Endoluminal Treatments for Gastroesophageal Reflux Disease (GERD)

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Preamble

The following clinical spotlight review regarding the endoluminal treatment of gastroesophageal reflux disease is intended for physicians who manage and treat GERD. It is meant to critically review these techniques and the available evidence supporting their safety and efficacy. Based on the level of evidence, recommendations may or may not be given for their use in clinical practice.

Disclaimer

Guidelines for clinical practice and spotlight reviews are intended to indicate preferable approaches to medical problems as established by experts in the field. These recommendations will be based on existing data or a consensus of expert opinion when little or no data are available. Spotlight reviews are applicable to all physicians who address the clinical problem(s) without regard to specialty training or interests, and are intended to convey recommendations based on a focused topic; within the defined scope of review, they indicate the preferable, but not necessarily the only acceptable approaches due to the complexity of the healthcare environment. Guidelines and recommendations are intended to be flexible. Given the wide range of specifics in any health care problem, the surgeon must always choose the course best suited to the individual patient and the variables in existence at the moment of decision.

Guidelines, spotlight reviews, and recommendations are developed under the auspices of the Society of American Gastrointestinal Endoscopic Surgeons and its various committees, and approved by the Board of Governors. Each clinical spotlight review has been systematically researched, reviewed and revised by the guidelines committee, and, when appropriate, reviewed by an appropriate multidisciplinary team. The recommendations are therefore considered valid at the time of production based on the data available.

Literature Review

A systematic literature search was performed using PubMed for each of the technologies discussed in this Clinical Spotlight Review. The literature was reviewed through the dates as listed below for the individual technologies (June – September, 2012).

The volume of literature available for each procedure varied, mostly depending on the length of existence of each device. Strength and level of evidence therefore is variable too, and is determined by review of available literature.

Levels of Evidence/Definitions

Both the quality of the evidence and the strength of the recommendation for each of the guidelines were assessed according to the GRADE system. This uses a 4-tiered system for denoting the quality of evidence (very low (+), low (+ +), moderate (+ + +), or high (+ + + +)) and a 2-tiered system for strength of recommendation (weak, or strong) [1, 2].

I. Introduction

Gastroesophageal reflux disease (GERD) is a complex disorder resulting from multiple contributing factors, including acid production, lower esophageal sphincter tone and location, and anatomic barriers to reflux created by the angle of His and the diaphragmatic hiatus. GERD is a common problem that affects approximately 30-40% of the adult population with at least 20% of Americans reporting weekly symptoms. [1,2] GERD symptoms can be bothersome, resulting in interference with quality of life, and treatment can result in lifelong lifestyle changes and inadequate symptom relief. The estimated US population cost according to the American Gastroenterology Association is approximately 24 billion dollars annually, the majority of which stems from loss of work productivity.[2] Symptoms can range from a simple episode of heartburn, to regurgitation, persistent cough, and dysphagia.[1] Some symptoms easily are overcome using over-the-counter antacids. Persistent symptoms, however, often require lifelong treatment. The downstream risks of esophagitis, esophageal stricture, Barrett esophagus, and adenocarcinoma of the esophagus are significant causes for concern, and justify effective therapy for patients with GERD. Although a mainstay of GERD therapy for many patients, a discussion of long-term pharmacologic therapy, and its hazards, falls outside the scope of this document. Instead, the remainder of this review will focus on techniques designed to impact the anatomic mechanisms associated with GERD and its remedy.

Laparoscopic fundoplication remains the gold standard in interventions for GERD in both adults and children. Multiple studies document the long term success of laparoscopic Nissen fundoplication.[3,4] Notwithstanding the successes of surgical fundoplication, patients and providers continue to search for increasingly less invasive approaches to GERD, especially emphasizing techniques that seek to reduce the risks of dysphagia, bloating, and adverse outcomes sometimes associated with surgery. The endoscopic approach to treating GERD has been proposed by a number of devices and unique procedures, the majority of which are no longer available because ultimately, they failed to provide significant and durable relief from GERD symptoms or to effectively restore normal physiology.

The review that follows considers two procedures based on an endoscopic platform that provide alternatives to the pharmacologic and surgical treatment of GERD. In considering the clinical application of these and other alternatives to the effective therapy provided by laparoscopic fundoplication for patients with GERD, the reader is asked to consider the degree of symptom relief and restoration of physiologic function provided by each therapy, and further, to consider the implications of treatment failures related to endoluminal therapies. Some endoluminal therapies may not offer the same degree of relief provided by surgery, but might still represent viable alternatives for patients seeking relief from lifelong dependence on pharmacologic

therapy, its cost, associated side effects, and long-term adverse outcomes.

1. Pohle T and Domschke. Results of short- and long-term medical treatment of gastroesophageal reflux disease (GERD). Langenbeck's Archive of Surgery. 2000. 385: 317-323.
2. Brook RA, Wahlqvist P et al. Cost of gastro-oesophgeal reflux disease to the employer: a prospective from the United States. Alimentary Pharmacology and Therapeutics. 2007. 26. 889-898.
3. Papasavas PK, Keenan RJ et al. Effectiveness of laparoscopic fundoplication in relieving the symptoms of gastroesophageal reflux disease (GERD) and eliminating antireflux medical therapy. Surgical Endoscopy. 2003. 17. 1200 – 1205.
4. Dallemagne B, Weerts J et al. Clinical results of laparoscopic fundoplication at ten years after surgery. Surgical Endoscopy. 2006. 20. 159-165.

II. Statement of Focus

The intent of this Clinical Spotlight Review is to critically review literature related to currently available endoluminal therapies for GERD. The devices and techniques selected for this Clinical Spotlight Review include: EsophyX and Stretta.

III. Endoluminal Treatments for GERD

A. EsophyX

EsophyX, developed by Endogastric Solutions (Redwood City, WA), is a device reported to create an incisionless fundoplication. Transoral Incisionless Fundoplication (TIF) was first approved for clinical use in the United States by the Food and Drug Administration in September of 2007.[1] Once placed using the endoscopic approach, the instrument is deployed in the stomach and used to create a full thickness plication secured by "H-shaped" fasteners fashioned from polypropylene. The polypropylene stitch used as a fastener during TIF has been identified as one of the unique mechanisms of the device, and is thought to aid in the "serosa to serosa" fusion seen after completion of endoscopic fundoplication.

The EsophyX device has gone through a number of revisions. The first technique was called endoluminal fundoplication (ELF) and used the TIF 1 device. The TIF 1 procedure produced a gastrogastric wrap at the level of the gastroesophageal junction (GEJ); critics likened this to a slipped fundoplication. The TIF 2 device was developed to more closely replicate laparoscopic fundoplication. H-fasteners are placed 3-5 cm above the GEJ resulting in creation of an esophagogastric fundoplication that more typifies what can be created surgically.

(Figure 1)

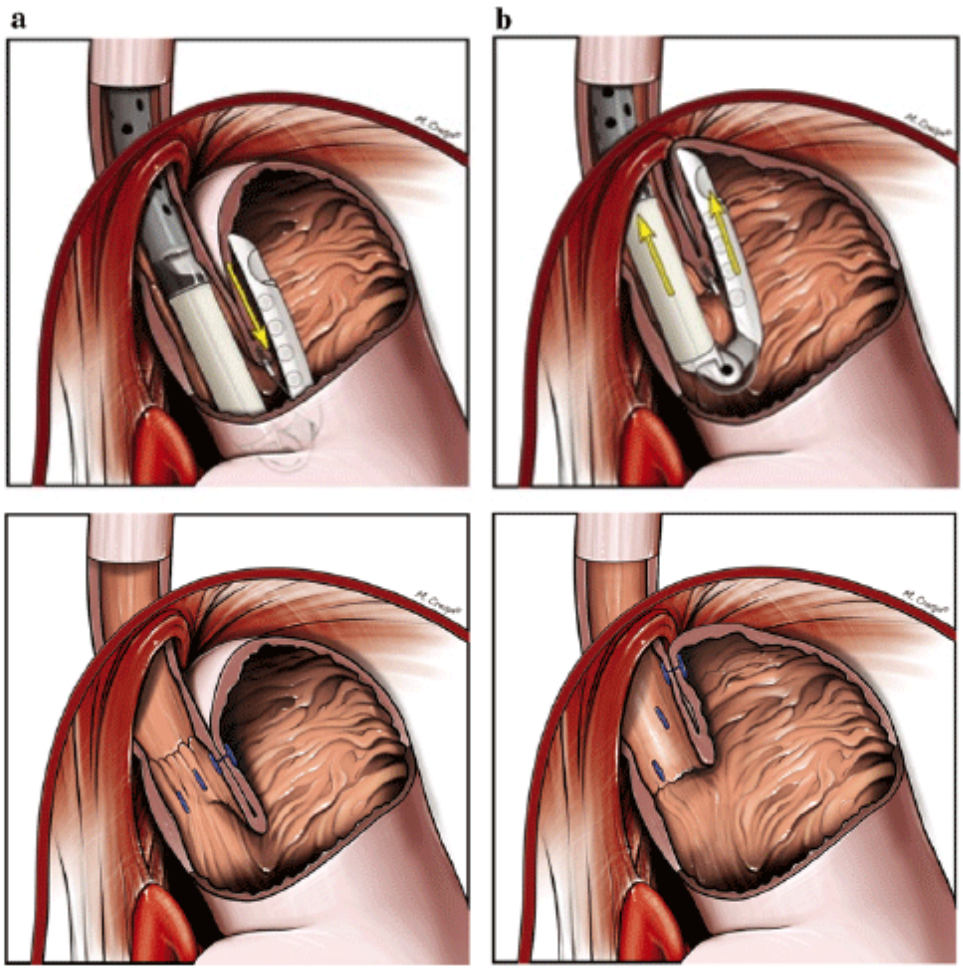


Fig. 2 A TIF 1 procedure with gastrogastric plications placed at the level of the Z-line. **B** TIF 2 technique creates an esophagogastric fundoplication proximal to the Z-line

(Bell & Cadiere. Transoral rotational esophagogastric fundoplication: technical, anatomical and safety considerations. Surgical Endoscopy. 2010.)

Transoral Incisionless Fundoplication (TIF) (Literature Review through September, 2012)

The TIF 1.0 protocol data first was collected in 2005 by Cadiere and colleagues, and published in Europe in 2006. Initially, the technique was called endoluminal fundoplication (ELF). This initial publication described the evolution and progression of the EsophyX device though its preclinical bench testing and animal studies, as well as its phase 1 and phase 2 clinical trials. At the time of this initial publication, the phase 2 clinical trial still was in progress. The phase 2 trial enrolled 17 patients. The study compared ELF to Laparoscopic Anti-Reflux Surgery (LARS) and a then existing competing Endoscopic Plication System (EPS); the authors did not specify the type of laparoscopic fundoplication performed. Six months after ELF, 80% of treated patients were reported to have stopped daily use of proton inhibitor medications (PPI); the reported cessation of PPI was 92-96% for patients treated using LARS, and 74% for patients treated with EPS. Esophageal pH was normalized in 67% of patients treated using ELF, 91 -96% of patients after LARS and 30% of patients after EPS.[2]

In 2008, Cadiere et al published a prospective clinical trial with one year follow-up; enrollment

began in 2005. Nineteen patients with chronic GERD lasting at least 6 months, grade A-C esophagitis per the LA classification, or chronic PPI dependence were enrolled. At 12 months, 16 patients were available for follow-up: 63% had a normal esophageal pH; 82% were off PPI medications; 53% improved pre-treatment HRQL scores by >50%. [3]

A multi-center trial performed in 2008 enrolled 84 patients and reported on 79 patients available for 12 month follow-up. Additionally, the authors stratified results for 21 patients who maintained a grade 1 Hill Valve at 12 months after treatment. Within this subset, 48% had normal esophageal pH compared with 37% of the aggregated study group; 81% discontinued PPI use compared with 85% of the aggregated patients; and 86% improved their pre-treatment HRQL scores while 73% of the aggregated group had improved scores. Three procedure related complications were reported, including esophageal perforation (2 patients) and hemorrhage (1 patient) requiring transfusion; endoscopic control was reported as effective.[1]

Bergman and colleagues at Ohio State reported one of the first US studies of EsophyX. They published a retrospective review of 8 patients in 2008; patients were treated using the second generation EsophyX device that was applied in the same fashion as had been reported by Cadiere and associates during their trial of the first generation device. Mean follow-up was 60 days ± 44 which consisted of an office visit or a follow up telephone call. The interviewer recorded the HRQL survey, symptom severity score, and questions regarding GERD medication use, as well as any other pertinent data. Four patients reported taking the same PPI dose after treatment; 2 patients were taking ?50% of their pre-treatment dose, and 2 patents had stopped using PPI medications. The HRQL mean score was 8±8 and the mean symptom severity score was 17±15 at follow-up.[4]

This group went on to further report their findings on 26 additional patients; mean follow up was 10 months, and primary end points used were the Anvari and HRQL scores at 3 months, medication use, and patient satisfaction with procedure. At 3 months, 45% of patients improved pre-treatment HRQL scores ? 50%. At mean follow-up of 10 months, 68% of patients still were taking PPI; 45% of patients reported satisfaction with the procedure. There were two complications reported; both were hemorrhage requiring transfusion and therapeutic endoscopy. [5]

In 2009, Cadiere et al published two year follow-up data for 14 patients initially enrolled in the original feasibility trial published in 2008. Follow-up data included HRQL survey, upper endoscopy, PPI and GERD medication use, diet, and lifestyle changes enacted. No esophageal pH assessment was performed. Determinants for success were cessation of PPI use, no interval development of hiatus hernia, absence of esophagitis, and relief of heartburn symptoms and regurgitation. Twenty-none percent of treated patients met these criteria for successful treatment at 2 year follow up. An additional fifty percent of patients were improved but reported occasional heartburn, regurgitation, or had developed a hiatus hernia or persistent esophagitis during follow up. Twenty-one percent of patients had ongoing symptoms and required daily PPI medication; they were deemed treatment failures. [6]

A prospective trial of 20 patients treated using TIF was performed by Testoni and colleagues. GERD HRQL and GERD QUAL questionnaires were administered preoperatively, once with

patients on PPI medications, and again with the patient off PPI medication. Endoscopy and esophageal pH studies were performed preoperatively. All patients underwent the TIF 2.0 procedure. There were no operative complications reported. At six months, all patients underwent endoscopy, esophageal pH and impedance testing, and all were given both questionnaires again. PPI medication use was reduced in 22% of patients and eliminated entirely in 55%; 61% of patients no longer exhibited hiatus hernia after undergoing the procedure. No significant change in pre-operative and post-operative DeMeester scores was reported.[7]

Velanovich reported his experience with 26 patients; 20 reported typical GERD symptoms, 4 had been diagnosed with laryngopharyngeal reflux, and 4 reported recurrent GERD symptoms after prior Nissen fundoplication. The first ten procedures were done using the TIF 1.0 device; the remaining 16 were performed using the TIF 2.0 device. Velanovich explains the differences between the devices to include a smaller diameter main tube, a more flexible tissue mold, and multi-load H-fastener cartridges. Two procedures were aborted because of inability to pass the device through the pharynx; one complication, hemorrhage requiring transfusion and therapeutic endoscopy, was reported. Mean follow-up was 7 weeks. Thirteen of 24 treated patients reported symptom resolution; 19 were satisfied with the procedure. The median GERD HRQL score decreased from 25 to 5. The 79% of patients who reported satisfaction with the procedure were no longer taking PPI medications.[8]

A retrospective review of 124 patients treated using a combination of the TIF 1.0 and TIF 2.0 technique has been published; median follow-up was 7 months. This review combined patients treated at 2 community hospitals; esophageal pH testing was unavailable at both institutions. Follow up data were available for 110 patients. All patients treated prior to TIF 2.0 exhibited moderate deterioration of their post-treatment gastroesophageal valves; 64% had hiatus hernias determined to be 2 or 3cm in size. Forty-three percent of study patients were ? than 65 years old, and 97% reported inadequate pre-treatment symptom relief on PPI therapy. One procedure was abandoned when a hematoma developed; this was reported to be related to patient failure to stop anticoagulant medication at the recommended time. Four percent of patients underwent laparoscopic Nissen fundoplication (LNF) within 2 months following TIF; treatment failure was the indication in each. PPI medication was stopped successfully in 93% of patients after TIF. Post-treatment endoscopy was performed in 53 patients; 89% exhibited a grade 1 Hill Valve, and 97% of pre-treatment hiatus hernias reduced during performance of TIF remained reduced at the time of post-treatment endoscopy. One new hiatus hernia was identified and 1 patient was found to have active esophagitis after TIF; the authors concluded that 79% of their patients had been treated successfully by TIF.[9]

Outcomes have varied by study, and untoward outcomes have been reported in a variety of studies. A multi-institutional study of 19 patients with mean follow up of 10.8 months published by Hoppo et al reported three complications; esophageal perforation in 1 patient; permanent numbness of the tongue in 1 patient; and hemorrhage requiring transfusion in 1 patient. Eventually 10 of these 19 patients went on to have surgical treatment for GERD, undergoing LNF. Hoppo determined that 68.4% of their patients experienced treatment failure.[10] Bell and Freeman reported 37 patients with median 6 month follow-up after TIF, with 2 complications reported; one mediastinal abscess and 1 patient experiencing hemorrhage. PPI cessation was

reported in 82%, and 5 patients required additional treatment; 3 underwent LNF and 2 underwent repeat TIF. [11] Trad et al reported on 32 patients undergoing TIF, where 82% of the 28 patients available for follow up were off PPI medications; no complications were reported, and 1 patient underwent LNF six months post-treatment. [12] Narsule et al performed TIF for 46 patients, and during median follow up of 83 days, 2 patients underwent repeat TIF and 1 was converted to LNF.[13]

Testoni and colleagues treated 42 patients with TIF 2.0, and report mean follow up of 27 months ± 4.6 months. Thirty-five patients completed 6 month follow up assessment and 26 patients completed 24 month follow up assessment. At 6 months, 60% of patients had stopped using PPI medication; at 24 months, 42.3% of patients were off PPI. There was no significant difference between PPI use at 12 months and 24 months, and there was no significant change in DeMeester scores. Two patients developed pneumothorax related to TIF; 4 patients went on to have LNF.[14]

Svoboda and colleagues published the only randomized clinical trial comparing endoluminal fundoplication and LNF identified during this literature review. Initiated in 2007, patients were randomized to either full thickness plication using a then available endoscopic plication device, or to surgical treatment with LNF. When the plication device became unavailable because of insolvency of its manufacturer, patients were then randomized either to TIF or LNF. Fifty-two patients were enrolled; 18 were randomized to plication, 16 to TIF, and 18 to LNF. At 12 month follow up, there were no statistically significant differences between the endoscopic fundoplication group and the LNF.[15]

A recent modification of the approach to endoscopic fundoplication using the TIF device is the “hybrid” technique. Ihde and colleagues published one of very few reports to include patients who underwent combined laparoscopic repair of hiatus hernia followed immediately by the TIF procedure. These authors enrolled all patients with a hiatus hernia ? 3 cm into the hybrid approach. Of 48 total patients with 6 month median follow up, 18 had undergone a hybrid approach that included laparoscopic posterior cruroplasty and standard TIF. Distal esophageal perforation in 1 patient was the only reported complication. Results were not stratified according to TIF alone or TIF plus laparoscopic cruroplasty. Sixty-seven percent of patients available for follow up reported cessation of daily PPI use; symptom severity scores were significantly reduced.[16]

Bell and colleagues published a multi-centered prospective trial of 100 patients undergoing the EsophyX2 procedure with mean six month follow-up. The centers involved in the study participated in the TIF registry. Included patients reported a one year or greater history of GERD, and at least 6 months of daily PPI use. Patients with a body mass index (BMI) > 35 or Barrett esophagus greater than 2 cm in length were excluded from this study. The majority of enrolled patients had been diagnosed with laryngeal pharyngeal reflux (LPR) (51%). The primary endpoint of the study was improvement in GERD symptoms as related to symptom severity monitored by various symptom surveys; GERD-HRQL (GERD – Health Related Quality of Life), RSI (Reflux Symptom Index), GERSS (GERD Symptom Score). Secondary endpoints included cessation of PPI use, improvement or normalization of esophageal pH, healing of esophagitis, and reduction in hiatus hernia size. For patients treated for typical GERD

symptoms, 66% recorded normalized HRQL scores, 87% recorded normalized regurgitation scores, and 71% were able to stop PPI use after TIF. For patients with LPR, 69% recorded normalized RSI scores, and 82% were able to stop PPI use after TIF. Overall, 80% of study patients stopped PPI use after TIF. Esophageal pH testing was reported for 44 of 100 patients; just 28 had esophageal pH testing both before and after TIF. This subgroup exhibited a significant reduction in percentage of esophageal acid exposure time, number of reflux episodes, and DeMeester scores. There were no untoward outcomes reported in this study.[17]

Considerations in the Pediatric Population

The reader is advised that the EsophyX System is not approved by the FDA for use in pediatric patients, nor is the device recommended for use in children by its manufacturer. There is one available study that reports the use of the EsophyX system in the pediatric population. Chen et al. reported results for eleven patients who underwent transoral fundoplication for either primary GERD (6/11) or recurrent GERD following Nissen fundoplication (5/11) [18]. The children had a mean age of 16 years and weighed 45 kg. The majority (9/11) were neurologically impaired. All required general anesthesia with a mean procedure time of 113 ± 31 minutes. Resolution of reflux was measured by the improvement in clinical symptoms, absence of reflux on upper GI or pH-probe study. Mean follow up was 8.2 ± 4.2 months. Overall, 7 patients underwent upper GI study and 3 underwent pH-probe all demonstrating the absence of reflux. The minority of patients had post-procedure gagging or feeding difficulties. There was one episode of recurrent reflux during the study period that ultimately went on to require gastroesophageal disconnect.

This study is limited by its small size, short follow up, and uncontrolled patient selection. There was one device failure, and one hemorrhagic complication requiring a four unit blood transfusion and therapeutic endoscopy, reported in these 11 patients. Results were, on average, good though the study lacked a uniform objective measurement of post-procedure outcome. The device itself requires a delivery system of 54-French diameter, limiting application to patients larger than 25kg, excluding infants and toddlers from consideration for TIF. Presently, there is insufficient data to support the routine use of TIF in the pediatric population. Future controlled studies conducted under Institutional Review Board supervision are required before recommendations regarding its safety and efficacy in the pediatric population can be made.

TIF Conclusions

The EsophyX device has been studied across a broad range of adult patient populations, and reported in one adolescent study. Numerous published series have reported significant untoward events, although the safety profile for the procedure appears to be evolving in parallel with the procedural technique. Results appear mixed with some series reporting disappointing outcomes, and others reporting promising short-term results; yet, there still is a significant gap in the literature. The majority of available literature is significantly underpowered, mostly observational studies with routinely brief follow-up periods. There has been a paucity of sham controlled trials and studies that directly compare TIF with laparoscopic anti-reflux surgery. The device has been modified through multiple revisions, and the technique of the procedure has evolved as well; long term data that will be available in the near future will most likely be based upon the first generation device and the TIF 1.0 technique. The creation of the EsophyX

database and registry will aid in future research important to making more meaningful recommendations with respect to placement of TIF in the treatment of patients with GERD. Further study in the pediatric population will be necessary to consider TIF a treatment option for children.

Recommendation:

Long term data is not yet available for EsophyX. In short term follow-up, from 6 months to 2 years, EsophyX may be effective in patients with a hiatal hernia ? 2 cm with typical and atypical GERD. Further studies are required to define optimal techniques and most appropriate patient selection criteria, and to further evaluate device and technique safety.

Quality of Evidence: (++). GRADE Recommendation: Weak

Literature Cited

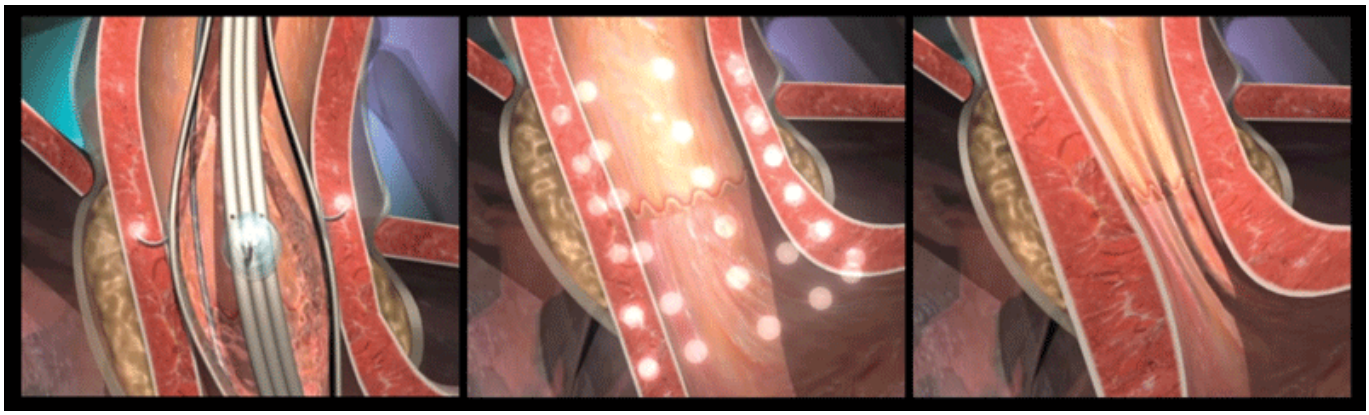
1. Cadiere GB, Buset M, Muls V et al. Antireflux Transoral Incisionless fundoplication using EsophyX: 12-Month Results of a prospective multicenter study. *World Journal of Surgery*. 2008. 32:1676-1688.
2. Cadiere GB; Rajan A et al. Endoluminal fundoplication (ELF) – evolution of EsophyX, a new surgical device for transoral surgery. *Minimally invasive therapy*. 2006. 15:6. 348-355.
3. Cadiere GB; Rajan A et al. Endoluminal fundoplication by a transoral device for the treatment of GERD: a feasibility study. *Surgical Endoscopy*. 2008. 22: 333-342.
4. Bergman S, Mikami J et al. Endoluminal fundoplication with EsophyX: The initial North American Experience. *Surgical Innovation*. 2008. 15:3. 166-170.
5. Demyttenaere S; Bergman S et al. Transoral Incisionless fundoplication for gastroesophageal reflux disease in an unselected patient population. *Surgical Endoscopy*. 2010. 24: 854-858.
6. Cadiere GB; Sante N et al. Two year results of a feasibility study on antireflux transoral incisionless using EsophyX. *Surgical Endoscopy*. 2009. 23:957 -964.
7. Testoni P; Corsetti M et al. Effect of transoral Incisionless fundoplication on symptoms, PPI use, and pH impedance refluxes of GERD patients. *World Journal of Surgery*. 2010. 34: 750-757.
8. Velanovich V. Endoscopic, endoluminal fundoplication for gastroesophageal reflux disease: initial experience and lessons learned. *Surgery*. 148. 4. 648-653.
9. Barnes, W; Hoddinott, K et al. Transoral Incisionless Fundoplication offers high patient satisfaction and relief of therapy-resistant typical and atypical symptoms of GERD in community practice. *Surgical Innovation*. 2011. 18.
10. Hoppo T; Immanuel A et al. Transoral Incisionless fundoplication 2.0 procedure using EsophyX for gastroesophageal reflux disease. *Journal of Gastrointestinal Surgery*. 2010.

14: 1895-1901.
11. Bell R and Freeman K. Clinical and pH-metric outcomes of transoral esophogogastric fundoplication for the treatment of gastroesophageal reflux disease. *Surgical Endoscopy*. 2011. 25: 1975 – 1984.
12. Trad K; Turgeon D et al. Long term outcomes after transoral Incisionless fundoplication in patients with GERD and LPR symptoms. *Surgical Endoscopy*. 2012. 26: 650-660.
13. Narsule C; Burch M et al. Endoscopic Fundoplication for the treatment of gastroesophageal reflux disease: initial experience. *The Journal of Thoracic and Cardiovascular Surgery*. 2012: 143.1.
14. Testoni P; Vailati C et al. Transoral Incisionless fundoplication (TIF 2.0) with EsophyX for gastroesophageal reflux disease: long term results and findings affecting outcome. *Surgical Endoscopy*. 2011.
15. Svoboda P; Kantorova I et al. Our experience with transoral Incisionless plication of gastroesophageal reflux disease: NOTES Procedure. *Hepatogastroenterology*. 2011. 58: 1208-1213.
16. Ihde G; Besancon K et al. Short term safety and symptomatic outcomes of transoral Incisionless fundoplication with or without hiatal hernia repair in patients with chronic gastroesophageal reflux disease. *The American Journal of Surgery*. 2011. 202. 740-747.
17. Bell R; Mavrelis P et al. A prospective multicenter registry of patients with chronic gastroesophageal reflux disease receiving transoral incisionless fundoplication. Journal of the American College of Surgeons. 2012.
18. Chen S; Jarboe MD; Teitlebaum DH; Effectiveness of a transluminal endoscopic fundoplication for the treatment of pediatric gastroesophageal reflux disease. Pediatr Surg Int. 2012 28:229-234

B. Stretta

Mederi Therapeutics Inc. (Greenwich CT) acquired all rights to the Stretta system for the radiofrequency treatment of GERD, including its specialized catheters and radiofrequency (RF) generators. The FDA originally cleared Stretta for use in 2000 and issued an updated clearance on the RF generator in 2011. The transoral Stretta catheter system uses a proprietary algorithmic application of low power (5 Watts) RF energy and generates low tissue temperatures (65C to 85C) during a series of one-minute treatment cycles. Stretta therapy remodels the musculature of the lower esophageal sphincter (LES) and gastric cardia. Clinical studies demonstrate that the Stretta RF treatment results in significant reductions in tissue compliance and transient LES relaxations. These mechanisms act to restore the natural barrier function of the LES as well as to significantly reduce spontaneous regurgitation caused by transient inappropriate relaxations of the sphincter.

(Figure 2)



Stretta (Literature Review through July, 2012)

Meta Analysis:

In a meta-analysis recently accepted for publication in *Surgical Laparoscopy Endoscopy and Percutaneous Techniques,* Perry et al performed a comprehensive search of randomized controlled, cohort series and reviews of literature. The meta-analysis reported on 18 studies published over a 10 year span and included 1441 patients. Subjective and objective outcome measures of GERD were identified from all studies (see Table 1). The results show that radiofrequency treatment significantly improved heartburn scores (mean heartburn score decreased in each individual study and showed a significant change from 3.55 to 1.19 in the pooled analysis), and produced significant improvements in quality of life as measured by GERD-HRQL scale and QOLRAD. Esophageal acid exposure decreased from a pre-procedure DeMeester score of 44.4 to 28.5 but did not normalize, and while the procedure did not significantly increase LES pressure, there was a trend toward improvement. The most common untoward outcomes encountered were minor and transient.[1]

Table 1.

Results Summary of Meta-Analysis

Outcome Variable	Studies (n)	Patients (n)	Mean Follow-up (mo)	Pre-Stretta	Post-Stretta	P-value
Subjective Measurements						
GERD-HRQL	9	433	19.8	26.11	9.25	0.0001
QOLRAD	4	250	25.2	3.30	9.25	0.0010
SF-36 Physical	6	299	9.5	36.45	46.12	0.0001
SF-36 Mental	5	264	10.0	46.79	55.16	0.0015
Heartburn Score	9	525	24.1	3.55	1.19	0.0001
Satisfaction Score	5	366	21.9	1..43	4.07	0.0006
Objective Measurements						
Esophageal Acid Exposure (%Ph<4)	11	364	11.9	10.29	6.51	0.0003
DeMeester score	7	267	13.1	44.37	28.53	0.0074
LES pressure	7	263	8.7	16.54	20.24	0.0302

Table 1. Perry K, Banerjee A, Melvin S. **Radiofrequency Energy Delivery To The Lower Esophageal Sphincter Reduces Esophageal Acid Exposure And Improves GERD Symptoms: A Systematic Review and Meta-Analysis.** *Surg Lap Endosc Percut Tech., Accepted for publication scheduled for August 2012, manuscript reviewed.*

Randomized Controlled Trials:

Arts et al reported in 2012 on 22 patients at 3 and 6 months follow-up in a double-blind randomized sham-controlled cross-over study of the Stretta procedure. In a single center, consecutive GERD patients were randomized in a double-blinded manner and underwent two procedures, either sham or active Stretta at a 3 month interval. The primary outcome measurement was a barostat distensibility test of the GEJ before and after administration of sildenafil. The GEJ compliance was not significantly altered after the sham procedure (14.0± 5.3 vs. 13.3± 4.30 ml/ mm Hg, NS), but the active Stretta procedure was associated with a significant decrease in tissue compliance (17.8± 3.6 vs. 7.4± 3.4 ml/ mm Hg, *P*

Aziz et al (2009) reported on 36 patients with GERD in a prospective, randomized, sham-controlled multicenter study. Patients were randomly assigned (12/12/12) to one of three treatment arms; a single session RF energy procedure, a repeat RF procedure if the GERD-HRQL score had not improved by 75% after 4 months, and a sham RF energy procedure. Complete 12-month clinical data were available in all patients. Improvement from baseline in the primary outcome measure, mean, off medication GERD-HRQL scores, were reported as 18.2% for the sham group, 51.3% for the single RF treatment group and 65.5% for the repeat RF procedures group; improvements in the single and repeat RF procedure groups were significantly greater than for the sham group. Secondary outcomes evaluated were changes in

GERD medication use, measured LES basal pressures, distal esophageal acid exposure, and endoscopic esophagitis grade. At 12 months, 50% of patients were off all antisecretory and antacid medications, while the remaining patients experienced a significant decline in use of antisecretory agents. In the sham group, none of the patients were off antisecretory therapy at the end of the follow-up period. No serious adverse events occurred, but two patients developed significant delay in gastric emptying after undergoing the second Stretta treatment.[3]

Galmiche and colleagues (2008) reported on a prospective, randomized, controlled multicenter study of PPI-dependent patients with established diagnoses of GERD. Forty-three patients were randomized to either an RF treatment group (n=23) or PPI regimen alone (n=20). An Intent-to-treat analysis performed at 6 and 12 months follow-up reported on the primary endpoint, defined as the possibility for the patient to stop or decrease PPI use to 50% improvement in GERD Quality of Life Scores compared with the 30% improvement reported by the sham group. Symptom improvement persisted at 12-month follow-up. There were no serious adverse events, perforations or deaths.[5]

Long Term Follow-up Studies:

In 2011 Dughera and colleagues published a long term prospective trial of safety and efficacy with 24 and 48 month follow-up of 56 patients treated with the Stretta procedure who underwent follow up esophageal manometry. The study found that treatment with the Stretta procedure significantly improved heartburn scores, GERD specific quality of life scores and general quality of life scores at both 24 and 48 months in 92.8% of patients. Both mean heartburn and GERD-HRQL scores decreased significantly and both mental and physical quality of life as measured by SF-36 improved. At 48 months 72.3% of patients were completely off PPI medications. Minor adverse outcomes consisted of temporary post procedure chest discomfort, mild fever, transient vomiting and transient dysphagia. A single major adverse event occurred in one patient with prolonged but transient gastroparesis; the patient required hospitalization for 3 weeks, and gastroparesis resolved completely within 8 weeks. [6]

In a prospective case series study Noar (2007) reported long term safety and efficacy in a series of 109 consecutive drug refractory patients treated with the Stretta procedure and followed for 48 months. Heartburn scores decreased, patient satisfaction improved and medication use was eliminated or significantly reduced. Complete long term follow-up assessment was available for 96 patients at 48 months. Medication use decreased significantly from 100% of patients requiring twice-daily PPI therapy at study initiation, to just 25% of patients requiring daily PPI use at 48 months. Patient satisfaction improved from a mean of 1.4 to 3.8 and heartburn scores decreased from 3.6 to 1.18, total heartburn score on the GERD-related quality of life questionnaire decreased from 27.8 to 7.1 and patient satisfaction improved from 1.4 to 3.8. There were no serious adverse events noted. Minor adverse outcomes included dyspepsia (10.1%), chest discomfort (25%), and minor gastric bleeding (1.8%), each resolving within 2 weeks.[7]

In a prospective single center case series in 2007, Reymunde et al evaluated the long term safety and efficacy of the Stretta procedure on 83 patients with GERD, measuring improvement in symptom control, quality of life and medication use with 4 year follow-up on a matched data

set of 80 complete patients. In follow-up evaluations at 12, 36, and 48 months the study reported a significant improvement in mean GERD symptom score from 2.7 (baseline), to 0.3 at 36 months, and 0.6 at 48 months. The mean GERD QOL score improved from 2.4 at baseline to 4.6 (36 months) and 4.3 (48 months). Daily medication use decreased significantly from 100% at baseline to 13.6% at 48 months. No serious adverse events associated with the Stretta procedure were reported.[8]

Other studies of note:

In a comparison study Richards (2003) reported on 140 consecutive patients with GERD, 65 of whom had the radiofrequency energy (RF) procedure with a mean follow-up of 7.3 months and 75 who had laparoscopic fundoplication (LF) with a mean follow-up of 5.2 months. There were no significant differences in improvement between the two groups as measured by the QOLRAD and SF-12 scores. At follow-up, 58% of the patients in the RF treatment group and 97% of the patients in the LF treatment group had discontinued all use of PPI medication. At follow-up 89% of the RF group and 96% of the LF group reported being “highly satisfied” with the outcome of their procedure. Reported adverse events in the RF group included 1 patient with transient gastroparesis. Reported adverse events in the LF group included enterotomies (2), pneumothorax (1), slipped Nissen fundoplication (1), paraesophageal hernia (1), and incisional hernias (2). Twenty-two patients in the RF group had follow-up 24-h esophageal pH testing at mean of 7.2 months revealing a 46.3% improvement in their mean esophageal acid exposure time; DeMeester scores improved by 32.5% and mean LES pressure remained unchanged. [9]

Noar (2008) studied the potential for Stretta to correct the gastroparesis sometimes associated with GERD and resulting in failure of even twice daily PPI therapy, by screening 227 patients undergoing Stretta between July 2000 and July 2004 for gastric anomalies. Thirty one patients were classified as abnormal at baseline. He reported that 23 patients (74%) experienced normalization of gastric emptying (responders) and reported 4 others who showed improvement but remained abnormal and 4 with no improvement for a total of 8 non-responders. At 6 months post Stretta procedure emptying scores had improved significantly for responders, with the percentage of solid food emptied at 90 minutes improved from 41% to 66% and at 120 minutes from 55% to 84%. All patients had a 1-year follow-up symptom assessment which showed significant improvements in GERD HRQL, dyspepsia and heartburn scores. No significant differences in patient satisfaction or quality of life were observed compared with the group’s baseline assessment, whether medication was received or not. Both the responder and non-responder groups demonstrated significant improvements in GERD-HRQL scores. Responders improved from 18.74 (on medications) to 8.0-4 at 6 months and showed continued, lasting improvement measured at 5.35 at 12 months. Non-responders improved from 25.13 to 14.00 at 6 months and further to 11.75 at 12 months follow-up. Heartburn scores also improved significantly for responders from 2.43 to 1.0 at 6 months and for non-responders from 3.0 to 1.75. Medication usage decreased significantly in the responder group with 22 of 24 patients moving from PPI BID to no medications or to antacids/H2RA as needed. Of the 8 non-responders 4 patients transitioned from twice daily PPI to antacid/H2RA as needed, 2 transitioned from twice daily PPI to once per day PPI, and 2 experienced no change in PPI dose. Minor adverse events included 4 cases of transient dyspepsia and one case of minor

gastric bleeding.[10]

In 2007 Meier and colleagues reported on a prospective, multicenter study of 60 patients. Outcomes assessed included changes in scores for heartburn, GERD-HRQL and SF-36, medication use, patient reported satisfaction with the RF energy procedure, esophageal acid exposure, LES pressure and grade of esophagitis. Responders were defined as patients who were off all PPIs, used medication other than PPIs as needed, but less than twice weekly, or reduced their medication requirements by >50%. At 12 month follow-up, 75% of patients were either off medication or using less medication than before treatment. It was reported that patients were more satisfied with their symptom control and had statistically significantly fewer GERD symptoms (mean lower esophageal sphincter (LES) pressure improved from 14.89/9.1 to 16.79/10.0 mmHg, and mean total reflux time from 16.79/12.8 to 8.89/6.6%. Quality of life and overall physical and mental health also improved significantly.[11]

In 2005 Lufti and colleagues published a prospective, single center study of patients with GERD who had the RF energy procedure, with a mean follow up time of 26.2 months. The study qualified 77 patients with 61 completing the GERD QOLRAD and SF-12 questionnaires, queries about satisfaction with their Stretta procedure and medication use. Twenty-four returned for post-treatment 24-hour pH study. At follow-up 39 patients were considered responders. Patients were divided into two groups according to their response also as a means to test for correlation between symptomatic improvement and improvement in esophageal acid exposure. The results showed a significant difference between the two groups on all of the quality of life scales, as well as in esophageal acid exposure. No significant change was reported in the non-responder group in total reflux time or DeMeester score before and after Stretta, whereas both decreased significantly in the responder group with normal total reflux time achieved in more than half of responders. Twenty six of 39 (67%) responders were off PPIs.[12]

A prospective single center study of 50 patients was published by Go and colleagues in 2004. Follow-up surveys at a mean of 10 months were completed by 37 patients, including 10 who had failed previous antireflux surgery. The mean heartburn score improved from 3.19 to 1.74 and overall symptom satisfaction score improved from 3.92 to 1.63. Four patients went on to have antireflux surgery after the Stretta procedure. [13]

Torquati and colleagues published a prospective single center study in 2004 with 36 patients reporting long-term outcomes with mean follow-up of 27.1 months. These authors report that 83% of patients were highly satisfied with the procedure and 56% had completely discontinued PPI use. Based on their post-procedure PPI use, patients were divided into two groups; responders (20) and non-responders (16). It was reported that responders scored higher in QOLRAD scores, SF-12 physical scores, and SF-12 mental scores. In a 24-hour pH study, responders demonstrated a significant decrease in distal esophageal acid exposure time.[14]

Tam and colleagues in 2003 studied the impact of a reduced rate of transient lower esophageal sphincter relaxations (TLESRs) on the clinical and symptom improvement for patients with GERD. They reported on 20 patients at 6 months follow-up post radiofrequency energy treatment who experienced a reduced rate of TLESRs from 6.8 per hour at baseline to 5.2 per hour. The number of reflux events was reduced significantly from 10 per 3 hours to 5 per 3

hours with an associated significant reduction in acid exposure time from 5.4% to 3.9%. Acid suppressant medication was required for all patients for symptom control prior to treatment. It was reported that 15 patients (75%) were off medication completely at 6 months and 13 (65%) remained off all medications at 12 months. One patient underwent laparoscopic fundoplication at 9 months. While 1 patient required readmission for post procedural pain, an esophageal perforation was ruled out and the patient responded successfully to analgesic and antibiotic therapy.[15]

In 2004 Triadafilopoulos published a post hoc subgroup analysis from the 118 patient Stretta 6-month open label trial. Outcomes included analysis of the decrease in both proximal and distal esophageal acid exposure times. Patients were assigned to responder or non-responder groups on the basis of post-treatment responses for GERD health-related quality of life heartburn, satisfaction, and proton pump inhibitor use. Responder subgroups demonstrated significant improvements in esophageal acid exposure, whereas non-responders had no change or less improvement. There was a positive correlation between esophageal acid exposure and both GERD-HQRL and heartburn episodes suggesting that symptomatic improvement after Stretta is attributable to a decrease in esophageal acid exposure.[16]

In 2002 Wolfsen and Richards evaluated standardized patient reported outcomes from 558 patients across 33 institutions treated with Stretta with a mean follow-up of 8 months. Outcomes provided at baseline and at follow-up included GERD severity, percentage of GERD symptom control, patient satisfaction, and antisecretory medication use. At baseline, 76% of patients were dissatisfied with antisecretory therapy. GERD symptom relief began less than 2 months after Stretta treatment for 68.7% of patients, and relief was achieved between 2 and 6 months for 14.6% of patients. The median drug requirement reported by patients improved significantly, from twice daily PPI, to antacids as needed. Satisfactory GERD control was reported by 26.3% of patients at baseline while on medication, and improved to 77.0% after the Stretta procedure. Median baseline symptom control for patients on medication was 50%, compared to 90% at follow-up for those treated with Stretta. Baseline patient satisfaction improved from 23.2% while on medication to 86.5% at follow-up after Stretta. Subgroup analysis (1 year) demonstrated a superior effect on symptom control (86.6% vs. 75.3%) and current required drug use (59% vs. 49.8% off all anti-secretory drugs) in Stretta patients with longer than 1-year follow up.[17]

In 2002 DiBaise and colleagues published a study of 18 patients with 6-month follow-up. The study demonstrated a significant improvement in mean symptom scores. The GERD Activity Index decreased from 112.5 to 81.0 after Stretta, and antacid use decreased from 17 doses per week (range 0–81) to0 (range 0–10). No adverse effect on vagal function was identified and no significant change in esophageal motility was seen. A trend was noted toward a reduction in the number of transient lower esophageal sphincter relaxations induced by gastric air distension (3.5/h *vs.* 1.0/h). There were no serious adverse events reported.[18]

In 2002 Triadafilopoulos and colleagues published a multicenter prospective open label trial reporting on 6 and 12 month results for 118 patients with chronic heartburn and/or regurgitation requiring daily anti-secretory medication who were treated using the Stretta procedure. Patients demonstrated improvement at 12 months in median heartburn scores (4 to 1), GERD scores (27

to 9), satisfaction (1 to 4), SF-36 mental quality of life scores (46.3 to 55.4), and SF-36 physical quality of life scores (40.9 to 53.1). The required use of PPIs for symptom relief decreased from 88.1% to 30% of patients. Esophageal acid exposure improved significantly (10.2% to 6.4%). Minor adverse events were reported in 10 patients, none of which required therapeutic intervention.[19]

Considerations in the Pediatric Population

The reader is advised that the Stretta Procedure is not approved by the FDA for use in pediatric patients, nor is the device recommended for use in children by its manufacturer. There are two available studies reporting the results of Stretta in the pediatric population. Islam et al. reported the use of Stretta in 6 patients with recurrent reflux following fundoplication [20]. Mean age was 18 years. All patients required general anesthesia and the mean procedure time was 80 ± 15 minutes. A modified GERD score was used to assess post-procedure symptoms. At a mean of 11 months, there was a decrease in the post-procedure GERD score from 5.2 ± 1.0 to 1.6 ± 1.9. Fifty percent (3/6) were able to come off their antisecretory agents and four of five with > 6 month follow up were asymptomatic. One patient had early recurrence of symptoms requiring a revision fundoplication.

Liu et al reported the results of 8 children undergoing Stretta as initial therapy for medically refractory GERD [21]. Three children were neurologically impaired requiring concomitant gastrostomy. Age range of the children was 11-16 years. All children received a general anesthetic with a mean procedure time of 46 ± 8 minutes. There was one complication reported, aspiration, which was successfully managed. Follow-up ranged 6-15 months. For the neurologically impaired children, all were tolerating bolus tube feeds at follow-up without clinical signs of reflux. In the neurologically normal patients, 3 of 5 were asymptomatic and off antisecretory medications. The remaining children had early recurrence of GERD symptoms. One has been successfully managed with medications, the other required fundoplication.

There is a paucity of data from which conclusions can be drawn regarding the use of Stretta in the pediatric population. Combined, the results of 14 patients are available in the literature. Overall, the data are encouraging with most children experiencing symptom relief after Stretta. Both studies are limited by the lack of consistent objective pre- and post-treatment testing, their enrollment size, and short follow up periods. There were no significant complications associated with the procedure in these series and the published morbidity profile in adults is quite acceptable. Future controlled studies conducted under Institutional Review Board supervision are required before recommendations regarding its safety and efficacy in the pediatric population can be made, although the typically excellent outcomes in adults suggest that future controlled studies in children may enable comparisons to fundoplication.

Conclusion

More than 30 peer reviewed studies, including 4 adequately powered randomized, controlled studies, a comprehensive meta-analysis and multiple prospective clinical trials have documented the safety and efficacy of the Stretta procedure. Durable treatment outcomes to at least to 48 months also have been demonstrated in multiple studies, with significant reduction or

elimination of medications used to treat the symptoms of GERD, as well as improvement in GERD QOL and symptom scores. Stretta may be recommended as an appropriate therapeutic option for patients with GERD who meet current indications and patient selection criteria and choose endoluminal therapy over laparoscopic fundoplication. Those criteria include:

Adult patients (age >=18) with symptoms of heartburn, regurgitation, or both for >= 6 months who have been partially or completely responsive to antisecretory pharmacologic therapy.

The procedure has not been studied and should not be applied in treating patients with severe esophagitis, hiatus hernias > 2 cm, long segment Barrett esophagus, dysphagia, or those with a history of autoimmune disease, collagen vascular disease, and/or coagulation disorders. Further studies are needed to evaluate the role of Stretta in children if it is to be considered a therapeutic option.

Recommendation:

Stretta is considered appropriate therapy for patients being treated for GERD who are 18 years of age or older, who have had symptoms of heartburn, regurgitation, or both for 6 months or more, who have been partially or completely responsive to anti-secretory pharmacologic therapy, and who have declined laparoscopic fundoplication.

Quality of Evidence: (++++). GRADE Recommendation: Strong

Literature Cited

1. Perry K, Banerjee A, Melvin S. Radiofrequency Energy Delivery To The Lower Esophageal Sphincter Reduces Esophageal Acid Exposure And Improves GERD Symptoms: A Systematic Review and Meta-Analysis. *Surg Lap Endosc Percut Tech., Accepted for publication scheduled for August 2012, manuscript reviewed.*
2. Arts J, Bisschops R, Blondeau K, Farré R, Vos R, Holvoet L, Caenepeel P, Lerut A, Tack J, A Double-Blind Sham-Controlled Study of the Effect of Radiofrequency Energy on Symptoms and Distensibility of the Gastro-Esophageal Junction in GERD. *Am J Gast*, 2012 Feb;107(2):222-30.
3. Abdel Aziz AM, El-Khayat HR, Sadek A, Mattar SG, McNulty G, Kongkam P, Guda MF, Lehman GA. A prospective randomized trial of sham, single-dose Stretta, and double-dose Stretta for the treatment of gastroesophageal reflux disease. *Curr Opin Gastroenterol.* 2009 Jul;25(4):352-7.
4. J. P. Galmiche, E. Coron, V. Sebille, G. Cadiot, F. Zerbib, P. Ducrotte, F. Drucote, P. Pouderoux, J. Arts, M. Le Rhun, T. Pivhe, S. Bruley Des Varannes. Clinical trial: radiofrequency energy delivery in proton pump inhibitor-dependent gastro-oesophageal reflux disease patients. *Aliment Pharmacol Ther* 28, July 2008 1147-1158

5. Douglas A. Corley, Philip Katz, John M. Wo, Andreas Stefan, Marco Patti, Richard Rothstein, Michael Kline, Rodney Mason, and M. Michael Wolfe. Improvement of Gastroesophageal Reflux Symptoms After Radiofrequency Energy: A Randomized, Sham-Controlled Trial. *Gastroenterology* 2003;125-668-676
6. Luca Dughera MD, Monica Navino MD, Paola Cassolino MD, Mariella De Cento MD, Luca Cacciotella, Fabio Cisarò MD, Michele Chiaverina MD, Turin Italy. Long-term results of radiofrequency energy delivery for the treatment of GERD. Results of a 48 month prospective study. *Diagnostic and Therapeutic Endoscopy,* August 2011.
7. Noar MD, Lotfi-Emran S. Sustained improvement in symptoms of GERD and antisecretory drug use: 4-year follow-up of the Stretta procedure. *Gastrointest Endosc.*2007 Mar;65(3):367-72.
8. Reymunde A, Santiago N. Long-term results of radiofrequency energy delivery for the treatment of GERD: sustained improvements in symptoms, quality of life, and drug use at 4-year follow-up. *Gastrointest Endosc.* 2007 Mar;65(3):361-6.
9. Richards WO, Houston HL, Torquati A, Khaitan L, Holzman MD, Sharp KW. Paradigm shift in the management of gastroesophageal reflux disease. *Ann Surg.* 2003 May;237(5):638-47; discussion 648-9.
10. Noar MD, Noar E. Gastroparesis associated with gastroesophageal reflux disease and corresponding reflux symptoms may be corrected by radiofrequency ablation of the cardia and esophagogastric junction. *Surg Endosc.* 2008 Nov;22(11):2440-4.
11. Peter N. Meier, Tina Nietzschmnn, Ibrahim Akin, Stefanie Klose, and Michael P. Manns. Improvement of objective GERD parameters after radiofrequency energy delivery: A European study. *Scandinavian Journal of Gastroenterology,* 2007; 42: 911-916
12. R. E. Lutfi, A. Torquati, J. Kaiser, M. Holzman, W. O. Richards. Three year's experience with the Stretta procedure. Did it really make a difference? *Surg Endosc,*2005;19: 289–295
13. Go MR, Dundon JM, Karlowicz DJ, Domingo CB, Muscarella P, Melvin WS. Delivery of radiofrequency energy to the lower esophageal sphincter improves symptoms of gastroesophageal reflux. *Surgery.* 2004 Oct;136(4):786-94.
14. Torquati A, Houston HL, Kaiser J, Holzman MD, Richards WO. Long-term follow-up study of the Stretta procedure for the treatment of gastroesophageal reflux disease. *Surg Endosc.* 2004 Oct;18(10):1475-9. Epub 2004 Jul 22.
15. Tam WCE, Schoeman MN, Zhang Q, Dent J, Ridga R, Utley D, Holloway RH. Delivery of radiofrequency energy to the lower oesophageal sphincter and gastric cardia inhibits transient lower oesophageal sphincter relaxations and gastro-oesophageal reflux in patients with reflux disease. *Gut* 2003;52:479-285
16. Triadafilopoulos G. Changes in GERD symptom scores correlate with improvement in esophageal acid exposure after the Stretta procedure. *Surg Endosc.* 2004 Jul;18(7):1038-44. Epub 2004 May 27.
17. Wolfsen HC, Richards WO. The Stretta procedure for the treatment of GERD: a registry of 558 patients. *J Laparoendosc Adv Surg Tech* A. 2002 Dec;12(6):395-402.
18. John K. DiBaise, M.D., Randall E. Brand, M.D., and Eamonn M. M. Quigley, M.D. Endoluminal Delivery of Radiofrequency Energy to the Gastroesophageal Junction in Uncomplicated GERD: Efficacy and Potential Mechanism of Action. *The American Journal Of Gastroenterology*, 2002;97:833-842.
19. Triadafilopoulos G, DiBaise JK, Nostrant TT, Stollman NH, Anderson PK, Wolfe MM,

Rothstein RI, Wo JM, Corley DA, Patti MG, Antignano LV, Goff JS, Edmundowicz SA, Castell DO, Rabine JC, Kim MS, Utley DS. The Stretta procedure for the treatment of GERD: 6 and 12 month follow-up of the U.S. open label trial. *Gastrointest Endosc.*2002 Feb;55(2):149-56.

20. Islam S; Geiger JD et al. Use of radiofrequency ablation of the lower esophageal sphincter to treat recurrent gastroesophageal reflux disease. J Ped Surg. 2004, 39: 282-286
21. Liu DC; Somme S et al. Stretta as the initial antireflux procedure in children. J Ped Surg. 2005,40: 148-152

Not detailed above:

Louis O. Jeansonne IV, MD; Brent C. White, MD; Vien Nguyen, MD; Syed M. Jafri, BS; Vickie Swafford, RN; Mina Katchooi, DDS; Leena Khaitan, MD, PhD; S. Scott Davis, MD; C. Daniel Smith, MD; Shahriar Sedghi, MD; Edward Lin, DO. Endoluminal Full-Thickness Plication and Radiofrequency Treatments for GERD. *An Outcomes Comparison. Arch Surg.* 2009;144(1):19-24

Arts J, Sifrim D, Rutgeerts P, Lerut A, Janssens J, Tack J. Influence of radiofrequency energy delivery at the gastroesophageal junction (the Stretta procedure) on symptoms, acid exposure, and esophageal sensitivity to acid perfusion in gastroesophagal reflux disease. *Dig Dis Sci.* 2007 Sep;52(9):2170-7.

Cipolletta L, Rotondano G, Dughera L, Repici A, Bianco MA, De Angelis C, Vingiani AM, Battaglia E. Delivery of radiofrequency energy to the gastroesophageal junction (Stretta procedure) for the treatment of gastroesophageal reflux disease. *Surg Endosc.* 2005 Jun;19(6):849-53. Epub 2005 May 3.

Fanelli RD, Gersin KS, Bakhsh A. The Stretta procedure: effective endoluminal therapy for GERD. *Surg Technol Int.* 2003;11:129-34. Review.

Triadafilopoulos G. Clinical Experience With The Stretta Procedure. *Gastrointest Endosc Clin N Am.* 2003 Jan;13(1):147-55. Review.

Houston H, Khaitan L, Holzman M, Richards WO. First year experience of patients undergoing the Stretta procedure. *Surg Endosc.* 2002 Mar;17(3):401-4. Epub 2002 Nov 20.

Triadafilopoulos G, Utley DS. Temperature-controlled radiofrequency energy delivery for gastroesophageal reflux disease: the Stretta procedure. *J Laparoendosc Adv Surg Tech A.* 2001 Dec;11(6):333-9. Review.

Richards WO, Scholz S, Khaitan L, Sharp KW, Holzman MD. Initial experience with the Stretta procedure for the treatment of gastroesophageal reflux disease. *J Laparoendosc Adv Surg Tech A.* 2001 Oct;11(5):267-73.

Donald E Mansell. Community practice evaluation of the effectiveness on the STRETTA

procedure for the treatment of GERD. *AJG* – September, Suppl., 2001:S21

Gao Xiang, Wang Zhong-Gao, WU Ji-Min, JI Feng, ZHANG Cheng-Chao, Ning Ya-Chan, LI Zhi-Tong, HU Zhi-Wei, Chen Xiu And TIAN Shu-Rui . Radiofrequency treatment on respiratory symptoms due to gastroesophageal reflux disease. *Chin Med J 2011;124(7):1006-1009*

D. A. McClusky III, L. Khaitan, V. A. Swafford, C. D. Smith, Radiofrequency energy delivery to the lower esophageal sphincter (Stretta procedure) in patients with recurrent reflux after antireflux surgery. *Surg Endosc* (2007) 21: 1207–1211.

Kazuhide Higuchi, Yasuhiro Fujiwara, Hirotoshi Okazaki, Masahiko Tabuchi, Natsuhiko Kameda, Kaori Kadouchi, Hirohisa Machida, Tetsuya Tanigawa, Masatsugu Shiba, Toshio Watanabe, Kazunari Tominaga, Nobuhide Oshitani, and Tetsuo Arakawa. Feasibility, safety, and efficacy of the Stretta procedure in Japanese patients with gastroesophageal reflux disease: first report from Asia. *J Gastroenterol* 2007; 42:205–210

Mattar SG, Qureshi F, Taylor D, Schauer PR. Treatment of refractory gastroesophageal reflux disease with radiofrequency energy (Stretta) in patients after Roux-en-Y gastric bypass. *Surg Endosc.* 2006 Jun;20(6):850-4. Epub 2006 May 12.

Review Articles and Clinical Guidelines

Grzegorz Wallner, Micha? Solecki, Wies?aw Tarnowski, Tadeusz Wróblewski, Edward Stanowski, Andrzej Budzy?ski, Maciej Michalik. Gastroesophageal Reflux Disease – Clinical Practice Guidelines. *Videosurgery and other miniinvasive techniques* 2009; 4 (Suppl 1)

Jafri SM, Arora G, Triadafilopoulos G. What is left of the endoscopic antireflux devices? *Curr Opin Gastroenterol.* 2009 Jul;25(4):352-7. Review.

C. Daniel Smith, Editorial, Stretta: ahead of its time or has its time passed? *Gastrointestinal Endoscopy*, Volume 65, No. 3: 2007

Yeh RW, Triadafilopoulos G. Endoscopic antireflux therapy: the Stretta procedure. *Thorac Surg Clin.* 2005 Aug;15(3):395-403. Review.

Soji Ozawa, Md, PhD, Masashi Yoshida, MD, PhD, Koichiro Kumai, MD, PhD, and Masaki Kitajima, MD, PhD New Endoscopic Treatments for Gastroesophageal Reflux Disease.*Thorac Cardiovasc Surg* 2005; 11: 146-153

Torquati A, Richards W. The Stretta procedure for the treatment of gastroesophageal reflux disease (GERD). *Min Invas Ther & Allied Technol* 2002: 11(5/6); 217-277.

Cost Analysis

Harewood GC, Gostout CJ. Cost analysis of endoscopic antireflux procedures: endoluminal plication vs. radiofrequency coagulation vs. treatment with a proton pump inhibitor. *Gastrointest*

Endosc. 2003 Oct;58(4):493-9.

IV. Summary of Recommendations

EsophyX

Long term data is not yet available for EsophyX. In short term follow-up, from 6 months to 2 years, EsophyX may be effective in patients with a hiatal hernia ? 2 cm with typical and atypical GERD. Further studies are required to define optimal techniques and most appropriate patient selection criteria, and to further evaluate device and technique safety.

Quality of Evidence: (++). GRADE Recommendation: Weak

Stretta

Stretta is considered appropriate therapy for patients being treated for GERD who are 18 years of age or older, who have had symptoms of heartburn, regurgitation, or both for 6 months or more, who have been partially or completely responsive to anti-secretory pharmacologic therapy, and who have declined laparoscopic fundoplication.

Quality of Evidence: (++++). GRADE Recommendation: Strong

V. Author Financial Disclosure/Conflict of Interest Statement Addendum

Auyang – No disclosures, Carter – No disclosures, Fanelli – No relevant disclosures

VI. Additional References

1. Guyatt G H, Oxman A D, Kunz R, Falck-Ytter Y, Vist G E, Liberati A, Schunemann H J (2008) Going from evidence to recommendations. BMJ 336:1049-1051
2. Guyatt G H, Oxman A D, Vist G E, Kunz R, Falck-Ytter Y, Alonso-Coello P, Schunemann H J (2008) GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 336:924-926