Significant improvement from baseline for FAM in domain of mental health (P<0.05).	B
Hansen 2006 ²³ [16409423]	EsOME 20 mg (O-D) vs EsOME 20 mg (QD) vs RAN 150 mg (BD)	1902 (1797) 6 mo	QOLRAD ^a : EsOME 20 mg QD & EsOME 20 mg O-D > RAN in all dimensions (emotional, sleep, food, physical, vitality); P< 0.005. EsOME 20 mg QD > EsOME 20 mg O-D in 4 dimensions (Emotional, sleep, food, vitality), P< 0.005. EsOME 20 mg O-D > EsOME 20 mg QD in physical activity, P< 0.005.	B
Fujiwara 2005 ²⁵ [15943841]	OME 20 mg (QD) vs FAM 20 mg (BD)	106 (98) 4 wk	SF-36 ^b (all scales): No significant differences between FAM & OME in changes from baseline . GSRs (total & all dimensions): No significant differences between FAM & OME .	C Study methods not reported

^a Quality of Life in Reflux and Dyspepsia (QOLRAD) questionnaire: Disease-specific questionnaire covering 5 dimensions with 7-grade Likert scale (lower score indicating a more severe impact on daily functioning).

^b SF-36 contains 8 scales and 2 summary scores. SF-36 Japanese version 1.2 was used in this study. Range of scores was 0 -100; higher scores indicate better functioning and well-being.

Table 8. Comparison of PPI w/ H2 Receptor Antagonist - Esophagitis Healing

Study Year [UI]	Comparisons: Drug Name Dose (Frequency)	$\frac{N_E}{(N_{FU})}$ F/U duration	Results	Quality
Peura 2009 ²⁶ [18726153]	LAN 15 mg (QD) vs RAN 150 mg (BD)	$\frac{206}{195}$ 1 y	↑ healing rate ^a at 1 y w/ LAN (67%) vs RAN (13%), P<0.001	B

Table 9. Comparison of PPI w/ H2 Receptor Antagonist - Relapse rate, patient satisfaction, time to recurrence and medication use

Study Year [UI]	Comparisons: Drug Name Dose (Frequency)	$\frac{N_E}{(N_{FU})}$ F/U duration	Results	Quality
Norman 2005 ²² [15924594] / Hansen 2006 ²³ [16409423]	EsOME 20 mg (O-D) vs EsOME 20 mg (QD) vs RAN 150 mg (BD)	$\frac{1902}{(Norman\ 2005:\ 1648 / Hansen\ 2005:\ 1797)}$ 6 mo	↑ % of patients w/ 1 relapse in RAN (34.4%) vs EsOME 20 mg QD (7%) & EsOME 20 mg O-D (10.9%), P<0.0001 ²² ↑ satisfaction w/ study medication for EsOME 20 mg QD (82.2%) vs EsOME 20 mg O-D (75.4%) & RAN (33.5%) P<0.01 for EsOME 20 mg QD vs EsOME 20 mg O-D; P<0.0001 for EsOME 20 mg QD vs RAN; P<0.0001 for EsOME 20 mg O-D vs RAN. ²³	B
Peura 2009 ²⁶ [18726153]	LAN 15 mg (QD) vs RAN 150 mg (BD)	$\frac{206}{195}$ 1 y	Improved median time to recurrence of day and night heartburn w/ LAN (92 d) vs RAN (36 d). ↑ number of days on maintenance therapy w/ LAN (mean 236.9 days) vs RAN (mean 88.7 days), P<0.05.	B

^a Defined as absence of endoscopic recurrence of erosive esophagitis (≥ Grade 2 on the modified Hetzel–Dent grading scale ⁶²)

Table 10. Comparison of different PPIs – Symptom Assessment

Study Year [UI]	Comparisons: Drug Name Dose (Frequency)	N _E (N _{FU})	Results	Quality
		F/U duration		
Goh 2007 ²⁷ [17301646]	PAN 20 mg (QD) vs EsOME 20 mg (QD)	1316 (ITT–1303 / PP-1005) 6 mo	Same mean sum score of GI symptoms ^a (0.1) for PAN 20 mg (QD) & EsOME 20 mg (QD), NS.	A
Labenz 2009 ²⁸ [19222417]	PAN 40 mg (QD) vs EsOME 40 mg (QD)	3151 (3151) 4 wk	Heartburn resolution was similar in PAN (66.9%) & EsOME (72.5%) arms.	B
Labenz 2009 ³³ [19298581] ^b	PAN 20 mg (QD) vs EsOME 20 mg (QD)	2766 (2766) 6 mo	Heartburn relapse was higher in PAN (17.4%) vs EsOME (9.8%).	B
Eggleston 2009 ³⁵ [19210493]	RAB 20 mg (QD) vs EsOME 20 mg (QD) vs EsOME 40 mg (QD)	1392 (1201) 4 wk	Similar rates of complete resolution of heartburn in RAB (58.4%), EsOME 40 mg QD (64.4%), & EsOME 20 mg QD (60.6%), P=0.184 Similar rates of complete resolution of regurg in RAB (60.6%), EsOME 40 mg QD (60.3%) & EsOME 20 mg QD (60.1%), P=0.363.	B
Glatzel 2007 ²⁹ [17489035]	PAN 40 mg (QD) vs EsOME 40 mg (QD)	585 (ITT - 561/ PP- 476) 4 wk	PAN non-inferior to EsOME (97.5% CI upper bound of PAN score w/in non-inferiority margin - Δ1.73). Median 3-day mean ReQuest GI score ^c similar for PAN (0.24) & EsOME (0.31), Higher rates of symptom relapse post Tx in EsOME (61%) vs PAN (51.1%), P=0.0216.	B
Bardhan 2007 ³⁰ [17539986]	PAN 40 mg (QD) vs EsOME 40 mg (QD)	582 (418) 12 wk	Same rates of complete endoscopic & symptomatic remission with PAN (76%) & EsOME (76%) in ITT population, & slightly higher rates in per protocol population (PAN: 93%, EsOME: 90%) Comparable rates of symptom relief in PAN (79%) & EsOME: (77%) which is also seen in per protocol population (PAN: 95%, EsOME: 92%)	B
Fass 2006 ³⁴ [16431305]	LAN 30 mg (BD) vs EsOME 40 mg (QD)	328 (282) 8 wk	LAN non-inferior to EsOME (lower limit of the 90%CI > -10). Similar % of heartburn free days (EsOME: 54.4%, LAN: 57.5%), % of epigastric pain free days (EsOME: 65%, LAN: 66.9%) & % of acid regurg free days (EsOME: 60.3%, LAN: 65.3%) NS differences in change in heartburn, epigastric pain & acid regurg from baseline to end of study in both groups.	B
Scholten 2007 ³¹ [17358101]	PAN 20 mg (O-D) vs EsOME 20 mg (O-D)	236 (199) 24 wk	Lower mean intensity of heartburn ^d in PAN (1.12) vs EsOME (1.32), P=0.012. Mean intensity of acid eructation: NS	B
Vcev 2006 ³² [17058517]	PAN 40 mg (QD) vs EsOME 40 mg (QD)	180 (176) 8 wk	Similar heartburn-free days for EsOME (70.2%) & PAN (69.8%).	B
Fock 2005 ³⁶	RAB 10 mg (QD) vs	134 (127)	NS differences in Time to first 24-hr	B

Study Year [UI]	Comparisons: Drug Name Dose (Frequency)	N_E (N_{FU}) F/U duration	Results	Quality
[15918196]	EsOME 20 mg (QD)	4 wk	<p>heartburn & regurg free interval (RAB<EsOME), Time to first 48-hr heartburn (RAB>EsOME)& regurg free interval(RAB<EsOME)</p> <p>Among pts w/ both heartburn & acid regurg, satisfactory symptom relief ↑ in RAB (92.5%) vs EsOME (79.4%), P< 0.05</p> <p>NS difference in patient-perceived symptom improvement (RAB: 96.4%, EsOME: 87.9%).</p> <p>RAB led to a more rapid resolution of heartburn (8.5 days versus 9 days for EsOME, P=0.265) and acid regurgitation (6 days versus 7.5 days for EsOME, P=0.405)</p>	
Pai 2007 ³⁷ [17696229]	DexRAB 10 mg (QD) vs RAB 20 mg (QD)	50 (50) 28 d	<p>NS change in heartburn & regurg scores^c from baseline in DexRAB (-34.8, -40 respectively) & RAB (-32.4, -28.4 respectively)</p> <p>↑ proportion of patients w/ ≥50% improvement of regurg scores in DexRAB (96%) vs RAB (60%), P<0.05.</p>	C Details of outcome measure not reported, no power calculations

^a Symptoms included heartburn, acid regurgitation, dysphagia, epigastric pain/discomfort, retrosternal tightness, burping/ belching, nausea/vomiting, fullness, lower abdominal pain, and flatulence. The intensity of symptoms was scored as none (0), mild (1), moderate (2), and severe (3) by investigators.

^b Maintenance phase study of Labenz 2009 [19222417] (which is the healing/active phase study).

^c ReQuest-GI comprises 4 dimensions of acid complaints, upper abdominal stomach complaints, lower abdominal/digestive complaints and nausea. Each dimension's score is a product of its intensity and frequency. The ReQuest-GI score is sum of the weighted scores of its four dimensions.

^d Intensity of heartburn on a 4-point scale.

^e Measured using visual analog scales. Details not provided.

Table 11. Comparison of different PPIs – Quality of Life

Study Year [U]	Comparisons: Drug Name Dose (Frequency)	N_E (N_{FU}) F/U duration	Results	Quality
Eggleston 2009 ³⁵ [19210493]	RAB 20 mg (QD) vs EsOME 20 mg (QD) vs EsOME 40 mg (QD)	1392 (1201) 4 wk	SF-36 ^a (all domains): ↑ from baseline for all PPI groups, P<0.05; Greatest improvements: Bodily pain, Role-physical, Role-emotional NS differences between Tx groups	B

^a SF-36 contains 8 scales and 2 summary scores with a range of scores from 0 -100; higher scores indicate better functioning and well-being.

Table 12. Comparison of different PPIs - Endoscopic Esophagitis Healing

Study Year [UI]	Comparisons: Drug Name Dose (Frequency)	N _E (N _{FU})	Results	Quality
		F/U duration		
Goh 2007 ²⁷ [17301646]	PAN 20 mg (QD) vs EsOME 20 mg (QD)	1316 (ITT– 1303 / PP- 1005)	Equal rates of endoscopic & symptomatic remission ^a for PAN (93%) and EsOME (93%) (ITT analysis: PAN (84%) and EsOME (85%)).	A
Bardhan 2007 ³⁰ [17539986]	PAN 40 mg (QD) vs EsOME 40 mg (QD)	582 (418) 12 wk	Similar rates for endoscopic healing for PAN (98%) and EsOME (94%) (ITT analysis: PAN (91%) and EsOME (88%)).	B
Vcev 2006 ³² [17058517]	PAN 40 mg (QD) vs EsOME 40 mg (QD)	180 (176) 8 wk	Similar healing rates of erosive oesophagitis w/ EsOME (92.2%) & PAN (91.1%).	B
Pai 2007 ³⁷ [17696229]	DexRAB 10 mg (QD) vs RAB 20 mg (QD)	50 (50) 28 d	Greater change in % of patients w/ esophagitis from baseline in DexRAB (52% points – 84% to 32%) vs RAB (32% points – 92% to 32 %).	C Details of outcome measure not reported, no power calculations

^a Combined symptomatic and endoscopic remission was defined as the absence of endoscopic findings (GERD Los Angeles grades A-D) and 'no' or 'mild' heartburn and acid regurgitation. Symptomatic non-relapse was defined as 'no' or 'mild' symptom severity for the variables of heartburn and acid regurgitation.

Table 13. Comparison of different PPIs – Antacid Medication Use

Study Year [U]	Comparisons: Drug Name Dose (Frequency)	N_E	Results	Quality
		(N_{FU}) F/U duration		
Scholten 2007 ³¹ [17358101]	PAN 20 mg (O-D) vs EsOME 20 mg (O-D)	236 (199) 24 wk	↑ average daily antacid use w/ PAN (0.31 tablets/d) vs EsOME (0.23 tablets/d).	B

Table 14. Comparison of different dosages as well as different dosing regimens of the same PPIs – Symptom Assessment

Study Year [UI]	Comparisons: Drug Name Dose (Frequency)	N _E (N _{FU}) F/U duration	Results	Quality
EsOME – Different Dosages				
Johnson 2005 ³⁹ [16128933]	EsOME 20 mg (QD) vs EsOME 40 mg (QD) vs Placebo	675 (642) 4 wk	Relief of nighttime heartburn symptoms w/ ESOME 40 mg QD (53.1%), ESOME 20 mg QD (50.5%) vs placebo (12.7%), P<0.0001	B
Giannini 2008 ³⁸ [18289194]	EsOME 40 mg (QD) vs EsOME 20 / 40 mg (QD, determined by endoscopy)	612 (551) 24 wk	Response to empirical Tx ^a (EsOME 40 mg, QD) – 71.8% was similar to endoscopy-based Tx (EsOME 20 / 40 mg, QD)- 68.3% at 24 wk (P=0.389)	B
LAN – Different Dosing Regimens				
Cibor 2006 ⁵³ [17357336]	LAN 30 mg (O-D) vs LAN 15 mg (QD) vs LAN 30 mg 4-wk course (intermittent therapy)	65 (60) 12 mo	↓ intensity of symptoms ^b for LAN 30 mg O-D and LAN 15 mg QD as compared to LAN 30 mg intermittent Tx, P<0.05	B
Mine 2005 ⁴² [16105122]	LAN 15 mg (QD) for 16 wk (No step group) vs LAN 30 mg (QD) for 8 wk, followed by FAM 20 mg (BD) for 8 wk (Step down to FAM group) vs LAN 30 mg (QD) or 8 wk followed by LAN 15 mg (QD) for 8 wk (Step down to LAN group)	43 (43) 16 wk	Heartburn, regurg and dysphagia disappeared in no step and step down to LAN groups (1 patient in no step had residual heartburn and 1 person in step down to LAN had residual regurg) but remained to some degree in step down to FAM group.	C Poor description of methods, small sample size
DexLAN – Different Dosages				
Fass 2009 ⁴³ [19392864]	DexLAN 30 mg (QD) vs DexLAN 60 mg (QD) vs Placebo	947 (873) 4 wk	The median % of 24-h heartburn-free days was significantly greater in both the DexLAN 30 mg (54.9%) and DexLAN 60 mg (50%) as compared w/ placebo (18.5%), P<0.00001 ↓ symptom scores for DexLAN 30 mg and DexLAN 60 mg vs placebo, P<0.005	A
Metz 2009 ⁴⁴ [19210298]	DexLAN 30 mg (QD) vs DexLAN 60 mg (QD) vs Placebo	445 (221) 6 mo	↑ proportion of patients w/ no heartburn in DexLAN 60 mg (63%) and DexLAN 30 mg (67%) as compared to placebo (17%), P<0.0025	C 50% loss to follow-up
Howden 2009 ⁴⁵ [19681809]	DexLAN 60 mg (QD) vs DexLAN 90 mg (QD) vs Placebo	451 (230) 6 mo	↑ proportion of patients w/ no heartburn in DexLAN 60 mg (95.8%) and DexLAN 90 mg (94.4%) as compared to placebo (19.2%), P<0.00001	C 88% loss to follow-up in the placebo group
PAN – Different Dosages				
Pai 2006 ⁴⁶ [17009401]	S-PAN (20 mg QD) vs racemic PAN (40 mg QD)	369 (369) 28 d	↓ in all symptom scores (heartburn, regurg, bloating, dysphagia, nausea) in both groups ↑ proportion of patients w/ relief from heartburn & acid regurg w/ s-PAN 20 mg QD (85.5% & 92.9%, respectively) than w/ racemic PAN 40 mg QD (74.4% & 82.4%, respectively), P=0.01 & P=0.004, respectively	C no power calculations, baseline characteristics not adequately reported, poor diagnostic quality
Scholten	PAN 40 mg (O-D) vs	548 (465)	↓ perceived average daily symptom	C

Study Year [UI]	Comparisons: Drug Name Dose (Frequency)	N_E (N_{FU}) <u>F/U duration</u>	Results	Quality
2005 ⁴⁷ [16113546]	PAN 20 mg (O-D) vs Placebo	28 wk	load (heartburn, epigastric pain, acid regurg) for PAN 40 mg O-D (2.71) and PAN 20 mg O-D (2.91) vs placebo (3.93), $P < 0.001$	Poor description of methods

^a Responders classified by symptom score. A responder at the 24-wk period was a patient whose sum of symptom scores over the last 7 days before the visit was 0 or 1.

^b Intensity of symptoms was rated each time using the Visual-Analog Scale (VAS) from 0-10 points.

Table 15. Comparison of different dosages as well as different dosing regimens of the same PPIs – Quality of Life

Study Year [UI]	Comparisons: Drug Name Dose (Frequency)	N_E (N_{FU}) F/U duration	Results	Quality
EsOME – Different Dosages				
Johnson 2005 ³⁹ [16128933]	EsOME 20 mg (QD) vs EsOME 40 mg (QD) vs Placebo	675 (642) 4 wk	↑ rates of complete resolution and relief of GERD-associated sleep disturbances in EsOME 40 mg QD & 20 mg QD groups versus placebo (P<0.0001) ↑ in good sleep quality (PSQI ≤ 5) ^a with EsOME 40 mg (46%), EsOME 20 mg (57%) versus placebo (36%), P<0.001 Greater improvement in global PSQI score (better sleep) with EsOME 40 mg (-3.64) and EsOME 20 mg (-4.00) versus placebo (-2.19), P<0.0001	B
Giannini 2008 ³⁸ [18289194]	EsOME 40 mg (QD) vs EsOME 20 / 40 mg (QD, determined by endoscopy)	612 (551) 4 wk	QOLRAD ^b : No difference in emotional, sleep, food/drink, vitality, physical / social components	B
DexLAN – Different Dosages				
Metz 2009 ⁴⁴ [19210298]	DexLAN 30 mg (QD) vs DexLAN 60 mg (QD) vs Placebo	445 (221) 6 mo	↑ (improvement) PAGI-QoL for DexLAN 60 mg QD and DexLAN 90 mg QD vs placebo, P<0.0025	C 50% loss to follow-up
Howden 2009 ⁴⁵ [19681809]	DexLAN 60 mg (QD) vs DexLAN 90 mg (QD) vs Placebo	451 (230) 6 mo	Higher mean change(improvement) in total PAGI-QoL scores ^a for DexLAN 60 mg QD and DexLAN 90 mg QD vs the placebo, P<0.0025 (except in relationship sub-scale). DexLAN 60 mg and DexLAN 90 mg maintained their PAGI-QoL while the placebo group reported a deterioration in QOL	C 88% loss to follow-up in the placebo group

^a Pittsburgh Sleep Quality Index (PSQI): 19-item questionnaire of sleep quality with 7 component scores with each component score ranged from 0 (best) –3 (worst) to get a global PSQI score range from 0 - 21. A global score >5 indicates poor sleep quality.

^b Quality of Life in Reflux and Dyspepsia (QOLRAD) 25 items questionnaire of five dimensions with each item scored on a 7-grade Likert scale; lower values indicate more severe impact on daily functioning.

Table 16. Comparison of different dosages as well as different dosing regimens of the same PPIs – Esophagitis healing

Study Year [UI]	Comparisons: Drug Name Dose (Frequency)	N_E (N_{FU}) F/U duration	Results	Quality
EsOME – Different Dosages				
Katz 2007 ⁴⁰ [17305763]	EsOME 10 mg (QD) vs EsOME 40 mg (QD)	169 (103) 4 wk	↑ healing of esophagitis in EsOME 40 mg (86%) as compared to EsOME 10 mg (55%)	C 39% drop-out rates
LAN – Different Dosing Regimen				
Mine 2005 ⁴² [16105122]	LAN 15 mg (QD) for 16 wk (No step group) vs LAN 30 mg (QD) for 8 wk, followed by FAM 20 mg (BD) for 8 wk (Step down to FAM group) vs LAN 30 mg (QD) or 8 wk followed by LAN 15 mg (QD) for 8 wk (Step down to LAN group)	43 (43) 16 wk	Esophagitis healing was seen in all groups (NS)	C Poor description of methods, small sample size
DexLAN – Different Dosages				
Metz 2009 ⁴⁴ [19210298]	DexLAN 30 mg (QD) vs DexLAN 60 mg (QD) vs Placebo	445 (221) 6 mo	↑ esophagitis healing in DexLAN 60 mg (82.5%) & DexLAN 30 mg (74.9%) vs placebo (27.2%), P<0.00001	C 50% loss to follow-up
Howden 2009 ⁴⁵ [19681809]	DexLAN 60 mg (QD) vs DexLAN 90 mg (QD) vs Placebo	451 (230) 6 mo	↑ esophagitis healing in DexLAN 60 mg (86.6%) & DexLAN 90 mg (82.1%) vs placebo (25.7%), P<0.00001	C 88% loss to follow-up in the placebo group
PAN – Different Dosages				
Pai 2006 ⁴⁶ [17009401]	S-PAN 20 mg (QD) vs racemic PAN 40 mg (QD)	369 (369) 28 d	NS differences in healing of esophagitis and erosions between the groups	C No power calculations, baseline characteristics not adequately reported, poor diagnostic quality

Table 17. Comparison of different dosages as well as different dosing regimens of the same PPIs – Acid Control

Study Year [UI]	Comparisons: Drug Name Dose (Frequency)	$\frac{N_E}{(N_{FU})}$ F/U duration	Results	Quality
EsOME – Different Dosages				
Katz 2007 ⁴⁰ [17305763]	EsOME 10 mg (QD) vs EsOME 40 mg (QD)	$\frac{169}{4 \text{ wk}}$ (103)	↑ acid control (Percent of time w/ pH >4 after 5 days of Tx) in EsOME 40 mg (72%) vs EsOME 10 mg (41%)	C 39% drop-out rates
EsOME – Different Dosing Regimen				
Vasiliadis 2010 ⁴¹ [19809412]	EsOME 40 mg (QD) vs EsOME 40 mg (BD) vs EsOME 40 mg (Once every other day)	$\frac{75}{30 \text{ d}}$ (73)	Abnormal acid exposure ($\geq 4\%$ of total time w/ Ph<4) in EsOME 40 mg taken once every other day (7%) and not in EsOME 40 mg BD (0.7%) & EsOME 40 mg QD (1.5%). Abnormal De Meester score (≥ 14.7) in EsOME 40 mg taken once every other day (29.4) and not in EsOME 40 mg QD (6.4) & EsOME 40 mg BD (3.9).	B

Table 18. Comparison of different dosages as well as different dosing regimens of the same PPIs - Antacid Medication Use and Treatment Satisfaction

Study Year [UI]	Comparisons: Drug Name Dose (Frequency)	N_E (N_{FU}) F/U duration	Results	Quality
EsOME – Different Dosages				
Johnson 2005 ³⁹ [16128933]	EsOME 20 mg (QD) vs EsOME 40 mg (QD) vs Placebo	675 (642) 4 wk	Lower use of daily antacid rescue tablets in EsOME 40 mg QD ($1.0 \pm$ 1.45 tablets/day) and EsOME 20 mg QD (0.9 ± 1.41 tablets/day) versus placebo (1.7 ± 1.61 tablets/day), $P < 0.001$	B
LAN – Different Dosing Regimen				
Cibor 2006 ⁵³ [17357336]	LAN 30 mg (O-D) vs LAN 15 mg (QD) vs LAN 30 mg 4-wk course (intermittent therapy)	65 (60) 12 mo	Satisfaction ^a : \uparrow % of patients completely satisfied w/ Tx in LAN 30 mg O-D group (90%) and LAN 15 mg QD (95%) vs LAN 30 mg intermittent Tx (85%), $P < 0.05$	B
DexLAN – Different Dosages				
Fass 2009 ⁴³ [19392864]	DexLAN 30 mg (QD) vs DexLAN 60 mg (QD) vs Placebo	947 (873) 4 wk	\uparrow % of days w/o rescue medication in DexLAN MR 30 mg (63%) and 60 mg (63%) groups vs placebo (37.3%), $P < 0.00001$	A
PAN – Different Dosages				
Scholten 2005 ⁴⁷ [16113546]	PAN 40 mg (O-D) vs PAN 20 mg (O-D) vs Placebo	548 (465) 28 wk	Lower average daily antacids intake w/ PAN 40 mg O-D ($0.33 \pm$ 0.52 tablets/day) and PAN 20 mg O-D (0.45 ± 0.79 tablets/day) vs placebo (0.68 ± 0.77 tablets/day), $P = 0.0034$	C Poor description of methods

^a Satisfaction was measured on a 4-point Verbal Rating Scale (VRS; 0 – completely dissatisfied from treatment, 1 – rather dissatisfied, 2 – rather satisfied, 3 – completely satisfied).

Table 19. Comparisons between once daily and on-demand dosing regimens of commonly used PPIs – Symptom Assessment

Study Year [UI]	Comparisons: Drug Name Dose (Frequency)	N_E (N_{FU}) F/U duration	Results	Quality
EsOME – Different Dosing Regimen				
Szucs 2009 ⁴⁹ [18783388]	EsOME 20 mg (O-D) vs EsOME 20 mg (QD)	1935 (1904) 6 mo	↑ proportion of patient w/o symptoms (heartburn & regurg) in EsOME 20 mg QD (86%) vs EsOME 20 mg O-D (80%), P<0.01	B
Sjosted 2005 ⁴⁸ [16091055]	EsOME 20 mg (O-D) vs EsOME 20 mg (QD)	477 (370) 6 mo	No difference for overall symptomatic relapse between EsOME 20 mg QD (5.0%) and EsOME 20 mg O-D (5.7%), P=0.77	B
RAB – Different Dosing Regimen				
Morgan 2007 ⁵¹ [18080054]	RAB 20 mg (O-D) vs RAB 20 mg (QD)	268 (234) 6 mo	↑ % of heartburn-free days w/ RAB 20 mg QD (90.3%) vs RAB 20 mg O-D (64.6%), P<0.0001	B
Bour 2005 ⁵² [15801915]	RAB 10 mg (O-D) vs RAB 10 mg (QD)	152 (132) 6 mo	↑ % of patients w/ symptoms relief w/ RAB 10 mg QD (86.4%) vs RAB 10 mg O-D (74.6%), P= 0.065 ↑ recurrence rate at the end of Tx w/ RAB 10 mg O-D (21.1%) vs. RAB 10 mg QD (13.6%), P=0.065	B

Table 20. Comparisons between once daily and on-demand dosing regimens of commonly used PPIs – Quality of Life

Study Year [UI]	Comparisons: Drug Name Dose (Frequency)	$\frac{N_E}{(N_{FU})}$ F/U duration	Results	Quality
EsOME – Different Dosing Regimen				
Pace 2005 ⁵⁰ [16098002]	EsOME 20 mg (O-D) vs EsOME 20 mg (QD)	$\frac{6017}{(5265)}$ 26 wk	QOLRAD ^b : Improvement in all dimensions w/ EsOME 20 mg QD vs EsOME 20 mg O-D, P<0.0001	C No blinding
RAB – Different Dosing Regimen				
Morgan 2007 ⁵¹ [18080054]	RAB 20 mg (O-D) vs RAB 20 mg (QD)	$\frac{268}{(234)}$ 6 mo	↑ QoL ^a in RAB 20 mg QD ↓ QoL in RAB 20 mg O-D (P<0.05). Change in QoL between groups: P<0.05.	B

^a Patient assessment of upper gastrointestinal disorders – quality of life questionnaire (PAGIQOL): 30-item questionnaire about the quality of life. The range for total PAGI-QOL is 0-5, with lower scores indicating better health.

Table 21. Comparisons between once daily and on-demand dosing regimens of commonly used PPIs – Esophagitis healing

Study Year [UI]	Comparisons: Drug Name Dose (Frequency)	N_E (N_{FU}) F/U duration	Results	Quality
EsOME – Different Dosing Regimen				
Sjosted 2005 ⁴⁸ [16091055]	EsOME 20 mg (O-D) vs EsOME 20 mg (QD)	477 (370) 6 mo	↑ proportion of pts in endoscopic remission in EsOME 20 mg QD (81%) vs EsOME 20 mg O-D (58%), P<0.0001	B

Table 22. Comparison of PPI w/ Over the Counter Doses of approved PPIs (OME 20 mg, LAN 15 mg) – Symptom Assessment

Study Year [UI]	Comparisons: Drug Name Dose (Frequency)	N_E (N_{FU}) F/U duration	Results	Quality
Lightdale 2006 ⁵⁴ [16773434]	EsOME 20 mg (QD) vs OME 20 mg (QD)	1176 (1106) 8 wk	NS differences b/w groups at 4 wk for resolution of heartburn (60.6% EsOME vs 60.5% OME; P=0.995), proportion of heartburn-free day (72.6% EsOME vs 70.9% OME; P = 0.354) or nights (85.7% EsOME vs 83.2% OME, P = 0.069)	A
Devault 2006 ⁶⁰ [16682260]	EsOME 20 mg (QD) vs LAN 15mg (QD)	1026 (1001) 6 mo	↑ endoscopic/symptomatic remission rate ^a in EsOME (84.8%) vs LAN (75.9), P=0.0007.	B
Pace 2005 ⁵⁷ [16024305]	RAB 20 mg (QD) vs OME 20 mg (QD)	560 (442) 8 wk	↓ time to the first day of satisfactory heartburn relief w/ RAB (2.8±0.2 d) vs OME (4.7±0.5 d), P= 0.0045 Similar time to complete heartburn relief for RAB (7.2 d) vs OME (8.4 d), NS Similar change in % of patients with good reflux control w/ RAB (7% to 90%) vs OME (5.5% to 90.7%).	B
Pilotto 2007 ⁵⁵ [17724802]	OME 20 mg (QD) vs LAN 30 mg (QD) vs PAN 40 mg (QD) vs RAB 20 mg (QD)	320 (301) 2 mo	↑ rates of disappearance of heartburn with PAN (100%) & RAB (100%) vs OME (86.9%) & LAN (82.4%), P<0.05 for PAN vs OME, RAB vs OME, LAN vs PAN, LAN vs RAB. ↑ rates of disappearance of acid regurg for OME (100%) & PAN (92.2%) vs LAN (75%) & RAB (90.1%), P<0.05 for LAN vs OME, LAN vs PAN, LAN vs RAB. ↑ rates of disappearance of epigastric pain for RAB (100%), PAN (95.2%) & OME (95%) vs LAN (82.6%), P<0.05 for LAN vs OME, LAN vs PAN, LAN vs RAB.	B
Chen 2005 ⁵⁹ [15918199]	EsOME 40 mg (QD) vs OME 20 mg (QD)	48 (44) 8 wk	Similar improvement in heartburn score from baseline for EsOME (-22.3 ± 2.1) and OME (-21.4 ± 2.2), NS	C Small sample size, no power calculation

^a Kaplan-Meier estimate of endoscopic and symptomatic remission rate of erosive esophagitis. Endoscopic / symptomatic remission was defined as no detectable EE and no study discontinuation as a result of reflux symptoms.

Table 23. Comparison of PPI w/ Over the Counter Doses of approved PPIs (OME 20 mg, LAN 15 mg) – Quality of Life

Study Year [UI]	Comparisons: Drug Name Dose (Frequency)	N_E (N_{FU}) F/U duration	Results	Quality
Pace 2005 ⁵⁷ [16024305]	RAB 20 mg (QD) vs OME 20 mg (QD)	560 (442) 8 wk	Similar change from baseline in % patients w/ very good/good general well being ^a on RAB (47.6%; 41.7 to 89.3%) & OME (42.8%; 43.5 to 86.3%).	B
Tepes 2009 ⁵⁸ [19453031]	OME 20 mg (O-D) vs OME 10 mg (QD) vs OME 20 mg (QD)	216 (186) 12 Mo	Similar mean health-related QoL scores ^b (range 1-10) after Tx period w/ OME 20 mg O-D (9.4), OME 10 mg QD (9.7) and OME 20 mg QD (9.8), NS.	B

^a General well being was self reported on a 5-point Likert scale: 0 (very good), 1 (good), 2 (fair), 3 (poor) 4 (very poor).

^b Health-related quality of life assessed using a visual analogue scale: Range 1 to 10 (1 worst; 10 best)

Table 24. Comparison of PPI w/ Over the Counter Doses of approved PPIs (OME 20 mg, LAN 15 mg) - Esophagitis Healing

Study Year [UI]	Comparisons: Drug Name Dose (Frequency)	N_E (N_{FU}) F/U duration	Results	Quality
Lightdale 2006 ⁵⁴ [16773434]	EsOME 20 mg (QD) vs OME 20 mg (QD)	1176 (1106) 8 wk	Similar healing rates for EsOME (90.6%) and OME (88.3%), P=0.621.	A
Zheng 2009 ⁵⁶ [19248200]	OME 20 mg (QD) vs LAN 30 mg (QD) vs PAN 40 mg (QD) vs EsOME 40 mg (QD)	274 (264) 8 wk	Similar healing rates for OME (87.7%), LAN (89.6%), PAN (91.1%), EsOME (95.4%), NS.	A
Devault 2006 ⁶⁰ [16682260]	EsOME 20 mg (QD) vs LAN 15mg (QD)	1026 (746) 6 mo	↑ rates of endoscopic remission ^a for EsOME (86.9%) vs LAN (77.8%), P=0.0003.	B
Pace 2005 ⁵⁷ [16024305]	RAB 20 mg (QD) vs OME 20 mg (QD)	560 (442) 8 wk	RAB (97.9%) similar to OME (97.5%) in endoscopic healing.	B
Pilotto 2007 ⁵⁵ [17724802]	OME 20 mg (QD) vs LAN 30 mg (QD) vs PAN 40 mg (QD) vs RAB 20 mg (QD)	320 (301) 2 mo	↑ healing rates for PAN (90%) & RAB (89%) vs OME (75%) & LAN (85%), P<0.05 for PAN vs OME, RAB vs OME.	B
Tepes 2009 ⁵⁸ [19453031]	OME 20 mg (O-D) vs OME 10 mg (QD) vs OME 20 mg (QD)	216 (186) 12 Mo	Stratified by baseline esophagitis status: 1) No esophagitis: ↑ endoscopic remission with OME 10 mg QD (90.5%,) vs OME 20 mg O-D (57.7%), P<0.05 (ITT analysis: OME 10 mg QD (76%,) vs OME 20 mg O-D (48.4%), P<0.05. 2) Grade A esophagitis: ↑ endoscopic remission with OME 10 mg QD (90.3%,) vs OME 20 mg O-D (65.1%), P<0.01. 3) Grade B esophagitis: NS difference in endoscopic remission rates.	B
Chen 2005 ⁵⁹ [15918199]	EsOME 40 mg (QD) vs OME 20 mg (QD)	48 (44) 8 wk	↑ rate of esophagitis healing w/ EsOME (72.7%) vs OME (50%), (ITT analysis: EsOME (76.4%) vs OME (45.5%).	C Small sample size, no power calculation

^a No detectable erosive esophagitis (endoscopic remission)

Key Question 1E. Surgical treatments

Synopsis

The 2005 CER found little to no difference between laparoscopic total and partial fundoplication, laparoscopic fundoplication with and without division of short gastric vessels, and open total and partial fundoplication in producing symptom relief, QoL improvement, or decreasing usage of antisecretory medications. In the present update, the inclusion of four additional RCTs and seven non-randomized comparative studies did not alter the conclusions of the original report with respect to these comparisons.

Detailed analysis

Comparative effectiveness of surgery (Table 25)

Five RCTs (a total of 595 patients) and seven non-randomized comparative studies (a total of 3482 patients) of fundoplication for the treatment of GERD were identified for inclusion in the present update. Three RCTs⁶³⁻⁶⁵ and five non-randomized comparative studies⁶⁶⁻⁷⁰ compared two different approaches to laparoscopic fundoplication techniques: total versus partial, and with versus without division of short gastric vessels. Two RCTs⁷¹⁻⁷³ and one non-randomized comparative study⁷⁴ examined laparoscopic versus open fundoplication.

Mean followup in these studies ranged from 5 to 10.3 years, and sample sizes from 99 to 844. All but one RCT⁶³ were graded C. Among the non-randomized comparative studies, two studies^{66,67} were graded B and four^{68-70,73} were graded C.

Total versus partial fundoplication

One RCT⁶³ and five non-randomized comparative studies⁶⁶⁻⁷⁰ compared laparoscopic total versus partial fundoplication. No significant differences in GERD symptoms between groups were observed among any of the studies. One non-randomized comparative study reported that patients who underwent partial fundoplication had an odds ratio of 1.427 (95 percent CI 1.009-2.019) of postoperative medication use compared with patients who had total fundoplication.⁷⁰ Similarly, another non-randomized comparative study reported a significantly lower proportion of PPI users in the total fundoplication group compared with the partial fundoplication group (total: 14 percent vs. partial: 41 percent, $P < 0.01$).⁶⁸ Two non-randomized comparative studies reporting GIQIL scores did not find any significant difference between groups.^{66,68}

Total laparoscopic fundoplication with versus without division of short gastric vessel

Two RCTs^{64,65} and two non-randomized comparative studies^{69,70} evaluated laparoscopic fundoplication with versus without division of the short gastric vessels. Both RCTs (one⁶⁵ grade B and one⁶⁴ grade C) followed patients for 10 years, and did not find differences in medication use, GERD symptoms, or quality of life measures. One of the two non-randomized studies followed 709 patients for 7.1 years and found no significant difference in recurrence of GERD, dysphagia, gas bloat, or Visick grades.⁶⁹ Similarly, the other non-randomized study, with 844 patients and 5.9 years of follow-up did not find significant differences in the proportion of antireflux medication users between the two groups (with division: 61 percent vs. without division: 63 percent).⁷⁰

Laparoscopic versus open total fundoplication

Two RCTs⁷¹⁻⁷³ and one non-randomized comparative study⁷⁴ compared laparoscopic with open total fundoplication. Both RCTs were graded C, and reported no significant differences in medication use, diagnostic test results, GERD symptoms, or quality of life.⁷¹⁻⁷³ Similarly, the non-randomized comparative study (grade C) did not find significant differences in GERD symptoms between the two groups.⁷⁴

Long-term effectiveness of surgery (Table 26)

Five cohort studies provided long-term outcome (mean 5 to 6.4 years) data on fundoplication.⁷⁵⁻⁷⁹ Sample sizes ranged from 100 to 515. Two^{75,79} were graded B and three were graded C.⁷⁶⁻⁷⁸

Three of the five cohort studies reported significant improvement in GERD symptoms.^{75,77,78} One study of laparoscopic partial fundoplication reported significant decreases in the percentage of time with pH < 4 after surgical treatment (17.8 percent vs. 0.9 percent, P < 0.0005), as well as significant decreases in DeMeester score (4.3 vs. 0.5, P < 0.0005).⁷⁵ The proportion of patients who were off all medications at followup was over 70 percent in two studies.^{76,79} One cohort study of laparoscopic total fundoplication reported significant improvements in quality of life measure (32-item QoL scale ranging from 0-96 points, 56.3 vs. 74, P < 0.001).⁷⁸

Table 25. Comparative studies evaluating the long-term outcomes of different types of fundoplication

Author Year	Study design Follow-up Duration	Enroll/ Final	Objective Outcomes			Subjective Outcomes		Quality Comments
			Off PPI	Off all meds	Diagnostic tests	Symptoms	Quality of life	
Laparoscopic total vs partial fundoplication								
Cai 2008 ⁶³ [18942055]	RCT 10 y	54/48	81%	nd	Nd	Heartburn 15% Dysphagia 52%	Satisfied 94%	B
		53/41	73%	nd	nd	Heartburn 20% Dysphagia 34%	Satisfied 93%	
Dallemagne 2006 ⁶⁶ [16333553]	nRCT 10.3 y	68/49	91% at 5 y	nd	Normal barium swallow at 5 y 100% (36/36)	Heartburn 29% Dysphagia 22% GERD-free 93%	GIQLI 115.5 ± 20.8	B
		32/20	92% at 10 y		Intrathoracic migration at 5 y 33% (7/21)	Heartburn 35% Dysphagia 25% GERD-free 82%	GIQLI 108.5 ± 27.9	
Hafez 2008 ⁶⁷ [18449599]	nRCT 7.8 y	89/89	nd	nd	nd	Insufficient GERD symptom control at 93 mo 14%	nd	B Inconsistent sample size, only p-value reported for multivariate analyses
		45/45	nd	nd	nd	Insufficient GERD symptom control at 93 mo 9%	nd	
Fein 2008 ⁶⁸ [18766417]	nRCT 5-10 y	85/74	86%	92%	Esophagitis 4% Haital hernia 6% LES pressure 9.1 ± 4.1 LES length 3.5 ± 0.7 (n=48)	Heartburn 30% Regurg 15% Dysphagia 31%	GIQLI 109.8 ± 24.4	C High loss to f/u, unclear pt flow, retrospective, historical control
		32/25 ^a	59%	6%	Esophagitis 0% Haital hernia 11% LES pressure 8.9 ± 5.9 LES length 3 ± 0.6 (n=19)	Heartburn 29% Regurg 32% Dysphagia 30%	GIQLI Anterior: 104.1 ± 26.9 Toupet: 115.1 ± 21.0	
Pessaux 2005 ⁶⁹ [16230543]	nRCT 7.1 y	711/711	nd	nd	nd	Dysphagia 8% Visick I and II 93%	nd	C Unclear eligibility criteria, incomplete medical f/u exam in some pt
		629/629	nd	nd	nd	Dysphagia 2% Visick I and II 93%	nd	

Wijnhoven 2008 ⁷⁰ [18071830]	nRCT 5.9 y	525/525 319/319	nd nd	67% 56% ^b	nd nd	Heartburn 38% Regurg 38%	nd nd	C
Laparoscopic total fundoplication with vs without division of short gastric vessels								
Yang 2008 ⁶⁵ [18156921]	RCT 10 y	50/44	91%	nd	nd	Heartburn 11% Regurg 9%	nd	B
		52/44	80%	nd	nd	Heartburn 18% Regurg 17%	nd	
Mardani 2009 ⁸⁰ [19016274]	RCT 10 y	52/42	nd	83%	nd	No reflux symptoms 90% Heartburn 10% Regurg 10% GSRs reflux score 1.4 ± 0.7* GSRs dysphagia score 2.0 ± 1.5*	PGWB 100.0 ± 17.2*	C Unclear recruitment criteria
		47/40		83%		No reflux symptoms 78% Heartburn 23% Regurg 18% GSRs reflux score 1.9 ± 1.4* GSRs dysphagia score 2.4 ± 1.6*	PGWB 92.7 ± 21.4*	
Pessaux 2005 ⁶⁹ [16230543]	nRCT 7.1 y	305	nd	nd	nd	GERD recurrence 13% Dysphagia 9% Visick I nad II 91%	nd	C Unclear eligibility criteria, incomplete medical f/u exam in some pt
		404	nd	nd	nd	GERD recurrence 9% Dysphagia 6% Visick I nad II 96%	nd	
Wijnhoven 2008 ⁷⁰ [18071830]	nRCT 5.9 y	110 734	nd nd	61% 63%	nd nd	Heartburn 38% Regurg 38%	nd nd	C
Laparoscopic vs open total fundoplication								
Draaisma 2006 ⁷¹ [16794387]; Broeders 2009 ⁷² [19801931]	RCT 5.3 y	98/79	nd	72%	% time pH<4 80% (n=10) End expiratory LES 1.7 ± 0.2 (n=48)	Heartburn 41% Regurg 29% Dysphagia 54% Visick I and II 92% (n=79)	General QoL VAS 65.3 (n=79)	C Objective data available in only a subset of pt

		79/69	nd	77%	% time pH<4 70% (n=10) End expiratory LES 1.5 ± 0.2 (n=49)	Heartburn 39% Regurg 19% Dysphagia 45% Visick I and II 91% (n=63)	General QoL VAS 61.4 (n=63)	
Salminen 2007 ⁷³ [17667497]	RCT 11 y	55/38	74%	59%	Esophagitis 5% Loose LES 5%	Heartburn/regurg 43% Dysphagia 59%	nd	C Treatment not given as randomized, high dropout, inconsistencies in reported results
		55/35	67%	60%	Esophagitis 6% Loose LES 26%	Heartburn/regurg 56% Dysphagia 39%	nd	
Trullenque 2005 ⁷⁴ [16004525]	nRCT 7 y	75/nd	nd	nd	nd	Heartburn 0% Regurg 0%	nd	C poor reporting of f/u length, dropout and pt characteristics, unclear analysis
		28/nd	nd	nd	nd	Heartburn 1 pt Regurg 0%	nd	

GIQLI: Gastrointestinal Quality of Life, PGWB: Psychological General Well-Being index, GSRS: Gastrointestinal Symptom Rating Scale

* mean ± SEM

^a This group includes 22 patients who underwent anterior fundoplication and 10 patients who underwent Toupet fundoplication.

^b Compared with patients with total fundoplication, patients with partial fundoplication had a odd ratio of 1.427 (95% CI 1.009-2.019) of postoperative medication use

Table 26. Cohort studies evaluating the long term outcomes of surgical procedures

Author Year	Study design Follow-up Duration	Enroll/ Final	Objective Outcomes			Subjective Outcomes		Quality Comments
			Off PPI	Off all meds	Diagnostic tests	Symptoms	Quality of life	
Zehetner 2006 ⁷⁵ [16391962]	Cohort laparoscopic partial fundoplication 5 y	100/87	nd ^a	nd	%time pH<4 Preoperative: 17.8% (normal value<4%) Postoperative: 0.9%	DeMeester score Preoperative: 4.27 @ 5 y: 0.47 Heartburn @ 5 y: 15%	Satisfaction: 96.6%	B Very small portion of patients for 24-h pH manometry
Rice 2006 ⁷⁶ [16549692]	Cohort laparoscopic partial fundoplication 6.4 y	117/100	5-11 y: 88%	5-11 y: 78%	nd	Heartburn using the analog scale (postoperative): score of 0 (n=46) score of 1-3 (n=34) score of 4-6 (n=11) score of ≥7 (n=9) less likely to describe dysphagia postoperatively	Overall satisfaction: score of 10 (n=35) score of 7-9 (n=35) score of 4-6 (n=17) score ≤3 (n=3)	C No information on patient characteristics
Biertho 2006 ⁷⁷ [16823657]	Cohort laparoscopic total fundoplication 5 y	515/277	nd	nd	nd	GERD score difference (pre-5yrs): 21.5 (p<0.001) GI score (pre-5yrs): 2.4 (p<0.05)	nd	C High loss to follow-up, no reason provided
Teixeira 2009 ⁷⁸ [19453033]	Cohort laparoscopic total fundoplication 5.4 y	168/143	nd	nd	nd	Average of the difference (pre vs. post, score 0-3), *p<0.001 Heartburn +2.2* Regurgitation +2.0* Dysphagia +0.9*	56.3 ^b (preop) 74.0 @ 5 yr Net difference (p<0.001)	C Retrospective, no adjustment; QoL scale not externally validated; no power calculation
Oelschlager 2008 ⁷⁹ [17970835]	Cohort laparoscopic total or partial fundoplication 5.8 y	288/288	nd	At 5 y: 73%	nd	Symptoms improved % (postop) Heartburn (90%), Regurgitation (92%) Dysphagia (75%)	nd	B

^a 3.5% of patients needed a regular PPI treatment postoperatively.

^b QoL (scale included GI and non-GI symptoms, medication, physical, emotional and psychosocial; maximum score of 96, the higher the score, the better)

Key Question 1F. Endoscopic treatments

Synopsis

The 2005 CER reviewed studies on four endoscopic procedures: EndoCinch™ Suturing System, Stretta®, Enteryx™, and the NDO Plicator™. The present report excluded Enteryx and the NDO Plicator because they are no longer available in the US. Stretta was removed from the US market but reintroduced in 2010 by a different manufacturer. Another device, EsophyX™, has been commercialized since the 2005 CER. Thus, we evaluated three endoscopic procedures: the EndoCinch Suturing System, Stretta, and EsophyX.

The EndoCinch Suturing System (Bard, Murray Hill, NJ) places sutures to create a submucosal plication in the gastric cardia. Stretta (Mederi Therapeutics, Greenwich, CT) involves application of radiofrequency energy to the lower esophageal sphincter through a catheter. EsophyX (EndoGastric Solutions, Redmond, WA) plicates the fundus to the anterior and left lateral wall of the distal esophagus slightly below the esophagogastric junction in order to tighten the lower esophageal sphincter.

The effectiveness of the endoscopic procedures for the long-term management of GERD remains substantially uncertain. Similar to the 2005 CER, we found no study of direct comparisons between the different endoscopic treatments in this update. We found little or no difference between EndoCinch and sham, and between Stretta and sham. Five cohort studies assessed the efficacy of EsophyX. Better quality studies with longer follow-up are needed to determine the value of endoscopic procedures in the treatment of chronic GERD.

Detailed analysis

In the present update, three RCTs evaluated the efficacy of endoscopic treatments for GERD.⁸¹⁻⁸³ All three studies had short study durations (3 months to 1 year) and small sample sizes (40 to 46 patients).

In addition to RCTs, six cohort studies⁸⁴⁻⁸⁹ of EndoCinch™, five cohort studies⁹⁰⁻⁹⁵ of EsophyX™, and seven cohort studies⁹⁶⁻¹⁰² of Stretta™ or endoscopic radiofrequency treatment were identified in the present update.

The effectiveness of the EndoCinch Suturing System (Tables 27 and 28)

Of the two sham-controlled trials that evaluated EndoCinch, one A-rated study followed 40 patients for 3 months,⁸¹ and one B-rated study enrolled 44 patients for 1 year.⁸² One study reported a significantly greater proportion of patients who stopped or decreased PPI use in the EndoCinch group compared with the sham group at 3 months (65 percent vs. 25 percent, $P = 0.01$),⁸¹ whereas no difference was observed in the other study at both 3 months (50 percent vs. 33 percent, $P = \text{NS}$) and 1 year (45 percent vs. 24 percent, $P = \text{NS}$).⁸² Compared with sham, patients in the EndoCinch group had significantly better improvement in heartburn score at 3 months (EndoCinch: -8.6 ± 9.0 vs. sham: -0.9 ± 4.3 , $P < 0.01$), but not in regurgitation score (EndoCinch: -5.2 ± 8.3 vs. sham: -1.1 ± 4.2 , $P = \text{NS}$).⁸¹ Neither trial found significant differences in 24-hour pH study measures and quality of life between EndoCinch and sham.

Of the six cohort studies that evaluated EndoCinch, follow-up durations ranged from 6 to 41 months. Analyzed sample sizes were small, from 20 to 95 patients. Three studies were graded B,^{84,87,89} and three graded C.^{85,86,88} Significant improvements in heartburn were found in four studies.^{85,87-89} Of the two studies that reported quality of life outcome,^{84,85} one reported

significant improvement in SF-36 general and mental scores.⁸⁵ Two studies reported increased proportion of patients without esophagitis over the follow-up period, but statistical significance were not reported.^{87,89}

The effectiveness of EsophyX (Table 28)

Of the five cohort studies that evaluated EsophyX, follow-up duration ranged from 6 to 25 months. Apart from one study⁹² that enrolled 86 patients and was rated B, all other studies^{90,91,93-95} of EsophyX enrolled 26 or less than patients and were rated C. The proportion of patients who were off PPI at the end of the followup period ranged from 47 to 71 percent.⁹⁰⁻⁹⁵ Improvement of GERD-HRQL was reported by all five studies, of which two found significant results.^{94,95}

The effectiveness of Stretta (Tables 27 and 28)

One B-rated RCT randomized 43 patients into Stretta procedure or control groups, and followed for 1 year.⁸³ The proportion of patients who stopped or decreased PPI use was significantly greater in the Stretta group compared with the control group at 6 months (78 percent vs. 40 percent, $P = 0.01$) but it was not significant at 1 year (56 percent vs. 35 percent, $P = 0.16$). Similarly, there was significant difference in mean regurgitation score (higher is worse) at 6 months (Stretta: 1.3 ± 0.6 vs. control: 2.2 ± 1.3 , $P = 0.01$), but not at 1 year (Stretta: 1.2 ± 0.4 vs. control: 1.7 ± 1.4 , $P = 0.58$). This RCT did not find significant differences in heartburn score, SF-36 and Global REFLUX-QUAL scores, 24-hour pH study measures, and the proportion of patients with esophagitis between the two arms.

Of the seven cohort studies that evaluated Stretta, follow-up durations ranged from 6 months to 4 years. Analyzed sample sizes were relatively small, from 32 to 93 patients. Three studies were graded B,^{96,99,102} and four graded C.^{97,98,100,101} Of the six studies that reported changes in GERD symptoms,^{96-98,100-102} four found significant improvements during the follow-up periods.^{96,100-102} Also, five studies reported statistically significant improvement in quality of life,^{96,99-102} and one did not.⁹⁷ Two studies reported increased proportion of patients without esophagitis during the follow-up period, but statistical significance were not reported.^{96,102} At the end of the follow-up, the proportion of patients who were off PPI in these seven studies ranged from 6 percent to 86 percent,⁹⁶⁻¹⁰² but only two studies reported statistical significant difference between baseline and follow-up.^{101,102}

Table 27. Comparative studies evaluating endoscopic treatment for GERD

Author Year	Study design Follow-up Duration	Intervention	Enroll/ Final	Objective Outcomes			Subjective Outcomes		Quality Comments
				Off PPI	Off All Meds	Diagnostic tests	Symptom improved	Quality of life	
Schwartz 2007 ⁸¹ [16763053] ^a	RCT ^b 3 mo	EndoCinch™	20/20	40% of pt reduced PPI use by >95%	nd	% time pH<4 -2.7 ± 4.4 LES pressure 0 ± 0.7	Heartburn 60% Heartburn score -8.6 ± 9.0 Regurg score -5.2 ± 8.3	In SF-20, there were no sig difference between treatment groups in the change in physical function, social function, and mental health sub-scores. Compared with sham, EndoCinch had sig greater increase in role function and general health sub-scores, and sig greater decrease in bodily pain perception.	A
		sham	20/20	5% of pt reduced PPI use by >95%	nd	% time pH<4 -1.9 ± 4.6 LES pressure -0.3 ± 0.8	Heartburn 60% Heartburn score -0.9 ± 4.3 Regurg score -1.1 ± 4.2		
Montgomery 2006 ⁸² [17101568]	RCT 1 y	EndoCinch	22/22	3 mo: 50% 1 y: 45%	nd	Esophagitis 5% % time pH<4 4.7 (IQR 3.18-7.13) LES length 5cm (IQR 4.0-7.0) LES pressure 9.9 mmHg (IQR 5.9-13.9)	There were no sig differences in GSRS at 1 y between the two groups.	There were no sig differences in SF-36 PCS, and SF-36 MCS at 1 y between the two groups.	B Small sample size without power calculation, unclear sample population

Author Year	Study design Follow-up Duration	Intervention	Enroll/ Final	Objective Outcomes			Subjective Outcomes		Quality Comments
				Off PPI	Off All Meds	Diagnostic tests	Symptom improved	Quality of life	
		sham	24/21	3 mo: 33% 1 y: 24%	nd	Esophagitis 11% % time pH<4 7.4 (IQR 4.03-12.45) LES length 5.5cm (IQR 4.2-6.0) LES pressure 14.0 mmHg (IQR 11.6-19.0)	nd		
Coron 2008 ⁸³ [18616516]	RCT 1 y	Stretta®	23/20	ITT 17% PP 20%	nd	Esophagitis at 6 mo 53% % time pH<4 at 6 mo 11.4 ± 6.3%	Heartburn score 1.7 ± 0.8 Regurg score 1.2 ± 0.4 Epigastric burning score 1.3 ± 0.6	SF-36 physical 53 ± 7 SF-36 mental 51 ± 9 REFLUX- QUAL global 84 ± 9	B Small sample size
		Control	20/14	ITT 0% PP 0%	nd	Esophagitis at 6 mo 54% % time pH<4 at 6 mo 8.8 ± 6.1%	Heartburn score 2.3 ± 1.5 Regurg score 1.7 ± 1.4 Epigastric burning score 2.0 ± 1.4	SF-36 physical 40 ± 10 SF-36 mental 50 ± 7 REFLUX- QUAL global 77 ± 18	

ITT: intention-to-treat analysis, PP: per-protocol analysis, GLQI: Gastrointestinal Life Quality Index, PCS: physical component score, MCS: mental component score, IQR: inter-quartile range

SF-36 contains 8 scales - physical functioning (PF), role limitation-physical (RP), bodily pain (BP), general health perceptions (GH), vitality (VT), social functioning (SF), role limitation-emotional (RE), mental health (MH) – and 2 summary scores - the physical component summary score (PCS) and mental component summary score (MCS). SF-36 Japanese version 1.2 was used in this study. Range of scores was 0 -100; higher scores indicate better functioning and well-being.

Table 28. Cohort studies evaluating endoscopic treatment

Study Year [UI]	N enrolled/ N follow-up	Follow-up duration	Results						Quality
		Excluded ≥ grade 3 esophagitis (y/n)	Change in symptoms	QoL	Esophagitis healing	Medication	pH study	Other	
EndoCinch™									
Schiefke 2005 ⁸⁹ [15888777]	70/56 Prosp	18 mo n	heartburn score improved (58.2 vs. 36.8, P=0.001)	nd	Grade 0 (37.1% vs. 45.7%; no P value)	off PPI (0% vs. 6%; no P value)	%time pH <4: 9.1% vs. 8.5% (NS)	B	
Ozawa 2009 ⁸⁷ [19440812]	48/48	24 mo y	heartburn symptom score improved (14.9±4.6 vs. 2.7±2.9, P<0.0001)	nd	Grade 0 (0% vs. 80%)	off PPI (66%)	nd	B	
Domagk 2006 ⁸⁴ [16542275]	26/26 RCT ^c	6 mo nd	Heartburn severity score 20.9 ± 24.2	SF-36 physical 50.3 ± 8.1 SF-36 mental 43.5 ± 8.9 GLQI 85.2 ± 14.2		Off PPI 77%	Improved esophagitis % % time pH<4 9.6 ± 8.9% LES pressure 38.4 ± 10.4 Modified DeMeester symptom score 2.2 ± 2.4	B Small sample size	
Paulssen 2008 ⁸⁸ [18938771]	119/80 ?Prosp	41 mo n	heartburn score improved (baseline 21.4±4.72 (SD) vs. final 8.5±8.43, P <0.01); no regurg (baseline 37% vs. final 66%, no P value)	nd	nd	no sig change compared to baseline	%time pH <4: 11.7% vs. 13.5% (NS)	C Large drop out	
Liu 2006 ⁸⁶ [16484118]	95/95 Retro	12 mo y	complete resolution of heartburn and regurg: 72%	nd	nd	nd	nd	C Retrospective study without adjustment	

Study Year [UI]	N enrolled/ N follow-up	Follow-up duration	Results						Quality
			Excluded \geq grade 3 esophagitis (y/n)	Change in symptoms	QoL	Esophagitis healing	Medication	pH study	
Liao 2008 ⁸⁵ [18318824]	21/20 Prosp	24 mo y	heartburn score improved (64 \pm 25.9 vs. 21.1 \pm 26.4, P <0.001); regurg improved (2.4 \pm 0.7 vs. 1.3 \pm 1, P <0.001)	SF-36 general and mental health improved (31.2 \pm 14.5 vs. 38.3 \pm 15.3, P=0.032; 49.7 \pm 19.5 vs. 57 \pm 16.4, P=0.03)	nd	nd	nd		C Small sample
EsophyX™									
Cadiere 2008 ⁹² [18443855]	86/79 Prosp	12 mo y	Heartburn eliminated: 61/79 (77%) Regurgitation eliminated: 34/79 (59%)	improved GERD-HRQL of \geq 50% 58/79 (73%)	Esophagitis none (17% vs. 45%)	Off PPI (0% vs. 68%) Off any medication (0% vs. 48%)	DeMeester score ^d (34 vs. 28, p<0.001) Significant increase in LES resting pressure by 53% (p<0.001)		B
Cadiere 2009 ^{90,91} [19288158]	19/14 Prosp	25 mo y	heartburn resolved: 13/14 (93%)	improved GERD-HRQL of \geq 50% 9/14 (64%)	nd	Off PPI: 10/14 (71%)	nd		C Small sample
Repici 2010 ⁹³ [19902310]	20/15	12 mo n		improved GERD-HRQL of \geq 50% 11/15 (73%)		Off PPI 7/15 (47%)	LES pressure (NS)		C Small sample
Testoni 2010 ⁹⁴ [20091308]	20/18	6 mo n	GERD-HRQL when off PPI (45 \pm 20 vs. 16 \pm 14, P < 0.001) Number of reflux (63 \pm 43 vs. 43 \pm 41, P = 0.02)	GERD-QUAL when off PPI (114 \pm 29 vs. 74 \pm 21, P < 0.001)	Grade 0 (17% vs. 22%, NS)	Off PPI (0% vs. 55.6%) Reduced PPI use: 22%	DeMeester score (20 \pm 13 vs. 18 \pm 17, NS) LES pressure (8 \pm 5 vs. 10 \pm 3,	nd	C small sample, short followup

Study Year [UI]	N enrolled/ N follow-up	Follow-up duration	Results						Quality
		Excluded ≥ grade 3 esophagitis (y/n)	Change in symptoms	QoL	Esophagitis healing	Medication	pH study	Other	
Meier 2007 ¹⁰⁰ [17613919]	60/60? Prosp	12 mo n	heartburn score improved (3.4±1.1 vs. 1.3±1.3, P <0.05)	GERD-HRQL improved (19.2±9 vs. 6.6±7.3; P <0.0001); SF-36 physical & mental improved (P<0.05)	nd	off meds (0% vs. 38%)	DeMeester improved (72.9±63 vs. 35.1±28.6; P=0.003)	C Heterogeneous sample; no objective testing for GERD	
Dundon 2008 ⁹⁷ [18829607]	37/32 Retro	53 mo nd	heartburn score in those who did not require other surgery (2.43 vs. 1.43, NS)	GERD QoL in those who did not require other surgery (3.14 vs. 1.46, NS)	nd	2/32 (?) completely off meds	nd	C 53 mo data only on 13 patients	
Jeansonne 2009 ⁹⁸ [19153320]	68/35 ⁹ RCT ^h	6 mo nd	Severe heartburn 22% Severe regurg 18.8% Dysphagia 0%			50% off PPI	% time pH < 4 9.1%	C High dropout, poor GERD diagnostic criteria	

^a Data presented is change from baseline.

^b Data presented in this table refers to the first 3 mo of the study where patients were randomized and blinded. After 3 mo, patients in the sham or observation groups were offered the EndoCinch treatment.

^c This intervention group is subset of a larger RCT.

^d Median

^e Range 0 to 72. Lower score indicates improved symptom score

^f Range 0 to 50. Lower score indicates improved symptom score

^g A total of 51% follow-up rate was reported for this study. Exact numbers of participants followed per group were not reported

^h This intervention group is subset of a larger RCT.

Key Question 1G. Comparative effectiveness of treatment for extra-esophageal Manifestation of Gastroesophageal Reflux Disease

Synopsis

Key findings from comparative effectiveness of treatment for extra-esophageal manifestation of GERD are summarized as follows:

Medical treatment for Extra-esophageal manifestations of GERD.

Asthma

- A systematic review evaluating the effect of medical treatment did not find consistent effects of PPI or H2RA versus placebo in improving asthma symptoms, nocturnal asthma, use of asthma medications or in objective indicators such as forced expiratory volume in 1 second (FEV1), and morning and evening peak expiratory flow.
- An update to the systematic review did not find evidence from 8 primary RCTs to contradict the conclusions of the systematic review. Studies that used either omeprazole 20 mg in combination with domperidone 10 mg or esomeprazole 40 mg reported an improvement in morning and evening peak expiratory flow rate. Studies using lansoprazole 30 mg or pantoprazole 40 mg did not report an improvement in either asthma symptoms or lung function tests. While rabeprazole 20 mg taken two times a day improved respiratory symptoms during exercise in patients with exercise induced asthma, as compared to a placebo, it did not improve quality of life or pulmonary function tests results.
- An RCT comparing surgery with an H2RA and antacids, and lifestyle modification as a co-intervention in all arms, did not find statistically significant differences in pulmonary function tests among the three groups, though the proportion of patients reporting an improvement ≥ 40 percent in asthma symptom score was significantly higher in the surgery group (75 percent) as compared to the H2RA group (0 percent) and the control group (20 percent) ($P < 0.05$).

Hoarseness

- Two of the six RCTs in the systematic review assessing the effect of PPI treatment on hoarseness found a significant higher percentage of patients who reporting resolution of hoarseness symptom with PPI treatment, as compared to a placebo.

Chronic Cough

- A meta-analysis of data from 4 studies in the review demonstrated no significant difference in total resolution of cough between PPIs and placebo, odds ratio 0.46 (95 percent CI: 0.19 to 1.15). A meta-analysis of data from 4 RCTs reporting mean cough scores at the end of the trial in 109 participants found a borderline significant improvement in the mean cough scores at the end of the trial with PPIs as compared to placebo -0.38 units (95 percent CI: -0.77 to 0.00, $P = 0.05$).

Surgical Treatment for Extra-esophageal symptoms

- All of the data on the impact of surgical treatment for GERD on of extra-esophageal symptoms come from surgical cohort studies, with a wide variation in the population treated, the severity of the underlying GERD as well as its extra-esophageal manifestation, the outcome measures used to assess efficacy, the surgical interventions used, as well as the intensity and duration of followup. Within these parameters, there is an improvement of extra-esophageal symptoms with surgical treatment for GERD, with cough (13 to 96 percent in 11 out of 13 studies reporting outcome) and laryngeal symptoms (64 to 94 percent in 5 out of 8 studies reporting outcome) showing a better range of complete resolution of symptoms than asthma (0 to 64 percent in 3 out of 7 studies reporting outcome).

Detailed analysis

In this update to the 2005 CER,² we expanded the population of interest to include patients with both chronic GERD and symptomatic extra-esophageal GERD (with a focus on chronic cough, hoarseness/laryngitis and asthma). We included systematic reviews or meta-analyses that synthesized studies focusing exclusively on treatment of patients with chronic GERD, and their impact on extra-esophageal GERD (with a focus on chronic cough, hoarseness/laryngitis and asthma). The interventions assessed included both medical (PPI, H2RA, lifestyle modification and patient education) and surgical treatment (fundoplication as well as non-fundoplication repairs).

From the 107 reviews in the search results, 5 systematic reviews qualified for inclusion, which assessed various treatment strategies for chronic cough, hoarseness/laryngitis and asthma.^{12,103-106} One systematic review focused solely on the efficacy of medical and surgical treatment on asthma;¹² one studied the effect of medical and surgical treatment on chronic cough;¹⁰³ one assessed the effect of surgical and non-surgical treatment on hoarseness/laryngitis,¹⁰⁴ and two^{105,106} included all of the outcomes of interest - chronic cough, hoarseness/laryngitis and asthma.

In addition to reviewing the systematic review on the efficacy of medical and surgical treatment modalities on asthma,¹² we conducted an update by searching for primary studies on the same topic published since 2002 – including a period of 9 months prior to the date of the last search listed in the Gibson review to make sure we did not miss any studies.

On closer examination of the studies included in the qualified systematic reviews, it was noticed that all of the studies from the systematic review by Hungin 2005¹⁰⁵ were already included in the later reviews that assessed the same outcomes – asthma,¹² chronic cough,¹⁰³ and hoarseness/laryngitis.¹⁰⁴ Furthermore, the quality of Hungin 2005 was assessed to be inferior to the other reviews (e.g., no assessment of the quality of the included primary studies). Therefore, Hungin 2005 was excluded in this report.

All of the systematic reviews included studies on adults but two also included studies on both adults and children.^{12,103} However, data on children were excluded from our analyses.

When the systematic reviews included both RCTs and observational studies, their results are reported separately.

The quality of the systematic reviews were assessed by the AMSTAR checklist.¹⁰ The quality of the systematic reviews of RCTs on asthma outcomes,¹² hoarseness/laryngitis outcome,¹⁰⁴ and chronic cough outcomes¹⁰³ was adequate. The quality of the systematic review

of surgical cohort studies on all outcomes¹⁰⁶ was suboptimal: data on study design details, independent reviews, list of excluded studies, study quality and publication bias assessment were not provided.

Medical treatment for Extra-esophageal manifestations of GERD

Asthma

Synopsis

One systematic review that was included in this analysis evaluated the effect of PPI treatment on asthma with data from RCTs.¹² In addition, an update to this review found 8 primary RCTs of medical GERD therapy in patients with asthma.

Medical treatment does not show a consistent effect on asthma symptoms, nocturnal asthma, use of asthma medications, and objective lung function indicators, including Forced Expiratory Volume in 1 second (FEV1), morning peak expiratory flow and evening peak expiratory flow. Studies that used either omeprazole 20 mg in combination with domperidone 10 mg or esomeprazole 40 mg reported an improvement in morning and evening peak expiratory flow rate. Studies using lansoprazole 30 mg or pantoprazole 40 mg did not report an improvement in either asthma symptoms or lung function tests. While rabeprazole 20 mg taken two times a day improved respiratory symptoms during exercise in patients with exercise induced asthma, as compared to a placebo, it did not improve quality of life or pulmonary function tests results.

Detailed presentation (Table 29 and 30)

One systematic review was included in this analysis. The systematic review evaluated the effect of PPI treatment on asthma with data from RCTs.¹² The last search date for this review was September 21, 2002. Since recent RCTs have evaluated the impact of PPI on asthma in GERD patients, an update search was carried out to identify all RCTs of GERD therapy in patients with asthma. In the update search, the time period of search was limited from 2002 – 2009. A total of 277 abstracts were screened, and 8 RCTs qualified for inclusion.

In the systematic review by Gibson 2009,¹² 12 RCTs were included in the review. (Table 29) Nine were crossover studies and 3 were parallel arm studies. One study compared the effect of H2RA versus placebo on asthma in children and adolescents in the age group of 10 to 20 years. The omeprazole was the only PPIs used in these studies, in varying doses - 20 mg, 40 mg, 80 mg and 160 mg doses. H2RAs including ranitidine and cimetidine, non-pharmacological conservative reflux therapy, and surgical therapy (posterior gastropexy) were other interventions that were used. 10 of the 12 studies compared either PPI or H2RAs to control therapy, while of the remaining two, one study compared non-pharmacological conservative reflux therapy to a control and another study compared a H2RA to a placebo or surgery. The sample size in the 12 trials ranged from 11 to 90, totaling 432 participants. The range of followup was 1 to 4.5 months. In the 11 trials conducted on adults, the mean age was 48 years (range 22-80 years). Outcome measures reported were lung function, symptoms and use of asthma medications.

Medical treatment did not consistently improve asthma symptoms, nocturnal asthma, use of asthma medications and objective lung functions. Nine out of 12 RCTs did not report a significant improvement in asthma symptoms. Three out of 6 trials that reported nocturnal asthma symptoms scores did not report significant improvement between the treatment arm and the placebo arm. Four out of 7 trials that reported beta-agonists use in puffs per day did not find

statistically significant reduction in beta-agonist use. There was no significant improvement in FEV1 in groups using proton pump inhibitors, histamine antagonists, conservative therapy or surgical treatment. Using morning peak expiratory flow as an outcome, a meta-analysis of 3 studies (184 participants) showed no effect of PPI or H2RA over placebo (Mean difference: 5.28 L/min (95 percent CI: -35.43, 44.72)). Sub-group analysis of the same outcome in studies using PPI (3 studies, 88 participants) and H2RA (1 study, 96 participants) did not show significant differences between the drug and the placebo. With evening peak expiratory flow as an outcome, data from 3 studies (154 participants) showed no effect of PPI or H2RA over placebo (Mean difference: 7.03 L/min (95 percent CI: -25.88, 39.95)). Sub-group analysis of the same outcome in studies using PPI (2 studies, 58 participants) and H2RA (1 study, 96 participants) did not show significant differences between the drug and the placebo. Similar non-significant effects were seen with nocturnal symptoms score (Mean difference: -0.16 (95 percent CI: -0.42, 0.11)) and puffs of asthma medication per day (Mean difference: 0.52 puffs per day (95 percent CI: -1.7, 0.67)). Sub-group analysis of nocturnal symptoms score and puffs of asthma medication per day did not show significant differences between using PPI or H2RA as treatment versus the placebo.

In the update search, 8 RCTs were included for analysis.¹⁰⁷⁻¹¹⁴ The characteristics and results from the 8 studies are outlined in Table 30. The studies enrolled a total of 1538 adult participants and followup data were available from 1192 participants. Five RCTs compared PPIs – lansoprazole 30 mg, omeprazole 20 mg, pantoprazole 40 mg, esomeprazole 40 mg, rabeprazole 20 mg - with placebo,^{107,109-112} one compared a PPI (lansoprazole 30 mg/d) with an H2RA (Roxatidine 150 mg/d,¹¹³ one compared a PPI (omeprazole 20 mg) and antiemetic agent (Domperidone 10 mg three times a day) taken alongside anti-asthma medication with only anti-asthma medication,¹⁰⁸ and one study was a 3-arm comparison of surgery and with an H2RA (ranitidine 150 mg three time/d) and antacids.¹¹⁴ Of the 8 trials, the quality of 4 was graded as B and the 4 remaining trials were graded as C.

In the five RCTs comparing PPIs with placebo,^{107,109-112} the sample size of the trials ranged from 31 to 624. Of the 4 trials reporting the effect of PPIs therapy on asthma symptoms, 2 trials^{107,110} did not find any significant improvement in asthma symptom score with PPI therapy, while two others^{111,112} found a significant improvement. In addition, 4 trials reported objective measures of pulmonary function, including FEV1 and, morning and evening peak expiratory flow. 2 trials^{109,112} reported significantly higher *net difference* (i.e. difference in change from baseline between the intervention and control groups) with PPI therapy but 3 trials^{107,110,111} did not find any significant differences in pulmonary function tests between PPI and placebo therapy. Interestingly, one of the trials with rabeprazole 20 mg versus placebo, conducted in subjects with exercise triggered asthma, did not find a significant difference in pulmonary function tests while showing a significant improvement in asthma symptoms.¹¹¹ Two trials reported on use of albuterol in addition to GERD therapy.^{110,112} One trial comparing lansoprazole 30 mg versus placebo over 24 weeks did not find any significant difference in albuterol use (measured in puffs per day)¹¹⁰ while another found a significant decrease in albuterol use with omeprazole (20 mg taken twice a day) and Domperidone (10 mg taken three times a day), as compared to a placebo.

In an RCT comparing lansoprazole 30 mg per day with Roxatidine 150 mg per day, there was a significant decrease in asthma symptoms in the people taking lansoprazole 30 mg ($P < 0.05$), while no significant difference in change in asthma scores from baseline was found in people taking roxatidine 150 mg. Change in results of the pulmonary function test in both the groups were not significantly different. This RCT was graded B.

Another RCT, comparing a combination of omeprazole (20 mg taken once daily), domperidone (10 mg taken thrice daily) and anti-asthmatic medication (salbutamol 200 mg four times a day and budesonide 400 mg twice a day) with only anti-asthmatic medication in 30 subjects over 6 weeks found significantly higher *net difference* in bronchial hyperreactivity (measured by PC-20 in g/L: the amount of methacholine that causes a 20% reduction in FEV1) in the group taking omeprazole and domperidone with asthma medication as compared to only asthma medication (net difference: 0.54; 95 percent CI: 0.42,0.66), $P < 0.0001$.¹⁰⁸

In a 3-arm RCT, graded C, comparing surgery with an H2RA and antacids, lifestyle modification (including avoidance of tight garments, no eating after supper, avoiding eating fatty foods, and not reclining after meals, coupled with eating smaller, more frequent meals and elevating head of bed by 6 inches) was used as a co-intervention in all arms. There was statistically significant difference in pulmonary function test results among the three groups.¹¹⁴ Overall clinical improvement was significantly better in surgical group (12/16; 75 percent) as compared with medical (2/22, 9 percent) and control groups (1/24, 4 percent), $P < 0.01$. Overall asthma symptom score ($\geq 40\%$ improvement from baseline) was significantly better in the surgical (75 percent) versus medical (0 percent) /control (20 percent) groups, ($P < 0.05$).

In summary, medical treatment does not show a consistent effect on asthma symptoms, nocturnal asthma, use of asthma medications, and objective lung function indicators, including Forced Expiratory Volume in 1 second (FEV1), morning peak expiratory flow and evening peak expiratory flow. Studies that used either omeprazole 20 mg in combination with domperidone 10 mg or esomeprazole 40 mg reported an improvement in morning and evening peak expiratory flow rate. Studies using lansoprazole 30 mg or pantoprazole 40 mg did not report an improvement in either asthma symptoms or lung function tests. While rabeprazole 20 mg taken two times a day improved respiratory symptoms during exercise in patients with exercise induced asthma, as compared to a placebo, it did not improve quality of life or pulmonary function tests results.

Hoarseness/Laryngitis

Synopsis

One systematic review was included in this analysis, evaluating the effect of RCTs of PPI treatment versus a placebo on hoarseness,¹⁰⁴

Most of the RCTs (4/6, 67 percent) did not show a significant difference in resolution of hoarseness between the PPI and placebo arms.¹⁰⁴ The remaining 2 RCTs found a significant higher percentage of patients who reporting resolution of hoarseness symptom with PPI treatment, as compared to a placebo. The RCTs that included participants complaining of hoarseness could not objectively demonstrate reflux from the same participants using pH studies.

Detailed presentation (Table 31)

One systematic review was included in this analysis, evaluating the effect of RCTs of PPI treatment versus a placebo on hoarseness,¹⁰⁴

The search strategy for the systematic review of RCTs¹⁰⁴ included all controlled trials of anti-reflux therapy for adult patients presenting with hoarseness, irrespective of the objective diagnosis of laryngopharyngeal reflux and GERD. The databases searched included Cochrane ENT Group Specialised Register, Cochrane Central Register of Controlled Trials (The Cochrane Library, Issue 3, 2005), Medline (1951 to 2005), EMBASE (1974 to 2005), CINAHL (1982 to 2005), Biological Abstracts and review articles. The search was last updated on 15 November

2005. The interventions included in the search were non-surgical (including lifestyle modification and patient education, and drugs like PPIs, H2RAs, prokinetic agents and erythromycin) and surgical (including fundoplication repair - Nissen, Rossetti, Toupet partial fundoplication, Bore partial fundoplication, Collis gastroplasty followed by fundoplication – and non-fundoplication repairs - Hill repair (gastropexy), Belsey Mark IV). Only data from medical treatment is included in this analysis.

The sample size in the 6 trials that were included ranged from 15 to 145, totaling 275 participants randomized to either a PPI or a placebo. The range of followup was 2 to 3 months. The PPIs were all administered in a twice a day dose frequency. The various doses used included lansoprazole 30mg, omeprazole 40 mg, esomeprazole 40 mg, pantoprazole 40 mg and rabeprazole 20 mg. Most of the RCTs (4/6, 67 percent) did not show a significant difference in the resolution of hoarseness between the PPI and placebo arms. There were many issues with the primary studies included in the review. Even though the presenting symptom in these studies was hoarseness, the pH studies conducted in 4 of 6 trials could not objectively demonstrate GERD in the patients within the studies. Therefore, whether the efficacy of GERD treatment could be adequately evaluated was debatable. In addition, the symptom questionnaire varied across the 6 studies, so an inter-study comparison of resolution of hoarseness was not possible. The authors concluded that the sample sizes of these studies were not large enough to have the power to detect significantly different effects between the PPIs and the placebo. In addition, they hypothesized that the treatment period of 2 to 3 months may not have been adequate to demonstrate the effect on laryngeal symptoms.

Chronic Cough

Synopsis

One systematic reviews of RCTs that evaluated the effect of PPI treatment on non-specific dry cough of ≥ 3 weeks duration was included in this analysis.¹⁰³ Meta-analysis of 4 RCTs (191 participants) included in the systematic review did not find a significant difference between PPIs and placebo in total resolution of cough, reporting an odds ratio of 0.46 (95 percent CI: 0.19 to 1.15). Another meta-analysis of data from 6 RCTs (161 participants) reporting change in clough scores from the baseline in the same systematic review revealed a significant improvement in cough scores from baseline favoring PPIs as compared to placebo (-0.39 standardized mean difference units; 95 percent CI -0.71 to -0.08).

Detailed presentation (Table 32)

One systematic review of RCTs evaluating the effect of PPI treatment on non-specific dry cough of ≥ 3 weeks duration was included.¹⁰³ The search strategy for the systematic review of RCTs¹⁰³ included all RCTs of GERD treatment with cough as an outcome, where cough was unrelated to a respiratory disorder (e.g., cystic fibrosis, asthma, chronic obstructive airway disease, suppurative lung disease) or to medication use (e.g., ACE inhibitor). The following databases were searched: The Cochrane Controlled Trials Register (CENTRAL) including Airways Collaborative Review Group Specialised Trials Register, Medline (1951 to 2009) and EMBASE 1997 to 2009). The search was last updated in April 2009. The interventions included in the search were anti-reflux conservative measures, H2RA, PPI and surgical therapy. Only data from the medical treatment is presented. The primary outcome that was assessed was the failure to cure (defined as the proportions of participants who

were not cured or not substantially improved at follow up). Other outcomes included cough scores and change in cough scores from baseline.

The review contained results from 18 studies. Five of the 18 studies were in a pediatric age group population and thus excluded from this analysis. Out of 13 studies, 10 were parallel arm studies and 3 were crossover studies. The PPIs used were of varying doses and frequencies and included omeprazole, esomeprazole, lansoprazole, pantoprazole and rabeprazole. H2RAs like ranitidine, cisapride, and lifestyle modifications were other interventions that were used. The sample size in the 13 trials that were assessed ranged from 17 to 146, totaling 476 participants. The range of followup was 2 to 4 months. Outcome measures were subjective cough scales that had not been validated. Objective outcomes were not used in any of the trials.

Meta-analysis of 4 RCTs (191 participants) included in the systematic review did not find a significant difference between PPIs and placebo in total resolution of cough, reporting an odds ratio of 0.46 (95 percent CI: 0.19 to 1.15). Data from 4 studies (109 participants) reporting mean cough scores found a borderline significant difference in the mean cough scores at the end of the trial in comparisons of PPI versus placebo (Mean difference: -0.38 units (95 percent CI: -0.77 to 0.00, P=0.05)). Another meta-analysis of data from 6 RCTs (161 participants) reporting change in cough scores from the baseline in the same systematic review revealed a significant improvement in cough scores from baseline favoring PPIs as compared to placebo (-0.39 standardized mean difference units; 95 percent CI -0.71 to -0.08). There was evidence of heterogeneity ($I^2=12$ percent) between studies in this analysis.

A subgroup analysis was done comparing the differential effect when omeprazole was the PPI used, and when other PPIs were used. A meta-analysis of data from 2 studies (51 participants) revealed a significant difference in the change in cough scores from baseline in comparisons of Omeprazole versus placebo: -0.71 SMD (95 percent CI -1.29 to -0.14). There was no significant difference when other PPIs (lansoprazole, pantoprazole and rabeprazole) were compared with placebo (-0.26 SMD (95 percent CI -0.64 to 0.11)). It is noted that there was a considerable subjectivity in the assessment of outcomes across trials which can lead to biased results when combining the results to get a summary effect.

Surgical treatment for Extra-esophageal manifestations of GERD

Synopsis

Data from one systematic review was included in this report. The review evaluated the effect of anti-reflux surgical treatment on asthma, hoarseness/laryngitis and chronic cough with results from single-arm surgical cohort studies.¹⁰⁶

Data from surgical studies showed an improvement in the percentage of participants with resolution of asthma in 7 studies. With followup ranging from 6 to 65 months, the range of participants reporting either a partial or complete resolution of symptoms after surgery was 0 to 64 percent. Improvement in the percentage of participants with resolution of laryngeal symptoms was seen in 8 studies. With followup ranging from 6 to 65 months, the range of participants reporting either a partial or complete resolution of symptoms after surgery was 65 to 94 percent. In addition, improvement in the percentage of participants with chronic cough was seen in 13 studies. With followup ranging from 3.2 to 65 months, the range of participants reporting either a partial or complete resolution of symptoms after surgery was 60 to 100 percent.

Detailed presentation

Asthma (Table 29)

The search strategy for the systematic review of surgical case series included all retrospective and prospective studies, including RCTs, of surgical fundoplication in the treatment of the symptoms of extra-esophageal reflux.¹⁰⁶ The search period ranged from January 1991 to December 2006. Non-surgical interventions were excluded. 25 studies evaluating surgical fundoplication for treating extra-esophageal symptoms were screened. Of the 25 studies, 24 of those were case series, of which 10 were prospective and 14 were retrospective. One study was a RCT comparing medical and surgical therapy in asthmatics, which has been discussed under the section on Asthma.¹¹⁴ Overall, 7 studies reported asthma outcomes for patients receiving fundoplication, 13 studies had data on chronic cough outcomes, and eight studies reported laryngeal symptoms.

Out of the 24 case series that assessed the role of surgical fundoplication in treating all symptoms of extra-esophageal reflux, 7 studies had asthma as an outcome. One study was an RCT comparing Nissen fundoplication with medical therapy¹¹⁴ that was included in the update to the review by Gibson 2009.¹² Of the remaining 6 studies, 4 of the 6 studies (67 percent) were prospective cohort studies. The sample size in the 7 included studies ranged from 13 to 135, totaling 350 participants, on whom any one of the following surgical procedures was done: Nissen fundoplication, Toupet fundoplication, laparoscopic Nissen fundoplication, Collis Nissen fundoplication, Belsey Mark IV repair. The range of followup was 6 to 65 months. The various scoring methods were used for symptom evaluation were Asthma symptom score, medication frequency score and Likert scale. Quality of life was assessed in some studies before and after surgery, using the SF-36 medical outcomes survey.

In 3 out of 7 studies, 0 to 64 percent of the participants reported a complete resolution of asthma symptoms. In 6 studies, 15 to 84 percent of the participants reported a partial resolution of asthma symptoms after surgery.

Hoarseness/laryngitis (Table 31)

8 case-series studies had laryngeal manifestations as outcomes. 4 of the 8 studies were prospective, and the rest were retrospective. The sample size in the 8 included studies ranged from 9 to 86, totaling 272 participants, on whom any one of the following surgical procedures was done: Nissen fundoplication, Toupet fundoplication, laparoscopic Nissen fundoplication, Collis Nissen fundoplication, Belsey Mark IV repair. The range of followup was 6 to 65 months. The various scoring methods were used for symptom evaluation were Reflux Symptom Index scale, Reflux Finding Scores, Likert scale, and the Medication Frequency Score. Quality of life was assessed in some studies before and after surgery, using the Gastrointestinal Quality of Life Index (GIQLI).

All the studies showed an improvement in laryngeal symptoms. In 5 out of 8 studies, 65 to 94 percent of the participants reported a complete resolution of symptoms after undergoing surgery. In 3 studies, 74 to 83 percent of the participants reported a partial resolution of symptoms after surgery.

Chronic Cough (Table 32)

13 studies with surgical case series presented chronic cough as an outcome. 5 of the 13 studies (38 percent) were prospective, and the rest were retrospective. The sample size in the 13 included studies ranged from 11 – 354, totaling 1057 participants, on whom any one of the following surgical procedures was done: Nissen fundoplication, Toupet fundoplication,

laparoscopic Nissen fundoplication, Collis Nissen fundoplication, Belsey Mark IV repair. The range of followup was 3.2 - 65 months. The various scoring methods were used for symptom evaluation were symptom scales and Likert scale. Quality of life was assessed in some studies before and after surgery, using the Gastrointestinal Quality of Life Index (GIQLI) and other quality of life questionnaires.

All the studies showed an improvement in chronic cough symptoms. In 11 out of 13 studies, 13 to 96 percent of the participants reported a complete resolution of chronic cough after undergoing surgery. In 9 studies, 60 to 100 percent of the participants reported a partial resolution of cough after surgery.

Table 29. Treatment of GERD and its effect on Asthma – Data from Systematic reviews

Author Year	Gibson 2003 ¹²		
Design	A systematic review of GERD treatment for asthma in adults and children		
Population	Patients with asthma – adults (1 study of H2RA vs placebo included children and adolescents between 10-20 years of age).		
Intervention (Exposure) and Comparator	<ol style="list-style-type: none"> 1. H2 antagonist - ranitidine and cimetidine 2. Proton Pump Inhibitor (Only Omeprazole in varying doses - 20 mg, 40 mg, 80 mg and 160 mg) 3. Conservative anti-reflux therapy: raising the head of the bed, drinking warm water after meals, not eating for 3 hours prior to bed time, anti-reflux medication as required, avoid use of aspirin and anticholinergic preparations and avoidance of procedures increasing intra-abdominal pressure 4. Surgery 		
Results	<ul style="list-style-type: none"> • Database search yielded 262 abstracts, 22 full-text articles and 1 abstract were retrieved. Of these, 12 RCTs were included. • 9 cross-over trials and 3 parallel design, quality of studies (7 A studies, 4 B studies, and one C study), types of interventions: proton pump inhibitors (6 studies), histamine antagonists (5 studies), surgery (1 study), conservative management (1 study). With exception of 1 RCT comparing H2 antagonist with placebo who studied children and adolescents (aged 10-20 years old), all other RCTs investigated adults. • 9 of 12 studies failed to show a significant improvement in asthma symptoms. • Meta-analysis model and heterogeneity (if applicable): <ul style="list-style-type: none"> ○ H2 antagonist , Proton Pump inhibitor, conservative or surgical therapy vs. placebo on FEV1: No effect of treatment ○ H2 antagonist or Proton Pump inhibitor vs. placebo on morning peak expiratory flow, Fixed effect model, mean difference [95% CI]: 5.28 [-35.43, 44.72] Heterogeneity: Chi² = 0.3, df=2 (P=0.86); I²=0.0% ○ H2 antagonist or Proton Pump inhibitor vs. placebo on evening peak expiratory flow, Fixed effect model, mean difference [95% CI]: 7.03 [-25.88, 39.95] Heterogeneity: Chi² = 0.02, df=2 (P=0.99); I²=0.0% ○ H2 antagonist vs. placebo on nocturnal symptoms score (including a study on adolescents), Fixed effect model, mean difference [95% CI]: -0.16 [-0.42, 0.11] Heterogeneity: Chi² = 0.97, df=3, (P=0.81); I²=0.0% ○ Proton Pump inhibitor vs. placebo, Outcome: puffs per day, Fixed effect model, mean difference [95% CI]: -0.52 [-1.7, 0.67] Heterogeneity: Chi² = 0.59, df=2, (P=0.74); I²=0.0% 		
Comments	The duration of medical treatments was short in the most studies. Insufficient sample size in the pooled studies. One study included children and adolescents aged from 10 to 20 years.		
AMSTAR			
A priori design?	Y	Study quality assessment performed?	Y
Two independent reviewers?	Y	Study quality appropriately used in analysis?	N
Comprehensive literature search?	Y	Appropriate statistical synthesis?	Y
All publication types and languages included?	Y	Publication bias assessed?	N
Included and excluded studies listed?	Y	Conflicts of interest stated?	Y
Study characteristics provided?	Y		
Author Year [PMID]	Iqbal 2008 ¹⁰⁶ [19105666]		
Design	A systematic review of retrospective and prospective studies, including RCTs, of surgical fundoplication in the treatment of the symptoms of extra-esophageal reflux (EER).		
Population	Adults		
Intervention (Exposure) and Comparator	Surgery / fundoplication, versus placebo/medical therapy		
Results	Seven studies, 350 patients – 1 RCT, four prospective studies, 2 retrospective studies; In 3 out of 7 studies, 0 to 64 percent of the participants reported a complete resolution of asthma symptoms. In 6 studies, 15 to 84 percent of the		

	participants reported a partial resolution of asthma symptoms after surgery.		
Comments	Included both prospective and retrospective studies; only 1 RCT for asthma; no quantitative analysis; quality of studies was not assessed		
AMSTAR			
A priori design?	N	Study quality assessment performed?	N
Two independent reviewers?	N	Study quality appropriately used in analysis?	n/a
Comprehensive literature search?	Y	Appropriate statistical synthesis?	n/a
All publication types and languages included?	N	Publication bias assessed?	N
Included and excluded studies listed?	N	Conflicts of interest stated?	Y
Study characteristics provided?	Y		

Table 30. Treatment of GERD and its effect on Asthma: RCTs published between 2002 - 2010

Author year [PMID]	Interventions	N _E /N _{F/U}	F/U	Symptoms	Quality of Life	Pulmonary function tests	Asthma Medication use	Quality
Littner 2005 ¹¹⁰ [16162697]	Lansoprazole 30 mg vs. placebo	343/173	24 wk	No significant difference in overall asthma symptom score between LAN (1.57 ± 0.56 to 1.21 ± 0.58) vs. placebo (1.56 ± 0.55 to 1.35 ± 0.65), NS		No significant net difference in morning peak expiratory flow (L/min) between LAN vs. placebo (net difference: -5; 95 percent CI: -28, 18), NS; No significant net difference in evening peak expiratory flow (L/min) between LAN vs. placebo (net difference: -8; 95 percent CI: -32, 16), NS;	No significant difference in albuterol use (puffs/d) between LAN (4.3 ± 2.6 to 3.3 ± 2.6) vs. placebo (4.5 ± 3.1 to 3.6 ± 3.0), NS	B
Sharma 2007 ¹¹² [17461474]	Omeprazole 20 mg /d + Domperidone 10 mg three times/d vs. placebo	204/198	16 wk	Significant change in daytime asthma score between OME (17.4% decrease) vs. placebo (8.94% decrease), P=0.0001 Significant change in nighttime asthma score between OME (19.6% decrease) vs. placebo (5.4% decrease), P=0.0001		Significant higher net difference in morning peak expiratory flow (L/min) between OME vs. placebo (net difference: 22; 95 percent CI: 10, 34), P=0.004; difference in evening peak expiratory flow (L/min) between OME vs. placebo (net difference: 29; 95 percent CI: 14, 44), P=0.002; Significant change in post- bronchodilator FEV1 with OME (11.1% increase) vs. placebo (3.78% increase), P=0.0013	Significant decrease in albuterol use OME (23.2% decrease) vs. placebo (3.08% decrease), P=0.0001	B
Dos Santos 2007 ¹⁰⁷ [17724529]	Pantoprazole 40 mg/d vs. Placebo	49/44	90 d	No significant difference in diurnal asthma symptom score between PAN (69.2 ± 29 to 58.9 ± 23) vs. placebo (68.8 ± 26 to 64.92 ± 4), P=0.11 No significant difference in	Significant improvement in total quality of life score between PAN (61.61 ± 5 to 48.7 ± 12) vs. placebo (63.8 ± 13 to 61.8 ± 13), P=0.001	No significant net difference in morning peak expiratory flow (L/min) between PAN vs. placebo (net difference: 16; 95 percent CI: -45, 77), NS; No significant net difference in evening peak expiratory flow (L/min) between PAN vs. placebo		B

Author year [PMID]	Interventions	N _E /N _{F/U}	F/U	Symptoms	Quality of Life	Pulmonary function tests	Asthma Medication use	Quality
				nocturnal asthma symptom score between PAN (66.92 ± 7 to 57.9 ± 23) vs. placebo (66 ± 25 to 63.42 ± 6), P=0.16;		(net difference: 8; 95 percent CI: -54, 70), NS		
Shimizu 2006 ¹¹³ [16778364]	Lansoprazole 30 mg/d vs. Roxatidine 150 mg/d	30/30	2 mo	Significant difference in change from baseline in Asthma Control Questionnaire score in LAN (14.4 ± 4.2 to 9.4 ± 4.2), P<0.05 vs. no significant change in ROX (12.3 ± 2.1 to 9.0 ± 3.1), NS		No significant net difference in morning peak expiratory flow (L/min) between LAN vs. ROX (net difference: 17; 95 percent CI: -21, 55), NS;		B
Kiljander 2006 ¹⁰⁹ [16357331]	Esomeprazole 40 mg/d vs. placebo	770/624	16 wk			Significant higher net difference in morning peak expiratory flow (L/min) between EsOME vs. placebo (net difference: 8.7; 95 percent CI: 0.8, 17), P=0.03; Significant higher net difference in evening peak expiratory flow (L/min) between EsOME vs. placebo (net difference: 10.2; 95 percent CI: 2.3, 18), P=0.012		C no blinding, no details on method of randomization
Sontag 2003 ¹¹⁴ [12809818]	Nissen Fundoplication [surgical group] vs. Ranitidine 150 mg three times/d [medical group] vs. Antacids as needed [control group]. Lifestyle	75/62	2 y	Overall asthma symptom score (≥40% improvement from baseline) significantly better in the surgical (75 percent) versus medical (0 percent) / control (20 percent) P<0.05		No statistically significant difference in peak expiratory flow rate between the 3 groups, although trend toward improvement in surgical group compared to combined medical and control groups	No significant difference in requirement for bronchodilators or corticosteroids	C No blinding, subjective nature of symptom assessment

Author year [PMID]	Interventions	N _E /N _{F/U}	F/U	Symptoms	Quality of Life	Pulmonary function tests	Asthma Medication use	Quality
	modifications (Avoidance of tight garments, eating after supper, eating fatty foods, and reclining after meals with eating smaller, more frequent meals, elevating head of bed by 6 inches) was a co-intervention in all arms.							
Peterson 2009 ¹¹¹ [18688720]	Rabeprazole 20 mg one – two times /d vs. placebo	37/31	10 wk	Significant improvement in respiratory symptoms during exercise w/ patients taking RAB (70 percent) vs patients taking placebo (25 percent), P=0.03	No significant change in SF-36 scores w/ RAB vs placebo (P= 0.97,) or mini-Asthma quality of life questionnaire score (P=0.21)	No significant difference in pulmonary function tests (FEV1, FVC, and FEV1/FVC) between the RAB vs placebo.		C Small sample size, no detail of randomization
Jiang 2003 ¹⁰⁸ [12717871]	Omeprazole 20 mg /d & Domperidone 10 mg three times/d + anti-asthmatics (Salbutamol 200 mg four times /d & budesonide 400 mg twice a day) vs. anti-asthmatics	30/30	6 wk			Significant higher net difference in bronchial hyperreactivity (measured by PC-20 (g/L) OME & domperidone with asthma medication vs. only asthma medication (net difference: 0.54; 95 percent CI: 0.42,0.66), P<0.0001		C, no blinding, No details of method of randomization

Table 31. Treatment of GERD and its effect on extra-esophageal symptoms: Hoarseness and laryngitis

Author Year [PMID]	Hopkins 2009 [16437513] ¹⁰⁴		
Design	Randomised and quasi-randomised, controlled, double-blinded trials, controlled clinical trials (trials using a control group but no adequate randomisation procedure) and quasi-randomised trials of anti-reflux therapy for adult patients with hoarseness in the absence of other identifiable causes, irrespective of diagnosis of laryngopharyngeal reflux and GERD.		
Population	All adult (aged 18 or over) patients with hoarseness (dysphonia), regardless of GERD diagnosis, and who have undergone laryngoscopy to exclude other identifiable causes of hoarseness including malignancy, vocal cord paralysis and vocal cord nodules.		
Intervention (Exposure) and Comparator	<p>Non-surgical:</p> <p>a) Lifestyle modification and patient education</p> <p>b) Drugs: Proton pump inhibitors (PPIs), Antacids, H2-receptor antagonists, Prokinetic agents, Erythromycin</p> <p>Surgical:</p> <p>a) Fundoplication repair - Nissen, Rossetti, Toupet partial fundoplication, Bore partial fundoplication, Collis gastroplasty followed by fundoplication</p> <p>b) Non-fundoplication repairs: Hill repair (gastropexy), Belsey Mark IV</p>		
Results	<p>302 studies of hoarseness; 6 RCTs comparing gastric acid suppression with PPI vs placebo; no randomised trials of other methods of anti-reflux treatment.</p> <p>In all 6 RCT, 275 patients (sample size ranged from 15-145 participants) randomized to PPI or placebo. f/u ranged from 2 months - 3 months.</p> <p>Quality of outcome assessment (i.e. hoarseness) was not adequate as symptoms used for inclusion into the studies did not correlate with the results from the pH studies within these studies.</p> <p>The studies also used different and invalidated instruments to measure the outcome of interest, making inter-study comparisons invalid.</p> <p>4 of 6 studies included in the review could not find a significant difference in resolution of symptoms/hoarseness between the PPI and placebo groups;</p> <p>Authors state that excluded studies indicate a placebo effect (data not shown).</p>		
Comments	The SR was limited by the quality of the studies available in the literature. The outcome of interest, hoarseness, could not be ascertained reliably in all the RCTs that were screened.		
AMSTAR			
A priori design?	Y	Study quality assessment performed?	Y
Two independent reviewers?	Y	Study quality appropriately used in analysis?	N/A
Comprehensive literature search?	Y	Appropriate statistical synthesis?	N/A
All publication types and languages included?	nd	Publication bias assessed?	nd
Included and excluded studies listed?	Y	Conflicts of interest stated?	Y
Study characteristics provided?	N		
Author Year [PMID]	Iqbal 2008 [19105666] ¹⁰⁶		
Design	A systematic review of retrospective and prospective studies, including RCTs, of surgical fundoplication in the treatment of the symptoms of extra-esophageal reflux (EER).		
Population	Adults		
Intervention (Exposure) and Comparator	Surgery / fundoplication; no comparator		
Results	<p>Laryngeal symptoms: 8 published observational cohort studies (case series); 4/8 were prospective studies; f/u ranged from 6 - 65 months^a. Interventions included: Nissen fundoplication, Toupet fundoplication, laparoscopic Nissen fundoplication, Collis Nissen fundoplication, Belsey Mark IV repair.</p> <p>Complete resolution of symptoms: 5/8 studies</p> <p>Complete/ partial relief of symptoms: 65–94% of participants.</p> <p>Good pre-operative response to antacid medication predicted good response to surgery (2 studies)</p>		
Comments	Included both prospective and retrospective studies; no quantitative analysis; quality of studies was not assessed		

AMSTAR			
A priori design?	N	Study quality assessment performed?	N
Two independent reviewers?	N	Study quality appropriately used in analysis?	n/a
Comprehensive literature search?	Y	Appropriate statistical synthesis?	n/a
All publication types and languages included?	Y	Publication bias assessed?	N
Included and excluded studies listed?	N	Conflicts of interest stated?	Y
Study characteristics provided?	Y		

^a One study had a f/u range of 6-108 months

Table 32. Treatment of GERD and its effect on extra-esophageal symptoms: Chronic Cough

Author Year	Chang 2009¹⁰³		
Design	RCTs on GERD treatment for chronic cough (non-specific dry cough \geq 3 weeks duration unrelated to underlying respiratory disease (COPD, asthma or cystic fibrosis) or secondary to medication use).		
Population	Adults and pediatric patients with chronic cough		
Intervention (Exposure) and Comparator	Intervention 1- Anti reflux conservative measures 2- H2 receptor antagonists 3- Proton pump inhibitors 4- Surgical therapy Control- placebo		
Results	18 articles, 13 on adults, 5 on pediatric population. 10 parallel studies, 3 crossover studies (with a washout periods of two weeks). Meta-analysis model and heterogeneity (if applicable) <ul style="list-style-type: none"> - PPI vs. placebo (Adults >18 years) for failure to cure based on clinical features (still coughing at end of trial or reporting period). <ul style="list-style-type: none"> o Random effects model, Pooled OR 0.46 (95 percent CI 0.19 to 1.15) [Heterogeneity:- Tau²=0.00, Chi² = 1.14, df=3 (P=0.77); I²=0 percent] - PPI vs. placebo (Adults >18 years) for mean cough scores at end of intervention. <ul style="list-style-type: none"> o Random effects model, Pooled OR -0.38 (95 percent CI -0.77 to 0.00) [Heterogeneity:- Chi² = 1.98, df=3 (P=0.58); I²=0 percent] - PPI vs. placebo (Adults >18 years), for change in cough scores (end-beginning of intervention); data from parallel group / crossover studies: <ul style="list-style-type: none"> o SMD effect estimate -0.39 (95 percent CI -0.71 to -0.08) [Heterogeneity:- Chi² = 5.68, df=5 (P=0.34); I²=12 percent] o Only Crossover studies; standardized scale; fixed effects model. SMD effect estimate -0.41 (95 percent CI -0.75 to -0.07). [Heterogeneity:- Chi² = 0.10, df=1 (P=0.76); I²=0 percent] o Crossover studies; Absolute scores; fixed effects model. SD effect estimate -0.29 (95 percent CI -0.62 to -0.04). [Heterogeneity:- Chi² = 0.38, df=1 (P=0.54); I²= 0 percent] Meta-analysis revealed no significant difference in cure of cough between PPIs and placebo. Meta-analysis revealed significant improvement on cough outcomes at end of trial and in change in cough scores (both in overall scores as well as in data from crossover trials).		
Comments	1-Small number of studies and select availability of unpublished articles therefore potential for publication bias. 2-Lack of validated scales and objective data on cough. 3-lack of allocation concealment data due to clinical heterogeneity of participants and medications 4-Most studies did not use the GORD criteria specified by guidelines of American and European Gastroenterology Associations.		
AMSTAR			
A priori design?	Yes	Study quality assessment performed?	Yes
Two independent reviewers?	Yes	Study quality appropriately used in analysis?	Yes
Comprehensive literature search?	Yes	Appropriate statistical synthesis?	Yes
All publication types and languages included?	Yes	Publication bias assessed?	Yes
Included and excluded studies listed?	Yes	Conflicts of interest stated?	Yes
Study characteristics provided?	Yes		
Author Year [PMID]	Iqbal 2008 [19105666]¹⁰⁶		
Design	Retrospective and prospective studies of surgical fundoplication in the treatment of the symptoms of extra-esophageal reflux.		
Population	Adults		
Intervention (Exposure) and Comparator	Surgery / fundoplication		
Results	13 studies suggested that 60–100 percent of patients improve after surgery. Surgery		

	in cough was still less successful than surgery for classical GERD.		
Comments	Included both prospective and retrospective studies; no quantitative analysis; quality of studies was not assessed		
AMSTAR			
A priori design?	N	Study quality assessment performed?	N
Two independent reviewers?	N	Study quality appropriately used in analysis?	n/a
Comprehensive literature search?	Y	Appropriate statistical synthesis?	n/a
All publication types and languages included?	N	Publication bias assessed?	N
Included and excluded studies listed?	N	Conflicts of interest stated?	Y
Study characteristics provided?	Y		

Key Question 2: Is there evidence that effectiveness of medical, surgical and newer forms of treatment 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, and other demographic and medical factors? What are the provider characteristics for procedures including provider volume and setting (e.g., academic versus community)?

Synopsis

The 2005 CER identified a number of patient characteristics and baseline clinical factors that may influence the effectiveness of medical, surgical, or endoscopic treatment; however, the quality and consistency of these primary data were mixed and the strength of the identified associations remained unclear. Fifty additional studies were included in this update: 16 medical, 30 surgical, three endoscopic, and one medical versus surgical. For medical treatment, 17 percent (1/6) of RCTs and 40 percent (4/10) of cohort studies were rated C. For surgical treatment, the majority (77 percent) of studies were rated C. For endoscopic treatment, all three studies were rated C. The findings in this update are in general agreement with those from the 2005 report. In addition, the studies included in this update are similarly plagued with a number of methodological issues.

Key findings:

- One study showed that there was no significant difference in the effectiveness of surgical versus medical treatment between patients with or without Barrett's esophagus.
- Results from RCTs comparing different PPIs, or dosages and dosing regimens of PPIs showed mixed findings regarding the impacts of esophagitis severity at baseline on healing rates.
- Cohort studies found that sex was not significant modifying factors of medical treatment outcomes.
- Cohort studies consistently showed that obesity, presence of baseline typical GERD symptoms, and more severe esophagitis at baseline were significantly associated with worse medical treatment outcomes, but the associations between age and medical treatment outcomes were inconsistent.
- For surgical treatment, the following patient characteristics were inconsistently associated with worse surgical outcome: per year increase in patient's age, morbid obesity, female sex, presence of baseline symptoms, and esophagitis and hiatal hernia more than 3 centimeter at baseline.
- Preoperative esophageal motility did not significantly impact the effect of Nissen or Toupet laparoscopic fundoplication on dysphagia, recurrence of reflux, and 24-hour pH-metry and manometry outcomes 2 years after surgery.

Detailed analysis

No study examined the influences of provider characteristics on medical or surgical treatment outcomes, including provider volume and setting (e.g., academic versus community). For endoscopic treatment, one small study observed a learning curve in performance of a new endoscopic treatment device (EsophyX) comparing the technical procedure parameters in 17 patients.⁹¹

We first summarized the findings from a study that evaluated patient characteristics or clinical factors as modifying factors of comparative effectiveness of surgical versus medical treatment, followed by the findings from studies that evaluated patient characteristics or clinical factors as modifying factors of the outcomes of medical, surgical, or endoscopic treatment in this order.

Factors that influenced the comparative effectiveness of surgical versus medical treatment

One B-quality study, the Long-Term Usage of Acid Suppression Versus Antireflux Surgery (LOTUS) trial, was identified as comparing treatment outcomes in patients with versus those without Barrett's esophagus, randomized to laparoscopic antireflux surgery (LARS) or esomeprazole treatment.¹⁴ There were no major differences in demographics, disease specific characteristics, or allocation to treatment between patients with (n=60) and without (n=494) Barrett's esophagus. The study did not find significant differences in therapeutic outcomes (GI Symptom Rating Scale or quality of life) between the two groups after 3 years of followup.

Factors that influenced the outcome of medical therapy

Sixteen studies published after the 2005 CER evaluated whether baseline patient characteristics or clinical factors could differentially affect the outcomes of medical treatment (proton pump inhibitors or H₂ receptor antagonists). Six were RCTs that also examined whether the treatment outcomes differ by patients' baseline esophagitis severity,^{32,44,48,54,55,60} and 10 were cohort studies that examined patients characteristics or clinical factors as modifying factors of medical treatment outcomes.^{28,33,62,115-121} Of the six RCTs, four compared effects of different PPIs,^{32,54,55,60} one compared different dosing regimens of PPI,⁴⁸ and one compared different dosages of PPI.⁴⁴ In this section, we first summarized findings from the RCTs, followed by the findings from cohort studies.

RCTs comparing different proton pump inhibitors (Table 33)

Four RCTs (1 rated A, 2 rated B, and 1 rated C) compared effects of different PPIs and reported the treatment outcomes by baseline esophagitis severity.^{32,54,55,60} The PPI treatment comparisons were different across studies, and the treatment durations ranged from 1 to 6 months. Three of the four RCTs used the Los Angeles (LA) classification for the severity of esophagitis,^{32,54,60} while the remaining RCT used Savary-Miller classification.⁵⁵

Overall, two of the four RCTs found that the healing rates were similar between PPI treatment groups regardless of the baseline esophagitis severity, and the other two RCTs found opposite findings with regards to the effects of different PPIs by baseline esophagitis severity. Specifically, one RCT found that the healing rate was only significantly different between PPI treatment groups in patients with grade I (less severe) esophagitis, while the other RCT found that healing rate was only significantly different between PPI treatment groups in patients with grade C (more severe) esophagitis.

One A-quality RCT compared the effects of esomeprazole (20 mg/day) with that of omeprazole (20 mg/day) in a total of 1175 patients with erosive esophagitis and reported the cumulative healing rates by baseline severity grades.⁵⁴ The cumulative healing rates were similar between esomeprazole and omeprazole groups in patients with LA grade A (95 vs. 88 percent, respectively), grade B (85 vs. 85 percent, respectively), grade C (79 vs. 73 percent, respectively), or grade D (73 vs. 69 percent, respectively). The authors also reported that “sex, age (<65 vs. ≥65 years), race, and H. pylori status had no meaningful effect on treatment outcome in either group”.

One B-quality RCT compared effects of omeprazole (20 mg/day) with that of lansoprazole (15 mg/day) and reported the cumulative endoscopic or symptomatic remission rates by patients’ baseline severity of esophagitis over 6 months of treatment.⁶⁰ When patients were divided into two groups based on their baseline LA grades, the cumulative endoscopic or symptomatic remission rates were similar between omeprazole and lansoprazole groups in patients with LA grades A or B (88 vs. 81 percent, respectively) and in those with LA grade C or D (79 vs. 70 percent, respectively).

One B-quality RCT compared effects of four PPIs (omeprazole, lansoprazole, pantoprazole, rabeprazole) in elderly patients with esophagitis, and analyzed the healing rates by the baseline severity of esophagitis.⁵⁵ The healing rate was significantly lower in patients with grade I (less severe) esophagitis treated with omeprazole (20 mg/day) than in patients treated with lansoprazole (30 mg/day), pantoprazole (40 mg/day), or rabeprazole (20 mg/day) (81.8 vs. 100, 100 and 100 percent, respectively, $P = 0.012$). In patients with grade II, III, or IV esophagitis, there was no significant differences in the healing rates between the four PPIs.

The C-quality RCT found that esomeprazole (40 mg/day) was more effective than pantoprazole (40 mg/day) in healing erosive esophagitis among patients with more severe (LA grade B or C) esophagitis at baseline.³² The healing rates of erosive esophagitis after 4 weeks treatment of esomeprazole and pantoprazole were 84 and 83 percent ($P=NS$) respectively among patients with LA grade A at baseline, 78 and 72 percent ($P<0.05$) respectively among patients with LA grade B at baseline, and were 62 and 50 percent ($P<0.01$) respectively among patients with LA grade C at baseline. However, these results were based on only 75 percent of treated patients.

RCTs comparing different dosages and dosing regimens of proton pump inhibitors (Table 34)

We identified one RCT comparing different dosing regimen of PPI and one RCT comparing different dosages of PPI, and both RCTs reported the treatment outcomes by baseline esophagitis severity.^{44,48} Both RCTs used LA classification for the severity of esophagitis, and both were rated B quality.

One B-quality RCT compared effects of esomeprazole (20 mg/day) once daily with that of esomeprazole (20 mg/day) on-demand and examined the endoscopic remission rates by patients’ baseline severity of esophagitis over the 6 months of treatment.⁴⁸ The endoscopic remission rates were significantly higher in patients who received esomeprazole on-demand treatment than in those who received esomeprazole once daily regardless of the baseline severity (LA grades A to D). Overall, patients with more severe grades had more frequent endoscopic remission ($P=0.0017$). The endoscopic remission rates ranged from 7 to 20 percent in esomeprazole once daily group; and it ranged from 22 to 56 percent in esomeprazole on-demand group for patients with LA grades A to D.

One B-quality RCT compared the effects of two different dosages dexamprazole (30 or 60 mg/day) and reported the cumulative healing rates by patients' baseline severity of esophagitis over the 6 months of treatment.⁴⁴ Only patients with healed erosive esophagitis from previous healing studies were enrolled in this RCT. The maintained healing rates at were similar in the dexamprazole 30- and 60-mg treatment groups among patients with baseline grade A or B (80 vs. 82 percent, respectively). However, for patients with LA grades C and D at baseline, the maintained healing rates were lower in patients who received lower dose of dexamprazole than in patients who received higher dose of dexamprazole (63 vs. 85 percent, respectively).

Cohort studies of medical treatment (Table 35)

Ten cohort studies that examined patients characteristics or clinical factors as modifying factors of medical treatment outcomes.^{28,33,62,115-121} Medical treatment used in these studies include esomeprazole, pantoprazole, lansoprazole, rabeprazole, and nizatidine. As a particular study may have analyzed more than one factor, several studies appear multiple times in the present analyses. Of the 10 analyzed publications, five studies were on age,^{28,33,115,118,119} five on sex,^{28,33,118-120} six on BMI or obesity,^{28,33,117-119,121} one on severity of acid reflux,¹¹⁷ one on hiatal hernia,¹²¹ four on baseline symptoms,^{28,33,117,118} and six on esophagitis.^{58,62,116,118,119,122}

Overall, cohort studies found that sex was not significant modifying factors of medical treatment outcomes. Moreover, the studies found that obesity, baseline typical GERD symptoms, and severe esophagitis were significantly associated with worse medical treatment outcomes, but the associations between age and medical treatment outcomes were inconsistent. Study results are summarized below.

Age

Five studies (with a total of 14,645 patients) examined the influence of age on medical treatment outcomes.^{28,33,115,118,119} Three were rated B and two were rated C. Sample sizes ranged from 424 to 6,215.

Two studies found that there was no significant difference in medical outcome between older (≥ 65 or ≥ 60 years of age) and younger patients.^{115,119} Three studies (two graded B and one C) found that a per-year increase in patient age was significantly associated with better medical outcomes.^{28,33,118} Specifically, two B-quality studies examined factors associated with heartburn resolution in the Expo RCT (mean age 51 years old): one for the findings during the active phase of treatment (esomeprazole or pantoprazole 40 mg/day for 4 weeks),²⁸ and one for the findings during the maintenance phase of treatment (esomeprazole or pantoprazole 20 mg/day for 6 months).³³ Multivariate analyses showed that a per-year increase in patient age remained a significant predictor of odds of freedom from heartburn relapse during active phase of treatment (adjusted OR 1.01 [95 percent CI 1.01, 1.02]) and during maintenance phase of treatment (adjusted OR 1.02 [95 percent CI 1.01, 1.03]). One C-quality study analyzed data from a 10-year cohort study including 6215 patients (mean age 54 years old) and showed that a per-year increase in patient age was significantly associated with a reduced risk of continuous use of PPI (OR 0.97 [95 percent CI 0.96, 0.98]).

Sex

Five studies (with a total of 14,400 patients) examined the influence of sex on medical outcomes.^{28,33,118-120} Three studies were quality B and two were quality C. Sample sizes ranged

from 179 to 6,215. All five studies did not find a significant association between sex and medical outcomes.

Increase BMI or overweight

Six studies (with a total of 14,711 patients) examined the influence of body mass index (BMI, kg/m²) or obesity status on medical outcomes.^{28,33,117-119,121} Five studies were quality B and four were quality C. Sample sizes ranged from 113 to 6,215.

Only one study did not find significant association between obesity (BMI \geq 30) and medical outcomes,¹¹⁹ the other five studies consistently showed that overweight or obesity was significantly associated with worse medical outcomes, such as symptom relapse, continual use of PPIs, or treatment failure.^{28,33,117,118,121}

Hiatal hernia

One B-quality study (113 patients)¹²¹ did not find significant association between presence of hiatal hernia at baseline and medical outcomes.

Baseline symptoms

Four studies (a total of 8,383 patients) examined the influence of baseline symptoms on medical outcomes.^{28,33,117,118} Three studies was rated quality B and one was rated quality C. Sample sizes ranged from 377 to 4,855.

All four studies consistently showed that more severe baseline symptoms (e.g., heartburn, regurgitation, or symptom score) was significantly associated with worse medical outcomes, such as symptom relapse and continual use of PPIs.^{28,33,117,118} One of the four studies, however, reported that baseline heartburn severity was not significantly associated with the failure of on-demand treatment although it was significantly associated with an increased risk of symptom relapse during the active treatment period (adjusted OR 1.08 [95 percent CI 1.01, 1.12]).¹¹⁷

Esophagitis

Six studies (a total of 8538 patients) examined the influence of baseline status of esophagitis on medical outcomes.^{58,62,116,118,119,122} Four studies were rated quality B and two were rated quality C. Sample sizes ranged from 45 to 4,855.

One study did not find a significant association between baseline esophagitis and medical outcomes.⁵⁸ Five studies consistently showed that more severe esophagitis (based on Hill criteria, LA grades or other esophagitis severity scales) was significantly associated with worse medical outcomes, such as continual use of PPIs, or treatment failure.^{62,116,118,119,122} One of the five studies, however, reported that more severe esophagitis (based on Hill criteria) was not significantly associated with total symptom score although it was significantly associated with more PPI use.¹¹⁶

Factors that influenced the outcome of fundoplication (Table 36)

Thirty studies published after the 2005 CER evaluated whether preoperative patient characteristics or baseline clinical factors could differentially affect the outcomes of fundoplication.^{67,70,77-79,123-147} Surgical outcomes of interest included typical GERD symptoms (e.g., dysphagia, heartburn, and regurgitation), pH status, whether the patients were off PPIs or all medications, quality of life, and global success or failure (definitions of success or failure varied across studies). As a particular study may have analyzed more than one factor, several

studies appear multiple times in the present analyses. Of the 30 analyzed publications, nine studies were on age,^{67,70,78,79,125,128,137,142,144} six on sex,^{67,70,78,79,130,136} six on BMI or obesity,^{123,127,129-131,136} two on psychological profile,^{132,147} four on baseline symptoms,^{70,77,79,134} two on preoperative response to acid-suppression therapy,^{131,146} seven on esophagitis,^{78,131,133-136,143} one on esophageal pH,⁶⁷ one on LES competence,¹⁴⁰ four on esophageal motility,^{124,138,139,141} four on hiatal hernia,^{78,131,134,136} and two on reflux patterns.^{126,145}

Overall, firm conclusions are difficult to make concerning patient characteristics or baseline clinical factors as modifiers of fundoplication outcomes as many of the included studies were retrospective analyses relying on pre-existing patient records and/or self-reported outcomes with missing data, a lack of adjustment for potential confounding in the statistical analyses, or selection bias. Study results are summarized below.

Age

Nine studies (with a total of 3,750 patients) examined the influence of age on surgical outcomes.^{67,70,78,79,125,128,137,142,144} Of these, three were rated B and six were rated C. Sample sizes ranged from 82 to 1,340.

Seven studies found that a patient's age was not significantly associated with surgical outcomes, or that there was no significant difference in surgical outcomes between older (≥ 65 years of age was the most commonly used cutoff) and younger patients.^{67,78,125,128,137,142,144} Two studies (one graded B and one C) found that a per-year increase in patient's age was significantly associated with worse surgical outcomes.^{70,79} Specifically, the B-quality study (mean age: 47 years) conducted a multivariate analysis and showed that a per-year increase in patient's age remained a significant predictor for operation failure (success was defined as complete absence of the presenting symptom at the time of postoperative evaluation) after controlling for type of surgery (Nissen vs. Toupet) and other risk factors (adjusted OR 1.03 [95 percent CI, 1.01, 1.58]).⁷⁹ The C-quality study (mean age: 58 years) found that a per-year increase in patient age was a significant predictor for anti-reflux medication use after surgery (OR 1.04 [95 percent CI 1.02, 1.05]).⁷⁰

Sex

Six studies (with a total of 1,701 patients) examined the influence of sex on surgical outcomes.^{67,70,78,79,130,136} One study was quality B and five were quality C. Sample sizes ranged from 102 to 844.

Four studies did not find a significant association between sex and surgical outcomes.^{67,70,78,130} Two studies (one B, one C) found that male sex was significantly associated with better surgical outcomes.^{79,136} Specifically, the B-quality study conducted a multivariate analysis and showed that being male was significantly associated with a reduced risk of operation failure (success was defined as complete absence of the presenting symptom at the time of postoperative evaluation) after controlling for the type of surgery (Nissen vs. Toupet) other risk factors (adjusted OR 0.52 [95 percent CI, 0.29, 0.94]).⁷⁹ The C-quality study found that the male-to-female ratio was significantly lower in the poor outcome group (including patients whose outcomes were the same or worse than pre-op and those who were not happy with the results of the operation) than in the good outcome group (0.8 vs. 2.6, $P=0.001$).¹³⁶

Increase BMI or overweight

Six studies (with a total of 1,261 patients) examined the influence of body mass index (BMI, kg/m²) or obesity status on surgical outcomes.^{123,127,129-131,136} Two studies were quality B and four were quality C. Sample sizes ranged from 91 to 481.

Four studies did not find a significant association between BMI or obesity status and surgical outcomes.^{127,129,131,136} Two studies (both C-quality) found that higher BMI or obesity was significantly associated with worse surgical outcomes.^{123,130} Specifically, one study compared the surgical outcomes in patients with a BMI of 35 or more (mean BMI 38.4) with patients who had a BMI less than 30 (mean BMI 24.2).¹²³ This study found that morbidly obese patients reported significantly higher reflux symptom scores (indicates a worse outcome) 6 months postoperatively compared with patients who were of normal weight (P<0.0001); however, the difference in reflux symptom score was not associated with a significant difference in acid reflux as measured by 24-hour pH study. The other study also found that morbidly obese patients reported a significantly higher GERD-HRQL scores (indicating a worse outcome) than patients in the lower BMI groups (BMI 25-29.9, or 30-34.9).¹³⁰

Psychological profile

Two C-quality studies (with a total of 82 patients) examined the influence of psychological profile on surgical outcomes.^{132,147} One found that postoperative GERD symptoms and quality of life were not significantly different between patients with (n=28) and without (n=22) conversion disorder as diagnosed by the Minnesota Multiphasic Personality Inventory.¹³² The other reported similar findings having compared patients with (n=7) and without (n=25) depression documented by preoperative history and treatment with one or more antidepressants.¹⁴⁷ Additionally, this study also did not find a significant difference in postoperative PPI use between patients with and without depression.

Baseline symptoms

Four studies (with a total of 1,679 patients) examined the influence of baseline symptoms on surgical outcomes.^{70,77,79,134} One study was quality B and three were quality C. Sample sizes ranged from 31 to 844.

Two C-quality studies did not find significant associations between preoperative non-specific gastrointestinal symptoms or typical GERD symptoms and postoperative symptom outcomes.^{77,134} The other two studies (one B, one C) reported that preoperative typical GERD symptoms were significantly associated with poorer surgical outcomes. Specially, the B-quality study conducted a multivariate analysis and showed that preoperative dysphagia remained a significant predictor of operation failure (success was defined as complete absence of the presenting symptom at the time of postoperative evaluation) after controlling for type of surgery (Nissen vs. Toupet) and other risk factors (adjusted OR 2.17 [95 percent CI, 1.18, 3.98]).⁷⁹ The C-quality study found that preoperative heartburn and regurgitation were significantly associated with anti-reflux medication use after surgery (OR 6.5 [95 percent CI 4.5, 9.5] and OR 1.7 [95 percent CI 1.2, 2.4], respectively).⁷⁰

Preoperative response to acid-suppression therapy

Two studies (with a total of 415 patients) examined the influence of preoperative response to acid suppression treatment on surgical outcomes.^{131,146} One, a B-quality prospective study, found that a borderline significantly higher proportion of good responders to preoperative PPIs reported an excellent or good outcome with surgery (Visick I or II) compared to poor

responders (218/233 [94 percent] vs. 79/91 [87 percent]; $P=0.08$).¹⁴⁶ The other, a C-quality retrospective case-control study, found that preoperative good response to PPIs was associated with a reduced risk of treatment failure (OR 0.69 [95 percent CI, 0.48, 1.0]) in a univariate, but not in a multivariate analysis.¹³¹

Esophagitis

Seven studies (with a total of 782 patients) examined the influence of baseline status of esophagitis on surgical outcomes.^{78,131,133-136,143} All seven studies were quality C. Sample sizes ranged from 31 to 178.

Findings were mixed among the evaluated studies. Three reported no significant differences in surgical outcomes between patients with and without esophagitis at baseline,^{78,131,134} and two did not find a significant difference in surgical outcomes comparing patients with mild esophagitis at baseline to those with non-erosive or severe esophagitis at baseline.^{135,136} Another study did not find a significant difference in quality of life outcomes comparing patients with non-erosive esophagitis at baseline to those with erosive esophagitis at baseline. However, this study found a borderline significant effect in the rate of postoperative anti-reflux medication use (39 percent vs. 25 percent, respectively; $P=0.08$) and a significantly higher rate of postoperative symptoms (50 percent vs. 29 percent, respectively; $P=0.03$) between these two groups (non-erosive vs. erosive).¹⁴³ The seventh study found that patients with esophagitis reported a significantly lower gastrointestinal quality of life than patients without esophagitis at baseline ($P<0.05$).¹³³

Esophageal pH

One B-quality study conducted a multivariate analysis to examine the potential risk factors for recurrence of reflux symptoms among 133 patients who underwent partial or total fundoplication.⁶⁷ The study found that a DeMeester score greater or equal to 50 was the only significant predictor for recurrence of reflux symptoms in the multivariate model, which considered operation method (Nissen vs. Toupet) and other risk factors ($P=0.04$).

LES competence/pressure

One C-quality retrospective study aimed to examine the associations between preoperative LES manometry data and 1-year postsurgical outcomes among 351 patients.¹⁴⁰ Patients were grouped based on the main variables (i.e., intraabdominal length and lower esophageal sphincter pressure) representing LES competence in esophageal manometry. The results demonstrated that the preoperative manometric character of the LES was not significantly associated with either subjective or objective outcomes after laparoscopic antireflux surgery.

Esophageal motility

Four studies (with a total of 819 patients) examined the influence of esophageal dysmotility on surgical outcomes.^{124,138,139,141} One study was quality A, two quality B, and one quality C. Sample sizes ranged from 98 to 400.

The A-quality RCT randomized 200 patients (100 with normal and 100 with abnormal esophageal motility) to either Nissen or Toupet laparoscopic fundoplication.¹⁴¹ Two-year outcomes were assessed. The results indicated that preoperative esophageal motility did not significantly impact the effect of Nissen or Toupet laparoscopic fundoplication on dysphagia, recurrence of reflux and 24-hour pH-metry and manometry outcomes. The other three studies (2

B- and 1 C-quality) also did not find a significant association between esophageal motility and surgical outcomes.^{124,138,139}

Hiatal hernia

Four studies (with a total of 367 patients) examined the influence of hiatal hernia on surgical outcomes.^{78,131,134,136} All four studies were rated C. Sample sizes ranged from 31 to 143.

Three studies did not find a significant relationship between the presence of hiatal hernia and surgical outcomes.^{78,134,136} The remaining study indicated that a hernia size greater than 3 cm was significantly associated with an increased risk of surgical failure in the multivariate analysis (adjusted OR 3.17 [95 percent CI, 1.04, 9.69]).¹³¹

Reflux patterns (upright, bipositional, or supine)

Two C-quality studies (with a total of 382 patients) examined the influence of reflux patterns on surgical outcomes.^{126,145} Both found that reflux patterns were not significantly associated with surgical outcomes, including quality of life, reduction of symptoms, use of PPIs, or total acid exposure.

Factors that influenced the outcome of endoscopic treatment

Three C-quality studies examined the potential modifying factors of endoscopic treatment.^{86,91,94} One prospective study, did not find a significant difference between men and women (80 vs. 79 percent) in GERD symptom improvement or resolution after endoluminal gastroplication (EndoCinchTM).⁸⁶ Another study investigated the proportion of patients for complete cessation of PPI use at 6 months after transoral incisionless fundoplication with the EsophyXTM device.⁹⁴ They found that more patients with less severe esophagitis at baseline (base on Hill's grades) stopped PPI use than patients with more severe esophagitis (72 versus 0 percent, respectively; P=0.02). The third study reported a learning curve in endoscopic transoral fundoplication device performance (EsophyXTM) comparing the technical procedure parameters (e.g., procedure time and number of devices used) and found improvements in the last 10 treated patients compared with the first seven treated patients.⁹¹

Table 33. Summary of studies that evaluated patient characteristics as modifying factors in randomized, controlled trials comparing effects of different proton pump inhibitors

Author year [UI] Duration	Comparisons: Drug Name Dose (Frequency)	N analyzed	Potential modifying factor: outcome	P between treatments	Quality Comments
Outcome: healing rate of oesophagitis					
Lightdale 2006 ⁵⁴ [16773434] 8 weeks	Esomeprazole 20 mg (once daily)	587	LA grade A: 95% LA grade B: 85% LA grade C: 78% LA grade D: 73%	nd	A
	Omeprazole 20 mg (once daily)	588	LA grade A: 88% LA grade B: 85% LA grade C: 73% LA grade D: 69%		
Pilotto 2007 ⁵⁵ [17724802] 2 months	Omeprazole 20 mg (once daily)	74	SM grade I: 82% SM grade II: 82% SM grade III-IV: 79%	SM grade I: 0.012 SM grade II: NS	B Unclear outcome definition
	Lansoprazole 30 mg (once daily)	75	SM grade I: 100% SM grade II: 97% SM grade III-IV: 71%	SM grade III-IV: NS	
	Pantoprazole 40 mg (once daily)	77	SM grade I: 100% SM grade II: 90% SM grade III-IV: 94%		
	Rabeprazole 20 mg (once daily)	75	SM grade I: 100% SM grade II: 96% SM grade III-IV: 84%		
Vcev 2006 ³² [17058517] 4 weeks	Esomeprazole 40 mg (once daily)	70	LA grade A: 84% LA grade B: 78% LA grade C: 62%	LA grade A: NS LA grade B: <0.05	C Unclear outcome definition; only 75% patients in the analysis
	Pantoprazole 40 mg (once daily)	65	LA grade A: 83% LA grade B: 72% LA grade C: 50%	LA grade C: <0.01	
Outcome: endoscopic/symptomatic remission rate					
Devault 2006 ⁶⁰ [16682260] 6 months	Esomeprazole 20 mg (once daily)	501	LA grade A/B: 88% LA grade C/D: 79%	nd	B Large dropout
	Lansoprazole 15 mg (once daily)	500	LA grade A/B: 81% LA grade C/D: 70%		

SM, Savary-Miller classification (grade I: non-confluent erosions; grade II: confluent erosions; grade III: lesions extending to the entire circumference of the lower esophagus; and grade IV: deep ulcer or esophagitis with complications, i.e. stenosis and/or hemorrhagic lesions.)

Table 34. Summary of studies that evaluated patient characteristics as modifying factors in randomized, controlled trials comparing different dosages and dosing regimens of commonly used proton pump inhibitors

Author year [UI] Duration	Comparisons: Drug Name Dose (Frequency)	N analyzed	Potential modifying factor: outcome	P between	Quality Comments
Outcome: endoscopic remission rate					
Sjostedt 2005 ⁴⁸ [16091055] 6 months	Esomeprazole 20 mg (once daily)	241	LA grade A: 7% LA grade B: 10% LA grade C: 10% LA grade D: 20%	LA grade A: 0.03 LA grade B: <0.001	B More patients receive on- demand treatment withdrew due to relapse
	Esomeprazole 20 mg (on-demand)	229	LA grade A: 22% LA grade B: 35% LA grade C: 49% LA grade D: 56%	LA grade C: 0.0002 LA grade D: 0.09	
Outcome: esophagitis healing rate					
Metz 2009 ⁴⁴ [19210298] 6 months	Dexlansoprazole 30 mg (once daily)	137	LA grade A/B: 80% LA grade C/D: 63%	nd	B
	Dexlansoprazole 60 mg (once daily)	153	LA grade A/B: 82% LA grade C/D: 85%		

SM, Savary-Miller classification (grade I: non-confluent erosions; grade II: confluent erosions; grade III: lesions extending to the entire circumference of the lower esophagus; and grade IV: deep ulcer or esophagitis with complications, i.e. stenosis and/or hemorrhagic lesions.)

Table 35. Summary of studies that evaluated patient characteristics as modifying factors of medical treatment outcome

Potential modifying factor	Number of Studies (quality)	Outcomes				
		Total patients (range)	Symptoms ^a	Medications		Global Success/ Failure ^b
				Off PPIs	Off all meds	
Older age (≥65 years old)	5 (3 B; ^{28,33,119} 2 C ^{115,118})	Labenz, 2009 [19222417]; Labenz, 2009 [19298581]: 1 yr increase in age adj. OR of heartburn resolution 1.01 (95%CI 1.007, 1.019); 1.02 (95%CI 1.01, 1.03) ^d	Nocon, 2007 [17311605]: 1 yr increase in age OR 0.97 (95%CI 0.96, 0.98)		Malfertheiner, 2005 [15888776]: No diff ^e	
	14,645 ^c (424 to 6215)				DeVault, 2007 [17760655]: No diff	
Male sex	5 (3 B; ^{28,33,119} 2 C ^{118,120})	Labenz, 2009 [19222417]; Labenz, 2009 [19298581]: adj. OR 1.35 (95%CI 1.14, 1.59); No diff ^e	Nocon, 2007 [17311605]: No diff		Malfertheiner, 2005 [15888776]: No diff	
	14,400 ^f (179 to 6215)	Calleja, 2005 [15810621]: No diff				
Increase BMI or weight	6 (5 B; ^{28,33,117,119,121} 1 C ¹¹⁸)	Sheu, 2007 [17850409]: BMI≥25 vs. <25 adj. OR of SSR 0.90 (95%CI 0.89, 0.95) ⁱ	Nocon, 2007 [17311605]: 1 yr increase in BMI OR 0.96 (95% 0.94, 0.99)		Sheu, 2007 [17850409]: BMI≥25 vs. <25 adj. OR of ODT failure 2.9 (95%CI 2.3, 3.5)	
	14,711 ^h (113 to 6215)	Labenz, 2009 [19222417]; Labenz, 2009 [19298581]: No diff; BMI≥30 vs. <30 adj. OR of heartburn resolution 0.76 (95%CI 0.60, 0.93) ^j			BMI≥25 vs. <25 adj. OR of complete healing 0.43 (95%CI 0.29, 0.53)	
Hiatal hernia	1 (1 B ¹²¹)				Malfertheiner, 2005 [15888776]: No diff ^k	
	113				Sheu, 2008 [18702650]: No diff (multivariate analysis)	
Baseline symptoms	4 (3 B; ^{28,33,117} 1 C ¹¹⁸)	Sheu, 2007 [17850409]: heartburn severity adj. OR of SSR 0.93 (95%CI 0.89, 0.99); No diff ^m	Nocon, 2007 [17311605]: 1 unit increase in baseline symptom score OR 0.96 (95%CI 0.95, 0.97)		Sheu, 2007 [17850409]: No diff ⁿ	
	8383 ^l (377 to 4855)	Labenz, 2009 [19222417]; Labenz, 2009 [19298581]: regurgitation adj. OR of heartburn resolution 0.77 (95%CI 0.61, 0.98); heartburn severity adj. OR of heartburn resolution 0.72 (95%CI 0.57, 0.91) ⁿ				

Potential modifying factor	Number of Studies (quality)	Outcomes			
		Symptoms ^a	Medications	Quality of life	Global Success/ Failure ^b
	Total patients (range)		Off PPIs	Off all meds	
Esophagitis (any severity)	6 (4 B; ^{58,116,119,122} 2 C ^{62,118})	Xirouchakis, 2009 [18600453]: No diff ^p	Xirouchakis, 2009 [18600453]: more rabeprazole use among Hill IV group than Hill II or Hill III groups (P=0.02; P=0.001, respectively)		Hamamoto, 2005 [15683433]: LA grade B vs. A non-remission rate 30% vs. 63%, P=0.02; LA grade C/D vs. A non-remission rate 15% vs. 63%, P=0.002
	8538 (45 to 4855)		Nocon, 2007 [17311605]: mild vs. non-erosive OR 0.51 (95%CI 0.22, 0.61); severe vs. non-erosive OR 0.27 (95%CI 0.20, 0.38)		Tepes, 2009 [19453031]: No diff Malfertheiner, 2005 [15888776]: LA grade C/D vs. A/B healing rate 76.9% vs. 90.3%, P<0.001 ^q Kovacs, 2009 [19267194]: healed vs. unhealed EE ^r OR of recurrence 0.46, (95% CI 0.22, 0.97)

ODT, On-demand therapy; SSR, sustained symptomatic response defined as free from symptoms for the last 7 days

^a Symptoms include dysphagia.

^b Individual study's definition of success or failure defined by multiple variables.

^c Two studies analyzed the same patients: one study analyzed 3151 patients during active treatment (4 weeks), while another stud analyzed 2766 patients during maintenance phase (6 months)

^d Odds ratio (95%CI) in active treatment (4 weeks) / maintenance phase (6 months)

^e Comparison: age ≥60 vs. <60

^f Two studies analyzed the same patients: one study analyzed 3151 patients during active treatment (4 weeks), while another stud analyzed 2766 patients during maintenance phase (6 months)

^g Odds ratio (95%CI) in active treatment (4 weeks) / maintenance phase (6 months)

^h Two studies analyzed the same patients: one study analyzed 3151 patients during active treatment (4 weeks), while another stud analyzed 2766 patients during maintenance phase (6 months)

ⁱ Rate of sustained symptomatic response: symptoms of both acid regurgitation and heartburn for the last 7 continuous days in any week and thereafter of the active-phase therapy

^j Odds ratio (95%CI) in active treatment (4 weeks) / maintenance phase (6 months)

^k Comparison: BMI ≥30 vs. <30

^l Two studies analyzed the same patients: one study analyzed 3151 patients during active treatment (4 weeks), while another stud analyzed 2766 patients during maintenance phase (6 months)

^m Comparison: acid regurgitation severity

ⁿ Comparison: severe vs. moderate heartburn

^o Outcome: on-demand therapy failure until the fourth month

^p Comparison: Hill's grading II, III, or IV

^q Erosive reflux patients only

^r Healed erosive esophagitis (EE) was defined by a esophagitis grading scale of 0 to 1; unhealed EE was defined by a esophagitis grading scale of 2 to 4

Table 36. Summary of studies that evaluated patient characteristics as modifying factors of fundoplication outcome

Potential modifying factor	Number of Studies (Quality)	Outcomes					
		Symptoms ^a	pH	Off PPIs	Medications Off all meds	Quality of life	Global Success/ Failure ^b
Older age (≥65 years old)	9 (3 B; ^{67,79,137} 6 C ^{70,78,125,128,142,144}) 3750 (82 to 1340)	Brehant, 2006 [16504893]: No diff	Pizza, 2007 [17278197]: ^f No diff ^g		Wijnhoven, 2008 [18071830]: 1 y increased in age OR: 0.97 (95%CI 0.95, 0.98)	Brehant, 2006 [16504893]: No diff	Brehant, 2006 [16504893]: No diff
		Cowgill, 2006 [16986386]: No diff ^c				Wang, 2008 [18368318]: No diff	Oelschlager, 2008 [17970835]: 1 y increased in age adj. OR of operation failure
		Tedesce, 2006 [16549695]: No diff				Teixeira, 2009 [19453033]: No diff ^h	1.03 (95%CI, 1.01, 1.58) ⁱ
		Hafez, 2008 [18449599]: No diff ^j					
		Wang, 2008 [18368318]: No diff					
		Pizza, 2007 [17278197]: ^c No diff					
Male sex	6 (1 B; ⁶⁷ 5 C ^{70,78,79,130,136}) 1701 (102 to 844)	Hafez, 2008 [18449599]: No diff			Wijnhoven, 2008 [18071830]: No diff	Teixeira, 2009 [19453033]: No diff	Manning, 2006 [16872031]: Male:female ratio sig. lower in poor outcome group ⁱ (0.8 vs. 2.6, P=0.001)
						Gee, 2008 [18490558]: No diff	Oelschlager, 2008 [17970835]: adj. OR of operation failure OR 0.52 (95%CI: 0.29, 0.94)

Potential modifying factor	Number of Studies (Quality)	Outcomes					
		Symptoms ^a	pH	Off PPIs	Medications Off all meds	Quality of life	Global Success/ Failure ^b
Increase BMI or weight	6 (2 B; ^{127,129} 4 C ^{123,130,131,136})	D'Alessio, 2005 [16137590]: No diff ^k	Anvari, 2006 [16341568]: No diff ^m			Gee, 2008 [18490558]: sig. worse HRQL (P<0.05) ⁿ	Iqbal, 2006 [16368486]: No diff
	1261 (91 to 481)	Anvari, 2006 [16341568]: BMI≥35 vs. <30 net Δ in reflux symptom score: +5.64 (95%CI 1.04, 10.24) ^l					Manning, 2006 [16872031]: No diff
Psychological	2 (2 C ^{132,147})	Kalinowska, 2006 [17427490]: No diff		Yano, 2009 [19207552]: No diff		Kalinowska, 2006 [17427490]: No diff	
	82 (32; 50)	Yano, 2009 [19207552]: No diff				Yano, 2009 [19207552]: No diff	
Baseline symptoms	4 (1 B; ⁷⁹ 3 C ^{70,77,134})	Biertho, 2006 [16823657]: No diff			Wijnhoven, 2008 [18071830]: heartburn OR: 0.15 (95%CI 0.10, 0.22); regurgitation OR: 0.60 (95%CI 0.42, 0.87)		Oelschlager, 2008 [17970835]: adj. OR of operation failure 2.17 (95%CI: 1.18, 3.98) ^o
	1678 (31 to 844)	Lee, 2009 [19259354]: No diff					

Potential modifying factor	Number of Studies (Quality)	Outcomes					
		Symptoms ^a	pH	Off PPIs	Medications Off all meds	Quality of life	Global Success/ Failure ^b
Preoperative good response to acid-suppression therapy	2 (1 B; ¹⁴⁶ 1 C ¹³¹)	Wilkerson, 2005 [16025197]: No diff					Iqbal, 2006 [16368486]: No diff ^o
	415 (91; 324)						Wilkerson, 2005 [16025197]: good vs. poor responders +4% good surgery outcome (Visick I or II), P=0.08
Esophagitis	7 (7 C ^{78,131,133-136,143})	Thibault, 2006 [16907894]: Non-erosive vs. erosive 50% vs. 29% daily symptoms, P=0.03			Thibault, 2006 [16907894]: Non-erosive vs. erosive 39% vs. 25%, P=0.08	Kamolz, 2005 [15959712]: Esophagitis positive vs. negative net Δ GI QoL: -12.4 (nd), P<0.05	Iqbal, 2006 [16368486]: No diff
	782 (31 to 178)	Lord, 2009 [19050984]: No diff ^l				Thibault, 2006 [16907894]: No diff ^o	Manning, 2006 [16872031]: grade III/ IV vs. I/II No diff
		Lee, 2009 [19259354]: No diff					Teixeira, 2009 [19453033]: No diff
Severity of acid reflux	1 (1 B ⁶⁷) 133	Hafez, 2008 [18449599]: DeMeester score ≥50 sig. predicting time until recurrence of reflux symptom (P=0.04 ^s)					
Preoperative LES incompetence or low LES	1 (1 C ¹⁴⁰) 351	Riedl, 2009 [19370381]: No diff	Riedl, 2009 [19370381]: No diff			Riedl, 2009 [19370381]: No diff	

Potential modifying factor	Number of Studies (Quality)	Outcomes					
		Symptoms ^a	pH	Off PPIs	Medications Off all meds	Quality of life	Global Success/ Failure ^b
Esophageal dysmotility	4 (1 A, ¹⁴¹ 2 B, ^{124,138} 1 C ¹³⁹) 819 (98 to 400)	Strate, 2008 [18027055]: No diff	Strate, 2008 [18027055]: No diff ^u			Ravi, 2005 [16105534]: No diff	
		Ravi, 2005 [16105534]: No diff	Ravi, 2005 [16105534]: No diff				
		Pizza, 2008 [18197944]: ^l No diff	Pizza, 2008 [18197944]: ^v No diff ^w				
		Booth, 2008 [18076018]: No diff					
Hiatal hernia	4 (4 C ^{78,131,134,136}) 367 (31 to 143)	Lee, 2009 [19259354]: No diff				Teixeira, 2009 [19453033]: No diff	Iqbal, 2006 [16368486]: hernia size >3 cm adj. OR of failure: 3.17 (95%CI 1.04, 9.69); P=0.04
							Manning, 2006 [16872031]: No diff
Reflux patterns (upright, bipositional, or supine)	2 (2 C ^{126,145}) 382 (148; 234)	Wayman, 2007 [17377929]: No diff	Broeders, 2009 [19491839]: No diff	Broeders, 2009 [19491839]: No diff		Broeders, 2009 [19491839]: No diff	
		Broeders, 2009 [19491839]: No diff					

HRQoL, health-related quality of life

^a Symptoms include dysphagia.

^b Individual study's definition of success or failure defined by multiple variables.

-
- ^c Comparison: ≥ 70 vs. < 60 years old
- ^d Comparison: > 54 vs. ≤ 54 years old
- ^e Pizza, 2007 and Pizza, 2008 are the same study but examining different predictor
- ^f Pizza, 2007 and Pizza, 2008 are the same study but examining different predictor
- ^g Based on 50% patients at 1-year follow-up
- ^h Comparison: > 45 vs. ≤ 45 years old
- ⁱ Operation success was defined as complete resolution, meaning a complete absence of the presenting symptom at the time of the study
- ^j Poor outcome group included all patients whose outcomes were the same or worse than pre-op and those who were not happy with the
- ^k Comparison: BMI < 25 , 25-30, vs. > 30 kg/m²
- ^l Higher symptom score indicates worse outcome
- ^m Comparison: BMI ≥ 35 vs. < 30 kg/m²
- ⁿ Comparison: BMI ≥ 35 vs. 25-29.9, or 30-34.9 kg/m²
- ^o Comparison: baseline dysphasia vs. no dysphasia symptom
- ^p Odds ratio of treatment failure: 0.69 (95%CI 0.48, 1.0); P=0.05 but good response to PPI was not a significant predictor for treatment failure
- ^q Comparison: mild vs. non-erosive vs. severe esophagitis
- ^r Comparison: non-erosive vs. erosive esophagitis
- ^s Multivariate Cox regression after adjusting for operation method (Nissen vs. Toupet) and other risk factors
- ^t Pizza, 2007 and Pizza, 2008 are the same study but examining different predictor
- ^u 24-pH monitoring data only available for 144 (out of 200) patients
- ^v Pizza, 2007 and Pizza, 2008 are the same study but examining different predictor
- ^w Based on 68% patients at 1-year follow-up

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

Synopsis

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

Detail analysis

Adverse events comparing different treatment (Table 37)

We identified two RCTs (published in 4 publications) that compared the adverse events associated with medical treatment to those associated with surgical treatment.^{1,15,16,148} We did not identify any study that directly compared the adverse events between medical treatment and endoscopic treatment, or between endoscopic treatment and surgical treatment.

One death (from pneumonia) was reported in the medical treatment arm in one RCT;¹ another death was reported in the surgical treatment arm in another RCT.¹⁴⁸ In followup publications of the later RCT, that investigators found that fatal outcome and heart-related cause of adverse events were more common in the medical treatment group than in the surgical treatment group.^{15,16} However, these data were from FDA database, and claimed that FDA concluded that baseline differences and other confounding factors (eg, withdrawal from the surgical group and/or receiving both therapies) could have biased the safety data; thus were not considered in this review. The summary findings from these two RCTs are described below.

One study (published in 3 publications) examined the long-term (7 and 12 years) gastric mucosa, esophageal cancer, and myocardial infarction outcomes in an RCT comparing medical with surgical treatment.^{15,16,148} The original RCT randomized 310 patients to either omeprazole (n=154) or antireflux surgery (n=155) treatment group. No death was observed in patients who were randomized to omeprazole treatment. One patient (0.69 percent), who was randomized to antireflux surgery group and had an uneventful post-operative course, died 3 months after the operation due to myocardial infarction. Eleven (7 percent) and three (2 percent) patients withdrew from the study due to unacceptable adverse events in the omeprazole and antireflux

surgery group, respectively. Only 168 patients (96 in omeprazole and 72 in antireflux surgery group) had gastric mucosa outcomes after 7 years of followup. There were no significant differences in the rates of gastritis (17.7 vs. 22.2 percent), or atrophic gastritis (5.2 vs. 4.2 percent), but the difference in argyrophil cell hyperplasia (14.6 vs. 5.6 percent, $P=0.06$) was borderline significant between the two groups (omeprazole vs. antireflux surgery, respectively) after 7 years of followup. At 12 years of followup, there was one case of esophageal cancer in the antireflux surgical treatment group but none in the omeprazole group.

Another study investigated serious adverse events comparing medical with surgical treatment in patients with GERD during the 3 years of followup.¹ The original RCT randomized 554 patients to either esomeprazole ($n=266$) or laparoscopic antireflux surgery group ($n=288$). One death (0.4 percent) was reported in the esomeprazole treatment group, but no death was observed in the antireflux surgery group. There were significantly more patients withdrew from the study due to adverse events in esomeprazole than in surgery group ($P=0.03$). Overall rates of serious adverse events were lower in patients who received the esomeprazole treatment than in patients who had antireflux surgery (14 vs. 21 percent, respectively; $P=0.06$). Specific serious adverse event include myocardial infarction, injury, infections, infestations, neoplasms and gastrointestinal, musculoskeletal, connective tissue, cardiac, reproductive system (including breast), respiratory, thoracic, mediastinal vascular or hepatobiliary disorders.

Adverse events associated with medical treatment

Adverse events reported in postmarketing surveillance studies

One postmarketing surveillance study analyzed the safety profile of esomeprazole in 11,595 patients (median age 56 years old; 46 percent male) had a record of receiving prescriptions for esomeprazole between September 2000 and April 2001.¹⁴⁹ Thirty-six percent of these patients reported GERD as their primary indication for the use of esomeprazole. The top ranked adverse events include diarrhea, nausea or vomiting, abdominal pain, dyspepsia, headache or migraine, lower/upper respiratory tract infection, intolerance, general discomfort, and joint pain in descending order. The incidence densities (number of event per 1000 patient-month) for these adverse events were from 2.65 to 1.9 per 1000 patient-months. Furthermore, there were 101 “medically important events” cases probably or possibly related to esomeprazole based primarily on followup information obtained from clinicians. These events were reported in 71 patients (0.61 percent). There were a total of 1,331 “medically important events” involved 11 system organ classes (SOCs): immunological (9 events), cardiovascular (122 events), eye (36 events), central or peripheral nervous system (198 events), alimentary (480 events), skin (134 events), musculoskeletal (185 events), psychiatric (2 events), ear (17 events), respiratory (144 events), and metabolic and endocrine (12 events). There were 223 deaths (1.9%) reported, of which 57 cases with no information on the cause of death. The causes of death for the other 166 patients were mostly cancer (60 percent), or cardiovascular cause (20 percent).

Another postmarketing study analyzed the safety profile of rabeprazole (20 mg/day) in an open label, community-based interventional study.¹⁵⁰ During the 8-week followup, the most commonly reported adverse events among 2,579 GERD patients include abdominal pain (1.2 percent), chest pain (0.5 percent); diarrhea (1.5 percent); dizziness (0.7 percent); dyspepsia (0.6 percent); belching (0.5 percent); headache (1.6 percent); nausea (1.0 percent); rash (0.5 percent), and upper respiratory tract infection (0.5 percent)

Adverse events reported in randomized, controlled trials (Table 38)

A total of 28 RCTs of PPIs or H₂RAs reported adverse events in trial participants.^{22,26,27,29-32,34-37,39-46,48,51,54,55,57-60,115} The durations of these RCTs ranged from 1 to 12 months. The common adverse events reported in these RCTs were similar to those reported in the postmarketing surveillance studies (see the section above), and none reported a significant difference in the common adverse events between different medical treatment. One RCT reported that there were significantly more common adverse events in patients received dexlansoprazole (60 or 90 mg/day) than in those who received placebo,¹⁵¹ but another RCT comparing dexlansoprazole (30 or 60 mg/day) to placebo did not find significant differences in common adverse events between groups.⁴³

Of the 28 RCTs, two RCTs reported a total of three deaths among 1,546 patients.^{27,48} These deaths were thought not related to study medications by the investigators. Eleven RCTs reported “serious adverse events” (not defined) ranged from 0.3 to 9 percents.^{26,27,29-31,43,45,48,54,57,60} These “serious” adverse events were also thought not related to study medications by the investigators. One RCT reported 2 to 6 percent of patients had elevated liver function test results after PPI treatment, although the investigators stated that these changes were not clinically significant.³⁶ Another RCT reported 1 case (0.3 percent) of memory impairment that was thought possibly related to rabeprazole treatment.⁵¹ No other RCTs reported serious adverse events after PPI or H₂RA treatment.

Use of PPIs or H₂RAs and Fracture Risk (Table 39)

We identified nine observational studies (7 case-control and 2 cohort studies) that examined the relationships between the use of PPIs or H₂RA and fracture risk.¹⁵²⁻¹⁶⁰ We did not identify a RCT that specifically focused on fracture risk, and none of the RCTs that reported adverse events of medical therapy included fractures as an outcome..(see Key Question 1D)

The nine observational studies enrolled older men and/or women (>45 years old). The total number of fracture cases ranged from 356 to 124,655 in case-control studies.¹⁵⁴⁻¹⁶⁰ The total sample sizes were 11,094 and 161,806 in the two cohort studies in US.^{152,153} Both had about 8 years of followup duration. All studies performed multivariate analyses to adjust for potential confounding factors, but the factors included in the analyses varied across studies. The summary findings from these nine observational studies are summarized in Table 39. Below are the key findings:

- Two cohort studies in the US found mixed results on the relationships between the use of PPIs or H₂RAs and fracture risk during the 8 years of followup.^{152,153} Findings from one cohort study suggest that men and women, and different types of medical treatment (i.e., PPIs or H₂RAs) may have different strengths of association with fracture risk. Specifically, non-spine fracture risk was higher with PPI use than with H₂RA use, but the hip fracture risk was similar between PPI and H₂RA.
- Six (86%) of the seven case-control studies reported an increased risk of fractures with the use of PPIs.¹⁵⁵⁻¹⁶⁰ Exposure to PPIs ranged from 1 to 12 years, depending on the study.
- Three case-control studies found an increased risk of hip fracture with a longer duration of PPI use.^{155,157,160}

In summary, the available data suggest a possible association between the use of PPI for more than 1 year and an increased risk of fractures in older adults. However, all of the available

data are based on observational studies and the mechanisms leading to an increased fracture risk are unknown. Thus, the magnitude of risk remains unclear and the association could in part be due to residual confounding.

Drug Interaction

Another potential serious complication recognized since our 2005 report was a drug interaction between clopidogrel and PPIs, potentially leading to an increased risk of cardiovascular events. As a result, the Food and Drug Administration issued a warning in late 2009 about the interaction,¹⁶¹ although the importance of this interaction on clinical endpoints remains unsettled. Our search strategy did not focus on the clopidogrel PPI drug interaction since most such studies were based on observational data and a detailed review was beyond the scope of this update. Only one of the studies included in our review specifically addressed the issue of drug interactions with PPIs and that study did not find a drug interaction between PPIs and concomitant medications (medication not specified).¹²⁰

Adverse events associated with surgical treatment

We identified 37 studies published after the 2005 CER and reported intraoperative complications or adverse events occurring past 30 days after anti-reflux surgical procedures.^{17-19,63-66,68-76,78,79,124,130,134,136-138,141,144,162-172} Anti-reflux surgical procedures of interest include total or partial (Nissen or Toupet) fundoplication. Because one study may have reported more than one adverse event; it could appear multiple times in our analyses. The reported intraoperative complications include mortality,^{74,75,134,137,163,170,171} reoperation,^{75,76,170} conversion,^{74,75,134} gastrointestinal injury/perforation,^{18,69,123,133,134,137,166,167,170} pneumothorax,^{18,69} splenic injury,¹⁶⁶ bleeding,^{18,69,74,137,167,168,172} pulmonary event,^{18,69,168} infection/fever,^{18,69,168} dysphagia,^{74,141} and pain/discomfort.¹⁶⁸ The reported adverse events occurring past 30 days after anti-reflux surgical procedures include mortality,^{18,19,63,66,69,76,78,125,129,137,144,162,166-168} reoperation,^{18,65,66,70-76,79,130,141,162,163,167-169,171} bleeding,^{17,125,165} pulmonary event,^{78,125,129,162,171} gastrointestinal event,^{17,63,68,74,75,79,80,124,125,129,137,141,165,166,170,171} infection/fever,^{19,125,129,144,162,165,171,173} dysphagia,^{17,19,66,68,69,74,75,78,79,133,137,141,144,164,167,168,170,173} bloating,^{19,63,66,68,69,74,79,124,133,137,141,168,170} and pain.^{19,68,70,124,137,170}

Intra- and perioperative complications after surgical procedures

Four studies reported no deaths,^{74,134,137,170} but one study reported 0.8 percent of thirty-day all-cause mortality for Laparoscopic Nissen Fundoplication(LNF).¹⁷¹ No deaths were reported for Open Nissen Fundoplication(ONF),⁷⁴ Laparoscopic Toupet Fundoplication(LTF),⁷⁵ and Laparoscopic Nissen/Toupet Fundoplication (LNF/LTF) respectively.¹⁶³ One study reported 0.8 percent of reoperation for LNF.¹⁷⁰ Re-operation rates ranged from 0 to 1.8 percent for LTF.^{75,76} One study reported no gastrointestinal perforation for ONF.¹⁸ Gastrointestinal perforation rates ranged: from 0 to 3.2 percent for LNF^{134,166,167} and from 0.1 to 0.5 percent for LNF/LTF.^{18,69} Bleeding event rate ranged: from 0 to 3.6 percent for ONF;^{18,74} from 0.5 to 1.8 percent for LNF^{74,137,167,168,172} and from 0 to 1.5 percent for LNF/LTF.^{18,69} Dysphagia event rate ranged from 2.7 to 23 percent for LNF.^{74,141} The incidence of dysphagia was 7.1 percent for ONF⁷⁴ and 10 percent for LTF respectively.¹⁴¹ More detailed information about intra- and perioperative complications can be found in Table 40.

Complications occurring more than 30 days after surgical procedures

One study reported 0.6% of all-cause mortality for ONF.¹⁸ Mortality event rate ranged: from 0 to 8.8 percent for LNF,^{19,63,66,78,129,137,166-168} from 3.1 to 15.1 percent for LTF^{63,66,76} and from 0 to 0.9 percent for LNF/LTF.^{18,69,125,144,162} Reoperation rate ranged: from 3.2 to 34.8 percent for ONF,^{18,71-73} from 0 to 15 percent for LNF,^{65,66,71-74,141,167-169,171} from 4 to 9.4 percent for LTF^{66,75,76,141} and from 0.8 to 8 percent for LNF/LTF.^{18,70,79,130,162,163} Dysphagia event rate ranged: from 0 to 4.4 percent for ONF,^{74,167,173} from 1.3 to 30.6 percent for LNF,^{17,19,66,68,74,78,133,137,168,170} from 2 to 28.0 percent for LTF;^{66,68,75} and from 2 to 13.5 percent for LNF/LTF.^{69,79,141,144,164} One study reported no bloating for ONF.⁷⁴ Bloating event rate ranged; from 1 to 84.9 percent for LNF,^{19,63,66,68,74,124,133,137,168,170} from 46 to 70 percent for LTF,^{63,66,68,124} and from 7.5 to 53 percent for LNF/LTF.^{69,79,141} There was only one study include both open and laparoscopic Rossetti Nissen fundoplication and this study reported 22.4 percent of esophageal dysmotility.¹³⁹ More detailed information about complications occurred more than 30 days after surgical procedures can be found in Table 41.

Adverse events associated with endoscopic treatment

For endoscopic studies, we identified 12 studies published after the 2005 CER.^{81,83-85,88,91-93,95,99,174,175} Endoscopic treatment include EndoCinch, Stretta, or EsophyX. Intraoperative complications include dysphagia^{91,92} and bleeding.^{92,175} Complications occurring more than 30 days after endoscopic procedures include reoperation,⁸⁴ bleeding,⁹⁵ infection/fever,⁸⁸ dysphagia,^{81,85,99} bloating^{81,85,99} and pain.^{81,85}

Intra- and perioperative complications after endoscopic procedures

All-cause mortality rate was not reported for EndoCinch, Stretta, and EsophyX. Dysphagia event rate ranged from 0 to 4 percent for EsophyX.^{91,92} One study reported 11.1 percent of bleeding within 30 days after EndoCinch and another study reported 6 percent of bleeding for EsophyX.^{92,175} More detailed information about intra- and perioperative complications for endoscopic procedures can be found in Table 42.

Complications occurring more than 30 days after endoscopic procedures

There are no data on all-cause mortality for EndoCinch, Stretta, and EsophyX. One study reported 30.4 percent of reoperation for EndoCinch.⁸⁴ Dysphagia rate ranged from 14.3 to 50 percent for EndoCinch and one study reported that there was no dysphagia for Stretta.^{81,85,99} Bloating rate ranged from 10 to 19 percent and pain event rate ranged from 5 to 23.8 percent for EndoCinch.^{81,85} More detailed information about complications occurring more than 30 days after endoscopic procedures can be found in Table 43.

Adverse events reported in FDA/MAUDE (Manufacturer and User Facility Device Experience) database

A total of 38 events were reported for the three devices between 2000 and 2010 (Table 44). Almost half of these adverse events required hospitalization (47 percent), while nearly a fifth (18 percent) required surgery. Four deaths were noted, all within the radiofrequency ablation therapy group. Bleeding requiring blood transfusions was observed in 3 patients. A list of the reported adverse events is compiled in a second table (Table 45).

Table 37. Adverse events in RCTs comparing medical to surgical treatments

Author year [UI] Trail Name Follow-up duration	Treatment	Death	Other reported adverse events	P value between groups
Lundell 2008 ¹ [18469091] LOTUS	Esomeprazole 20 mg/d	1/266 (0.4%) ^a	Any serious adverse events: 42/266 (14.3%) <ul style="list-style-type: none"> • Myocardial infarction: 1/266 (0.4%) • Injury, poisoning, procedural: 2/266 (0.8%) • GI disorders: 5/266 (1.9%) • Musculoskeletal/connective tissue: 8/266 (3.0%) • Infections and infestations: 6/266 (2.3%) • General disorders: 4/266 (1.5%) • Cardiac disorders: 3/266 (1.1%) • Neoplasms, benign/malignant: 6/266 (2.3%) • Reproductive system including breast: 4/266 (1.5%) • Respiratory, thoracic, mediastinal: 1/266 (0.4%) • Vascular disorders: 3/266 (1.1%) • Hepatobiliary disorders: 0/266 (0%) 	nd ^b
3 years	Laparoscopic antireflux surgery	0/288	Any serious adverse events: 55/248 (21%) <ul style="list-style-type: none"> • Myocardial infarction: 1/248 (0.4%) • Injury, poisoning, procedural: 15/248 (6.0%) • GI disorders: 12/248 (4.8%) • Musculoskeletal/connective tissue: 2/248 (0.8%) • Infections and infestations: 3/248 (1.2%) • General disorders: 5/248 (2.0%) • Cardiac disorders: 4/248 (1.6%) • Neoplasms, benign/malignant: 2/248 (0.8%) • Reproductive system including breast: 1/248 (0.4%) • Respiratory, thoracic, mediastinal: 5/248 (2.0%) • Vascular disorders: 3/248 (1.2%) • Hepatobiliary disorders: 3/248 (1.2%) 	
Lundell 2006 ^{14b} [16480403]; Lundell 2007 ¹⁵ [17256807]; Ludell 2009 ^{c16} [19490952] SOPRAN	Omeprazole 20-40 mg/d	0% 7 year 8/154 ^d (5.2%) 12 year	7 year follow up <ul style="list-style-type: none"> • Gastritis: 17/96 (17.7%) • Atrophic gastritis: 5/96 (5.2%) • Argrophil cell hyperplasia: 14/96 (14.6%) 12 year follow up <ul style="list-style-type: none"> • Esophageal cancer: 0/78 (0%) • Non-fatal heart attacks: 9/78 (11.5%) 	nd ^e

12 years	Open antireflux surgery: Nissen (primarily)	1/144 (0.7%) ^f 7 year	7 year follow up
		2/144 ^g (1.4%) 12 year	<ul style="list-style-type: none"> • Gastritis: 16/72 (22.2%) • Atrophic gastritis: 3/72 (4.2%) • Argrophil cell hyperplasia: 4/72 (5.6%)
			12 year follow up
			<ul style="list-style-type: none"> • Esophageal cancer: 1/59^h (1.7%) • Non-fatal myocardial infarction: 2/59 (3.4%)

n/a, not applicable; GI gastrointestinal

^a One patient died from pneumonia

^b Estimated by chi-square testing: Significantly more patients withdrew from the study due to adverse events in esomeprazole than in surgery group (P=0.03). Marginal significant for any serious adverse events (P=0.06) between esomeprazole and surgery groups.

^c The FDA concluded that there are baseline differences between surgical and medical treatment groups (e.g., age, history of previous myocardial infarction).

^d Patients died of heart-related causes. These data were from FDA database, and claimed that FDA concluded that baseline differences and other confounding factors (eg, withdrawal from the surgical group and/or receiving both therapies) could have biased the safety data.

^e Estimated by chi-square testing: Significantly more patients withdrew from the study due to adverse events in omeprazole than in surgery group (P=0.04). Not significant for gastritis and atrophic gastritis, and marginally significant for argyrophil cell hyperplasia (P=0.06) between omeprazole and surgery groups.

^f One patient, who had an uneventful post-operative course, died 3 months after the operation due to myocardial infarction

^g Patients died of heart-related causes. These data were from FDA database, and claimed that FDA concluded that baseline differences and other confounding factors (eg, withdrawal from the surgical group and/or receiving both therapies) could have biased the safety data.

^h Barrett's diagnosed at baseline endoscopy

Table 38. Adverse events reported in randomized, controlled trials of PPIs or H2RA

Author, year [UI] Medical treatment (sample size) Duration	Common adverse events ^a	Death	“Serious” adverse events
Bardhan 2007 ³⁰ [17539986] • Pantoprazole 40mg (n=289) • Esomeprazole 40mg (n=293) 3 months	0.5% to 1.2%	nd	“Serious adverse events” not related to study medications • Pantoprazole: 2/289 (0.7%) • Esomeprazole: 7/293 (2.4%)
Chen 2005 ⁵⁹ [15918199] • Esomeprazole 40mg (n=25) • Omeprazole 20mg (n=23) 1 month	0% to 13% Similar for all treatment groups	nd	nd
Devault 2006 ⁶⁰ [16682260] • Esomeprazole 20mg/day (n=510) • Lansoprazole 15mg/day (n=514) 6 months	5.8% to 8% Similar for all treatment groups	nd	“Serious adverse events” not related to study medications • Esomeprazole: 10/510 (2%) • Lansoprazole: 5/514 (1%)
Devault 2007 ¹¹⁵ [17760655] • Pantoprazole 10/20/40mg/day (n=254) • Nizatidine 150mg twice/day (n=82) • Placebo once daily (n=82) 2 months	50% to 59% Similar for all treatment groups	nd	nd
Eggleston 2009 ³⁵ [19210493] • Rabeprazole 20mg (n=464) • Esomeprazole 20mg (n=459) • Esomeprazole 40mg (n=469) 1 month	2.1% to 18.5%	nd	nd
Fass 2006 ³⁴ [15918196] • Lansoprazole 30 mg twice/day (n=167) • Esomeprazole 40 mg/day (n=159) 2 months	0% to 7.2%	nd	nd
Fass 2009 ⁴³ [19392864] • Dexlansoprazole 30 mg/day (n=315) • Dexlansoprazole 60 mg/day (n=315) • Placebo (n=317) 1 month	≥ 5% Similar for all treatment groups	nd	“Serious adverse events” not related to study medications • Dexlansoprazole 30 mg: 2/315 (0.6%) • Dexlansoprazole 60 mg: 1/315 (0.3%) • Placebo: 1/317 (0.3%)

Author, year [UI] Medical treatment (sample size) Duration	Common adverse events ^a	Death	“Serious” adverse events
Fock 2005 ³⁶ [15918196] • Rabeprazole 10 mg/day (n=63) • Esomeprazole 20 mg/day (n=66) 1 month	18.2% to 22% Similar for all treatment groups	nd	Elevation of ALT ^b • Rabeprazole: 1/63 (1.6%) • Esomeprazole: 4/66 (6.1%) Elevation of AST • Rabeprazole: 1/63 (1.6%) • Esomeprazole: 2/66 (3%)
Glatzel 2007 ²⁹ [17489035] • Pantoprazole 40 mg/day (n=284) • Esomeprazole 40 mg/day (n=277) 1 month	1.2% Similar for all treatment groups	nd	“Serious adverse events” not related to study medications • Pantoprazole: 1/284 (0.4%) • Esomeprazole: 2/277 (0.7%)
Goh 2007 ²⁷ [17301646] Acute phase (4-8 weeks): • Pantoprazole 40 mg/day (n=1268) Maintenance phase (6 months) • Pantoprazole 20 mg/day (n=636) • Esomeprazole 20 mg/day (n=667) 6 months	Considered by investigators to be related to study medication: 0.9% to 3%	Deaths unrelated to treatment: 2/1303 (0.2%)	“Serious adverse events” not related to study medications • Pantoprazole: 1.4% • Esomeprazole: 2.5% Serious adverse event (loss of consciousness) attributable to esomeprazole: 1/1303 (0.08%)
Howden 2009 ⁴⁵ [19681809] • Dexlansoprazole 60 mg/day (n=159) • Dexlansoprazole 90 mg/day (n=152) • Placebo (n=140) 1 month	0% to 7% Significantly greater in Dexlansoprazole 60 mg (P<0.01) and 90 mg (P=0.003) than placebo	0%	“Serious adverse events” not related to study medications • Dexlansoprazole 60 mg: 2/159 (1.3%) • Dexlansoprazole 90 mg: 5/152 (3.3%)
Johnson 2005 ³⁹ [16128933] • Esomeprazole 20 mg/day (n=220) • Esomeprazole 40 mg/day (n=226) 1 month	1.3% to 5% Similar for all treatment groups	nd	Nd
Katz 2007 ⁴⁰ [17305763] • Esomeprazole 10 mg/day (n=80) • Esomeprazole 40 mg/day (n=89) 1 month	2%	nd	nd

Author, year [UI] Medical treatment (sample size) Duration	Common adverse events ^a	Death	“Serious” adverse events
Lightdale 2006 ⁵⁴ [16773434] • Esomeprazole 20 mg/day (n=585) • Omeprazole 20 mg/day (n=588) 2 months	1.5% to 9.9 Similar for all treatment groups	nd	“Serious adverse events” not related to study medications • Esomeprazole: 1/585 (0.2%) • Omeprazole: 6/588 (1%)
Metz 2009 ⁴⁴ [19210298] • Dexlansoprazole MR 30 mg/day • Dexlansoprazole MR 60 mg/day 6 months	2.1% to 10.8% Similar for all treatment groups	nd	No oesophageal ulcers and perforation
Mine 2005 ⁴² [16105122] • 15 mg of lansoprazole once daily for 16 weeks (n=14) • 30 mg of lansoprazole once daily for 8 weeks followed by another 8-week treatment with 20 mg of famotidine twice daily (n=14) • 30 mg of lansoprazole once daily for 8 weeks followed by another 8-week treatment with 15 mg of lansoprazole once daily (n=15) 4 months	0% (No side effects reported)	nd	nd
Morgan 2007 ⁵¹ [18080054] • Rabeprazole 20mg/day (n=137) • Rabeprazole 20mg on-demand (n=131) 6 months	<3% to 8.8%	nd	1 (0.3%) memory impairment was categorized as possibly related to study medication 6 (2.2%) serious adverse events not related to study medications: post-op tonsillectomy hemorrhage, malignant melanoma, atrial fibrillation, headache, skin cancer, intestinal infection
Norman 2005 ²² [15924594] • Esomeprazole 20 mg on-demand • Esomeprazole 20 mg/day • Ranitidine 150 mg/day 6 months	0.5% to 2% Similar for all treatment groups	nd	nd

Author, year [UI] Medical treatment (sample size) Duration	Common adverse events ^a	Death	“Serious” adverse events
Pace 2005 ⁵⁷ [16024305] Acute phase (4-8 weeks): • Rabeprazole 20 mg/day (n=283) • Omeprazole 20 mg/day (n=277) Maintenance phase (48 weeks) • Rabeprazole 10 mg 1-2 times/day (n=502) 48 weeks	Acute Phase: Omeprazole (13/272, 4.8%) > Rabeprazole (4/277), P=0.0241 Long-term Phase: 1% to 2%	nd	Acute Phase: “Serious adverse events” not related to study medications Omeprazole: 3/272 (1.1%) Maintenance Phase: “Serious adverse events” Rabeprazole: 12/502 (2.4%)
Pai 2006 ⁴⁶ [17009401] • S- Pantoprazole 20 mg/day (n=187) • Racemic Pantoprazole 40 mg/day (n=182) 1 month	0% (“none of the patients in either groups reported adverse events”)	nd	nd
Pai 2007 ³⁷ [17696229] • Dexrabeprazole 10 mg/day (n=25) • Rabeprazole 20 mg/day (n=25) 1 month	0% (“no adverse drug reaction seen in either group”)	nd	nd
Peura 2009 ²⁶ [18726153] • Lansoprazole 15 mg/day (n=100) • Ranitidine 150 mg/day (n=100) 12 months	5% to 6%	nd	“Serious adverse events” not related to study medications • Lansoprazole: 9/100 (9%) • Ranitidine: 1/100 (1%)
Pilotto 2007 ⁵⁵ [17724802] • Omeprazole 20 mg/day (n=80) • Lansoprazole 30 mg/day (n=80) • Pantoprazole 40 mg/day (n=80) • Rabeprazole 20 mg/day (n=80) 2 months	0.1%	nd	nd
Scholten 2007 ³¹ [17358101] Acute phase (4 weeks): • Pantoprazole 20 mg on-demand (n=236) Long-term phase (6 months) • Pantoprazole 20 mg on-demand (n=100) • Esomeprazole 20 mg on-demand (n=100) 6 months	Acute Phase: 0.8% Long-term Phase: 1% to 6%	nd	“Serious adverse events” not related to study medications • Pantoprazole: 2/100 (2%) • Esomeprazole: 2/100 (2%)

Author, year [UI] Medical treatment (sample size) Duration	Common adverse events ^a	Death	“Serious” adverse events
Sjostedt 2005 ⁴⁸ [16091055] • Esomeprazole 20 mg/day (n=243) • Esomeprazole 20mg on-demand (n=234) 6 months	0.4% to 2.9% Similar for all treatment groups	20 mg/day: 1/243 (0.4%) ^c 20 mg on-demand: 0	“Serious adverse events” • 20 mg/day: 9/243 (3.7%) • 20 mg on demand: 7/234 (3.0%)
Tepes 2009 ⁵⁸ [19453031] • Omeprazole 10mg/day (n=94) • Omeprazole 20 mg/day (n=102) • Omeprazole 20mg on-demand (n=20) 12 months	0.8% to 2.5%	nd	nd
Vasiliadis 2010 ⁴¹ [19809412] • Esomeprazole 40mg twice daily (n=25) • Esomeprazole 40mg once daily (n=25) • Esomeprazole 40mg every other day (n=25) 1 month	0% (No adverse events reported)	nd	nd
Vcev 2006 ³² [17058517] • Esomeprazole 40 mg/day (n=90) • Pantoprazole 40 mg/day (n=90) 1 month	11% to 12% Similar for all treatment groups	nd	nd

ALT, alanine aminotransferase; AST, aspartate aminotransferase

^a diarrhea, nausea or vomiting, abdominal pain, dyspepsia, headache or migraine, respiratory track infection intolerance, general discomfort, joint pain, gastritis, dizziness, rash, chest pain, and nausea

^b Investigators stated that ALT and AST changes were not clinically significant

^c This death was not considered to be due to esomeprazole treatment.

Table 39. Observational studies that examined the relationships between the use of PPIs or H2RAs and fracture risk

Author year [UI]	Study design country	Population (N)	Outcomes	Adjusted OR (95% CI)
Cohort studies				
Gray 2010 ¹⁵³ [20458083]	WHI observational study and clinical trials US	50-79 y Postmenopausal women 161806	7.8 y follow-up <ul style="list-style-type: none"> • Risk of hip fracture of PPI use • Risk of clinical spine fracture of PPI use • Risk of forearm or wrist of PPI use • Risk of total fracture PPI use • Risk of hip fracture of H₂RA use • Risk of clinical spine fracture of H₂RA use • Risk of forearm or wrist of H₂RA use • Risk of total fracture of H₂RA use 	HR 1.0 (0.71, 1.40) HR 1.47 (1.18, 1.82) HR 1.26 (1.05, 1.51) HR 1.25 (1.15, 1.36) HR 1.07 (0.87, 1.30) HR 1.02 (0.87, 1.20) HR 1.05 (0.93, 1.19) HR 1.08 (1.02, 1.14)
Yu 2008 ¹⁵² [18813868]	Cohort study US	79 y Men & Women 11094	7.6 y follow-up <ul style="list-style-type: none"> • Risk of non-spine fracture of PPI use (Women) • Risk of non-spine fracture of PPI use (Men) • Risk of hip fracture of PPI use (Women) • Risk of hip spine fracture of PPI use (Men) • Risk of non-spine fracture of H₂RA use (Women) • Risk of non-spine fracture of H₂RA use (Men) • Risk of hip fracture of H₂RA use (Women) • Risk of hip spine fracture of H₂RA use (Men) 	HR 1.34 (1.10, 1.64) HR 1.21 (0.91, 1.62) HR 1.16 (0.80, 1.67) HR 0.62 (0.26, 1.44) HR 1.08 (0.90, 1.31) HR 0.88 (0.58, 1.35) HR 1.27 (0.92, 1.75) HR 1.22 (0.54, 2.76)
Case control studies				
Grisso 1997 ¹⁵⁴ [9143208]	Case-control US	>45 y Men (cases, 356) (controls, 402)	<ul style="list-style-type: none"> • Risk of hip spine fracture of H₂RA use (users vs. non-users) 	2.5 (1.4, 4.6)
Yang 2006 ¹⁵⁵ [17190895]	Nested case-control UK	>50 y Men & Women (cases, 13556) (controls, 135386)	<ul style="list-style-type: none"> • Risk of hip fracture with PPI therapy > 1 year • Risk of hip fracture with > 1.75 average daily-dose PPI 	1.44 (1.30, 1.59) 2.65 (1.80, 3.90)
Vestergaard 2006 ¹⁵⁶ [16927047]	Case-control Denmark	Mean age: 43.3 y Men & Women (cases, 124655) (controls, 373962)	<ul style="list-style-type: none"> • Risk of any fracture with PPI use within last year • Risk of hip fracture with PPI use within last year • Risk of spine fracture with PPI use within last year 	1.18 (1.12, 1.43) 1.45 (1.28, 1.65) 1.60 (1.25, 2.04)
Targownik 2008 ¹⁵⁷ [18695179]	Case-control Canada	>50 y Men & Women (cases, 15792) (controls, 47289)	<ul style="list-style-type: none"> • Risk of hip fracture after 5+ years of PPI use • Risk of hip fracture after 7+ years of PPI use • Risk of any osteoporosis-related fracture after 7+ years of PPI use 	1.62 (1.02, 2.58) 4.55 (1.68, 12.29) 1.92 (1.16, 3.18)
Kaye 2008 ¹⁵⁸ [18657011]	Nested case-control study UK	50–79 y Men & Women (cases, 4414) (controls, 10923)	<ul style="list-style-type: none"> • Risk of hip fracture after 2+ years of PPI use 	RR 0.9 (0.7, 1.1)
Roux 2009 ¹⁵⁹	Case-control	65.8 y	<ul style="list-style-type: none"> • Risk of vertebral fracture after 6 years of PPI use 	3.50 (1.14, 8.44) ^a

Author year [UI]	Study design country	Population (N)	Outcomes	Adjusted OR (95% CI)
[19023510]	Europe	Postmenopausal women 1211		
Corley 2010 ¹⁶⁰ [20353792]	Case-control US	≥ 18 y Men & Women (cases, 33752) (controls, 130471)	<ul style="list-style-type: none"> • Risk of hip fracture after 4-5.9 years of PPI use • Risk of hip fracture after 6-7.9 years of PPI use • Risk of hip fracture after 8-9.9 years of PPI use • Risk of hip fracture after 10+ years of PPI use 	1.21 (1.10, 1.33) 1.33 (1.19, 1.49) 1.33 (1.12, 1.57) 1.85 (1.41, 2.43)

WHI, Women's Health Initiative

^a Adjusted for current use of thiazide diuretics, corticosteroids, thyroid hormone supplementation, calcium, vitamin D, and hormone replacement therapy (HRT)

Table 40: Intraoperative complications (and those occurring within 30 days) for surgical procedures

	Surgical			
	Open Nissen Fundoplication	Laparoscopic Nissen Fundoplication	Laparoscopic Toupet Fundoplication	Laparoscopic Nissen Fundoplication /Laparoscopic Toupet Fundoplication
Mortality event rate ^{74,75,134,137,163,170,171}	<u>Trullenque, 2005 [16004525]</u> 0/28 (0%)	<u>del Genio, 2007 [17426906]</u> 0/380 (0%) <u>Cowgill, 2007 [17879678]</u> 2/239 (0.8%) <u>Trullenque, 2005 [16004525]</u> 0/75 (0%) <u>Pizza, 2007 [17278197]</u> 0/420 (0%) <u>Lee, 2009 [19259354]</u> 0/31 (0%)	<u>Zehetner, 2006 [16391962]</u> 0/100 (0%)	<u>Gill, 2007 [17436134]</u> 0/400 (0%)
Re-operation event rate ^{75,76,170}		<u>del Genio, 2007 [17426906]</u> 3/380 (0.8%)	<u>Zehetner, 2006 [16391962]</u> 0/100 (0%) <u>Rice, 2006 [16549692]</u> 2/113 (1.8%)	
Conversion event rate ^{74,75,134}	<u>Trullenque, 2005 [16004525]</u> 0/28 (0%)	<u>Trullenque, 2005 [16004525]</u> 1/75 (1.3%) <u>Lee, 2009 [19259354]</u> 0/31 (0%)	<u>Zehetner, 2006 [16391962]</u> 0/100 (0%)	
Gastrointestinal injury /perforation event rate ^{18,69,123,133,134,137,166,167,170}	<u>Olberg, 2005 [15932167]</u> Gastric perforation: 0/158 (0%)	<u>Zacharoulis, 2006 [17024541]</u> • Esophageal perforation: 3/808 (0.4%) • Stomach perforation: 4/808 (0.5%) <u>Csendes, 2005 [16137596]</u> • Esophageal or gastric perforation: 0/225 (0%) <u>Lee, 2009 [19259354]</u> • Gastric perforation: 1/31		<u>Olberg, 2005 [15932167]</u> Gastric perforation: 1/215 (0.5%) <u>Pessaux, 2005 [16230543]</u> • Gastric perforation: 1/1340 (0.1%) • Esophageal perforation: 4/1340 (0.3%) • Paraesophageal herniation: 2/1340 (0.1%) • Persistent esogastric

	Surgical			
	Open Nissen Fundoplication	Laparoscopic Nissen Fundoplication	Laparoscopic Toupet Fundoplication	Laparoscopic Nissen Fundoplication /Laparoscopic Toupet Fundoplication
		(3.2%) <u>del Genio, 2007 [17426906]</u> • Mucosal tear: 1/380 (0.3%) <u>Pizza, 2007 [17278197]</u> • Mucosal tear: 1/420 (0.2%) <u>Anvari, 2006 [16341568]</u> • Acute trans-hiatal herniation of the wrap 1/70 (1.4%) <u>Kamolz, 2005 [15959712]</u> • Severe flatulence 9/178 (5.3%) • Severe diarrhea 6/178 (3.6%)		perforation: 2/1340 (0.1%)
Pneumothorax event rate ^{18,69}	<u>Olberg, 2005 [15932167]</u> • Pneumothorax: 0/158 (0%)			<u>Pessaux, 2005 [16230543]</u> • Pneumothorax: 4/1340 (0.3%)
Splenic injury event rate ¹⁶⁶		<u>Csendes, 2005 [16137596]</u> • Splenectomy: 0/225 (0%)		
Bleeding event rate ^{18,69,74,137,167,168,172}	<u>Trullenque, 2005 [16004525]</u> • Abdominal hemorrhage: 1/28 (3.6%) <u>Olberg, 2005 [15932167]</u> • Intraabd. Bleeding: 2/158 (1.3%) • Bleeding, transfusion: 0/158 (0%)	<u>Zacharoulis, 2006 [17024541]</u> 4/808 (0.5%) <u>Salminen, 2006 [16921296]</u> 8/444 (1.8%) <u>Jensen, 2009 [18855057]</u> 1/113 (0.9%) <u>Trullenque, 2005 [16004525]</u> • Abdominal hematoma: 1/75 (1.3%) <u>Pizza, 2007 [17278197]</u>		<u>Pessaux, 2005 [16230543]</u> • Bleeding: 20/1340 (1.5%) • Hematoma: 5/1340 (0.4%) <u>Olberg, 2005 [15932167]</u> • Intraabd. Bleeding: 0/215 (0%) • Bleeding, transfusion: 2/215 (0.9%)

	Surgical			
	Open Nissen Fundoplication	Laparoscopic Nissen Fundoplication	Laparoscopic Toupet Fundoplication	Laparoscopic Nissen Fundoplication /Laparoscopic Toupet Fundoplication
		<ul style="list-style-type: none"> • Bleeding, 3/420 (0.7%) 		
Pulmonary event rate ^{18,69,168}	<u>Olberg, 2005 [15932167]</u> <ul style="list-style-type: none"> • Pulmonary embolism: 0/158 (0%) 	<u>Salminen, 2006 [16921296]</u> <ul style="list-style-type: none"> • Pneumonia: 1/444 (0.2%) 		<u>Pessaux, 2005 [16230543]</u> <ul style="list-style-type: none"> • Venous thrombosis or pulmonary embolism: 2/1340 (0.1%) • Pleural effusion: 5/1340 (0.4%) • Pneumonia: 11/1340 (0.8%)
Infection/ Fever event rate ^{18,69,168}	<u>Olberg, 2005 [15932167]</u> <ul style="list-style-type: none"> • Lung infection: 4/158 (2.5%) • Wound infection: 2/158 (1.3%) 	<u>Salminen, 2006 [16921296]</u> 4/444 (0.9%)		<u>Pessaux, 2005 [16230543]</u> <ul style="list-style-type: none"> • Urinary infection: 3/1340 (0.2%) • Wound infection: 3/1340 (0.2%) • Abdominal abscess: 1/1340 (0.1%) <u>Olberg, 2005 [15932167]</u> <ul style="list-style-type: none"> • Lung infection: 8/215 (3.7%) • Wound infection: 0/215 (0%)
Dysphagia event rate ^{74,141}	<u>Trullenque, 2005 [16004525]</u> <ul style="list-style-type: none"> • Solid-induced dysphagia: 2/28 (7.1%) 	<u>Trullenque, 2005 [16004525]</u> <ul style="list-style-type: none"> • Solid-induced dysphagia: 2/75 (2.7%) <u>Strate, 2008 [18027055]</u> 23/100 (23%)	<u>Strate, 2008 [18027055]</u> 10/100 (10%)	
Pain /discomfort event rate ¹⁶⁸		<u>Salminen, 2006 [16921296]</u> <ul style="list-style-type: none"> • Port sign pain: 1/444 (0.2%) 		
Other event rate ^{18,69,74,134,168}	<u>Trullenque, 2005 [16004525]</u> <ul style="list-style-type: none"> • Hemothorax: 1/28 (3.6%) • Surgical wound complication: 3/28 (10.7%) <u>Olberg, 2005 [15932167]</u> <ul style="list-style-type: none"> • Pneumothorax: 0/158 (0%) • Crural rupture: 1/158 (0.6%) 	<u>Salminen, 2006 [16921296]</u> <ul style="list-style-type: none"> • Urinary retention: 4/444 (0.9%) • Neural injury of the diaphragm: 1/444 (0.2%) • Wrap herniation (early): 1/444 (0.2%) 		<u>Pessaux, 2005 [16230543]</u> <ul style="list-style-type: none"> • Cardiac arrhythmia: 1/1340 (0.1%) <u>Olberg, 2005 [15932167]</u> <ul style="list-style-type: none"> • Pneumothorax: 6/215 (2.8%) • Crural rupture: 0/215 (0%)

	Surgical			
	Open Nissen Fundoplication	Laparoscopic Nissen Fundoplication	Laparoscopic Toupet Fundoplication	Laparoscopic Nissen Fundoplication /Laparoscopic Toupet Fundoplication
	<ul style="list-style-type: none"> • Pulmonary embolism: 0/158 (0%) • Acute paraesoph. Herniation: 0/158 (0%) 	<p><u>Trullenque, 2005 [16004525]</u></p> <ul style="list-style-type: none"> • Wound complication: 2/75 (2.7%) • Subcutaneous emphysemas: 3/75 (4.0%) <p><u>Lee, 2009 [19259354]</u></p> <ul style="list-style-type: none"> • Atelectasis and prolonged ileus: 2/31 (6.5%) • Subcutaneous emphysemas: 2/31 (6.5%) 		<ul style="list-style-type: none"> • Pulmonary embolism: 1/215 (0.5%) • Acute paraesoph. Herniation: 3/215 (1.4%)

Table 41: Complications occurring more than 30 days after surgical procedures

	Surgical			
	Open Nissen Fundoplication	Laparoscopic Nissen Fundoplication	Laparoscopic Toupet Fundoplication	Laparoscopic Nissen Fundoplication /Laparoscopic Toupet Fundoplication
<p>Mortality event rate^{18,19,63,66,69,76,78,125,129,137,144,162,166-168}</p>	<p>Olberg, 2005 [15932167] 1/158 (0.6%)</p>	<p><u>Csendes, 2005</u> [16137596] 0/225 (0%)</p> <p><u>Zacharoulis, 2006</u> [17024541] 13/808 (1.6%)</p> <p><u>Salminen, 2006</u> [16921296] 4/468 (0.9%)</p> <p><u>Dallemagne, 2006</u> [16333553] 6/68 (8.8%)</p> <p><u>Cai, 2008 [18942055]</u> 3/54 (5.6%)</p> <p><u>Pizza, 2007 [17278197]</u> 2/65 (3%)</p> <p><u>Teixeria, 2009</u> [19453033] • Operation mortality: 0/143 (0%)</p> <p><u>Dalessio, 2005</u> [16137590] 0/257 (0%)</p> <p><u>Anvari, 2006</u> [17227922] 0/52 (0%)</p>	<p><u>Dallemagne, 2006</u> [16333553] 1/32 (3.1%)</p> <p><u>Cai, 2008 [18942055]</u> 8/53 (15.1%)</p> <p><u>Rice, 2006</u> [16549692] 12/113 (11%)</p>	<p><u>Rosenthal, 2006</u> [17243869] 0/186 (0%)</p> <p><u>Pessaux, 2005</u> [16230543] 0/1340 (0%)</p> <p><u>Wang, 2008 [18368318]</u> 0/231 (0%)</p> <p><u>Brehant, 2006</u> [16504893] 3/2684 (0.1%)</p> <p><u>Olberg, 2005</u> [15932167] 2/215 (0.9%)</p>
<p>Re-operation event rate^{18,65,66,70-76,79,130,141,162,163,167-169,171}</p>	<p><u>Draaisma, 2006</u> [16794387]; <u>Broeders, 2009</u> [19801931] 24/69 (34.8%)</p>	<p><u>Dallemagne, 2006</u> [16333553] 1/68 (1.5%)</p>	<p><u>Dallemagne, 2006</u> [16333553] 3/32 (9.4%)</p>	<p><u>Gill, 2007 [17436134]</u> 3/400 (0.8%, ≤ 3mo) 21/400 (5.3%, > 3mo)</p>

	Surgical			
	Open Nissen Fundoplication	Laparoscopic Nissen Fundoplication	Laparoscopic Toupet Fundoplication	Laparoscopic Nissen Fundoplication /Laparoscopic Toupet Fundoplication
	<p><u>Salminen, 2007 [17667497]</u> 3/35 (8.6%)</p> <p><u>Olberg, 2005 [15932167]</u> 5/158 (3.2%)</p>	<p><u>Draaisma, 2006 [16794387]; Broeders, 2009 [19801931]</u> 12/79 (15.2%)</p> <p><u>Trullenque, 2005 [16004525]</u> 0/75 (0%)</p> <p><u>Yang, 2008 [18156921]</u> 13/88 (14.8%)</p> <p><u>Zacharoulis, 2006 [17024541]</u> 12/808 (1.5%)</p> <p><u>Salminen, 2006 [16921296]</u> 9/468 (1.9%)</p> <p><u>Morgenthal, 2007 [17562117]</u> 18/166 (10.8%)</p> <p><u>Cowgill, 2007 [17879678]</u> 28/239 (12%)</p> <p><u>Salminen, 2007 [17667497]</u> 3/38 (7.9%)</p> <p><u>Strate, 2008 [18027055]</u> 15/100 (15%)</p>	<p><u>Zehetner, 2006 [16391962]</u> 5/100 (5%)</p> <p><u>Rice, 2006 [16549692]</u> 8/113 (7.1%)</p> <p><u>Strate, 2008 [18027055]</u> 4/100 (4%)</p>	<p><u>Wijnhoven, 2008 [18071830]</u> 70/844 (8%)</p> <p><u>Rosenthal, 2006 [17243869]</u> 6/186 (3%)</p> <p><u>Oelschlager, 2008 [17970835]</u> 10/288 (3%)</p> <p><u>Gee, 2008 [18490558]</u> 2/173 (1.2%)</p> <p><u>Olberg, 2005 [15932167]</u> 17/215 (7.0%)</p>
Bleeding event rate ^{17,125,165}	<p><u>Huttl, 2005 [16211438]</u></p> <ul style="list-style-type: none"> Bleeding (without spleen): 5/1062 (0.5%) 	<p><u>Mehta, 2006 [17114017]</u></p> <ul style="list-style-type: none"> Splenic bleeding: 2/91 (2.2%) 	<p><u>Huttl, 2005 [16211438]</u></p> <ul style="list-style-type: none"> Bleeding (without spleen): 1/470 (0.2%) 	<p><u>Brehant, 2006 [16504893]</u></p> <ul style="list-style-type: none"> Bleeding: 10/2684 (0.4%)

	Surgical			
	Open Nissen Fundoplication	Laparoscopic Nissen Fundoplication	Laparoscopic Toupet Fundoplication	Laparoscopic Nissen Fundoplication /Laparoscopic Toupet Fundoplication
<p>Pulmonary event rate 78,125,129,162,171</p>		<p><u>Cowgill, 2007 [17879678]</u></p> <ul style="list-style-type: none"> • Postpneumonic empyema: 1/239 (0.4%) • Atelectasis: 1/239 (0.4%) <p><u>Teixeria, 2009 [19453033]</u></p> <ul style="list-style-type: none"> • Respiratory complications: 6/143 (4.2%) <p><u>Dalessio, 2005 [16137590]</u></p> <ul style="list-style-type: none"> • Pleural effusion: 1/257 (0.4%) 		<p><u>Rosenthal, 2006 [17243869]</u> 3/186 (1.6%)</p> <p><u>Brehant, 2006 [16504893]</u></p> <ul style="list-style-type: none"> • Pulmonary infection: 25/2684 (0.9%) • Pleural effusion: 12/2684 (0.4%) • Pulmonary embolism: 7/2684 (0.3%)
<p>Gastrointestinal event rate 17,63,68,74,75,79,80,124,125,129,137,141,165,166,170,171</p>	<p><u>Trullenque, 2005 [16004525]</u></p> <ul style="list-style-type: none"> • Early satiety: 0/28 (0%) • Diarrhea: 0/28 (0%) <p><u>Huttl, 2005 [16211438]</u></p> <ul style="list-style-type: none"> • Esophageal perforation: 6/1062 (0.6%) • Injuries of the stomach wall: 6/1062 (0.6%) <p><u>Cowgill, 2007 [17879678]</u></p> <ul style="list-style-type: none"> • Early postoperative gastroesophageal junction edema: 4/239 (1.7%) • Gastric/esophageal leak: 3/239 (1.3%) • Gastrotomy/esophagotomy: 2/239 (0.8%) 	<p><u>del Genio, 2007 [17426906]</u></p> <ul style="list-style-type: none"> • Hyperflautulence: 7/368 (1.9%) • Early satiety: 14/368 (3.8%) <p><u>Booth, 2008 [18076018]</u></p> <ul style="list-style-type: none"> • Restriction in belching: 26/59 (44%) • Unable to belch: 8/59 (14%) • Increased flatus: 44/59 (75%) • Diarrhoea: 4/59 (7%) <p><u>Cai, 2008 [18942055]</u></p> <ul style="list-style-type: none"> • Able to belch 	<p><u>Booth, 2008 [18076018]</u></p> <ul style="list-style-type: none"> • Restriction in belching: 21/58 (36%) • Unable to belch: 3/58 (5%) • Increased flatus: 39/58 (67%) • Diarrhoea: 6/58 (10%) <p><u>Cai, 2008 [18942055]</u></p> <ul style="list-style-type: none"> • Able to belch normally: 27/41 (66%) <p><u>Zehetner, 2006</u></p>	<p><u>Oelschlager, 2008 [17970835]</u></p> <ul style="list-style-type: none"> • New or increased diarrhea: 32/288 (11%) <p><u>Brehant, 2006 [16504893]</u></p> <ul style="list-style-type: none"> • Esophagus injury: 10/2684 (0.4%)

	Surgical			
	Open Nissen Fundoplication	Laparoscopic Nissen Fundoplication	Laparoscopic Toupet Fundoplication	Laparoscopic Nissen Fundoplication /Laparoscopic Toupet Fundoplication
	<ul style="list-style-type: none"> • Ileus: 1/239 (0.4%) <p><u>Csendes, 2005 [16137596]</u></p> <ul style="list-style-type: none"> • Necrosis: 0/225 (0%) 	<p>normally: 24/48 (50%)</p> <p><u>Trullenque, 2005 [16004525]</u></p> <ul style="list-style-type: none"> • Early satiety: 1/75 (1.3%) • Diarrhea: 2/75 (2.7%) <p><u>Mardani, 2009 [19016274]</u></p> <ul style="list-style-type: none"> • Ability to belch: 43/82 (52.4%) <p><u>Pizza, 2007 [17278197]</u></p> <ul style="list-style-type: none"> • Early satiety: 11/400 (2.8%) • Hyperflatulence: 7/400 (1.8%) <p><u>Strate, 2008 [18027055]</u></p> <ul style="list-style-type: none"> • Inability to belch: 25/100 (25%) <p><u>Trullenque, 2005 [16004525]</u></p> <ul style="list-style-type: none"> • Hindered vomiting and burping 15/75 (20.0%) 	<p><u>[16391962]</u></p> <ul style="list-style-type: none"> • Early satiety: 35/87 (41%) • Burp impossibility: 28/87 (33%) • Flatulence: 8/87 (10%) • Diarrhea: 9/87 (11%) <p><u>Huttl, 2005 [16211438]</u></p> <ul style="list-style-type: none"> • Esophageal perforation: 2/470 (0.4%) • Injuries of the stomach wall: 1/470 (0.2%) <p><u>Strate, 2008 [18027055]</u></p> <ul style="list-style-type: none"> • Inability to belch: 13/100 (13%) <p><u>Fein, 2008 [18766417]</u></p> <p>Vomiting: 6/25 (24%)</p>	
		<p><u>Fein, 2008 [18766417]</u></p> <ul style="list-style-type: none"> • Vomiting: 13/74 (18.8%) <p><u>Mardani, 2009 [19016274]</u></p> <ul style="list-style-type: none"> • Ability to vomit: 12/82 (14.6%) 		

	Surgical			
	Open Nissen Fundoplication	Laparoscopic Nissen Fundoplication	Laparoscopic Toupet Fundoplication	Laparoscopic Nissen Fundoplication /Laparoscopic Toupet Fundoplication
		<p><u>Dalessio, 2005</u> [16137590]</p> <ul style="list-style-type: none"> • Ileus: 1/257 (0.4%) • Small bowel perforation: 1/257 (0.4%) <p><u>Mehta, 2006</u> [17114017]</p> <ul style="list-style-type: none"> • Inadvertent Esophageal injury: 2/91 (2.2%) 		
<p>Infection/ fever event rate <small>^{19,125,129,144,162,165,171,173}</small></p>		<p><u>Huttl, 2005</u> [16211438]</p> <ul style="list-style-type: none"> • Wound infections: 9/1062 (0.85%) • Intraabdominal infections: 2/1062 (0.2%) <p><u>Jensen, 2009</u> [18855057]</p> <ul style="list-style-type: none"> • Wound infection: 2/113 (1.8%) <p><u>Cowgill, 2007</u> [17879678]</p> <ul style="list-style-type: none"> • Superficial wound infection: 2/239 (0.8%) <p><u>Dalessio, 2005</u> [16137590]</p> <ul style="list-style-type: none"> • Urinary tract infection: 2/257 (0.8%) • Pneumonia: 1/257 (0.4%) <p><u>Anvari, 2006</u></p>	<p><u>Huttl, 2005</u> [16211438]</p> <ul style="list-style-type: none"> • Wound infections: 0/470 (0%) • Intraabdominal infections: 0/470 (0%) 	<p><u>Rosenthal, 2006</u> [17243869]</p> <ul style="list-style-type: none"> • Urinary tract infection: 3/186 (1.6%) <p><u>Wang, 2008</u> [18368318]</p> <ul style="list-style-type: none"> • Pneumonia 2/33 (6.1%) <p><u>Brehant, 2006</u> [16504893]</p> <ul style="list-style-type: none"> • Wound infection: 14/2684 (0.5%)

	Surgical			
	Open Nissen Fundoplication	Laparoscopic Nissen Fundoplication	Laparoscopic Toupet Fundoplication	Laparoscopic Nissen Fundoplication /Laparoscopic Toupet Fundoplication
		[17227922] • Fever 2/52 (3.8%)		
<p style="text-align: center;">Dysphagia event</p> <p>rate ^{17,19,66,68,69,74,75,78,79,133,137,141,144,164,167,168,170,173}</p>	<p>Trullenque, 2005 [16004525] 0/28 (0%)</p> <p>Zacharoulis, 2006 [17024541] 15/808 (1.9%)</p> <p>Jensen, 2009 [18855057] 5/113 (4.4%)</p>	<p>Salminen, 2006 [16921296] 97/439 (22.1%)</p> <p>del Genio, 2007 [17426906] 13/368 (3.5%)</p> <p>Dallempagne, 2006 [16333553] 11/49 (22.4%)</p> <p>Trullenque, 2005 [16004525] 1/75 (1.3%)</p> <p>Fein, 2008 [18766417] 22/74 (30.6%)</p> <p>Pizza, 2007 [17278197] 13/400 (3.3%)</p> <p>Teixeria, 2009 [19453033] • Serious dysphagia: 6/143 (4.2%)</p> <p>Kamolz, 2005 [15959712] 21/178 (11.8%)</p> <p>Mehta, 2006 [17114017] 4/91 (4.4%)</p> <p>Anvari, 2006</p>	<p>Dallempagne, 2006 [16333553] 5/20 (25.0%)</p> <p>Fein, 2008 [18766417] 7/25 (28.0%)</p> <p>Zehetner, 2006 [16391962] • Mild dysphagia: 1/87 (2%)</p>	<p>Pessaux, 2005 [16230543] 68/1340 (5.1%)</p> <p>Fumagalli, 2008 [18430108] 25/259 (9.1%)</p> <p>Oelschlager, 2008 [17970835] 7/288 (2%)</p> <p>Strate, 2008 [18027055] • Moderate to severe dysphagia: 27/200 (13.5%)</p> <p>Wang, 2008 [18368318] • Dysphagia+vomiting: 1/33 (3.0%)</p>

	Surgical			
	Open Nissen Fundoplication	Laparoscopic Nissen Fundoplication	Laparoscopic Toupet Fundoplication	Laparoscopic Nissen Fundoplication /Laparoscopic Toupet Fundoplication
		[17227922] 4/52 (7.7%)		
<p style="text-align: center;">Bloating</p> <p>event rate ^{19,63,66,68,69,74,79,124,133,137,141,168,170}</p>	<p>Trullenque, 2005 [16004525]</p> <ul style="list-style-type: none"> • Gas bloat: 0/28 (0%) • Meteorism: 0/28 (0%) 	<p>Salminen, 2006 [16921296]</p> <ul style="list-style-type: none"> • Bloating/flatulence: 320/441 (72.6%) <p>del Genio, 2007 [17426906]</p> <p>9/368 (2.4%)</p> <p>Dallemagne, 2006 [16333553]</p> <ul style="list-style-type: none"> • Abdominal bloating: 40/49 (81.6%) • Gas: 22/49 (44.9%) <p>Cai, 2008 [18942055]</p> <ul style="list-style-type: none"> • Abdominal bloating: 14/48 (29%) <p>Trullenque, 2005 [16004525]</p> <ul style="list-style-type: none"> • Gas bloat: 1/75 (1.3%) • Meteorism: 4/75 (5.3%) <p>Booth, 2008 [18076018]</p> <ul style="list-style-type: none"> • Postprandial fullness: 37/59 (63%) <p>Fein, 2008 [18766417]</p> <ul style="list-style-type: none"> • Bloating: 62/74 (84.9%) • Epigastric fullness 44/74: (60.3%) 	<p>Dallemagne, 2006 [16333553]</p> <ul style="list-style-type: none"> • Abdominal bloating: 14/20 (70.0%) • Gas: 15/20 (75.0%) <p>Cai, 2008 [18942055]</p> <ul style="list-style-type: none"> • Abdominal bloating: 19/41 (46%) <p>Fein, 2008 [18766417]</p> <ul style="list-style-type: none"> • Bloating: 16/25 (64%) • Epigastric fullness: 15/25 (60%) <p>Booth, 2008 [18076018]</p> <ul style="list-style-type: none"> • Postprandial fullness: 37/58 (64%) 	<p>Pessaux, 2005 [16230543]</p> <ul style="list-style-type: none"> • Gas bloat syndrome: 101/1340 (7.5%) <p>Oelschlager, 2008 [17970835]</p> <ul style="list-style-type: none"> • Bloating: 27/288 (9%) <p>Strate, 2008 [18027055]</p> <ul style="list-style-type: none"> • Gas bloating: 106/200 (53%)

	Surgical			
	Open Nissen Fundoplication	Laparoscopic Nissen Fundoplication	Laparoscopic Toupet Fundoplication	Laparoscopic Nissen Fundoplication /Laparoscopic Toupet Fundoplication
		<p><u>Pizza, 2007 [17278197]</u></p> <ul style="list-style-type: none"> • Bloating: 4/400 (1.0%) <p><u>Kamolz, 2005 [15959712]</u></p> <ul style="list-style-type: none"> • Bloating 14/178 (7.9%) <p><u>Anvari, 2006 [17227922]</u></p> <ul style="list-style-type: none"> • Postprandial bloating 7/52 (13.5%) 		
<p>Pain event rate^{19,68,70,124,137,170}</p>		<p><u>del Genio, 2007 [17426906]</u></p> <ul style="list-style-type: none"> • Chest pain: 2/368 (0.5%) <p><u>Booth, 2008 [18076018]</u></p> <ul style="list-style-type: none"> • Abdominal pain: 13/59 (22%) <p><u>Fein, 2008 [18766417]</u></p> <ul style="list-style-type: none"> • Epigastric pain; 32/74 (43.8%) • Chest pain: 28/74 (38.4%) <p><u>Pizza, 2007 [17278197]</u></p> <ul style="list-style-type: none"> • Chest pain: 0/400 (0%) <p><u>Anvari, 2006 [17227922]</u></p> <ul style="list-style-type: none"> • Abdominal pain 2/52 (3.8%) 	<p><u>Booth, 2008 [18076018]</u></p> <ul style="list-style-type: none"> • Abdominal pain: 15/58 (26%) <p><u>Fein, 2008 [18766417]</u></p> <ul style="list-style-type: none"> • Epigastric pain: 13/25 (52%) • Chest pain: 12/25 (48%) 	<p><u>Wijnhoven, 2008 [18071830]</u></p> <ul style="list-style-type: none"> • Chest pain: 332/833 (39.9%)

	Surgical			
	Open Nissen Fundoplication	Laparoscopic Nissen Fundoplication	Laparoscopic Toupet Fundoplication	Laparoscopic Nissen Fundoplication /Laparoscopic Toupet Fundoplication
Other ^{74,78,79,125,136,141,165-168}	<p><u>Trullenque, 2005 [16004525]</u></p> <ul style="list-style-type: none"> • Hindered vomiting and burping: 1/28 (3.6%) • Hiccup: 0/28 (0%) <p><u>Huttl, 2005 [16211438]</u></p> <ul style="list-style-type: none"> • Injuries of the spleen: 4/1062 (0.4%) • Injuries of the pleura with thoracic drain: 5/1062 (0.5%) • Injuries of the pleura without drain: 19/1062 (1.8%) <p><u>Csendes, 2005 [16137596]</u></p> <ul style="list-style-type: none"> • Conversions: 3/225 (1.3%) • Necrosis: 0/225 (0%) <p><u>Zacharoulis, 2006 [17024541]</u></p> <ul style="list-style-type: none"> • Intrathoracic wrap migration: 11/808 (1.4%) <p><u>Salminen, 2006 [16921296]</u></p> <ul style="list-style-type: none"> • Conversion: 10/468 (2.1%) • Difficulties with swallowing: 47/468 (10.0%) 	<p><u>Trullenque, 2005 [16004525]</u></p> <ul style="list-style-type: none"> • Hiccup: 1/75 (1.3%) <p><u>Manning, 2006 [16872031]</u></p> <ul style="list-style-type: none"> • Conversion: 2/124 (2%) <p><u>Strate, 2008 [18027055]</u></p> <ul style="list-style-type: none"> • Conversion: 6/100 (6%) <p><u>Teixeria, 2009 [19453033]</u></p> <ul style="list-style-type: none"> • Conversion: 4/143 (2.7%) 		<p><u>Oelschlager, 2008 [17970835]</u></p> <ul style="list-style-type: none"> • New or increased diarrhea: 32/288 (11%) <p><u>Brehant, 2006 [16504893]</u></p> <ul style="list-style-type: none"> • Pneumothorax: 6/2684 (0.2%) • Esophagus injury: 10/2684 (0.4%) • Arterial hypertension: 6/2684 (0.2%) • Acute coronary syndrome: 5/2684 (0.2%) • Postoperative ileus: 7/2684 (0.3%) • Acute pancreatitis: 1/2684 (0.04%) • Subcutaneous emphysema: 3/2684 (0.1%) • Pulmonary embolism: 7/2684 (0.3%) • Pyrexia: 7/2684 (0.3%)
Other ^{18,66,69,129,144,162,165,171,172}	<p><u>Jensen, 2009 [18855057]</u></p> <ul style="list-style-type: none"> • Conversions: 0/113 (0%) • Readmission to hospital: 4/113 (3.5%) <p><u>Cowgill, 2007 [17879678]</u></p> <ul style="list-style-type: none"> • Conversion: 35/239 (15%) • Dysrhythmia: 3/239 (1.3%) • Urinary retention: 3/239 (1.3%) 	<p><u>Dallemagne, 2006 [16333553]</u></p> <ul style="list-style-type: none"> • Conversions: 0/68 (0%) <p><u>Dalessio, 2005 [16137590]</u></p> <ul style="list-style-type: none"> • Urinary retention: 5/257 (1.9%) • Uncomplicated CO2 	<p><u>Huttl, 2005 [16211438]</u></p> <ul style="list-style-type: none"> • Injuries of the spleen: 4/470 (0.85%) • Injuries of the pleura with thoracic drain: 2/470 (0.4%) • Injuries of the pleura without 	<p><u>Rosenthal, 2006 [17243869]</u></p> <ul style="list-style-type: none"> • Neuropsychiatric: 2/186 (1.1%) • Cardiac: 1/186 (0.5%) • Endocrinological: 1/186 (0.5%) <p><u>Pessaux, 2005 [16230543]</u></p>

	Surgical			
	Open Nissen Fundoplication	Laparoscopic Nissen Fundoplication	Laparoscopic Toupet Fundoplication	Laparoscopic Nissen Fundoplication /Laparoscopic Toupet Fundoplication
	<ul style="list-style-type: none"> • CO2 pneumothorax: 3/239 (1.3%) • Urinary tract infection: 1/239 (0.4%) • Fascial dehiscence: 1/239 (0.4%) • Intraabdominal abscess: 1/239 (0.4%) • Splenic laceration: 1/239 (0.4%) • Postoperative hemorrhage: 1/239 (0.4%) <p><u>Olberg, 2005 [15932167]</u></p> <ul style="list-style-type: none"> • Ventral hernia: 2/158 (1.3%) • Port site hernia: 0/158 (0%) • Diaphragmatic hernia: 1/158 (0.6%) • Paraesophageal herniation: 0/158 (0%) • Slipped Nissen: 1/158 (0.6%) • Disrupted Nissen or Toupet: 0/158 (0%) 	<ul style="list-style-type: none"> • pneumothorax: 4/257 (1.6%) • Atelectasis: 4/257 (1.6%) • Atrial fibrillation: 2/257 (0.8%) • Myocardial infarctions: 0/257 (0%) • Strokes: 0/257 (0%) • Pulmonary emboli: 0/257 (0%) 	<ul style="list-style-type: none"> • drain: 3/470 (0.6%) <p><u>Dallemagne, 2006 [16333553]</u></p> <ul style="list-style-type: none"> • Conversions: 0/32 (0%) 	<ul style="list-style-type: none"> • Conversions: 112/1340 (8.4%) <p><u>Wang, 2008 [18368318]</u></p> <ul style="list-style-type: none"> • Subcutaneous emphysema: 1/198 (0.5%) <p><u>Olberg, 2005 [15932167]</u></p> <ul style="list-style-type: none"> • Ventral hernia: 0/215 (0%) • Port site hernia: 13/215 (6.0%) • Diaphragmatic hernia: 0/215 (0%) • Paraesophageal herniation: 9/215 (4.2%) • Slipped Nissen: 6/215 (2.8%) • Disrupted Nissen or Toupet: 3/215 (1.4%)
Other ^{17,19,133}		<p><u>Kalmoz, 2005 [15959712]</u></p> <ul style="list-style-type: none"> • Early satiety 11/178 (6.1%) • Hiccups 12/178 (6.7%) • Severe weight loss (>5Kg) 12/178 (6.7%) <p><u>Mehta, 2006 [17114017]</u></p> <ul style="list-style-type: none"> • Wrap migration: 2/91 (2.2%) 		

	Surgical			
	Open Nissen Fundoplication	Laparoscopic Nissen Fundoplication	Laparoscopic Toupet Fundoplication	Laparoscopic Nissen Fundoplication /Laparoscopic Toupet Fundoplication
		<ul style="list-style-type: none"> • Postoperative sequelae: 0/91 (0%) <p><u>Anvari, 2006</u> <u>[17227922]</u></p> <ul style="list-style-type: none"> • Dilation of the wrap 2/52 (3.8%) • Delayed oral intake 3/52 (5.8%) 		

Table 42: Intraoperative complications (and those occurring within 30 days) for endoscopic procedures

	Endoscopic		
	Endocinch™	Stretta™	EsophyX
Mortality event rate	ND	ND	ND
Dysphagia event rate^{91,92}			<p><u>Cadiere, 2008 [18443855]</u> 3/86 (4%)</p> <p><u>Cadiere, 2008 [18071818]</u> 0/17 (0%)</p>
Bleeding event rate^{92,175}	<p><u>Mosler, 2008 [18629586]</u> 2/18 (11.1%)</p>		<p><u>Cadiere, 2008 [18443855]</u> • Application site bleeding: 5/86 (6%)</p>
Other event rate^{91-93,99}		<p><u>Lutfi, 2005 [15624052]</u> • Transient gastroparesis: 1/77 (1.3%)</p>	<p><u>Cadiere, 2008 [18443855]</u> • Musculoskeletal pain: 8/86 (9%) • Perforation: 2/86 (2%) • Abdominal pain upper: 8/86 (9%) • Pharyngolaryngeal pain: 6/86 (7%) • Nausea: 6/86 (7%) • Epigastric pain: 4/86 (5%) • Pyrexia: 3/86 (4%) • Diarrhea: 2/86 (2%) • Vomiting: 2/86 (2%)</p> <p><u>Repici, 2010 [19902310]</u> • Hematemesis: 2/20 (10%)</p> <p><u>Cadiere, 2008 [18071818]</u> • Bloating: 3/17 (18%) • Diarrhea: 0/17 (0%) • Difficulty swallowing: 2/17 (12%) • Epigastric pain: 1/17 (6%) • Eructation: 6/17 (35%) • Fever: 0/17 (0%) • Flatulence: 1/17 (6%) • Globus: 0/17 (0%) • Hematesis: 0/17 (0%) • Left shoulder pain: 0/17 (0%) • Nausea: 0/17 (0%) • Pharynx irritation: 3/17 (18%) • Vomiting: 1/17 (6%)</p>

Table 43: Complications occurring more than 30 days after endoscopic procedures

	Endoscopic		
	Endocinch™	Stretta™	EsophyX
Mortality event rate	nd	nd	nd
Re-operation event rate⁸⁴	<u>Domagk, 2006 [16542275]</u> 7/23 (30.4%)		
Bleeding event rate^{85,95}	<u>Liao, 2008 [18318824]</u> • Delayed bleeding with hematemesis: 1/21 (4.8%)		<u>Demyttenaere, 2010 [19730949]</u> 2/26 (7.7%)
Infection/ fever event rate⁸⁸	<u>Paulssen, 2008 [18938771]</u> • Oesophageal fungal infections: 2/119 (1.6%)		
Dysphagia event rate^{81,85,99}	<u>Schwartz, 2007 [16763053]</u> • Dysphagia <7 days: 10/20 (50%) <u>Liao, 2008 [18318824]</u> • Minor dysphasia 3/21 (14.3%)	<u>Lutfi, 2005 [15624052]</u> • Dysphagia: 0/77 (0%)	
Bloating event rate^{81,85,99}	<u>Schwartz, 2007 [16763053]</u> • Bloating: 2/20 (10%) <u>Liao, 2008 [18318824]</u> • Bloating 4/21 (19.0%)	<u>Lutfi, 2005 [15624052]</u> • Severe gas bloat: 0/77 (0%)	
Pain event rate^{81,85}	<u>Schwartz, 2007 [16763053]</u> • Abdominal pain: 1/20 (5%) <u>Liao, 2008 [18318824]</u> • Abdominal pain: 5/21 (23.8%)		
Other event rate^{81,83,85,88,92,95,99}	<u>Schwartz, 2007 [16763053]</u> • Sore throat: 8/20 (40%) • Chest soreness: 6/20 (30%) • Belching: 1/20 (5%) • Early satiety: 1/20 (5%) • Hiccups: 1/20 (5%) • Sedation-related: 0/20 (0%) <u>Paulssen, 2008 [18938771]</u> • Suture removal due to difficulty in swallowing: 1/119 (1%) <u>Liao, 2008 [18318824]</u> • Sore throat: 13/21 (61.9%) • Vomiting: 2/21 (9.5%)	<u>Lutfi, 2005 [15624052]</u> • Stricture: 0/77 (0%) <u>Coron, 2008 [18616516]</u> • Severe complication: 0/23 (0%) ^a	<u>Cadiere, 2008 [18443855]</u> • Abdominal pain upper: 1/86 (1%) • Nausea: 1/86 (1%) <u>Demyttenaere, 2010 [19730949]</u> • Esophageal perforation: 0/26 (0%)

^a No detailed information about complication

Table 44: Devices and Adverse events from the MAUDE database

Therapy	Device name	Manufacturer	Time Period	No. of Adverse events
Radiofrequency ablation	Stretta®	Curon Medical Inc., Fremont, CA Curon Medical Inc., Sunnyvale, CA	2000-2007	29
Endoluminal Suture	EndoCinch®	CR BARD/BARD Endoscopic Technologies, Billerica, MA Daval INC. (Subsidiary of CR BARD), Warwick RI	2001-2010	5
Endoluminal Suture	Esophyx®	Endogastric Solutions, Redmond, WA Redmond Inc., Redmond, WA	2009-2010	4

Table 45: List of Adverse events from the MAUDE database

Device	Adverse events
Stretta	<ol style="list-style-type: none"> 1. Death 2. Device malfunction 3. Gastrointestinal perforation 4. Perioperative bloating 5. Perioperative pain in stomach and abdomen 6. Perioperative gas and belching 7. Gastroparesis 8. Cutaneous burn 9. Perioperative chest pain 10. Gastrointestinal injury 11. Cardiac arrhythmia 12. Pneumonia 13. Pleural effusion 14. Post operative infection 15. Esophageal leak 16. Esophageal necrosis 17. Bleeding 18. Esophageal ulcer
EndoCinch	<ol style="list-style-type: none"> 1. Bleeding 2. Suture site ulcer 3. Ulcer at incision site 4. Operator error /device malfunction
Esophyx	<ol style="list-style-type: none"> 1. Device malfunction 2. Infection and abscess

Discussion

The present update found that many of the 2005 CER's original conclusions remained valid. In addition to these findings, additional data were identified and aided in the expansion of previous results. Notably, we added a section on the treatment of extra-esophageal manifestations of GERD, which was not covered in the 2005 review. Furthermore, the present update also reviewed two new PPIs and one new endoscopic procedure.

With regard to comparisons between surgery and medical therapy, we found that laparoscopic fundoplication in patients whose GERD symptoms were already well-controlled by medical treatments was at least as effective as continued medical treatment (and in some cases superior) in controlling GERD-related symptoms for the first 1 to 3 years following surgery, provided that the procedure was performed by experienced surgeons in high volume centers.

Bearing these findings in mind, the choice of laparoscopic fundoplication would be mainly targeted at those who wished to avoid the potential burden of lifelong medical treatments.

Therefore, it is important to know how well the laparoscopic fundoplication actually succeeds in doing so. Of the three trials on laparoscopic fundoplication versus medical treatment reviewed, one reported that no patients treated with surgery were on medications at 1 year followup;¹⁹ one reported 13 percent of the surgically treated patients were on medications at 1 year;¹³ and one (with a 3 year followup) did not report medication use.¹ It appears clear that laparoscopic fundoplication is efficacious in helping patients to decrease the use of antireflux medications in the short term (≤ 1 year), but the longer term effect is uncertain. Of note, a long-term trial on open fundoplication versus medical treatments found that one-third of the surgically treated patients had received some form of antireflux medication by 12 years.¹⁶

Adverse events from surgery must also be considered. Fundoplication is associated with procedural complications like postoperative infections and incisional hernia, and morbidities like dysphagia and postprandial bloating, some of which may require surgical revisions. It would be helpful if one can predict preoperatively who would be at a higher risk of some of these postoperative complications. However, our review did not identify reliable patient or operative predictors of clinical outcome; age, morbid obesity, female sex, baseline symptoms, esophagitis, and hiatal hernia were all inconsistently associated with worse surgical outcomes.

Medical therapy has also been associated with potentially serious complications. As in our previous review, serious complications reported with the use of PPIs include an increased risk of enteric infections (including *Campylobacter* and *C. difficile*) and pneumonia. An observation made since the 2005 review is a possible association between the use of PPIs and an increased risk of fractures.

For patients with GERD symptoms that cannot be adequately managed by standard medical treatments, published evidence to guide the choice of further therapy is not particularly helpful, as the available data are restricted to cohort studies lacking a proper control group. Of note, the two studies reviewed that explicitly included patients with an unsatisfactory response to medical treatments found that GERD symptoms had significantly improved after laparoscopic fundoplication in more than 5 years of followup.^{75,76}

Another important consideration is whether medical therapy or surgery is more effective in preventing long-term complications of GERD such as the development of Barrett's esophagus or esophageal adenocarcinoma. We did not identify sufficient evidence to conclude whether one or the other approach was more effective in preventing these adverse outcomes.

In addition to comparing medical and surgical therapies, our review also evaluated several new studies comparing specific medications, including two new PPIs. No consistent comparative difference in symptom relief was observed between esomeprazole (20 to 40 mg), lansoprazole (15 to 30 mg), pantoprazole (20 to 40 mg), dexlansoprazole (10 mg) or rabeprazole (10 to 20 mg). However, there is some evidence that rabeprazole 10 mg may provide better symptom relief than esomeprazole 40 mg at 4 weeks, and pantoprazole 40 mg better than esomeprazole 40 mg over 24 weeks. With respect to dosing intervals, continuous dosing with PPIs was found to be more effective than on-demand dosing. For example, continuous daily intake of esomeprazole 20 mg or rabeprazole 20 mg appeared to provide better symptom control and quality of life relative to on-demand dosing over a period of 6 months. As for comparisons of different PPIs with over-the-counter dosages of omeprazole (20 mg), it was observed that pantoprazole 40 mg and rabeprazole 20 mg provided significantly better symptom relief and healing of esophagitis at 8 weeks, and esomeprazole 20 mg provided better endoscopic remission rates as compared to over-the-counter dosages of lansoprazole (15 mg) at 6 months. While significant, the observed magnitude of these differences was generally small and the clinical relevance remains uncertain. It is possible that the variations in effectiveness may have been due to the specific doses examined.

As for the three available endoscopic procedures (EndoCinch™, Stretta™, EsophyX™) for the long-term management of GERD, effectiveness remains substantially uncertain. EndoCinch (suturing) and Stretta (radiofrequency ablation) had been previously examined in the 2005 CER; EsophyX (endoscopic fundoplication) is a new introduction. While some clinical benefits were observed in patients who had these procedures, the studies were generally small, of variable quality, and of short duration. In addition, all of these procedures have been associated with complications including dysphagia, infection/fever, and bloating.

For the treatment of patients with extra-esophageal manifestations of GERD symptoms, no consistent benefit could be attributed to either medication or surgery. Despite the focus on only those patients with asthma, chronic cough, or laryngeal symptoms, we surmise that the considerable clinical heterogeneity within these subgroups precluded the detection of a reliable effect, if one exists. A small RCT did find patients' asthma symptoms improved after antireflux surgery compared to antireflux medical treatments, but these improvements could not be substantiated by objective testing.¹¹⁴ Similarly, some observational studies reported that antireflux surgery could be beneficial for those with asthma, chronic cough, or laryngeal symptoms.

While we have made every attempt to address the Key Questions set out in the present review, it should be noted that the available evidence had several important limitations:

- Studies directly comparing surgery to medical therapy generally had high dropout-rates in long-term followup (e.g., 58 percent of patients were lost to followup at 12 years in a study comparing medical treatment and open fundoplication).
- There was a great deal of variability in the rigor of how the outcomes were evaluated across studies, particularly in subjective endpoints (e.g., some used a validated measure of quality of life, while others used symptom scales whose measurement properties have not been well characterized).
- Most studies were non-randomized or lacked a suitable control group.
- The majority of the included studies had a relatively short followup (typically no longer than 1 year), particularly those concerned with medical treatments.

- Pharmacologically equivalent doses of various PPIs have not been well established (or universally agreed upon), thus clouding interpretation of existing comparative PPI studies.
- Reporting of adverse events was often incomplete and inconsistent across studies; some studies did not report specific adverse events and the definitions of adverse events differed across studies.

Remaining Issues and Future Research Needs

- Longer term followup is necessary to determine the efficacy of laparoscopic fundoplication versus medical treatments. One available study reviewed reported 3-year interim data; that study is still ongoing.¹
- Higher quality studies are necessary to determine the role and value of endoscopic procedures in the treatment of patients with GERD.
- Retrospective analyses exploring potential modifiers of treatment outcomes need to carefully consider confounders and perform appropriate adjustments.
- Comparative studies are needed to determine the optimal treatment(s) for patients who did not respond to medication.
- The potential necessity of life-long medical therapy raises the possibility of unidentified long-term safety issues. Therefore, a systematic monitoring of long-term safety data on PPIs should be put in place, as well as better baseline reporting of patient characteristics and potential confounders. Both could help ferret out any possible association between treatment and adverse events.

Table 46. Summary of evidence

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

		<p>H2RA (ranitidine 150 mg taken twice daily) in symptom remission.</p> <ul style="list-style-type: none"> - In maintenance treatment, patients taking lansoprazole 15 mg are likely to stay longer on their treatment as compared to ranitidine 150 mg taken twice daily and thus tend to have a longer median time to relapse of symptoms. - Studies with larger sample sizes suggested PPIs to be more efficacious than H2RAs with respect to GERD symptoms.
Comparisons between different PPIs	Moderate	<ul style="list-style-type: none"> - No consistent comparative difference in symptom relief was observed between esomeprazole (20 to 40 mg), lansoprazole (15 to 30 mg), pantoprazole (20 to 40 mg), dexlansoprazole (10 mg) or rabeprazole (10 to 20 mg) over a period ranging from 4 weeks to 6 months. - There is some evidence that rabeprazole 10 mg may provide better symptom relief than esomeprazole 40 mg at 4 weeks, and also that pantoprazole 20 mg provides better control of heartburn than esomeprazole 40 mg over 24 weeks.
Comparisons between different dosages and dosing regimens of PPIs	Moderate	<ul style="list-style-type: none"> - There was no significant difference in symptom resolution rates at 4 weeks between esomeprazole 20 mg taken once a day and esomeprazole 40 mg taken once a day. - A significantly higher rate of healing of esophagitis at 4 weeks was observed with esomeprazole 40 mg once a day compared with esomeprazole 20 mg once a day.
Comparisons between once daily and on-demand dosing regimens of PPIs	Moderate	<ul style="list-style-type: none"> - Continuous daily intake of esomeprazole 20 mg appears to provide better symptom control and quality of life relative to on-demand dosing over a period of 6 months. - Continuous daily intake of esomeprazole 20 mg appears to provide significantly better endoscopic remission compared with on-demand dosing over a period of 6 months. <p>Continuous daily intake of rabeprazole 20 mg appears to provide better symptom control and quality of life relative to on-demand dosing over a period of 6 months.</p>
Comparisons between PPIs and over-the-counter dosages of PPIs (omeprazole 20 mg, lansoprazole 15 mg)	Moderate	<ul style="list-style-type: none"> - Pantoprazole 40 mg and rabeprazole 20 mg provide significantly better symptom relief and healing of esophagitis than omeprazole 20 mg at 8 weeks. - Esomeprazole 20 mg provides higher endoscopic remission rates compared with lansoprazole 15 mg over 6 months.
Surgical treatment comparisons Total versus partial fundoplication	Moderate	<ul style="list-style-type: none"> - One RCT and five non-randomized comparative studies compared laparoscopic total versus partial fundoplication. - No consistent significant differences in GERD symptoms, diagnostic test results, or quality of life were observed between groups.
Fundoplication with versus without division of short gastric vessel	Moderate	<ul style="list-style-type: none"> - Two RCTs and two non-randomized comparative studies compared laparoscopic fundoplication with versus without division of short gastric vessel. - No significant differences in medication use, GERD symptoms, or quality of life were found between groups.
Laparoscopic versus open fundoplication	Moderate	<ul style="list-style-type: none"> - Two RCTs and one non-randomized comparative study compared laparoscopic versus open fundoplication.

		- No significant differences in medication use, GERD symptoms, diagnostic test results, or quality of life were found between groups.
Endoscopic treatments		
Comparison between endoscopic treatments	insufficient	- No direct comparisons between the different endoscopic treatments were identified.
EndoCinch™	Low	- Two sham-controlled studies and six non-comparative cohort studies evaluated the effectiveness of EndoCinch™. - No consistent differences between EndoCinch™ and sham were reported. - Significant improvements in heartburn, quality of life, and esophagitis healing were found in some but not all cohort studies.
EsophyX™	Insufficient	- Five small cohort studies evaluated the effectiveness of EsophyX™. - The reported proportion of patients who were off PPI at the end of the followup period ranged from 47 to 71 percent. - Significant improvement of GERD-HRQL was reported by two of five studies.
Stretta™	Insufficient	- One sham-controlled study and seven non-comparative cohort studies evaluated Stretta™. - In the RCT, the proportion of patients who stopped or decreased PPI use was significantly greater in the Stretta™ group compared with the control group at 6 months (but it was not significant at 1 year). No significant differences in heartburn symptoms, QoL, acid exposure and esophagitis outcomes were found. - The majority of cohort studies found significant improvements in GERD symptoms, QoL, and medication use.
Medical treatment for extra-esophageal symptoms		
Asthma	Insufficient	- A systematic review did not find consistent effects of PPI or H2RA (versus placebo) in improving asthma symptoms, nocturnal asthma, use of asthma medications or FEV1. - 8 primary RCTs in the update to the systematic review also reported inconsistent effects. Omeprazole 20 mg (combined with domperidone 10 mg) or esomeprazole 40 mg showed an improvement in peak expiratory flow rate. Lansoprazole 30 mg or pantoprazole 40 mg did not show an improvement in asthma symptoms or lung function tests. Rabeprazole 20 mg twice a day improved respiratory symptoms during exercise in patients with exercise induced asthma, as compared to a placebo, but not QoL or pulmonary function measures.
Hoarseness	Low	- Four of six RCTs did not find a significant difference in resolution of hoarseness between PPI and placebo.
Chronic cough	Low	- Meta-analysis of 6 studies (191 participants) showed no significant difference in total resolution of cough between PPIs and placebo, odds ratio 0.46 (95% CI: 0.19 to 1.15). A second meta-analysis of 6 studies (161 participants) showed a significant difference in the change in cough scores from baseline comparing PPI with placebo: -0.39 standardized mean difference (SMD) units (95% CI -0.71 to -0.08).
Surgical Treatment for extra-esophageal symptoms	Insufficient	- All of the data on surgical treatment are from cohort studies, with a wide variation in the population treated, the severity of the underlying GERD and its extra-

		<p>esophageal manifestation, the outcome measures, the surgical interventions, the intensity and duration of followup.</p> <ul style="list-style-type: none"> - The majority of the cohort studies found that surgery may help improve cough and laryngeal symptoms more so than asthma, but there is a wide range of effect estimates in these studies.
<p>Key Question 2: Is there evidence that the effectiveness of medical, surgical and newer forms of 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 (e.g., academic versus community)?</p>		
Factors that influenced the comparative effectiveness of surgical versus medical treatment	Insufficient	<ul style="list-style-type: none"> - One study found that there was no significant difference in the effectiveness of medical vs. surgical treatment between patients with and without Barrett's esophagus.
Factors that influenced the outcome of medical therapy	Moderate	<ul style="list-style-type: none"> - Six RCTs comparing different PPIs, or dosages and dosing regimens of PPIs showed mixed findings regarding the impacts of esophagitis severity at baseline on healing rates. - Ten cohort studies examined patient characteristics or clinical factors as modifying factors of medical treatment outcomes. <ul style="list-style-type: none"> • Sex was not a significant modifying factor of medical treatment outcomes. • Obesity, presence of baseline typical GERD symptoms, and more severe esophagitis were significantly associated with worse medical treatment outcomes • The associations between age and medical treatment outcomes were inconsistent.
Factors that influenced the outcome of surgical treatment	Low	<ul style="list-style-type: none"> - One RCT found that preoperative esophageal motility did not significantly impact the effect of laparoscopic fundoplication on dysphagia, recurrence of reflux, and acid exposure and manometry outcomes. - Thirty cohort studies showed the following were inconsistently associated with worse surgical outcome: per year increase in patient's age, morbid obesity, female sex, presence of baseline symptoms or esophagitis, and hiatal hernia greater than 3 cm at baseline.
Factors that influenced the outcome of endoscopic treatment	Low	<ul style="list-style-type: none"> - Three cohort studies examined different modifying factors of endoscopic treatment: <ul style="list-style-type: none"> • One study did not find a significant difference between men and women in symptom improvement. • One study found more patients with less severe esophagitis at baseline stopped PPI use than patients with more severe esophagitis. • One study observed a learning curve in performance of a new endoscopic treatment device (EsophyX) comparing the technical procedure parameters.
<p>Key Question 3: What are the short-term and long-term adverse events associated with specific</p>		

medical, surgical and newer forms of therapies for GERD? Does the incidence of adverse events vary with duration of follow-up, specific surgical intervention, or patient characteristics?

Adverse events

Low

- None of the adverse event quantitative estimates are reliable because of a lack of standard definition and uniform system of reporting.
 - One RCT reported that the rate of serious adverse events was higher with surgery than with medical treatment (P=0.06).
 - Potential serious complications possibly associated with PPIs included an increased risk of bone fracture, as well as enteric infections and pneumonia previously reported in our 2005 CER.
 - Common adverse events reported in patients who underwent fundoplication included bloating and dysphagia.
 - Common adverse events after endoscopic suturing included chest or abdominal pain, bleeding, dysphagia, and bloating.
-

References

1. Lundell L, Attwood S, Ell C, et al. Comparing laparoscopic antireflux surgery with esomeprazole in the management of patients with chronic gastro-oesophageal reflux disease: a 3-year interim analysis of the LOTUS trial. *Gut* 57 (9):1207 -13, 2008.
2. Ip S, Bonis P, Tatsioni A et al. Effectiveness of management strategies for gastroesophageal reflux disease. 1. 2005. Agency for Healthcare Research and Quality. Evidence Report/Technology Assessment.
3. Vakil N, van Zanten SV, Kahrilas P, Dent J, Jones R. The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. *Am J Gastroenterol* 2006; 101(8):1900-1920.
4. Brook RA, Wahlqvist P, Kleinman NL, et al. Cost of gastro-oesophageal reflux disease to the employer: a perspective from the United States. *Aliment Pharmacol Ther* 2007; 26(6):889-898.
5. Forgacs I, Loganayagam A. Overprescribing proton pump inhibitors. *BMJ* 2008; 336(7634):2-3.
6. Ip S, Tatsioni A, Conant A, et al. Predictors of clinical outcomes following fundoplication for gastroesophageal reflux disease remain insufficiently defined: a systematic review. *Am J Gastroenterol* 2009; 104(3):752-758.
7. U.S.Food and Drug Administration, <http://www.fda.gov/cdrh/maude.html>. Manufacturer and User Facility Device experience Database - (MAUDE). Internet website . 2005.
8. Altman DG, Schulz KF, Moher D, et al. The revised CONSORT statement for reporting randomized trials: explanation and elaboration.[see comment]. [Review] [204 refs]. *Annals of Internal Medicine* 134(8):663-94, 2001.
9. Moher D, Schulz KF, Altman D, CONSORT GROUP (Consolidated Standards of Reporting Trials). The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomized trials.[see comment]. [Review] [30 refs]. *JAMA* 285(15):1987-91, 2001.
10. Shea BJ, Grimshaw JM, Wells GA, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. *BMC Med Res Methodol* 2007; 7:10.
11. Moher D, Cook DJ, Eastwood S, et al. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. Quality of Reporting of Meta-analyses.[see comment]. [Review] [49 refs]. *Lancet* 354(9193):1896-900, 1999.

12. Gibson PG, Henry R, Coughlan JJ. Gastro-oesophageal reflux treatment for asthma in adults and children [Systematic Review]. *Cochrane Database of Systematic Reviews* 2009;(3).
13. Grant AM, Wileman SM, Ramsay CR, et al. Minimal access surgery compared with medical management for chronic gastro-oesophageal reflux disease: UK collaborative randomised trial.[see comment]. *BMJ* 337 :a2664 , 2008.
14. Attwood SE, Lundell L, Hatlebakk JG, et al. Medical or surgical management of GERD patients with Barrett's esophagus: the LOTUS trial 3-year experience. *J Gastrointest Surg* 2008; 12(10):1646-1654.
15. Lundell L, Miettinen P, Myrvold HE, et al. Seven-year follow-up of a randomized clinical trial comparing proton-pump inhibition with surgical therapy for reflux oesophagitis.[see comment]. *British Journal of Surgery* 94 (2):198 -203 , 2007.
16. Lundell L, Miettinen P, Myrvold HE, et al. Comparison of outcomes twelve years after antireflux surgery or omeprazole maintenance therapy for reflux esophagitis. *Clin Gastroenterol Hepatol* 2009; 7(12):1292-1298.
17. Mehta S, Bennett J, Mahon D, Rhodes M. Prospective trial of laparoscopic nissen fundoplication versus proton pump inhibitor therapy for gastroesophageal reflux disease: Seven-year follow-up. *Journal of Gastrointestinal Surgery* 10(9):1312 -6 ; discussion 1316 -7 , 2006.
18. Olberg P, Johannessen R, Johnsen G, et al. Long-term outcome of surgically and medically treated patients with gastroesophageal reflux disease: a matched-pair follow-up study. *Scandinavian Journal of Gastroenterology* 40 (3):264 -74 , 2005.
19. Anvari M, Allen C, Marshall J, et al. A randomized controlled trial of laparoscopic nissen fundoplication versus proton pump inhibitors for treatment of patients with chronic gastroesophageal reflux disease: One-year follow-up. *Surgical Innovation* 13(4):238 -49 , 2006.
20. Mahon D, Rhodes M, Decadt B, et al. Randomized clinical trial of laparoscopic Nissen fundoplication compared with proton-pump inhibitors for treatment of chronic gastro-oesophageal reflux.[see comment]. *British Journal of Surgery* 92 (6):695 -9 , 2005.
21. Mahmood Z, Byrne PJ, McMahan BP, et al. Comparison of transesophageal endoscopic plication (TEP) with laparoscopic Nissen fundoplication (LNF) in the treatment of uncomplicated reflux disease.[see comment]. *American Journal of Gastroenterology* 101 (3):431 -6 , 2006.
22. Norman HA, Bergheim R, Fagertun H, Lund H, Moum B. A randomised prospective study comparing the effectiveness of esomeprazole treatment strategies in clinical practice for 6 months in the management of patients with symptoms of gastroesophageal reflux disease.[erratum appears in *Int J Clin Pract*. 2005 Nov;59(11):1371]. *International Journal of Clinical Practice* 59 (6):665 -71 , 2005.

23. Hansen AN, Bergheim R, Fagertun H, et al. Long-term management of patients with symptoms of gastro-oesophageal reflux disease -- a Norwegian randomised prospective study comparing the effects of esomeprazole and ranitidine treatment strategies on health-related quality of life in a general practitioners setting. *International Journal of Clinical Practice* 60 (1):15 -22 , 2006.
24. Wada T, Sasaki M, Kataoka H, et al. Efficacy of famotidine and omeprazole in healing symptoms of non-erosive gastro-oesophageal reflux disease: randomized-controlled study of gastro-oesophageal reflux disease. *Alimentary Pharmacology & Therapeutics* 21 Suppl 2:2-9 , 2005.
25. Fujiwara Y, Higuchi K, Nebiki H, et al. Famotidine vs. omeprazole: a prospective randomized multicentre trial to determine efficacy in non-erosive gastro-oesophageal reflux disease. *Alimentary Pharmacology & Therapeutics* 21 Suppl 2:10-8 , 2005.
26. Peura DA, Freston JW, Haber MM, et al. Lansoprazole for long-term maintenance therapy of erosive esophagitis: double-blind comparison with ranitidine. *Digestive Diseases & Sciences* 54(5):955 -63 , 2009.
27. Goh KL, Benamouzig R, Sander P, Schwan T, EMANCIPATE. Efficacy of pantoprazole 20 mg daily compared with esomeprazole 20 mg daily in the maintenance of healed gastroesophageal reflux disease: a randomized, double-blind comparative trial - the EMANCIPATE study.[see comment]. *European Journal of Gastroenterology & Hepatology* 2007;(3):205-211.
28. Labenz J, Armstrong D, Zetterstrand S, Eklund S, Leodolter A. Clinical trial: factors associated with resolution of heartburn in patients with reflux oesophagitis--results from the EXPO study.[see comment]. *Alimentary Pharmacology & Therapeutics* 29 (9):959 -66 , 2009.
29. Glatzel D, bdel-Qader M, Gatz G, Pfaffenberger B. Pantoprazole 40 mg is as effective as esomeprazole 40 mg to relieve symptoms of gastroesophageal reflux disease after 4 weeks of treatment and superior regarding the prevention of symptomatic relapse. *Digestion* 75 Suppl 1:69 -78 , 2007.
30. Bardhan KD, Achim A, Riddermann T, Pfaffenberger B. A clinical trial comparing pantoprazole and esomeprazole to explore the concept of achieving 'complete remission' in gastro-oesophageal reflux disease. *Alimentary Pharmacology & Therapeutics* 25 (12):1461 -9 , 2007.
31. Scholten T, Teutsch I, Bohuschke M, Gatz G. Pantoprazole on-demand effectively treats symptoms in patients with gastro-oesophageal reflux disease. *Clinical Drug Investigation* 27 (4):287 -96 , 2007.
32. Vcev A, Begic I, Ostojic R, et al. Esomeprazole versus pantoprazole for healing erosive oesophagitis. *Collegium Antropologicum* 30 (3):519 -22 , 2006.

33. Labenz J, Armstrong D, Zetterstrand S, Eklund S, Leodolter A. Clinical trial: factors associated with freedom from relapse of heartburn in patients with healed reflux oesophagitis--results from the maintenance phase of the EXPO study. *Alimentary Pharmacology & Therapeutics* 2009; 29(11):1165-1171.
34. Fass R, Sontag SJ, Traxler B, Sostek M. Treatment of patients with persistent heartburn symptoms: a double-blind, randomized trial. *Clinical Gastroenterology & Hepatology* 4(1):50 -6 , 2006.
35. Eggleston A, Katelaris PH, Nandurkar S, et al. Clinical trial: the treatment of gastro-oesophageal reflux disease in primary care--prospective randomized comparison of rabeprazole 20 mg with esomeprazole 20 and 40 mg. *Alimentary Pharmacology & Therapeutics* 29 (9):967 -78 , 2009.
36. Fock KM, Teo EK, Ang TL, et al. Rabeprazole vs esomeprazole in non-erosive gastro-oesophageal reflux disease: a randomized, double-blind study in urban Asia. *World Journal of Gastroenterology* 11(20):3091 -8 , 2005.
37. Pai V, Pai N. Randomized, double-blind, comparative study of dexrabeprazole 10 mg versus rabeprazole 20 mg in the treatment of gastroesophageal reflux disease.[see comment]. *World Journal of Gastroenterology* 13(30):4100 -2, 2007.
38. Giannini EG, Zentilin P, Dulbecco P, et al. Management strategy for patients with gastroesophageal reflux disease: a comparison between empirical treatment with esomeprazole and endoscopy-oriented treatment.[see comment]. *American Journal of Gastroenterology* 103 (2):267 -75 , 2008.
39. Johnson DA, Orr WC, Crawley JA, et al. Effect of esomeprazole on nighttime heartburn and sleep quality in patients with GERD: a randomized, placebo-controlled trial. *American Journal of Gastroenterology* 100 (9):1914 -22 , 2005.
40. Katz PO, Ginsberg GG, Hoyle PE, et al. Relationship between intragastric acid control and healing status in the treatment of moderate to severe erosive oesophagitis. *Alimentary Pharmacology & Therapeutics* 25 (5):617 -28 , 2007.
41. Vasiliadis KV, Viazis N, Vlachogiannakos J, et al. Efficacy of three different dosages of esomeprazole in the long-term management of reflux disease: a prospective, randomized study, using the wireless Bravo pH system. *American Journal of Gastroenterology* 2010; 105(2):308-313.
42. Mine S, Iida T, Tabata T, Kishikawa H, Tanaka Y. Management of symptoms in step-down therapy of gastroesophageal reflux disease. *Journal of Gastroenterology & Hepatology* 2005;(9):1365-1370.
43. Fass R, Chey WD, Zakko SF, et al. Clinical trial: the effects of the proton pump inhibitor dexlansoprazole MR on daytime and nighttime heartburn in patients with non-erosive reflux disease. *Alimentary Pharmacology & Therapeutics* 2009; 29(12):1261-1272.

44. Metz DC HCPML. Clinical trial: Dexlansoprazole MR, a proton pump inhibitor with dual delayed-release technology, effectively controls symptoms and prevents relapse in patients with healed erosive oesophagitis. *Alimentary Pharmacology and Therapeutics* 2009;(7):742-754.
45. Howden CW, Larsen LM, Perez MC, Palmer R, Atkinson SN. Clinical trial: efficacy and safety of dexlansoprazole MR 60 and 90 mg in healed erosive oesophagitis - maintenance of healing and symptom relief. *Alimentary Pharmacology & Therapeutics* 2009; 30(9):895-907.
46. Pai VG, Pai NV, Thacker HP, et al. Comparative clinical trial of S-pantoprazole versus racemic pantoprazole in the treatment of gastro-oesophageal reflux disease. *World Journal of Gastroenterology* 12 (37):6017 -20 , 2006.
47. Scholten T, Dekkers CP, Schutze K, et al. On-demand therapy with pantoprazole 20 mg as effective long-term management of reflux disease in patients with mild GERD: the ORION trial. *Digestion* 72 (2-3):76 -85 , 2005.
48. Sjostedt S, Befrits R, Sylvan A, et al. Daily treatment with esomeprazole is superior to that taken on-demand for maintenance of healed erosive oesophagitis. *Alimentary Pharmacology & Therapeutics* 22 (3):183 -91 , 2005.
49. Szucs T. Cost analysis of long-term treatment of patients with symptomatic gastroesophageal reflux disease (GERD) with esomeprazole on-demand treatment or esomeprazole continuous treatment: An open, randomized, multicenter study in Switzerland. *Value in Health* 2009;(2):273-281.
50. Pace F, Negrini C, Wiklund I, et al. Quality of life in acute and maintenance treatment of non-erosive and mild erosive gastro-oesophageal reflux disease. *Alimentary Pharmacology & Therapeutics* 22 (4):349 -56 , 2005.
51. Morgan DG, O'Mahony MF, O'Mahony WF, et al. Maintenance treatment of gastroesophageal reflux disease: an evaluation of continuous and on-demand therapy with rabeprazole 20 mg. *Canadian Journal of Gastroenterology* 21(12):820 -6 , 2007.
52. Bour B, Staub JL, Chousterman M, et al. Long-term treatment of gastro-oesophageal reflux disease patients with frequent symptomatic relapses using rabeprazole: on-demand treatment compared with continuous treatment. *Alimentary Pharmacology & Therapeutics* 21(7):805 -12 , 2005.
53. Cibor D, Ciecko-Michalska I, Owczarek D, Szczepanek M. Optimal maintenance therapy in patients with non-erosive reflux disease reporting mild reflux symptoms--a pilot study. *Advances in Medical Sciences* 51 :336 -9 , 2006.
54. Lightdale CJ, Schmitt C, Hwang C, Hamelin B. A multicenter, randomized, double-blind, 8-week comparative trial of low-dose esomeprazole (20 mg) and standard-dose omeprazole (20 mg) in patients with erosive esophagitis.[erratum appears in *Dig Dis*

Sci. 2006 May;51(5):851 Note: dosage error in text]. *Digestive Diseases & Sciences* 51 (5):852 -7 , 2006.

55. Pilotto A, Franceschi M, Leandro G, et al. Comparison of four proton pump inhibitors for the short-term treatment of esophagitis in elderly patients. *World Journal of Gastroenterology* 13(33):4467 -72 , 2007.
56. Zheng RN. Comparative study of omeprazole, lansoprazole, pantoprazole and esomeprazole for symptom relief in patients with reflux esophagitis. *World Journal of Gastroenterology* 15 (8):990 -5, 2009.
57. Pace F, Annese V, Prada A, et al. Rabeprazole is equivalent to omeprazole in the treatment of erosive gastro-oesophageal reflux disease. A randomised, double-blind, comparative study of rabeprazole and omeprazole 20 mg in acute treatment of reflux oesophagitis, followed by a maintenance open-label, low-dose therapy with rabeprazole. *Digestive & Liver Disease* 37 (10):741 -50 , 2005.
58. Tepes B, Stabuc B, Kocijancic B, Ivanusa M. Maintenance therapy of gastroesophageal reflux disease patients with omeprazole. *Hepato -Gastroenterology* 56 (89):67 -74 , 2009;-Feb.
59. Chen CY, Lu CL, Luo JC, et al. Esomeprazole tablet vs omeprazole capsule in treating erosive esophagitis. *World Journal of Gastroenterology* 11(20):3112 -7 , 2005.
60. Devault KR, Johanson JF, Johnson DA, Liu S, Sostek MB. Maintenance of healed erosive esophagitis: a randomized six-month comparison of esomeprazole twenty milligrams with lansoprazole fifteen milligrams. *Clinical Gastroenterology & Hepatology* 4(7):852 -9 , 2006.
61. Svedlund J, Sjodin I, Dotevall G. GSRS--a clinical rating scale for gastrointestinal symptoms in patients with irritable bowel syndrome and peptic ulcer disease. *Dig Dis Sci* 1988; 33(2):129-134.
62. Kovacs TO, Lee CQ, Chiu YL, Pilmer BL, Metz DC. Intravenous and oral lansoprazole are equivalent in suppressing stimulated acid output in patient volunteers with erosive oesophagitis. *Aliment Pharmacol Ther* 2004; 20(8):883-889.
63. Cai W, Watson DI, Lally CJ, et al. Ten-year clinical outcome of a prospective randomized clinical trial of laparoscopic Nissen versus anterior 180(degrees) partial fundoplication. *British Journal of Surgery* 95 (12):1501 -5, 2008.
64. Mardani J. Ten-year results of a randomized clinical trial of laparoscopic total fundoplication with or without division of the short gastric vessels. *The British journal of surgery* 2009;(1):61-65.
65. Yang H, Watson DI, Lally CJ, et al. Randomized trial of division versus nondivision of the short gastric vessels during laparoscopic Nissen fundoplication: 10-year outcomes. *Annals of Surgery* 247 (1):38 -42 , 2008.

66. Dallemagne B, Weerts J, Markiewicz S, et al. Clinical results of laparoscopic fundoplication at ten years after surgery. *Surgical Endoscopy* 2006;(1):159-165.
67. Hafez J, Wrba F, Lenglinger J, Miholic J. Fundoplication for gastroesophageal reflux and factors associated with the outcome 6 to 10 years after the operation: multivariate analysis of prognostic factors using the propensity score. *Surgical Endoscopy* 22 (8):1763 -8 , 2008.
68. Fein M, Bueter M, Thalheimer A, et al. Ten-year outcome of laparoscopic antireflux surgery. *Journal of Gastrointestinal Surgery* 12 (11):1893 -9 , 2008.
69. Pessaux P, Arnaud JP, Delattre JF, et al. Laparoscopic antireflux surgery: five-year results and beyond in 1340 patients. *Archives of Surgery* 140 (10):946 -51 , 2005.
70. Wijnhoven BP, Lally CJ, Kelly JJ, Myers JC, Watson DI. Use of antireflux medication after antireflux surgery. *Journal of Gastrointestinal Surgery* 12 (3):510 -7 , 2008.
71. Draaisma WA, Rijnhart-De Jong HG, Broeders IA, et al. Five-year subjective and objective results of laparoscopic and conventional Nissen fundoplication: a randomized trial. *Annals of Surgery* 244 (1):34 -41 , 2006.
72. Broeders JA, Rijnhart-De Jong HG, Draaisma WA, et al. Ten-year outcome of laparoscopic and conventional nissen fundoplication: randomized clinical trial. *Annals of Surgery* 2009; 250(5):698-706.
73. Salminen PT, Hiekkanen HI, Rantala AP, Ovaska JT. Comparison of long-term outcome of laparoscopic and conventional nissen fundoplication: a prospective randomized study with an 11-year follow-up. *Annals of Surgery* 246 (2):201 -6 , 2007.
74. Trullenque JR, Torres ST, Marti ME, et al. Surgery for gastroesophageal reflux disease: a comparative study between the open and laparoscopic approaches. *Revista Espanola de Enfermedades Digestivas* 97 (5):328 -37 , 2005.
75. Zehetner J, Holzinger F, Breuhahn T, Geppert C, Klaiber C. Five-year results of laparoscopic Toupet fundoplication as the primary surgical repair in GERD patients: is it durable? *Surgical Endoscopy* 2006;(2):220-225.
76. Rice S, Watson DI, Lally CJ, et al. Laparoscopic anterior 180 degrees partial fundoplication: five-year results and beyond. *Archives of Surgery* 141 (3):271 -5, 2006.
77. Biertho L, Sebjang H, Allen C, Anvari M. Does laparoscopic Nissen fundoplication lead to chronic gastrointestinal dysfunction? *Surgical Endoscopy* 2006;(9):1360-1363.
78. Teixeira JP, Mosquera V, Flores A. Long-term outcomes of quality of life after laparoscopic Nissen fundoplication. *Hepato -Gastroenterology* 56 (89):80 -4, 2009;- Feb.

79. Oelschlager BK, Quiroga E, Parra JD, et al. Long-term outcomes after laparoscopic antireflux surgery.[see comment]. *American Journal of Gastroenterology* 103 (2):280 -7 ; quiz 288 , 2008.
80. Mardani J, Lundell L, Lonroth H, Dalenback J, Engstrom C. Ten-year results of a randomized clinical trial of laparoscopic total fundoplication with or without division of the short gastric vessels. *British Journal of Surgery* 96 (1):61 -5, 2009.
81. Schwartz MP, Wellink H, Gooszen HG, et al. Endoscopic gastroplication for the treatment of gastro-oesophageal reflux disease: a randomised, sham-controlled trial.[see comment]. *Gut* 56 (1):20 -8 , 2007.
82. Montgomery M, Hakanson B, Ljungqvist O, Ahlman B, Thorell A. Twelve months' follow-up after treatment with the EndoCinch endoscopic technique for gastro-oesophageal reflux disease: a randomized, placebo-controlled study. *Scandinavian Journal of Gastroenterology* 41 (12):1382 -9 , 2006.
83. Coron E, Sebillé V, Cadiot G, et al. Clinical trial: Radiofrequency energy delivery in proton pump inhibitor-dependent gastro-oesophageal reflux disease patients. *Alimentary Pharmacology & Therapeutics* 28 (9):1147 -58 , 2008.
84. Domagk D, Menzel J, Seidel M, et al. Endoluminal gastroplasty (EndoCinch) versus endoscopic polymer implantation (Enteryx) for treatment of gastroesophageal reflux disease: 6-month results of a prospective, randomized trial.[see comment]. *American Journal of Gastroenterology* 101 (3):422 -30 , 2006.
85. Liao CC, Lee CL, Lin BR, et al. Endoluminal gastroplication for the treatment of gastroesophageal reflux disease: a 2-year prospective pilot study from Taiwan. *Journal of Gastroenterology & Hepatology* 23(3):398 -405 , 2008.
86. Liu JJ, Di S, V, Ookubo R, Carr-Locke DL, Saltzman JR. Endoscopic treatment of gastroesophageal reflux disease: effect of gender on clinical outcome. *Scandinavian Journal of Gastroenterology* 41 (2):144 -8 , 2006.
87. Ozawa S, Kumai K, Higuchi K, et al. Short-term and long-term outcome of endoluminal gastroplication for the treatment of GERD: the first multicenter trial in Japan. *Journal of Gastroenterology* 44 (7):675 -84 , 2009.
88. Paulssen EJ, Lindsetmo RO. Long-term outcome of endoluminal gastroplication in the treatment of gastro-oesophageal reflux disease: effect of a second procedure. *Scandinavian Journal of Gastroenterology* 43 (1):5-12 , 2008.
89. Schiefke I, Zabel-Langhennig A, Neumann S, et al. Long term failure of endoscopic gastroplication (EndoCinch).[see comment]. *Gut* 54(6):752 -8 , 2005.
90. Cadiere GB, Van SN, Graves JE, Gawlicka AK, Rajan A. Two-year results of a feasibility study on antireflux transoral incisionless fundoplication using EsophyX. *Surgical Endoscopy* 23(5):957 -64 , 2009.

91. Cadiere GB, Rajan A, Gerday O, Himpens J. Endoluminal fundoplication by a transoral device for the treatment of GERD: A feasibility study. *Surgical Endoscopy* 22 (2):333 -42 , 2008.
92. Cadiere GB, Buset M, Muls V, et al. Antireflux transoral incisionless fundoplication using EsophyX: 12-month results of a prospective multicenter study. *World J Surg* 2008; 32(8):1676-1688.
93. Repici A, Fumagalli U, Malesci A, et al. Endoluminal fundoplication (ELF) for GERD using EsophyX: a 12-month follow-up in a single-center experience. *J Gastrointest Surg* 2010; 14(1):1-6.
94. Testoni PA, Corsetti M, Di PS, et al. Effect of transoral incisionless fundoplication on symptoms, PPI use, and ph-impedance refluxes of GERD patients. *World J Surg* 2010; 34(4):750-757.
95. Demyttenaere SV, Bergman S, Pham T, et al. Transoral incisionless fundoplication for gastroesophageal reflux disease in an unselected patient population. *Surg Endosc* 2010; 24(4):854-858.
96. Cipolletta L, Rotondano G, Dughera L, et al. Delivery of radiofrequency energy to the gastroesophageal junction (Stretta procedure) for the treatment of gastroesophageal reflux disease. *Surgical Endoscopy* 2005;(6):849-853.
97. Dundon JM, Davis SS, Hazey JW, et al. Radiofrequency energy delivery to the lower esophageal sphincter (Stretta procedure) does not provide long-term symptom control. *Surgical Innovation* 15 (4):297 -301 , 2008.
98. Jeansonne LO, White BC, Nguyen V, et al. Endoluminal full-thickness plication and radiofrequency treatments for GERD: an outcomes comparison. *Archives of Surgery* 144 (1):19 -24 ; discussion 24 , 2009.
99. Lutfi RE, Torquati A, Kaiser J, Holzman M, Richards WO. Three year's experience with the Stretta procedure: did it really make a difference? *Surgical Endoscopy* 2005;(2):289-295.
100. Meier PN, Nietzschmann T, Akin I, Klose S, Manns MP. Improvement of objective GERD parameters after radiofrequency energy delivery: a European study. *Scandinavian Journal of Gastroenterology* 42 (8):911 -6 , 2007.
101. Noar MD, Lotfi-Emran S. Sustained improvement in symptoms of GERD and antisecretory drug use: 4-year follow-up of the Stretta procedure.[see comment]. *Gastrointestinal Endoscopy* 65 (3):367 -72 , 2007.
102. Reymunde A, Santiago N. Long-term results of radiofrequency energy delivery for the treatment of GERD: sustained improvements in symptoms, quality of life, and drug use at 4-year follow-up.[see comment]. *Gastrointestinal Endoscopy* 65 (3):361 -6 , 2007.

103. Chang AB, Lasserson TJ, Gaffney J, Connor FL, Garske LA. Gastro-oesophageal reflux treatment for prolonged non-specific cough in children and adults [Systematic Review]. *Cochrane Database of Systematic Reviews* 2009;(3).
104. Hopkins C, Yousaf U, Pedersen M. Acid reflux treatment for hoarseness [Systematic Review]. *Cochrane Database of Systematic Reviews* 2009;(3).
105. Hungin AP, Raghunath AS, Wiklund I. Beyond heartburn: a systematic review of the extra-oesophageal spectrum of reflux-induced disease. [Review] [138 refs]. *Family Practice* 22 (6):591 -603 , 2005.
106. Iqbal M, Batch AJ, Spychal RT, Cooper BT. Outcome of surgical fundoplication for extraesophageal (atypical) manifestations of gastroesophageal reflux disease in adults: a systematic review. [Review] [44 refs]. *Journal of Laparoendoscopic & Advanced Surgical Techniques Part A* 18 (6):789 -96 , 2008.
107. dos Santos LH, Ribeiro IO, Sanchez PG, et al. Evaluation of pantoprazol treatment response of patients with asthma and gastroesophageal reflux: a randomized prospective double-blind placebo-controlled study.[see comment]. *Jornal Brasileiro De Pneumologia: Publicacao Oficial Da Sociedade Brasileira De Pneumologia E Tisiologia* 2007; 33(2):119-127.
108. Jiang SP, Liang RY, Zeng ZY, et al. Effects of antireflux treatment on bronchial hyper-responsiveness and lung function in asthmatic patients with gastroesophageal reflux disease. *World Journal of Gastroenterology* 2003; 9(5):1123-1125.
109. Kiljander TO, Harding SM, Field SK, et al. Effects of esomeprazole 40 mg twice daily on asthma: a randomized placebo-controlled trial. *American Journal of Respiratory & Critical Care Medicine* 2006; 173(10):1091-1097.
110. Littner MR, Leung FW, Ballard ED, et al. Effects of 24 weeks of lansoprazole therapy on asthma symptoms, exacerbations, quality of life, and pulmonary function in adult asthmatic patients with acid reflux symptoms.[see comment]. *Chest* 2005; 128(3):1128-1135.
111. Peterson KA, Samuelson WM, Ryujin DT, et al. The role of gastroesophageal reflux in exercise-triggered asthma: a randomized controlled trial. *Digestive Diseases & Sciences* 2009; 54(3):564-571.
112. Sharma B, Sharma M, Daga MK, Sachdev GK, Bondi E. Effect of omeprazole and domperidone on adult asthmatics with gastroesophageal reflux. *World Journal of Gastroenterology* 2007; 13(11):1706-1710.
113. Shimizu Y, Dobashi K, Kobayashi S, et al. A proton pump inhibitor, lansoprazole, ameliorates asthma symptoms in asthmatic patients with gastroesophageal reflux disease. *Tohoku Journal of Experimental Medicine* 2006; 209(3):181-189.

114. Sontag SJ, O'Connell S, Khandelwal S, et al. Asthmatics with gastroesophageal reflux: long term results of a randomized trial of medical and surgical antireflux therapies.[see comment]. *American Journal of Gastroenterology* 2003; 98(5):987-999.
115. Devault KR, Morgenstern DM, Lynn RB, Metz DC. Effect of pantoprazole in older patients with erosive esophagitis. *Diseases of the Esophagus* 2007;(5):411-415.
116. Xirouchakis E, Kamberoglou D, Kalos D, et al. The effect of gastroesophageal flap valve appearance on the management of patients with symptoms of gastroesophageal reflux disease. *Digestive Diseases & Sciences* 54(2):328 -32 , 2009.
117. Sheu BS, Cheng HC, Chang WL, Chen WY, Kao AW. The impact of body mass index on the application of on-demand therapy for Los Angeles grades A and B reflux esophagitis. *American Journal of Gastroenterology* 102 (11):2387 -94 , 2007.
118. Nocon M, Labenz J, Jaspersen D, et al. Long-term treatment of patients with gastro-oesophageal reflux disease in routine care - results from the ProGERD study. *Alimentary Pharmacology & Therapeutics* 25 (6):715 -22 , 2007.
119. Malfertheiner P, Lind T, Willich S, et al. Prognostic influence of Barrett's oesophagus and *Helicobacter pylori* infection on healing of erosive gastro-oesophageal reflux disease (GORD) and symptom resolution in non-erosive GORD: report from the ProGORD study.[see comment]. *Gut* 54(6):746 -51 , 2005.
120. Calleja JL, Suarez M, De Tejada AH, Navarro A, Pantogerd Group. *Helicobacter pylori* infection in patients with erosive esophagitis is associated with rapid heartburn relief and lack of relapse after treatment with pantoprazole. *Digestive Diseases & Sciences* 50 (3):432 -9 , 2005.
121. Sheu BS, Chang WL, Cheng HC, Kao AW, Lu CC. Body mass index can determine the healing of reflux esophagitis with Los Angeles Grades C and D by esomeprazole. *American Journal of Gastroenterology* 103 (9):2209 -14, 2008.
122. Hamamoto N, Hashimoto T, Adachi K, et al. Comparative study of nizatidine and famotidine for maintenance therapy of erosive esophagitis. *Journal of Gastroenterology & Hepatology* 2005;(2):281-286.
123. Anvari M, Bamehriz F. Outcome of laparoscopic Nissen fundoplication in patients with body mass index ≥ 35 . *Surgical Endoscopy* 2006; 20(2):230-234.
124. Booth MI, Stratford J, Jones L, Dehn TC. Randomized clinical trial of laparoscopic total (Nissen) versus posterior partial (Toupet) fundoplication for gastro-oesophageal reflux disease based on preoperative oesophageal manometry.[see comment]. *British Journal of Surgery* 95 (1):57 -63 , 2008.
125. Brehant O, Pessaux P, Arnaud JP, et al. Long-term outcome of laparoscopic antireflux surgery in the elderly. *Journal of Gastrointestinal Surgery* 10(3):439 -44 , 2006.

126. Broeders JA, Draaisma WA, de Vries DR, et al. The preoperative reflux pattern as prognostic indicator for long-term outcome after Nissen fundoplication. *American Journal of Gastroenterology* 104 (8):1922 -30 , 2009.
127. Chisholm JA, Jamieson GG, Lally CJ, et al. The effect of obesity on the outcome of laparoscopic antireflux surgery. *Journal of Gastrointestinal Surgery* 13(6):1064 -70 , 2009.
128. Cowgill SM, Arnaoutakis D, Villadolid D, et al. Results after laparoscopic fundoplication: does age matter? *American Surgeon* 72 (9):778 -83 ; discussion 783 -4, 2006.
129. D'Alessio MJ, Arnaoutakis D, Giarelli N, Villadolid DV, Rosemurgy AS. Obesity is not a contraindication to laparoscopic Nissen fundoplication. *Journal of Gastrointestinal Surgery* 9 (7):949 -54, 2005;-Oct.
130. Gee DW, Andreoli MT, Rattner DW. Measuring the effectiveness of laparoscopic antireflux surgery: long-term results. *Archives of Surgery* 143 (5):482 -7 , 2008.
131. Iqbal A, Kakarlapudi GV, Awad ZT, et al. Assessment of diaphragmatic stressors as risk factors for symptomatic failure of laparoscopic nissen fundoplication. *Journal of Gastrointestinal Surgery* 2006; 10(1):12-21.
132. Kalinowska E, Tarnowski W, Bielecki K, Banasiewicz J. Quality of life before and after laparoscopic fundoplication. Does quality of life depend on psychological factors? Preliminary report. *Wiadomosci Lekarskie* 59 (11-12):772 -7 , 2006.
133. Kamolz T, Granderath FA, Schweiger UM, Pointner R. Laparoscopic Nissen fundoplication in patients with nonerosive reflux disease. Long-term quality-of-life assessment and surgical outcome. *Surgical Endoscopy* 2005;(4):494-500.
134. Lee SK, Kim EK. Laparoscopic Nissen fundoplication in Korean patients with gastroesophageal reflux disease. *Yonsei Medical Journal* 50 (1):89 -94 , 2009.
135. Lord RV, DeMeester SR, Peters JH, et al. Hiatal hernia, lower esophageal sphincter incompetence, and effectiveness of Nissen fundoplication in the spectrum of gastroesophageal reflux disease. *Journal of Gastrointestinal Surgery* 13(4):602 -10, 2009.
136. Manning BJ, Salman R, Gillen P. Laparoscopic Nissen fundoplication: predicting outcome from peri-operative evaluation. *Irish Journal of Medical Science* 175 (2):55 -8 , 2006;-Jun.
137. Pizza F, Rossetti G, Limongelli P, et al. Influence of age on outcome of total laparoscopic fundoplication for gastroesophageal reflux disease. *World Journal of Gastroenterology* 13(5):740 -7 , 2007.

138. Pizza F, Rossetti G, del GG, et al. Influence of esophageal motility on the outcome of laparoscopic total fundoplication.[erratum appears in Dis Esophagus. 2008;21(3):279 Note: Rosetti, G [corrected to Rossetti, G]]. Diseases of the Esophagus 21(1):78 -85 , 2008.
139. Ravi N, Al-Sarraf N, Moran T, et al. Acid normalization and improved esophageal motility after Nissen fundoplication: equivalent outcomes in patients with normal and ineffective esophageal motility. American Journal of Surgery 2005;(3):445-450.
140. Riedl O, Gadenstatter M, Lechner W, et al. Preoperative lower esophageal sphincter manometry data neither impact manifestations of GERD nor outcome after laparoscopic Nissen fundoplication. Journal of Gastrointestinal Surgery 13(7):1189 -97 , 2009.
141. Strate U, Emmermann A, Fibbe C, Layer P, Zornig C. Laparoscopic fundoplication: Nissen versus Toupet two-year outcome of a prospective randomized study of 200 patients regarding preoperative esophageal motility.[see comment]. Surgical Endoscopy 22 (1):21-30 , 2008.
142. Tedesco P, Lobo E, Fisichella PM, Way LW, Patti MG. Laparoscopic fundoplication in elderly patients with gastroesophageal reflux disease. Archives of Surgery 141 (3):289 -92 ; discussion 292 , 2006.
143. Thibault R, Coron E, Sebillé V, et al. Antireflux surgery for non-erosive and erosive reflux disease in community practice. Alimentary Pharmacology & Therapeutics 24 (4):621 -32 , 2006.
144. Wang W, Huang MT, Wei PL, Lee WJ. Laparoscopic antireflux surgery for the elderly: a surgical and quality-of-life study. Surgery Today 38 (4):305 -10, 2008.
145. Wayman J, Myers JC, Jamieson GG. Preoperative gastric emptying and patterns of reflux as predictors of outcome after laparoscopic fundoplication. British Journal of Surgery 94 (5):592 -8 , 2007.
146. Wilkerson PM, Stratford J, Jones L, et al. A poor response to proton pump inhibition is not a contraindication for laparoscopic antireflux surgery for gastro esophageal reflux disease. Surgical Endoscopy 2005;(9):1272-1277.
147. Yano F, Sherif AE, Turaga K, et al. Gastrointestinal quality of life in patients after anti reflux surgery. Diseases of the Esophagus 22 (2):177 -84 , 2009.
148. Lundell L, Havu N, Miettinen P, et al. Changes of gastric mucosal architecture during long-term omeprazole therapy: results of a randomized clinical trial. Alimentary Pharmacology & Therapeutics 23(5):639 -47 , 2006.
149. Davies M, Wilton LV, Shakir SA. Safety profile of esomeprazole: results of a prescription-event monitoring study of 11 595 patients in England. Drug Safety 31 (4):313 -23, 2008.

150. Cutler A, Robinson M, Murthy A, Delemos B. Rabeprazole 20 mg for erosive esophagitis-associated symptoms in a large, community-based study: additional results. *Digestive Diseases & Sciences* 2010; 55(2):338-345.
151. Howden CW, Ballard ED, Koch FK, Gaultille TC, Bagin RG. Control of 24-hour intragastric acidity with morning dosing of immediate-release and delayed-release proton pump inhibitors in patients with GERD. *Journal of Clinical Gastroenterology* 43 (4):323 -6 , 2009.
152. Yu EW, Blackwell T, Ensrud KE, et al. Acid-suppressive medications and risk of bone loss and fracture in older adults. *Calcified Tissue International* 2008; 83(4):251-259.
153. Gray SL, LaCroix AZ, Larson J, et al. Proton pump inhibitor use, hip fracture, and change in bone mineral density in postmenopausal women: results from the Women's Health Initiative. *Arch Intern Med* 2010; 170(9):765-771.
154. Grisso JA, Kelsey JL, O'Brien LA, et al. Risk factors for hip fracture in men. Hip Fracture Study Group. *American Journal of Epidemiology* 1997; 145(9):786-793.
155. Yang YX, Lewis JD, Epstein S, Metz DC. Long-term proton pump inhibitor therapy and risk of hip fracture. *JAMA* 2006; 296(24):2947-2953.
156. Vestergaard P, Rejnmark L, Mosekilde L. Proton pump inhibitors, histamine H2 receptor antagonists, and other antacid medications and the risk of fracture. *Calcified Tissue International* 2006; 79(2):76-83.
157. Targownik LE, Lix LM, Metge CJ, et al. Use of proton pump inhibitors and risk of osteoporosis-related fractures. *CMAJ Canadian Medical Association Journal* 2008; 179(4):319-326.
158. Kaye JA, Jick H. Proton pump inhibitor use and risk of hip fractures in patients without major risk factors. *Pharmacotherapy* 2008; 28(8):951-959.
159. Roux C, Briot K, Gossec L, et al. Increase in vertebral fracture risk in postmenopausal women using omeprazole. *Calcified Tissue International* 2009; 84(1):13-19.
160. Corley DA, Kubo A, Zhao W, Quesenberry C. Proton pump inhibitors and histamine-2 receptor antagonists are associated with hip fractures among at-risk patients. *Gastroenterology* 2010; 139(1):93-101.
161. U.S. Food and Drug Administration. Clopidogrel (marketed as Plavix) and Omeprazole (marketed as Prilosec) - Drug Interaction. <http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm190848.htm> . 11-17-2009.
162. Rosenthal R, Peterli R, Guenin MO, von FM, Ackermann C. Laparoscopic antireflux surgery: long-term outcomes and quality of life. *Journal of Laparoendoscopic & Advanced Surgical Techniques Part A* 16 (6):557 -61 , 2006.

163. Gill J, Booth MI, Stratford J, Dehn TC. The extended learning curve for laparoscopic fundoplication: a cohort analysis of 400 consecutive cases. *Journal of Gastrointestinal Surgery* 11(4):487 -92 , 2007.
164. Fumagalli U, Bona S, Battafarano F, et al. Persistent dysphagia after laparoscopic fundoplication for gastro-esophageal reflux disease. *Diseases of the Esophagus* 21(3):257 -61 , 2008.
165. Huttel TP, Hohle M, Wichmann MW, Jauch KW, Meyer G. Techniques and results of laparoscopic antireflux surgery in Germany. *Surgical Endoscopy* 2005;(12):1579-1587.
166. Csendes A, Burdiles P, Korn O. Laparoscopic Nissen fundoplication: the "right posterior" approach. *Journal of Gastrointestinal Surgery* 9 (7):985 -91 , 2005;-Oct.
167. Zacharoulis D, O'Boyle CJ, Sedman PC, Brough WA, Royston CM. Laparoscopic fundoplication: a 10-year learning curve. *Surgical Endoscopy* 2006;(11):1662-1670.
168. Salminen PT, Laine SO, Ovaska JT. Late subjective results and symptomatic outcome after laparoscopic fundoplication. *Surgical Laparoscopy , Endoscopy & Percutaneous Techniques* 16 (4):203 -7 , 2006.
169. Morgenthal CB, Shane MD, Stival A, et al. The durability of laparoscopic Nissen fundoplication: 11-year outcomes.[see comment]. *Journal of Gastrointestinal Surgery* 11(6):693 -700 , 2007.
170. del GG, Rossetti G, Bruscianno L, et al. Laparoscopic Nissen-Rossetti fundoplication with routine use of intraoperative endoscopy and manometry: technical aspects of a standardized technique. *World Journal of Surgery* 31 (5):1099 -106 , 2007.
171. Cowgill SM, Gillman R, Kraemer E, et al. Ten-year follow up after laparoscopic Nissen fundoplication for gastroesophageal reflux disease. *American Surgeon* 73 (8):748 -52 ; discussion 752 -3, 2007.
172. Jensen CD, Gilliam AD, Horgan LF, Bawa S, Attwood SE. Day-case laparoscopic Nissen fundoplication. *Surgical Endoscopy* 2009; 23(8):1745-1749.
173. Jensen CD, Gilliam AD, Horgan LF, Bawa S, Attwood SE. Day-case laparoscopic Nissen fundoplication. *Surgical Endoscopy* 23(8):1745 -9 , 2009.
174. Madan AK, Ternovits CA, Tichansky DS. Emerging endoluminal therapies for gastroesophageal reflux disease: adverse events. *American Journal of Surgery* 2006;(1):72-75.
175. Mosler P, Aziz AM, Hieston K, Filipi C, Lehman G. Evaluation of supplemental cautery during endoluminal gastroplication for the treatment of gastroesophageal reflux disease. *Surgical Endoscopy* 22 (10):2158 -63 , 2008.

Abbreviation

AHRQ	Agency for Healthcare Research and Quality
AMSTAR	Assessment of multiple systematic reviews
ARS	anti-reflux surgery
BD	Twice daily
BMI	body mass index
CI	Confidence Interval
CONSORT	Consolidated Standards of Reporting Trials
CVD	Cardiovascular disease
d	day, days
DBP	Diastolic blood pressure
DexLAN	Dexlansoprazole
DexRAB	Dexrabeprazole
diff	difference
DM	Diabetes Mellitus
Dx	Diagnosis
ECH	Endocinch
EPC	Evidence-based Practice Center
ERX	Enteryx
EsOME	Esomeprazole
f/u	follow-up
FAM	Famotidine
GERD	gastroesophageal Reflux Disease
GERD-HRQL	Gastroesophageal Reflux Disease-Health-Related Quality-Of-Life
GERSS	Gastroesophageal Reflux Score
GI	gastrointestinal
GSRS	Gastrointestinal Symptoms Rating Scale
H2RA	H2 receptor antagonist
HR	Hazard ratio
ht	Height
HTN	Hypertension
hx	history
IOM	Institute of Medicine
IQR	Interquartile range
IU	International unit
LAN	Lanzoprazole
LAS	laparoscopic anti reflux surgery, laparoscopic fundoplication
LES	lower esophageal sphincter
LNF	laparoscopic Nissen fundoplication, laparoscopic Nissen Rossetti
LOS	length of stay

LPA	laparoscopic partial fundoplication, laparoscopic Toupet
MA	Meta-analysis
MED	all medical interventions
MI	Myocardial infarction
mil	Million
mo	month, months
N	Number of subjects
n	Number of subjects had event(s)
N _E	N enrolled
NA	not applicable
nd	no data
NDO	NDO plication
N _{FU}	N follow up
NIH	National Institutes of Health
NIZ	Nizatidine
nRCT	non-randomized controlled trial
NS	Not significant
OAS	Open anti-reflux surgery
O-D	On-Demand
OME	Omeprazole
OME	omeprazole
ONF	Open Nissen fundoplication, Open total fundoplication, Open Nissen Rossetti
OPA	Open partial fundoplication, Open Toupet
OR	Odds Ratio
P	P value (note upper case P; not lower case p)
P Btw	P value of difference between two interventions
PAGI-QOL	The Patient Assessment of Upper Gastrointestinal Disorders Quality of Life
PAN	Pantoprazole
PGWB	Psychological General Well-Being Index
PI(E)CO	Population, Intervention (or Exposure), Comparison and Outcome
PMID	PubMed (unique) identifier
postop	postoperative
PPI	Proton Pump Inhibitor
PSQI	Pittsburgh Sleep Quality Index
pt	patient, patients
QD	Once daily
QoL	quality-of-life
QOLRAD	GERD-specific quality-of-life questionnaire
RAB	Rabeprazole

RAN	ranitidine
RAN	Ranitidine
RCT	randomized controlled trial
regurg	regurgitation
RR	Relative risk
SBP	Systolic blood pressure
SD	Standard deviation
SE	Standard error
SF-36-M	SF-36 mental
SF-36-P	SF-36 physical
STR	Stretta
STROBE	STrengthening the Reporting of OBservational studies in Epidemiology
Suppl	supplement
TEP	Technical Expert Panel
TIA	Transient ischemic attach
TOO	Task order officer
Tx	Treatment
UK	United Kingdom
US	United States
vol	volume
vs	versus
w/	with
w/o	without
wk	week, weeks
WMD	Weighted mean difference
wt	weight
XO	crossover design
y	year, years