Policy Number	**MED201.016**
Policy Effective Date	**06/15/2024**
Policy End Date	**12/31/2025**

Device Therapies for Gastroesophageal Reflux Disease (GERD)

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Related Policies (if applicable)
SUR716.003 Bariatric Surgery
SUR709.036 Magnetic Esophageal Ring to Treat Gastroesophageal Reflux Disease (GERD)

Disclaimer

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Coverage

Transendoscopic therapy as a treatment for gastroesophageal reflux disease (GERD**) may be considered medically necessary** for transesophageal endoscopic gastroplasty, also known as endoscopic gastroplication, fundoplication, or transoral incisionless fundoplication [TIF] (e.g., StomaphyX™, EsophyX®, MUSE) OR transesophageal radiofrequency to create submucosal thermal lesions of the gastroesophageal junction (e.g., Stretta™ procedure), for individuals meeting ALL of the following criteria:

- 18 years of age or older;
- Confirmed GERD by endoscopy, ambulatory pH, or barium swallow testing;
- >1 year of GERD symptoms (reflux symptoms that occur 2 to 3 times per week);
- History of daily proton pump inhibitor's (PPI's) for >6 months;
- Body mass index (BMI) ≤ 35;
- No hiatal hernia >2 cm;
- No Los Angeles classification system (LA) grade C or D esophagitis;
- No Barrett's esophagus >2 cm;
- Absence of achalasia and esophageal ulcer;

- No altered esophageal anatomy that would prevent insertion of a device;
- Absence of esophageal motility disorder; and
- No previous history of failed antireflux surgery.

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

NOTE 1: See Medical Policy SUR716.003 Bariatric Surgery for coverage description of StomaphyX™ when performed for bariatric indications.

Policy Guidelines

None.

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.

Gastroesophageal Reflux Disease
Gastroesophageal reflux disease 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 (LES) 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 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 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 histamine$_2$-receptor (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 is 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).

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 (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 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 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 LES 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 randomized controlled trial (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 U.S. Food and Drug Administration (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 were cleared for marketing by the FDA through the 510(k) (K171307) for expanded indications, including patients who require and respond to pharmacologic therapy and patients with hiatal hernia larger than 2 cm when 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 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.

Rationale

This policy was created in August 2002 and has been updated regularly with searches of the PubMed database. The most recent literature update was performed October 18, 2023.

Medical policies assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are 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 to 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 balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one 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. RCTs 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.

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 policy.

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.

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. (8) 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.

Richter et al. (2018) published a network meta-analysis of RCTs comparing TIF or laparoscopic Nissen fundoplication (LNF) with sham or PPIs. (9) The meta-analysis was limited by low-quality studies (one 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). (10) 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%.

Rausa et al. (2023) published a network meta-analysis of 33 RCTs comparing TIF (n=188) to anterior partial fundoplication (APF) (n=322), laparoscopic Toupet fundoplication (LTF)

(n=1120), laparoscopic Nissen fundoplication (LNF) (n=1740), and PPI therapy (N=80) in patients with recalcitrant GERD. (11) The outcomes of interest were differences in the rate of heartburn, regurgitation, dysphagia, bloating, and PPI discontinuation. Surgical and endoscopic treatments have similar RR for heartburn, regurgitation, bloating. LTF has a lower risk ratio (RR) of post-operative dysphagia when compared to APF (RR 3.3; Crl 1.4–7.1) and LNF (RR 2.5; Crl 1.3–4.4). The pooled network meta-analysis did not observe any significant improvement regarding lower esophageal sphincter (LES) pressure and pH < from baseline. LTF, APF, LNF, magnetic augmentation sphincter (MSA), radiofrequency ablation (RFA), and TIF had have a similar post-operative PPI discontinuation rate.

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) (8)	2008-2016	32	Patients met standard criteria for the TIF procedure[a]	1475 (10-124)	5 RCTs, 21 prospective and 6 retrospective studies	NR
Richter et al. (2018) (9)	NR	7	Patients had GERD, established by endoscopic results indicating erosive esophagitis and/or abnormal ambulatory esophageal pH monitoring[b]	1128 (range NR)	2 RCTs (TIF vs PPI); 2 RCTs (TIF vs sham); 3 RCTs (LNF vs PPIs)	TIF: 6-12 mo LNF vs PPI: 1-5 y
Testoni et al. (2021) (10)	Inception to May 2020	8	Patients had refractory GERD and underwent a TIF procedure	418 (15 to 86)	1 RCT, 3 multicenter, prospective studies, and 4 single-center prospective studies	Median follow-up: 5.3 years (range: 3 to 10 years)
Rausa et al. (2023) (11)	Inception to April 2022	33	Patients with refractory GERD who underwent	4382	33 RCTs	NR

			APF, LTF, LNF, or TIF			

APF: anterior partial fundoplication; GERD: gastroesophageal reflux disease; LNF: laparoscopic Nissen fundoplication; LTF: laparoscopic Toupet fundoplication; MSA: magnetic sphincter augmentation; mo: month; N: number; NR: not reported; PPI: proton pump inhibitor; RCT: randomized controlled trial; TIF: transoral incisionless fundoplication; y: year.

[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) (8)					
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	<0.001	<0.001	<0.001	<0.001	<0.001
I^2 (p)	93.6 (0.00)	94 (<0.001)	98 (<0.001)	95 (<0.001)	86 (<0.001)
Mean follow-up (SD), mo	15.5 (14.6)				
		TIF-2 Subgroup			*TIF-2 Subgroup*
N		997 (15 studies)			
MD (95% CI)		17.62 (17.19 to 18.05)			53.18 (49.49 to 56.87)
p		<0.001			<0.001
Richter et al. (2018) (9)					
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) (10)					
	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) (11)					
	Heartburn RR (95% CrI)	**Regurgitation RR (95% CrI)**	**Dysphagia RR (95% CrI)**	**Bloating RR (95% CrI)**	**PPI Discontinuation RR (95% CrI)**
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; mo: month; N: Number; NR: not reported; OR: odds ratio; PPI: proton pump inhibitor; RR: relative risk; RSI: Reflux Symptom Index; 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 (see 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. (12) 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. (13) The primary outcome in both trials was the elimination of symptoms, measured in slightly different ways (see Table 3).

In both trials, the primary outcome was achieved by a higher percentage of patients treated with TIF than with PPIs (see 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=0.023). In TEMPO, the relative risk of achieving the primary outcome was 12.9 (95% confidence interval [CI], 1.9 to 88.9; p<0.001).

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.

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 RCTs Comparing TIF With Medical Management in Patients Whose Symptoms Were Not Controlled on PPIs

Study; Trial	TIF/CTL, n	Patient Symptoms or Other Characteristics	Comparator	FU, month	Principal Clinical Outcome

Hunter et al. (2015) (12); 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) (13); 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; n: number; 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 RCTs Comparing TIF With Medical Management in Patients Whose Symptoms Were Not Controlled on PPIs

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) (12)					
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	0.023	0.072	0.936	0.313	
	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) (13)					
TIF	62%	-21.1	-14	-17.4	54%
Maximum-dose PPI	5%	-7.6	-5.2	-3.0	52%

RR (95% CI)	-12.9 (1.9-88.9)				
p	0.001	NR	NR	NR	0.914
TIF	62%-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). (14) All patients in the control group (maximum PPIs) had crossed over to TIF and were included in the follow-up. Symptom scores, esophagastroduodenoscopy, 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 5-year follow-up for the TEMPO trial (Table 5). (15) 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)
pH normalization[b]		41% (24/59)	37% (18/49)	40% (16/40)	

Adapted from Trad et al. (2017) and Trad et al. (2018). (14, 15)
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 of ≥5.3%.

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) (12)			2. Not compared to fundoplication 3. Measurement off PPIs group		
Trad et al. (2015) (13)			2. Not compared to fundoplication 3. No sham surgery		
Hakansson et al. (2015) (16)			2. Sham only (no active treatment)		
Witteman et al. (2015) (17)			3. Continued PPI only (no sham surgery)		

The study limitations stated in this table are those notable in the current literature review; this is not a comprehensive limitations 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) (12)						
Trad et al. (2015) (13)		1, 2. No blinding				1. Within-group analysis only
Hakansson et al. (2015) (16)				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) (17)		1, 2. No blinding		1. Study stopped following unplanned interim	1. Power calculations not reported	

The study limitations stated in this table are those notable in the current literature 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.

<u>Nonrandomized Studies</u>

Two nonrandomized comparative studies have compared TIF with laparoscopic fundoplication in patients whose symptoms were not controlled on PPIs. (18, 19)

A nonrandomized study by Toomey et al. (2014) compared 20 patients undergoing TIF, 20 patients undergoing Nissen fundoplication, and 20 patients undergoing Toupet fundoplication. (18) 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 to 10 patients undergoing laparoscopic fundoplication with the first-generation EsophyX procedure. (19) 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 zero 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 as 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	Treatment	Follow-Up
Toomey et al. (2014) (18)	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) (19)	Prospective open-label	Italy	2000-2008	Patients had heartburn and/or regurgitation despite high-dose PPIs	10 patients chose first-generation EsophyX fundoplica-tion	10 patients chose laparoscopic fundoplica-tion	3 mo

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

Table 9. Nonrandomized Study Results in Patients Whose Symptoms Were Not Controlled by PPIs

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) (19)						
TIF, %	70	50	20	40	10	0
Fundoplication, %	0	100	90	100	20	20
p	0.003	0.03	0.005	0.011	NR	NR

NR: not reported; PPI: proton pump inhibitor; TIF: transoral incisionless fundoplication.

Case Series

Bell et al. (2021) evaluated the durability of TIF with the EsophyX2 in 151 patients via a single institution prospective registry between November 2008 and July 2015. (20) 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: TIF for Symptoms Uncontrolled by PPIs

Studies Comparing TIF With Continued PPIs

The evidence on TIF in patients whose symptoms are not controlled by PPIs includes two RCTs, one 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. The TEMPO trial reported significant improvements in subjective measures with TIF compared with maximum PPI treatment. At a 3-year follow-up, about twice as many patients reported symptom improvement. 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 laparoscopic Nissen fundoplication (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. 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.

TIF for Symptoms Controlled by PPIs

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 policy.

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.

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 (see Table 10). Hakansson et al. (2015) compared TIF (n=22) to sham only (n=22). (16) 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 (see Table 10). (17) 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 ($p<0.001$, 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%, $p=0.01$). 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 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).

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 TIF in Patients Whose Symptoms Were Controlled by PPIs

Study	TIF/CTL, n	Patient Symptoms or Other Characteristics	Comparator	FU, mo	Principal Clinical Outcome
Hakansson et al. (2015) (16)	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) (17)	40/20	Controlled on PPI; those who received TIF had	Continued PPI only	6	Mean GERD symptoms, percent with >50% improvement

		GERD with hiatal hernias ≤ 2 cm			

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

Table 11. Results of RCTs Comparing TIF With Nonsurgical Treatment in Patients Whose Symptoms Were Controlled on PPIs

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) (16)						
TIF	197	13 (59%)	4	1.5		3.6%
Sham only	107	4 (18%)	1.4	0.4		9.8%
p	0.001	0.01	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) (17)						
TIF			55%	-14.1	-19%	50%
Continued PPI			5%	-3.1	-20%	63%
p			<0.001	<0.001	>0.05	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; RCT: randomized controlled trial; 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 LES 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 ($p<0.05$), 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 hiatal hernia. Although this RCT met its principal endpoint at 6 months, and improvements in GERD symptoms appeared to be maintained to 12 months, long-term reflux control was not achieved.

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. (21)

In a prospective cohort study of 50 individuals by Testoni et al. (2015, 2019), 72% of the patients were completely responsive to PPIs at baseline, and 24% were partially responsive. (22, 23) 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 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. (24) 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 PPIs

Study	Country	Participants	Treatment Delivery	Mean FU, mo

Stefanidis et al. (2017) (21)	Greece	PPI-controlled, hiatal hernia ≤ 2 cm	EsophyX2	59
Testoni et al. (2015, 2019) (22, 23)	Prospective study from 1 center in Italy	Daily PPI, esophagitis or abnormal pH, hiatal hernia ≤ 2 cm	EsophyX2	53
Testoni et al. (2022) (24)	Italy	Daily PPI, chronic GERD, endoscopic GERD or Barrett's esophagus <3 cm	MUSE	Mean NR; total follow-up 36 m

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

Table 13. Long-Term Durability of TIF in Patients Whose Symptoms Were Controlled by PPIs

Outcomes	Mean Baseline	6 Months	1 Year	2 Years	3 Years	6-7 Years	10 Years
Stefanidis et al. (2017) (21)							
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) (22, 23)							
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) (24)							
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; TIF: transoral incisionless fundoplication.

[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 meta-analysis of TIF for the treatment of GERD. (25) 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: TIF for Symptoms Controlled by PPIs

The evidence on TIF in patients whose symptoms are controlled by PPIs includes two 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, although the limited evidence beyond 2 years is consistent with some loss in treatment effectiveness.

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 policy.

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 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.

Systematic Reviews

A meta-analysis of 4 RCTS (N=165 patients) was published by Lipka et al. (2015) (Table 14). (26) Three trials (27, 28, 29) compared Stretta with sham, and one trial (30) 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. (29) Aziz et al. (2010) found statistically significant improvements in GERD-HRQL scores in all

treatment groups. (28) Arts et al. (2012) reported that the symptom score and QOL score for bodily pain improved, but no changes were observed in PPI use, esophageal acid exposure, or lower esophageal sphincter (LES) pressure after radiofrequency (RF). (27) 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 discontinue 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. (31) Pooled results showed that the Stretta reduced (improved the health-related quality of life score by -14.6 [-16.48, -12.13] (P<0.001). Stretta also reduced (improved) the pooled heartburn standardization score by -1.53 [-1.97, -1.09] (P<0.001). After Stretta treatment, only 49% of the patients using proton inhibitors (PPIs) at baseline required PPIs at follow-up (P<0.001). The Stretta treatment reduced the incidence of erosive esophagitis by 24% (P 0.001) and reduced esophageal acid exposure by a mean of -3.01 [-3.72, -2.30] (P<0.001). Lower esophageal sphincter (LES) basal pressure was increased post Stretta therapy by a mean of 1.73 (-0.374] mmHg (P=NS). The study concluded that the Stretta procedure significantly improves subjective and objective clinical endpoints (with the exception of LES basal pressure) and therefore should be considered as a viable alternative in managing GERD.

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. (32) 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 quality of life 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.

Table 14. Meta-Analytic Characteristics

Study	Dates	Trials	Participants	N (Range)	Design	Duration, months
Fass et al. (2017) (31)	Inception to May 2016	28	Patients with GERD undergoing endoscopic radiofrequency (Stretta)	2468 (9-558)	Meta-analysis of 4 RCTs, 23 cohort studies, and 1 registry	3-120

Lipka et al. (2015) (26)	Inception to Feb 2014	4	Patients with physiologic evidence of GERD who were on PPI therapy	165 (22-64)	Meta-analysis of RCTs	6-12
Xie et al. (2021) (32)	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; N: Number; PPI: proton pump inhibitor; RCT: randomized controlled trial.

Table 15. Meta-Analytic 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) (31)					
Patients (studies), n	637 (12)	507 (11)	1795 (23)	364 (11)	407 (8)
Change (95% CI)	-0.53 (-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 (0.49 to 0.60)	-3.01 (-3.72 to -2.30)	-13.79 (-20.01 to -7.58)
p	<0.001	<0.001	<0.001	<0.001	<0.001
I^2 (p)	Significant in all subgroups (p<0.001)	RCTs: NS Cohort: 85% (<0.001)	RCTs: NS Cohort: 95% (<0.001)	Not significant in any subgroup	77%
	Ability to Stop PPI Therapy				*Mean LES Pressure*

Lipka et al. (2015) (26)					
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 mm Hg (-2.66 to 2.02 mm Hg)
p	0.06	0.18		0.46	0.79
I^2 (p)	0%	96% (<0.001)		99% (<0.001)	96% (<0.001)
Range of N	24-51	22-64		22-64	

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

Observational Studies

In 2023, Joel et al. published a prospective observational study that evaluated the clinical outcomes of Stretta in patients with medically refractory GERD. (33) The data of all patients who underwent Stretta from October 2014 were included in the analysis. A total of 195 patients underwent Stretta between October 2014 and June 2022 in a UK tertiary center. Patients and primary care professionals were contacted to obtain information regarding the initiation of PPI and reintervention after Stretta. No procedure-related complications occurred. Of the 195 patients, 144 (73.8%) patients were contacted, and PPI-free period (PFP) and reintervention details were confirmed. Overall, 66 patients (45.8%) did not receive PPI after a median follow-up of 55 months. Six patients (3.1%) underwent further interventions. The median PFP after Stretta was 41 months. There was a significant negative correlation between PFP and age (p=0.007), with no differences between sexes (p=0.96). Patients younger than 55 years of age had a longer PFP than their older counterparts (p=0.005). Younger males had a significantly longer PFP than older males (p=0.021). However, this was not observed in the female cohort (p=0.09) or between the younger men and women (p=0.66). As one of the largest studies in Europe, researchers suggest that Stretta is a safe and feasible option for treating refractory GERD, especially in younger patients. It prevents further anti-reflux interventions in most patients and increases the lead-time to surgery in patients with refractory GERD.

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) After 3 months post-procedure, the QOL score increased from 20% to 80% in the Stretta group compared to 20% to 30% in the sham group (p<0.05). There was a significant decrease in the score for heartburn, regurgitation, chest pain, and cough in the Stretta group but not the control group (p<0.05). There were no significant differences in LES pressure between the groups. PPI therapy was eliminated in 60% of the Stretta group, whereas there was no change in the control group. Overall, 80% of the

Stretta group was satisfied compared to 30% of the control group. Short-term outcomes such as GERD symptoms and cessation of PPIs appeared improved for the Stretta group.

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). 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 (TERF) With Laparoscopic Fundoplication

Liang et al. (2015) reported a prospective comparison of laparoscopic Toupet fundoplication with the Stretta procedure (Table 16). (36) Of the 165 patients treated, 125 (76%) completed the 3-year follow-up (65 fundoplication, 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.

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).

Table 16. Characteristics of Studies Comparing TERF 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, y: year.

Table 17. Results Comparing TERF With Laparoscopic Fundoplication

Study	PPI Indepen-dence	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	0.627	0.01	0.004	0.005	0.006	0.120
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) (39) reported symptom improvement in 72% of patients and elimination of dysplasia in 85% of patients.

Table 18. Cohort Study and Case Series Characteristics

Study	Country/Institution	Participants	Follow-Up, years	Loss to Follow-Up
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)

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: TERF (Stretta Procedure)
Based on existing evidence, Stretta has been shown to improve GERD-related symptoms such as heartburn, regurgitation, chest pain, and cough. Additionally, PPI cessation was achieved in more than 50% of treated patients. Although the effectiveness of the procedure diminishes some over time, persistent effects have been described up to 10 years after the procedure in appropriately selected patients with GERD.

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 policy.

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.

Durasphere
The available evidence for Durasphere consists of a single case series. One open-label pilot study by Ganz et al. (2009) assessed of 10 GERD patients injected Durasphere (Carbon Medical Technologies), a bulking agent approved for treatment of urinary and fecal incontinence, at the gastroesophageal junction. (40) At 12 months, 7 patients (70%) discontinued all antacid

medication completely. No erosion, ulceration, or sloughing of 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 preclude 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.

Summary of Evidence

For individuals who have gastroesophageal reflux disease (GERD) and a hiatal hernia of 2 cm or less that is not controlled by proton pump inhibitors (PPIs) who receive transoral incisionless fundoplication (TIF) (e.g., EsophyX; MUSE), the evidence includes 2 randomized controlled trials (RCTs) comparing TIF with PPI therapy, nonrandomized studies comparing TIF with fundoplication, and case series with longer term follow-up. The relevant outcomes are symptoms, change in disease status, quality of life (QOL), medication use, and treatment-related morbidity. The highest quality RCT (RESPECT) was sham-controlled and compared TIF with PPI therapy while the other RCT (TEMPO) compared TIF with maximum PPI therapy. Both trials found a significant benefit of TIF on the primary outcome measure in about 65% of patients. The evidence is considered sufficient to determine the effects of the technology on health outcomes.

For individuals who have GERD and a hiatal hernia of 2 cm or less that is controlled by PPIs who receive TIF (e.g., EsophyX; MUSE), the evidence includes 2 RCTs and observational studies with longer-term follow-up. The relevant outcomes are symptoms, change in disease status, quality of life, medication use, and treatment-related morbidity. A sham-controlled trial found that 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 evidence is considered sufficient to determine the effects of the technology on health outcomes.

For individuals who have GERD who receive endoscopic radiofrequency energy (e.g., Stretta), the evidence includes 2 meta-analyses, a network meta-analysis, 6 small RCTs, 2 nonrandomized comparative studies, and observational studies with longer term follow-up. The

relevant outcomes are symptoms, change in disease status, QOL, medication use, and treatment-related morbidity. The RCTs reported some improvements in symptoms and QOL following treatment with radiofrequency energy compared with sham controls. The evidence is considered sufficient to determine the effects of the technology on health outcomes.

For individuals who have GERD who receive esophageal bulking agents, the evidence includes case series. The relevant outcomes are symptoms, change in disease status, QOL, medication use, and treatment-related morbidity. 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 whether subjective improvement (e.g., discontinuation of medication therapy, GERD-HRQL scores) is supported by objective improvement (e.g., esophageal acid exposure). The evidence is insufficient to determine that the technology results in an improvement in the net health outcomes.

Practice Guidelines and Position Statements

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)."

Society of American Gastrointestinal and Endoscopic Surgeons

In 2017, the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) provided a clinical spotlight review on endoluminal treatments for GERD. (44) The SAGES gave a strong recommendation based on moderate-quality evidence that transoral incisionless fundoplication (TIF) using EsophyX can be performed with an acceptable safety risk in selected patients. The SAGES concluded that EsophyX results in better control of GERD symptoms than PPI treatment in the short term (six months), and lead to similar improvements 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. The SAGES found no comparative, controlled trials between TIF and surgical fundoplication, but preliminary evidence suggested that surgical fundoplication can be used safely after TIF failure.

The 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 was found to decrease PPI use by about 50%, and be more effective than PPIs, but less effective compared to fundoplication.

American Society for Gastrointestinal Endoscopy

In 2015, the American Society for Gastrointestinal Endoscopy published guidelines on endoscopic procedures for GERD. (45) 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 end point could be useful in defining the clinical role of these procedures.

American Society of General Surgeons

In 2011, the American Society of General Surgeons (ASGS) issued a position statement on transoral fundoplication in 2011 stating that "ASGS supports the use of transoral fundoplication by trained General Surgeons for the treatment of symptomatic chronic 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." (46)

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. (47) 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, the National Institute for Health and Care Excellence (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…" (48) 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, the 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…" (49)

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this policy are listed in Table 20.

Table 20. Summary of Key Trials

NCT Number	Trial Name	Planned Enrollment	Completion Date
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

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	43192, 43201, 43210, 43212, 43236, 43253, 43257, 43266, 43289, 43499
HCPCS Codes	None

*Current Procedural Terminology (CPT®) ©2023 American Medical Association: Chicago, IL.

References

1. Katz PO, Gerson LB, Vela MF. Guidelines for the diagnosis and management of gastroesophageal reflux disease. Am J Gastroenterol. Mar 2013; 108(3):308-328; quiz 329. PMID 23419381
2. van Pinxteren B, Sigterman KE, Bonis P, et al. Short-term treatment with proton pump inhibitors, H2-receptor antagonists and prokinetics for gastro-oesophageal reflux disease-like symptoms and endoscopy negative reflux disease. Cochrane Database Syst Rev. Nov 10, 2010; (11):CD002095. PMID 21069670
3. Khan F, Maradey-Romero C, Ganocy S, et al. Utilisation of surgical fundoplication for patients with gastro-oesophageal reflux disease in the USA has declined rapidly between 2009 and 2013. Aliment Pharmacol Ther. Jun 2016; 43(11):1124-1131. PMID 27060607
4. Ihde GM. The evolution of TIF: transoral incisionless fundoplication. Therap Adv Gastroenterol. 2020; 13:1756284820924206. PMID 32499834
5. U.S. Food and Drug Administration (FDA). 510(k) Summary: EsophyX (K160960) (2016). Available at: <https://www.accessdata.fda.gov> (accessed October 18, 2023).
6. U.S. Food and Drug Administration (FDA). EsophyX Summary (K171307) (2017). Available at: <https://www.accessdata.fda.gov> (accessed October 19, 2023).
7. U.S. Food and Drug Administration (FDA). EsophyX Summary (K172811) (2017). Available at: <https://www.accessdata.fda.gov> (accessed October 20, 2023).
8. McCarty TR, Itidiare M, Njei B, et al. Efficacy of transoral incisionless fundoplication for refractory gastroesophageal reflux disease: a systematic review and meta-analysis. Endoscopy. Jul 2018; 50(7):708-725. PMID 29625507
9. Richter JE, Kumar A, Lipka S, et al. Efficacy of laparoscopic Nissen fundoplication vs transoral incisionless fundoplication or proton pump inhibitors in patients with gastroesophageal reflux disease: a systematic review and network meta-analysis. Gastroenterology. Apr 2018; 154(5):1298-1308 e1297. PMID 29305934
10. Testoni S, Hassan C, Mazzoleni G, et al. Long-term outcomes of transoral incisionless fundoplication for gastro-esophageal reflux disease: systematic-review and meta-analysis. Endosc Int Open. Feb 2021; 9(2):E239-E246. PMID 33553587
11. Rausa E, Ferrari D, Kelly ME, et al. Efficacy of laparoscopic Toupet fundoplication compared to endoscopic and surgical procedures for GERD treatment: a randomized trials network meta-analysis. Langenbecks Arch Surg. Jan 21 2023; 408(1):52. PMID 36680602
12. Hunter JG, Kahrilas PJ, Bell RC, et al. Efficacy of transoral fundoplication vs omeprazole for treatment of regurgitation in a randomized controlled trial. Gastroenterology. Feb 2015; 148(2):324-333 e325. PMID 25448925
13. Trad KS, Barnes WE, Simoni G, et al. Transoral incisionless fundoplication effective in eliminating GERD symptoms in partial responders to proton pump inhibitor therapy at 6 months: the TEMPO Randomized Clinical Trial. Surg Innov. Feb 2015; 22(1):26-40. PMID 24756976
14. Trad KS, Fox MA, Simoni G, et al. Transoral fundoplication offers durable symptom control for chronic GERD: 3-year report from the TEMPO randomized trial with a crossover arm. Surg Endosc. Jun 2017; 31(6):2498-2508. PMID 27655380

15. Trad KS, Barnes WE, Prevou ER, et al. The TEMPO Trial at 5 years: transoral fundoplication (TIF 2.0) Is safe, durable, and cost-effective. Surg Innov. Apr 2018; 25(2):149-157. PMID 29405886
16. Hakansson B, Montgomery M, Cadiere GB, et al. Randomised clinical trial: transoral incisionless fundoplication vs. sham intervention to control chronic GERD. Aliment Pharmacol Ther. Dec 2015; 42(11-12):1261-1270. PMID 26463242
17. Witteman BP, Conchillo JM, Rinsma NF, et al. Randomized controlled trial of transoral incisionless fundoplication vs. proton pump inhibitors for treatment of gastroesophageal reflux disease. Am J Gastroenterol. Apr 2015; 110(4):531-542. PMID 25823768
18. Toomey P, Teta A, Patel K, et al. Transoral incisionless fundoplication: is it as safe and efficacious as a Nissen or Toupet fundoplication? Am Surg. Sep 2014; 80(9):860-867. PMID 25197871
19. Frazzoni M, Conigliaro R, Manta R, et al. Reflux parameters as modified by EsophyX or laparoscopic fundoplication in refractory GERD. Aliment Pharmacol Ther. Jul 2011; 34(1):67-75. PMID 21539587
20. Bell RCW, Freeman K, Heidrick R, et al. Transoral incisionless fundoplication demonstrates durability at up to 9 years. Therap Adv Gastroenterol. 2021; 14:17562848211004827. PMID 33948113
21. Stefanidis G, Viazis N, Kotsikoros N, et al. Long-term benefit of transoral incisionless fundoplication using the esophyx device for the management of gastroesophageal reflux disease responsive to medical therapy. Dis Esophagus. Feb 01, 2017; 30(3):1-8. PMID 27868281
22. Testoni PA, Testoni S, Mazzoleni G, et al. Long-term efficacy of transoral incisionless fundoplication with Esophyx (Tif 2.0) and factors affecting outcomes in GERD patients followed for up to 6 years: a prospective single-center study. Surg Endosc. Sep 2015; 29(9):2770-2780. PMID 25480624
23. Testoni PA, Testoni S, Distefano G et al. Transoral incisionless fundoplication with EsophyX for gastroesophageal reflux disease: clinical efficacy is maintained up to 10 years. Endosc Int Open. May 2019; 7(5):E647-E654. PMID 31058207
24. Testoni SGG, Cilona MB, Mazzoleni G, et al. Transoral incisionless fundoplication with Medigus ultrasonic surgical endostapler (MUSE) for the treatment of gastro-esophageal reflux disease: outcomes up to 3 years. Surg Endosc. Jul 2022; 36(7):5023-5031. PMID 34799745
25. Huang X, Chen S, Zhao H, et al. Efficacy of transoral incisionless fundoplication (TIF) for the treatment of GERD: a systematic review with meta-analysis. Surg Endosc. Mar 2017; 31(3):1032-1044. PMID 27495332
26. Lipka S, Kumar A, Richter JE. No evidence for efficacy of radiofrequency ablation for treatment of gastroesophageal reflux disease: a systematic review and meta-analysis. Clin Gastroenterol Hepatol. Jun 2015; 13(6):1058-1067 e1051. PMID 25459556
27. Arts J, Bisschops R, Blondeau K, et al. A double-blind sham-controlled study of the effect of radiofrequency energy on symptoms and distensibility of the gastro-esophageal junction in GERD. Am J Gastroenterol. Feb 2012; 107(2):222-230. PMID 22108449

28. Aziz AM, El-Khayat HR, Sadek A, et al. A prospective randomized trial of sham, single-dose Stretta, and double-dose Stretta for the treatment of gastroesophageal reflux disease. Surg Endosc. Apr 2010; 24(4):818-825. PMID 19730952
29. Corley DA, Katz P, Wo JM, et al. Improvement of gastroesophageal reflux symptoms after radiofrequency energy: a randomized, sham-controlled trial. Gastroenterology. Sep 2003; 125(3):668-676. PMID 12949712
30. Coron E, Sebille V, Cadiot G, et al. Clinical trial: Radiofrequency energy delivery in proton pump inhibitor-dependent gastro-oesophageal reflux disease patients. Aliment Pharmacol Ther. Nov 1, 2008; 28(9):1147-1158. PMID 18616516
31. Fass R, Cahn F, Scotti DJ, et al. Systematic review and meta-analysis of controlled and prospective cohort efficacy studies of endoscopic radiofrequency for treatment of gastroesophageal reflux disease. Surg Endosc. Dec 2017; 31(12):4865-4882. PMID 28233093
32. Xie P, Yan J, Ye L, et al. Efficacy of different endoscopic treatments in patients with gastroesophageal reflux disease: a systematic review and network meta-analysis. Surg Endosc. Apr 2021; 35(4):1500-1510. PMID 33650003
33. Joel A, Konjengbam A, Viswanath Y, et al. Endoscopic radiofrequency Stretta therapy reduces proton pump inhibitor dependency and the need for anti-reflux surgery for refractory gastroesophageal reflux disease. Clin Endosc. Jan 2024; 57(1):58-64. PMID 37157958
34. Kalapala R, Shah H, Nabi Z, et al. Treatment of gastroesophageal reflux disease using radiofrequency ablation (Stretta procedure): An interim analysis of a randomized trial. Indian J Gastroenterol. Sep 2017; 36(5):337-342. PMID 29030802
35. Zerbib F, Sacher-Huvelin S, Coron E, et al. Randomised clinical trial: oesophageal radiofrequency energy delivery versus sham for PPI-refractory heartburn. Aliment Pharmacol Ther. Aug 2020; 52(4):637-645. PMID 32656869
36. Liang WT, Yan C, Wang ZG, et al. Early and midterm outcome after laparoscopic fundoplication and a minimally invasive endoscopic procedure in patients with gastroesophageal reflux disease: a prospective observational study. J Laparoendosc Adv Surg Tech A. Aug 2015; 25(8):657-661. PMID 26258269
37. Ma L, Li T, Liu G, et al. Stretta radiofrequency treatment vs Toupet fundoplication for gastroesophageal reflux disease: a comparative study. BMC Gastroenterol. May 27 2020; 20(1):162. PMID 32460696
38. Liang WT, Wang ZG, Wang F, et al. Long-term outcomes of patients with refractory gastroesophageal reflux disease following a minimally invasive endoscopic procedure: a prospective observational study. BMC Gastroenterol. 2014; 14:178. PMID 25304252
39. Noar M, Squires P, Noar E, et al. Long-term maintenance effect of radiofrequency energy delivery for refractory GERD: a decade later. Surg Endosc. Aug 2014; 28(8):2323-2333. PMID 24562599
40. Ganz RA, Fallon E, Wittchow T, et al. A new injectable agent for the treatment of GERD: results of the Durasphere pilot trial. Gastrointest Endosc. Feb 2009; 69(2):318-323. PMID 19185691
41. Feretis C, Benakis P, Dimopoulos C, et al. Endoscopic implantation of Plexiglas (PMMA) microspheres for the treatment of GERD. Gastrointest Endosc. Apr 2001; 53(4):423-426. PMID 11275880

42. Yadlapati R, Gyawali CP, Pandolfino JE, et al. AGA Clinical Practice Update on the Personalized Approach to the Evaluation and Management of GERD: Expert Review. Clin Gastroenterol Hepatol. May 2022; 20(5):984-994.e1. PMID 35123084
43. Katz PO, Dunbar KB, Schnoll-Sussman FH, et al. ACG Clinical Guidelines for the Diagnosis and Management of Gastroesophageal Reflux Disease. Am J Gastroenterol. Jan 2022; 117:27-56. PMID 34807007
44. Society of American Gastrointestinal and Endoscopic Surgeons. Clinical Spotlight Review: Endoluminal Treatments for Gastroesophageal Reflux Disease (GERD) (2017). Available at: <https://www.sages.org> (accessed May 7, 2024).
45. Muthusamy VR, Lightdale JR, Acosta RD, et al. The role of endoscopy in the management of GERD. Gastrointest Endosc. 2015; 81(6):1305-1310. PMID 25863867
46. American Society of General Surgeons (ASGS). Coverage of Transoral fundoplication (2011). Available at: <https://www.theasgs.org> (accessed October 20, 2023).
47. Slater BJ, Collings A, Dirks R, et al. Multi-society consensus conference and guideline on the treatment of gastroesophageal reflux disease (GERD). Surg Endosc. Feb 2023; 37(2):781-806. PMID 36529851
48. National Institute for Health and Care Excellence (NICE). Endoscopic radiofrequency ablation for gastro-oesophageal reflux disease [IPG461] (2013). Available at: <https://www.nice.org> (accessed October 19, 2023).
49. National Institute for Health and Care Excellence (NICE). Endoluminal gastroplication for gastro-oesophageal reflux disease [IPG404] (2011). Available at: <https://www.nice.org> (accessed October 18, 2023).

Centers for Medicare and Medicaid Services (CMS)

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The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision

Date	Description of Change
06/15/2024	Document updated with literature review. No change to coverage. Added references 11, 24, 33, 42, 45, and 47.
09/15/2023	Reviewed. No changes.
08/15/2022	Document updated with literature review. The following change was made to Coverage: Added MUSE as an example of a transoral incisionless

	fundoplication procedure. The following references were added: 3, 4, 7, 10, 19, 29, 32, 34, and 40.
11/01/2021	Reviewed. No changes.
02/01/2021	Document updated with literature review. The following change was made to Coverage: Transesophageal radiofrequency to create submucosal thermal lesions of the gastroesophageal junction (e.g., Stretta™ procedure) was changed from experimental, investigational, and/or unproven to conditionally medically necessary. Reference 18 added.
06/15/2019	Document updated with literature review. Coverage unchanged. Added the following references: 4, 6, 7, 10, 11, 16, 18, 19, 26, and 34.
04/15/2018	Reviewed. No changes.
07/15/2017	Document updated with literature review. Coverage unchanged.
07/15/2016	Document partially updated with literature review. The following coverage change was made: "Transendoscopic therapy as a treatment for gastroesophageal reflux disease (GERD) maybe considered medically necessary for transesophageal endoscopic gastroplasty also known as endoscopic gastroplication, fundoplication or transoral incisionless fundoplication [TIF] (e.g., StomaphyX™, EsophyX™) when meeting ALL the following criteria:Age 18+; Confirmed GERD by endoscopy, ambulatory PH, or barium swallow testing; Greater than one year of GERD symptoms (reflux symptoms that occur 2 to 3 times per week); History of daily PPI's for > six months; GERD patients with BMI ≤ 35; No Hiatal hernia >2 cm; No Esophagitis LA (Los Angeles classification system) grade C or D; No Barrett's esophagus >2 cm; Absence of achalasia and esophageal ulcer; No altered esophageal anatomy that would prevent insertion of a device; Esophageal motility disorder; and Previous history of failed antireflux surgery.
04/01/2016	Document updated with literature review. Coverage criteria regarding a laparoscopically implantable magnetic esophageal ring (LINX™ Reflux Management System) was removed and is now addressed on new medical policy document SUR709.036 Magnetic Esophageal Ring to Treat Gastroesophageal Reflux Disease (GERD). Otherwise coverage unchanged.
04/15/2015	Document updated with literature review. Coverage unchanged.
06/15/2013	Document updated with literature review. The following was added: (1) Durasphere and Gatekeeper Reflux Repair System added as examples of an endoscopic submucosal injection or implantation of a prosthetic or bulking agent. (2) A laparoscopically implantable magnetic esophageal ring (LINX™ Reflux Management System) as a treatment device for GERD is considered experimental, investigational and unproven. Title changed from Transendoscopic Therapies for Gastroesophageal Reflux Disease (GERD).
05/15/2011	Document updated with literature review. Coverage unchanged.
09/15/2009	Revised/updated entire document. No change in experimental, investigational, and unproven coverage position. Additional new trade name

	(EsophyX™) for performing transesophageal endoscopic gastroplasty or gastroplication added to the coverage section.
01/15/2007	Revised/updated entire document
10/01/2004	Revised/updated entire document
08/01/2002	New medical document