Update on novel endoscopic therapies to treat gastroesophageal reflux disease: A review

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Abstract
Endoscopic treatments for gastroesophageal reflux disease (GERD) have become increasingly popular in recent years. While surgical intervention with the Laparoscopic Nissen Fundoplication remains the gold standard, two endoscopic interventions, specifically, are gaining traction in clinical use (EsophyX and Stretta). The EsophyX (EndoGastric Solutions, Inc., Redmond, WA, United States) was developed as a method of restoring the valve at the GE junction through an endoluminal fundoplication (ELF) technique. Long-term data suggests that transoral incisional fundoplication (TIF) with EsophyX may be effective for symptom control and proton pump inhibitor reduction or cessation for up to 2-6 years. There is no evidence that EsophyX is more effective than surgical intervention. TIF may be most effective for patients with HH < 2 cm and Hill Grade I/II valves. Stretta (Mederi Therapeutics, Greenwich, CT, United States) was approved by the Food and Drug Administration in 2000. It delivers radiofrequency energy to the lower esophageal sphincter and gastric cardia. Published reviews of the literature are conflicted in their recommendations of Stretta in the management of GERD. The literature suggests that the Stretta procedure has an acceptable safety profile and may be effective in reducing symptom burden and quality of life scores up to 8 years post-intervention. However, there does not appear to be any sustained improvement in objective outcomes and there is no evidence that Stretta results in improved outcomes as compared to surgical intervention. Treatment modalities for GERD, as a field, suffer from a lack of standardization in primary and secondary outcomes. Although many studies have looked at health related quality of life, the tools used to do so are markedly heterogeneous. Future directions for the endoscopic treatment of GERD include novel techniques like endoscopic submucosal dissection.

Key words: Endoscopy; Reflux; Gastroesophageal reflux disease management; EsophyX; Stretta

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Core tip: While surgical intervention with the Laparoscopic Nissen Fundoplication remains the gold standard for reflux, endoscopic treatments for gastroesophageal reflux disease have become increasingly popular in recent years. This review of endoscopic methods focuses on two procedures: the Esophyx, a procedure involving endoluminal fundoplication of the gastroesophageal junction, and Stretta, a procedure involving radiofrequency ablation of the gastro-esophageal junction. While these techniques have an acceptable safety profile and lead to subjective improvement in reflux, their objective efficacy remains unclear. The review highlights the lack of standardisation of outcome measures and heterogeneity of assessment tools.

INTRODUCTION
The most widely accepted definition of gastroesophageal reflux disease (GERD), developed by the International consensus group, is "a condition that develops when stomach contents cause troublesome symptoms and/or complications"[6]. In North America, it has a prevalence of 18.1%-27.8%[7] and is estimated to be the most common reason for an outpatient gastrointestinal clinic visit[8]. This translates into significant economic burden through health-care associated costs, as well as reduced quality of life (QOL) for affected persons.

GERD is a multifactorial disease process. Factors affecting the development of GERD include mechanical impairment of the gastroesophageal (GE) junction, hiatal hernias (HH), and esophageal acid exposure (EAE). Pathological reflux can result in GERD type symptoms (heartburn, regurgitation, heartburn) and mucosal disease (esophagitis, strictures, metaplasia and cancer)[9].

The treatment of GERD changed dramatically after the advent of proton pump inhibitors (PPIs)[10]. In conjunction with lifestyle modifications, they are the current first line therapy for GERD[11]. While PPIs are often effective, there are patients who will be non-responders, require chronic PPI use or be subject to side effects of PPI therapy[12]. These side effects include enteric infections (Clostridium difficile), increased susceptibility to pneumonia, hypergastrinemia, osteoporosis and drug-drug interactions[13,14]. Furthermore, PPIs have a high drug expense and patient compliance with chronic daily use may be limited[15,16,17].

More invasive treatment options include surgical and endoscopic interventions. Laparoscopic Nissen Fundoplication (LNF) is considered the gold standard of treatment[18]. LNF differs from medical treatment in that it is directed at the underlying cause of GERD. The literature has demonstrated that LNF is able to provide improved relief of GERD symptoms and reduced PPI use with good long-term cost efficacity[13,14]. Furthermore, LNF may be more effective for those patients with abnormal symptoms[7,15].

Endoscopic treatments for GERD have become increasingly prevalent in recent years. There has been increased interest in these interventions by both patients and practitioners as an alternative to surgical intervention[12]. Endoscopic intervention is less invasive, typically involves a day procedure and avoids side effects of LNF such as bloating and dysphagia[9,16]. They are less permanent interventions; yet do not preclude the patient from being a future candidate for LNF[17-19]. Historically, endoscopic treatments have been divided into three separate categories: radiofrequency (RF) treatment of the GE junction, plication of the lower esophageal sphincter (LES) and injection of biopolymers[6,9]. Currently, there are two endoscopic interventions being used clinically - transoral incisional fundoplication (TIF) with the Esophyx device and RF treatment with the Stretta device.

The intent of this review is to provide an update on more recently published data regarding the two endoscopic interventions for GERD that are currently in clinical use (Stretta and Esophyx). Prior reviews have summarized short-term effects and suggest that long-term efficacy be studied and the appropriate patient populations be identified[18,20]. In the majority of published studies to date, the most common primary endpoint is subjective reduction in daily symptoms (> 50%) or improvement in health related quality of life (HRQL) scores. Objective end point outcomes (pH studies, resolution of esophagitis and reduction of HH) have not been routinely studied in all patients up to this point in time.

DISCUSSION
Esophyx
The Esophyx (EndoGastric Solutions, Inc., Redmond, WA, United States) was developed as a method of restoring the valve at the GE junction through an endoluminal fundoplication (ELF) technique. The device is inserted transorally under direct vision with an endoscope. It allows for creation of 2-3 cm and 210°-300° fundoplication at the level of the GE junction. Twelve or more polypropylene, full thickness fasteners are used to create the omega-shaped valve. In a revision of the device (TIF 2), the fasteners are deployed 3-5 cm above the GE junction to create a flap valve similar to that of a LNF[12,16,21].

Randomized controlled trials
The first published randomized controlled trial (RCT) in 2011 by Svoboda et al[22] compared TIF against the gold standard Nissen fundoplication. The authors concluded no significance difference between the two therapies,
with a significant reduction in length of stay in favor of TIF (2.9 d vs 6.4 d). The RESPECT trial was published in 2015[18]. It included 129 randomized patients. Results included a significant elimination of troublesome regurgitation in 67% (58 of 87) of TIF patients as compared to 45% (19 of 42) of PPI/sham patients. TIF patients also had significant decrease in EAE. At 18-mo follow, 71% (30 of 42) of the PPI/sham had crossed over to TIF and 28% (24 of 87) of the TIF group had resumed PPI.

The TEMPO trial was an open-label, randomized study of 60 patients who were followed up to 6 mo, with a primary end point of elimination of daily bothersome symptoms[23]. Troublesome regurgitation was eliminated in 97% (29/30) of patients undergoing TIF and off PPI, vs 50% (9 of 18) in the PPI group. At 6 mo, 90% (35 of 39) patients undergoing TIF had complete cessation of PPI use. EAE was normalized in 54% (21 of 39) of the TIF group vs 52% (11 of 21) in the PPI group. At 6 mo, 90% (18 of 20) of the TIF group had reduction of complete healing of esophagitis vs 38% (5 of 13) in the PPI group. Overall, the authors demonstrated that TIF had a more significant effect on controlling GERD symptoms compared to PPI.

A RCT was performed by Witteman et al[24], comparing TIF vs PPI treatment for GERD in 60 patients. They were followed up to 12 mo, with crossover of the PPI group to TIF at 6 mo. At 6 mo follow-up, HRQL scores were increased by ≥ 50% in 55% of the TIF group vs 5% of the PPI group. Change in EAE, normalization of pH and healing of esophagitis was non-significant between the groups. While TIF2 had a significant increase in LES pressure, the total number of reflux episodes did not improve. In the TIF group, PPI was discontinued in 74%. Hill grade I valves were created in 90% at the time of TIF, with only 35% remaining at 12 mo.

Long-term follow-up trials
Trials with long-term follow-up are limited in the literature. Bell et al[25] looked at prospectively collected data on TIF performed on 127 patients. Two year follow-up was completed on 100 patients with a primary endpoint of ≥ 50% improvement in their regurgitation score. Of the 88 patients presenting with daily symptoms, 70% (60) reached the primary endpoint. Of the 98 patients starting with daily PPI use, 69 (70%) had complete cessation of PPI. HRQL scores remained stable to the 24 mo follow-up point. In regards to objective endpoints, 31 patients underwent endoscopic screening with healing of esophagitis seen in 75% (12 of 16). Furthermore, pH testing was performed in 50 patients preoperatively and 14 patients at 2 years. Eight of 14 (57%) patients had normalization of esophageal acid exposure.

Testoni et al[26], followed 50 patients who underwent TIF 2.0 with EsophyX. Mean follow-up was 52.7 mo, with 14 patients reaching 6-year follow-up. HRQL scores were significantly reduced compared to pre-intervention. In regards to PPI use, ≥ 50% reduction or cessation was seen in 87.8% (36 of 41) at 24 mo, 84.4% (27 of 32) at 3 years, and 85.7% (12 of 14) at 6 years. There was no significant change in LES pressure at any time point. Overall, long-term response was best predicted by initial response in the first 6-12 mo, with best candidates for TIF being patients with Hill grade I/II valves and a hiatal hernia < 2 cm.

Literature reviews
In 2013, Wendling et al[19], published a systematic review of 15 observational studies of TIF. There was significant improvement in HRQL score compared to baseline score on PPI. Overall, the patient satisfaction rate with TIF was 72% at a mean of 8.5 mo. PPI cessation rates varied widely, with an overall rate of 67% at a mean follow-up time of 8.3 mo. There was weak correlation between discontinuation and follow-up length. None of the included studies were able to demonstrate reduced post-procedure EAE time. In total, there were 18 complications, with the most common being hemorrhage (1.1%) and an overall failure rate of 8.1%.

Overall, the limited long-term data reviewed here suggests that TIF with EsophyX may be effective for symptom control and PPI reduction or cessation for up to 2-6 years. There is no evidence that EsophyX is more effective than LNF. TIF may be most effective for patients with HH < 2 cm and Hill Grade I/II valves[23,26,27]. The ideal patient population has yet to be fully elucidated. The safety profile is acceptable, with low complication rates and no associated mortality.

STRETTA
Stretta (Mederi Therapeutics, Greenwich, CT, United States) was approved by the FDA in 2000. It delivers radiofrequency energy to the LES and gastric cardia. A gastroscope is first inserted to measure the distance to the Z-line. The gastroscope is then withdrawn and a catheter with a four channel RF generator is placed 1 cm proximal to the Z-line. Radiofrequency energy is then delivered to the muscularis propria for approximately 60 s to a target temperature of 65-85 degrees Fahrenheit. Tissue temperatures are constantly monitored using a thermocouple incorporated into the active electrodes[28]. Additional treatments are delivered by rotating the catheter circumferentially, as well as advancing it distally for a span of 2 cm towards the gastric cardia[12,16]. The mechanism of action of radiofrequency treatment for GERD has yet to be fully elucidated, but is thought to work via neurolysis or tissue necrosis causing local inflammation, collagen deposition and muscular thickening of the LES, resulting in fewer transient relaxations in LES pressure[28-30]. Clinical use was previously limited by safety concerns for esophageal perforation. In recent studies, the most commonly seen side effect was chest pain, which was self-limited and did not require intervention[31].
Gastroparesis has also been identified\[32\]. As it has been on the market for approximately 15 years, Stretta has been the topic of multiple studies and reviews, including four RCTs\[32,29-34\]. More recently published studies have focused on long-term efficacy of the procedure.

**RCTs**

In 2003, Corley et al\[33\] published the first randomized, sham-controlled trial for RFA in GERD patients, with follow-up at 0, 6, and 12 mo. At 6 and 12 mo, patients treated with RFA had significantly improved heartburn symptoms as well as improved QOL scores. No improvement was seen in the sham group. Prior to a medication withdrawal protocol there was no difference in daily PPI use between groups. Following this protocol the RF group reduced PPI usage by 46% compared to 29% in the sham group. There was no difference in EAE between RF and sham groups at 6 mo. A sub-group analysis of responders (> 50% reduction in QOL score) was shown to have significant decreases in 24-h acid exposure. Additionally, there was no difference in LES pressure or esophagitis between groups.

In 2008, Coron et al\[30\] published a prospective, randomized trial comparing PPI use vs RF energy in patients with PPI-dependent GERD. Results for their primary outcome demonstrated reduction or discontinuation of PPI in 18/23 (78%) of patients treated with RFA vs 8/20 (40%) in their control group at 6 mo follow-up. At 12 mo, this decreased to 12/23 (56%) and 7/20 (35%), respectively. Their secondary outcomes showed no difference in heartburn scores, no difference in QOL surveys, no difference in mean daily dose of PPI at 6 or 12 mo (P = 0.05) and no change in 24 h pH monitoring or endoscopic grade of esophagitis.

In another prospective, randomized, double-blinded, sham-controlled trial by Aziz et al\[32\] in 2010, patients were treated with either a single dose Stretta, a double dose of Stretta or with a sham procedure. At 12 mo there was a significant improvement in GERD-related symptoms in both active treatments, but not the sham group. In the double-dose group 50% were completely off their PPI, while only 16.6% in the single-dose group and none in the sham group were completely off of PPI therapy. LES pressure and esophageal acid exposure time was improved in both the single and double-dose treatment groups, with non-significant changes seen in the sham group.

In the latest RCT in 2012, Arts et al\[31\] reported outcomes of a double blind, sham-controlled study looking at the effect of the Stretta procedure on GERD symptoms, esophageal acid exposure and GE junction distensibility. They hypothesized that the procedure may decrease GE junction distensibility, thereby reducing the volume of refluxate and subsequently symptomatology. Symptom score was significantly reduced after the Stretta procedure, but not following a sham procedure. No change between the Stretta and sham groups was demonstrated in 3 or 6 mo follow-up endoscopy or 24-h pH monitoring. Medication use was not affected by initial Stretta procedure of sham. Finally, resting LES pressure did not change at 0, 3 or 6 mo following Stretta or sham procedure.

**Long-term follow-up trials**

Triadafilopoulos, in 2002, looked at Stretta durability at 6 and 12-mo follow-up\[31\]. They demonstrated significant improvement in heartburn scores, HRQL scores and patient satisfaction scores at both time periods. Eighty-eight percent of patients required daily PPI use at baseline, which decreased to 30% at 12 mo. Distal esophageal acid exposure time also decreased from 10.2% to 6.4%.

A prospective observational study of long term outcomes by Liang et al\[35\] in 2014, reported follow-up results on 138 of 152 initial patients. Overall symptom score was reduced at 6 mo and was sustained to the 5-year follow-up mark. At 6 mo, 38 (27.5%) of patients were completely off of PPI, which increased to 59 (42.8%) at 5 years.

Dughera et al\[36\] published long-term follow-up results of their single center study. Eight-year follow-up was achieved in 26 of 86 patients. In total, 7 patients restarted daily use of a PPI, of which 5 went on to have LNF. Overall, there was a significant decrease in heartburn score and increase in HRQL score that was still present at 8 year follow-up. Furthermore, 20/26 remained completely off a PPI. While none of the 26 patients developed endoscopic evidence of esophagitis, median LES pressure did not demonstrate any improvement at 8 years.

In the longest reported follow-up data, Noar et al\[37\] performed a 10-year, open label, prospective trial of patients with refractory GERD treated with Stretta. In total, 149 of 217 patients reached the 10-year follow-up, of which 72% had normalization of HRQL. Furthermore, 64% had ≥ 50% reduction in baseline PPI use with discontinuation in 41% at the 10 year mark. Fifty-one of 149 patients had no endoscopic evidence of erosive esophagitis at 10 years.

**Literature reviews**

Published reviews of the literature are conflicted in their recommendations of Stretta in the management of GERD. The most recent systematic review in 2014 by Lipka et al\[38\] concluded that was no evidence for the efficacy of radiofrequency ablation for the treatment of GERD. Their review included 4 randomized trials, all of which were determined to be of poor methodological quality. Overall outcomes showed no significant benefit of Stretta over sham therapy for mean time pH was less than 4, mean change in LES pressure, increase in discontinuation of PPI or improvement in HRQL scores\[38\]. This was in direct contrast to an earlier Review by Perry et al\[39\] and a subsequent recommendation review by the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES)\[3,20,39\]. Perry et al\[39\] found, in their 2012 review of 18 studies, that radiofrequency
produced significant improvement in reflux symptoms, with improved heartburn scores, esophageal acid exposure and QOL scores. The methodologically validity of both reviews continues to be debated\(^{38,39}\).

Overall, the data suggests that the Stretta procedure has an acceptable safety profile and may be effective in reducing symptom burden and QOL scores up to 8 years post-intervention. There does not appear to be any sustained improvement in objective outcomes and there is no evidence that Stretta results in improved outcomes as compared to surgical intervention.

**Limitations**

Treatment modalities for GERD, as a field, suffer from a lack of standardization in primary and secondary outcomes. Although many studies have looked at HRQL, the tools used to do so are markedly heterogeneous. Furthermore, whether more subjective measures such as QOL and symptom control are equivalent to objective measurements has not yet been elucidated\(^{27}\).

Subjective symptom improvement is clinically relevant, but there is no established correlation to severity of reflux\(^{12}\). PPI use is quantified in studies and is an objective outcome, but is not a specific marker for GERD and may be used for dyspepsia. Manometry and pH studies are more objective markers but may have less clinical relevance, particularly for the patient if symptom control is not improved.

**Future direction**

In a preliminary, prospective, single-arm trial, Ota et al.\(^{40}\), looked at a novel endoscopic fundoplication technique using endoscopic submucosal dissection (ESD) in 13 patients. Scarring post-ESD results in narrowing of the GE junction and reduced reflux. The demonstrated improved symptoms in 92% (12 of 13), cessation of PPI use in 23% (3 of 13) and reduced PPI use in 23% (3 of 13). There was no change demonstrated in pH studies. Future directions may be aimed more towards novel surgical interventions, such as the LINX reflux management system, a ring of linked magnetic beads laparoscopically placed around the LES that improves pressure without any anatomical change\(^{7,10}\). The EndoStim is another device placed laparoscopically that delivers electrical energy to the LES in order to increase resting pressure\(^{7,10}\).

**CONCLUSION**

In theory, endoscopic management of GERD is promising field with obvious advantages of a less invasive procedure, however the majority of procedures and devices released are no longer available for lack of reported efficacy. The published data for the two procedures with the most evidence, EsophyX and Stretta, generally show improvement over baseline (PPI therapy alone) or sham procedure but currently are second-line procedures to surgical intervention\(^{20}\).

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