Table A-1. Comparative effectiveness of management strategies for gastoesophageal reflux disease (GERD)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Original Key Questions/Conclusions | | Updated Key Questions/Conclusions (2011-2012) | 2009 Prediction | | Concordance | |
| Comparative Effectiveness of Management Strategies for Gastoesophageal Reflux Disease (GERD) (Original report date - Dec 2005[1](#_ENREF_1) and Update report date -  Sep 2011[2](#_ENREF_2)) | | | | | | |
| Key Question 1 - What is the evidence of the comparative effectiveness of medical, surgical, and endoscopic treatments for improving objective and subjective outcomes in patients with chronic GERD? Is there evidence that effectiveness varies by specific techniques/procedures or medications? Objective outcomes include esophagitis healing, ambulatory pH, other indicators of reflux, need for medication, health care utilization, and incidence of esophageal stricture, Barrett's esophagus, or esophageal adenocarcinoma. Subjective outcomes include symptom frequency and severity, sleep/productivity, and overall quality of life. | Key Question 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, health care utilization, and incidence of esophageal stricture, Barrett's esophagus or esophageal 4 adenocarcinoma. Subjective outcomes include symptom frequency and severity, sleep/productivity, and overall quality of life. | | |  | |  |
| Medical therapy with PPIs and surgery (fundoplication) appeared to be similarly effective for improving symptoms and decreasing esophageal acid exposure. 10 percent to 65 percent of surgical patients still require medications. The limited data available did not support a significant benefit of fundoplication compared with medical therapy for preventing Barrett's esophagus or esophageal adenocarcinoma. | 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 than patients who received medical treatment alone. However, some uncertainty remains in the true estimates of the efficacy of surgery versus medical treatment because of the large proportion of patient dropouts (33 to 58 percent) in studies with long followup. As with the 2005 CER, the studies in this review included patient populations with varying clinical characteristics and response to medical treatments at baseline. One of the previously reviewed studies with longterm followup data enrolled only patients with baseline esophagitis, without restriction on the degree of severity, while the other included patients with no higher than Los Angeles grade Besophagitis at randomization. | | | Conclusion is still valid and this portion of the CER does not need updating. | | Poor - update indicates symptoms are better with surgery. However, 5 of the 8 studies contributing evidence to the update conclusion were published in 2008/2009, and the limited literature search used for the identification of signals was done in 2008 and hence certainly was not capable of detecting some of this new evidence. |
| Of the three nonrandomized studies that compared an endoscopic procedure with laparoscopic fundoplication in patients with GERD documented by pH or endoscopy, the longest follow-up was 8 months, and all three studies had significant bias that may invalidate the results. Two studies reported that more patients treated with laparoscopic fundoplication were satisfied with their results compared with those who had EndoCinchTM. One of these studies and a study of Stretta® also found less need for PPIs in patients who had fundoplication. | Based on analysis of 4 RCTs and 3 nonrandomized trials with varied: Medical (PPI and/or H2RA) vs. 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. | | | Original conclusion should probably be deleted as the endoscopic procedure is no longer in use. | | Fair - Two of the three considered endoscopic procedures had been withdrawn at the time of the 2009 surveillance, but since then 1 was reintroduced, and another was developed about 2007. The 2009 prediction probably should have been more nuanced than saying the whole conclusion should be deleted since the procedures were withdrawn, since that did not anticipate the development of new procedures. But it worked well as a signal that the procedural landscape for GERD was changing and needed updating. |
| There was no head-to-head comparison of medical treatments with endoscopic treatments. | No study was identified for this comparison (medical vs. endoscopic treatments). 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 EndoCinchTM. There were no significant differences in other outcomes. | | | Original conclusion should probably be deleted as the endoscopic procedure is no longer in use. | | Fair - Same as above |
| PPIs were superior to H2RAs (histamine 2 receptor inhibitors) in resolution of GERD symptoms at 4 weeks and healing of esophagitis at 8 weeks.There was no difference between omeprazole, lansoprazole, pantoprazole, and rabeprazole for relief of symptoms at 8 weeks.No significant difference was found in the comparisons of esomeprazole 40 mg with lansoprazole 30 mg or pantoprazole 40 mg for relief of symptoms at 4 weeks. Similarly, there was no difference in the comparison of esomeprazole 20 mg with omeprazole 20 mg in relief of symptoms at 4 weeks. | 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. Data from one RCT reported that lansoprazole 15 mg, taken once daily, was more effective than ranitidine 150 mg taken twice daily for healing of esophagitis at 1 year.Data from one RCT reported that esomeprazole 20 mg, taken once daily or on demand, was more effective than ranitidine 150 mg taken twice daily for prevention of symptom relapse at 6 months.Data from two RCTs reported that maintenance treatment (≥ 6 months) with PPIs (esomeprazole 20 mg taken once daily or on demand, lansoprazole 15 mg taken once daily) appears to be more efficacious than maintenance treatment with H2RA (ranitidine 150 mg taken twice daily) in symptom remission.  Data from one RCT reported that 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. Based on analysis of 10 RCTs, no consistent comparative difference in symptom relief and esophagitis healing rates was observed between esomeprazole (20 to 40 mg), lansoprazole (15 to 30 mg), pantoprazole (20 to 40 mg) or rabeprazole (10to 20 mg) over a period ranging from 4 weeks to 6 months.  Data from one RCT reported that 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. Based on analysis of 10 RCTs, no consistent comparative difference in symptom relief and esophagitis healing rates was observed between esomeprazole (20 to 40 mg), lansoprazole (15 to 30 mg), pantoprazole (20 to 40 mg) orrabeprazole (10to 20 mg) over a period ranging from 4 weeks to 6 months.  There is some evidence from individual studies that rabeprazole 10 mg may provide better symptom relief than esomeprazole 40 mg at 4 weeks, and also that pantoprazole 20 mg provides better control of heartburn than esomeprazole 40 mg over 24 weeks. Results from three acute treatment trials showed similar esophagitis healing rates for both pantoprazole 40 mg and esomeprazole 40 mg as demonstrated by endoscopy, with the rates increasing with trial duration from 8 to 12 weeks, and being equivalent over 6 months. Based on analysis of 12 RCTs, no consistent difference in doses and dosing regiments with different PPIs in relation to symptom resolution and esophagitis healing rates. One RCT reported that there was no significant difference in symptom resolution rates at 4 weeks between esomeprazole 20 mg taken once a day and esomeprazole 40 mg taken once a day. One RCT reported 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.  Three RCTs comparing 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.One RCT reported that continuous daily intake of esomeprazole 20 mg appears to provide significantly better endoscopic remissioncompared with on-demand dosing over a period of 6 months. Two RCTs reported that continuous daily intake of rabeprazole 20 mg appears to provide better symptom control and quality of life relative. Based on analysis of eight RCTs, no consistent comparative difference in symptom relief and esophagitis healing rates was observed between esomeprazole (20 to 40 mg), lansoprazole 30 mg, pantoprazole 40 mg or rabeprazole 20 mg with omeprazole 20 mg or lansoprazole 15 mg over a period ranging from 4 weeks to 1 year.  One RCT reported that pantoprazole 40 mg and rabeprazole 20 mg provide significantly better symptom relief and healing of esophagitis than omeprazole 20 mg at 8 weeks. One RCT reported that esomeprazole 20 mg provides higher endoscopic remission rates compared with lansoprazole 15 mg over 6 months. | | | Conclusion is probably out of date and this portion of the CER may need updating based on a wealth of new data. | | Good - Even though the overall conclusion didn't change, the reason for the 2009 conclusion - a wealth of new data-was supported by the update, with many of the same studies being noted. |
| For maintenance medical treatment of 6 months to 1 year, PPIs taken at a standard dose were more effective than those taken at a lower dose. | No comparable conclusion in the update | | | Conclusion is still valid and this portion of the CER does not need updating. | | Not applicable as there is no comparable conclusion in the update |
| Laparoscopic fundoplication was as effective as open fundoplication for relieving heartburn and regurgitation, improving quality of life, and decreasing use of antisecretory medications. Almost 90 percent of patients who were followed for 5 or more years in both surgical arms reported improvement in symptoms. | Two RCTs and two non-randomized comparative studies compared laparoscopic fundoplication with vs. without division of short gastric vessel. No significant differences in medication use, GERD symptoms, or quality of life were found between groups. Two RCTs and one non-randomized comparative study compared laparoscopic vs. open fundoplication. No significant differences in medication use, GERD symptoms, diagnostic test results, or quality of life were found between groups. One RCT and five non-randomized comparative studies compared laparoscopic total vs. partial fundoplication. No consistent significant differences in GERD symptoms, diagnostic test results, or quality of life were observed between groups. | | | Conclusion is still valid and this portion of the CER does not need updating. | | Good |
| Compared to sham, StrettaTM was more effective in improving symptoms of reflux and improving quality of life at 6 months and was associated with a decrease in the need for antisecretory medications. Improvement of esophageal pH exposure compared with sham could not be demonstrated for StrettaTM. | One sham-controlled study and seven noncomparative 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. Two sham-controlled studies and six noncomparative 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. 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. | | | Original conclusion should probably be deleted as the endoscopic procedure is no longer in use. | | Fair - Same rationale as above |
|  | A systematic review did not find consistent effects ofPPI or H2RA (vs. 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 functionmeasures. Four of six RCTs did not find a significant differencein resolution of hoarseness between PPI andplacebo.  Meta-analysis of 4 studies (191 participants) showed no significant difference in total resolution of cough between PPIs and placebo, odds ratio 0.46 (95% CI: 0.19 to 1.15). A meta-analysis of data from 4 RCTs reporting mean cough scores at the end of the trial in 109 participants found a borderline significant improvement in the mean cough scores at the end of the trial with PPIs as compared to placebo 0.38 units (95 percent CI: 0.77 to 0.00, P=0.05). Another meta-analysis examining the improvement in cough scores 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). 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 surgical interventions, the intensity and duration of followup. 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. | | |  | | These conclusions have no counterpart in the original report, and present new data. |
| Key Question 2 - Is there evidence that effectiveness of medical, surgical, and endoscopic treatments varies for specific patient subgroups? What are the characteristics of patients who have undergone these therapies, including the nature of previous medical therapy, severity of symptoms, age, sex, weight, other demographic and medical factors, or by specific patient subgroups, and provider characteristics for procedures including provider volume and setting (eg, academic versus community)? | Key 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 vs. community)? | | |  | |  |
| Patients on maintenance antireflux medications may have higher rates of esophagitis if they have any of the following factors: increased severity of esophagitis at baseline (pretreatment), younger age, and moderate to severe regurgitation. | 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. 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. 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. The 2005 CER identified a number of patient characteristics and baseline clinical factors that may influence the effectiveness of medical, surgical, or endoscopic treatment. However, the quality and consistency of these primary data were mixed and the strength of the identified associations remained unclear. The studies included in this update were plagued with similar methodological issues. | | | Conclusion is still valid and this portion of the CER does not need updating. | | Good |
| There is no substantial evidence to support a difference in surgical outcome based on age, preoperative presence or severity of esophagitis, lower esophageal sphincter incompetence, or esophageal body hypomotility. Patients treated surgically who have a history of psychiatric disorders may have worse symptom and satisfaction outcomes than those without a significant psychiatric history. | 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 cmat baseline. Three cohort studies examined different modifying factors of endoscopic treatment: 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. | | | Conclusion is still valid and this portion of the CER does not need updating. | | Good |
| Key Question 3 - What are the short- and long-term adverse effects associated with specific medical, surgical, and endoscopic therapies for GERD? Does the incidence of adverse effects vary with duration of follow-up, specific surgical intervention, or patient characteristics? | Key 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? | | |  | |  |
| Higher adverse event rates were described for PPIs than for H2RAs or placebo. The most commonly cited events for PPIs and H2RAs were headache, diarrhea, and abdominal pain. | One RCT reported that the rate of serious adverse events was higher in patients who underwent fundoplication than in those who had medical treatment (P = 0.06). Adverse events reported with PPIs included diarrhea, nausea or vomiting, abdominal pain, dyspepsia, and headache. These occurred in fewer than 2 percent of patients. Potential serious complications possibly associated with PPI use that were reported in the 2005 CER included enteric infections(Campylobacter and Clostridium difficile) and pneumonia. An increased risk of bone fracture is now added to this list, although the strength of association is uncertain. Common adverse events reported in patients who underwent fundoplication included bloating (up to 85 percent) and dysphagia (up to 23 percent). Reoperation rates ranged from 3 to 35 percent. Common adverse events after endoscopic suturing included chest or abdominal pain (up to 24 percent), bleeding (up to 11 percent), dysphagia (up to 50 percent), and bloating (up to 19 percent). None of these quantitative estimates are reliable because of the lack of a standard definition and uniform system of reporting. The strength of evidence was rated low. | | | Conclusion is possibly out of date and this portion of the CER may need updating based on expert opinion about newly recognized adverse events. | | Good - the new AE of bone fracture is an important conclusion |
| The most commonly reported complications occurring intra operatively or within 30 days after open fundoplication were the need for splenectomy, dysphagia, inability to belch, and inability to vomit. The most commonly reported complications for laparoscopic procedures were gastric or esophageal injury or perforation, splenic injury or splenectomy, pneumothorax, bleeding, pneumonia, fever, wound infections, bloating, and dysphagia. Major complications were generally reported at very low rates. | Common adverse events reported in patients who underwent fundoplication included bloating and dysphagia. | | | Conclusion is still valid and this portion of the CER does not need updating. | | Good |
| Frequently reported complications for endoscopic treatments (intra operatively or within 30 days after the procedure) included chest or retrosternal pain, gastrointestinal injury, bleeding, and short-term dysphagia. The frequency and types of complications varied with the different procedures. Serious complications, including fatalities, have also been described. | Common adverse events after endoscopic suturing included chest or abdominal pain, bleeding, dysphagia, and bloating. | | | Original conclusion should probably be deleted as the endoscopic procedure is no longer in use. | | Fair - Same rationale as above for other conclusions about endoscopy procedures. |

**References**

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

2. Ip S, Chung M, Moorthy D, et al. Comparative Effectiveness of Management Strategies for Gastroesophageal Reflux Disease: Update. Comparative Effectiveness Review No. 29. (Prepared by Tufts Medical Center Evidence-based Practice Center under Contract No. HHSA 290-2007-10055-I.) AHRQ Publication No. 11-EHC049-EF. Rockville, MD: Agency for Healthcare Research and Quality. September 2011. [www.effectivehealthcare.ahrq.gov/reports/final.cfm](http://www.effectivehealthcare.ahrq.gov/reports/final.cfm).