Medical Policy

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Title: Transesophageal Endoscopic Therapies for Gastroesophageal Reflux Disease

Related Policies:	▪ *Endoscopic Radiofrequency Ablation or Cryoablation for Barrett Esophagus* ▪ *Injectable Bulking Agents for the Treatment of Urinary and Fecal Incontinence*

Professional / Institutional
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Populations	Interventions	Comparators	Outcomes
Individuals: • With gastroesophageal reflux disease and hiatal hernia ≤2 cm that is not controlled by proton pump inhibitors	Interventions of interest are: • Transoral incisionless fundoplication (e.g., EsophyX; MUSE)	Comparators of interest are: • Laparoscopic fundoplication	Relevant outcomes include: • Symptoms • Change in disease status • Quality of life • Medication use • Treatment-related morbidity

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Individuals: • With gastroesophageal reflux disease	Interventions of interest are: • Endoscopic radiofrequency energy (e.g., Stretta)	Comparators of interest are: • Proton pump inhibitor therapy • Laparoscopic fundoplication	Relevant outcomes include: • Symptoms • Change in disease status • Quality of life • Medication use • Treatment-related morbidity
Individuals: • With gastroesophageal reflux disease	Interventions of interest are: • Esophageal bulking agents	Comparators of interest are: • Proton pump inhibitor therapy • Laparoscopic fundoplication	Relevant outcomes include: • Symptoms • Change in disease status • Quality of life • Medication use • Treatment-related morbidity

DESCRIPTION

Transesophageal endoscopic therapies are being developed for the treatment of gastroesophageal reflux disease (GERD). A variety of procedures are being evaluated, including transesophageal (or transoral) incisionless fundoplication (TIF), application of radiofrequency energy, and injection/implantation of prosthetic devices or bulking agents.

OBJECTIVE

The objective of this evidence review is to determine whether transoral incisionless fundoplication, application of radiofrequency energy, or injection or implantation of prosthetic devices or bulking agents is an effective treatment for gastroesophageal reflux disease.

BACKGROUND

Gastroesophageal Reflux Disease

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,]

Pathophysiology
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 or incompetence of the diaphragm. Another mechanism is an abnormally slow clearance of stomach acid. 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 a 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.

Treatment
Guidelines on the management of GERD emphasize initial medical management. Weight loss, smoking cessation, head of the 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, van Pinxteren et al (2010) reported that PPIs demonstrated superiority to H_2-receptor antagonists and prokinetics in both network meta-analyses and direct comparisons.[2,]

Surgical Treatment
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 lower esophageal sphincter pressure. If a hiatal hernia is present, the procedure also restores the position of the lower esophageal sphincter 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).

Other Treatment Options
Due in part to the high prevalence of GERD, 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 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 4 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 the 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) used a soft, pliable, expandable prosthesis made of a polyacrylonitrile-based hydrogel. The prosthesis was implanted into the esophageal submucosa, and with time, the prosthesis absorbed water and expanded, creating bulk in the region of implantation. However, the only identified RCT was terminated early due to lack of efficacy and it was voluntarily withdrawn by the manufacturer. Endoscopic submucosal implantation of polymethylmethacrylate beads into the lower esophageal folds has also been investigated.

REGULATORY STATUS

The EsophyX® (EndoGastric Solutions) is a transesophageal (or transoral) incisionless fundoplication (TIF) device that was originally cleared for marketing by the FDA through the 510(k) process in 2007 and has subsequently undergone 2 evolutions: Generation 2=EsophyX2 iterations (E2-Plus, HD) and Generation 3=Z iterations (EZ/ZR, Z+).[4,] Some of the key Regulatory Status changes are summarized herein. In 2007, EsophyX® (EndoGastric Solutions) was cleared for marketing by the FDA through the 510(k) process for full-thickness plication. In 2016, EsophyX® Z Device with SerosaFuse Fasteners was cleared for marketing by the FDA through the 510(k) process (K160960) for use in transoral tissue approximation, full-thickness plication, ligation in the gastrointestinal tract, narrowing the gastroesophageal junction, and reduction of hiatal hernias of 2 cm or less in patients with symptomatic chronic GERD.[5,] In June 2017, EsophyX2 HD and the third-generation EsophyX Z Devices with SerosaFuse fasteners and accessories were cleared for marketing by the FDA through the 510(k) process (K171307) for expanded indications, including patients who require and respond to pharmacologic therapy and patients with hiatal hernias larger than 2 cm when a laparoscopic hiatal hernia repair reduces a hernia to 2 cm or less.[6,] The most recent FDA 510(k) clearance (K172811) occurred in October 2017 for new product specification iterations of EsophyX2 HD and EsophyX Z Devices. This clearance allows for "a moderate increase in the upper limit of the temporary Tissue Mold clamping pressure occurring during each fastener deployment."[7,] FDA product code: ODE.

The Medigus SRS Endoscopic Stapling System (MUSE, Medigus) was cleared for marketing by the 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 the 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 the FDA through the 510(k) process for general use in the electrosurgical coagulation of tissue and was specifically intended for use in the treatment of GERD. In 2010, Mederi Therapeutics began manufacturing the Stretta® device. Mederi was acquired by Respiratory Technology Corporation in 2018. FDA product code: GEI.

Durasphere® is a bulking agent approved for the 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 the Durasphere® GR product is "intended to treat problems associated with GERD" but is considered an investigational device in the U.S.

POLICY

A. Transoral incisionless fundoplication (TIF) (e.g., Esophyx; MUSE) is considered **experimental / investigational** as a treatment of gastroesophageal reflux disease.

B. Transesophageal radiofrequency to create submucosal thermal lesions of the gastroesophageal junction (i.e., Stretta procedure) is considered **experimental / investigational** as a treatment of gastroesophageal reflux disease.

C. Endoscopic submucosal implantation of a prosthesis or injection of a bulking agent (e.g., polymethylmethacrylate beads, zirconium oxide spheres) is considered **experimental / investigational** as a treatment of gastroesophageal reflux disease.

Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

RATIONALE

This evidence review has been updated regularly with searches of the PubMed database. The most recent literature update was performed through October 18, 2023.

This evidence review was informed, in part, by a TEC Assessment (2003) of transesophageal endoscopic treatments for gastroesophageal reflux disease (GERD) and an Evidence Street Assessment (2016) on transoral incisionless fundoplication (TIF).[8,] This review addresses procedures currently available for use in the U.S.

Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life (QOL), and ability to function including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, 2 domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent 1 or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. Randomized controlled trials are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA (Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations."

TRANSORAL INCISIONLESS FUNDOPLICATION FOR SYMPTOMS UNCONTROLLED BY PROTON PUMP INHIBITORS

Clinical Context and Therapy Purpose

The purpose of transoral incisionless fundoplication (TIF) (e.g., EsophyX; MUSE) is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with gastroesophageal reflux disease (GERD) and hiatal hernias of 2 cm or less not controlled by proton pump inhibitors (PPIs).

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

Populations

The relevant population of interest is individuals with GERD and a hiatal hernia of 2 cm or less uncontrolled by PPIs.

Interventions

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

Comparators

The following practice is currently being used to treat GERD: laparoscopic fundoplication.

Outcomes

The general outcomes of interest are symptoms, change in disease status, QOL, medication use, and treatment-related morbidity. Follow-up at 3 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.
- Studies with duplicative or overlapping populations were excluded.

REVIEW OF EVIDENCE

Systematic Reviews

McCarty et al (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.[9,] 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 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 et al (2018) published a network meta-analysis of RCTs comparing TIF or laparoscopic Nissen fundoplication (LNF) with sham or PPIs.[10,] The meta-analysis was limited by low-quality studies (1 did not report the 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 the 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.

Testoni et al (2021) published a systematic review and meta-analysis focusing on long-term (≥3 years) outcomes of patients with GERD undergoing TIF (using either EsophyX or MUSE).[11,] 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 5 studies, 97% in 1 study, and was not provided in the other 2 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 1 open-label RCT among the 8 studies included, and the high heterogeneity across studies for patient reported overall satisfaction after the TIF procedure.

Rausa et al (2023) published a network meta-analysis of RCTs comparing TIF (n=188) to anterior partial fundoplication (n=322), laparoscopic Toupet fundoplication (n=1120), laparoscopic Nissen fundoplication (n=1740), and PPI therapy (N=80) in patients with recalcitrant GERD.[12,] The outcomes of interest were differences in the rate of heartburn, regurgitation, dysphagia, bloating, and PPI discontinuation. TIF did not differ significantly from the other treatments in the pooled network analysis for any outcome. Treatment failure was not included in the quantitative analysis due to the considerable heterogeneity across studies.

Tables 1 and 2 summarize the characteristics and results of selected systematic reviews.

Table 1. Characteristics of Systematic Reviews

Study	Dates	Trials	Participants	N (Range)	Design	Duration
McCarty et al (2018)[9,]	2008-2016	32	Patients met standard criteria for the TIF procedure[a]	1475 (10 to 124)	5 RCTs, 21 prospective and 6 retrospective studies	NR
Richter et al (2018)[10,]	NR	7	Patients had GERD, established by endoscopic results indicating erosive	1128 (range NR)	2 RCTs (TIF vs. PPI); 2 RCTs (TIF vs. sham);	TIF: 6 to 12 mo LNF vs. PPI: 1 to 5 y

Study	Dates	Trials	Participants	N (Range)	Design	Duration
			esophagitis and/or abnormal ambulatory esophageal pH monitoring[b]		3 RCTs (LNF vs. PPI)	
Testoni et al (2021)[11,]	Inception to May 2020	8	Patients had refractory GERD and underwent a TIF procedure	418 (15 to 86)	1 RCT, 3 muticenter, prospective studies, and 4 single-center prospective studies	Median follow-up: 5.3 years (range , 3 to 10 years)
Rausa et al (2023)[12,]	Inception to April 2022	33	Patients with refractory GERD who underwent APF, LTF, LNF, or TIF	4382	33 RCTs	NR

APF: anterior partial fundoplication; GERD: gastroesophageal reflux disease; LNF: laparoscopic Nissen fundoplication; LTF: laparoscopic Toupet fundoplication; MSA: magnetic sphincter augmentation; NR: not reported; PPI: proton pump inhibitor; RCT: randomized controlled trial; TIF: transoral incisionless fundoplication.
[a] Body mass index <35 kg/m^2; hiatal hernia size ≤2 cm; grade A, B, or C esophagitis using the Los Angeles classification; no underlying esophageal motility disorder.
[b] DeMeester score >14.7 and/or percentage total time at a pH <4 of ≥4.0%.

Table 2. Results of Systematic Reviews

Study	Complete PPI Cessation	GERD-HRQL Score	GERSS	RSI Score	Other Objective Measures
					Esophageal Acid Exposure (% time with pH <4)
McCarty et al (2018)[9,]					
N	1407 (28 studies)	1236 (25 studies)	NR (6 studies)	NR (8 studies)	722 (15 studies)
% (95% CI)	89 (82 to 95)				
MD (95% CI)		17.72 (17.31 to 18.14)	23.78 (22.96 to 24.60)	14.28 (13.56 to 15.01)	3.43 (2.98 to 3.88)
p	<.001	<.001	<.001	<.001	<.001
I^2 (p)	93.6 (.00)	94 (<.001)	98 (<.001)	95 (<.001)	86 (<.001)
Mean follow-up (SD), mo	15.5 (14.6)				
		TIF-2 Subgroup			*TIF-2 Subgroup*
N		997 (15 studies)			

Study	Complete PPI Cessation	GERD-HRQL Score	GERSS	RSI Score	Other Objective Measures
MD (95% CI)		17.62 (17.19 to 18.05)			53.18 (49.49 to 56.87)
p		<.001			<.001
Richter et al (2018)[10,]					
N		• TIF=293 (4 studies) • LNF=875 (3 studies)			
OR (95% CrI)		TIF vs. LNF: 2.08 (0.71 to 6.09)			LNF vs. TIF: 0.08 (0.02 to 0.36)
Ranking probability (SUCRA)		• TIF=0.96 • LNF=0.66 • Sham=0.35 • PPI=0.042			• LNF=0.99 • PPI=0.64 • TIF=0.32 • Sham=0.05
Testoni et al (2021)[11,]					
	Patient Satisfaction with TIF (median %)	**PPI Use (pooled % off/occasional use)**		**Normalized Heartburn Scores (median pooled %)**	**Normalized Regurgitation Scores (median pooled %)**
After 3 years	74	53.5/73.8		68.6	79
After 4 to 5 years	86.2	57.5/76.4		86.2	87.1
After 8 years	78	34.4/91.7			
			GERD-HRQL (pooled estimated mean [95% CI])		
Before TIF (off PPI)			26.1 (21.5 to 30.7)		
After TIF (mean follow-up 5.3 years)			5.9 (0.35 to 11.4)		
p value			<.001		
Rausa et al (2023)[12,]					
	Heartburn RR (95% CrI)	**Regurgitation RR (95% CrI)**	**Dysphagia RR (95% CrI)**	**Bloating RR (95% CrI)**	**PPI Discontinuation RR (95% CrI)**

Study	Complete PPI Cessation	GERD-HRQL Score	GERSS	RSI Score	Other Objective Measures
TIF vs. LNF	0.76 (0.28 to 2.20)	0.80 (0.31 to 2.07)	0.47 (0.18 to 1.27)	0.65 (0.24 to 1.89)	
TIF vs. LTF	1 (0.32 to 3.28)	1.10 (0.36 to 3.24)	1.17 (0.46 to 1.97)	0.95 (0.32 to 2.97)	-0.45 (-3.6 to 2.8)
TIF vs. APF	0.51 (0.15 to 1.88)	0.65 (0.21 to 2.06)	0.35 (0.11 to 1.15)	0.70 (0.23 to 2.28)	
TIF vs. PPI	0.71 (0.32 to 1.57)	0.66 (0.35 to 1.38)	0.95 (0.46 to 1.97)	0.72 (0.35 to 1.54)	
Global heterogeneity (I^2)	53%	32%	36%	54%	85%

APF: anterior partial fundoplication; CI: confidence interval; CrI: credible interval; GERD-HRQL: Gastroesophageal Reflux Disease Health-Related Quality of Life questionnaire; GERSS: Gastroesophageal Reflux Symptom Score; LNF: laparoscopic Nissen fundoplication; MD: mean difference; NR: not reported; OR: odds ratio; PPI: proton pump inhibitor; RR: relative risk; RSI: Reflux Symptom Index; SD: standard deviation; SUCRA: surface under the cumulative ranking curve; TIF: transoral incisionless fundoplication.

Randomized Controlled Trials

Two RCTs (the RESPECT and TEMPO trials) have evaluated TIF using EsophyX2 in patients with troublesome symptoms despite daily PPI therapy (Table 3). Hunter et al (2015) compared treatment using TIF2.0 plus placebo pills (n=87) with treatment using sham TIF plus PPIs (n=42) in the RESPECT trial.[13,] Increases in medication (placebo or PPI depending on treatment group) were allowed at 2 weeks. At 3 months, patients with continued troublesome symptoms were declared early treatment failures and failed TIF patients were given PPI and failed sham patients were offered TIF. Trad et al (2015) compared TIF2.0 (n=40) with maximum PPI therapy (n=23) without a sham procedure in the TEMPO trial.[14,] The primary outcome in both trials was the elimination of symptoms, measured in slightly different ways (Table 3).

In both trials, the primary outcome was achieved by a higher percentage of patients treated with TIF than with PPIs (Table 4). Elimination of symptoms was reported by 62% to 67% of patients treated by TIF compared with 5% of patients treated with maximum PPIs and 45% of patients who had a sham procedure plus PPIs (p=.023). In TEMPO, the relative risk of achieving the primary outcome was 12.9 (95% confidence interval [CI], 1.9 to 88.9; p<.001).

Secondary outcomes for the RESPECT trial showed no significant differences between treatments, except for Reflux Disease Questionnaire scores, which showed significant improvement in the TIF group compared with baseline. Physiologic measurements such as the number of reflux episodes, percentage of total time pH less than 4, and DeMeester score (a composite score of acid exposure based on esophageal monitoring) showed statistically significant differences between groups, but these measurements were performed when off PPIs for 7 days and the difference in pH between TIF and continued PPI therapy cannot be determined from this trial.

In TEMPO, self-reported troublesome regurgitation was eliminated in 97% (29/30) of TIF patients who were off PPIs. However, the objective measure of esophageal acid exposure did not differ significantly between groups.

Table 3. Characteristics of Randomized Controlled Trials Comparing Transoral Incisionless Fundoplication With Medical Management in Patients Whose Symptoms Were Not Controlled on Proton Pump Inhibitors

Study; Trial	TIF/CTL, n	Patient Symptoms or Other Characteristics	Comparator	FU, mo	Principal Clinical Outcome
Hunter et al (2015)[13]; RESPECT	87/42	• Hiatal hernia ≤2 cm • Troublesome regurgitation[a] not controlled on PPI	Sham + PPI	6	Relief of regurgitation without PPI in TIF group vs. PPI escalation in control group
Trad et al (2015)[14];TEMPO	40/23	• Hiatal hernia ≤2 cm • Troublesome symptoms not controlled on PPI[b]	Maximum-dose PPI	6	Elimination of daily symptoms other than heartburn

CTL: control; FU: follow-up; PPI: proton pump inhibitor; TIF: transoral incisionless fundoplication.
[a] Troublesome regurgitation was defined as mild symptoms for ≥2 days a week or moderate-to-severe symptoms >1 day a week.
[b] Gastroesophageal reflux disease for >1 year and a history of daily PPI use for >6 months.

Table 4. Results for Randomized Controlled Trials Comparing Transoral Incisionless Fundoplication With Medical Management in Patients Whose Symptoms Were Not Controlled on Proton Pump Inhibitors

Trial	Symptoms[a]	Regurgitation	Heartburn	Reflux	Esophageal pH
	Elimination of Troublesome Regurgitation	*Change in RDQ Regurgitation Score*	*Change in RDQ Heartburn Score*	*Change in RDQ Heartburn Plus Regurgitation Score*	
RESPECT (2015)[13]					
TIF + placebo, % (n/N)	67% (58/87)	-3	-2.1	-2.5	
Sham + PPI, % (n/N)	45% (19/42)	-3	-2.2	-2.4	
p	.023	.072	.936	.313	
	Elimination of Symptoms Other Than Heartburn[b]	*Change in GERD-HRQL Score*	*Change in GERD-HRQL Heartburn Score*	*RSI Score*	*Percent Time With pH >4*
TEMPO (2015)[14]					

Trial	Symptoms[a]	Regurgitation	Heartburn	Reflux	Esophageal pH
TIF	62%	-21.1	-14	-17.4	54%
Maximum-dose PPI	5%	-7.6	-5.2	-3.0	52%
RR (95% CI)	-12.9 (1.9 to 88.9)				
p	.001	NR	NR	NR	.914
TIF	62% to 67%				

CI: confidence interval; GERD-HRQL: Gastroesophageal Reflux Disease Health-Related Quality of Life; NR: not reported; PPI: proton pump inhibitor; RCT: randomized controlled trial; RDQ: Reflux Disease Questionnaire; RR: relative risk; RSI: Reflux Symptom Index; TIF: transoral incisionless fundoplication.
[a] Primary outcome measure.
[b] Primary outcome measure a composite of 3 GERD symptom scales: the GERD-HRQL, RSI, and RDQ.

Trad et al (2017) reported a 3-year follow-up for patients treated with TIF in the TEMPO trial (Table 5).[15,] All patients in the control group (maximum PPIs) had crossed over to TIF and were included in the follow-up. Symptom scores, esophagogastroduodenoscopy, and 48-hour pH monitoring were conducted off PPIs, and the 2 TIF failures who had undergone fundoplication were assigned the worst scores. Of 63 patients treated with TIF, data on PPI use was available for 52 (83%), with 71% of patients reporting a cessation of PPI use. However, completion of the Reflux Disease Questionnaire and assessment of pH normalization were available for 77% of patients. pH normalization was available for 40% of available patients following TIF, whereas 90% reported the elimination of troublesome regurgitation.

Trad et al (2018) also reported a 5-year follow-up for the TEMPO trial (Table 5).[16,] 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.

Table 5. Follow-Up of Patients Treated With EsophyX2 in the TEMPO Trial

Outcome Measure	Baseline	1 Year	2 Years	3 Years	5 Years
Sample size (% of 63)		60 (95%)	55 (87%)	52 (83%)	44 (70%)
Elimination of troublesome regurgitation (RDQ)[a]		88% (42/48)	90% (41/44)	90% (37/41)	86% (37/43)
Elimination of atypical symptoms (RSI ≤13)[a]		82% (45/55)	84% (43/51)	88% (42/48)	80% (31/39)
GERD-HRQL score	32.8 (/60)	7.1 (/58)	7.3 (/52)	5.0 (/43)	6.8 (/31)
Esophagitis	55% (33/60)	5% (3/59)	10% (5/50)	12% (5/41)	
Cessation of PPI use		78% (47/60)	76% (42/55)	71% (37/52)	46% (20/44)

Outcome Measure	Baseline	1 Year	2 Years	3 Years	5 Years
pH normalization[b]		41% (24/59)	37% (18/49)	40% (16/40)	

Adapted from Trad et al (2017) and Trad et al (2018).[15,16,]
Values are % (n/N) unless otherwise noted.
GERD-HRQL: Gastroesophageal Reflux Disease Health-Related Quality of Life; PPI: proton pump inhibitor; RDQ: Reflux Disease Questionnaire; RSI: Reflux Symptom Index.
[a] Primary outcome: elimination of daily troublesome regurgitation and atypical symptoms as measured with the RDQ and RSI. Troublesome symptoms are defined as mild symptoms, occurring ≥2 days a week, or moderate-to-severe symptoms, occurring >1 day a week.
[b] Normality was defined as percent of total recorded time pH <4 with 5.3% as the threshold for normality.

Tables 6 and 7 summarize the important limitations of the RCTs discussed above.

Table 6. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Hunter et al (2015)[13,]			2. Not compared to fundoplication 3. Measurement off PPI group		
Trad et al (2015)[14,]			2. Not compared to fundoplication 3. No sham surgery		
Hakansson et al (2015)[17,]			2. Sham only (no active treatment)		
Witteman et al (2015)[18,]			3. Continued PPI only (no sham surgery)		

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
PPI: proton pump inhibitor
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms

Table 7. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Hunter et al (2015)[13,]						
Trad et al (2015)[14,]		1, 2. No blinding				1. Within-group analysis only
Hakansson et al (2015)[17,]				1. Unequal dropout rates in both treatment groups	1. Power calculations not reported	2. Adjusted for baseline values but not for repeated measures
Witteman et al (2015)[18,]		1, 2. No blinding		1. Study stopped following unplanned interim analysis	1. Power calculations not reported	

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4.Comparative treatment effects not calculated.

Nonrandomized Studies

Two nonrandomized comparative studies have compared TIF with laparoscopic fundoplication in patients whose symptoms were not controlled on PPIs.[19,20,]

A nonrandomized study by Toomey et al (2014) compared 20 patients undergoing TIF, 20 patients undergoing Nissen fundoplication, and 20 patients undergoing Toupet fundoplication.[19,] Age, body mass index, and preoperative DeMeester score were controlled; however, the indications for each procedure differed. Patients with abnormal esophageal motility underwent Toupet fundoplication, and only patients who had a hiatal hernia of 2 cm or less were offered TIF. As a result, only 15% of the TIF group had a hiatal hernia versus 65% and 55% of the 2 fundoplication groups, limiting comparison of both treatments. Adverse events were not reported.

Frazzoni et al (2011) compared 10 patients undergoing TIF with 10 patients undergoing laparoscopic fundoplication with the first-generation EsophyX procedure.[20,] The patients selected which treatment they wanted, but the groups were comparable to a baseline. Regarding clinical outcomes assessed at 3 months, 7 patients undergoing TIF reported only partial/no symptom

remission versus 0 patients undergoing fundoplication. Mild dysphagia was reported by 2 patients after fundoplication and 1 patient after TIF. Two patients reported epigastric bloating after fundoplication. Several measures of GERD assessed by manometry and impedance-pH monitoring showed greater improvement in the fundoplication group than in the TIF group. This study reported that TIF with the first-generation EsophyX device is less effective than fundoplication in improving symptoms of GERD.

Tables 8 and 9 summarize the characteristics and results of selected nonrandomized studies.

Table 8. Nonrandomized Study Characteristics

Study	Study Type	Country	Dates	Participants	Treatment	Comparator	Follow-Up
Toomey et al (2014)[19,]	Case-control	U.S.	2010-2013	Patients with GERD undergoing TIF, LNF, or LTF	20 patients underwent TIF	20 patients each had LTF or LNF	NR
Frazzoni et al (2011)[20,]	Prospective open-label	Italy	2000-2008	Patients had heartburn and/or regurgitation despite high-dose PPIs	10 patients chose first-generation EsophyX fundoplication	10 patients chose laparoscopic fundoplication	3 mo

GERD: gastroesophageal reflux disease; LNF: laparoscopic Nissen fundoplication; LTF: laparoscopic Toupet fundoplication; NR: not reported; PPI: proton pump inhibitor; TIF: transoral incisionless fundoplication.

Table 9. Nonrandomized Study Results in Patients Whose Symptoms Were Not Controlled by Proton Pump Inhibitors

Study	Percent Partial or No Symptom Remission	Normalization Esophageal Acid Exposure Time	Normalization of Distal Refluxes	Normalization of Proximal Refluxes	Mild Dysphagia	Bloating
Frazzoni et al (2011)[20,]						
TIF, %	70	50	20	40	10	0
Fundoplication, %	0	100	90	100	20	20
p	.003	.03	.005	.011	NR	NR

NR: not reported; TIF: transoral incisionless fundoplication.

Case Series

Bell et al (2021) evaluated the durability of TIF with EsophyX2 in 151 patients via a single institution prospective registry between November 2008 and July 2015.[21,] 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.

SECTION SUMMARY: TRANSORAL INCISIONLESS FUNDOPLICATION FOR SYMPTOMS UNCONTROLLED BY PROTON PUMP INHIBITORS

Studies Comparing Transoral Incisionless Fundoplication With Continued Proton Pump Inhibitors

The evidence on TIF in patients whose symptoms are not controlled by PPIs includes 2 RCTs, 1 of which followed TIF patients for up to 5 years. The highest quality study is the sham-controlled RESPECT trial by Hunter et al (2015). RESPECT found a significantly greater proportion of patients who reported the elimination of troublesome regurgitation compared with sham plus PPIs; elimination of regurgitation was achieved in 67% of patients treated with TIF. Other symptom measures did not differ between the TIF and sham-PPI groups. A strong placebo effect of the procedure is suggested by the subjective outcome measures in the sham group, in which 45% of patients whose symptoms were not previously controlled on PPIs reported elimination of troublesome regurgitation. The strong placebo effect suggested by the RESPECT trial raises questions about the validity of the nonblinded TEMPO trial. TEMPO reported significant improvements in subjective measures with TIF compared with maximum PPI treatment, but there was no significant difference in the objective measure of esophageal acid exposure. At a 3-year follow-up, about twice as many patients reported symptom improvement compared with improvement in the objective measure. It is not clear whether the discrepancy is due to a general lack of correlation between pH and symptoms, or to a placebo effect on the subjective assessment. Together, these data would suggest the most appropriate comparator for patients whose symptoms are not controlled on PPIs is laparoscopic fundoplication. However, a 5-year follow-up of the TEMPO trial found sustained cessation of PPI therapy in most patients with data available, as well as the resolution of several types of trouble symptoms. These results may suggest long-term safety and durability of TIF 2.0 as an alternative to LNF.

Studies Comparing Transoral Incisionless Fundoplication With Laparoscopic Fundoplication

Each study comparing TIF with laparoscopic fundoplication has methodologic problems that do not permit conclusions on the comparative efficacy of the 2 procedures. The Frazzoni et al (2011) nonrandomized study showed that TIF is less effective than a fundoplication. However, this study was conducted with an earlier device. In the Toomey et al (2014) study, patients were assigned to different procedures based on specific baseline characteristics. Two of the studies concluded that TIF and fundoplication were similarly effective based on a lack of statistically significant differences across symptom outcomes. However, because of the small sizes of these samples, the lack of a statistically significant difference in outcomes cannot be interpreted as equivalent outcomes. For these studies, several outcomes favored fundoplication over TIF. The studies did not report adverse events or rates of postoperative symptoms associated with fundoplication (e.g., dysphagia, bloating). Thus, it is not possible to evaluate whether a difference in

effectiveness between procedures might be accompanied by a difference in adverse events. Limited data suggest that the first-generation TIF is considerably inferior to laparoscopic fundoplication in patients who have failed PPI therapy, and this treatment is no longer available. Current data are insufficient to determine the risks and benefits of the second-generation TIF procedure compared with laparoscopic fundoplication in patients whose symptoms are not controlled by PPIs.

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 individuals with GERD and hiatal hernias of 2 cm or less controlled by PPIs.

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; MUSE).

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.
- Studies with duplicative or overlapping populations were excluded.

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 (Table 10). Hakansson et al (2015) compared TIF (n=22) with sham only

(n=22).[17,] 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 (Table 10).[18,] 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 (Table 11). 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.

Table 10. Characteristics of Randomized Trials Assessing Transoral Incisionless Fundoplication in Patients Whose Symptoms Were Controlled by Proton Pump Inhibitors

Study	TIF/CTL, n	Patient Symptoms or Other Characteristics	Comparator	FU, mo	Principal Clinical Outcome
Hakansson et al (2015)[17,]	22/22	Controlled on PPI, run-in to confirm PPI dependence	Sham only	>6	Time to resumption of PPI, percent needing PPI at 6 mo
Witteman et al (2015)[18,]	40/20	Controlled on PPI; those who received TIF had GERD with hiatal hernias ≤2 cm	Continued PPI only	6	Mean GERD symptoms, percent with >50% improvement

CTL: control; FU: follow-up; GERD: gastroesophageal reflux disease; PPI: proton pump inhibitor; TIF: transoral incisionless fundoplication.

Table 11. Results of Randomized Controlled Trials Comparing Transoral Incisionless Fundoplication With Nonsurgical Treatment in Patients Whose Symptoms Were Controlled on Proton Pump Inhibitors

Study	Days to PPI Resumption	Change in PPI Therapy	Change in Symptoms	Change in QOL	Change in Esophagitis	Esophageal pH
		Remission at 6 Months	*Median GSRS Score*	*Median QOLRAD Score*		*Percent Time pH <4*
Hakansson et al (2015)[17,]						
TIF	197	13 (59%)	4	1.5		3.6%
Sham only	107	4 (18%)	1.4	0.4		9.8%
p	.001	.01	NR	NR		NR
			Percent >50% Improvement in GERD-HRQL Score	*Mean GERD-HRQL Score*	*Percentage With Esophagitis*	*Percent Patients With Normalized pH[a]*
Witteman et al (2015)[18,]						
TIF			55%	-14.1	-19%	50%
Continued PPI			5%	-3.1	-20%	63%
p			<.001	<.001	>.05	NR

GERD-HRQL: Gastroesophageal Reflux Disease Health-Related Quality of Life; GSRS: Gastrointestinal Symptom Rating Scale; NR: not reported; PPI: proton pump inhibitor; QOL: quality of life; QOLRAD: Quality of Life in Reflux and Dyspepsia; TIF: transoral incisionless fundoplication.
[a] Defined as <4% for ≤4.2% of recording time.

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 TIF with EsophyX2 (Tables 12 and 13). 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 of 45 individuals, about 75% of whom had the elimination of esophagitis and had discontinued PPI use at 5 years. Of the 13 patients with hiatal hernias, 62% had a reduction in hernia size at follow-up.[22,]

In a prospective cohort study of 50 individuals by Testoni et al (2015, 2019), 72% of patients were completely responsive to PPIs at baseline, and 24% were partially responsive.[23,24,] 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 TIF procedures were considered unsuccessful. Nine percent of patients had additional surgery for poor response by 2 years. The Johnson-DeMeester score, an objective measure of acid exposure due to reflux, 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.

An additional prospective cohort study of the MUSE by Testoni et al (2022) included 46 individuals with full or partial response to PPIs at baseline.[25,] Recurrent hiatal hernia <2.5 cm occurred in 6.5% of patients at 6 months and 4.4% at 1 year follow-up. There was no significant change in Johnson-DeMeester score at 6-month and 1 year follow-up. In addition to the outcomes summarized in Table 13, 2 individuals (4.3%) had perforations requiring surgical repair.

Table 12. Characteristics of Observational Studies With Long-Term Outcomes in Patients Whose Symptoms Were Controlled by Proton Pump Inhibitors

Study	Country	Participants	Treatment Delivery	Mean FU, mo
Stefanidis et al (2017)[22,]	Greece	PPI-controlled, hiatal hernia ≤2 cm	EsophyX2	59
Testoni et al (2015, 2019)[23,24,]	Italy	Daily PPI, esophagitis or abnormal pH, hiatal hernias ≤2 cm	ExophyX2	53
Testoni et al (2022)[25,]	Italy	Daily PPI, chronic GERD, endoscopic GERD or Barrett's esophagus <3 cm	MUSE	Mean NR; total follow-up 36 m

FU: follow-up; GERD: gastroesophageal reflux disease;NR: not reported; PPI: proton pump inhibitor.

Table 13. Long-Term Durability of Transoral Incisional Fundoplication in Patients Whose Symptoms Were Controlled by Proton Pump Inhibitors

Outcomes	Mean Baseline	6 Months	1 Year	2 Years	3 Years	6 to 7 Years	10 Years
Stefanidis et al (2017)[22,]							
Sample size	45					44	
GERD-HRQL score off PPI	27					4	
PPI discontinuation						72.7%	
Elimination of esophagitis	n=33		81.8%			72.7%	
Reduction in hiatal hernia	n=13					61.5%	
Testoni et al (2015, 2019)[23,24,]							
Sample size	50	49[a]	49	45[b]	45	30	14
GERD-HRQL score off PPI (SD)	46 (19)			18 (13)	19 (14)	10 (7.7)	9.5 (6.1)
GERD-QUAL score off PPI (SD)	114 (20)			71 (24)	80 (21)		
Johnson-DeMeester score (SD)	22 (12)	18 (15)		19 (20)			
PPI discontinuation n (%)		61.2%	51.0%	25/45 (55.6)	24/45 (53.3)	11/30 (36.7)	5/14 (35.7)
Additional surgery for poor response n (%)				4/45 (8.8)	4/45 (8.8)	6/30 (20.0)	2/14 (14.1)
Testoni et al (2022)[25,]							
Sample size	31 to 46[c]						
GERD-HRQL score off PPI (95% CI)	22.0 (16.0 to 25.0)	9.0 (6.0 to 12.0)	7.0 (3.3 to 10.0)	8.5 (3.0 to 12.0)	2.5 (0.5 to 8.7)		
Johnson-DeMeester score (95% CI)		20.0 (6.0 to 37.7)	16.4 (5.6 to 26.9)				
PPI discontinuation n (%)		27/46 (58.7%)	27/46 (58.7%)	22/39 (56.4%)	23/35 (65.7%)		
Additional surgery for poor response n (%)		1/46 (2.2%)					

CI: confidence interval; GERD-HRQL: Gastroesophageal Reflux Disease Health-Related Quality of Life; GERD-QUAL: Gastroesophageal Reflux Disease Quality of Life; PPI: proton pump inhibitor; SD: standard deviation.
[a] Excluding 1 failed procedure due to pneumothorax.
[b] Excluding 4 patients who underwent Nissen fundoplication for failed procedure.
[c] Number with follow-up data varied according to outcome measure

Adverse Events

Huang et al (2017) conducted a systematic review with a meta-analysis of TIF for the treatment of GERD.[26,] 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.

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 RADIOFREQUENCY

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 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.
- Studies with duplicative or overlapping populations were excluded.

REVIEW OF EVIDENCE

Systematic Reviews

A meta-analysis of 4 RCTs (N=165 patients) was published by Lipka et al (2015) (Table 14).[27,] Three trials[28,29,30,]compared Stretta with sham, and 1 trial[31,]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.[30,] Aziz et al (2010) found statistically significant improvements in GERD-HRQL scores in all treatment groups.[29,] 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.[28,] 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.

Fass et al (2017) published a meta-analysis of the same 4 RCTs plus 23 prospective cohort studies and 1 registry that evaluated the Stretta procedure for patients with GERD.[32,] Pooled results showed clinically significant improvements in subjective outcome measures and a reduction in PPI use from a baseline of 97% of patients to 49% of patients after treatment, but there was a smaller difference from the sham group in the RCTs and high heterogeneity in the cohort studies. For objective outcome measures, erosive esophagitis was not significantly improved using a random-effects model, and there was high heterogeneity in the cohort studies. The time that esophageal acid exposure was less than 4 was significantly improved in the cohort studies but was not significantly different from sham in the RCTs. The authors are business advisors to Mederi Therapeutics.

Xie et al (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.[33,] Table 14 summarizes its overall characteristics. 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 QOL score 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.

Table 14. Meta- Analysis Characteristics

Study	Dates	Trials	Participants	N (Range)	Design	Duration, mo
Fass et al (2017)[32,]	Inception to May 2016	28	Patients with GERD undergoing endoscopic radiofrequency (Stretta)	2468 (9 to 558)	Meta-analysis of 4 RCTs, 23 cohort studies, and 1 registry	3 to 20
Lipka et al (2015)[27,]	Inception to Feb 2014	4	Patients with physiologic evidence of GERD who were on PPI therapy	165 (22 to 64)	Meta-analysis of RCTs	6 to 12
Xie et al (2021)[33,]	Inception to Dec 2019	10	Patients with GERD diagnosed by typical symptoms, abnormal esophageal acid exposure, or esophagitis	516 (20 to 129)	Network meta-analysis of RCTs	3 to 60

GERD: gastroesophageal reflux disease; PPI: proton pump inhibitor; RCT: randomized controlled trial.

Table 15. Meta- Analysis Results

Study	Heartburn	GERD-HRQL Score	Use of PPI Therapy	Acid Exposure Time (pH <4)	Other Objective Outcome Measures
	Heartburn Score				*DeMeester score*
Fass et al (2017)[32,]					
Patients (studies), n	637 (12)	507 (11)	1795 (23)	364 (11)	407 (8)
Change (95% CI)	-1.53 (-1.97 to -1.09)	RCT: -14.56 (-16.63 to -12.48) Cohort: -14.69 (-16.90 to -12.47)	Baseline: 1743 (97.1%) Post-treatment: 850 (49%) RR: 0.49 (0.40 to 0.60)	-3.01 (-3.72 to -2.30)	-13.79 (-20.01 to -7.58)

Study	Heartburn	GERD-HRQL Score	Use of PPI Therapy	Acid Exposure Time (pH <4)	Other Objective Outcome Measures
p	<.001	<.001	<.001	<.001	<.001
I^2 (p)	Significant in all subgroups (<.001)	RCTs: NS Cohort: 85% (<.001)	RCTs: NS Cohort: 95% (<.001)	NS in any subgroup	77%
	Ability to Stop PPI Therapy				*Mean LES Pressure*
Lipka et al (2015)[27,]					
Patients (studies), n	118 (3)	88 (2)		153 (4)	110 (3)
MD (95% CI)	RR , 0.87 (0.75 to 1.00)	-5.24 (-12.95 to 2.46)		1.56% (-2.56% to 5.69%)	0.32 mmHg (-2.66 to 2.02 mmHg)
p	.06	.18		.46	.79
I^2 (p)	0%	96% (<.001)		99% (<.001)	96% (<.001)
Range of N	24 to 51	22 to 64		22 to 64	

CI: confidence interval; GERD-HRQL: Gastroesophageal Reflux Disease Health-related Quality of Life; LES: lower esophageal sphincter; MD: mean difference; NS: nonsignificant; PPI: proton pump inhibitor; RCT: randomized controlled trial; RR; relative risk.

Randomized Controlled Trials

Additional RCTs have been published since the meta-analyses summarized in Table 14.

Kalapala et al (2017) published interim results from a small RCT of 20 patients randomized to PPI plus Stretta or PPI alone, with 3 months of follow-up.[34,] While short-term outcomes such as GERD symptoms and cessation of PPIs appeared improved for the Stretta group, the study sample was small and power calculations were not conducted.

Zerbib et al (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 from 8 French centers.[35,] 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.

Controlled Trials Comparing Transesophageal Radiofrequency With Laparoscopic Fundoplication

Liang et al (2015) reported on a prospective comparison of laparoscopic Toupet fundoplication with the Stretta procedure (Table 16).[36,] 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 (Table 17). 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.

Ma et al (2020) reported on a retrospective comparison of laparoscopic Toupet fundoplication with the Stretta procedure (Table 16).[37,] 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 17), 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.

Table 16. Characteristics of Studies Comparing Transesophageal Radiofrequency With Laparoscopic Fundoplication

Study	Study Type	Country	Dates	Participants	Treatment 1	Treatment 2	FU, y
Liang et al (2015)[36,]	Prospective cohort	China	2011	165	TERF	Laparoscopic fundoplication	3
Ma et al (2020)[37,]	Retrospective cohort	China	2014-2017	230	TERF	Laparoscopic fundoplication	1

FU: follow-up; TERF: transesophageal radiofrequency.

Table 17. Results Comparing Transesophageal Radiofrequency With Laparoscopic Fundoplication

Study	PPI Independence	Improvement in Heartburn Score	Improvement in Regurgitation Score	Improvement in Chest Pain Score	Reoperation	Bloating
Liang et al (2015)[36,]						
TERF	68.3%	2.53	2.41	2.96	11.8%	0%
LF	72.3%	4.05	4.03	5.50	0%	6.2%
p	.627	.01	.004	.005	.006	.120
Ma et al (2020)[37,]						
TERF	NR	NR	NR	NR	NR	5.7%
LF	NR	NR	NR	NR	NR	4.7%
p	NR	NR	NR	NR	NR	.866

LF: laparoscopic fundoplication; NR: not reported; PPI: proton pump inhibitor; TERF: transesophageal radiofrequency.

Prospective Cohort Studies

Long-term follow-up from case series and cohort studies can inform the durability of TERF. For example, 5- and 10-year follow-ups after TERF were reported in 2014 (Table 18).[38,39,] Elimination of PPI use was similar for both studies at around 42% (Table 19). Liang et al (2014) reported that symptoms of heartburn, regurgitation, chest pain, cough, and asthma were all decreased compared with baseline. Noar et al (2014) reported symptom improvement in 72% of patients and elimination of dysplasia in 85% of patients, but the interpretation of these findings is limited due to the 34% loss to follow-up in this study.

Table 18. Cohort Study and Case Series Characteristics

Study	Country/Institution	Participants	FU, y	Loss to FU
Liang et al (2014)[38,]	China	152 who failed PPI therapy	5	9%
Noar et al (2014)[39,]	University of Pittsburgh	149 who failed PPI therapy	10	34% (7% deceased)

FU: follow-up; PPI: proton pump inhibitor.

Table 19. Cohort Study and Case Series Results at Follow-Up

Study	Elimination of PPI Use	Symptom Improvement	Elimination of Dysplasia	Bloating
Liang et al (2014)[38,]	42.8%	p<.001 vs. pretreatment		8.7%
Noar et al (2014)[39,]	41%	72%	85%	

PPI: proton pump inhibitor.

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.

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 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.

REVIEW OF EVIDENCE

Durasphere

The available evidence for Durasphere consists of a single case series. One open-label pilot study by Ganz et al (2009) assessed 10 GERD patients injected with Durasphere (Carbon Medical Technologies), a bulking agent approved for the treatment of urinary and fecal incontinence, at the gastroesophageal junction.[40,] At 12 months, 7 (70%) patients discontinued all antacid medication completely. No erosion, ulceration, or sloughing of the material was noted at any injection site.

Polymethylmethacrylate Beads

The available evidence for polymethylmethacrylate beads consists of a single case series. A case series by Feretis et al (2001) evaluated transesophageal submucosal implantation of polymethylmethacrylate beads in 10 patients with GERD who were either refractory to or dependent on PPIs.[41,] 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.

SUPPLEMENTAL INFORMATION

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Clinical Input From Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

2015 Input

In response to requests for clinical input on transesophageal radiofrequency (Stretta) as a treatment of gastroesophageal reflux disease (GERD), input was received from 1 physician specialty society (2 reviewers) and 3 academic medical centers while this policy was under review in 2015. Input was mixed on the treatment of GERD with transesophageal radiofrequency to create submucosal thermal lesions of the gastroesophageal junction (i.e., Stretta). Potential conflicts of interest were noted by 2 reviewers.

2011 Input

In response to requests for clinical input on transoral incisionless fundoplication (TIF) using EsophyX, input was received from 2 physician specialty societies and 4 academic medical centers while this policy was under review in 2011. Reviewers agreed that TIF differed sufficiently from

laparoscopic Nissen fundoplication to warrant evaluation as a separate procedure. Reviewers considered TIF (i.e., EsophyX) to be investigational for the treatment of GERD.

Practice Guidelines and Position Statements
Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American Gastroenterological Association
In 2022, the American Gastroenterological Association issued a clinical practice update on the personalized approach to the evaluation and management of GERD.[42,] The guideline stated that "transoral incisionless fundoplication is an effective endoscopic option in carefully selected patients" with proven GERD. The guideline further stated that TIF has "demonstrable value in patients with regurgitation-predominant GERD" and that "further research into risks/benefits, durability, effectiveness, and treatment outcomes will enhance optimal utilization" as part of a personalized approach to treatment.

American College of Gastroenterology
The American College of Gastroenterology (2022) guidelines on the diagnosis and management of GERD include the following statements regarding TIF and Stretta[43,]:

- 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).
- 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).

According to the guideline methods, a conditional recommendation equates to a suggestion, and low level of evidence signifies "very little confidence in the effect estimate to support a particular recommendation, based on the risk of bias of the studies, evidence of publication bias, heterogeneity among studies, directness of the evidence, and precision of the estimate of effect." The guideline additionally noted that if TIF or Stretta is used, such use should be limited to patients with milder forms of GERD.

American Society for Gastrointestinal Endoscopy
In 2015, the American Society for Gastrointestinal Endoscopy published guidelines on endoscopic procedures for GERD.[44,] In its review of the EsophyX and Stretta procedures, the Society noted some positive findings but discrepancies between subjective and objective outcome measures or a lack of objective outcome measures in reported trials, concluding that these techniques represent "potentially new therapeutic indications for GI endoscopy", but that prospective trials using objective measures of GERD as the primary endpoint could be useful in defining the clinical role of these procedures.

American Society of General Surgeons
In 2011, the American Society of General Surgeons issued a position statement on transoral fundoplication stating that "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."[45,]

Multi-Society Consensus Guidance on GERD
In 2023, consensus guidance was issued by the Society of American Gastrointestinal and Endoscopic Surgery, American Society for Gastrointestinal Endoscopy, American Society for Metabolic and Bariatric Surgery, European Association for Endoscopic Surgery, Society for Surgery of the Alimentary Tract, and The Society of Thoracic Surgeons on the diagnosis and treatment of GERD. [46,] The relevant questions and recommendations for TIF and Stretta are as follows:

- Should endoscopic treatment with TIF 2.0 versus fundoplication be used for patients with GERD?
    - The panel suggests that adult patients with GERD may benefit from fundoplication over TIF 2.0. (Expert Opinion recommendation; GRADE recommendation was unable to be determined due to lack of evidence).
- Should endoscopic treatment with TIF 2.0 versus medical treatment (PPI) be used for patients with GERD?
    - The panel suggests that adult patients with GERD may benefit from TIF 2.0 over continued PPI (conditional recommendation, moderate certainty of evidence).
- Should endoscopic treatment with Stretta versus fundoplication be used for patients with GERD?
    - The panel suggests that adult patients with GERD may benefit from fundoplication over Stretta. (conditional recommendation, very low certainty of evidence).
- Should endoscopic treatment with Stretta versus medical treatment (PPI) be used for patients with GERD?
    - The panel suggests that adult patients with GERD may benefit from Stretta over PPI. (conditional recommendation, low certainty of evidence).

National Institute for Health and Care Excellence
In 2013, NICE updated its guidance on endoscopic radiofrequency treatment for GERD, concluding: "The evidence on the safety of endoscopic radiofrequency ablation for gastro-esophageal 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....."[47,] The NICE 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."

In 2011, NICE issued guidance on endoluminal gastroplication for GERD, concluding that "The evidence on endoluminal gastroplication for gastroesophageal reflux disease raises no major safety concerns. Evidence from a number of RCTs [randomized controlled trials] shows a degree of efficacy in terms of reduced medication requirement in the short term, but changes in other

efficacy outcomes are inconsistent, and there is no good evidence of sustained improvement in esophageal pH measurements...."[48,]

U.S. Preventive Services Task Force Recommendations
Not applicable.

Ongoing and Unpublished Clinical Trials
Some currently ongoing and unpublished trials that might influence this review are listed in Table 20.

Table 20. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date (status)
Ongoing			
NCT04306380	Transoral Incisionless Fundoplication Database Repository (TIF)	500	Dec 2030
NCT05066594	Observational Registry of Transoral Incisionless Fundoplication (Creation of a New Gastroesophageal Valve) in Patients With Gastroesophageal Reflux Disease	100	May 2029
NCT03669874	Endoscopic Fundoplication With MUSE System	80	Sept 2026
NCT04795934	Multicenter Single-Blind RCT of CTIF Versus LNF For Treatment of GERD in Patients Requiring Hiatal Hernia Repair Combined With Transoral Incisionless Fundoplication Versus Laparoscopic Nissen Fundoplication for Treatment of Gastroesophageal Reflux Disease in Patients Requiring Hiatal Hernia Repair	142	Dec 2026
Unpublished			
NCT01118585[a]	Prospective Outcome Evaluation of Transoral Incisionless Fundoplication (TIF) for the Treatment of Gastroesophageal Reflux Disease (GERD): The TIF Registry Study	278	Dec 2018 (completed)
NCT02366169[a]	A Worldwide Post-Market Surveillance Registry to Assess the Medigus Ultrasonic Surgical Endostapler (MUSE™) System for the Treatment of GERD	200	Dec 2019 (unknown)

NCT: national clinical trial.
[a] Denotes industry-sponsored or cosponsored trial.

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. This may not be a comprehensive list of procedure codes applicable to this policy.

Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

The code(s) listed below are medically necessary ONLY if the procedure is performed according to the "Policy" section of this document.

CPT/HCPCS	
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-dilatation and guide wire passage, when performed)
43236	Esophagogastroduodenoscopy, flexible, transoral; with directed submucosal injection(s), any substance
43257	Esophagogastroduodenoscopy, flexible, transoral; with delivery of thermal energy to the muscle of lower esophageal sphincter and/or gastric cardia, for treatment of gastroesophageal reflux disease
43266	Esophagogastroduodenoscopy, flexible, transoral; with placement of endoscopic stent (includes pre- and post-dilation and guide wire passage, when performed)

REVISIONS	
12-15-2009	In Header Section: ▪ Changed title From: Endoscopic gastroplasty for gastroesophageal reflux disease (GERD) and weight reduction To: Transesophageal Endoscopic Therapies for Gastroesophageal Reflux Disease
	Updated Description Section.
	In Policy Section: ▪ No change in policy intent was made, however, wording was updated to current version From: "The following transesophageal endoscopic therapies are considered experimental/investigational for all indications, including but not limited to gastroesophageal reflux disease and weight reduction due to the lack of long-term studies: 1. Transesophageal endoscopic gastroplasty (i.e., the Endocinch procedure) 2. Transesophageal radiofrequency energy to create submucosal thermal lesions of the gastroesophageal junction (i.e., the Stretta® procedure) 3. Endoscopic submucosal implantation of a biocompatible polymer (i.e., Enteryx) 4. Endoscopic submucosal implantation of polymethylmethacrylate beads into the lower esophageal folds"
	Added Rationale Section.

REVISIONS	
	In Coding Section: ▪ Removed CPT codes: 0008T, 0133T.
	Updated Revision and References Sections.
01-03-2012	Updated Description Section
	Updated Rationale Section
	In Policy Section: ▪ Combined Items #3 and #4 of "3. Endoscopic submucosal implantation of a biocompatible polymer (e.g., Enteryx) is considered experimental / investigational as a treatment of gastroesophageal reflux disease. 4. Endoscopic submucosal implantation of polymethylmethacrylate beads into the lower esophageal folds is considered experimental / investigational as a treatment of gastroesophageal reflux disease." to read: "3. Endoscopic submucosal implantation of a prosthesis or injection of a bulking agent (e.g., biocompatible liquid polymer, polymethylmethacrylate beads, zirconium oxide spheres) is considered experimental / investigational as a treatment of gastroesophageal reflux disease." This update does include the addition of "Endoscopic submucosal implantation of a prosthesis" to the policy language as experimental / investigational.
	In Coding Section: ▪ Added CPT code: 43219
	Updated References section
06-05-2012	Updated Description section
	Updated References
03-12-2013	Description section updated
	Rationale section updated
	In Coding section: ▪ Coding notations added.
	References updated
01-01-2014	Description section updated
	Rationale section updated
	In Coding section: ▪ Added CPT code: 43212, 43236, 43266 (Eff 01-01-2014) ▪ Revised nomenclature on CPT codes: 43201, 43257 (Eff 01-01-2014) ▪ Terminated CPT code: 43219 (Eff 12-31-2013) ▪ Removed the Diagnosis section as the policy is experimental / investigational for all diagnoses related to this policy.
	References updated
07-21-2015	Description section updated
	In Policy section: ▪ In Item 1 removed "Transesophageal endoscopic gastroplasty" and "(e.g., the EndoCinch ™, NDO Plicator™, or EsophyX™ procedures)" to read, "Transoral incisionless fundoplication (TIF) (i.e., Esophyx®) is considered experimental / investigational as a treatment of gastroesophageal reflux disease." ▪ In Item 3 removed "biocompatible liquid polymer" as a bulking agent example.
	Rationale section updated
	In Coding section: ▪ Removed CPT Code 43219 as the code terminated 12-31-2013. ▪ Coding notations updated.
	In Revision section:

REVISIONS	
	▪ Corrected a code effective date in 01-01-2014 Revision.
	References updated
01-01-2016	In Coding section: ▪ Added CPT code: 43210
02-09-2016	In Title section: ▪ Added "See Also: Injectable Bulking Agents for the Treatment of Urinary and Fecal Incontinence" ▪ Corrected Professional and Institutional Current Effective Date from January 1, 2016 back to July 21, 2015.
	Description section updated
	Rationale section updated
	In Coding section: ▪ Coding notations updated ▪ Added "Experimental / Investigational for all diagnoses related to this medical policy." as this was erroneously left off of prior versions.
	References updated
03-10-2017	Description section updated
	Rationale section updated
	In Coding section: ▪ Coding notations updated
	References updated
03-01-2018	Description section updated
	Rationale section updated
	References updated
04-24-2019	Description section updated
	Rationale section updated
	References updated
03-23-2021	Description section updated
	Rationale section updated
	References updated
02-25-2022	Updated Description Section
	Updated Policy Section ▪ Section A: Added MUSE as an example
	Updated Rationale Section
	Updated Coding Section ▪ Removed 43499 and 43659 ▪ Remove coding notations
	Updated References Section
01-24-2023	Updated Description Section
	Updated Rationale Section
	Updated References Section
01-23-2024	Updated Description Section
	Updated Rationale Section
	Updated Coding Section ▪ Removed ICD-10 Diagnoses Box
	Updated References Section

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