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Medical Policy Manual Surgery, Policy No. 110

Transesophageal Endoscopic Therapies for Gastroesophageal Reflux Disease (GERD)

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IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Transesophageal endoscopic therapies are a group of minimally invasive antireflux procedures being investigated as alternatives to medical management or fundoplication surgery in the treatment of GERD.

MEDICAL POLICY CRITERIA

Transesophageal endoscopic therapies are considered **investigational** for the treatment of gastroesophageal reflux disease (GERD). These procedures include but are not limited to the following:

I. Transesophageal endoscopic gastroplasty procedure (i.e., MUSE)
II. Transoral incisionless fundoplication (TIF) procedure, (i.e., EsophyX)
III. Transesophageal radiofrequency energy procedure (i.e., Stretta)
IV. Endoscopic submucosal implantation of a prosthesis or injection of a bulking agent (i.e., Durasphere, polymethylmethacrylate [PMMA] beads, the Gatekeeper Reflux Repair system)

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

CROSS REFERENCES

1. Bariatric Surgery, Surgery, Policy No. 58
2. Gastric Reflux Surgery, Surgery, Policy No. 186
3. Magnetic Esophageal Ring to Treat Gastroesophageal Reflux Disease (GERD), Surgery, Policy No. 190

BACKGROUND

Gastroesophageal reflux disease (GERD) is a common disorder characterized by heartburn and other symptoms related to reflux of stomach acid into the esophagus. Nearly all individuals experience such symptoms at some point in their lives; a smaller number have chronic symptoms and are at risk for complications of GERD. The prevalence of GERD has been estimated to be 10% to 20% in the Western world, with a lower prevalence in Asia.[1]

The pathophysiology of GERD involves excessive exposure to stomach acid, which occurs for several reasons. There can be an incompetent barrier between the esophagus and stomach, either due to dysfunction of the lower esophageal sphincter (LES) or incompetence of the diaphragm. Another mechanism is abnormally slow clearance of stomach acid by the esophagus. In this situation, delayed clearance leads to an increased reservoir of stomach acid and a greater tendency to reflux.

In addition to troubling symptoms, some patients will have more serious disease, which results in complications such as erosive esophagitis, dysphagia, Barrett esophagus, and esophageal carcinoma. Pulmonary complications may result from aspiration of stomach acid into the lungs and can include asthma, pulmonary fibrosis and bronchitis, or symptoms of chronic hoarseness, cough, and sore throat.

Guidelines on the management of GERD emphasize initial medical management. Weight loss, smoking cessation, head of bed elevation, and elimination of food triggers are all recommended in recent practice guidelines.[1] Proton pump inhibitors (PPIs) have been shown to be the most effective medical treatment. In a Cochrane systematic review, PPIs demonstrated superiority to H_2-receptor agonists and prokinetics in both network meta-analyses and direct comparisons.[2]

The most common surgical procedure used for GERD remains laparoscopic Nissen fundoplication, however, the utilization of this procedure steadily declined between 2009 and 2013 with the advancement of novel nonmedical (endoscopic and surgical) techniques.[3] Fundoplication involves wrapping a portion of the gastric fundus around the distal esophagus to increase LES pressure. If a hiatal hernia is present, the procedure also restores the position of the LES to the correct location. Laparoscopic fundoplication was introduced in 1991 and has been rapidly adopted because it avoids complications associated with an open procedure.

Although fundoplication results in a high proportion of patients reporting symptom relief, complications can occur, and sometimes require conversion to an open procedure. Patients who have relief of symptoms of GERD after fundoplication may have dysphagia or gas-bloat syndrome (excessive gastrointestinal gas).

Due in part to the high prevalence of gastroesophageal reflux disease, there has been interest in creating a minimally invasive transesophageal therapeutic alternative to open or laparoscopic fundoplication or chronic medical therapy. This type of procedure may be

considered natural orifice transluminal surgery. Three types of procedures have been investigated.

1. Transesophageal endoscopic gastroplasty (gastroplication, transoral incisionless fundoplication) can be performed as an outpatient procedure. During this procedure, the fundus of the stomach is folded, and then held in place with staples or fasteners that are deployed by the device. The endoscopic procedure is designed to recreate a valve and barrier to reflux.

2. Radiofrequency (RF) 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, RF energy is applied through four electrodes inserted into the esophageal wall at multiple sites both 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 and fibrosis.

3. Submucosal injection or implantation of a prosthetic or bulking agent to enhance the volume of the lower esophageal sphincter has also been investigated.

One bulking agent, pyrolytic carbon-coated zirconium oxide spheres (Durasphere®), has been evaluated. The Gatekeeper™ Reflux Repair System (Medtronic) 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. However, the only identified RCT on this system was terminated early due to lack of efficacy (NCT00200044). Endoscopic submucosal implantation of polymethylmethacrylate (PMMA) beads into the lower esophageal folds has also been investigated.

REGULATORY STATUS

In 2007, EsophyX® (EndoGastric Solutions, Redmond, WA) was cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process for full-thickness plication. In 2016, EsophyX® Z Device with SerosaFuse Fasteners was cleared for marketing (K160960) by FDA through the 510(k) process for use in transoral tissue approximation, full thickness plication, ligation in the gastrointestinal tract, narrowing the gastroesophageal junction, and reduction of hiatal hernia of 2 cm or less in patients with symptomatic chronic gastroesophageal reflux disease (GERD).[4] In June 2017, EsophyX2 HD and the third-generation EsophyX Z Devices with SerosaFuse fasteners and accessories were cleared for marketing by FDA through the 510(k) process (K171307) for expanded indications, including patients who require and respond to pharmacologic therapy and in patients with hiatal hernias larger than 2 cm when a laparoscopic hiatal hernia repair reduces the hernia to 2 cm or less.[5] FDA product code: ODE.

The Medigus SRS Endoscopic Stapling System (MUSE, Medigus) was cleared for marketing by FDA through the 510(k) process in 2012 (K120299) and 2014 (K132151). MUSE is intended for endoscopic placement of surgical staples in the soft tissue of the esophagus and stomach to create anterior partial fundoplication for treatment of symptomatic chronic GERD in patients who require and respond to pharmacologic therapy. FDA product code: ODE.

In 2000, the CSM Stretta® System was cleared for marketing by FDA through the 510(k) process for general use in the electrosurgical coagulation of tissue and is specifically intended for use in the treatment of GERD. Stretta® is currently manufactured by Mederi Therapeutics (Greenwich, CT). FDA product code: GEI.

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. The website of Carbon Medical Technologies states that Durasphere GR is an investigational device in the United States "intended to treat problems associated with GERD."

EVIDENCE SUMMARY

MULTIPLE ENDOSCOPIC PROCEDURES

Systematic Reviews

A 2005 report of the Agency for Healthcare Research and Quality (AHRQ), on "Comparative Effectiveness of Management Strategies for Gastroesophageal Reflux Disease," indicated additional efficacy and safety data on new endoscopic approaches were needed.[6] A 2011 update of the AHRQ report excluded Enteryx and the NDO Plicator, since they were no longer available in the U.S., and added the EsophyX procedure (endoscopic fundoplication), which was commercialized after the 2005 review.[7] The 2011 update reported the following:

> The AHRQ report concluded that for the 3 available endoscopic procedures (EndoCinch, Stretta, EsophyX), effectiveness remains substantially uncertain for the long-term management of GERD. While some clinical benefits were observed in patients who had these procedures, the studies were generally small, of variable quality, and of short duration. In addition, all of these procedures have been associated with complications, including dysphagia, infection/fever, and bloating; complications which are also side effects associated with laparoscopic fundoplication[8] Higher quality studies are needed to determine the role and value of endoscopic procedures in the treatment of patients with GERD. A 2015 review of endoscopic treatment of GERD noted that EndoCinch is no longer manufactured.[9]

A systematic review was conducted in 2009 to examine 7 endoscopic treatments for GERD that included 33 studies, only 2 of which were RCTs.[10] The remainder were case series. The authors concluded, "…despite the potential benefits of these procedures, there is insufficient evidence at present to establish their safety and efficacy, particularly in the long term."

TRANSESOPHAGEAL ENDOSCOPIC GASTROPLASTY AND TRANSORAL INCISIONLESS FUNDOPLICATION (TIF)

Systematic Reviews

Haseeb (2023) conducted a systematic review and meta-analysis that assessed the efficacy of TIF, using the EsophyX device, which uses a minimally invasive endoscopic fundoplication method, for atypical GERD symptoms in patients with chronic or refractory GERD.[11] All study types were included that assessed atypical GERD using the reflux symptom index questionnaire. Data on TIF with concomitant hiatal hernia repair were also included. 10 studies (n=564 patients) were analyzed. At 6- and 12- month follow-up, there was a mean reduction of 15.72 (95% confidence interval, 12.15 to 19.29) and 14.73 (95% confidence interval, 11.74 to 17.72) points, respectively, in the reflux symptom index score post-TIF. At both follow-ups,

more than two-thirds of patients were satisfied with their health condition and approximately three-fourths of patients were no longer taking daily proton pump inhibitors. Limitations of this meta-analysis include heterogeneity across studies for self-reported patient satisfaction and methodological quality of included studies.

Testoni (2021) published a systematic review with meta-analysis focusing on long-term (≥3 years) outcomes of patients with GERD undergoing TIF (using either EsophyX or MUSE).[12] Outcomes of interest included patient satisfaction, QOL, and PPI use. The mean follow-up time across studies was 5.3 years (range: 3 to 10 years). Daily PPI use was 100% in five studies, 97% in one study, and was not provided in the other two studies. Overall, the pooled proportion of patient-reported satisfaction before and after TIF was 12.3% and 70.6%, respectively. Additionally, the pooled rates of patients completely off, or on occasional, PPIs post-TIF was 53.8% and 75.8%. The analysis was limited by various factors including the nature of included studies, which involved only one open-label RCT among the eight studies included, and the high heterogeneity across studies for patient reported overall satisfaction after the TIF procedure.

McCarty (2018) published a systematic review of RCTs and nonrandomized studies that showed significant improvement in a number of clinical outcomes for patients treated with TIF.[13] For example, 89% of TIF patients discontinued PPI therapy after the procedure, and the Gastroesophageal Reflux Disease Health-Related Quality of Life (GERD-HRQL) questionnaire, Gastroesophageal Reflux Symptom Score, and Reflux Symptom Index (RSI) measures showed significant improvement. The review had several limitations, including the risk of heterogeneity bias, due to the inclusion of studies of first- and second-generation TIF devices and protocols.

Richter (2018) published a network meta-analysis of RCTs comparing TIF or laparoscopic Nissen fundoplication (LNF) with sham or PPIs.[14] The meta-analysis was limited by low-quality studies (one did not report randomization method, others lacked data on allocation concealment, blinding of outcome assessors, or other aspects of study protocol). It should be noted that a reason behind for scarcity of direct comparisons between TIF and LNF is the discrepancy in populations requiring the respective treatments: consequently, TIF studies included patients with mild esophagitis and small hiatal hernias (<2 cm), while LNF studies included patients with Los Angeles grade A, B, C, or D esophagitis and all sizes of hiatal hernias.

Randomized Controlled Trials

In 2018, Trad reported five-year outcomes on the manufacturer-sponsored TEMPO randomized controlled trial (RCT).[15] Three-year results were reported in 2016[16], other interim results were previously reported as well.[17, 18] Below are highlights from each publication:

- Participants with small or absent hiatal hernias (<2cm) and GERD symptoms while on PPI therapy for at least six months who also had abnormal esophageal acid exposure (EAE) were randomized to either EsophyX® (n=40) treatment or PPI therapy (n=23). After six months of evaluation, 21 remaining PPI therapy participants elected to crossover to EsophyX.
- At three years follow-up, 52 participants were assessed for (1) GERD symptom resolution, (2) healing of esophagitis using endoscopy, (3) EAE, and (4) discontinuation of PPI use. Two participants required revision surgery. As assessed by questionnaire

(the Reflux Disease Questionnaire [RDQ], and the Reflux Symptom Index [RSI]), primary outcomes of GERD resolution and elimination of all troublesome atypical symptoms was observed in 37/40 participants, and 42/48 participants, respectively.

- At five years follow-up, data were available for 44 patients, of whom 37 (86%) showed elimination of troublesome regurgitation at 5 years. Twenty (43%) patients were completely off PPIs at the 5-year follow-up, and 31 (70%) patients expressed satisfaction with the procedure, as assessed by the GERD-HRQL scores. While data on pH normalization were available for 24 patients at the 3-year follow-up, at 5 years, 22% (n=5) of these patients could not be assessed for pH normalization.
- Although mean symptom scores were reportedly improved, standard deviations for primary (and secondary) outcomes suggest a wide range of responses and further well-designed studies may be warranted.

In 2015, four RCTs that compared the EsophyX® device to proton pump inhibitor (PPI) treatment or to a sham control were identified, two of which were industry sponsored. The studies differed in whether patients' symptoms were or were not controlled on PPI therapy, in the control used (i.e., sham, sham plus PPI, PPI alone), whether patients were blinded to treatment, and in outcome measures. Included in the studies were patients on daily PPI therapy for moderate-to-severe GERD symptoms. Exclusion criteria common to the RCTs are body mass index (BMI) over 35 kg/m^2, hiatal hernia greater than 2 cm; esophagitis grade C or D; Barrett esophagus greater than 2 cm, and esophageal ulcer. Most studies allowed crossover to the other intervention with continued follow-up after the randomized portion of the study.

The largest RCT with the lowest risk of bias was an industry-sponsored, double-blind, sham-controlled multicenter study (RESPECT) that evaluated TIF in patients whose symptoms were not well controlled on PPIs.[19] Of 696 patients screened, 129 met inclusion and exclusion criteria and were randomized in a 2:1 ratio; 87 patients received TIF with EsophyX®-2 combined with 6 months of placebo (TIF/placebo) and 42 patients received sham surgery with 6 months of daily PPI therapy (sham/PPI). The primary outcome measure was elimination of troublesome regurgitation, defined as mild symptoms for 2 or more days per week or moderate-to-severe symptoms for more than 1 day per week. Crossover was allowed at 3 months in the case of treatment failure or at 6 months when the blind was broken. Lack of response at 3 months was observed in 36% of patients in the sham/PPI group compared with 11% in the TIF/placebo group (p=0.002). Self-reported regurgitation was eliminated in 22% more patients following TIF compared to continued PPI therapy patients (67% vs 45%, p=0.023), while reductions in GERD symptoms scores were similar in the 2 groups. The objective measure of control of esophageal pH was significantly reduced after TIF (mean percent time esophageal pH <4 decreased from 9.3% to 6.3%, p<0.001), but not after sham surgery (from 8.6% to 8.9%). By the 18-month follow-up, 71% of patients in the sham/PPI group had crossed over to TIF, compared with 28% of patients in the TIF/placebo group who resumed PPI therapy (p<0.001). There were 5 moderate-to-severe complications in the TIF group compared to one in the sham group. Strengths of this study include the use of both sham surgery and placebo control to maintain double-blinding, adequate power, objective as well as subjective outcome measures, and use of intention-to-treat analysis. A limitation is the relatively short duration of follow-up for most outcome measures.

Several other RCTs from 2015 have evaluated TIF in patients whose symptoms are at least partially controlled by PPI therapy.

Hakonsson reported a double-blind, sham-controlled randomized trial with 44 patients who had moderate-to-severe GERD symptoms without PPI therapy.[20] Controls received a sham procedure, and the primary outcome was the time in remission, which was longer following TIF than sham (197 days vs 107 days, p<0.0001). Secondary outcomes measuring GERD symptoms 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 were reported as not statistically different, however, it is unlikely that the study was powered to detect differences in these outcomes.

Witteman reported an unplanned interim analysis of an RCT of 60 patients randomized to TIF using EsophyX®-2 or continued PPI therapy.[21] Sixty of the planned 120 patients had been recruited at the time of analysis. The patients' symptoms were adequately controlled by PPIs but they wanted to avoid lifelong PPI therapy. At 6 months, subjective GERD symptoms improved to a greater extent in the TIF group (p<0.001), and satisfaction scores were higher (50% satisfied vs 0%), but there was no significant difference in esophageal acid exposure (p=0.228) or pH normalization (50% vs 63%) between the TIF and PPI groups, respectively. At 12 months after TIF, normalization of pH was achieved in only 29% of patients and there was deteriorated valve appearance at endoscopy; 61% of TIF patients had resumed use of PPIs.

Trad reported 6- and 12-month results of an industry-funded, multicenter RCT (TEMPO) that compared TIF using EsophyX®-2 (n=40) versus maximal dose PPI therapy (n=23) in partial responders to PPI therapy.[17, 18] At the 6-month follow-up, the subjective measure of troublesome regurgitation was eliminated in 97% of TIF patients versus 50% of PPI patients (relative risk, 1.9; p=0.006). At 6 months, 90% of patients in the TIF group had completely stopped PPI therapy. However, the objective measure of normalized esophageal acid exposure did not differ significantly between groups (TIF=54% vs PPI=52%, p=0.914). At 12 months after TIF, 77% of patients had symptom control, 82% had stopped PPI therapy, 100% had healed esophagitis, and 45% had normalized esophageal acid exposure.

Additional controlled trials (RCTs) comparing transesophageal endoscopic gastroplasty or plication procedures to sham or other endoscopic procedures have been identified.[18, 22-27] Though these studies showed a promising decrease in PPI use and symptom control at 3 to 12 months, they do not allow conclusions regarding long-term health outcomes, safety or durability of the procedure in patients with GERD for one or more of the following reasons:

Insufficient study durations – Only short-term follow-up of 3 to 12 months is available, which does not address the long-term safety and durability of the procedures.[18, 23-28] For example, there may be suture loss over time. One study reported up to 29 % of study subjects required a second procedure at 12-month follow-up.[23] Of these patients, 72% of sutures were still present but only 19% were judged functional. A second study noted marked loss of sutures with 67% remaining at 12 months.[25]

Small sample size – Given the prevalence of GERD in the general population, available randomized trials include very small sample sizes. The largest study of 159 patients had an almost 10% loss in reported data with an intention to treat analysis that did not include these patients. All other studies include sample sizes of 60 or fewer patients. It is unclear if these studies are adequately powered.[18, 23, 25-29]

Unreliable endpoints – The use of subjective, point in time GERD questionnaires as a primary endpoint may give variable results depending upon symptoms present at the time the subject completes the questionnaire.[18, 23, 24]

Improvement over the gold standard procedures was not demonstrated. In order to establish the efficacy of transoral procedures, an improvement in symptoms of gastric reflux over the current open or laparoscopic anti-reflux procedures, must be shown.[18, 27, 29]

There is a single randomized trial of the TIF procedure, which compares TIF to Nissen laparoscopic fundoplication.[28] Although the authors reported comparable results at 12 months, conclusions based upon this trial are limited by the small sample size (n=52) and the different methods used for TIF (both the Plicator® and the EsophyX).

Nonrandomized Studies

Observational studies[30-63], registry data[64, 65] nonrandomized comparative studies[66] of gastroplication and fundoplication (specifically, transoral incisionless fundoplication) procedures do not allow conclusions about their long-term effectiveness and durability.

Case Series

Bell (2021) evaluated the durability of TIF with the EsophyX2 in 151 patients via a single institution prospective registry between November 2008 and July 2015.[62] Of these patients, the average duration of GERD symptoms was 11.3 years and 78% reported moderate to severe ongoing symptoms preoperatively despite PPI therapy. Eighty-six percent (n=131) were available for follow-up at a median of 4.92 years (0.7 to 9.7 years). Results revealed a reduction in the median GERD-HRQL scores from 21 (off PPI) and 14 (on PPI) at baseline to 4 (at 4.92 years) and 5 (at 5 to 9 years post-TIF). A successful (>50%) reduction in GERD-HRQL score at 4.92 years was seen in 64% of evaluable patients and 68% of patients followed for ≥5 years. Thirty-three (22%) of TIP patients underwent laparoscopic revisional surgery at a median of 14.7 months after surgery. Approximately 70% of patients remained free of daily PPI use throughout follow-up. The authors concluded that TIF provides durable relief of GERD symptoms for up to 9 years with a significant portion of patients having a successful outcome by symptom response and PPI use.

Harms

Although harms are not systematically reported across observational studies, there have been several publications on potential harms of TIF procedures.

Ramai (2021) published a report of complications associated with TIF from post-marketing surveillance data from the FDA Manufacturer and User Facility Device Experience (MAUDE) database from Jan 2011 through Jan 2021.[67] During the period studied, approximately 95 event cases were reported to the FDA and approximately 131 patient complications were identified. The most common adverse events were perforation (19.8%), laceration 17.6%, bleeding (9.2%), and pleural effusion (9.2%). Patient complications were treated using endoscopic clips (12.3%), chest tube or drain insertion (12.3%), use of endoscopic retriever device (11.1%), esophageal stent (8.6%), and emergent or open surgery (11.1%).

Furnee reported an increased risk of gastric injury with laparoscopic Nissen fundoplication after failed EsophyX fundoplication.[68] Of 88 patients in their database who underwent EsophyX fundoplication, 11 (12.5%) subsequently underwent Nissen fundoplication for

persistent or recurrent symptoms at a mean 8.1 months after the primary procedure. Endoscopy showed partial or total disruption of fasteners in 8 of the 11 patients (72.7%). Nissen fundoplication after EsophyX resulted in gastric perforation (n=2), conversion to laparotomy (n=1), subphrenic abscess requiring surgical exploration (n=1) and symptom-worsening in four patients.

In 2017, Huang conducted a systematic review with meta-analysis of TIF for the treatment of GERD.[69] Authors included 5 RCTs and 13 prospective observational studies, of which 14 were performed with the TIF 2 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. Follow-up out to six 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%) out of 781 patients. This included seven perforations, five cases of post-TIF bleeding, four cases of pneumothorax, one case requiring intravenous antibiotics, and one case of severe epigastric pain.

TRANSESOPHAGEAL RADIOFREQUENCY ENERGY (I.E., THE STRETTA PROCEDURE)

Systematic Reviews

Xie (2021) 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.[70] Of the included RCTs, five compared Stretta to control (PPI or sham + PPI) and five compared TIF to control (PPI or sham + PPI). Results of the network meta-analysis revealed that improvements in the HRQoL score in patients treated 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 in this outcome. Additionally, both Stretta and TIF were significantly better than PPIs at improving heartburn scores. Regarding reduction in PPI use and esophagitis incidence, no significant difference between TIF and Stretta was 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.

Fass (2017) published a meta-analysis of cohort studies and RCTs evaluating the Stretta procedure for patients with GERD (N=2468 total, 9-558 per study).[71] The meta-analysis included 4 RCTs, 23 cohort studies, and one registry. Follow-up time varied from 3 to 120 months. When RCT and cohort results were pooled, there were clinically significant treatment effects for several of end points; however, the analysis was limited by the lack of control groups in many studies. Also, only 1 end point was shared between the four included RCTs.

A meta-analysis of four RCTs (total N=165 patients) was published by Lipka in 2015.[72] Three trials compared Stretta with sham, and one trial 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 (2008) reported improvement in heartburn symptoms, quality of life, and general physical quality of life in the active treatment group compared with the sham group, but there were no significant differences in medication use and esophageal acid exposure.[73] Aziz (2010) found

statistically significant improvements in GERD-HRQL in all treatment groups.[74] Arts (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 RF.[75] Pooled results of the meta-analysis showed no significant difference 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 may be due to small sample sizes, differences in measures, and differences in follow-up time.

A 2014 systematic review and meta-analysis of four randomized trials; three reviewed previously[73-75] and one trial which compared Stretta with PPI therapy,[76] included a total of 165 patients. The overall quality of the evidence was considered to be very low with a high risk of bias. The pooled results showed no significant difference between Stretta and sham or PPI management for the measured outcomes. The meta-analysis was limited by heterogeneity in the included studies, which may be due to small sample sizes, differences in measures, and differences in follow-up time. The author also identified significant risks associated with Stretta, including pneumonia, gastroparesis, esophageal perforation, cardiac arrest, and at least 4 deaths from review of the Manufacturer and User Facility Device Experience database.

A meta-analysis completed by Perry, included 20 studies, only 2 of which were RCTs. This meta-analysis was limited by the inclusion of lower quality studies and by the analysis, which only examined within-subject differences and did not include between-subject differences, as reported in the RCTs.[77]

Randomized Controlled Trials

Zerbib (2020) 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.[78] The primary endpoint was clinical success at week 24, defined as an intake of fewer than seven PPI doses over the previous two 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.

There are several randomized trials comparing transesophageal radiofrequency (RF) energy with a sham procedure that involved balloon inflation but no needle deployment or RF energy delivery.[73-75]

Results of the first study failed to include 20% of the randomized patients in analysis of primary endpoints, and no intention to treat analysis was provided. Therefore, reported results of improved heartburn symptoms and GERD quality of life scores are not reliable.

Results of the second, third and fourth studies were flawed due to a small patient population and inadequate timeframe for follow up.

Other small RCT's have been published. Two compared RF to PPI therapy. One trial showed promising short-term (6 months) results but does not permit conclusions about mid- to long-term effectiveness and durability.[76] Another compared RF with PPI therapy to PPI therapy alone.[79] Results at 3 months appeared favorable to the Stretta group, however, the study sample was small (N=20) and power calculations were not conducted.

Nonrandomized Studies

Other clinical studies concerning transesophageal radiofrequency are limited to observational case series that do not allow conclusions about long-term effectiveness and durability.[22, 80-92] Though several case series report up to 4-10 year outcomes, there was a significant loss to follow-up in these studies such that conclusions on durability and health outcomes cannot be made.[93]

INJECTION OR IMPLANTATION OF BIOCOMPATIBLE POLYMERS

Randomized Controlled Trials

The available evidence for the Gatekeeper Reflux Repair System consists of one RCT.[94] This industry-funded sham-controlled single-blind multicenter study randomized 118 patients into Gatekeeper (n=75) or sham (n=43) treatment. An additional 25 patients were treated as lead-ins during the initial training of investigators and included only in the safety analysis. The patients were implanted initially with 4 Gatekeeper prostheses. At three months, 44% of implanted patients received retreatment with up to four additional prostheses due to unsatisfactory symptom control. The primary safety end point was reduction in serious device- and procedure-related adverse device effects, compared with a surgical procedure composite complication rate of 15%. Four serious adverse events were reported (2 perforations, 1 pulmonary infiltrate related to a perforation, 1 severe chest pain). The primary efficacy end point was reduction in heartburn symptoms using the GERD-HRQL questionnaire. Planned interim analysis after 143 patients were enrolled found that heartburn symptoms and esophageal acid exposure had improved significantly in both the Gatekeeper and sham groups at six months, but there was no significant difference between the two groups. The study was terminated early due to a lack of efficacy.

There is one randomized sham-controlled trial which reports results of patients randomized to receive either injection of Enteryx biopolymer or a sham procedure.[95] At 3- and 6-months follow-up, patients in the Enteryx group had greater reductions in PPI use and more improvement in GERD health-related quality of life heartburn scores. However, the small size and short duration of the study limit interpretation of findings.

Nonrandomized Studies

Other data on injectable or implantable polymers consists of very small case series.[22, 96] The small number of patients and lack of long-term follow-up precludes scientific analysis.

PRACTICE GUIDELINE SUMMARY

Several clinical practice guidelines consider the use of transoral fundoplication or other endoscopic procedures, although none were able to recommend this treatment based upon high level evidence.

AMERICAN SOCIETY OF GENERAL SURGEONS

The American Society of General Surgeons (ASGS) consensus-based position statement on transoral fundoplication states, “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.”[97]

AMERICAN GASTROENTEROLOGICAL ASSOCIATION

The 2008 Medical Position Statement of the American Gastroenterological Association (AGA), makes no recommendation for or against “the use of currently commercially available endoluminal antireflux procedures in the management of patients with an esophageal syndrome” based on insufficient evidence (Grade Insufficient).[98]

AMERICAN COLLEGE OF GASTROENTEROLOGY

In 2022, the American College of Gastroenterology (ACG) released updated guidelines for the diagnosis and management of gastroesophageal reflux disease.[99] The guidelines state the following:

- 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 (conditional recommendation, low level of evidence).
- 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 (conditional recommendation, low level of evidence).
- For patients who have regurgitation as their primary PPI-refractory symptom and who have had abnormal gastroesophageal reflux documented by objective testing, we suggest consideration of antireflux surgery or TIF (conditional recommendation, low level of evidence).

SOCIETY OF AMERICAN GASTROINTESTINAL ENDOSCOPIC SURGEONS

In 2021, the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) published guidelines for the surgical treatment of gastroesophageal reflux (GERD).[100] Although several recommendations regarding fundoplication were provided, the guideline does not mention transesophageal endoscopic approaches.

In 2017, SAGES updated its evidence-based guidelines on endoluminal treatments for GERD.[101] SAGES gave a strong recommendation based on moderate quality evidence that TIF with EsophyX can be performed with an acceptable safety risk in selected patients. SAGES concluded that EsophyX results in better control of GERD symptoms compared with proton pump inhibitor (PPI) treatment in the short term (six months) but leads to similar improvement in objective GERD measures compared with PPIs. TIF appears to lose effectiveness during longer term follow-up and is associated with moderate patient satisfaction scores. SAGES found no comparative, controlled trials between TIF and surgical fundoplication, but preliminary evidence suggested that the surgical fundoplication can be used safely after TIF failure. SAGES gave a strong recommendation based on moderate quality evidence that Stretta is safe for adults and significantly improves health-related quality of life

score, heartburn scores, the incidence of esophagitis, and esophageal acid exposure in patients with GERD. Stretta is more effective than PPI, but less so than fundoplication.

SUMMARY

There is not enough research to show that transesophageal endoscopic therapies for the treatment of gastroesophageal reflux disease (GERD) improves health outcomes. Although clinical guidelines based on research may recommend treating GERD with one or more of the therapies mentioned, there is not enough research to know if or how well these procedures work to treat people with GERD. This does not mean that it does not work, but more research is needed to know. Therefore, the use of any of these procedures is considered investigational for the treatment of GERD.

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CODES

Codes	Number	Description
CPT	43192	Esophagoscopy; rigid, transoral; with directed submucosal injection(s), any substance

Codes	Number	Description
	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
	43236	Esophagogastroduodenoscopy, flexible, transoral, with direct submucosal injections, any substance
	43257	Esophagogastroduodenoscopy, flexible transoral; with deliver of thermal esophageal sphincter and/or gastric cardia, for treatment of gastroesophageal reflux disease
	43499	Unlisted procedure, esophagus
HCPCS	None	

Date of Origin: *February 2001*