Treatment for Gastroesophageal Reflux Disease (GERD)

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DESCRIPTION

Gastroesophageal Reflux Disease (GERD)

The esophagus is, tube-like and connects the mouth to the stomach. Within the esophagus there are sphincter(s), which allows movement of stomach contents into the lower esophagus. Gastroesophageal reflux disease (GERD) is a weakening or inappropriate relaxation of the lower esophageal sphincter. More than 60 million people in United States suffer from GERD and it has generated interest in creating minimally invasive transesophageal therapeutic alternatives to open, laparoscopic fundoplication, or chronic medical therapy.

There are multiple therapies and surgical interventions being studied for the treatment of gastroesophageal and laryngopharyngeal reflux disease. Non-surgical treatments continue to be first-line treatment for all reflux disease. Treatment GERD generally involves a stepwise approach. The goals are to control symptoms, to heal esophagitis, and to prevent

recurrent esophagitis or other complications. The treatment is based on lifestyle modification and control of gastric acid secretion.

Some patients continue to have issues with GERD symptoms after treatment. According to most experts, patients with GERD who exhibit partial or lack of response to proton pump inhibitor (PPI) twice daily are considered to have failed a PPI therapy. However, some experts suggest a lack of satisfactory symptomatic response to a PPI once a day should be considered a failure of PPI therapy. The definition of refractory GERD remains controversial.

The Food and Drug Administration (FDA) has approved treatments based on a variety of technologies to improve the function of the lower esophageal sphincter. Treatments which have been investigated which include but are not limited to the following:

1. **Endoscopic Submucosal Implantation or Injection of a Bulking Agent**
   - Submucosal injection, implantation of a prosthetic, or bulking agent is utilized to enhance the volume of the lower esophageal sphincter thus creating an anti-reflux barrier.
2. **Magnetic Esophageal Ring (LINX)**
   - Magnetic sphincter augmentation device (MSAD) restores the competency of the lower esophageal sphincter with a device rather than a tissue fundoplication.
3. **Transesophageal Endoscopic Radiofrequency Ablation (e.g., Stretta)**
   - Radiofrequency energy has been used to produce submucosal thermal lesions at the gastroesophageal junction. This technique has also been referred to as the Stretta® procedure. Specifically, radiofrequency energy is applied through four electrodes inserted into the esophageal wall at multiple sites, above and below the squamocolumnar junction. The mechanism of action of the thermal lesions is not precisely known but may be related to ablation of the nerve pathways responsible for sphincter relaxation or may induce a tissue-tightening effect related to heat-induced collagen contraction.
4. **A Transoral Incisionless Fundoplication (TIF)**
   - A procedure that involves wrapping the stomach's upper portion over the lower esophagus to strengthen the gastroesophageal sphincter. TIF is intended as a less-invasive alternative to laparoscopic Nissen fundoplication (LNF) surgery in patients who experience insufficient relief with proton pump inhibitor (PPI) pharmacotherapy or are concerned about lifelong PPI consumption.
5. **Transesophageal Endoscopic Suturing and Plication**
   - Transesophageal Endoscopic Gastroplasty (Gastroplication or Fundoplication) is an outpatient procedure where suture(s) are placed in the lower esophageal sphincter. The sutures are designed to strengthen and lengthen the sphincter to decrease reflux.
6. **Upper Esophageal Sphincter Assist Device**
   - It is a novel medical device designed to prevent the reflux of gastric contents into the laryngopharynx. It is a non-pharmacologic, non-surgical medical

device worn while sleeping and applies a standardized external pressure to the cricoid cartilage in order to decrease retrograde reflux of gastroduodenal contents

Review of Evidence: Esophageal Bulking Agents

Clinical Context and Therapy Purpose
The purpose of esophageal bulking agents is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with GERD.

The question addressed in this evidence review is: Does the use of esophageal bulking agents improve the net health outcomes in individuals with GERD?

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is individuals with GERD.

Interventions
The therapy being considered is esophageal bulking agents.

Comparators
The following therapies and practices are currently being used to treat GERD: PPI therapy and laparoscopic fundoplication.

Outcomes
The general outcomes of interest are symptoms, change in disease status, QOL, medication use, and treatment-related morbidity. Though not completely standardized, follow-up for GERD symptoms would typically occur in the months to years after starting treatment.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.

In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.

To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.

Studies with duplicative or overlapping populations were excluded.

Endoscopic Submucosal Implantation/Injection of a Bulking Agent: Enteryx
(2004) Hubert et al reported Enteryx (ethylene vinyl alcohol copolymer) was developed as a bulking agent to be injected endoscopically at the lower esophageal sphincter (LOS) to increase the competency of the gastroesophageal barrier in patients suffering from gastroesophageal reflux disease (GORD). Preliminary clinical studies have shown that Enteryx implantation is a fast, minimally invasive, and safe procedure. In prospective multicenter studies, significant improvement in reflux symptoms, reduction in the use of proton pump inhibitors (PPIs), and objective improvement in acid esophageal exposure time were observed after 6 months of follow-up. Improvement of GORD symptoms seems to be correlated with the persistence of the implant. Preliminary data suggest a lengthening and an increase in the LOS relaxation pressure as mechanisms of action of this injection technique. Longer follow-up and controlled sham studies are needed to confirm the efficacy of this technique before it can be proposed as a routine alternative to medical or surgical therapies for GORD.

Endoscopic Submucosal Implantation/Injection of a Bulking Agent: Durasphere
(2009) Ganz et al. assessed the long-term safety and effectiveness of Durasphere (Carbon Medical Technologies, St Paul, Minn), a new injectable bulking agent, in the treatment of mild-moderate GERD with an initial human pilot study.

Ten GERD subjects, confirmed by pH monitoring, on daily proton pump inhibitor (PPI) therapy, hiatal hernia <3 cm, and no or mild erosive esophagitis. Endoscopic injection with Durasphere, a new submucosal bulking agent, at the gastroesophageal junction. Change in symptom scores, PPI use, pH scores, and endoscopic findings; monitoring of safety profile. Nine of 10 patients completed the 12-month trial. There were no adverse events. The procedure was well tolerated with minimal patient discomfort and no dysphagia. At 12 months 70% of patients discontinued all antacid medication completely; 90% of patients reduced PPI use by greater than 50%. DeMeester scores improved from a mean of 44.5 at baseline to 26.5 at 12 months; 4 patients achieved normal pH scores. There was no esophagitis at 12 months, and no erosion, ulceration or sloughing of material was noted at any injection site. The Durasphere material did not appear to migrate. The limitations included nonrandomized study design without a control group and a small number of subjects. The concluded Durasphere appears to be a promising new injectable bulking agent for the treatment of mild-moderate GERD, with demonstrable efficacy and no significant adverse events in a small cohort

Endoscopic Submucosal Implantation/Injection of a Bulking Agent: Gatekeeper
(2018) Rodrigues et al. reported "…The Gatekeeper was a previously used device in which expandable hydrogel prosthesis were endoscopically implanted in the submucosa of the distal esophagus to create a reflux barrier. Theoretically, the number of prostheses could be titrated to the desired treatment effect and were also easily removable. Although initially attractive because of its simplicity, this device lacked compelling efficacy data and had a poor record on safety, with chest pain, pleural effusion, and even perforations. Accordingly, it was voluntarily withdrawn by the manufacturer.

To the best of our knowledge, there are no reports of the Gatekeeper after its suspension. Considering the wide range of endoscopic techniques for gastroesophageal reflux disease that were developed and discontinued in the past, it is important for the endoscopist to be aware of this type of prosthesis and its endoscopic appearance. This information might simplify the differential diagnosis with esophageal subepithelial lesions and avoid hazardous fine-needle aspiration or resection attempts."

Endoscopic Submucosal Implantation/Injection of a Bulking Agent: Plexiglass or Polymethylmethacrylate (PMMA) Beads

(2001) Feretis et al. noted an endoscopic submucosal implantation of PMMA was carried out in 10 patients with GERD who were either refractory to or dependent on proton pump inhibitors. Symptom severity score, 24-hour pH monitoring, upper GI endoscopy, and EUS were performed to evaluate the efficacy of implantation.

A significant decrease in the symptom severity score and mean total time with esophageal pH less than 4 was noted after the implantation of PMMA ($p < 0.05$). Seven of 10 patients were taking no medication after PMMA implantation. There were no serious procedure-related complications. Endoscopic implantation of PMMA into the submucosa of the lower esophageal folds may be a new method for treating GERD. While a significant decrease in symptom scores was noted at posttreatment follow-up (time not specified), the small number of patients and lack of long-term follow-up precluded scientific analysis. No additional studies have been identified evaluating this treatment option.

Section Summary: Esophageal Bulking Agents

The evidence on the injection of bulking agents includes case series. High-quality data from large RCTs are needed to compare bulking procedures with both sham controls and with the currently accepted treatments for GERD (i.e., drug therapy, laparoscopic fundoplication). Well-designed trials should use standardized outcome measures to examine both subjective (e.g., GERD-HRQL scores) and objective (e.g., esophageal acid exposure) effects on health outcomes.

Roux-en-Y Gastric Bypass (RYGBP)

Roux-en-Y gastric bypass (RYGBP) (open or laparoscopic) is commonly known as gastric bypass. A small stomach pouch is created to restrict food intake. A Yshaped section of the small intestine is attached to the pouch to allow food to bypass the lower stomach, the duodenum and the first portion of the jejunum.

This reduces the number of calories and amount nutrients the body absorbs. Long-limb Roux-en-Y gastric bypass is similar to standard RYGBP, except that the limb through which food passes is long, which purportedly eases symptoms of GERD.

(2020) Butti et al. completed a review on gastroesphageal reflux disease following roux-en-y gastric bypass. They found six studies, four case reports, and two retrospective studies about surgical and endoscopic options to treat this subgroup of patients.

Discussion: Pharmacological therapy and lifestyle optimization are the first line of treatment. For resistant GERD, new surgical and endoscopic strategies are proposed in the past years to manage this subgroup of patients related to anatomic limitation of RYGB. The authors concluded more studies are needed to compare surgical and endoscopic solutions. The choice of treatment depends on local resources and skills, and if necessary, refer the patient to a specialist center.

(2019) Holmberg et al. noted in a nationwide cohort study of all adults with preoperative reflux who underwent gastric bypass in Sweden between 2006 and 2015, with complete follow-up through 2016. The outcome was remaining/recurring reflux symptoms, defined as use of proton pump inhibitors or histamine-2 receptor antagonists for >6 months after surgery. Cumulative incidence and risk factors of reflux were assessed with multivariable Poisson regression. Among 2454 participants (81.7% female; mean age: 46.1 years, SD: 9.8 years), who were followed for median 4.6 years (interquartile range: 3.1-6.3 years), reflux recurred in 48.8% (95% confidence interval [95% CI], 46.8-51.0) of participants within 2 years of gastric bypass and remained stable up to 10 years after surgery (yearly change in incidence rate ratio [IRR] of 1.00; 95% CI, 0.99-1.02). Risk factors for recurring reflux were high preoperative dose of anti-reflux medication (IRR 1.77; 95% CI, 1.60-1.96 compared with low dose), older age (IRR 1.12; 95% CI 1.02-1.24 comparing age >50 with <40 years), female sex (IRR 1.28; 95% CI, 1.16-1.42) and comorbidity (IRR 1.26; 95% CI, 1.14-1.39 comparing Charlson Comorbidity Index ≥2 with 0). Reflux symptoms decrease rapidly after gastric bypass, but around half of operated patients require continuous anti-reflux medication. The treatment efficacy of gastric bypass on reflux symptoms might have been overestimated.

Magnetic Sphincter Augmentation (MSA) (LINX)

Clinical Context and Therapy Purpose
The purpose of magnetic sphincter augmentation (MSA) in patients who have gastroesophageal reflux disease (GERD) is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does the use of MSA improve the net health outcome in individuals with GERD who have not responded to optimal medical management?

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is individuals with GERD who have not responded to optimal medical management.

The severity of GERD varies widely. Many patients have mild, intermittent symptoms that do not require treatment or only require episodic use of medications. Other patients

have chronic, severe GERD that can lead to complications such as Barrett esophagus and esophageal cancer.

The Los Angeles (LA) classification system is used to describe the endoscopic appearance of reflux esophagitis and grade its severity. Esophagitis is confirmed by endoscopy according to a 5-grading severity scale.

- Not present: No breaks (erosions) in the esophageal mucosa (edema, erythema, or friability may be present).
- Grade A: One or more mucosal breaks confined to the mucosal folds, each not more than 5 mm in maximum length.
- Grade B: One or more mucosal breaks more than 5 mm in maximum length, but not continuous between the tops of 2 mucosal folds.
- Grade C: Mucosal breaks that are continuous between the tops of 2 or more mucosal folds, but which involve less than 75% of the esophageal circumference.
- Grade D: Mucosal breaks which involve at least 75% of the esophageal circumference.

Interventions

The therapy being considered is MSA. The LINX Reflux Management System is composed of a small flexible band of 10 to 18 interlinked titanium beads with magnetic cores. Using standard laparoscopic techniques, the band is placed around the esophagus at the level of the gastroesophageal junction. The magnetic attraction between the beads is intended to augment the lower esophageal sphincter to prevent gastric reflux into the esophagus, without compressing the esophageal wall. It is proposed that swallowing food or liquids creates sufficient pressure to overcome the magnetic bond between the beads, allowing the beads to separate and temporarily increase the size of the ring. Magnetic sphincter augmentation is a 30-minute surgical procedure performed under general anesthesia that includes testing of the esophageal sphincter. This is a minimally invasive procedure conducted in an inpatient surgical center and requires an overnight stay. The device manufacturer claims patients resume a normal diet within 24 hours postsurgery. The device can be removed by a laparoscopic procedure if severe adverse events occur or if magnetic resonance imaging is needed for another condition.

Comparators

The following therapies and practices are currently being used to treat GERD that has not responded to optimal medical therapy: lifestyle modifications, continued medical therapy, and interventions to strengthen the lower esophageal sphincter.

Lifestyle modifications may include weight loss, elevation of the head of the bed, avoidance of meals close to bedtime, and elimination of dietary triggers. For patients with severe disease, chronic treatment with acid suppressive therapies is an option. For some patients, medications are inadequate to control symptoms; other patients prefer to avoid the use of indefinite, possibly lifelong medications. Surgical treatments are available for these patients, primarily a Nissen fundoplication performed either laparoscopically or by open surgery. A number of less invasive procedures are also being evaluated as an

intermediate option between medical therapy and surgery (see review 2.01.38 on endoscopic procedures).

In patients who continue to have symptoms despite once daily proton pump inhibitors (PPIs) (e.g., omeprazole 20 mg), guideline-based recommendations include increasing and/or splitting the PPI dose and switching to a different PPI to optimize pharmacologic treatment.

Outcomes
Relevant outcomes of interest are a reduction in symptoms such as heartburn and regurgitation, reduction in acid suppression medication use, QOL, treatment-related adverse events, device failure, device erosion, the need to explant if magnetic resonance imaging is necessary, and progression to Barrett esophagus and esophageal cancer. Additional outcomes of interest include objective measures such as the DeMeester score or percent time esophageal pH < 4 based on impedence-pH findings. Objective measures are of special interest as a lack of correlation between subjective and objective measures of GERD have been reported in the literature.

A variety of scales have been developed to measure patient and investigator-reported GERD symptoms. Frequently used measures of QOL include the GERD-health-related QOL (GERD-HRQL), a scale with 11 items focusing on heartburn symptoms, dysphagia, medication effects, and the patient's present health condition. Each item is scored from 0 to 5, with a higher score indicating a better QOL, and GERD-QOL, a scale with 16 items clustered into the following 4 subscales: daily activity, treatment effect, diet, and psychological well-being. The total score of this questionnaire is the average of the 4 subscale scores. The final score can range from 0 to 100, with a higher score indicating a better QOL.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.

Review of Evidence
Data submitted to the U.S. Food and Drug Administration (FDA) for the LINX Reflux Management System included 2 single-arm FDA regulated investigational device exemption (IDE) trials (N=144 subjects) and follow-up data between 2 and 4 years. The feasibility IDE trial enrolled 44 subjects at 4 clinical sites (2 U.S., 2 Europe) and had published data out to 4 years. The pivotal IDE trial included 100 subjects from 14 clinical sites (13 U.S., 1 Europe) who had documented symptoms of GERD for more than 6 months (regurgitation or heartburn that responds to acid neutralization or suppression),

required daily PPI or other antireflux drug therapy, had symptomatic improvement on PPI therapy, and had a total distal ambulatory esophageal pH less than 4 for 4.5% or more of the time when off GERD medications. The primary safety endpoint measured the rate of related device and procedure serious adverse events. Efficacy endpoints were assessed off PPI therapy and measured esophageal acid exposure, total GERD-HRQL scores, and PPI usage. Subjects served as their own controls.

(2021) Bonavina et al. published 3-year outcomes from a prospective, observational registry evaluating MSA and laparoscopic fundoplication in 631 patients (465 MSA; 166 laparoscopic fundoplication) enrolled between 2009-2014 across 22 medical centers in Europe. Patients had a diagnosis of GERD confirmed by abnormal esophageal acid exposure and chronic reflux symptoms despite daily use of PPIs. Patients with severe GERD marked by hiatal hernia >3 cm, Barrett esophagus, motility disorder, and Grade C or D esophagitis by Los Angeles classification were also included. The type of anti-reflux procedure performed was provisionally determined by the surgeon in consultation with the patient. MSA was recommended when patients met labeling requirements for MSA (hiatal hernia ≤ 3 cm, esophagitis < Grade C, absence of Barrett esophagus, and absence of motility disorders); however, the final choice of procedures was made by the surgeon at the time of laparoscopy. Various forms of laparoscopic fundoplication were performed, including Nissen (62%), Toupet (31%), and Other/Unspecified (eg, Dor; 7%). Improvements in total GERD-HRQL scores were observed in both MSA (22.0 to 4.6) and laparoscopic fundoplication (23.6 to 4.9) groups with similar increases in GERD-HRQL satisfaction. A higher proportion of patients maintained the ability to vomit in the MSA group compared to laparoscopic fundoplication (91.2% vs. 68.0%). Similar declines in PPI usage were observed in both groups (MSA 97.8% to 24.2% and laparoscopic fundoplication 95.8% to 19.5%). Limitations of the study include lack of randomization and blinding, heterogeneity in laparoscopic fundoplication techniques, and selection bias as patients with less severe symptoms received MSA. It is unclear to what extent study results are generalizable to U.S. populations and broader settings of care. Additionally, the minimal dissection protocol for MSA implantation utilized in this study has since evolved to include full crural and gastroesophageal junction dissection.

FDA Manufacturer and User Facility Device Experience (MAUDE) reports and manufacturer complaint databases were analyzed from 2013-2020 by DeMarchi and coworkers (2021) to determine rates of surgical device erosion and explants. Overall, 7-year cumulative risk of removal was 4.81% (95% CI, 4.31% to 5.36%), with 2.2% of devices (609/27779) having been reported as removed. Primary reasons for device removal included dysphagia/odynophagia (47.9%), persistent GERD (20.5%), and unknown/other (11.2%). The 7-year cumulative risk of erosion was 0.28% (95% CI, 0.17% to 0.46%), with 27 reports of erosion. Smaller device size was found to be associated with increased removal and erosion rates.

(2020) Ayazi et al. published a retrospective review of 380 patients treated with MSA with a mean follow-up duration of 11.5 ± 8.7 months. Persistent dysphagia was reported in 59 (15.5%) patients with 31% requiring at least 1 dilation for dysphagia or chest pain.

The overall response rate to dilation was 67%, with 7 (1.8%) patients requiring device removal for dysphagia. Independent predictors of persistent dysphagia included the absence of a large hiatal hernia (p=.035), the presence of preoperative dysphagia (p=.037) and having less than 80% peristaltic contractions on high-resolution impedance manometry (p=.031).

Additional single-arm observational studies have reported on outcomes after MSA in sample sizes ranging from 79 to 500 patients, some of which focused on specific subpopulations of individuals with GERD, such as those with large hiatal hernias (e.g., Rona et al. [2017] and Dunn et al. [2021]).,Other studies have highlighted independent predictors of favorable outcomes, such as age of intervention <40-45 years, male sex, abnormal DeMeester scores, and baseline GERD-HRQL scores >15.

(2020) An ECRI custom product brief on the LINX® Reflux Management System for treating GERD identified a review of evidence from 2017 through 2020 that included two systematic reviews, one randomized control trial, one retrospective pre-post study and two economic studies. It was concluded longer follow-up and comparisons of LINX with other GERD devices would be useful and there are currently 3 ongoing trials that may partially address these evidence gaps.

(2020) Schizas et al. conducted a systematic review to investigate the safety and efficacy of the LINX® Reflux Management System. After screening 614 articles, a total of 35 studies fit the criteria and were analyzed. According to the authors, although laparoscopic fundoplication (LF) and magnetic sphincter augmentation (MSA) both appear to be safe and effective procedures, MSA appears to have a few distinct advantages such as a less technical procedure, less bloating and superiority in the ability to vomit/belch, easily reversible and if it fails, LF is still a viable option after device removal. The authors' findings suggested that MSA with the Linx device is a safe procedure and has the potential to bridge the treatment gap between maxed out medical treatment and laparoscopic fundoplication. The authors also concluded that further studies with longer follow-up are needed. A prospective, multicenter, randomized control trial was conducted by Bell et al. (2019, included in the ECRI report) comparing sphincter augmentation (MSA) (n-50) to double-dose proton-pump inhibitor (PPI) therapy (omeprazole, 20 mg, twice a day) (n-102). The goal of the study was to compare the effect of the two treatments for elimination of moderate to severe regurgitation. As reported on a foregut symptom questionnaire, at six months, 89% of patients treated with MSA reported relief of regurgitation, with 81% reporting ≥ 50% improvement in GERD-health-related quality of life scores. Ten percent of the PPI group reported relief of regurgitation with eight percent of the PPI group reporting ≥ 50% improvement in GERD-health-related quality of life scores. However, twenty-eight percent of MSA patients reported transient dysphagia, with 4% reporting ongoing dysphagia. The authors concluded that patients who continue to experience moderate to severe regurgitation despite PPI treatment should be considered for MSA. Randomized controlled trials with larger patient populations and long term follow up are needed to further assess the long-term safety and efficacy of MSA.

(2020) Bell et al. completed a 1-year randomized trial on magnetic sphincter augmentation superior to proton pump inhibitors for regurgitation. Patients with moderate to severe regurgitation (assessed by the foregut symptom questionnaire) despite once-daily PPI therapy (n = 152) were randomly assigned to groups given twice-daily PPIs (n = 102) or laparoscopic MSA (n = 50) at 20 sites, from July 2015 through February 2017. Patients answered questions from the foregut-specific reflux disease questionnaire and GERD health-related quality of life survey about regurgitation, heartburn, dysphagia, bloating, diarrhea, flatulence, and medication use, at baseline and 6 and 12 months after treatment. Six months after PPI therapy, MSA was offered to patients with persistent moderate to severe regurgitation and excess reflux episodes during impedance or pH testing on medication. Regurgitation, foregut scores, esophageal acid exposure, and adverse events were evaluated at 1 year. Patients in the MSA group and those who crossed over to the MSA group after PPI therapy (n = 75) had similar outcomes. MSA resulted in control of regurgitation in 72/75 patients (96%); regurgitation control was independent of preoperative response to PPIs. Only 8/43 patients receiving PPIs (19%) reported control of regurgitation. Among the 75 patients who received MSA, 61 (81%) had improvements in GERD health-related quality of life improvement scores (greater than 50%) and 68 patients (91%) discontinued daily PPI use. Proportions of patients with dysphagia decreased from 15% to 7% ($P < .005$), bloating decreased from 55% to 25%, and esophageal acid exposure time decreased from 10.7% to 1.3% ($P < .001$) from study entry to 1-year after MSA (Combined $P < .001$). Seventy percent (48/69) of patients had pH normalization at study completion. MSA was not associated with any peri-operative events, device explants, erosions, or migrations. Considerations and potential limitations in this study include the relatively limited duration of follow-up. Other studies of MSA have documented little decrease in efficacy between 1 and 5 years of follow-up, and additional long-term studies of MSA are ongoing. The current study compared medical and surgical therapy, and lacking evidence to suggest that medical therapy results improve over time, longer-term follow-up comparison of the 2 arms was deemed unnecessary. Another consideration was the use of transnasal impedance or pH testing at the 6-month endpoint but 48-hour telemetry capsule pH testing at the 12-month endpoint. Transnasal impedance or pH testing was the only method to evaluate ongoing nonacid regurgitation in the double-dose PPI cohort, as it measures both acidic and acid-neutralized reflux episodes and was appropriate to determine crossover eligibility. Telemetry capsule pH testing was utilized at 12 months when all patients were evaluated off PPIs and were undergoing follow-up endoscopy. Keeping these considerations in mind, we reached the following conclusions. The authors concluded the yhe final results of this RCT found that MSA was superior to BID PPI therapy in patients with moderate-to-severe regurgitation despite daily PPI therapy. The response was sustained over 12 months. Regurgitation and associated heartburn symptoms responded to MSA even when completely nonresponsive to PPI therapy, in line with the mechanical, volume origin of regurgitative symptoms. Dysphagia improved by quality-of-life measures; bloating and gas were not significant after MSA.

(2019) Guidozzi et al. noted magnetic sphincter augmentation (MSA) has been proposed as a less invasive, more appealing alternative intervention to fundoplication for the

treatment of gastroesophageal reflux disease (GERD). The aim of this study was to evaluate clinical outcomes following MSA for GERD control in comparison with laparoscopic fundoplication. A systematic electronic search for articles was performed in Medline, Embase, Web of Science, and Cochrane Library for single-arm cohort studies or comparative studies (with fundoplication) evaluating the use of MSA. A random-effects meta-analysis for postoperative proton pump inhibitor (PPI) use, GERD-health-related quality of life (GERD-HRQOL), gas bloating, ability to belch, dysphagia, and reoperation was performed. The systematic review identified 6 comparative studies of MSA versus fundoplication and 13 single-cohort studies. Following MSA, only 13.2% required postoperative PPI therapy, 7.8% dilatation, 3.3% device removal or reoperation, and esophageal erosion was seen in 0.3%. There was no significant difference between the groups in requirement for postoperative PPI therapy (pooled odds ratio, POR = 1.08; 95%CI 0.40-2.95), GERD-HRQOL score (weighted mean difference, WMD = 0.34; 95%CI -0.70-1.37), dysphagia (POR = 0.94; 95%CI 0.57-1.55), and reoperation (POR = 1.23; 95%CI 0.26-5.8). However, when compared to fundoplication MSA was associated with significantly less gas bloating (POR = 0.34; 95%CI 0.16-0.71) and a greater ability to belch (POR = 12.34; 95%CI 6.43-23.7). In conclusion, magnetic sphincter augmentation achieves good GERD symptomatic control similar to that of fundoplication, with the benefit of less gas bloating. The safety of MSA also appears acceptable with only 3.3% of patients requiring device removal. There is an urgent need for randomized data directly comparing fundoplication with MSA for the treatment of GERD to truly evaluate the efficacy of this treatment approach.

(2019) Louie et al. reported one-year results from a mandated post-approval multicenter, prospective case series of 200 patients with pathologic acid reflux confirmed by esophageal pH testing, who underwent magnetic sphincter augmentation (MSA). Predefined clinical outcomes were assessed at the annual visit including a validated, disease-specific questionnaire, esophagogastroduodenoscopy (EGD) and esophageal pH monitoring, and use of proton pump inhibitors. At 1 year, the mean total acid exposure time decreased from 10.0% at baseline to 3.6%, and 74.4% of patients had normal esophageal acid exposure time (% time pH<4 ≤5.3%). GERD Health-Related Quality of Life scores improved from a median score of 26.0 at baseline to 4.0 at 1 year, with 84% of patients meeting the predefined success criteria of at least a 50% reduction in total GERD Health-Related Quality of Life score compared with baseline. The device removal rate at 1 year was 2.5%. There was a report of one erosion, and no serious adverse events were reported. The authors conclude safety and effectiveness of MSA has been demonstrated outside of an investigational setting It is important to note study limitations include lack of concurrent comparison group receiving a different GERD treatment and relatively short follow-up period.

(2018) Warren et al. noted in a retrospective observational study, analyzed factors influencing the outcome of MSA for chronic GERD using data from a pivotal trial (N = 99) and the authors prospectively maintained esophageal database (N = 71). A priori outcomes were defined as excellent (GERD-HRQL <5, no PPI, no esophagitis), good (GERD-HRQL 6-15, no PPI, grade A esophagitis), fair (GERD-HRQL 16 to 25, PPI use,

grade B esophagitis), and poor (GERD-HRQL >25, PPI use, grade C/D esophagitis). Univariable and multivariable logistic regression analyses were performed to determine predictors of achieving an excellent/good outcome. A total of 170 patients underwent MSA with a median age of 53 years, [43-60] and a median BMI of 27 (IQR = 24-30). At baseline, 93.5% of patients experienced typical symptoms and 69% atypical symptoms. At univariable analysis, excellent/good outcomes were negatively impacted by BMI, preoperative LES residual pressure, Hill grade, and hiatal hernia. At multivariable analysis, BMI >35 (OR = 0.05, 0.003-0.78, p = 0.03), structurally defective LES (OR = 0.37, 0.13-0.99, p = 0.05), and preoperative LES residual pressure (OR = 0.89, 0.80-0.98, p = 0.02) were independent negative predictors of excellent/good outcome. The authors' conclusion is that MSA results in excellent/good outcomes in most patients but a higher BMI, structurally defective sphincter, and elevated LES residual pressure may prevent this goal. The authors' conclusion is that a higher BMI, structurally defective sphincter, and elevated LES residual pressure may prevent optimal treatment with MSA. The findings however do not provide evidence for the safety and efficacy of MSA compared to other therapeutic approaches.

(2018) Aiolfi et al. conducted a systematic review and meta-analysis of early results of MSA versus fundoplication for the treatment of GERD. Seven observational cohort studies, published between 2014 and 2017, matched the inclusion criteria. Overall, 1211 patients, 686 MSA and 525 LF, were included. Postoperative morbidity ranged from 0 to 3% in the MSA group and from 0 to 7% in the LF group, and there was no mortality. Dysphagia requiring endoscopic dilatation occurred in 9.3% and 6.6% of patients respectively (OR = 1.56, 95% CI = 0.61-3.95, p = 0.119). The pooled OR of gas/bloat symptoms, ability to vomit, and ability to belch were 0.39 (95% CI 0.25-0.61; p < 0.001), 10.10 (95% CI 5.33-19.15; p < 0.001), and 5.53 (95% CI 3.73-8.19; p < 0.001), respectively. The postoperative GERD-HRQL was similar (p = 0.101). The pooled OR of PPI suspension, endoscopic dilation, and reoperation were similar in the two patients' groups (p = 0.548, p = 0.119, p = 0.183, respectively). The authors concluded that both anti-reflux procedures are safe and effective up to 1-year follow-up. PPI suspension rate, dysphagia requiring endoscopic dilatation, and disease-related quality of life are similar in the two patient groups. MSA is associated with less gas/bloat symptoms and increased ability to vomit and belch. The findings are limited by inclusion of observational studies only and relatively short follow-up periods.

(2018) Alicuben et al. reported on the worldwide experience with erosion of the MSA device in a large case series. In total, 9453 devices were placed and there were 29 reported cases of erosions. The median time to presentation of an erosion was 26 months with most occurring between 1 and 4 years after placement. The risk of erosion was 0.3% at 4 years after device implantation. Most patients experienced new-onset dysphagia prompting evaluation. Devices were successfully removed in all patients most commonly via an endoscopic removal of the eroded portion followed by a delayed laparoscopic removal of the remaining beads. At a median follow-up of 58 days post-removal, there were no complications and 24 patients have returned to baseline. Four patients reported ongoing mild dysphagia. The authors concluded that erosion of the LINX device is an

important but rare complication to recognize that has been managed via minimally invasive approaches without long-term consequences. Continued monitoring and reporting of MSA erosion will provide longer-term experience.

Per the American Gastroenterological Association (AGA) current guideline for the diagnosis and management of gastroesophageal reflux disease, the FDA approval of the LINX device was based on 100 GERD patients and this study found that the performance of the LINX resulted in symptom relief and pH control with fewer side effects than traditional laparoscopic fundoplication in well-selected patients. More data is required before widespread usage can be recommended.

(2017) SAGES LINX® Safety and Effectiveness Analysis Committee finds:
With regards to safety:

Safety analyses suggest the LINX procedure was associated with few serious adverse events and no reported mortality.

- The most common anticipated side effect was acute dysphagia.
- The reported rate of erosion is in the range of 0.1% to 0.2%. The published literature on erosions suggests that the device can be safely removed endoscopically or laparoscopically without serious adverse outcomes.
- Some devices require removal, most often for recurrent GERD or persistent and/or severe dysphagia
- No new patterns of failure or complications have been reported in long-term follow-up.
- Longer-term follow-up supports the FDA conclusion that the device is safe.

With regards to efficacy, the panel concludes:

- LINX implant results in pH normalization, improved quality of life, and complete cessation of regular PPI use on a consistent basis. The ability to belch and vomit is maintained following implantation of LINX, and de novo moderate-severe gas-bloat is uncommon.
- When compared to laparoscopic fundoplication, rates of success in alleviating GERD symptoms and dysphagia are similar following LINX. Bloating side effects may be lower.
- Longer-term follow-up data demonstrates that the LINX Reflux Management System is effective in the management of GERD.

Conclusions:

- Longer-term (3-5 years) experience with the LINX Reflux Management System confirms the initial safety profile that led to FDA approval of the device.
- The LINX device has been demonstrated to result in long-term GERD control based on symptomatic outcomes, PPI utilization, and pH studies.
- LINX is a reasonable treatment option for appropriately selected patients with GERD who meet indications for antireflux surgery. The LINX procedure is part of the armamentarium in the treatment of GERD. As such, it should be performed

by surgeons familiar with the workup and different management alternatives of GERD and not offered in isolation.

Section Summary: Magnetic Sphincter Augmentation (MSA) (LINX)
For individuals who have GERD who receive MSA, the evidence includes 1 RCT comparing MSA to PPI therapy, a single nonrandomized registry study comparing MSA to laparoscopic fundoplication, single-arm cohort studies, and systematic reviews of observational studies comparing MSA to LNF. Relevant outcomes are symptoms, change in disease status, medication use, and treatment-related morbidity. A RCT comparing MSA to omeprazole 20 mg twice daily found significantly more patients who received MSA reported improvements in symptoms and QOL at 6 months. A major limitation of the trial was that the patients had not received optimal medical treatment prior to enrollment. A prospective, observational registry study comparing MSA to laparoscopic fundoplication found similar improvements in QOL, satisfaction, and medication use. Limitations of the study included lack of randomization and blinding, heterogeneity in fundoplication techniques, use of an outdated MSA protocol, and selection bias as patients with less severe symptoms received MSA. In the 2 single-arm, uncontrolled pivotal trials submitted to the FDA with materials for device approval, subjects showed improvements in GERD-health-related QOL scores and reduced PPI use. Similarly, observational comparative studies included in systematic reviews, most often comparing MSA with LNF, generally have shown that GERD-health-related QOL scores do not differ significantly between fundoplication and MSA, and patients can reduce PPI use after MSA. However, the comparative studies are retrospective and nonrandomized, and may be affected by selection bias. Randomized comparisons of MSA with LNF are needed to evaluate the relative risk-benefit of these 2 procedures. The evidence is insufficient to determine that the technology results in an improvement in the net health outcomes.

Radiofrequency Treatment

Clinical Context and Therapy Purpose
The purpose of endoscopic radiofrequency energy (e.g., Stretta) is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with GERD.

The question addressed in this evidence review is: Does the use of endoscopic radiofrequency energy improve the net health outcomes in individuals with GERD?

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is individuals with GERD.

Interventions
The therapy being considered is endoscopic radiofrequency energy (e.g., Stretta).

Comparators
The following therapies and practices are currently being used to treat GERD: PPI therapy and laparoscopic fundoplication.

Outcomes
The general outcomes of interest are symptoms, change in disease status, QOL, medication use, and treatment-related morbidity.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.

In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.

To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.

(2021) Xie et al. published a systematic review and network meta-analysis of 10 RCTs that evaluated the comparative effects of Stretta, TIF, and PPIs in patients with GERD, Of the included RCTs, 5 compared Stretta to control (PPI or sham + PPI) and 5 compared TIF to control (PPI or sham + PPI). Results of the network meta-analysis revealed that improvements in the health-related quality of lifes core induced by Stretta were not significantly different than the improvements seen with TIF (mean difference [MD], 2.45; 95% CI, -2.37 to 7.26); however, both Stretta and TIF were significantly superior to PPIs. Additionally, both Stretta and TIF were significantly better than PPIs at improving heartburn scores. With regard to reduction in PPI use and esophagitis incidence, no significant differences between TIF and Stretta were observed. This network meta-analysis had several limitations including a lack of assessment of long-term efficacy, the inclusion of only 10 studies with even fewer studies evaluated for each individual outcome, and lack of RCTs directly comparing Stretta and TIF. Additionally, some of the comparisons were significantly affected by heterogeneity and the evidence quality of each outcome (as assessed by GRADE) ranged from moderate to very low.

(2020) Zerbib et al. published a double-blind RCT that compared Stretta plus PPI therapy (n=29) to sham plus PPI therapy (n=33) in individuals with PPI-refractory heartburn from 8 French centers. The primary endpoint was clinical success at week 24, defined as an intake of fewer than 7 PPI doses over the previous 2 weeks and adequate subjective patient-reported symptom control. Fewer patients achieved the primary endpoint in the Stretta group, but the difference was not statistically significant (3.4% vs. 15.1%; odds ratio [OR]=0.20; 95% CI, 0.02 to 1.88). Severe adverse events were more frequent in the Stretta group (7 vs. 2) and included epigastric pain (n=3), delayed gastric emptying, vomiting, headache, and 1 leiomyoma. Limitations of this RCT include that

pH-impedance monitoring was not performed either at enrollment or during follow-up. Thus, baseline status of GERD diagnosis is unclear and the physiologic effects of Stretta are unknown.

(2019) Viswanath et al. reported a prospective case series of 50 patients who underwent endoscopic antireflux radiofrequency treatment **(Stretta)** for refractory gastroesophageal reflux disease (GORD), Assessment involved the use of the Gastroesophageal Reflux Disease-Health-Related Quality of Life (GERD-HRQL) questionnaire, which evaluated symptoms and proton pump inhibitor (PPI) dependency, before and after treatment. Median follow-up post treatment was 771 days. The average GERD-HRQL score improved from 46.2/75 (±14.2) before Stretta treatment to 15.2/75 (±17.3) after Stretta treatment. The authors concluded that in select patients with GORD, Stretta improves quality of life and decreases PPI dependency, and is a viable option for patients who are unwilling or unable to undergo surgery. The also concluded that randomized controlled trials with larger patient populations are needed to further assess Stretta. Limitations of this study include lack of concurrent comparison group, its small numbers and that the pre-Stretta assessments were carried out by a variety of teams thus the potential for inconsistencies.

(2017) Fass et al. conducted a systematic review and meta-analysis of randomized controlled and cohort studies to determine the efficacy of the **Stretta** procedure in treating patients with GERD. Twenty-eight studies (4 RCTs, 23 cohort studies, and 1 registry) representing 2468 unique Stretta patients were included in the meta-analysis. The (unweighted) mean follow-up time for the 28 studies was 25.4 [14.0, 36.7] months. The pooled results showed that the Stretta reduced (improved) the health-related quality of life score by -14.6 [-16.48, -12.73] ($P < 0.001$). Stretta also reduced (improved) the pooled heartburn standardized score by -1.53 [-1.97, -1.09] ($P < 0.001$). After Stretta treatment, only 49% of the patients using proton pump inhibitors (PPIs) at baseline required PPIs at follow-up ($P < 0.001$). The Stretta treatment reduced the incidence of erosive esophagitis by 24% ($P < 0.001$) and reduced esophageal acid exposure by a mean of -3.01 [-3.72, -2.30] ($P < 0.001$). Lower esophageal sphincter (LES) basal pressure was increased post Stretta therapy by a mean of 1.73 [-0.29, 3.74] mmHg (P = NS). The authors concluded that the Stretta procedure significantly improves subjective and objective clinical endpoints, except LES basal pressure, and therefore should be considered as a viable alternative in managing GERD. Longer-term outcomes are needed to further evaluate the Stretta procedure. (Author Dugher et al. (2014) and Noar et al. (2014) which were previously cited in this policy are included in Fass et al. (2107) meta-analysis).

(2017) Kalapala et al. reported short outcomes (3 months) from a prospective randomized study comparing the **Stretta** treatment with controls receiving proton pump inhibitors (PPIs). Patients (n = 20) with symptoms of heartburn, regurgitation, abnormal esophageal acid exposure (≥ 4%), and endoscopically confirmed esophagitis were included into the study. The primary measure was improvement in quality of life (QOL) and decrease in the frequency and severity of GERD symptoms. The mean age of the patients was 39 (±

15) years and controls were 34 (± 11) years. Three months after Stretta, 80% reported improvement in QOL compared to 40% in the control group. At the end of 3 months, significant ($p < 0.05$) improvement in GERD symptom score for heartburn, regurgitation, chest pain, and cough compared with the control group was observed. After Stretta treatment, 60% of the patients were free of PPIs whereas there was no change in the control group. Almost 80% of the patients on Stretta treatment were satisfied with the treatment compared to 30% of the patients in the control group. The study was limited by the small sample size and short follow-up, therefore, randomized controlled trials with larger patient populations and longer follow-up periods are needed to further assess Stretta.

(2017) Noar et al. noted in a case series, prospectively assessed and compared patient-reported outcomes in 18 patients refractive to laparoscopic Nissen fundoplication (LNF) and 81 patients with gastrointestinal reflux disease (GERD) refractory to medical management that all underwent **Stretta** during 10-year follow-up. Patient-reported outcomes measured were GERD-HRQL (health-related quality of life), patient satisfaction scores, and daily medication requirements. The refractory LNF subset demonstrated median improvements in GERD-HRQL, satisfaction, and medication use at all follow-up time points ≥6 months to 10 years, which was significant from a baseline of both on- and off-medications ($p < 0.05$). Specifically, at 10 years, median GERD-HRQL decreased from 36 to 7 ($p < 0.001$), satisfaction increased from 1 to 4 ($p < 0.001$), and medication score decreased from 7 to 6 ($p = 0.040$). Nine patients decreased medication use by half at 10 years. No significant differences existed between refractory LNF and standard refractory GERD subsets at any follow-up time point ≥6 months to 10 years ($p > 0.05$) after Stretta. At 10 years, no significant differences were noted between refractory LNF and standard Stretta subsets regarding medication use ($p = 0.088$), patient satisfaction ($p = 0.573$), and GERD-HRQL ($p = 0.075$). Stretta procedures were completed without difficulty or significant intraoperative or long-term adverse events. The authors concluded that within a small cohort of refractory LNF patients, Stretta resulted in sustained improvement over 10 years with equivalent outcomes to non-LNF standard Stretta patients. Study limitations include lack of concurrent comparison group, non-randomization and small patient population.

A meta-analysis of 4 RCTs (N=165 patients) was published by Lipka et al. (2015). Three trials compared Stretta with sham, and 1 compared Stretta with PPI therapy. Results of the individual sham-controlled trials were inconsistent, generally supporting some improvement in symptoms, but not in objective measures of esophageal acid exposure. For example, Corley et al (2003) reported improvements in heartburn symptoms, QOL, and general physical QOL in the active treatment group compared with the sham group, but there were no significant differences in medication use or esophageal acid exposure. Aziz et al (2010) found statistically significant improvements in GERD-HRQL scores in all treatment groups. Arts et al (2012) reported that the symptom score and quality-of-life score for bodily pain improved, but no changes were observed in PPI use, esophageal acid exposure, or lower esophageal sphincter pressure after radiofrequency. Pooled results of the meta-analysis showed no significant differences between Stretta and either

sham treatment or PPI management for the measured outcomes, including the ability to stop PPI therapy. The overall quality of evidence was considered to be very low with a high risk of bias, and the meta-analysis was limited by heterogeneity in the included studies, which might have been due to small sample sizes, differences in measures, and differences in follow-up times.

Controlled Trials Comparing Transesophageal Radiofrequency With Laparoscopic Fundoplication

(2020) Ma et al. reported on a retrospective comparison of laparoscopic Toupet fundoplication with the Stretta procedure, GERD relapse was the primary endpoint. The 2 groups were comparable at baseline in demographic characteristics, body mass index, GERD family history, and comorbid hypertension, coronary disease, and diabetes. Two patients in each group were lost to follow-up and excluded from the final analyses. At 12 months, there were no statistically significant differences between the laparoscopic Toupet fundoplication and Stretta groups in GERD relapse (0 vs. 1.4%; p=.744), reflux outcomes (e.g., reflux time [hours]: 1.7 vs. 2.0; p=.390), dysphagia (2.3% vs. 5.7%; p=.486), bloating (Table 18), diarrhea (2.3% vs. 4.3%; p=.792), or chronic stomach pain (2.3% vs. 4.3%; p=.792). However, compared to laparoscopic Toupet fundoplication, the Stretta group had a high DeMeester score (8.8 vs. 7.3; p<.05) and less lower esophageal sphincter pressure (11.6 vs 12.8 mmHg; p<.05). Important limitations of this study are its single-center design and short follow-up time.

(2015) Liang et al. reported on a prospective comparison of laparoscopic Toupet fundoplication with the Stretta procedure, Of 165 patients treated, 125 (76%) completed the 3-year follow-up (65 fundoplications, 60 Stretta) and were included in the analysis. Although the 2 groups were comparable in symptoms at baseline, 9 patients in the Stretta group had revised treatment and were not included in the final symptom scores. A similar percentage of remaining patients in the 2 groups achieved complete PPI independence and had similar improvements in belching, hiccup, cough, and asthma. The Stretta procedure was less effective than laparoscopic fundoplication in reducing symptoms of heartburn, regurgitation, and chest pain. Significantly more patients in the Stretta group underwent reoperation, while more patients in the fundoplication group complained of bloating, but this difference was not statistically significant. This study lacked randomization and, along with not reporting the transesophageal radiofrequency (TERF) failures, had a high loss to follow-up. Also, while symptom scores were comparable at baseline, the study might have been subject to selection bias related to treatment choice, which affected baseline differences for other variables.

UpToDate: Radiofrequency Treatment for Gastroesophageal Reflux Disease (GERD)

(2021) Long-term studies — Studies with long-term follow-up have found radiofrequency treatment to be effective. The durability of radiofrequency treatment was assessed in 26 patients who were followed for eight years. At eight years, 77 percent of patients were completely off PPIs. In a study with 217 patients with refractory GERD who underwent RF treatment, normalization of GERD health-related quality of life (the

primary outcome) was seen in 72 percent of patients at 10 years. Secondary outcomes were 50 percent reduction or elimination of PPIs, and 60 percent or greater improvement in satisfaction at 10 years. A 50 percent or greater reduction in PPI use occurred in 64 percent of patients (41 percent eliminating PPIs entirely), and a 60 percent or greater increase in satisfaction occurred in 54 percent of patients. A prospective study evaluated the outcomes of 138 patients with refractory GERD who were followed for five years after RF treatment. At the end of the five-year follow-up, all symptom scores (heartburn, regurgitation, chest pain, cough, and asthma) had decreased. In addition, 59 patients (43 percent) achieved complete PPI therapy independence, and 104 patients (75 percent) were completely or partially satisfied with their GERD symptom control. In a case series including 50 patients who were followed for a median of 771 days, radiofrequency treatment was associated with improvement in post-procedure GERD-HRQL scores.

Comparison with surgical treatment — Studies have compared RF treatment with fundoplication for the treatment of GERD with variable results:

- One group stratified patients to either endoscopic therapy or laparoscopic fundoplication. Patients were offered RF treatment if they did not have a hiatal hernia greater than 2 cm, had a lower esophageal pressure of at least 8 mmHg, and did not have Barrett's esophagus. At six months, the quality-of-life scores were similar in both groups, and both groups were satisfied with their procedures (89 percent of RF treated patients and 96 percent of fundoplication patients). Fifty-eight percent of RF patients and 97 percent of fundoplication patients were off proton pump inhibitors (PPI) and an additional 31 percent of RF patients had reduced their PPI dose significantly.
- In a non-randomized cohort of 32 patients referred to a surgical practice who underwent RF treatment with an average follow-up of 53 months, 19 patients (59 percent) subsequently required anti-reflux surgery. Those not undergoing surgery showed a significant improvement in their GERD satisfaction scores from 3.1 to 1.5 but had significantly lower pre-procedure heartburn scores (2.4) than those who proceeded to surgery. The RF treatment was effective in reducing symptoms in 40 percent of patients.
- A non-randomized study prospectively evaluated outcomes of 215 patients with refractory GERD five years after laparoscopic Nissen fundoplication (LNF) or RF treatment. At the end of the five-year follow-up, the post-treatment symptoms scores for regurgitation, heartburn, chest pain, belching, hiccup, cough, and asthma were lower compared with the pre-treatment scores in both groups. However, the symptom improvements after RF treatment were lower than those after LNF. After LNF, 81 patients (91 percent) achieved complete PPI therapy independence, compared with 47 patients (51 percent) after RF treatment.
- In an observational study including 226 patients with GERD, there were no significant differences in acid exposure time at one year following radiofrequency treatment (Stretta) compared with Toupet fundoplication [26]. However, radiofrequency treatment was associated with higher post-procedure DeMeester score and lower LES pressure compared with fundoplication.

Section Summary: Transesophageal Radiofrequency
Six RCTs (n range, 20 to 64 patients), 4 of which were sham-controlled, reported some improvements in symptoms following treatment with TERF. However, measures of esophageal acid exposure were typically not improved. Also, meta-analyses of 4 of these same studies found no significant improvements in outcomes. The findings of improvements in symptoms but not esophageal acid exposure have led to questions about whether TERF is acting by reducing sensation in the esophagus. Although single-arm studies have shown maintenance of symptom relief at 5 to 10 years, the interpretation depends on the efficacy of the procedure in the short term. Nonrandomized comparative studies have suggested that clinical success and symptom relief with TERF is lower than with fundoplication and there is a greater incidence of reoperations and severe adverse events. Larger RCTs with longer follow-up are needed to define the risks and benefits of this procedure with greater certainty.

Transoral Incisionless Fundoplication for Symptoms Controlled by Proton Pump Inhibitors

Clinical Context and Therapy Purpose
The purpose of TIF (e.g., EsophyX; MUSE) is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with GERD and hiatal hernias of 2 cm or less controlled by PPIs.

The question addressed in this evidence review is: Does TIF using the EsophyX System improve the net health outcomes in individuals with GERD?

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is individuals with GERD and hiatal hernias of 2 cm or less controlled by PPIs.

Interventions
The therapy being considered is TIF (e.g., EsophyX).

Comparators
The following therapy is currently being used to treat GERD: PPI therapy.

Outcomes
The general outcomes of interest are symptoms, change in disease status, QOL, medication use, and treatment-related morbidity. Follow-up at 2, 3, and 6 years is of interest to monitor outcomes.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.

In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.

To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.

Review of Evidence
Randomized Trials
Two published RCTs have evaluated the efficacy of TIF in patients whose symptoms were adequately controlled on PPIs, but who were considering an intervention over lifelong drug dependence. Hakansson et al. (2015) compared TIF (n=22) with sham only (n=22). The expected outcome in the sham group was that, without PPIs, GERD symptoms would eventually recur. Witteman et al. (2015) compared TIF (n=40) with continued PPI therapy (n=20) without a sham procedure, The objective was to demonstrate that outcomes with TIF were not significantly worse than those with continued PPI therapy.

The primary outcome of the Hakansson et al. (2015) trial was treatment failure, defined as the need to resume PPIs. The primary outcome of the Witteman et al. (2015) trial was treatment success, defined by an improvement of 50% or more on the GERD-HQRL score.

In Hakansson et al. (2015), Kaplan-Meier curves showed a higher rate of treatment failure in the sham group than in the TIF group ($p<.001$, time to treatment failure), with significantly more patients in the TIF group in remission at 6 months (59%) compared with the sham without PPI group (18%, $p=.01$). In Witteman et al. (2015), PPI therapy was stepped up or down as necessary during follow-up. At 6 months, 55% of TIF patients had more than a 50% improvement in subjective GERD symptoms versus 5% of patients on continued PPI therapy. Mean change in GERD symptoms from baseline was consistent with this result (TIF, -14.1; control, -3.1); however, it is uncertain whether the difference between groups was due to a combination of TIF plus PPI, or if the PPI therapy in the control group was at maximum following the step-up protocol.

Secondary outcomes measuring GERD symptoms in the Hakansson et al. (2015) trial showed results consistent with more favorable outcomes in the TIF group. However, no statistical between-group analysis was reported for these outcomes. Dysphagia, bloating, and flatulence were reported in twice as many patients undergoing TIF (4, 4, and 2, respectively) compared with sham (2, 2, and 1, respectively). These results were reported as not statistically different. However, it is unlikely that the trial was powered to detect differences in these outcomes.

In the trial by Witteman et al. (2015), 26% of TIF patients resumed at least occasional PPI use by 6 months, and 100% of control patients remained on PPI therapy. With the exception of lower esophageal sphincter resting pressure, physiologic and endoscopic outcome measures did not differ significantly between groups. No adverse events related to fundoplication were identified on the Symptom Rating Scale.

TIF patients were followed beyond 6 months, with additional control patients who crossed over to have TIF. Sixty patients eventually underwent TIF. Although GERD symptoms remained improved over baseline ($p<.05$), esophageal acid exposure did not differ significantly from baseline. At least occasional use of PPI increased between 6 months and 12 months, from 34% to 61%. Endoscopy findings at 6 months and 12 months showed several findings indicating possible worsening of GERD in terms of esophagitis rating, Hill grade rating of the gastroesophageal valve, and size of a hiatal hernia. Although this RCT met its principal endpoint at 6 months and improvements in GERD symptoms appeared to be maintained for 12 months, long-term reflux control was not achieved, and the trialists concluded that "TIF is not an equivalent alternative for PPIs in GERD treatment, even in this highly selected population." The trial was originally designed as a dual-center study, but it was terminated following interim analysis showing loss of reflux control.

Observational Studies

Observational case series and prospective cohort studies can provide information on the durability of the TIF procedure. Studies were included if they provided additional information on treatment durability or addressed treatment safety.

A case series and a cohort study have evaluated outcomes to 6 years after TIF2.0. Both studies were performed in patients with hiatal hernias of 2 cm or less in size whose symptoms were adequately controlled on PPIs but did not want to take medication indefinitely. Stefanidis et al. (2017) reported on a retrospective series that about 75% of patients had the elimination of esophagitis and had discontinued PPI use at 5 years, while 62% of the 13 patients with hiatal hernias had a reduction in hernia size at follow-up.

In a prospective cohort by Testoni et al (2015, 2019), 72% of patients were completely responsive to PPIs at baseline, and 24% were partially responsive. Hiatal hernias had recurred by 12 months in 46% of the patients who had hernias at baseline, and at the 24-month follow-up, 20% of TIF2.0 procedures were considered unsuccessful. Nine percent of patients had additional surgery for poor response by 2 years. The Johnson-DeMeester score was not significantly improved. A poor response to treatment was associated with a hiatal hernia of 2 cm, higher Hill grade, the presence of esophagitis at baseline, and the use of fewer fasteners. About half the patients with a complete response initially resumed PPI use by 6 years and 20% had undergone additional surgery for a poor response, although these findings are limited by the low number of patients at follow-up. The number of fasteners used in this study might also be lower than current procedures.

Adverse Events
Huang et al. (2017) conducted a systematic review with a meta-analysis of TIF for the treatment of GERD. The authors included 5 RCTs and 13 prospective observational studies, of which 14 were performed with the TIF2.0 procedure. Efficacy results from the RCTs were combined for patients whose symptoms were controlled by PPIs and for those whose symptoms were not controlled by PPIs and are not further discussed here. The follow-up to 6 years in prospective observational studies indicated a decrease in efficacy over time. The reported incidence of severe adverse events, consisting of gastrointestinal perforation and bleeding, was 19 (2.4%) of 781 patients. This included 7 perforations, 5 cases of post-TIF bleeding, 4 cases of pneumothorax, 1 case requiring intravenous antibiotics, and 1 case of severe epigastric pain.

Transesophageal Endoscopic Fundoplication: EsophyX
(2016, Updated 2021) An ECRI reported the following information in relation to EsophyX in a Clinical Evidence Assessment: EsophyX® is an endoscopic surgical device intended for treating chronic gastroesophageal reflux disease (GERD) with transoral incisionless fundoplication (TIF). The report focuses on EsophyX's safety and effectiveness and how they compare with those of LNF or other GERD treatments.

EsophyX is safe and improves symptoms and quality of life (QOL) in most patients with persistent GERD symptoms despite PPI therapy, based on evidence from five systematic reviews (SRs). Unlike LNF, EsophyX allows an incisionless anatomic correction, but SRs with network meta-analysis assessed too few patients per comparison to determine how well it works compared with LNF or the Stretta® procedure. Network meta-analysis suggests that EsophyX is as effective as LINX® for improving QOL. (Somewhat favorable)

None of the SRs included studies that performed head-to-head comparisons between EsophyX and other GERD devices. All SRs reported high heterogeneity across studies for most outcomes and combined results from studies with widely differing follow-up times, thereby possibly combining outcomes for short-term and long-term follow-up.

Randomized controlled trials (RCTs) that directly compare EsophyX with other devices and procedures for treating GERD and report on long-term patient-oriented outcomes would be useful to support stronger conclusions. Ongoing trials may partially address this gap.

Transesophageal Endoscopic Fundoplication: MUSE
(2016) Kim et al. reported the initial 6-month data for MUSE™ (Medigus, Omer, Israel) endoscopic stapling device was reported (Zacherl et al. in Surg Endosc 29:220–229, 2015). The current study aims to evaluate the long-term clinical outcome of 37 patients who received endoscopic gastroesophageal reflux disease (GERD) treatment with the MUSE™ device.

Efficacy and safety data for 37 patients were analyzed at baseline, 6 months, and 4 years post-procedure. In one center (IU), efficacy and safety data were evaluated at baseline, 6 months post-procedure, and then annually up to 4 years. No new complications have been reported in our long-term analysis. The proportions of patients who remained off daily PPI were 83.8 % (31/37) at 6 months and 69.4 % (25/36) at 4 years post-procedure. GERD-Health Related Quality of Life (HRQL) scores (off PPI) were significantly decreased from baseline to 6 months and 4 years post-procedure. The daily dosage of GERD medications, measured as omeprazole equivalents (mean ± SD, mg), decreased from 66.1 ± 33.2 at baseline to 10.8 ± 15.9 at 6 months and 12.8 ± 19.4 at 4 years post-procedure ($P < 0.01$).

In our multi-center prospective study, the MUSE™ stapling device appears to be safe and effective in improving symptom scores as well as reducing PPI use in patients with GERD. These results appeared to be equal to or better than those of the other devices for endoluminal GERD therapy. Future studies with larger patient series, sham control group, and greater number of staples are awaited.

Transesophageal Endoscopic Fundoplication: SRS Endoscopic Stapling System
(2014) Danalioglu et al. noted the SRS Endoscopic Stapling System (Medigus Ltd, Omer, Israel) The present study assessed the safety and efficacy of SRS compared with laparoscopic anti-reflux surgery (LARS).

Of 27 participants, 11 underwent SRS and 16 LARS. Symptoms were assessed using Velanovich GERD-health-related quality of life (GERD-HRQL) scores. The groups were compared in reference to operation time, improvement in GERD-HRQL scores, and postoperative course. Chi-squared and Mann-Whitney-U-tests were used for statistical analysis. Of 16 (59.3%) male and 11 (40.7%) female patients, mean age was 39.6 (range: 24-60) years and mean body mass index was 26.2 kg/m(2). Both groups were statistically similar. An esophageal perforation observed in the SRS group completely recovered after over-the-scope clipping. Procedure times for SRSand LARS were 89 and 47 min, respectively ($P < 0.05$). Mean discharge time was longer for SRS than LARS (3 days vs 1.2 days, $P < 0.05$). However, this difference disappeared with the exclusion of a complicated patient with long hospitalization in the SRS group. During six months mean follow up, proton-pump inhibitor use was insignificantly higher in the SRS group ($P > 0.05$). Mean GERD-HRQL scores dropped in 87% and in 64% of patients ($P > 0.05$) from 29.3 to 4.1 and from 24.8 to 8.9 ($P = 0.016$) in LARS and SRS groups, respectively.

The short-term results of SRS are promising. The forthcoming new-generation devices and increasing experience may further improve efficacy and decrease untoward effects.

Section Summary: Transoral Incisionless Fundoplication for Symptoms Controlled by Proton Pump Inhibitors
The evidence on TIF in patients whose symptoms are controlled by PPIs includes 2 RCTs and observational studies with long-term follow-up. The sham-controlled trial by Hakansson et al. (2015) found the time to resume PPI therapy was longer following TIF

and the remission rate was higher, indicating that TIF is more effective than no therapy. The nonblinded trial by Witteman et al. (2015) found a benefit of TIF compared with continued PPI therapy for subjective measures, but not for the objective measures of pH normalization and esophagitis, raising questions about a possible placebo effect. Extended follow-up of the TIF patients in the Witteman trial found the use of PPI increased over time, while endoscopy showed several findings indicating possible worsening of GERD. The limited evidence beyond 2 years is consistent with some loss of treatment effectiveness. Increased use of PPIs beyond 2 years occurred in Testoni et al (2015). Adverse events associated with the procedure may be severe. Current evidence is insufficient to determine the effect of this intervention on the net health outcome in patients whose symptoms are adequately controlled by PPIs.

Transesophageal Endoscopic Suturing and Plication: OverStitch Endoscopic Suturing System

(2018) Han et al. completed a preliminary study was conducted to determine the feasibility and safety of endoscopic augmentation of the gastroesophageal junction (GEJ) using the Apollo OverStitch endoscopic suturing system in patients with gastroesophageal reflux disease (GERD) symptoms. Patients and methods Endoscopic augmentation of GEJ was performed on 10 consecutive patients and the data were analyzed retrospectively. Using a double channel gastroscope affixed to the endoscopic suturing platform, interrupted sutures were placed on the gastric side of the GEJ in two layers in order to create a narrowed and elongated GEJ.

Technical success was achieved in all patients, including those with a history of previous antireflux procedures (n = 7) and those with a hiatal hernia (n = 6). The median follow-up duration was five mo (range: 2 - 12). The median pre-procedure GERD-Health Related Quality of Life Questionnaire improved from 20 (range: 11 - 45) to a post-procedure score of 6 (range: 3 - 25) (P = 0.001). The median duration of GERD symptom improvement after the procedure was 1 mo (range: 0.5 - 4). Adverse events were limited to 1 patient who developed nausea and vomiting, which was self-limited.
The use of a novel endoscopic suturing technique for the treatment of GERD is feasible and safe. The procedure resulted in short-term GERD symptom improvement. Further prospective studies using refined techniques are currently underway to improve durability and to prove efficacy.

Transesophageal Endoscopic Suturing and Plication: EndoCinch

(2005) Schiefke et al. reported the aim of this study was to evaluate prospectively the long-term outcome after EndoCinch.

A total of 70 patients treated with EndoCinch at a single referral center were studied prospectively. All patients were interviewed using a standardized questionnaire regarding their symptoms and medication prior to and 18 months after EndoCinch. In addition, follow up included endoscopy, 24-hour pH monitoring, and esophageal manometry.

The procedure was well tolerated without major short- or long-term complications. Eighteen months after EndoCinch, 56/70 patients (80%) were considered treatment failures as their heartburn symptoms did not improve or proton pump inhibitor medication exceeded 50% of the initial dose. Endoscopy showed all sutures in situ in 12/70 (17%) patients while no remaining sutures could be detected in 18/70 (26%). In 54 and 50 patients examined, respectively, no significant changes in 24-hour pH monitoring (median pH <4/24 hours, 9.1% v 8.5%; p=0.82) or lower esophageal sphincter (LOS) pressure (7.7 v 10.3 mm Hg; p=0.051) were observed while median LOS length slightly increased (3.0 to 3.2 cm; p<0.05). Endoscopic gastroplication (EndoCinch) is a safe and minimally invasive endoscopic treatment for GORD with reasonable short-term results. In contrast, long term outcome is disappointing, probably due to suture loss in the majority of patients. Therefore, technical improvements to ensure suture durability are mandatory before endoscopic suturing can evolve as a therapeutic option for GORD treatment.

Transesophageal Endoscopic Suturing and Plication: GERDx System

(2021) Kalapala et al. reported the majority of endoscopic antireflux procedures for GERD are cumbersome to use and randomized long-term data are sparse. We conducted such a trial to determine the efficacy and safety of a novel, easy to use endoscopic full-thickness fundoplication (EFTP) device in patients with GERD. Patients with proton pump inhibitor (PPI)-dependent GERD were randomized to either EFTP or a sham procedure in 1:1 ratio. The primary endpoint was ≥50% improvement in the health-related quality of life (GERD-HRQL) score at 3 months. Secondary end points included improvement in GERD-HRQL, reflux symptom scores, PPI usage, oesophageal acid exposure and reflux episodes and endoscopic findings at 3, 6 and 12 months.

Seventy patients were randomized: 35 in each group with a median (IQR) age of 36 (29–42) years, 71.4% males. 70% had non-erosive reflux disease on endoscopy with a mean DeMeester score of 18.9 (±19.93). The mean (±SD) duration of EFTP procedure was 17.4 (±4) min. The primary end point was more frequently achieved in the EFTP group (65.7% vs 2.9%; p<0.001). Median (IQR) % improvement in GERD-HRQL was significantly higher in the EFTP group at 6 (81.4 (60.9–100.0) versus 8.0 (2.2–21.6); p<0.001) and 12 (92.3 (84.4–100.0) versus 9.1 (4.8–36.0); p<0.001) months. In the EFTP group, 62.8% patients were off-PPI at 12 months compared with 11.4% in the sham group (p<0.001). pH-metry parameters partially improved at 3 months, (n=70; total reflux episodes in EFTP arm and non-acid reflux episodes for EFTP vs sham) but not at 12 months (n=27); endoscopic esophagitis was seen in 0% in the treatment (n=18) and 5 (29.4%) in the control group (n=17) at 12 months. No major procedure-related adverse events were encountered in either group. EFTP using a novel device is safe and effective in improving quality of life in patients with PPI dependent mostly non-erosive reflux disease at short and long terms; objective parameters showed a limited response rate.

Transesophageal Endoscopic Suturing and Plication: NDO Surgical Endoscopic Plication System

(2007) Pleskow et al. reported the purpose of the present study was to assess the long-term safety and durability of effect for endoscopic full-thickness plication for the treatment of symptomatic gastroesophageal reflux disease (GERD). The Plicator (NDO Surgical, Inc., Mansfield, MA) used delivers a transmural suture through the gastric cardia to restructure the antireflux barrier. Published reports have shown the Plicator procedure to be effective in reducing GERD symptoms and medication use at 1-year post-plication.

Twenty-nine patients with chronic heartburn requiring maintenance daily anti-secretory therapy were treated at five sites. Patients received a single full-thickness plication in the gastric cardia 1 cm below the gastroesophageal junction (GE) junction. Re-treatments were not permitted. Patients were evaluated at baseline for GERD symptoms and medication use. Intermediate (12 month) and long-term subject follow-up (median follow-up: 36.4 months; range, 31.2-43.9 months) were completed to evaluate procedure safety and durability of effect.

Twenty-nine patients completed the 12-month and 36-month follow-up. All procedure-related adverse events occurred acutely, and no new events were observed during extended follow-up. At 36-months post-procedure, 57% (16/28) of baseline proton pump inhibitor (PPI)-dependent patients remained off daily PPI therapy. Treatment effect remained stable from 12- to 36-months, with 21/29 patients off daily PPI at 12 months compared to 17/29 patients at 36-months. Median GERD- Health Related Quality of Life (HRQL) scores remained significantly improved at 36 months versus baseline off-meds scores (8 versus 19, $p < 0.001$). In addition, the proportion of patients achieving > or = 50% improvement in GERD-HRQL score was consistent from 12 months (59%) to 36 months (55%). Endoscopic full-thickness plication can reduce GERD symptoms and medication use for at least 3-years post-procedure. Treatment effect is stable from 1 to 3 years, and there are no long-term procedural adverse effects.

Upper Esophageal Sphincter Assist Device

(2018) Yadlapati et al. completed a prospective single-center pragmatic exploratory clinical trial was conducted from 9/2015–3/2017, approved by the Northwestern Institutional Review Board (STU#00201370;8/24/2015), and registered with clinicaltrials.gov (NCT#02552966). The study included adult patients experiencing ≥1 month of laryngeal complaints (e.g., throat clearing, sore throat, dysphonia, cough, globus) with a reflux symptom index (RSI) score ≥13. Exclusion criteria included pregnancy, inability to consent in English, active imprisonment, altered mental status and preexisting conditions preventing UESAD use per manufacturer guidelines. Proton pump inhibitor use was permitted if not initiated or modified within four weeks of study initiation.

The 20-day study protocol included a baseline assessment, an intervention period during which subjects wore the UESAD over 14 consecutive nights, and a post-intervention

assessment. At each assessment participants completed three validated patient-reported questionnaires (RSI3, GerdQ4, and the Nocturnal GERD Symptom Severity & Impact Questionnaire [N-GSSIQ]5) and provided three consecutive fasting salivary samples which were analyzed via Peptest™ (RD Biomed Ltd) to quantify pepsin concentration. The primary outcome was symptom response measured by the RSI. Participants were categorized into three responder groups (complete responder: >50% reduction from baseline RSI and post-intervention RSI<13; partial responder: reduction from baseline RSI, not meeting criteria for complete response; non-responder: no reduction from baseline RSI). The secondary outcomes included change in GerdQ, N-GSSIQ, and salivary pepsin.

Of 20 enrolled subjects: 3 withdrew due to poor tolerance, two were lost to follow-up, and 15 were included in the final analysis (mean age: 45.7±13.4 years, 60% female, and 60% on continued PPI). Compared to baseline, mean questionnaire scores significantly decreased following intervention (RSI: 26.0±7.8 vs 19.4±8.5, $p<0.01$; GerdQ: 10.4±2.1 vs 8.6±2.4, $p<0.01$; and N-GSSIQ 43.4±20.1 vs 26.8±20.8, $p<0.01$). Mean salivary pepsin concentrations did not significantly differ (146.5±172.7 vs 158.4±150.2 ng/mL, $p=0.61$). Responder type distribution was as follows: 29% complete responders, 58% partial responders, and 14% non-responders. Reduction in salivary pepsin was significantly greater among complete responders ($p<0.01$). While not statistically significant, mean age and body mass index were lower and baseline salivary pepsin higher among complete responders.

Current treatment options for RALS are limited and often ineffective. In this pilot clinical trial of 15 patients with suspected RALS use of the UESAD was associated with significant symptom improvement. Overall, the majority demonstrated a partial symptom response. Additionally, symptom improvement was associated with reductions in salivary pepsin.

These results suggest that the UESAD is an effective non-invasive therapeutic option for RALS. Furthermore, the salivary pepsin data is thought provoking. Reductions in pepsin appear to track with symptom response, and in this study significant reductions in salivary pepsin were only seen among complete responders. This suggests that patients with complete response and reduction in pepsin likely had RALS and derived an actual benefit with the UESAD whereas patients reporting symptom response without a reduction in pepsin may be experiencing a placebo effect. Although the sample size in this study is small, particularly when comparing responder groups, the sample size is similar to other previously published studies and abstracts, and trends seen in this study are sufficiently hypothesis generating. Future work is needed to assess the long-term physiologic responses to the UESAD and the potential placebo response to the UESAD. In conclusion, the UESAD is a potentially effective therapeutic tool for RALS, and salivary pepsin may be a reliable diagnostic and prognostic biomarker of RALS. The UESAD should be considered and further examined as a treatment tool for this difficult to manage patient population.

(2016) Slivers et al. noted patients with Reflux Symptom Index (RSI) >13 were enrolled. The device was fit and adjusted to at least 20 mmHg applied external cricoid pressure. The primary effectiveness endpoint was reduction in RSI at 4-weeks compared to baseline. 36-Item Short Form Health Survey or SF-36® Health Survey (SF-36), patient and physician satisfaction, and Functional Outcomes of Sleep Questionnaire (FOSQ) were secondary endpoints. Safety was based on reported adverse reactions.

Eighty-nine of 95 patients completed the study [mean (Standard Deviation (SD)) age=48.8(+/-13.7); mean (SD) Body Mass Index (BMI)=25.5(+/-4.2); 69.5% female, 81.1% Caucasian]. Most common troublesome symptoms included chronic cough (21.3%) and excess mucus/postnasal drip (20.2%). There was a significant ($p<0.0001$) reduction in median (Intelligence Quotient (IQ)) RSI at 2- and 4-weeks [12.5(8.0-20.0) and 10.0(5.8-16.5), respectively] compared to baseline [25.6(21.0-30.0)]. Eighty-two percent (82%) reported improvement greater than 25% with 30.1% having an improvement of 75% or more. 84.7% of patients and 95.2% of providers reported satisfaction. Adverse events were generally mild and transient with no withdrawals due to adverse events. Limitations might include the uncontrolled and non-randomized nature of the study. However, plans are in place to address these limitations within future trials. Overall, our findings are unique and provide alternative treatment options for patients with suspected extraesophageal reflux based on physiologically confirmed mechanisms. The UES Assist Device resulted in significant symptom improvement within two weeks which was sustained for the duration of the study at four weeks. In conclusion, the study showed that the UES Assist Device is a safe and effective non-invasive method for the treatment of extraesophageal symptoms. Given the poor response to PPI therapy in many such patients this device may serve as a potential alternative for this difficult to treat group of patients. Future controlled studies will further validate the importance of this device in this group of difficult to treat patient population.

Summary of Evidence

For individuals who have gastroesophageal reflux disease (GERD) several minimally invasive alternatives have been developed to alter either the lower esophagus or upper stomach to create a barrier from reflux of stomach contents into the esophagus. The evidence includes systematic reviews, randomized controlled trials (RCTs) and case series. Relevant outcomes are symptoms, change in disease status, quality of life (QOL), medication use, and treatment-related morbidity. While some RCTs reported some improvements in symptoms and QOL, meta- analysis of these RCTs found no significant improvements in outcomes, raising the questions about the mechanisms of the symptom relief. Further well-designed comparative trials are needed to include the use of standardized outcome measures to examine the subjective improvement (e.g., discontinuation of medication therapy, Gastroesophageal Reflux Disease Health-Related Quality of Life Scores) to support objective improvement (e.g., esophageal acid exposure. The evidence is insufficient to determine the effects of the technology on health outcomes.

Note: *(2020) An ECRI custom product brief on the LINX® Reflux Management System for treating GERD identified a review of evidence from 2017 through 2020 that included two systematic reviews, one randomized control trial, one retrospective pre-post study and two economic studies. It was concluded longer follow-up and comparisons of LINX with other GERD devices would be useful and there are currently three ongoing trials that may partially address these evidence gaps.*

Practice Guidelines and Position Statements

American Gastroenterological Association (AGA)
(March 2022) The American Gastroenterological Association (AGA) issued updated guidelines for the diagnosis and management of gastroesophageal reflux disease which included the following recommendations:

Surgical and Endoscopic Options for GERD

Recommendation	GRADE Quality of Evidence	GRADE Strength of Recommendation
We recommend antireflux surgery performed by an experienced surgeon as an option for long-term treatment of patients with objective evidence of GERD. Those who have severe reflux esophagitis (LA grade C or D), large hiatal hernias, and/or persistent, troublesome GERD symptoms who are likely to benefit most from surgery.	Moderate	Strong
We recommend consideration of magnetic sphincter augmentation (MSA) as an alternative to laparoscopic fundoplication for patients with regurgitation who fail medical management.	Moderate	Strong
We recommend consideration of RYGB as an option to treat GERD in obese patients who are candidates for this procedure and who are willing to accept its risks and requirements for lifestyle alterations.	Low	Conditional
Because data on the efficacy of radiofrequency energy (Stretta) as an antireflux procedure is inconsistent and highly variable, we cannot recommend its use as an alternative to medical or surgical antireflux therapies.	Low	Conditional
We suggest consideration of TIF for patients with troublesome regurgitation or heartburn who do not wish to undergo antireflux surgery and who do not have severe reflux esophagitis (LA grade C or D) or hiatal hernias > 2 cm.	Low	Conditional

(*Accessed October 2022*)

American Society for Gastrointestinal Endoscopy (ASGE)
(2015) The American Society for Gastrointestinal Endoscopy (ASGE) Standards of Practice Committee noted, "Endoluminal antireflux techniques represent potentially new therapeutic indications for GI endoscopy. Prospective trials comparing these therapies with existing medical and surgical options by using objective measures of GERD as the primary endpoint could be useful in further defining the clinical role of these procedures. Appropriate patient selection and endoscopist experience and training should be carefully considered before pursuing these therapies" (*Accessed October 2022*)

American Society of General Surgeons (ASGS)
The ASGS released a position statement on Transoral Fundoplication. The ASGS supports the use of transoral fundoplication by trained General Surgeons for the treatment of symptomatic chronic gastroesophageal reflux disease (GERD) in patients who fail to achieve satisfactory response to a standard dose of Proton Pump Inhibitor (PPI) therapy or for those who wish to avoid the need for a lifetime of medication dependence. The purpose of surgical fundoplication is to reconstruct the biomechanics and physiology of the esophagogastric junction in order to prevent stomach contents from refluxing into the patient's esophagus. The General Surgeon has a choice on how to achieve a surgical fundoplication – open incisional, laparoscopic or transoral. Transoral fundoplication adheres to the same fundamental surgical principles, which have guided surgical care of GERD for more than 50 years. Specifically, a trained General Surgeon can create a full thickness esophagogastric fundoplication to correct an incompetent lower esophageal sphincter with a transoral approach.

During transoral fundoplication, a General Surgeon constructs an anterior partial fundoplication of 270-300 degrees by attaching the fundus to the anterior and left lateral wall of the distal esophagus slightly above the esophagogastric junction through full thickness plications using multiple fasteners around the gastroesophageal junction. In clinical studies, the transoral fundoplication procedure has been shown to offer comparable results to traditional open and laparoscopic approaches. Transoral fundoplication is also indicated to narrow the gastroesophageal junction and reduce hiatal hernia < 2 cm in patients with chronic GERD.

The ASGS continues to supports the adoption of this procedure by trained General Surgeons as a less invasive alternative to more conventional surgical techniques. However, ASGS believes that in patients who are candidates for fundoplication, the preferred surgical technique for creating the fundoplication should be left to the discretion of the General Surgeon and should be based on the surgeon's independent medical judgment and the individual patient's clinical circumstances." (*Accessed October 2022*)

National Institute for Health and Care Excellence (NICE)
(2013) NICE issued updated interventional procedure guidance in on endoscopic radiofrequency treatment for GERD, concluding: "The evidence on the safety of endoscopic radiofrequency ablation for gastroesophageal reflux disease is adequate in the

short and medium term but there is uncertainty about longer term outcomes. With regard to efficacy, there is evidence of symptomatic relief but objective evidence on reduction of reflux is inconclusive. Therefore, this procedure should only be used with special arrangements for clinical governance, consent and audit or research." The reviewing committee noted "concern on the part of some specialists about the possibility that symptoms may improve as a result of denervation caused by the procedure; if that were the case then failure to recognize and treat reflux might lead to complications in the long term." (*Accessed October 2022*)

The Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) (2017) Clinical Spotlight Review: Endoluminal Treatments for Gastroesophageal Reflux Disease (GERD)

- Based on existing evidence, TIF can be performed with an acceptable safety risk in appropriately selected patients. The procedure leads to better control of GERD symptoms compared with PPI treatment in the short term (6 months) but appears to lose effectiveness during longer term follow-up and is associated with moderate patient satisfaction scores. Objective GERD measures improve similarly after TIF 2.0 compared with PPI. No comparative, controlled trials exist between TIF and surgical fundoplication, but preliminary evidence suggests that the latter can be used safely after TIF failure. (Level of evidence +++, strong recommendation) (*Accessed October 2022*)

Regulatory Status
Currently, the Food and Drug Administration (FDA) has approved 510(k) marketing clearance for use in the treatment of GERD includes but is not limited to the following devices:

Device	Manufacturer	Description
Durasphere®	Coloplast Corporation	Durasphere® is a *bulking agent* approved for treatment of urinary and fecal incontinence. *Use of this product for esophageal reflux would be considered off-label use.*
EndoCinch™	CR Bard	EndoCinch™ is a suture technique for *partial-thickness plication* intended to improve the function of the sphincter near the gastroesophageal junction. A review of endoscopic treatment of GERD by Hummel and Richards (2015) noted that EndoCinch is no longer manufactured.

Enteryx™	Boston Scientific Corporation	Enteryx™ received FDA approval in 2003 through the premarket approval process for the treatment of symptomatic GERD. However, in September 2005, Boston Scientific Corporation issued a recall due to the device polymerizing shortly after injection into a spongy material that cannot be removed. Serious adverse events involved unrecognized transmural injections of Enteryx™ into structures surrounding the esophagus, potentially resulting in serious injury or death.
EsophyX®/ EsophyX2 HD/ EsophyX Z	EndoGastric Solutions, Inc.	*Transoral Incisionless Fundoplication* (TIF) ® with EsophyX® is a less *invasive procedure* performed to construct an antireflux valve and tighten the lower esophageal sphincter. The intended outcomes include creating a sufficient reflux barrier and improving the integrity of the gastroesophageal junction for patients with GERD.
GERDx™	G-SURG	GERDx™ is an endoscopic *full-thickness plication* device that uses hydraulic elements for controlling. This device does not have FDA approval at this time.
Inert Polymers or polymethylmethacrylate (PMMA) beads	_____	A PMMA bead implant contain polymethylmethacrylate used as a submucosal injection of the microspheres into the lower esophageal folds to decrease the severity of symptoms and acid reflux in patients with GERD.
LINX™ Reflux Management System	Torax® Medical	In 2012, the LINX® Reflux Management System (Torax Medical) was approved by the U.S. Food and Drug Administration (FDA) through the premarket approval process (P100049) for patients diagnosed with GERD, as defined by abnormal pH testing, and who continue to have chronic GERD symptoms despite maximal therapy for the treatment of reflux. The FDA initially required a 5-year follow-up of 100 patients from the investigational device exemption pivotal study to evaluate the safety and efficacy of the device, which was

		completed in March 2016. In 2018, the manufacturer initiated a device recall due to a possible separation of the bead component with the adjacent wire link causing a potential discontinuous or open LINX device. This recall was terminated on November 4, 2020. FDA product code: LEI. In March 2018, the FDA approved an update of the LINX® Reflux Management System precautions statement, stating that the use of the system "in patients with a hiatal hernia larger than 3 cm should include hiatal hernia repair to reduce the hernia to less than 3 cm and that the LINX Reflux Management System has not been evaluated in patients with an unrepaired hiatal hernia greater than 3 cm, add a hiatal hernia clinical data summary in the instructions for use, update the instructions for use section to highlight the recommendation to repair a hiatal hernia, if present, at the time of the LINX Reflux Management System implantation, and update the patient information booklet to align with the instructions for use and include 5 year clinical study results."
Medigus Ultrasonic Surgical Endostapler (MUSE™ System)	Medigus	MUSE is intended for endoscopic placement of *surgical staples* in the soft tissue of the esophagus and stomach to create *anterior partial fundiplication* for treatment of symptomatic chronic GERD in patients who require and respond to pharmacologic therapy.
NDO Plicator™	Ethicon Endo-Surgery	NDO Plicator™ is an endoluminal therapy intended for *full thickness plication* to restore the valvular mechanism of the gastroesophageal junction
OverStitch™	Apollo Endosurgery	Endoscopic suturing system to allow placement of sutures and approximation of soft tissue
Reza Band™		Designed to prevent the reflux of gastric contents into the laryngopharynx. It is a non-pharmacologic non-surgical medical device

		worn while sleeping and applies a standardized external pressure to the cricoid cartilage in order to decrease retrograde reflux of gastroduodenal contents
Stretta®	Mederi Therapeutics	*Radiofrequency energy* is applied through four electrodes inserted into the esophageal wall at multiple sites both above and below the squamocolumnar junction for the treatment of GERD.
SRS Endoscopic Stapling System™	Medigus	An endoscopic method to rebuild the sphincter between the esophagus and the stomach creating a partial anterior fundoplication and helps restore the angle of His to help treat GERD.
The Gatekeeper Reflux Repair System™	Medtronic	The Gatekeeper Reflux Repair System utilizes a soft, pliable, expandable prosthesis made of a polyacrylonitrile-based hydrogel. The prosthesis is implanted into the esophageal submucosa and with time the prosthesis absorbs water and expands, creating bulk in the region of implantation. **Voluntarily withdrawn by the manufacturer in 2005*

PRIOR APPROVAL

Not applicable.

POLICY

See Related Medical Policies

- 02.01.63 Endoscopic Radiofrequency Ablation or Cryoablation for Barrett Esophagus
- 02.04.81 Biomarker Testing for Barrett's Esophagus and Other Esophageal Disorders
- 02.01.66 Confocal Laser Endomicroscopy

The following procedures for the treatment of gastroesophageal reflux disease (GERD) are considered **investigational** to include, but not limited to the following because evidence is insufficient to determine that the technology results in an improvement in the net health outcomes:

- Endoscopic submucosal implantation or injection of a bulking agent, including, but not limited to:

    - Ethylene-vinyl alcohol (e.g., Enteryx)
    - Zirconium oxide spheres (e.g., Durasphere GR)
    - Gatekeeper Reflux Repair System
    - Plexiglass or polymethylmethacrylate (PMMA) beads
- Gastric Bypass Roux-en-Y (RYGBP) (open or laparoscopic)
- Magnetic esophageal ring, including, but not limited to:
    - LINX Reflux Management System
- Transesophageal radiofrequency ablation, including, but not limited to:
    - Stretta Therapy, Stretta® System
- Transesophageal endoscopic fundoplication, including, but not limited to:
    - A transoral incisionless fundoplication (TIF) using EsophyX, EsophyX2, EsophyX2 HD, EsophyX Z
    - MUSE System
    - SRS Endoscopic Stapling System
- Transesophageal endoscopic suturing and plication, including, but not limited to:
    - ~~o~~ OverStitch Endoscopic Suturing System
    - GERDx System
    - NDO Surgical Endoscopic Plication System, NDO Plicator
- Upper Esophageal Sphincter Assist Device
    - Reza Band

PROCEDURE CODES AND BILLING GUIDELINES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnosis codes.

- 43192 Esophagoscopy, rigid, transoral; with directed submucosal injection(s), any substance
- 43201 Esophagoscopy, flexible, transoral; with directed submucosal injection(s), any substance
- 43210 Esophagogastroduodenoscopy, flexible, transoral; with esophagogastric fundoplasty, partial or complete, includes duodenoscopy when performed
- 43212 Esophagoscopy, flexible, transoral; with placement of endoscopic stent (includes pre- and post-dilation and guide wire passage, when performed)
- 43236 Esophagogastroduodenoscopy, flexible, transoral, diagnostic, including collection of specimen(s) by brushing or washing, when performed: with directed submucosal injection(s), any substance.
- 43257 Upper gastrointestinal endoscopy including esophagus, stomach, and either the duodenum and/or jejunum, as appropriate; with delivery of thermal energy to the muscle of lower esophageal sphincter and/or gastric cardia, for treatment of gastroesophageal reflux disease
- 43284 Laparoscopy, surgical, esophageal sphincter augmentation procedure, placement of sphincter augmentation device (i.e., magnetic band), including cruroplasty when performed

- 43285 Removal of esophageal sphincter augmentation device
- 43289 Unlisted laparoscopy procedure, esophagus
- 43499 Unlisted procedure, esophagus
- 43644 - Laparoscopy, surgical, gastric restrictive procedure; with gastric bypass and Roux-en-Y gastroenterostomy (roux limb 150 cm or less)
- 43645 - Laparoscopy, surgical, gastric restrictive procedure; with gastric bypass and small intestine reconstruction to limit absorption
- 43659 Unlisted laparoscopy procedure, stomach
- 43846 - Gastric restrictive procedure, with gastric bypass for morbid obesity; with short limb (150 cm or less) Roux-en-Y gastroenterostomy
- 43847 - Gastric restrictive procedure, with gastric bypass for morbid obesity; with small intestine reconstruction to limit absorption
- 43999 Unlisted procedure, stomach
- C9724 Endoscopic full-thickness plication in the gastric cardia using endoscopic plication system (EPS); includes endoscopy.
- E1399 Durable medical equipment, Miscellaneous

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POLICY HISTORY		
Date	**Reason**	**Action**
October 2022	Annual Review	Policy Revised
October 2021	Annual Review	Policy Revised
October 2020	Annual Review	Policy Revised
November 2019	Annual Review	Policy Revised
October 2018	Annual Review	Policy Revised
October 2017	Annual Review	Policy Revised
October 2016	Annual Review	Policy Revised
October 2015	Annual Review	Policy Revised
November 2014	Annual Review	Policy Revised
January 2014	Annual Review	Policy Revised
July 2013	Annual Review	Policy Renewed
August 2012	Annual Review	Policy Renewed
December 2010	Interim Review/EsophyX®	Policy Revised

New information or technology that would be relevant for Wellmark to consider when this policy is next reviewed may be submitted to:

Wellmark Blue Cross and Blue Shield
Medical Policy Analyst
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