Medical Policy

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Title: Transesophageal Endoscopic Therapies for Gastroesophageal Reflux Disease (GERD) (*Transoral Incisionless Fundoplication – TIF)*

Description/Background

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 (RF) energy, and injection/implantation of prosthetic devices or bulking agents.

Gastroesophageal Reflux Disease

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

Pathophysiology

The pathophysiology of GERD involves excessive exposure to stomach acid, which occurs for 1 of 3 reasons. There can be an incompetent barrier between the esophagus and stomach, due to either dysfunction of the lower esophageal sphincter (LES) or incompetence of the diaphragm. Another mechanism is abnormally slow clearance of stomach acid by the esophagus. A third mechanism is abnormally slow clearance of acid by the stomach. 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] PPIs have been shown to be the most effective medical treatment. In a Cochrane systematic review, PPIs demonstrated superiority to H_2-receptor agonists and prokinetics in both network meta-analyses and direct comparisons.[2]

Surgical Treatment

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

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

Other Treatment Options

Due in part to the high prevalence of gastroesophageal reflux disease (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 or transoral incisionless fundoplication [TIF]) 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 lower esophageal sphincter has also been investigated. One bulking agent, pyrolytic carbon-coated zirconium oxide spheres (Durasphere®), is being evaluated. The Gatekeeper™ Reflux Repair System (Medtronic, Shoreview, MN) uses a soft, pliable, expandable prosthesis made of a polyacrylonitrile-based hydrogel. The prosthesis is implanted into the esophageal submucosa, and with time, the prosthesis absorbs water and expands, creating bulk in the region of implantation.

The Agency for Healthcare Research and Quality published a systematic review of management strategies for GERD in 2005, which was updated by Ip et al (2011).[4,5,] The 2005 comparative effectiveness review evaluated studies on the EndoCinch Suturing System, Stretta, Enteryx, and the NDO Plicator.[4,] The 2011 update excluded Enteryx and the NDO Plicator, because they were no longer available in the US, and added the EsophyX procedure (endoscopic fundoplication), which was commercialized after the 2005 review.[5,] The 2011 report, which is now archived meaning that the findings may be used for research purposes but should not be considered current, concluded that, for the 3 available endoscopic procedures (EndoCinch, Stretta, EsophyX), effectiveness remained substantially uncertain for the long-term management of GERD. All procedures have been associated with complications, including dysphagia, infection/fever, and bloating, although bloating and dysphagia are also adverse events of laparoscopic fundoplication.[6,] A review of endoscopic treatment of GERD by Hummel and Richards (2015) noted that EndoCinch is no longer manufactured.[7,]

Regulatory Status:

The EsophyX® (EndoGastric Solutions) is a TIF device that was originally cleared for marketing by the FDA through the 510(k) process in 2007 and has subsequently undergone 2 evolutions: Generation 2=EsophyX2 iterations (E2-Plus, HD) and Generation 3=Z iterations (EZ/ZR, Z+).[8] In 2007, EsophyX® (EndoGastric Solutions, Redmond, WA) was cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process for full-thickness plication. In 2016, EsophyX® Z Device with SerosaFuse Fasteners was cleared for marketing (K160960) by FDA through the 510(k) process for use in transoral tissue approximation, full thickness plication, ligation in the gastrointestinal tract, narrowing the gastroesophageal junction, and reduction of hiatal hernia of 2 cm or less in patients with symptomatic chronic gastroesophageal reflux disease (GERD).[9] In June 2017, EsophyX2 HD and the third-generation EsophyX Z Devices with SerosaFuse fasteners and accessories were cleared for marketing by the FDA through the 510(k) process (K171307) for expanded indications, including patients who require and respond to pharmacologic therapy and patients with hiatal hernias larger than 2 cm when a laparoscopic hiatal hernia repair reduces a hernia to 2 cm or less.[10,] 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."[11,] FDA product code: ODE.

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

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

Durasphere® is a bulking agent approved for treatment of urinary and fecal incontinence. Use of this product for esophageal reflux would be considered off-label use. The website of Carbon Medical Technologies states that Durasphere GR is an investigational device in the United States "intended to treat problems associated with GERD."

Medical Policy Statement

Transesophageal endoscopic therapies are considered experimental/investigational as a treatment of gastroesophageal reflux disease. These procedures include, but are not limited to the following:

- Transesophageal endoscopic gastroplasty (gastroplication or transoral incisionless fundoplication [TIF]) procedures, including but not limited to the EndoCinch™ procedure, the EsophyX® procedure, the Syntheon ARD Plicator, the Bard™ Endoscopic Suturing System [BESS], StomaphyX™, the Endoscopic Plication System etc.
- Transesophageal radiofrequency to create submucosal thermal lesions of the gastroesophageal junction (i.e., the Stretta™ procedure).
- Endoscopic submucosal implantation of a prosthesis or injection of a bulking agent (e.g., polymethylmethacrylate beads, zirconium oxide spheres).

These procedures have not been scientifically demonstrated to be as safe and effective for the treatment of GERD as conventional medical and/or surgical management.

Inclusionary and Exclusionary Guidelines

N/A

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure)*

Established codes:

43201** 43212 43236**

***Note: 43201 and 43236 are considered experimental/investigational when used for the treatment of gastroesophageal reflux (GERD), diagnosis codes K21.0 and K21.9. 43201 and 43236 are considered established for all other indications (e.g., esophageal tattooing, injection of corticosteroids, etc.)*

Other codes (investigational, not medically necessary, etc.):

43210 43257 43499

Rationale

Evidence reviews 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, 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 (ESOPHYX®) FOR PATIENTS WHOSE SYMPTOMS ARE NOT CONTROLLED BY PROTON PUMP INHIBITORS

Clinical Context and Therapy Purpose

The purpose of transoral incisionless fundoplication (TIF; e.g., EsophyX) 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 hernia of 2 cm or less that is not controlled by proton pump inhibitors (PPIs).

The following **PICOs** were used to select literature to inform this review.

Populations

The relevant population of interest are individuals with GERD and hiatal hernia of 2 cm or less that is not controlled by PPIs.

Interventions

The therapy being considered is TIF2.0 (e.g., EsophyX2).

Comparators

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

Outcomes

The general outcomes of interest are symptoms, change in disease status, quality of life, mediation use, and treatment-related morbidity.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

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

Systematic Reviews

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

Richter et al (2018) published a network meta-analysis of RCTs comparing TIF and laparoscopic Nissen fundoplication (LNF) with sham or PPIs.[14] The meta-analysis was limited by low-quality studies (one did not report randomization method, others lacked data regarding allocation concealment, blinding of outcome assessors, or other aspects of study protocol). It should be noted that one reason behind the scarcity of direct comparison 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 esophagitis grades A-D (LA) and all sizes of hiatal hernia.

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).[15,] Outcomes of interest included patient satisfaction, QOL, and PPI use. The mean follow-up time across studies was 5.3 years (range: 3 to 10 years). Daily PPI use was 100% in 5 studies, 97% in 1 study, and was not provided in the other 2 studies. Overall, the pooled proportion of patient-reported satisfaction before and after TIF was 12.3% and 70.6%, respectively. Additionally, the pooled rates of patients completely off, or on occasional, PPIs post-TIF was 53.8% and 75.8%. The analysis was limited by various factors including the nature of included studies, which involved only 1 open-label RCT among the 8 studies included, and the high heterogeneity across studies for patient reported overall satisfaction after the TIF procedure.

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

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

Table 1. Characteristics of Systematic Reviews

Study	Dates	Trials	Participants	N (Range)	Design	Duration
McCarty et al (2018)	2008-2016	32	Patients me standard criteria for the TIF procedure[a]	1475 (10-124)	5 RCTs, 21 prospective studies, 6 retrospective	NR
Richter et al (2018)	NR	7	Patients had GERD, established by endoscopic results indicating erosive esophagitis and/or		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

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

GERD: gastroesophageal reflux disease; LNF: laparoscopic Nissen fundoplication; NR: not reported; PPI: proton pump inhibitor; RCT: randomized controlled trial; TIF: transoral incisionless fundoplication.
[a] Body mass index <35 kg/m^2; hiatal hernia size of ≤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 pH <4 of ≥4.0%.

Table 2. Results of Systematic Reviews

Study	Complete PPI Cessation	GERD HRQOL	GERSS Score	RSI Score	Other Objective Measures
McCarty et al (2018)					
				Esophageal Acid Exposure (1% time with pH <4)	
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			53.18
		(17.19 to 18.05)			(49.49 to 56.87)
p		<0.001			<0.001
Richter et al (2018)					
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)					
	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			<0.001		
Rausa et al (2023)					
	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%

CI: confidence interval; GERD: gastroesophageal reflux disease; GERSS: Gastroesophageal Reflux Symptom Score; HRQOL: health-related quality of life; LNF: laparoscopic Nissen fundoplication; MD: mean difference; NR: not reported; OR: odds ratio; PPI: proton pump inhibitor; RSI: Reflux Symptom Index; TIF: transoral incisionless fundoplication.

Randomized Controlled Trials

Two RCTs have evaluated TIF using ExophyX2 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.[16] 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.[17] The primary outcome in both trials was the elimination of symptoms, measured in slightly different ways (see Table 1).

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 in the case of Reflux Disease Questionnaire, which showed significant improvement in the TIF group compared with baseline. Physiologic measurements such as

number of reflux episodes, percent total time pH less than 4, and DeMeester score (a composite score of acid exposure based on esophageal monitoring) showed statistically significant differences between groups, but these measurements were performed when off PPIs for 7 days, and the difference in pH between TIF and continued PPI therapy cannot be determined from this trial.

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

Table 3. Characteristics of Randomized Trials Comparing TIF With Medical Management in Patients Whose Symptoms Were Not Controlled on PPIs

Study	TIF:CTL, n	Patient Symptoms or Other Characteristics	Comparator	FU, mo	Principal Clinical Outcome
Hunter et al (2015) (RESPLECT)	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) (TEMPO)	40:23	• Hiatal hernia ≤2 cm • Troublesome symptoms not controlled on PPI[b]	Maximum-dose PPI	6	Elimination of daily symptoms other than heartburn

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

Table 4. Summary of Key Results for RCTs Comparing TIF With Medical Management in Patients Whose Symptoms Were Not Controlled on PPIs

Trial	Elimination of Symptoms[a]	Change in Regurgitation	Change in Heartburn	Reflux Symptoms	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)					
TIF + placebo	67% (58/87)	-3	-2.1	-2.5	
Sham + PPI	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)					
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
Summary					
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 - composite of 3 gastroesophageal reflux disease symptom scales: the GERD-HRQL, RSI, and RDQ.

Trad et al (2017) reported 3-year follow-up for patients treated with TIF in the TEMPO trial (see Table 5).[18] 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 elimination of troublesome regurgitation.

Trad et al (2018) also reported 5-year follow-up for the TEMPO trial (see Table 5).[19] 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 5-yar follow-up, and 31 (70%) patients expressed satisfaction with the procedure, as assessed by GERD-HRQOL. While data regarding pH normalization were available for 24 patients at 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 (98%)
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). 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 the 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

Table 6. Relevance Limitations

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

The study limitations stated in this table are those notable in the current review; this is not a comprehensive 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[d]	Data Completeness[e]	Power[d]	Statistical[f]
Hunter et al (2015)						
Trad et al (2015)		1, 2. No blinding				1. Within-group analysis only
Hakansson et al (2015)				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)		1, 2. No blinding		1. Study stopped following unplanned interim analysis	1. Power calculations not reported	

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

Nonrandomized Studies

Two nonrandomized comparative studies have compared TIF with laparoscopic fundoplication in patients whose symptoms were not controlled on PPIs.[22,23]

A nonrandomized study by Toomey et al (2014) compared 20 patients undergoing TIF, 20 patients undergoing Nissen fundoplication, and 20 patients undergoing Toupet fundoplication.[22] 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 vs. 65% and 55% of the 2 fundoplication groups, limiting comparison of both treatments. Adverse events were not reported.

Frazzoni et al (2011) compared 10 patients undergoing TIF with 10 patients undergoing laparoscopic fundoplication with the first-generation EsophyX procedure.[23] 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 vs. 0 patients undergoing fundoplication (see Table 8). Mild

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

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

Table 8. Key Nonrandomized Study Characteristics

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

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

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

Study	% 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)						
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.[24,] 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.

Studies Comparing TIF With Continued PPIs

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

Studies Comparing TIF to 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 fundoplication. However, this study was conducted with an earlier device. The Svoboda RCT included patients who underwent the TIF procedure using a different 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 lack of statistically significant differences across symptom outcomes. However, because of the small sizes of these samples, lack of a statistically significant difference in outcomes cannot be interpreted as equivalent outcomes. For these studies, several outcomes favored fundoplication over TIF. The studies did not report adverse events or rates of postoperative symptoms associated with fundoplication (e.g., dysphagia, bloating). Thus, it is not possible to evaluate whether a difference in effectiveness between procedures might be accompanied by a difference in adverse events. Limited data suggest that the first-generation TIF is considerably inferior to laparoscopic fundoplication in patients who have failed PPI therapy, and this treatment is no longer available. Current data are insufficient to determine the risks and benefits of the second-generation TIF procedure compared with laparoscopic fundoplication in patients whose symptoms are not controlled by PPIs.

TIF IN PATIENTS WHOSE SYMPTOMS ARE CONTROLLED BY PPIs

Clinical Context and Therapy Purpose

The purpose of TIF (e.g., EsophyX2) is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with GERD and hiatal hernia of 2 cm or less that is controlled by PPIs.

The following **PICOs** were used to select literature to inform this review.

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

Interventions
The therapy being considered is TIF (e.g., EsophyX2).

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

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

Study Selection Criteria
Methodologically credible studies were selected using the principles outlined in indication 1.

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) with sham only (n=22).[20] 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).[21] 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 trial was treatment failure, defined as the need for resumption of PPIs (see Table 10). The primary outcome of the Witteman 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, 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 vs. 5% of patients on continued PPI therapy (see Table 11). Mean change in GERD symptoms from baseline was consistent with this result (TIF, -14.1; control, -3.1), however, it is uncertain whether the difference between groups was due to a combination of TIF plus PPI, or if the PPI therapy in the control group was at maximum following the step-up protocol.

Secondary outcomes measuring GERD symptoms in Hakansson et al (2015) 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 was reported in twice as many patients undergoing TIF (four, four, and two, respectively) compared

with sham (two, two, and one, 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 RCTs 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)	22/22	Controlled on PPI, run-in to confirm PPI dependence	Sham only	36	Time to resumption of PPI, percent needing PPI at 6 mo
Witteman et al (2015)	40/20	Controlled on PPI; those who received TIF had GERD with hiatal hernias ≤2 cm	Continued PPI only	6	Mean GERD symptoms, percent with >50% improvement

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

Table 11. Results of 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 QOL RAD Score**		**Percent Time pH<4**
Hakansson et al (2015)						
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 GERDHRQL Score	**Mean GERDHRQL Score**	**Percentage With Esophagitis**	**Percent Patients With Normalized pH[a]**
Witteman et al (2015)						
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 Witteman et al (2015), 26% of TIF patients resumed at least occasional PPI use by 6 months, and 100% of control patients remained on PPI therapy. With the exception of lower esophageal sphincter resting pressure, physiologic and endoscopic outcome measures did not differ significantly between groups. No adverse events related to fundoplication were identified on the Symptom Rating Scale.

TIF patients were followed beyond 6 months, with additional control patients who crossed over to have TIF. Sixty patients eventually underwent TIF. Although GERD symptoms remained improved over baseline ($p<0.05$), 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 end point at 6 months, and improvements in GERD symptoms appeared to be maintained for 12 months, long-term reflux control was not achieved, and the authors concluded that "TIF is no[t an] equivalent alternative for PPIs in GERD treatment, even in this highly selected population." The trial was originally designed as a dual-center study, but it was terminated following interim analysis showing loss of reflux control.

Observational Studies

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

A case series and a cohort study have evaluated outcomes to 6 years after TIF 2.0 (see Tables 12 and 13). Both of these 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 in a retrospective series that about 75% of patients had elimination of esophagitis and had discontinued PPI use at 5 years, while 62% of the 13 patients with a hiatal hernia had a reduction in hernia size at follow-up.[25]

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.[26,27] 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. Eight percent of patients had additional surgery for poor response by 2 years. The Johnson-DeMeester score was not significantly improved. A poor response to treatment was associated with a hiatal hernia of 2 cm, higher Hill grade, presence of esophagitis at baseline, and use of fewer fasteners. About half the patients with a complete response initially had gone back to PPI use, although this finding is limited by the low number of patients followed to 6 years. The number of fasteners used in this study might also be lower than current procedures.

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)	Greece	PPI-controlled, hiatal hernia ≤2 cm	EsophyX2	59
Testoni et al (2015, 2019)	Prospective study from 1 center in Italy	Daily PPI, esophagitis or abnormal pH, hiatal hernias ≤2 cm	ExophyX2	53
Testoni et al (2022)	Italy	Daily PPI, chronic GERD, endoscopic GERD or Barrett's esophagus <3 cm	MUSE	Mean NR; total follow-up 36 m

FU: follow-up; 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)							
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)							
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)							
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%)					

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.

Adverse Events

Huang et al (2017) conducted a systematic review with meta-analysis of TIF for the treatment of GERD.[28] They included 5 RCTs and 13 prospective observational studies, of which 14 were performed with the TIF 2 procedure. Efficacy results from the RCTs were combined for patients whose symptoms were controlled by PPIs and for those whose symptoms were not controlled by PPIs and are not further discussed here. Follow-up 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 in Patients Whose Symptoms Are Controlled by PPIs
The evidence on TIF in patients whose symptoms are controlled by PPIs includes 2 RCTs and observational studies with long-term follow-up. The sham-controlled trial by Hakansson et al (2015) found 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 nonblinded trial by Witteman et al found a benefit of TIF compared with continued PPI therapy for subjective measures, but not for the objective measures of pH normalization and esophagitis, raising questions about a possible placebo effect. Extended follow-up of the TIF patients in the Witteman trial found the use of PPI increased over time, while endoscopy showed several findings indicating possible worsening of GERD. The limited evidence beyond 2 years is consistent with some loss of treatment effectiveness. Increased use of PPIs beyond 2 years occurred in Testoni et al (2015). Adverse events associated with the procedure may be severe. Current evidence is insufficient to determine the effect of this intervention on the net health outcome in patients whose symptoms are adequately controlled by PPIs.

TRANSESOPHAGEAL RADIOFREQUENCY (STRETTA PROCEDURE)

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 **PICOs** were used to select literature to inform this review.

Populations
The relevant population of interest are 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 make treat GERD: proton pump inhibitor therapy and laparoscopic fundoplication.

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

Study Selection Criteria
Methodologically credible studies were selected using the principles outlined in indication 1.

Systematic Reviews
A meta-analysis of 4 RCTs (total N=165 patients) was published by Lipka et al (2015) (see Table 14).[29] Three trials compared Stretta with sham, and one compared Stretta with PPI therapy (see Table 15). 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 improvement in

heartburn symptoms, quality of life, and general physical quality of life in the active treatment group compared with the sham group, but there were no significant differences in medication use and esophageal acid exposure.[30] Aziz et al (2010) found statistically significant improvements in GERD-HRQL score in all treatment groups.[31] Arts et al (2012) reported that the symptom score and quality-of-life score for bodily pain improved, but no changes were observed in PPI use, esophageal acid exposure or lower esophageal sphincter pressure after RF.[32] Pooled results of the meta-analysis showed no significant difference between Stretta and either sham treatment or PPI management for the measured outcomes, including the ability to stop PPI therapy (see Table 16). 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 time.

Fass et al (2018) published a meta-analysis of cohort studies and RCTs evaluating Stretta for patients with GERD.[33] When RCT and cohort results were pooled, there were clinically significant treatment effects for several of the endpoints; however, the analysis was limited by the lack of control group in many of the studies. Also, only one of the end points was shared between the four included RCTs.

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.[34,] 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 core induced by Stretta were not significantly different than the improvements seen with TIF (mean difference [MD], 2.45; 95% CI, -2.37 to 7.26); however, both Stretta and TIF were significantly superior to PPIs. Additionally, both Stretta and TIF were significantly better than PPIs at improving heartburn scores. With regard to reduction in PPI use and esophagitis incidence, no significant differences between TIF and Stretta were observed. This network meta-analysis had several limitations including a lack of assessment of long-term efficacy, the inclusion of only 10 studies with even fewer studies evaluated for each individual outcome, and lack of RCTs directly comparing Stretta and TIF. Additionally, some of the comparisons were significantly affected by heterogeneity and the evidence quality of each outcome (as assessed by GRADE) ranged from moderate to very low.

Table 14. Meta-Analytic Characteristics of RCTs Assessing TERF

Study	Dates	Trials	Participants	N (Range)	Design	Duration, mo
Fass et al (2017)	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)	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)	Inception to Dec 2019	10	Patients with GERD diagnosed by typical symptoms, abnormal esophageal acid	516 (20 to 129)	Network meta-analysis of RCTs	3 to 60

			exposure, or esophagitis			

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

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)					
Patients (studies), n	637 (12)	507 (11)	1795 (23)	364 (11)	407 (8)
Change (95% CI)	-1.53 (-1.97 to -1.09)	RCT: -14.56 (-16.63 to -12.48) Cohort: -14.69 (-16.90 to -12.47)	Baseline: 1743 (97.1%) Posttreatment: 850 (49%) RR: 0.49 (0.40 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)					
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)
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; MD: mean difference; PCS: Physical Component Summary; PPI: proton pump inhibitor. RCT: randomized controlled trial; RR; relative risk

Randomized Controlled Trials

Although not included in the meta-analyses tabulated in Tables 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.[36] While short-term outcomes such as GERD symptoms and cessation of PPIs appeared improved for the Stretta group, the study sample was small and power calculations were not conducted.

Zerbib et al (2020) published a double-blind RCT that compared Stretta plus PPI therapy (n=29) to sham plus PPI therapy (n=33) in individuals with PPI-refractory heartburn from 8 French centers.[37] The primary endpoint was clinical success at week 24, defined as an intake of fewer than 7 PPI doses over the previous 2 weeks and adequate subjective patient-reported symptom control. Fewer patients achieved the primary endpoint in the Stretta group, but the difference was not statistically significant (3.4% vs 15.1%; odds ratio [OR]=0.20; 95% CI, 0.02 to 1.88). Severe adverse events were more frequent in the Stretta group (7 vs 2) and included epigastric pain (n = 3), delayed gastric emptying, vomiting, headache, and 1 leiomyoma.

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

Controlled Trials Comparing TERF With Laparoscopic Fundoplication

Liang et al (2015) reported on a prospective comparison of laparoscopic Toupet fundoplication with the Stretta procedure (see Table 17).[38] Of 165 patients treated, 125 (76%) completed the 3-year follow-up (65 fundoplications, 60 Stretta) and were included in the analysis. Although the 2 groups were comparable in symptoms at baseline, 9 patients in the Stretta group had revised treatment and were not included in the final symptom scores. A similar percentage of remaining patients in the 2 groups achieved complete PPI independence and had similar improvements in belching, hiccup, cough, and asthma. The Stretta procedure was less effective than laparoscopic fundoplication in improving symptoms of heartburn, regurgitation, and chest pain (see Table 18). Significantly more patients in the Stretta group underwent reoperation, while more patients in the fundoplication group complained of bloating, but this difference was not statistically significant. This study lacked randomization and, along with not reporting the TERF failures, had a high loss to follow-up. Also, while symptom scores were comparable at baseline, the study may have been subject to selection bias related to treatment choice, which affected baseline differences for other variables.

Ma et al (2020) reported on a retrospective comparison of laparoscopic Toupet fundoplication with the Stretta procedure (see Table 17).[39] 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 (see Table 18), diarrhea (2.3% vs 4.3%; *P*=.792), or chronic stomach pain (2.3% vs 4.3%; *P*=.792). However, compared to laparoscopic Toupet fundoplication, the Stretta group had a high DeMeester score (8.8 vs 7.3; *P*<.05) and less lower esophageal sphincter pressure (11.6 vs 12.8 mmHg; *P*<.05). Important limitations of this study are its single-center design and short follow-up time.

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)[38],	Prospective cohort	China	2011	165	TERF	Laparoscopic fundoplication	3
Ma et al (2020)[39],	Retrospective cohort	China	2014-2017	230	TERF	Laparoscopic fundoplication	1

FU: follow-up; TERF: transesophageal radiofrequency.

Table 17. Results Comparing TERF With Laparoscopic Fundoplication

Study	PPI Independence	Improvement in Heartburn Score	Improvement in Regurgitation Score	Improvement in Chest Pain Score	Reoperation	Bloating
Liang et al (2015)[38],						

TERF	68.3%	2.53	2.41	2.96	11.8%	0%
LF	72.3%	4.05	4.03	5.50	0%	6.2%
p	.627	.01	.004	.005	.006	.120
Ma et al (2020)[39,]						
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-up after TERF were reported in 2014 (see Table 19).[40,41] Elimination of PPI use was similar for both studies at around 42% (see Table 20). Liang et al reported that symptoms of heartburn, regurgitation, chest pain, cough, and asthma were all decreased compared with baseline. Noar et al reported symptom improvement in 72% of patients and elimination of dysplasia in 85% of patients, but the interpretation of these findings is limited due to the 34% loss to follow-up in this study.

Table 18. Cohort Study and Case Series Characteristics

Study	Country/Institution	Participants	FU, y	Loss to FU
Liang et al (2014)[40,]	China	152 who failed PPI therapy	5	9%
Noar et al (2014)[41,]	University of Pittsburgh	149 who failed PPI therapy	10	34% (7% deceased)

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

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

Study	Elimination of PPI Use	Symptom Improvement	Elimination of Dysplasia	Bloating
Liang et al (2014)[40,]	42.8%	p<.001 vs. pretreatment		8.7%
Noar et al (2014)[41,]	41%	72%	85%	

PPI: proton pump inhibitor.

Section Summary: Transesophageal Radiofrequency (Stretta Procedure)

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

ESOPHAGEAL BULKING AGENTS

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

The following **PICOs** were used to select literature to inform this review.

Populations
The relevant population of interest are individuals with GERD.

Interventions
The therapy being considered is esophageal bulking agents.

Comparators
The following therapies and practices are currently being used to make treat GERD: proton pump inhibitor therapy and laparoscopic fundoplication.

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

Study Selection Criteria
Methodologically credible studies were selected using the principles outlined in indication 1.

Durasphere
The available evidence for Durasphere consists of a single case series. One open-label pilot study (2009) of 10 GERD patients injected Durasphere (Carbon Medical Technologies), a bulking agent approved for treatment of urinary and fecal incontinence, at the gastroesophageal junction.[42] At 12 months, 7 (70%) patients 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 2001 case series on transesophageal submucosal implantation of polymethylmethacrylate beads evaluated 10 patients with GERD who were either refractory to or dependent on PPIs.[43] 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 injection of bulking agents includes an RCT terminated early due to lack of efficacy and 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 GERD and hiatal hernia of 2 cm or less that is not controlled by proton pump inhibitors (PPIs) who receive TIF (e.g., EsophyX), 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. Relevant outcomes are symptoms, change in disease status, quality of life, medication use, and treatment-related morbidity. The highest quality RCT (RESPECT) was a sham-controlled together 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, but the sham-controlled trial found improvement in 45% of the sham-controlled group and no benefit on secondary subjective outcome measures. The nonblinded RCT found significant improvements in subjective measures but no difference in objective outcome measures when compared with PPI therapy. Together, these trials suggest a strong placebo effect of the surgery and a modest benefit of TIF in patients whose symptoms are not controlled by PPIs. For these patients, the most appropriate comparator is laparoscopic fundoplication. Studies comparing TIF with fundoplication have limitations that include earlier TIF procedures and unequal groups at baseline and are inadequate to determine relative efficacy. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have GERD and hiatal hernia of 2 cm or less that is controlled by PPIs who receive TIF (e.g., EsophyX), the evidence includes 2 RCTs and observational studies with longer term follow-up. 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 nonblinded RCT found a benefit of TIF compared with continued PPI therapy for subjective measures, but not for the objective measures of pH normalization and esophagitis. These results raise questions about a possible placebo effect for the procedure. Also, observational studies have indicated a loss of treatment effectiveness over time. Adverse events associated with the procedure (e.g., perforation) may be severe. At present, the available evidence does not support the use of this intervention in patients whose symptoms are adequately controlled by medical therapy. The evidence is insufficient 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 6 small RCTs, 2 nonrandomized comparative study, and observational studies with longer term follow-up. Relevant outcomes are symptoms, change in disease status, quality of life, medication use, and treatment-related morbidity. The RCTs report improvements in symptoms and quality of life following treatment with RF energy, however, a meta-analysis of these same studies found no significant improvement in outcomes. Nonrandomized studies show maintenance of efficacy at 3 to 10 years, although symptom relief may be lower than after fundoplication, and reoperations greater. Larger RCTs with longer follow-up are needed to better define the risks and benefits of this procedure. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have GERD who receive esophageal bulking agents, the evidence includes 1 RCT and case series. Relevant outcomes are symptoms, change in disease status, quality of life, medication use, and treatment-related morbidity. The RCT for 1 product was terminated early due to lack of efficacy, while other products have only case series to support use. 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–Health-Related Quality of Life scores) is supported by objective improvement (e.g., esophageal acid exposure). The evidence is insufficient to determine the effects of the technology on health outcomes.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 21.

Table 21. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT04306380	Transoral Incisionless Fundoplication Database Repository (TIF)	500	Dec 2030
NCT03669874	Endoscopic Fundoplication With MUSE System	80	Sept 2026
NCT05066594	Observational Registry of Transoral Incisionless Fundoplication (Creation of a New Gastroesophageal Valve) in Patients With Gastroesophageal Reflux Disease	100	May 2029
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)
NCT02366169a	A worldwide post-market surveillance registry to assess the Medigus Ultrasonic Surgical Endostapler (MUSE™) System for the treatment of GERD	200	Dec 2019

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

SUPPLEMENTAL INFORMATION

Clinical Input Received through Physician Specialty Societies and Academic Medical Centers

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

2015 Input

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

2011 Input

In response to requests for clinical input on TIF using EsophyX, BCBSA received input from 2 physician specialty societies and 4 academic medical centers while this policy was under review in 2011. The reviewers agreed that TIF is sufficiently different from laparoscopic Nissen fundoplication to warrant evaluation as a separate procedure. The reviewers considered TIF (i.e., EsophyX®) to be investigational for the treatment of GERD.

PRACTICE GUIDELINES AND POSITION STATEMENTS

American Society for Gastrointestinal Endoscopy

In 2015, the American Society for Gastrointestinal Endoscopy (ASGE) published guidelines on endoscopic procedures for GERD.[44] ASGE gave a number of recommendations based on moderate or high-quality evidence for the endoscopic evaluation of GERD. ASGE gave a suggestion, based on low quality evidence, that antireflux therapy be considered for selected patients with uncomplicated GERD.

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[1,]:

- We suggest consideration of TIF for patients with troublesome regurgitation or heartburn who do not wish to undergo antireflux surgery and who do not have severe reflux esophagitis (LA grade C or D) or hiatal hernias >2 cm (conditional recommendation, low level of evidence).
- Because data on the efficacy of radiofrequency energy (Stretta) as an antireflux procedure is inconsistent and highly variable, we cannot recommend its use as an alternative to medical or surgical antireflux therapies (conditional recommendation, low level of evidence).

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

American Society of General Surgeons (ASGS)

In 2011, the American Society of General Surgeons issued a position statement on transoral fundoplication stating that “ASGS supports the use of transoral fundoplication by trained General Surgeons for the treatment of symptomatic chronic gastroesophageal reflux disease (GERD) in patients who fail to achieve satisfactory response to a standard dose of Proton Pump Inhibitor (PPI) therapy or for those who wish to avoid the need for a lifetime of medication dependence.”[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.[46,] The relevant questions and recommendations for TIF and Stretta are as follows:

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

National Institute for Health and Care Excellence (NICE)

2017

NICE updated its guidance on bulking agents for GERD found that “Current evidence on the safety and efficacy of endoscopic injection of bulking agents for gastro-esophageal reflux disease does not appear adequate for this procedure to be used without special arrangements….” In 2016, NICE removed guidance on endoscopic bulking agents/hydrogel implants from guidelines on treatment for “dyspepsia and gastro-esophageal reflux” because the product had been withdrawn by the manufacturer

2013

The National Institute for Health and Clinical Excellence of the National Health Service of Great Britain issued interventional procedure guidance on endoscopic radiofrequency treatment for GERD, concluding: “The evidence on safety and efficacy of endoscopic radiofrequency (RF) ablation for gastro-oesophageal reflux disease is adequate in the short and medium term but there is uncertainty about longer-term outcomes. With regard to efficacy, there is evidence of symptomatic relief but objective evidence on reduction of reflux is inconclusive. Therefore, this procedure should only be used with special arrangements for clinical governance, consent and audit or research.”[47] The reviewing committee noted “concern on the part of some specialists about the possibility that symptoms may improve as a result of denervation caused by the procedure; if that were the case then failure to recognize and treat reflux might lead to complications in the long term.”

2011

NICE issued guidance in 2011 on endoluminal gastroplication for GERD, concluding that "The evidence on endoluminal gastroplication for gastro-esophageal reflux disease raises no major safety concerns. Evidence from a number of randomized controlled trials (RCTs) 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. Therefore, this procedure should only be used with special arrangements for clinical governance, consent and audit or research."[48]

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

Government Regulations

National:

There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

Local:

Wisconsin Physicians Service Insurance Corporation LCD for Endoscopic Treatment of GERD (L34659). Last updated 08/29/2024.

Indications and Limitations of Coverage and/or Medical Necessity
Benefits are not available for endoluminal treatment for Gastroesophageal Reflux Disease (GERD) using the Stretta® procedure, the Bard EndoCinch Suturing System, Plicator, Enteryx, or similar treatments as these procedures are not considered reasonable and necessary for the diagnosis or treatment of an injury or disease.

Currently, these procedures are considered non-covered due to the fact that current peer-reviewed literature does not support the efficacy of the services. Claims will be denied as "not proven effective."

The Stretta procedure is an endoluminal treatment for GERD in which radiofrequency energy is delivered to smooth muscle of the lower esophageal sphincter (LES). A flexible catheter equipped with special needle electrodes for precise energy delivery is placed by mouth into the esophagus and carefully controlled radiofrequency energy is then delivered to the LES and gastric cardia, creating thermal lesions. The manufacturer maintains that the changes that occur immediately, and over time, result in a "tighter" LES and a less compliant gastric cardia. Additionally, the interruption of nerve pathways in the LES area is believed to reduce the incidence of inappropriate LES "relaxations," leading to an improvement in GERD symptoms. Substantial peer-reviewed evidence to fully support these assumptions remains to be published.

The Bard EndoCinch™ Suturing System and the Plicator™ are intended for use in endoscopic placement of suture(s) in the soft tissue of the esophagus and stomach and for approximation of tissue for treatment of symptomatic gastroesophageal reflux disease.

These procedures are promising for treatment of patients in whom proton pump inhibitor therapy fails. Clinical data from various studies are emerging. At this time, open-label studies or patient registries with short term follow-ups are the dominant source of data. The overwhelming preponderance of reviewers remains equivocal in their support and has called for randomized controlled trials with long-term follow-ups. In the absence of evidence from

such studies, and in the absence of wide acceptance, endoscopic treatments for GERD are not proven effective. Therefore, they are not reimbursable even though some of the treatments may have associated CPT or OPPS codes.

Coverage for the TIF (Transoral Incisionless Fundoplication) procedure is for treatment of patients in whom proton pump inhibitor therapy fails. An example of the device used in TIF is EsophyX™. TIF using EsophyX™ for performing surgery for treating gastroesophageal reflux disease (GERD) reconstructs the valve at the top of the stomach that helps prevents acid reflux.

Indications

Coverage is appropriate for TIF if done by a well-trained surgeon for the following indications:

1. Symptomatic chronic gastroesophageal reflux (chronic being defined as > 6 months of symptoms), and
2. Symptoms must not be completely responsive to Proton Pump Inhibitors (PPIs) as judged by GERD HRQL scores of < or equal to 12 while on PPIs and > or equal to 20 when off for 14 days (also acceptable would be the difference of > or equal to 10 of the scores between off and on therapy), and
3. Hiatal hernia < or equal to 2 cm, except where the hernia has been reduced to 2 cm or less by a successful laparoscopic hernia reduction procedure prior to the TIF procedure. (Based on FDA approval).

Limitations

Coverage is not extended:

1. For those patients who may have recurrent symptoms or may fail this procedure. No literature has been submitted for repeat TIF use. These procedures (repeat TIF) would be considered investigational at this time.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

- Endoscopic Radiofrequency Ablation or Cryoablation for Barrett's Esophagus
- Magnetic Esophageal Ring to Treat Gastroesophageal Reflux Disease (GERD)
- Fecal Incontinence-Investigational Treatments

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): 308-28; 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): 1124-31. PMID 27060607
4. Ip S, Bonis P, Tatsoni A, et al. Comparative Effectiveness of Management Strategies for Gastroesophageal Reflux Disease (Evidence Report/Technology Assessment No. 1). Rockville, MD: Agency for Healthcare Research and Quality; 2005.
5. Ip S, Chung M, Moorthy D, et al. Management strategies for gastroesophageal reflux disease: An update (Comparative Effectiveness Review No. 29). Rockville, MD: Agency for Healthcare Research and Quality; 2011.
6. Humphries LA, Hernandez JM, Clark W, et al. Causes of dissatisfaction after laparoscopic fundoplication: the impact of new symptoms, recurrent symptoms, and the patient experience. Surg Endosc. May 2013; 27(5): 1537-45. PMID 23508812
7. Hummel K, Richards W. Endoscopic treatment of gastroesophageal reflux disease. Surg Clin North Am. Jun 2015; 95(3): 653-67. PMID 25965137
8. Ihde GM. The evolution of TIF: transoral incisionless fundoplication. Therap Adv Gastroenterol. 2020; 13: 1756284820924206. PMID 32499834
9. Food and Drug Administration (FDA). 510(k) Summary: EsophyX (K160960). 2016; https://www.accessdata.fda.gov/cdrh_docs/pdf16/K160960.pdf. Accessed November 2024.
10. Food and Drug Administration (FDA). EsophyX Summary K171307. 2017; https://www.accessdata.fda.gov/cdrh_docs/pdf17/K171307.pdf. Accessed November 2024.
11. Food and Drug Administration (FDA). EsophyX Summary K172811. 2017; https://www.accessdata.fda.gov/cdrh_docs/pdf17/K172811.pdf. Accessed November 2024.
12. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Transesophageal Endoscopic Treatments for Gastroesophageal Reflux Disease. TEC Assessment. 2003;Volume 18:Tab 20. PMID
13. 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
14. 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.e7. PMID 29305934
15. 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
16. 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.e5. PMID 25448925
17. 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
18. 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

19. Trad S, 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
20. 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): 1261-70. PMID 26463242
21. 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): 531-42. PMID 25823768
22. 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): 860-7. PMID 25197871
23. 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
24. 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
25. 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
26. 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): 2770-80. PMID 25480624
27. 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
28. 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
29. 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): 1058-67.e1. PMID 25459556
30. 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): 668-76. PMID 12949712
31. 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): 818-25. PMID 19730952
32. 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): 222-30. PMID 22108449
33. 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

34. 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
35. 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 01 2008; 28(9): 1147-58. PMID 18616516
36. 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
37. 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
38. 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): 657-61. PMID 26258269
39. 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
40. 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. Oct 10 2014; 14: 178. PMID 25304252
41. 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): 2323-33. PMID 24562599
42. 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): 318-23. PMID 19185691
43. 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): 423-6. PMID 11275880
44. Muthusamy VR, Lightdale JR, Acosta RD, et al. The role of endoscopy in the management of GERD. Gastrointest Endosc. 2015; 81(6): 1305-10. PMID 25863867
45. American Society of General Surgeons (ASGS). Coverage of Transoral fundoplication. 2011; https://theasgs.org/position-statements/coverage-of-transoral-fundoplication-2/. Accessed November 2024.
46. National Institute for Health and Care Excellence (NICE). Endoscopic radiofrequency ablation for gastro-oesophageal reflux disease [IPG461]. 2013; https://www.nice.org.uk/guidance/ipg461. Accessed November 2024.
47. National Institute for Health and Care Excellence (NICE). Endoluminal gastroplication for gastro-oesophageal reflux disease [IPG404]. 2011; https://www.nice.org.uk/guidance/ipg404. Accessed November 20254.
48. 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
49. 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

50. 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
51. Katz PO, Dunbar KB, Schnoll-Sussman FH, et al. ACG Clinical Guideline for the Diagnosis and Management of Gastroesophageal Reflux Disease. Am J Gastroenterol. Jan 01 2022; 117(1): 27-56. PMID 34807007
52. 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

The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through November 2025, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
8/9/02	8/9/02	7/31/02	Joint medical policy established
9/30/04	9/30/04	9/28/04	Scheduled review of noncovered services; new treatment option added (Enteryx®, PMMA).
1/1/07	11/1/06	9/24/06	Routine maintenance
3/1/09	12/9/08	2/2/09	Routine maintenance; deleted terminal T codes from policy
1/1/11	10/12/10	10/27/10	Routine maintenance. Additional references added
5/1/11	2/15/11	3/3/11	Added information on the EsophyX procedure to the medical policy statement; additional references added.
9/1/12	6/12/12	6/19/12	Updated policy to mirror BCBSA policy. Added CPT codes 43257 to policy. Updated rationale and references. Title changed from "Transendoscopic Therapies for Gastroesophageal Reflux Disease" to "Transesophageal Endoscopic Therapies for GERD (*Transoral Incisionless Fundoplication)"*
9/1/13	6/18/13	6/26/13	Routine review, references added. No change in policy status.
11/1/14	8/19/14	8/19/14	Routine review; references updated. Procedures remain experimental/ investigational.
3/1/16	12/10/15	12/10/15	Routine review; references updated.
3/1/17	12/13/16	12/13/16	Routine policy review. References and rationale updated. No change in policy status.
3/1/18	12/12/17	12/12/17	Updated specialty society and practice guideline sections.
3/1/19	12/11/18		Routine policy update. No changes in policy status.
3/1/20	12/17/19		Routine policy update, added reference # 44. No change in policy status.

3/1/21	12/15/20		Routine policy maintenance. No change in policy status.
3/1/22	12/14/21		Updated rationale, references added. No change in policy status.
3/1/23	12/20/22		Updated rationale, references 15, 24 and 34 added. No change in policy status.
3/1/24	12/19/23		Updated rationale, added references 49-53. Received request from Spectrum health reconsideration for EsophyX. No change in policy status. Vendor managed: N/A (ds)
3/1/25	12/17/24		Routine policy maintenance, no change in status. Vendor managed: N/A (ds)

Next Review Date: 4th Qtr. 2025

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: TRANSESOPHAGEAL ENDOSCOPIC THERAPIES FOR GERD
(*TRANSORAL INCISIONLESS FUNDOPLICATION)*

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Not covered.
BCNA (Medicare Advantage)	See government section.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

N/A