

TRANSORAL INCISIONLESS FUNDOPLICATION (TIF[®])
FOR THE TREATMENT OF
GASTROESOPHAGEAL REFLUX DISEASE (GERD)

CLINICAL DOSSIER

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Executive Summary – Clinical and Economic Value of the Product

1. Clinical Benefits

Transoral Incisionless Fundoplication (TIF) performed with the EsoPHYX® device is an endoscopic procedure for the treatment of gastroesophageal reflux disease (GERD). The TIF procedure clinical objectives are a) to mechanically repair a defective gastroesophageal valve and b) to reduce small hiatal hernias. The goal of therapy is to control both the symptoms and mucosal damage. Based on the most recent data, the TIF procedure appears to be a valuable treatment alternative for the management of appropriately selected patients with moderate to severe chronic GERD symptoms. These studies establish the TIF procedure's ability to provide complete symptom relief across the spectrum of typical and atypical GERD manifestations, including regurgitation and laryngopharyngeal reflux.

2. Economic Benefits

GERD is one of the most prevalent gastrointestinal disorders in the United States affecting 30-40% of the US population with \$12 billion annual healthcare expenditures.¹ More than 80 million Americans experience symptoms at least monthly, 19 million experience daily symptoms and 60% of those over 65 have GERD.² The cost of treating GERD continues to grow, both in terms of financial resources and in terms of the impact on the quality of life for many patients.

Traditional fundoplication, most commonly Nissen fundoplication, has been the leading surgical intervention for GERD. Medicare reimbursement for anti-reflux surgery (ARS) e.g. laparoscopic surgical fundoplication--can range from \$8,000 to \$32,000. ARS has been associated with post-operative complications and long-term side-effects including dysphagia, inability to belch or vomit, diarrhea, bloating, abdominal pain and constipation. On the other hand, the TIF procedure is reimbursed by Medicare at around \$7,600 and has a low procedural complication rate and little evidence of negative side-effects long-term.

3. Conclusions

Recent high-level clinical studies support the safety, effectiveness, and durability of the TIF procedure and justify its use as a therapeutic option for well selected patients with chronic GERD. The TIF procedure has been proven to work in select cases where PPIs fail to achieve symptomatic control. The evidence demonstrates sustainable improvement in health outcomes, symptom relief, decrease in PPI utilization, healed esophagitis and improvement in objective pH measurements of esophageal acid exposure.

Gastroesophageal Reflux Disease (GERD)

1. Disease Overview

GERD, also known as acid reflux, occurs when acid or other stomach contents back up in the esophagus. The most common symptom of GERD is heartburn, which, while rarely life-threatening, can greatly reduce a patient's quality of life by affecting daily activities, sleep and what they can eat. GERD patients may present with typical symptoms that include troublesome heartburn, epigastric pain, reflux and/or regurgitation, chest pain and difficulty sleeping or atypically with chronic cough, sinusitis, asthma, chronic laryngitis/voice disturbances or dental erosion.³

2. Treatment Options

GERD has often been described as a spectrum of disease. GERD symptoms may respond positively to lifestyle changes and this is typically the first recommendation of medical practitioners. Where lifestyle changes are impractical or do not reduce symptom frequency or severity effectively, medical treatment may be considered. Initial response to medical therapy is favorable for many GERD patients, especially those suffering from troublesome heartburn.

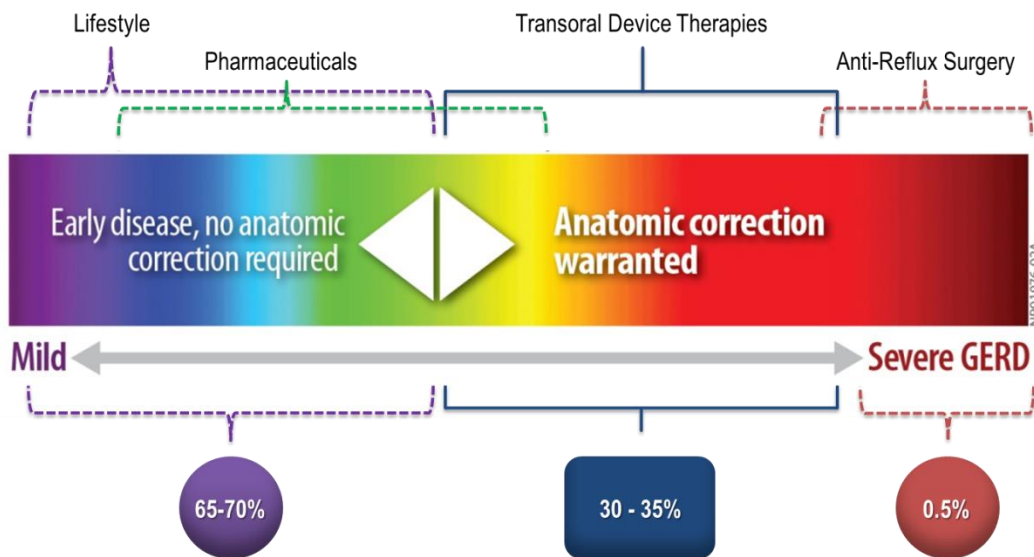


Figure 1. GERD Symptom and Treatment Continuum

a. Lifestyle

Lifestyle modifications are usually the appropriate first step in the treatment pathway for GERD. For GERD sufferers with infrequent symptoms, simple dietary and lifestyle changes may offer symptom relief. Examples of lifestyle changes include:

- Lose weight
- Avoid foods known to cause reflux
- Eat smaller well-timed meals hours before sleeping
- Review medications that may contribute symptoms
- Quit smoking
- Limit alcohol intake

b. Pharmaceuticals

Where lifestyle changes alone are impractical or do not reduce symptom frequency or severity effectively, medical treatment may be considered. Initial response to medical therapy is favorable for many GERD patients, especially those suffering from troublesome heartburn. There are several medications available including antacids, H₂-receptor antagonists, and Proton Pump Inhibitors (PPIs). PPIs are used most commonly with more than 100 million courses of PPI treatment dispensed annually in the United States.

Long term use of PPIs, however, has documented safety concerns that include dementia⁴, interference with Plavix, increased pneumonia risk, Vitamin B12 and magnesium deficiencies, increased risk of fundic gland polyps⁵, increased risk of osteoporosis fractures, chronic kidney damage, reduced gall bladder motility, and increased risk of bacterial gastroenteritis and *C. difficile*⁶ with small bowel bacterial overgrowth.

c. Procedural Interventions

Over time, approximately 17-32% of GERD patients do not experience adequate symptom relief with medication and could become candidates for procedural intervention.⁷ Literature comparing conventional ARS, like the laparoscopic Nissen fundoplication, to PPI therapy suggests that procedural intervention provides superior control of primary GERD symptoms at the expense of a higher rate of ARS side-effects including gas bloat, dysphagia, and flatulence.⁸

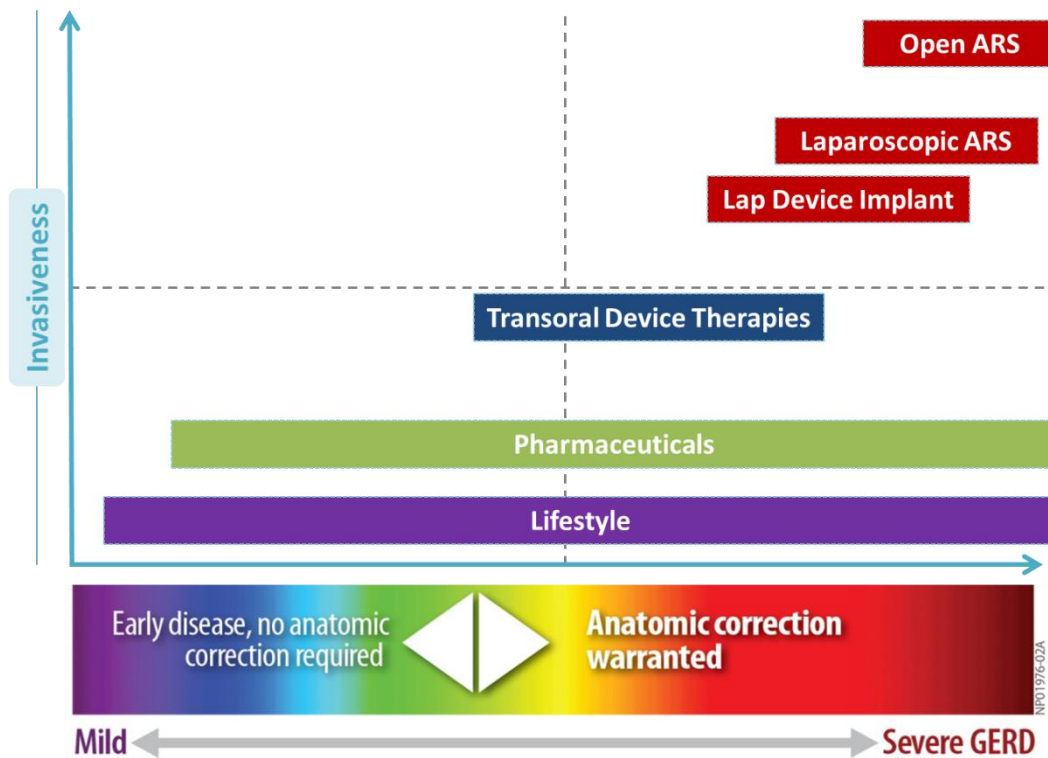


Figure 2. GERD Treatment Comparison Matrix

i. Conventional ARS

The current most common ARS treatment for GERD, Nissen fundoplication, has been employed since 1955. The Nissen surgical procedure is technically demanding and requires expertise and experience to achieve optimal outcomes. Postoperative complication rates from both laparoscopic and open Nissen are reportedly high, at 8.3 and 12.6%, respectively.⁹ In fact, there was a significant decline in the number of surgical funduplications from 2009 to 2013.¹⁰ Despite this, no alternative, conventional surgical therapy has emerged to date as a viable option to Nissen fundoplication.

Nissen fundoplication is total (360°). Partial funduplications, such as Dor (anterior 180-200°) and Toupet funduplications (posterior 270°), are less common alternative procedures with different indications and outcomes. These funduplications are typically done laparoscopically but can also be performed as an open procedure.

Conventional ARS has been shown to be a viable, though not optimal option to treat severe GERD with fewer than 30,000 patients treated surgically each year. This figure contrasts to the 20-40% (3-6 million) of daily GERD sufferers whose symptoms are not adequately controlled by medical therapy. Further, it was recently concluded that risk of PPI use after ARS was higher than previously reported, and more than 50% of patients became long-term PPI users 10–15 years postsurgery.¹¹ This clearly underscores the need for alternatives to conventional ARS procedure for the treatment of GERD.

ii. Laparoscopic Device Implant

Other, newer, procedures include:

- Magnetic Esophageal Ring

- > Consists of a laparoscopically implanted ring composed of interlinked metal beads with magnetic cores. The metal ring is placed around the esophagus at the level of the gastroesophageal junction.

iii. Transoral Device Therapies

Due in part to the high prevalence of GERD and the dissatisfaction with available options, there has been interest in creating a minimally invasive, device therapy alternatives to open or laparoscopic fundoplication or chronic medical therapy.

The number of patients whose symptoms are not adequately controlled on medication but who are not candidates for conventional ARS is significant. The patients in this segment, referred to as the “treatment gap,” may be 1) aware of ARS but have decided the potential benefits do not outweigh the risk of side-effects, or 2) have not been made aware of ARS due to the perception by practitioners that ARS presents undesired side-effects.¹²

Transoral device therapies include:

- Transoral Incisionless Fundoplication (TIF)
 - > See full description below
- Radiofrequency (RF) Ablation
 - > RF energy is applied through multiple 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.

Transoral Incisionless Fundoplication (TIF) Procedure

1. Procedure Description

With the patient under general anesthesia, a flexible endoscope with the EsophyX® device, are introduced together into the stomach under constant endoscopic visualization. The endoscope and the device are retroflexed, a helical retractor is engaged into the tissue slightly beyond the juncture where the pink squamous esophageal mucosa abuts the darker red gastric mucosa, called the Z line. The fundus of the stomach is plicated around the distal esophagus, suction is applied to position the distal esophagus in the abdominal cavity beyond the diaphragm. Strong polypropylene fasteners (same material as 3-0 sutures) are deployed through the apposed layers of esophageal and fundal tissue to anchor the repair. This process is repeated multiple times to create a full thickness, 270° circumferential gastroesophageal fundoplication and form the valve.

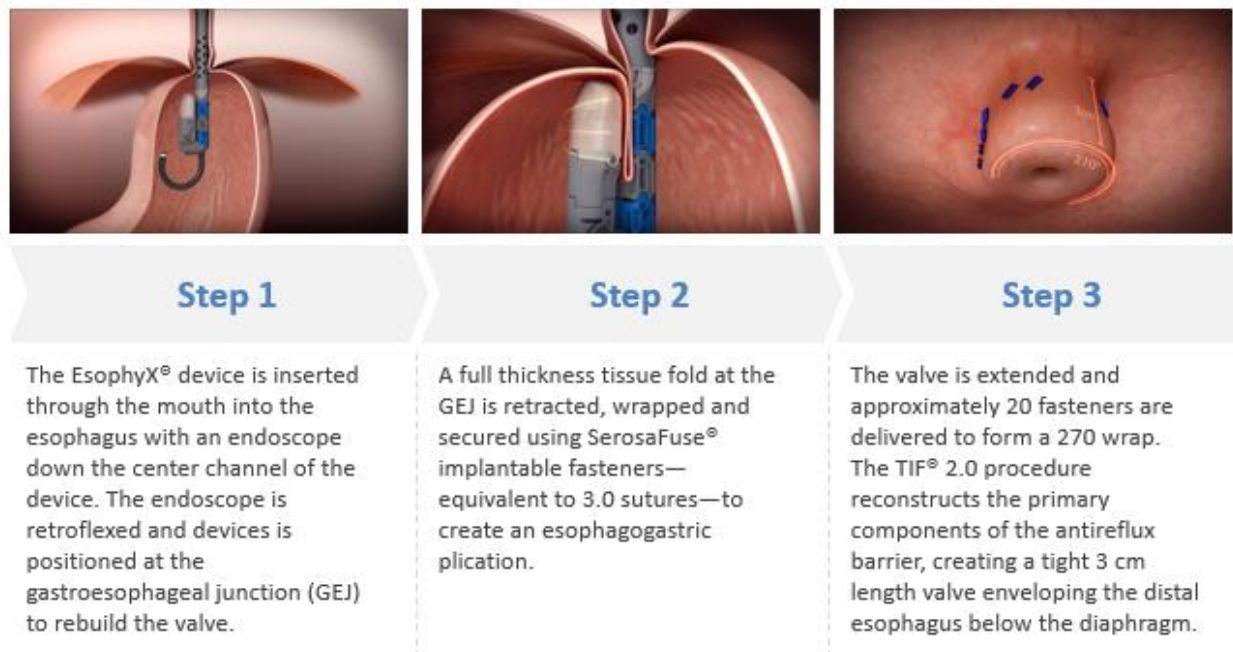


Figure 3. TIF Procedure Overview

The first transoral incisionless fundoplication (TIF) procedure using the EsophyX device was performed in 2005. Since then, more than 20,000 procedures have been completed. The currently performed version of the procedure (TIF 2.0) comprises the majority of the 20,000 procedures performed and is the version of the procedure studied in the most recent literature.

The original variation of the procedure performed early in U.S. experience, and predominantly in Europe was known as endoluminal fundoplication (ELF). This first-generation procedure was developed to assess the feasibility of the approach and was designed – first and foremost – to demonstrate safety and efficacy. At the time, investigators were concerned with placing fasteners through the distal esophagus and elected instead to create gastro-gastric plications distal to the gastroesophageal junction.

After experience was gained with the first-generation procedure and devices, subsequent iterations of the technique were pursued to more closely replicate the principles and outcomes of traditional surgical procedures.

Table 1. TIF Procedure Evolution¹³

Procedure	Commercial Introduction	# Commercial Cases to Date	% of Total Commercial Cases	Plication Type	Fastener Placement	Avg. # of Fasteners	Wrap
Transoral Incisionless Fundoplication 2.0 (TIF 2.0)	2009	22,051	96.3%	Esophagogastric	1-3cm above Z-line; more length along the greater curve of the stomach	12 to 23	Yes
Transoral Incisionless Fundoplication 1.0 (TIF 1.0)	2007	673	2.9%	Esophagogastric	Above Z-line, 1cm	12	No
EndoLuminal Fundoplication (ELF)	2005	186	0.8%	Gastrogastric	Below Z-line	10	No

2. Device Description

The EsophyX[®] device is a single use, hand-held flexible instrument that is introduced transorally with a flexible endoscope in the center of the device, so the entire procedure can be done safely under direct visualization. The device is designed so the physician can manipulate esophageal and gastric tissue and deploy strong, H-shaped fasteners in order to reconfigure lower esophageal anatomy to prevent GERD.

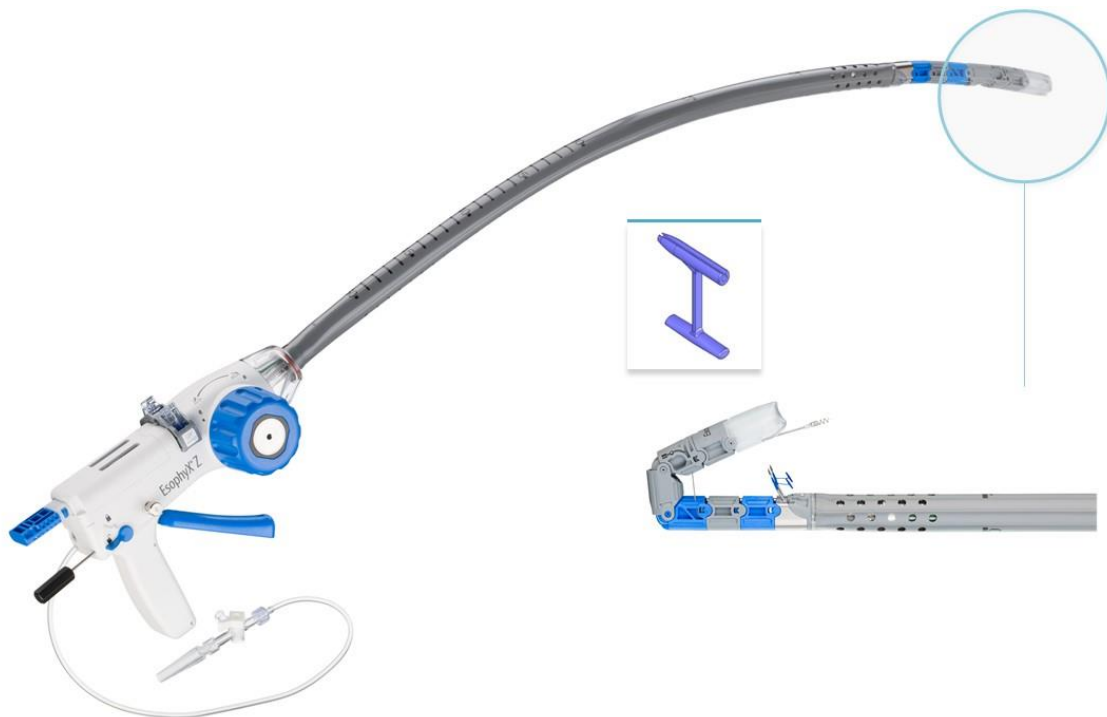


Figure 4. EsophyX[®] Z+ Device and SerosaFuse[®] Fastener

3. Patient Selection

Based on analysis of recent data, ideal candidates for the TIF procedure are chronic GERD patients with partial but inadequate symptom control on high-dose PPI therapy who have only mild to moderate deterioration of the GEJ (absent or small hiatal hernia ≤ 2 cm, or reducible to ≤ 2 cm, Hill grade I or II), and effective esophageal motility.¹⁴

Indications:

The TIF procedure is indicated for use in transoral tissue approximation, full thickness plication and ligation in the GI tract and is indicated for the treatment of symptomatic chronic gastroesophageal reflux disease in patients who require and respond to pharmacological therapy. It is also indicated to narrow the gastroesophageal junction and reduce hiatal hernia ≤ 2 cm in size in patients with symptomatic chronic gastroesophageal reflux disease. Patients with hiatal hernias larger than 2cm may be included when a laparoscopic hiatal hernia repair reduces the hernia to 2cm or less.

Contraindications:

Patients with bleeding disorders, strictures, severe esophagitis, esophageal diverticulae, obstructions, paraesophageal hernia, limited neck mobility, osteophytes of the spine, esophageal varices, esophageal infections or fungal disease, esophageal stenosis and any kind of normal or abnormal esophageal anatomy which would not permit insertion of a device of this size, chronic cough, BMI > 35 or hiatal hernia > 2 cm.

GERD Treatment Guidelines & Statements from National Medical Societies

1. *SAGES Clinical Spotlight Review: Endoluminal Treatments for Gastroesophageal Reflux Disease*
 - “Compared with sham controls, esophageal acid exposure time has been shown to improve significantly after TIF and be similar to that of patients on PPIs.”
 - “Patients undergoing TIF were found to have fewer [reflux] episodes compared with those on PPIs.”
 - “Based on existing evidence, TIF can be performed with an acceptable safety risk in appropriately selected patients.”
 - “Level of evidence +++, strong recommendation”
2. *AGA Institute Technology Coverage Statement on Minimally Invasive Surgical Options for GERD*
 - “Recognizing that the AGA medical position statement on the management of GERD has not been updated since 2008, AGA convened a multi-disciplinary workgroup to develop a framework for selected services and procedures related to the diagnosis and treatment of GERD.”
 - “The goal of therapy is to control both the symptoms and mucosal damage.”
 - “This procedure [TIF] delivers patient outcomes similar to those provided by conventional anti-reflux surgery (ARS) procedures and does not limit future treatment options.”
 - “In conclusion, the three-year plus evidence [for TIF] is sufficient to demonstrate sustainable improvement in health outcomes, symptom relief, decrease in PPI utilization and improvement in esophageal pH with transoral fundoplication.”
 - “Transoral fundoplication should be covered and reimbursed for appropriate patients who meet the selection criteria as described.”
3. *AGA: An Episode Payment Framework for Gastroesophageal Reflux Disease*^{15,16}
 - “Recent studies show that endoscopic procedures, such as transoral fundoplication, are safe and effective for treatment of patients with a hiatal hernia of ≤ 2 cm in length who have symptomatic regurgitation while taking a PPI.”
 - “Advantages of endoscopic procedures are the minimally invasive nature of the procedures, with reduced risk of complications and troublesome side effects, such as gas bloat, dysphagia, and diarrhea, which can plague some patients after laparoscopic fundoplication.”
4. *American Society of General Surgeons (ASGS) Position Statement: Transoral Fundoplication*¹⁷
 - “The ASGS supports the use of transoral fundoplication by trained General Surgeons for the treatment of symptomatic chronic gastroesophageal reflux disease (GERD) in patients who fail to achieve satisfactory response to a standard dose of Proton Pump Inhibitor (PPI) therapy or for those who wish to avoid the need for a lifetime of medication dependence.”

Clinical Evidence

Published clinical literature supports that it is now accepted by the medical community for the surgical treatment of GERD in appropriately selected patients; primarily, those patients with documented symptomatic GERD, elevated esophageal acid exposure, no precluding hiatal hernia and no reported dysphagia to indicate abnormal esophageal motility.

Table 2. Summary of Level I and II Clinical Studies (TIF 2.0)

	RESPECT ¹⁸	TEMPO ^{19,20,21,22}	TIF vs. Sham ²³	TIF Registry ^{24,25,26}
<i>Design</i>	A multi-center, randomized, single-blind, controlled TIF/Placebo vs. Sham/PPIs trial	A multi-center, randomized, open-label, controlled TIF vs. PPI trial	A multi-center, double-blind, sham controlled randomized trial	A multi-center, prospective, open-label, post market registry
<i>Objective</i>	To compare safety and effectiveness of TIF vs. Sham/PPIs in patients with “troublesome symptoms” specifically regurgitation	To compare safety and efficacy of TIF vs. PPIs for the treatment of chronic medically refractory GERD	To gauge the time to ‘treatment failure’ during the first 6 months after intervention	To evaluate the safety and efficacy of TIF in a broad range of GERD patients treated in routine clinical practice
<i>Patients</i>	2:1 ratio TIF/Placebo group (n=80) vs. Sham/PPI group (n=40)	2:1 ratio TIF group (n=40) vs. PPIs group (n=23)	1:1 ratio TIF group (n=22) vs. sham group (n=22)	274 patients treated with TIF procedure
<i>Duration(s)</i>	6 months, 1-year w/ crossover (abstract)	6 months, 1-year w/ crossover, 3 years, 5 years	6 months	6 months, 1-year, 2 years
<i>Key Outcomes</i>	<ul style="list-style-type: none"> ✓ Troublesome regurgitation was eliminated in 72% of TIF patients at > 1Y ✓ Median heartburn score decreased from 17 to 5 at 6 months and to 3, at > 1Y post-TIF ✓ Complete cessation of PPI therapy was achieved in 72% of TIF patients > 1Y 	<ul style="list-style-type: none"> ✓ All symptomatic outcome measures were stable between 1Y, 2Y, 3Y and 5Y follow-up ✓ Sustained elimination of regurgitation (86%) and atypical symptoms (80%) at 5Y follow-up ✓ Patient satisfaction w/ current health condition remains high (70%) at 5Y follow-up ✓ No serious adverse events or any safety concerns associated w/ the TIF 2.0 procedure 	<ul style="list-style-type: none"> ✓ Average of 197 days “time in remission” post-TIF vs. 107 days post-sham ✓ Six months post-op 13/22 (59%) of TIF patients were in clinical remission with complete cessation of PPIs consumption. ✓ 69% of the TIF group normalized esophageal acid exposure vs. 20% of the sham group 	<ul style="list-style-type: none"> At 2Y follow-up: <ul style="list-style-type: none"> ✓ 65% normalization in the Reflux Symptom Index score ✓ 74% normalization of Gastroesophageal Reflux Symptom Score ✓ A decrease from 91% to 29% in daily PPI use ✓ 75% of patients had esophagitis healed

The goal of the TIF 2.0 procedure is to rebuild the gastro-esophageal valve rather than to create a reflux barrier as is the objective in conventional ARS. Several RCTs support the safety, effectiveness, and durability of the TIF procedure and justify its use as a therapeutic option for well selected patients. In the study published by Trad et al., TIF 2.0 improved control of regurgitation and of atypical symptoms compared to six months of high dose PPIs.²² Of 20 patients with GERD symptoms after six months of high-dose PPI therapy, 65% (13/20) reported global elimination of troublesome regurgitation and atypical symptoms post TIF off PPIs; 67% (6/9) reported no troublesome regurgitation. Esophagitis further healed in 75% (6/8) of patients, normalization of esophageal acid exposure decreased from 52% after high-dose PPIs (on PPIs) to 33% after TIF (off PPIs), p=0.388. In the original TIF group, 12-month post TIF, 77% of patients achieved complete symptom control, 82% ceased PPI therapy, 100% healed esophagitis and 45% normalized esophageal acid exposure.²¹ The results of this study indicate that in patients with incomplete symptom control on high-dose PPI therapy, TIF 2.0 procedure provided further elimination of symptoms and esophagitis healing.

Hunter et al.¹⁸ selected patients with GERD and hiatal hernias < 2 cm who were randomly assigned to groups that underwent TIF 2.0 procedure and then received six months of placebo (n=87), or sham surgery and six months of once or twice daily omeprazole (controls, n=42). Patients were blinded to therapy during follow-up period and reassessed at 2, 12, and 26 weeks. At six months, patients

underwent 48-hr esophageal pH monitoring and esophagogastroduodenoscopy. The TIF procedure eliminated troublesome regurgitation in a larger proportion of patients (67%) than PPIs (45%), $p=.023$. A larger proportion of controls had no response at three months (36%) than subjects that received TIF (11%), $p=.004$. Control of esophageal pH improved following TIF (mean 9.3% before and 6.3% after, $p<.001$); but not after sham surgery (mean 8.6% before and 8.9% after). The authors concluded that TIF procedure was an effective treatment for patients with GERD particularly those with persistent regurgitation despite PPI therapy.

These studies are included in two recent meta-analyses. McCarty et al.²⁷ highlights the different protocols of the TIF procedure, with the major difference being the degree of circumference of the re-established valve and the location of the valve. Similarly, Gerson et al.¹³ evaluated outcomes of RCT trials of TIF 2.0 data in a meta-analysis. It is highlighted that very few ELF and TIF 1.0 procedures have been ever been performed – only 859 combined and all performed more than 10 years ago.

Longer-term, prospective case studies support the durability of the TIF 2.0 procedure. Testoni et al. has published follow-up at 10-²⁸ and 6-years²⁹. Stefanidis et al.³⁰ reported findings at 5-years. These long-term post-TIF results are similar to those of surgical fundoplication, without any of the surgery-related persistent side effects. The findings confirm that TIF 2.0 can offer a long-term, effective and safe therapeutic option for carefully selected symptomatic GERD patients.

The TIF 2.0 procedure has been proven to work in select cases where PPIs fail to achieve symptomatic control. The evidence demonstrates sustainable improvement in health outcomes, symptom relief, decrease in PPI utilization, healed esophagitis and improvement in objective pH measurements of esophageal acid exposure.

Comprehensive list of published literature on TIF 2.0 procedure is available in Appendix A.

Reimbursement Information

Table 3. CPT/HCPCS Codes Used to Report TIF

	CPT/HCPCS	Description
Jan. 1, 2016	43210	Esophagogastroduodenoscopy, flexible, transoral; with esophagogastric fundoplasty, partial or complete, includes duodenoscopy when performed.
Pre-Jan. 1, 2016	C9724	Endoscopic full-thickness plication of the stomach using endoscopic plication system (eps); includes endoscopy

The American Medical Association's (AMA) decision to create a unique CPT code that describes the transoral reconstruction of a defective gastroesophageal valve to prevent reflux in January 2016 acknowledges the significant clinical evidence, including data from two randomized trials, and that the TIF procedure has reached broad acceptance across the physician community. The application for the new code was jointly sponsored by four key specialty medical societies: American Gastroenterological Association (AGA), American College of Gastroenterology (ACG), American Society for Gastrointestinal Endoscopy (ASGE) and the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES).

Table 4. DRGs and Descriptors under which the TIF Procedure is Paid in the Inpatient Setting

MS-DRG	Description
326	Stomach, Esophageal and Duodenal Procedures with MCC
327	Stomach, Esophageal and Duodenal Procedures with CC
328	Stomach, Esophageal and Duodenal Procedures w/o CC/MCC

Table 5. ICD-10 Diagnosis and Procedure Codes

ICD-10-CM	Description
K21.0	Gastro-esophageal reflux disease with esophagitis
K21.9	Gastro-esophageal reflux disease without esophagitis
K30	Functional dysphasia
R10.13	Dyspepsia NOS
K44	Diaphragmatic hernia without obstruction or gangrene
R12	Heartburn

Note: These are the common ICD-10 diagnosis codes related to the TIF procedure. These codes would not trigger payment under a DRG with CC or MCC.

ICD-10-PSC	Description
0DV48DZ	Restriction of Esophagogastric Junction with Intraluminal Device, Via Natural or Artificial Opening Endoscopic

Economic Summary

In a study evaluating GERD-related costs at a large employer, the total healthcare-related costs were greater by \$3,355 for patients with GERD than those without (\$6,878 versus \$3,522, respectively).³¹ Additionally, it has been found that patients with GERD who were on twice-daily PPIs were associated with significantly higher utilization of healthcare resources and related costs for inpatient hospitalizations, emergency room visits, outpatient services, physician office visits, endoscopy procedures, and pharmacy services.³² These are the patients, assuming other criteria are met, that would be candidates for the TIF procedure.

Table 6 below lays out the CY2020 Medicare rates for the different procedures for treating GERD.

Table 6. Comparison of Medicare Reimbursement Rates CY2020 (Unadjusted)

	TIF	RF Ablation	Magnetic Esophageal Ring	Lap. Fundoplication	Lap Fund. w/ Mesh
CPT/HCPCS (APC)	43210 (5362)	43257 (5303)	43284 (5362)	43281 (5362)	43282 (5362)
Physician	\$451.48	\$243.24	\$704.11	\$1,624.75	\$1,826.86
Facility	\$8,412.18	\$2,998.75	\$8,412.18	\$8,412.18	\$8,412.18
Total Reimbursement	\$8,863.66	\$3,241.99	\$9,116.29	\$10,036.93	\$10,239.04
Procedure Time ³³	60	45	60	180	210

Coverage Status

Table 7. Coverage Status (as of January 11, 2020)

Type	Contractor/Carrier	LCD #/Policy #	Title
Medicare	CGS	N/A	Coverage confirmed with carrier
	NGS	L35080	Select Minimally Invasive GERD Procedures
	FCSO	N/A	Coverage confirmed with carrier
	Novitas	L34999	Transoral Incisionless Fundoplication
	Noridian	N/A	Coverage confirmed with carrier
	Palmetto	L34434	Upper Gastrointestinal Endoscopy and Visualization
	WPS	L34659	Endoscopic Treatment of GERD
Commercial	BCBS of Massachusetts	920	Surgical and Transesophageal Endoscopic Procedures to Treat Gastroesophageal Reflux Disease
	BCBS of North Dakota		Transesophageal Endoscopic Therapies for Gastroesophageal Reflux Disease (GERD)
	BCBS of South Carolina	CAM 20138	Transesophageal Endoscopic Therapies for Gastroesophageal Reflux Disease
	CareFirst		Coverage confirmed with carrier
	Cleveland Clinic		Coverage confirmed with carrier
	Geisinger Health Plan	MP256	Transoral Incisionless Fundoplication
	Health Alliance Plan of Michigan		Gastroesophageal Reflux Disease (GERD) Procedures
	Health Care Services Corporation (HCSC) [BCBS of Illinois, BCBS of Texas, BCBS of Oklahoma, BCBS of New Mexico, BCBS of Montana]	MED201.016	Device Therapies for Gastroesophageal Reflux Disease (GERD)
	Health Net (Centene)		Coverage confirmed with carrier
	Highmark BCBS	S-145-021	Transesophageal Endoscopic Therapies for Gastroesophageal Reflux Disease (GERD)
	Johns Hopkins HealthCare	CMS20.03	Gastroesophageal Reflux Disease (GERD) Devices
	Moda Health		Endoscopic Procedures for the Treatment of Gastroesophageal Reflux Disease
	Priority Health (MI)	91483-R7	Endoscopic Treatment of GERD and Barrett's Esophagus

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- ¹ National Hospital Discharge Survey, National Hospital Ambulatory Medical Care Survey, available at http://ftp.cdc.gov/pub/Health_Statistics/NCHS/Dataset_Documentation/NAMCS/doc09.pdf.
- ² Chen KY, Lou HY, Lin HC, Lee SH. *Seasonal variation in the incidence of gastroesophageal reflux disease*. Am J Med Sci. 2009 Dec;338(6):453-8.
- ³ Vakil N, van Zanten SV, Kahrilas P, Dent J, Jones R. *The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus*. Am J Gastroenterol. 2006 Aug;101(8):1900-20; quiz 1943.
- ⁴ Gomm W, von Holt K, Thomé F, Broich K, Maier W, Fink A, Doblhammer G, Haenisch B. *Association of Proton Pump Inhibitors With Risk of Dementia: A Pharmacoepidemiological Claims Data Analysis*. JAMA Neurol. 2016 Apr 1;73(4):410-6.
- ⁵ Thomson AB, Sauve MD, Kassam N, Kamitakahara H. *Safety of the long-term use of proton pump inhibitors*. World J Gastroenterol. 2010 May 21;16(19):2323-30.
- ⁶ McDonald EG, Milligan J, Frenette C, Lee TC. *Continuous Proton Pump Inhibitor Therapy and the Associated Risk of Recurrent Clostridium difficile Infection*. JAMA Intern Med. 2015 May;175(5):784-91.
- ⁷ Reavis KM, Perry KA. *Transoral incisionless fundoplication for the treatment of gastroesophageal reflux disease*. Expert Rev Med Devices. 2014 Jul;11(4):341-50.
- ⁸ Galmiche JP, Hatlebakk J, Attwood S, Ell C, Fiocca R, Eklund S, Långström G, Lind T, Lundell L. *Laparoscopic antireflux surgery vs esomeprazole treatment for chronic GERD: the LOTUS randomized clinical trial*. JAMA. 2011 May 18;305(19):1969-77.
- ⁹ Salminen PTP, Hiekkänen HI, Rantala APT, Ovaska JT. *Comparison of Long-term Outcome of Laparoscopic and Conventional Nissen Fundoplication: A Prospective Randomized Study With an 11-Year Follow-up*. Ann Surg. 2007 Aug; 246(2): 201–206.
- ¹⁰ Khan F, Maradey-Romero C, Ganocy S, Frazier R, Fass R. *Utilisation of surgical fundoplication for patients with gastro-oesophageal reflux disease in the USA has declined rapidly between 2009 and 2013*. Aliment Pharmacol Ther. 2016 Jun;43(11):1124-31.
- ¹¹ Lødrup A, Pottgård A, Hallas J, Bytzer P. *Use of proton pump inhibitors after antireflux surgery: a nationwide register-based follow-up study*. Gut. 2014 Oct;63(10):1544-9. doi: 10.1136/gutjnl-2013-306532. Epub 2014 Jan 28.
- ¹² Subramanian CR, Triadafilopoulos G. *Refractory gastroesophageal reflux disease*. Gastroenterol Rep (Oxf). 2015 Feb;3(1):41-53.
- ¹³ Gerson L., Stouch B., Lobonțiu A. (2018). *Transoral Incisionless Fundoplication (TIF 2.0): A Meta-Analysis of Three Randomized, Controlled Clinical Trials*. Chirurgia (Bucur), 113(2):173-184. doi: 10.21614/chirurgia.113.2.173.
- ¹⁴ Trad KS. *Transoral incisionless fundoplication: current status*. Curr Opin Gastroenterol. 2016 Apr 15. [Epub ahead of print].
- ¹⁵ Vaezi MF, Brill JV, Mills MR, Bernstein BB, Ness RM, Richards WO, Brillstein L, Leibowitz R, Strople K, Montgomery EA, Patel K. *An Episode Payment Framework for Gastroesophageal Reflux Disease: Symptomatic Gastroesophageal Reflux Disease, Dysplastic and Nondysplastic Barrett's Esophagus, and Anti-Reflux Surgical and Endoscopic Interventions*. Gastroenterology. 2016 Apr;150(4):1009-18.
- ¹⁶ Vaezi MF, Brill JV, Mills MR, Bernstein BB, Ness RM, Richards WO, Brillstein L, Leibowitz R, Strople K, Montgomery EA, Patel K. *An Episode Payment Framework for Gastroesophageal Reflux Disease*. Gastroenterology. 2016 Apr;150(4):1019–1025.
- ¹⁷ American Society of General Surgeons (ASGS). *Position statement: Transoral fundoplication*. 2011; <http://www.theasgs.org/aboutus/ASGS-Transoral-Fundoplication.pdf>. Accessed May 5, 2016.
- ¹⁸ Hunter JG, Kahrilas PJ, Bell RCW, Wilson EB, Trad KS, Dolan JP, Perry KA, Oelschlager BK, Soper NJ, Snyder BA, Burch MA, Melvin WS, Reavis K, Turgeon DG, Hungness ES, Diggs BS. *Efficacy of transoral fundoplication vs. omeprazole for treatment of regurgitation in a randomized controlled trial*. Gastroenterology. 2015 Feb;148(2):324-333.
- ¹⁹ Trad KS, Barnes WE, Prevou ER, Simoni G, Steffen JA, Shughoury AB, Raza M, Heise JA, Fox MA, Mavrelis PG. *The TEMPO Trial at 5 Years: Transoral Fundoplication (TIF 2.0) Is Safe, Durable, and Cost-Effective*. Surg Innov 2018; [ePub ahead of print].
- ²⁰ Trad KS, Fox MA, Simoni G, Shughoury AB, Mavrelis PG, Raza M, Heise JA, Barnes WE. *Transoral Fundoplication Offers Durable Symptom Control for Chronic GERD: 3-Year Report from the TEMPO Randomized Trial with a Crossover Arm*. Surg Endosc. 2016 Sep 21.
- ²¹ Trad KS, Fox MA, Simoni G, Ahmad B, Shughoury AB, Mavrelis PG, Raza M, Heise JA, Turgeon DG, Barnes WE. *Efficacy of Transoral Fundoplication For Treatment of Chronic Gastroesophageal Reflux Disease Incompletely Controlled with High-Dose PPI Therapy: A Randomized, Multicenter, Open Label, Crossover Study*. BMC Gastroenterol. 2014 Oct 6; 14(1):174.
- ²² Trad KS, Barnes WE, Simoni G, Shughoury AB, Mavrelis PG, Raza M, Heise JA, Turgeon DG, Fox MA. *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. 2015 Feb;22(1):26-40.
- ²³ Håkansson B, Montgomery M, Cadiere GB, Rajan A, Bruley des Varannes S, Lerhun M, Coron E, Tack J, Bishops R, Thorell A, Arnelo U, Lundell L. *Randomised clinical trial: transoral incisionless fundoplication vs. sham intervention to control chronic GERD*. Alimentary Pharmacology & Therapeutics.
- ²⁴ Bell RCW, Barnes WE, Carter BJ, Sewell RW, Mavrelis PG, Ihde GM, Hoddinott KM, Fox MA, Freeman KD, Gunsberger T, Hausmann MG, Dargis D, Gill BD, Wilson EB, Trad KS. *Transoral Incisionless Fundoplication: 2-year results from the prospective multicenter U.S. study*. Am Surg, 2014 Nov; 80(11):1093-1105.

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- ²⁵ Wilson EB, Barnes WE, Mavrelis PG, Carter BJ, Bell RCW, Sewell RW, Ihde GM, Dargis D, Hoddinott KM, Shughoury AB, Gill BD, Fox MA, Turgeon DG, Freeman K, Gunsberger T, Hausmann MG, LeBlanc KA, Deljkich E, Trad KS. *The Effects of Transoral Incisionless Fundoplication on Chronic GERD Patients: 12-Month Prospective Multicenter Experience*. Surg Laparosc Endosc Percutan Tech, Feb 2014; 24(1):36-46.
- ²⁶ Bell RCW, Mavrelis PG, Barnes WE, Dargis D, Carter BJ, Hoddinott KM, Sewell RW, Trad KS, Gill BD, Ihde GM. *A Prospective Multicenter Registry of Chronic Gastroesophageal Disease Receiving Transoral Incisionless Fundoplication*. J Am Coll Surg. 2012 Dec; 215(6):794-809.
- ²⁷ McCarty T., Itidiare M., Njei B., Rustagi T. (2018). *Efficacy of transoral incisionless fundoplication for refractory gastroesophageal reflux disease: a systematic review and meta-analysis*. Endoscopy, Jul;50(7):708-725. doi: 10.1055/a-0576-6589.
- ²⁸ Testoni PA, Testoni S. *Transoral fundoplication for gastroesophageal reflux disease*. Ann Esophagus 2018;1:7.
- ²⁹ Testoni PA, Testoni S, Mazzoleni G, Vailati C, Passaretti S. *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. 2015 Sep;29(9):2770-80. doi: 10.1007/s00464-014-4008-6. Epub 2014 Dec 6.
- ³⁰ Stefanidis G, Viazis N, Kotsikoros N, Tsoukalas N, Lala E, Theocharis L, Fassaris A, Manolakopoulos S. *Long-term benefit of transoral incisionless fundoplication using the Esophyx device for the management of gastroesophageal reflux disease responsive to medical therapy*. Dis Esophagus. 2017 Feb 1;30(3):1-8.
- ³¹ Brook RA, Wahlqvist P, Kleinman L, Wallander MA, Campbell SM, Smeeding JE. *Cost of gastro-oesophageal reflux disease to the employer: a perspective from the United States*. Aliment Pharmacol Ther. 2007;26:889-898.
- ³² Mody R, Eisenberg D, Hou L, Kamat S, Gerson LB. *Comparison of health care resource utilization and costs among patients with GERD on once-daily or twice-daily proton pump inhibitor therapy*. Clinicoecon Outcomes Res. 2013; 5: 161-169.
- ³³ Source: CY2018 PFS Physician Time, Median Intra-Service Time.

Appendix A. TIF® Procedure with EsophyX® Device Peer-Reviewed Bibliography - TIF 2.0

#	Reference	Publication Date	PMID	NCT	Patient Type (US/EU)	TIF Type	# of Patients Treated	Evidence Level	Study Type
1	Janu P, Shughoury AB, Venkat K, Hurwich D, Galouzis T, Siatras J, Streeter S, Korman K, Mavrelis G, Mavrelis P. Laparoscopic Hiatal Hernia Repair Followed by Transoral Incisionless Fundoplication. Surgical Innovation. Published Online August 20, 2019. https://doi.org/10.1177/155335061986944	Sep/19	31431138	3143608	US	2.0	99	IIb	Prospective
2	Fanous, M, Jaehne, A; Lorenson, D, Williams, S. Massive Caudate Lobe in Laparoscopic Hiatal Hernia Repair: Tying and Wrapping outside the Box. American Surgeon, Volume 85, Number 7, July 2019, pp. e336-e338(3).	Jul/19	31405438	n/a	US	2.0	1	IV	Case report
3	Nabi Z, Reddy DN. Update on Endoscopic Approaches for the Management of Gastroesophageal Reflux Disease. Gastroenterol Hepatol (NY). 2019 Jul;15(7):369-376.	Jul/19	31391807	n/a	EU/US	2.0	n/a	V	Review
4	Bazerbachi F, Krishnan K, Abu Dayyeh BK. Endoscopic GERD therapy: a primer to the transoral incisionless fundoplication procedure. Gastrointest Endosc. 2019 May 17. pii: S0016-5107(19)31720-1. doi: 10.1016/j.gie.2019.05.028. [Epub ahead of print]	Sep/19	31108091	n/a	US	2.0	n/a	V	Review
5	Testoni PA, Testoni S. Transoral fundoplication for gastroesophageal reflux disease. Ann Esophagus 2018;1:7.	Aug/18	n/a	n/a	EU/US	1.5, 2.0	50	IIb + V	Prospective + Review
6	Fanous M, Jaehne A, Lorenson D, Williams S. Outcome of Transoral Incisionless Fundoplication in Medicare Beneficiaries in a Critical Access Hospital. Am Surg, Volume 84, Number 9, September 2018, pp. e420-e422(3).	Sep/18	30454521	n/a	US	2.0	17	IV	Retrospective
7	Chimukangara M, Jalilvand AD, Melvin WS, Perry KA. Long-term reported outcomes of transoral incisionless fundoplication: an 8-year cohort study. Surg Endosc. 2018 Aug 27. doi: 10.1007/s00464-018-6403-x. [Epub ahead of print]	Aug/18	30167944	n/a	US	1.0, 2.0	57	IV	Retrospective
8	Fanous M, Jaehne, A, Lorenson, D, Williams, S. Impact of Endoscopic Training for Surgeons on Endolumenal and Laparoscopic Treatment for Gastroesophageal Reflux Disease: Data from a Rural, High-Volume Antireflux Program. The American Surgeon, Volume 84, Number 7, July 2018, pp. e245-e247(3).	Jul/18	n/a	n/a	US	2.0	136	IV	Retrospective
9	Fanous M, Wei W, Jaehne, A, Lorenson, D. Laparoscopic Repair of Hiatal Hernia in the Presence of Aberrant Left Hepatic Artery Using Extracorporeal Sliding Arthroscopic Knots. The American Surgeon, Volume 84, Number 7, July 2018, pp. e251-e253(3).	Jul/18	n/a	n/a	US	2.0	4	IV	Retrospective

Appendix A. TIF® Procedure with EsophyX® Device Peer-Reviewed Bibliography - TIF 2.0

#	Reference	Publication Date	PMID	NCT	Patient Type (US/EU)	TIF Type	# of Patients Treated	Evidence Level	Study Type
10	Yadlapati R, Vaezi MF, Vela MF, Spechler SJ, Shaheen NJ, Richter J, Lacy BE, Katzka D, Katz PO, Kahrilas PJ, Gyawali CP, Gerson L, Fass R, Castell DO, Craft J, Hillman L, Pandolfino JE. Management options for patients with GERD and persistent symptoms on proton pump inhibitors: recommendations from an expert panel. Am J Gastroenterol. 2018 Apr 24. doi: 10.1038/s41395-018-0045-4. [Epub ahead of print]	Apr/18	29683276	n/a	EU/US	ELF, 1.0, 2.0	n/a	V	Review
11	Puri R, Smith CD, Bowers SP. The Spectrum of Surgical Remediation of Transoral Incisionless Fundoplication-Related Failures. J Laparoendosc Adv Surg Tech A. 2018 May 16. doi: 10.1089/lap.2018.0063. [Epub ahead of print]	May/18	29733015	n/a	US	2.0	5	IV	Case series
12	Tyberg A, Choi A, Gaidhane M, Kahaleh M. Transoral incisional fundoplication for reflux after peroral endoscopic myotomy: a crucial addition to our arsenal. Endosc Int Open. 2018 May;6(5):E549-E552. doi: 10.1055/a-0584-6802. Epub 2018 May 8.	May/18	29756011	n/a	US	2.0	5	IV	Case series
13	Gerson L, Stouch B, Lobonțiu A. Transoral Incisionless Fundoplication (TIF 2.0): A Meta-Analysis of Three Randomized, Controlled Clinical Trials. Chirurgia (Bucur). 2018 Mar-Apr;113(2):173-184. doi: 10.21614/chirurgia.113.2.173.	May/18	29733015	n/a	EU/US	2.0	n/a	Ia	Meta-analysis
14	McCarty TR, Itidiare M, Njei B, Rustagi T. Efficacy of transoral incisionless fundoplication for refractory gastroesophageal reflux disease: a systematic review and meta-analysis. Endoscopy. 2018 Apr 6. doi: 10.1055/a-0576-6589. [Epub ahead of print]	Apr/18	29625507	n/a	EU/US	1.0, 2.0	n/a	V	Meta-analysis
15	Obuobi RB, Viswanath Y, Sathasivam R, Bussa G, Gill T, Reddy A, Shanmugam V, Gilliam A, Thambi P. Trans-oral incisionless fundoplication vs stretta, two recognized endoluminal anti-reflux therapies; a systematic review and meta-analysis. Int Surg J. 2018 Mar;5(3):765-772.	Mar/18	TBD	n/a	EU/US	1.0, 2.0	n/a	V	Review
16	Trad KS, Barnes WE, Prevou ER, Simoni G, Steffen JA, Shughoury AB, Raza M, Heise JA, Fox MA, Mavrelis PG. The TEMPO Trial at 5 Years: Transoral Fundoplication (TIF 2.0) Is Safe, Durable, and Cost-effective. Surg Innov. 2018 Feb.	Feb/18	29405886	16437958	US	2.0	44 (19 lost)	Ib	RCT

Appendix A. TIF® Procedure with EsophyX® Device Peer-Reviewed Bibliography - TIF 2.0

#	Reference	Publication Date	PMID	NCT	Patient Type (US/EU)	TIF Type	# of Patients Treated	Evidence Level	Study Type
17	Fanouso MY, Lorenson D, Williams S, Jaehne AK. Transoral incisionless fundoplication for Jehovah's Witnesses: A case report discussing safety and durability. SAGE Open Med Case Rep. 2017 Dec 21.	Dec/17	29318016	n/a	US	2.0	1	IIIa	Case report
18	Richter JE, Kumar A, Lipka S, Miladinovic B, Velanovich V. 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. 2018 Jan 3.	Jan/18	29305934	n/a	EU/US	ELF, 1.0, 2.0	n/a	V	Network meta-analysis
19	Fernando HC. Endoscopic fundoplication: patient selection and technique. J Vis Surg. 2017 Sep 14;3:121.	Sep/17	29078681	n/a	EU/US	2.0	n/a	V	Review
20	Thosani N, Goodman A, Manfredi M, Savaneethan U, Parsi M, Smith ZL, Sullivan SA, Banerjee S, Maple, JT; Endoscopic anti-reflux devices (with videos). Gastrointestinal Endoscopy 2017 Oct.	Oct/17	TBD	n/a	EU/US	ELF, 1.0, 2.0	n/a	V	Review
21	Ebright MI, Sridhar P, Little VR, Narsule CK, Daly BD, Fernando HC. Endoscopic Fundoplication: Effectiveness for Controlling Symptoms of Gastroesophageal Reflux Disease. Innovations (Phila). 2017 May/Jun;12(3):180-185.	May/17	28296655	n/a	US	2.0	80	IIIa	Case control
22	Stefanidis G, Viazis N, Kotsikoros N, Tsoukalas N, Lala E, Theocharis L, Fassaris A, Manolakopoulos S. Long-term benefit of transoral incisionless fundoplication using the esophyx device for the management of gastroesophageal reflux disease responsive to medical therapy. Dis Esophagus. 2016 Nov 21. [Epub ahead of print]	Nov/16	27868281	n/a	EU	2.0	45	IV	Case series
23	Brar TS, Draganov PV, Yang D; Endoluminal Therapy for Gastroesophageal Reflux Disease: In Between the Pill and the Knife? Dig Dis Sci. 2016 Oct 28. [Epub ahead of print].	Oct/16	27796767	n/a	EU, US	2.0	n/a	V	Review
24	Trad KS, Simoni G, Barnes WE, Shughoury AB, Raza M, Heise JA, Turgeon DG, Fox MA, Mavrelis PG. Transoral Fundoplication offers durable symptom control for chronic GERD: 3-year report from the TEMPO randomized trial with crossover arm. Surg Endosc. 2016 Sept 21 published online.	Sep/16	27655380	16437958	US	2.0	52 (9 lost)	Ib	RCT
25	Vohra S, Kuo V, Madani B, Sharaiha R, Kahaleh M, Tarnasky P, Kedia P. Real-time measurement of luminal compliance during transoral incisionless fundoplication. Endoscopy. 2015;47 Suppl 1 UCTN:E282-3.	Jun/15	TBD	n/a	US	2.0	1	V	Case report

Appendix A. TIF® Procedure with EsophyX® Device Peer-Reviewed Bibliography - TIF 2.0

#	Reference	Publication Date	PMID	NCT	Patient Type (US/EU)	TIF Type	# of Patients Treated	Evidence Level	Study Type
26	Huang X, Chen S, Zhao H, Zeng X, Lian J, Tseng Y, Chen J. Efficacy of transoral incisionless fundoplication (TIF) for the treatment of GERD: a systematic review with meta-analysis. <i>Surg Endosc.</i> 2016 Aug 5. [Epub ahead of print].	Aug/16	27495332	n/a	EU, US	ELF, 1.0, 2.0	n/a	V	Review
27	Testoni PA, Mazzoleni G, Testoni SG. Transoral incisionless fundoplication for gastro-esophageal reflux disease: Techniques and outcomes. <i>World J Gastrointest Pharmacol Ther.</i> 2016 May 6;7(2):179-89.	May/16	27158533	n/a	EU, US	2.0	n/a	V	Review
28	Jain D, Singhal S. Transoral Incisionless Fundoplication for Refractory Gastroesophageal Reflux Disease: Where Do We Stand? <i>Clin Endosc.</i> 2016 Mar;49(2):147-56.	Mar/16	26878326	n/a	EU, US	1.0, 2.0	n/a	V	Review
29	Chang CG, Thackeray L; Laparoscopic Hiatal Hernia Repair in 221 Patients: Outcomes and Experience. <i>JSLs.</i> 2016 Jan-Mar;20(1).	Mar/16	26884676	n/a	US	2.0	46	IV	Retrospective
30	Patti MG; An Evidence-Based Approach to the Treatment of Gastroesophageal Reflux Disease. <i>JAMA Surg.</i> 2016 Jan 1;151(1):73-78.	Jan/16	26629969	n/a	EU, US	1.0, 2.0	n/a	V	Review
31	Håkansson, B, Montgomery, M, Cadiere, GB, Rajan, A, Bruley des Varannes, S, Lerhun, M, Coron, E, Tack, J, Bischops, R, Thorell, A, Arnelo, U, Lundell. L. <i>Randomised clinical trial: transoral incisionless fundoplication vs. sham intervention to control chronic GERD.</i> <i>Aliment Pharmacol Ther.</i> 2015 Dec;42(11-12):1261-70.	Dec/15	26463242	1110811	EU	2.0	22 (22 sham)	Ib	RCT
32	Bell RC; <i>Randomized Controlled Trial of Transoral Incisionless Fundoplication Vs. Proton Pump Inhibitors for Treatment of Gastroesophageal Reflux Disease;</i> <i>Am J Gastroenterol.</i> 2015 Nov;110(11):1621-3.	Nov/15	26618423	n/a	EU	ELF, 1.0, 2.0	n/a	V	Retrospective
33	Ihde GM, Dill LA, Lister DG, Lucchese CF, Cottrell C, Krone PK, Stone RA. <i>A comparison of the endoscopic and laparoscopic view of the gastroesophageal junction in the use of transoral fundoplication.</i> <i>Am J Surg.</i> 2015 Sep 14.	Sep/15	26460056	n/a	US	2.0	53	V	

Appendix A. TIF® Procedure with EsophyX® Device Peer-Reviewed Bibliography - TIF 2.0

#	Reference	Publication Date	PMID	NCT	Patient Type (US/EU)	TIF Type	# of Patients Treated	Evidence Level	Study Type
34	Testoni PA, Testoni S, Mazzoleni G, Vailati C, Passaretti S. <i>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.</i> Surg Endosc. 2015 Sep;29(9):2770-80.	Sep/15	25480624	n/a	EU	1.0, 2.0	50	IIb	Prospective
35	Hopkins J, Switzer NJ, Karmali S. <i>Update on novel endoscopic therapies to treat gastroesophageal reflux disease: A review.</i> World J Gastrointest Endosc. 2015 Aug 25;7(11):1039-44.	Aug/15	PMC4549661	n/a	EU, US	ELF, 1.0, 2.0	n/a	V	
36	Bell RC, Kurian AA, Freeman KD. <i>Laparoscopic anti-reflux revision surgery after transoral incisionless fundoplication is safe and effective.</i> Surg Endosc. 2015 Jul;29(7):1746-52.	Jul/15	25380707	n/a	US	2.0	28 (failed TIF 2.0)	IV	
37	Subramanian, CR, Triadafilopoulos G; <i>Refractory Gastroesophageal Reflux Disease;</i> Gastroenterol. Rep. (2015) 3 (1): 41-53.	Feb/15	25274499	n/a	EU, US	2.0	n/a	V	
38	Hunter JG, Kahrilas PJ, Bell RCW, Wilson EB, Trad KS, Dolan JP, Perry KA, Oelschlager BK, Soper NJ, Snyder BA, Burch MA, Melvin WS, Reavis K, Turgeon DG, Hungness ES, Diggs BS. <i>Efficacy of transoral fundoplication vs omeprazole for treatment of regurgitation in a randomized controlled trial.</i> Gastroenterology. 2015 Feb;148(1):324-33.	Feb/15	25448925	1136980	US	2.0	87 (42 sham)	Ib	RCT
39	Rinsma NF, Farré R, Bouvy ND, Masclee AA, Conchillo JM. <i>The effect of endoscopic fundoplication and proton pump inhibitors on baseline impedance and heartburn severity in GERD patients.</i> Neurogastroenterol Motil. 2015 Feb;27(2):220-8.	Feb/15	25348594	n/a	EU	2.0	32 (15 PPI)	IV	
40	Trad KS, Barnes WE, Simoni G, Shughoury AB, Mavrelis PG, Raza M, Heise JA, Turgeon DG, Fox MA. <i>Transoral Incisionless Fundoplication Effective in Eliminating GERD Symptoms in Partial Responders to Proton Pump Inhibitor Therapy at 6 Months: The TEMPO Randomized Clinical Trial.</i> Surg Innov. 2015 Feb;22(1):26-40.	Feb/15	24756976	16437958	US	2.0	40 (23 PPI)	Ib	RCT

Appendix A. TIF® Procedure with EsophyX® Device Peer-Reviewed Bibliography - TIF 2.0

#	Reference	Publication Date	PMID	NCT	Patient Type (US/EU)	TIF Type	# of Patients Treated	Evidence Level	Study Type
41	Bell RC, Barnes WE, Carter BJ, Sewell RW, Mavrelis PG, Ihde GM, Hoddinott KM, Fox MA, Freeman KD, Gunsberger T, Hausmann MG, Dargis D, Gill BD, Wilson EB, Trad KS. <i>Transoral Incisionless Fundoplication: 2 year results from the prospective multicenter U.S. study.</i> Am Surg, 2014 Nov; 80(11):1093-1105.	Nov/14	25347499	1118585	US	2.0	100	IIb	Prospective
42	Edriss H, El-Bakush A, Nugent K. <i>Esophageal Perforation and Bilateral Empyema Following Endoscopic EsophyX Transoral Incisionless Fundoplication.</i> Clin Endosc. 2014 Nov;47(6):560-3.	Nov/14	PMC 4260105	n/a	US	2.0	1	IV	
43	Bell RC, Fox MA, Barnes WE, Mavrelis PG, Sewell RW, Carter BJ, Ihde GM, Trad KS, Dargis D, Hoddinott KM, Freeman KD, Gunsberger T, Hausmann MG, Gill BD, Wilson E. <i>Univariate and multivariate analyses of preoperative factors influencing symptomatic outcomes of transoral fundoplication.</i> Surg Endosc. 2014 Oct;28(10):2949-58.	Oct/14	24879134	1118585	US	2.0	158	IIb	Prospective
44	Trad KS, Simoni G, Barnes WE, Shughoury AB, Raza M, Heise JA, Turgeon DG, Fox MA, Mavrelis PG. <i>Efficacy of Transoral Fundoplication For Treatment of Chronic Gastroesophageal Reflux Disease Incompletely Controlled with High-Dose PPI Therapy: A Randomized, Multicenter, Open Label, Crossover Study.</i> BMC Gastroenterol. 2014 Oct 6;14(1):174.	Oct/14	25284142	16437958	US	2.0	61 (39 + 1 lost 6-12m + 21 crossover)	Ib	RCT
45	Toomey P, Teta A, Patel K, Ross S, Sukharamwala P, Rosemurgy AS. <i>Transoral Incisionless Fundoplication: Is It as Safe and Efficacious as a Nissen or Toupet Fundoplication?</i> Am Surg 2014 Sep;80(9):860-7.	Sep/14	25197871	n/a	US	2.0	20	IV	Prospective case control
46	Maradey-Romero C, Kale H, Fass R. C; Nonmedical therapeutic strategies for nonerosive reflux disease. J Clin Gastroenterol. 2014 Aug;48(7):584-9.	8/1/2014	25000345	n/a	EU	ELF, 2.0	n/a	V	
47	Reavis KM and Perry KA. <i>Transoral incisionless fundoplication for the treatment of gastroesophageal reflux disease.</i> Expert Rev. Med. Devices. 2014 Mar; 11(4), 341-350.	Mar/14	24918903	n/a	US	2.0	n/a	V	

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#	Reference	Publication Date	PMID	NCT	Patient Type (US/EU)	TIF Type	# of Patients Treated	Evidence Level	Study Type
48	Rinsma N, Smeets F, Bruls D, Kessing B, Bouvy N, Masclee AM, Conchillo J. <i>Effect of transoral incisionless fundoplication on reflux mechanisms.</i> Surg Endosc. 2014 Mar;28(3):941-9.	Mar/14	24149854	n/a	EU	2.0	15	IIb	Prospective
49	Wilson EB, Barnes WE, Mavrelis PG, Carter BJ, Bell RCW, Sewell RW, Ihde GM, Dargis D, Hoddinott KM, Shughoury AB, Gill BD, Fox MA, Turgeon DG, Freeman K, Gunsberger T, Hausmann MG, LeBlanc KA, Deljkich E, Trad KS. <i>The Effects of Transoral Incisionless Fundoplication on Chronic GERD Patients: 12-Month Prospective Multicenter Experience.</i> Surg Laparosc Endosc Percutan Tech, Feb 2014; 24(1):36-46.	Feb/14	24487156	1118585	US	2.0	100	IIb	Prospective
50	Wendling MR, Melvin WS, Perry KA. <i>Impact of transoral incisionless fundoplication (TIF) on subjective and objective GERD indices: a systematic review of the published literature.</i> Surg Endosc. 2013 Oct;27(10):3754-61.	Oct/13	23644835	n/a	EU, US	ELF, 1.0, 2.0	550+	IIIa	Case control
51	Titus JM, Mason DP, Raymond DP, Rice TW, Murthy SC; <i>Esophagopulmonary fistula and left lung abscess after transoral incisionless fundoplication.</i> Ann Thorac Surg. 2013 Aug;96(2):689-91.	Aug/13	23910114	n/a	US	2.0	1	IV	
52	Perry KA, Linn JG, Eakin JL, Onders RP, Velanovich V, Melvin WS. <i>Transoral Incisionless Fundoplication Does Not Significantly Increase Morbidity of Subsequent Laparoscopic Nissen Fundoplication.</i> Journal of Lap & Adv Surg Tech. 2013 May;23(5):456-8.	May/13	23578416	n/a	US	2.0	7	IIb	Retrospective
53	Bell RCW, Hufford RJ, Fearon J, Freeman KD. <i>Revision of failed traditional fundoplication using EsophyX® transoral fundoplication.</i> Surg Endosc. 2013 Mar;27(3):761-7.	Mar/13	23052519	n/a	US	2.0	11	IV	
54	Bell RCW, Mavrelis PG, Barnes WE, Dargis D, Carter BJ, Hoddinott KM, Sewell RW, Trad KS, Gill BD, Ihde GM. <i>A Prospective Multicenter Registry of Patients with Chronic Gastroesophageal Disease Receiving Transoral Incisionless Fundoplication.</i> J Am Coll Surg. 2012 Dec;215(6):794-809.	Dec/12	25347499	1118585	US	2.0	100	IIb	Prospective

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#	Reference	Publication Date	PMID	NCT	Patient Type (US/EU)	TIF Type	# of Patients Treated	Evidence Level	Study Type
55	Narsule CK, Wee JO, Fernando HC. <i>Endoscopic management of gastroesophageal reflux disease: A review.</i> J Thorac Cardiovasc Surg. 2012 Sep; 144(3):S74-8.	Sep/12	22513318	n/a	US	2.0	n/a	V	
56	Testoni PA, Vailati C. <i>Transoral incisionless fundoplication with EsophyX for treatment of gastro-oesophageal reflux disease.</i> Dig Liver Dis 2012 Aug; 44(8):631-5.	Aug/12	22622203	n/a	EU	1.5, 2.0	n/a	V	
57	Testoni PA, Vailati C, Testoni S, Corsetti M. <i>Transoral incisionless fundoplication (TIF 2.0) with EsophyX for gastroesophageal reflux disease: long-term results and findings affecting outcome.</i> Surg Endosc. 2012 May; 26(5):1425-35.	May/12	22170317	n/a	EU	1.0, 2.0	42	IIb	Prospective
58	Petersen RP, Filippa L, Wassenaar EB, Martin AV, Tatum R, Oelschlagel B. <i>Comprehensive evaluation of endoscopic fundoplication using the EsophyX device.</i> Surg Endosc. 2012 Apr; 26(4):1021-7.	Apr/12	22042587	n/a	US	2.0	21	IV	
59	Trad KS, Turgeon DS, Deljkich E. <i>Long-term outcomes after transoral incisionless fundoplication in patients with GERD and LPR symptoms.</i> Surg Endosc. 2012 Mar; 26(3):650-60.	Mar/12	21959689	1327963	US	2.0	34	IV	Retrospective
60	Narsule CK, Burch MA, Ebright MI, Hess DT, Rivas R, Daly BDT, Fernando HC. <i>Endoscopic fundoplication for the treatment of gastroesophageal reflux disease: initial experience.</i> J Thorac Cardiovasc Surg. 2012 Jan; 143(1):228-34.	Jan/12	22070927	n/a	US	2.0	46	IIIa	Case control
61	Rosen HR, Hussain A, Lechner M, Enserer, C. <i>Transoral fundoplication for recurrent gastro-oesophageal reflux disease following previous surgical repair.</i> Hamdan Medical Journal. 2012; 5:57-62.	Jan/12	n/a	n/a	EU	2.0	10	IV	
62	Ihde GM, Besancon K, Deljkich E. <i>Short-term safety and symptomatic outcomes of transoral incisionless fundoplication with or without hiatal hernia repair in patients with chronic gastroesophageal reflux disease.</i> Am J Surg. 2011 Dec; 202(6):740-7.	Dec/11	22014853	1327963	US	2.0	47	IIb	Prospective

Appendix A. TIF® Procedure with EsophyX® Device Peer-Reviewed Bibliography - TIF 2.0

#	Reference	Publication Date	PMID	NCT	Patient Type (US/EU)	TIF Type	# of Patients Treated	Evidence Level	Study Type
63	Nguyen A, Vo T, Nguyen XM, Smith BR, Reavis KM. <i>Transoral incisionless fundoplication: initial experience in patients referred to an integrated academic institution.</i> Am Surg. 2011 Oct; 77(10):1386-9.	Oct/11	22127095	n/a	US	2.0	10	IV	
64	Bell RCW, Cadiere GB. <i>Transoral rotation esophagogastric fundoplication: technical, anatomical, and safety considerations.</i> Surg Endosc. 2011 Jul;25(7):2387-99.	Jul/11	21184101	n/a	US	2.0	n/a	V	
65	Bell RCW, Freeman K. <i>Clinical and pH-metric outcomes of transoral esophagogastric fundoplication for the treatment of gastroesophageal reflux disease.</i> Surg Endosc. 2011 Jun; 25(6):1975-84.	Jul/11	21140170	n/a	US	2.0	37	IV	Retrospective
66	Hoppo T, McMahan BP, Witteman BPL, Kraemer SJM, O'Rourke RW, Gravesen F, Bouvy ND, Jobe BA. <i>Functional Lumen Imaging Probe to Assess Geometric Changes in Esophagogastric Junction Following Endolumenal Fundoplication.</i> J Gastrointest Surg. 2011 Jul;15(7):1112-20.	Jul/11	21597882	n/a	US	1.0, 2.0	10 human + 11 canine	V	
67	Barnes WE, Hoddinott KM, Mundy S, Williams M. <i>Transoral incisionless fundoplication offers high patient satisfaction and relief of therapy-resistant typical and atypical symptoms of GERD in community practice.</i> Surg Innov. 2011 Jun; 18(2):119-29.	Jun/11	21307014	1327963	US	2.0	123	IV	
68	Hoppo T, Immanuel A, Schuchert M, Dubrava Z, Smith A, Nottle P, Watson DI, Jobe BA. <i>Transoral incisionless fundoplication 2.0 procedure using EsophyX™ for gastroesophageal reflux disease.</i> J Gastrointest. Surg. 2010 Dec; 14(12):1895-901.	Dec/10	20878257	n/a	US	2.0	19	IIb	Prospective
69	Perretta S, Dallemagne B, Allemann P, Marescaux J; Multimedia manuscript. <i>Heller myotomy and intraluminal fundoplication: a NOTES technique.</i> Surg Endosc. 2010 Nov;24(11):2903.	Nov/10	20428893	n/a	EU	2.0	1 porcine	V	
70	Yushuva A, McMahan M, Goodman E; <i>Transoral incision free fundoplication (TIF) - A new paradigm in the surgical treatment of GERD.</i> J Surg Case Rep. 2010 Jul 1;2010(5):1.	Jul/10	24946319	n/a	US	2.0	1	IV	

Appendix A. TIF® Procedure with EsophyX® Device Peer-Reviewed Bibliography - TIF 2.0

#	Reference	Publication Date	PMID	NCT	Patient Type (US/EU)	TIF Type	# of Patients Treated	Evidence Level	Study Type
71	Testoni PA, Corsetti M, Di Pietro S, Castellana AG, Vailati C, Masci E, Passaretti S. <i>Effect of transoral incisionless fundoplication on symptoms, PPI use, and pH-impedance refluxes of GERD patients.</i> World J Surg. 2010 Apr; 34(4):750-7.	Apr/10	20091308	n/a	EU	1.0, 2.0	20	IIb	Prospective
72	Velanovich V. <i>Endoscopic, endoluminal fundoplication for gastroesophageal reflux disease: initial experience and lessons learned.</i> Surgery 2010 Apr; 148:646-53.	Apr/10	20708763	n/a	US	1.0, 2.0	24	IV	
73	Agostoni M, Boemo C; Bilateral pneumothorax during transoral incisionless fundoplication. Eur J Anaesthesiol. 2010 Feb;27(2):216-7.	Feb/10	19935074	n/a	EU	2.0	1	IV	
74	Jobe BA, O'Rourke RW, McMahon BP, Gravesen F, Lorenzo C, Hunter JG, Bronner M, Kraemer SJM. <i>Transoral endoscopic fundoplication in the treatment of GERD: the anatomic and physiologic basis for reconstruction of the esophagogastric junction using a novel device.</i> Ann Surg. 2008 Jul; 248(1):69-76.	Jul/08	18580209	n/a	US	1.0, 2.0	21 canine	V	