

New Options for the Management of GERD

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Abstract Novel GERD treatment modalities have emerged over the past decade as alternatives to proton pump inhibitors or traditional laparoscopic Nissen fundoplication. Four new devices—LINX, TIF, EndoStim and Stretta—have attempted to improve upon the limitations of these traditional therapies. While each is promising, only the LINX device addresses the patient's symptoms, achieves objective control of acid and has limited the need for additional therapies. Further comparative research and longer term follow-up are necessary to determine the role of these therapies in the algorithm of GERD management.

Keywords Gastroesophageal reflux disease · GERD · Management · LINX · EndoStim · TIF · EsophyX · Stretta · Reflux · Nissen · Fundoplication · Esophagitis · Hiatal hernia

Introduction

Gastroesophageal reflux (GERD) affects up to 27.8 % of adults in North America, and the incidence has been increasing worldwide [1]. The primary options for treatment have been proton pump inhibitors (PPI) or laparoscopic Nissen fundoplication (LNF). The vast majority of patients

are managed with PPIs with good control of their symptoms. However, what was once a panacea for treating GERD has been eroded by recent data, suggesting that PPIs are not as effective as believed, with only 32 % of patients achieving complete symptom relief [2], and other reports highlighting long-term side effects such as pneumonia, *Clostridium difficile* infection, fracture, impaired magnesium absorption, thrombocytopenia, iron deficiency, vitamin B12 deficiency, rhabdomyolysis and acute interstitial nephritis [3].

Despite these outcomes and concerns, a relatively small number of patients will choose the alternative and undergo fundoplication, which has been demonstrated to be as effective if not more effective than PPIs in a randomized control trial [4]. The patient's reticence may be due to the perceived invasiveness of a laparoscopic operation, the potential side effects such as symptomatic gas bloat (40 %), hyperflatulence (57 %) and dysphagia (11 %) or even the durability of LNF, which is estimated at 85 % at 5 years [5•]. This has resulted in a significant treatment gap with a large number of patients who are unsatisfied with PPIs yet are unwilling to undergo LNF. Alternative treatment modalities have been developed to attempt to close this treatment gap. In this report, we review the recently developed surgical and endoscopic options for managing GERD that hope to address this therapy gap.

Methods

Devices or systems included in this review were selected if they have received approval from the Food and Drug Administration (FDA) for use in the USA or have CE Mark approval in Europe. In addition, the device was required to have published results in a medical journal. The devices meeting these criteria were:

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- LINX reflux management system (Torax Medical, Shoreview, MN, USA).
- EsophyX₂ transoral incisionless fundoplication (TIF) (Endogastric Solutions, Redmond, WA, USA).
- Stretta (Mederi Therapeutics, Greenwich, CT, USA);
- EndoStim (Endostim BM, The Netherlands).

The success of most GERD treatments is often determined by the symptomatic improvement reported by the patient. However, this is not the only measure of success. In this review, each device or procedure was assessed by several factors including:

- (1) Symptom improvement (e.g., effect on presenting symptoms, durability, development of new symptoms and patient perception of overall success);
- (2) Effects on esophageal function and mucosal integrity (e.g., esophageal acid exposure, mucosal integrity);
- (3) Need for additional therapy (medication use and reoperations) [6•].

Results of Current Options for GERD Treatment

Both PPIs and antireflux surgery have been shown to be effective in the management of chronic GERD in two randomized trials at 5 [5•] and 12 years [7]. The LOTUS trial demonstrated similar rates of remission of GERD at 5 years (92 %-PPIs vs. 85 %-LNF, $p = 0.48$), but these rates dropped to 46 and 37 %, respectively, when patients reach 12 years of follow-up [7]. Subjectively, in these trials, the classic symptoms of heartburn and regurgitation were better controlled with surgery, but this comes in exchange for higher rates of dysphagia, flatulence and an inability to belch/vomit. Despite these differences, the quality of life of both treatment arms remained excellent and very similar across the groups. Only the LOTUS trial reported objective pH data [5•]. Patients treated with PPIs had % time pH < 4 increase from 12.1 to 62.1 %, whereas patients who underwent LNF remained stable from 12.4 % at baseline to 11.4 % at 5 years [5•].

New Options for GERD Treatment

LINX: Reflux Management System

The LINX Reflux Management System (LINX) consists of a ring of titanium-coated magnets that are designed to augment the lower esophageal sphincter (see Fig. 1). The mechanism of action of this device is based on the concept of a ‘loose ligature’ around the LES as first described in

1983 by Samelson et al. [8]. This loose ligature was shown to prevent LES shortening and thus opening of the LES to increasing gastric distension (see Fig. 1).

Current indications for implantation of the LINX device include patients with objective evidence of GERD, hiatal hernia <3 cm in axial length, normal esophagogastric motility, and the absence of Barrett’s esophagus. The full manufacturer recommended and FDA approved patient selection criteria are listed in Table 1.

The LINX device is implanted laparoscopically using four or five ports in a similar configuration to LNF. The location of device placement is identified on the patient’s right side at the level of the hepatic branch of the anterior vagus nerve. Next, the space between the lateral left crus and the posterior fundus is dissected. After opening the gastrohepatic ligament around the hepatic branch of the vagus nerve, a tunnel is created behind the esophagus directed toward the area dissected on the left crus. A ¼-inch penrose drain is placed through the tunnel behind the esophagus. The posterior vagus nerve is then identified and isolated by placing the penrose inside of the nerve and around the GEJ.

On the anterior surface, the peritoneum and fat are cleared with monopolar cautery taking care to preserve the anterior vagal nerve and thus creating a “trench” for the device to sit in on the surface of the esophagus. The sizing device is placed in the tunnel between the posterior vagus and the esophagus to guide size selection. After sizing, the appropriately sized device is situated in the tunnel and around the esophagus and secured with the clasp or sutures depending on which version of the device is implanted. Hiatal hernias up to 3 cm in size can usually be closed with a single crural suture in most cases.

Patients are allowed to drink liquids immediately after the procedure and start on a regular diet within 24 h of the procedure. PPIs are stopped the morning of the procedure. For most patients, only oral analgesics are necessary for up to 2–4 days.

Outcomes and Results of LINX

The current outcome data on LINX are derived from two major publications that evaluated 100 patients from the USA [9•] and 100 patients from Italy [10]. Patients in both trials were among the first to undergo device implantation, and the majority were part of a clinical trial.

In both studies, the patient’s GERD symptoms as measured by the GERD HRQL showed significant (≥ 50 %) improvement from baseline in 92 % [9•] and a normalization of the median GERD-HRQL from 16 to 2 on PPIs before placement [10]. The symptom of regurgitation was significantly improved from nearly 60–1 % 3 years after device implantation [9•]. Bloating was reported in only

Fig. 1 LINX system: **a** antireflux action; **b** relaxation with food bolus. Photos courtesy of Torax Medical Inc.

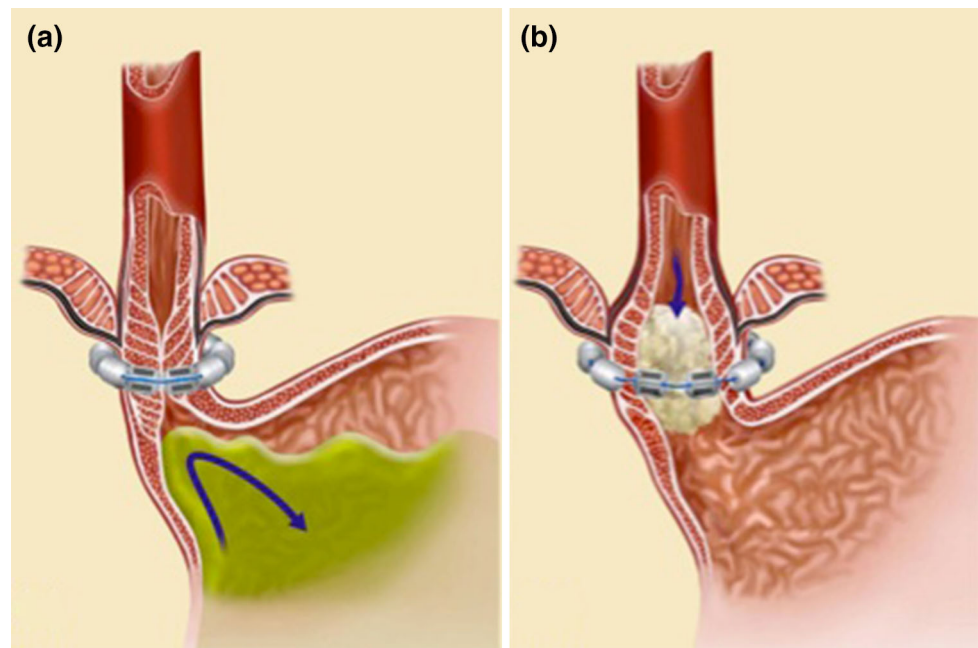


Table 1 LINX inclusion and exclusion criteria

Inclusion criteria	
18–85 years old	
Typical reflux symptoms at least partially responsive to PPI therapy	
Abnormal esophageal acid exposure	
Normal contraction amplitude and wave form in the esophageal body	
Exclusion criteria	
Symptoms of dysphagia	
Previous upper abdominal surgery	
Previous endoluminal antireflux procedures	
Sliding hiatal hernia ≥ 3 cm	
Grade B, C or D esophagitis (LA classification)	
Barrett's esophagus	
BMI > 35 kg/m ²	
Titanium, stainless steel, nickel or ferrous allergy	
Gross esophageal anatomic abnormalities	

Data from Bonavina et al. [10, 30]

PPI proton pump inhibitor, BMI body mass index

2 % (2/100) of patients, while 99 % (99/100) of patients reported ability to belch and vomit at follow-up [10]. Lastly, patient satisfaction was reported in 87 % (83/95) of patients at last follow-up [10].

Consistent with symptomatic improvements, the objective measures of reflux also improved after LINX placement. The mean DeMeester score decreased from 36.6 to 13.5 ($p < 0.001$), and % time pH < 4 decreased from 10.9 to 3.3 ($p < 0.001$) [9]. These results appear to be durable

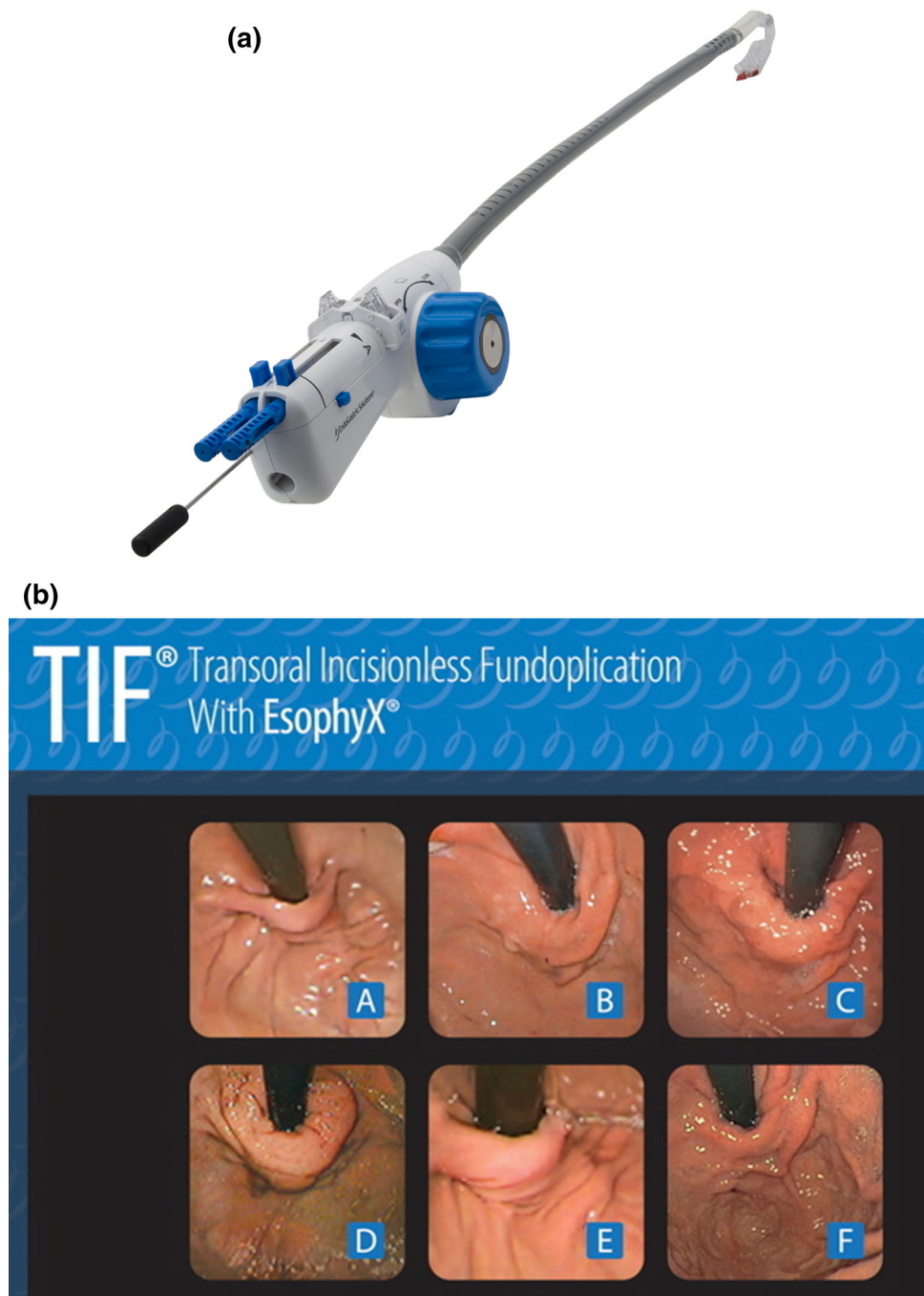
with post-implantation pH studies at a mean of 4.2 years in 20 patients showing % time pH < 4 was lowered from 8 to 3.2 %, and the DeMeester score was reduced from 30.1 to 11.2 [10]. Normalization of pH (% time pH < 4 for ≤ 4.5 % of the time) was 67 % (20/30) at last follow-up and 75 % (15/20) at 5 years [10]. Likewise, normalization of esophageal acid exposure or a ≥ 50 % reduction was achieved in 80 % (25 of 30) patients [10]. Additionally, over 85 % of patients were off PPIs at 3 years in both studies [9, 10].

It is recommended that patients with a LINX should have it removed before undergoing MRI. However, few data have been reported on this issue. Bonavina et al. [10] reported their results of 8/100 patients who underwent MRI scanning after LINX implantation, and two of these patients reported discomfort during the scan. One had odynophagia and dysphagia for 3 months, and one patient reported occasional heartburn after the MRI [10]. Due to this report, MRI should be avoided if possible in patients who have had a LINX implant.

Transoral Incisionless Fundoplication (TIF) with the EsophyX₂ Device

The EsophyX₂ antireflux device (see Fig. 2) used in conjunction with a flexible endoscope enables the creation of a partial anterior (up to 270–300°) esophagogastric full-thickness fundoplication by using proprietary tissue-manipulating elements and 12 or more polypropylene fasteners [11–13]. This system was designed to mimic a LNF by using an endoscopic technique.

Fig. 2 **a** TIF EsophyX device. **b** Endoscopic view post fundoplication. ©[2013] EndoGastric Solutions, Inc. *A*, *E* Endoscopic view post Nissen fundoplication. *B–D*, *F* Endoscopic view post TIF. Photos courtesy of EndoGastric Solutions Inc.



Current indications for transoral incisionless fundoplication include patients with objective evidence of GERD and hiatal hernia <3 cm in axial length. Inclusion and exclusion criteria are listed in Table 2 [14].

The procedure is performed endoscopically under general anesthesia with the patient in the left lateral decubitus position. The EsophyX₂ device has a handle where controls are located and a *chassis* (18 mm diameter) through which the endoscope is inserted and control channels run (see Fig. 2). The endoscopic plicating and suturing mechanism

works in a complex but coordinated way as described by Bell et al. [15]. Plication is facilitated by a vacuum-powered tissue invaginator, a *tissue mold*, which retroflexes to push tissue against the device for plication and a helical screw that allows caudal manipulation of tissue between the *mold* and *shaft*. Additionally, there are also two stylets that fire through the esophagus and fundus to guide H-shaped fastener deployment.

During the procedure, one physician controls fastener implantation and one physician operates the endoscope.

Table 2 EsophyX transoral incisionless fundoplication (TIF) inclusion and exclusion criteria

Inclusion criteria	
Age 18–75 years	
GERD for >1 year	
Daily PPI use for >6 months	
Moderate to severe typical or atypical GERD symptoms off PPIs	
Complete (responders) or partial (nonresponders) symptom control on PPIs	
Deteriorated gastroesophageal junction (Hill grade II or III)	
Proven gastroesophageal reflux by either endoscopy, ambulatory pH, or barium swallow testing	
Willingness to undergo pH/impedance testing, if required	
Willingness to adhere to postoperative diet for 6 week	
Availability for follow-up visits at 6 and 12 months	
Willingly and cognitively signed informed consent	
Exclusion criteria	
BMI > 35 kg/m ²	
Incompletely reducible hernia with residual >5 mm	
Portal hypertension and/or varices	
Esophagitis grade D; Barrett's esophagus >2 cm; esophageal ulcer; fixed esophageal stricture or narrowing	
Active gastroduodenal ulcer disease	
Gastric outlet obstruction or stenosis	
Gastroparesis or delayed gastric emptying confirmed by solid-phase gastric emptying study, if patient complains of postprandial satiety during assessment	
Coagulation disorder	
History of any of the following: resective gastric or esophageal surgery, antireflux surgery with anatomy unsuitable for TIF procedure per physician judgment, cervical spine fusion	
Zenker's diverticulum, esophageal epiphrenic diverticulum, achalasia, scleroderma, dermatomyositis, eosinophilic esophagitis or cirrhosis	
Pregnancy or plans of pregnancy in the next 12 months	
Enrollment in another device or drug study that may confound the results	

Data from Bell et al. [14•]

GERD gastroesophageal reflux disease, PPI proton pump inhibitor, BMI body mass index

First, an initial helical screw is deployed at 12 o'clock at the Z-line; next, three anterior rotation plication sets are created with the tissue mold, tissue invaginator, stylets and fasteners from 2 to 4 o'clock. The device is then rotated, and three posterior plication sets are deployed in a similar fashion from 7 o'clock toward 10 o'clock. The tissue mold is again rotated, and two anterior longitudinal plication sets are created at 12:30–2 o'clock. Next, the device is repositioned, and the final greater curve plication is created at 5 o'clock. Final endoscopy is performed to assess plication for bleeding or perforation.

Cadiere et al. [13] reported that the procedure took a median of 77 min, and either two gastroenterologists or

one surgeon and one gastroenterologist performed each procedure. Patients are typically discharged on post procedure day 1 and treated with PPIs for 2 weeks. A liquid diet without carbonation for 2 weeks followed by a soft diet for 2 weeks is recommended [13]. A water-soluble contrast study prior to discharge is recommended by some authors [15].

Outcomes and Results of TIF

The current results of the TIF procedure are based on ~25 publications. There was one multicenter review of 86 patients published in 2008 [13], and the remaining studies have been single-center reviews.

Subjective data for the TIF procedures showed significant improvements in the GERD-HRQL. At 6 months, scores were reduced by more than 50 % of patients, but only normalized in 50 % of patients [16], whereas at 12 months, reduced GERD-HRQL (≥ 50 %) scores were reported in 73 % (58/79) of patients [13]. Complete symptom elimination (GERD-HRQL score ≤ 12) occurred in 75 % of patients, and 65 % of patients were satisfied with their condition [13]. However, in this same study, only 56 % of patients were 'cured' of GERD (i.e., alleviated symptoms and off PPIs), while 22 % had improved symptoms and 22 % had ongoing GERD [13].

In a large study published in 2012 examining the TIF technique in 100 patients, 80 % discontinued acid suppression medications after surgery [14•]. Comparatively, in a different study, only 8/19 (42 %) of patients were completely off PPIs, while 32 % (6/19) were taking occasional PPIs and 26 % (5/19) were taking daily PPIs at 36 months [17]. Most patients that had dysphagia before the procedure had improved swallowing after TIF (24/27, 89 %), and no patients developed new dysphagia [14•]. Additionally, TIF did not affect the number of gas reflux episodes, allowing venting of gastric air as needed in a small series of 15 patients [18].

Objective measures of reflux control in 24 of 36 patients who underwent pre- and post-procedure pH testing off PPIs showed the mean % time pH < 4 was reduced from 10.4 to 1.7 ($p = 0.003$) and had normalized post TIF in 61 % of patients [16]. However, four patients actually had an increased (>5 %) time pH < 4 after TIF [16]. The average number of reflux episodes per 24 h was reduced from 20.8 to 8.4 ($p < 0.001$) after TIF and normalized in 89 % of patients [16]. DeMeester scores were also significantly reduced from 37.1 to 16.9 and normalized in 56 % of patients [16].

Complications occurring during TIF have been notable for esophageal perforation and post-procedure bleeds. In a series of 87 patients, there were two esophageal perforations during device insertion requiring operative

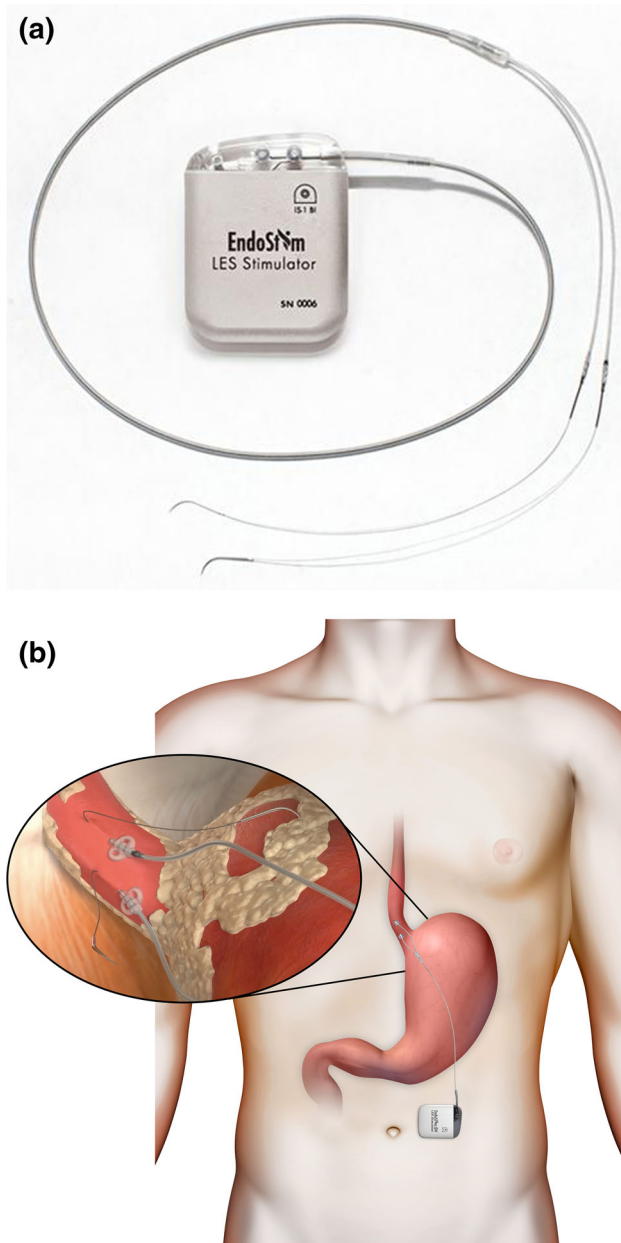


Fig. 3 **a** EndoStim device. **b** Implanted view. Photos courtesy of EndoStim Inc.

intervention with patients being discharged on day 6 and 21 [13]. There was also one patient who required blood transfusion of 4 units PRBC related to hemorrhage post TIF [13]. Bleeding was controlled endoscopically with clips and fibrin glue injection.

Two studies tracked patients who required additional procedures for refractory symptoms of GERD. First, a total of 5 (13.5 %) patients underwent additional procedures within 3–6 months including two patients who had a repeat TIF procedure and 3 that subsequently underwent LNF [16]. However, in a series of 38 patients at 36 months

Table 3 EndoStim inclusion and exclusion criteria

Inclusion

- 21–65 years
- Heartburn, regurgitation or both for >6 months necessitating daily PPI use
- Baseline GERD-HRQL heartburn score of ≥ 20 off PPI with at least 10-point improvement on PPI
- ASA class ≤ 2
- Distal esophageal pH < 4 on 24-h pH-metry off antisecretory therapy for >5 %
- Resting LES EEP ≥ 5 mmHg and ≤ 15 mmHg; esophageal body contraction amplitude > 30 mmHg for >70 % of swallows and >50 % peristaltic contractions
- Esophagitis \leq grade C (LA classification)
- Signed informed consent

Exclusion

- Non-GERD esophageal motility disorders or gastroparesis
- Subject has significant multisystem diseases (e.g., scleroderma, dermatomyositis, CREST, Sjogren's, etc.)
- Barrett's (>M2; >C1) or any dysplasia
- Hiatal hernia > 3 cm
- BMI > 35 kg/m²
- Type 1 diabetes mellitus or uncontrolled type II diabetes mellitus (T2DM) defined as HbA1c > 9.5 in previous 6 months or T2DM for >10 years)
- Suspected or confirmed esophageal or gastric malignancy or varices
- Significant cardiac arrhythmia, ectopy, significant cardiovascular disease
- Implanted electromedical device (e.g., pacemaker)
- Pregnancy
- Esophageal or gastric surgery, including antireflux surgery

Data from Rodriguez et al. [21]

PPI proton pump inhibitor, GERD-HRQL gastroesophageal reflux disease-health related quality of life, LES lower esophageal sphincter, BMI body mass index

follow-up, 37 % (14/38) of patients requested revisional LNF because of persistent GERD symptoms [17]. Further analysis of patients undergoing conversion from TIF to LNF have shown no increased operative morbidity [19]. The H fasteners were partially dislodged in all of these cases. However, another review of 11 patients after TIF that went on to require LNF did report increased operative morbidity [20]. In this series, previous TIF was associated with a risk of gastric injury during LNF (2/11, 18.2 %) and an increased rate of post-fundoplication dysphagia (3/11, 27.2 %) [20].

EndoStim

The EndoStim device is an implantable electrical stimulator that delivers long-term electrical stimulation therapy

to the lower esophageal sphincter (see Fig. 3). It consists of two bipolar stitch electrodes, an implantable pulse generator (IPG) and an external programming device. The programmable stimulator delivers electrical impulses into the LES at set intervals. The impulses have been shown to increase LES pressure in animals and humans, which is thought to result in GERD control [21].

The EndoStim device is not currently approved for sale in the US. However, it received the CE (Conformité Européenne) mark in 2012 for use in Europe. Patients eligible for this device have symptomatic reflux, are PPI dependent with no significant hiatal hernia and have a BMI < 35 m/kg². Inclusion and exclusion criteria are outlined in Table 3 [21].

The EndoStim device is placed laparoscopically as described by Rodriquez et al. [22]. The GEJ is dissected with care to preserve the phrenoesophageal ligament and vagus nerve branches. The goal is obtaining 2–3 cm of intra-abdominal esophageal length, which may require transhiatal mobilization of the distal esophagus. If this is the case, the posterior crura are closed after device implantation. Next, upper endoscopy is performed, and the Z line is identified via trans-illumination. Electrodes are placed laparoscopically while simultaneously performing an endoscopy to avoid esophageal perforation. The electrodes are placed away from the vagal nerves into the muscularis propria of the LES 10 mm away from one another. The electrode wires are then tunneled to a subcutaneous pocket and attached to the device. The device is tested intraoperatively and turned on 12 h after the procedure. Electrical stimulation parameters reported in prior studies were 20 Hz, 215 ms and 3–8 mA in 30-min sessions [22]. Patients are typically discharged home on postoperative day 1; it is unclear from these series whether they were on PPIs or diet restricted.

Outcomes and Results of EndoStim

Clinical results of EndoStim are based on a single open-labeled study of 25 patients reported in three different papers reflecting the duration of follow-up [21, 22, 23•].

Subjectively, the GERD HRQL was reduced from 9.0 on PPIs and 23.5 off PPI to 2.0 ($p < 0.001$) at 12 months in a study of 24 patients [22]. In this series, only 4 % of patients were unsatisfied with their current condition at 6-month follow-up [22]. Reflux impacting sleep decreased from 21/24 (88 %) off PPIs to 4 % (1/24; $p < 0.001$). Dysphagia or odynophagia also decreased from 58 % (14/24) off PPIs to 4 % (1/24; $p = 0.001$) [22].

Objectively, 96 % (23/24) of patients were off PPIs at 12 months [23•]. The DeMeester score was reduced from 36.7 to 11.7 ($p < 0.001$) [23•]. Similarly, the % time pH < 4 was reduced in the upright position [10.4 to 4.5 % ($p = 0.001$)] and in the supine position [6–0.4 %

($p = 0.02$)] [23•]. At 12 months, 96 % of patients were off PPIs, and 69 % of patients had either normalization or a > 50 % improvement in distal esophageal pH [23•].

None (0/24) of the patients reported bloating, inability to belch or new dysphagia [22]. In this series, one patient required hospitalization for chest pain and ultimately was diagnosed with esophageal spasms and discharged on antispasmodics without further symptoms. Three patients had implant site pain, one had a localized infection and one reported dyspepsia; three had transient nausea [22].

Stretta

The Stretta device delivers low-power radiofrequency energy to the LES and GEJ via endoscopic balloon-mounted needles, thereby altering the neuromuscular function of the LES (see Fig. 4). It is reported that the therapy remodels the LES and gastric cardia musculature, thereby improving reflux control by decreasing both the number of lower esophageal sphincter relaxation episodes (tLESRs) [24] and GEJ compliance, which is thought to be due to a neuro-ablative mechanism rather than tissue fibrosis [25].

Study inclusion criteria for Stretta include PPI responsive symptoms, abnormal 24-h pH study and normal esophageal motility. Exclusion criteria have included Barrett's esophagus and hiatal hernia >2 cm. Full inclusion and exclusion criteria are outlined in Table 4.

Radiofrequency ablative therapy is performed endoscopically under conscious sedation as described by Dughara et al. [26]. First, endoscopy is performed to measure the distance from the Z-line to the incisors, and then the endoscope is removed. The Stretta catheter is passed transorally and positioned up to 2 cm proximal to the squamocolumnar junction (Z line). The balloon is inflated, and four nickle-titanium electrodes are deployed into the esophageal wall. Temperature controlled (65–85 °C) RF energy (5 W) is delivered for a set time (1 min) while the device is irrigated with cooling solution. The needles are withdrawn, and the balloon is deflated prior to repositioning the device. The device is rotated 45° at a time, and treatment sets are repeated every 0.5 cm, covering an area 2 cm proximal and 1.5 cm distal to the Z line [26]. Six more sets of needle deployments are completed below the cardia for a total of 22 sets. All patients undergo endoscopy immediately after treatment to assess the mucosa. Dughara et al. [26] reported a mean procedure time of 50 min (range 45–70 min). The procedure is performed in the outpatient setting.

Outcomes and Results of Stretta

In 2012, Perry et al. published a meta-analysis containing 1,441 patients from 18 studies published until 2010 and demonstrated significant improvement in reflux symptoms

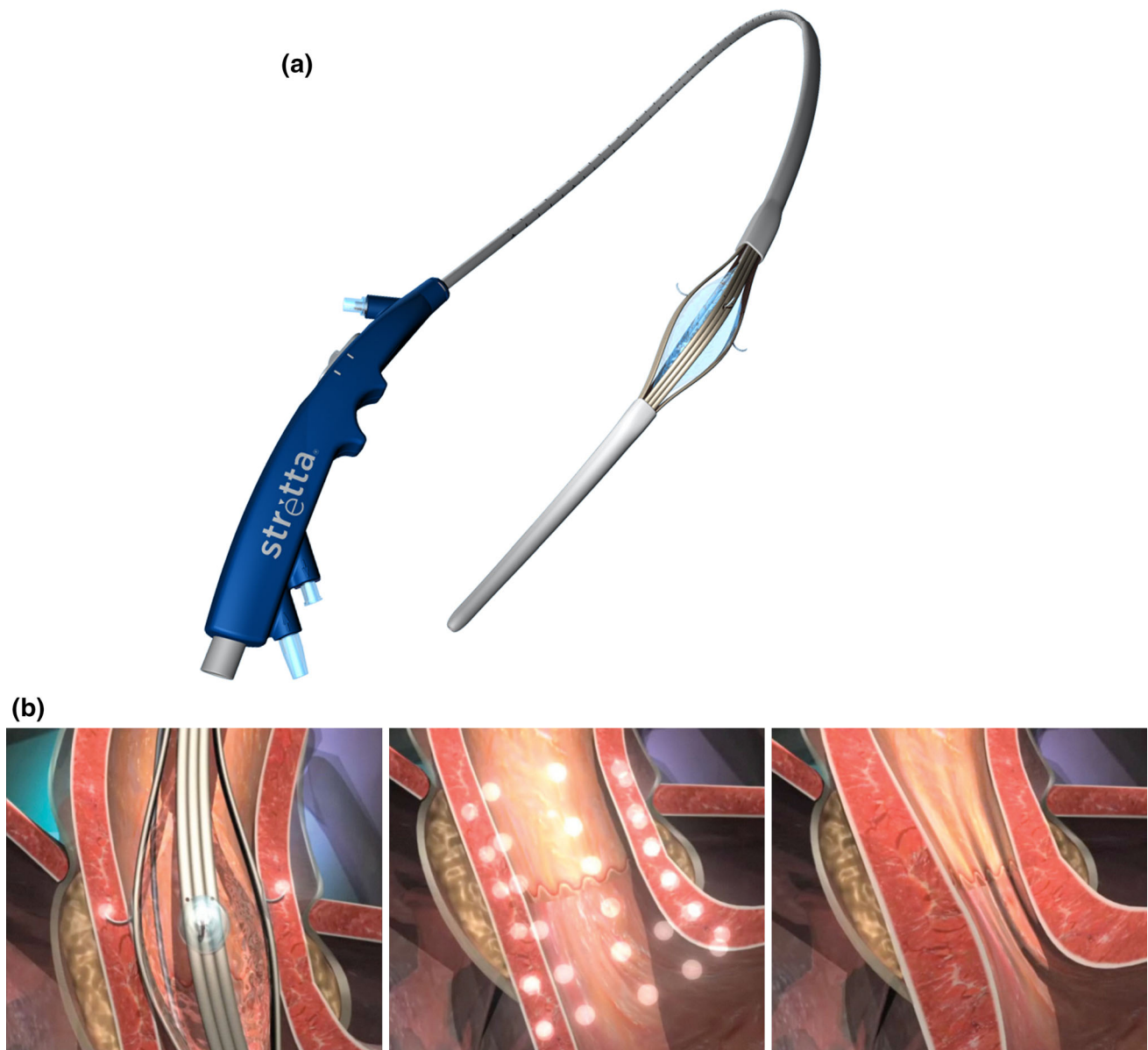


Fig. 4 **a** Stretta device; **b** how Stretta works. Photos courtesy of Mederi Therapeutics Inc. © 2013 Mederi Therapeutics Inc.

overall [27•]. They reported statistically significant improvements in subjective data of Stretta at mean follow-up intervals of 9.5–25.2 months. Significant improvements were reported for the GERD-HRQL (26.11–9.25, $p = 0.001$), QOLRAD (3.30–9.25, $p = 0.0010$), SF-36 physical (36.45–46.12, $p = 0.001$) and mental (46.7–55.1, $p = 0.0015$), heartburn score (3.55–1.19, $p = 0.001$) and satisfaction score (1.43–4.07, $p = 0.006$) [27•].

Objectively, the 6- and 12-month follow-up results of a US multicenter prospective open-label trial showed that PPI use in 94 patients decreased from 88 to 30 % at 12 months ($p = 0.0001$), and esophageal acid (% time $\text{pH} < 4$) exposure decreased from 10.2 to 6.4 % [28].

Similar results were also seen in the meta-analysis with % time $\text{pH} < 4$ (10.3–6.5, $p = 0.003$), DeMeester score (44.3–28.5, $p = 0.0074$) and LESP (16.5–20.2, $p = 0.0302$) after Stretta therapy [27•]. In longer term follow-up, additional procedures for reflux occurred in 11.9 % (13/109) of patients (6 Nissen, 7 Stretta) [27•].

Stretta was shown to be safe in several series with only minor complications reported [28, 29]. These self-limited complications occurred in 10 (8.6 %) of patients and included fever in two patients, superficial mucosal injury due to catheter movement in three patients (2.5 %) and chest pain requiring narcotic use in two (1.7 %). Hospitalization was required in one of these patients, sedation

Table 4 Stretta RFA inclusion and exclusion criteria

Inclusion criteria	
Age >18 years old	
24-h pH study (off medication) showing abnormal esophageal acid exposure	
GERD responsive to PPIs	
24-h pH study (off medications) showing abnormal esophageal acid exposure ($\geq 4\%$) and a DeMeester score of >14.7	
Esophageal manometry showing normal peristalsis and sphincter relaxation	
LES pressure > 5 mmHg and <10 mmHg	
Upper endoscopy showing low grade (LA grade A–B) or lack of esophagitis	
Exclusion criteria	
Barrett's esophagus	
Hiatal hernia >2 cm	
Prior esophageal or gastric surgery, including prior antireflux surgery	
Pregnancy	
Coagulation disorders	
Nutritional behavioral disorders: anorexia or bulimia	
Ineffective esophageal motility	

Data from Dughera et al. [26]

PPI proton pump inhibitor, *LES* lower esophageal sphincter

related self-limiting hypotension in one (0.8 %) and submental swelling in one (0.8 %). Similar results were shown in another trials with minor complications including dyspepsia 11/109 (10.1 %), chest discomfort 27/109 (25 %) and minor gastric bleeding 2/109 (1.8 %) [29]. There were no perforations, strictures, new onset dysphagia, bleeding or death reported [26, 28].

Future Roles and Trends

The ideal therapy for GERD requires restoration of the barrier function without altering normal physiologic function such as belching and is simple, reproducible, less invasive and reversible if necessary. Each of the reviewed modalities has altered the LES in a novel way to achieve this goal. The LINX system acts as a loose ligature around the LES preventing shortening and thus transient LES opening. TIF endoscopically creates a partial fundoplication that theoretically should enhance the angle of His and prevent LES opening. EndoStim increases LES pressure through electrical stimulation while allowing normal LES relaxation, and Stretta alters the neuromuscular function of the LES and gastric cardia via RFA.

The result, regardless of the mechanism, is an improvement in the patient's GERD symptoms and improved quality of life. What is surprising is that objective control of GERD based on pH data did not support the

subjective improvement except in patients who received a LINX device who had normal mean post-procedure DeMeester scores of 13.5 [9] or who underwent EndoStim with post-procedure DeMeester scores of 11.7 [23]. It is unclear why there is a discordance between the subjective and objective findings. It could represent a placebo effect or an alteration in the way the patient senses reflux.

However, when these new treatments are evaluated by the defined measures of successful GERD treatment—symptoms, objective measures of acid control and the need for additional therapy [6]—TIF and Stretta fall short when evaluated by control of acid reflux as measured by pH assessment. Moreover, both TIF and Stretta patients appear to require additional procedures or treatments frequently. EndoStim, while it meets the criteria, is very limited in the number of patients that have completed clinical trials. LINX device implantation appears to be the most promising new approach to GERD with symptomatic improvement, objective control of pH measures and very few additional procedures or treatments required for reflux control.

Lastly, it should be recognized that none of the four devices has been compared in either a cohort or randomized fashion to PPIs or fundoplication. The reported experience with any device has been limited, and the follow-up ranges from 6 months to 6 years. Obviously, greater experience is required particularly with the LINX and EndoStim devices to validate their early results with subjective and objective measures of durability over a longer follow-up period.

Conclusions

Each of the current GERD treatment options (PPIs, LNF) has limitations in terms of objective efficacy measures and may also have potentially unpalatable side effects for the patient. Four new devices, LINX, TIF, EndoStim and Stretta, have attempted to improve upon these limitations. While each is promising, only the LINX device addresses the patient's symptoms, achieves objective control of acid and has reported limited need for additional therapies. Further comparative research and longer follow-up are necessary to determine the role of these therapies in the algorithm of GERD management.

Compliance with Ethics Guidelines

Conflict of interest Jennifer L. Wilson declares that she has no conflict of interest. Brian E. Louie has had travel/accommodations expenses covered/reimbursed by Torax Medical.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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