



TITLE: Endoluminal Treatments for Gastroesophageal Reflux Disease (GERD):

- Stretta
- EndoCinch
- Enteryx

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ENDOLUMINAL TREATMENTS FOR GASTROESOPHAGEAL REFLUX DISEASE

INTRODUCTION

The California Technology Assessment Forum has received requests to review the published data regarding the efficacy and safety of currently available endoluminal treatment of gastroesophageal reflux disease. Treatments reviewed are radiofrequency-energy delivery (Stretta™, Curon Medical Inc, CA, USA), endoluminal suturing (Bard EndoCinch™, Bard Interventional Products, Billerica, MA), and endoluminal injection of a biodegradable polymer (Enteryx™, Enteric Medical Technology, Palo Alto, CA).

BACKGROUND

Gastroesophageal reflux disease (GERD) is a multifaceted illness defined by chronic symptoms or mucosal damage produced by the abnormal reflux of gastric contents into the esophagus (Katz, 2001). The most common manifestation of GERD is heartburn, which is a daily symptom for 30 million adults in the United States, though only about 2% of adults have objective evidence of reflux esophagitis (Spechler, 1992). The incidence of GERD increases with age, significantly rising after the age of 45. Exact epidemiological data are difficult to obtain, however, since there is no specific "gold standard" for establishing the diagnosis. Several factors may contribute to the development of GERD. In most patients, reflux occurs as a result of poor tone or incompetence of the lower esophageal sphincter and transient relaxations of the sphincter. Such transient lower esophageal sphincter relaxations occur normally, but are more frequent in patients with GERD (Spechler, 1992). Esophageal mucosal damage is related to the potency of the acidic gastric fluid and the amount of time it is in contact with the mucosa. In addition, about one-third of patients with severe GERD also have diminished peristaltic clearance and delayed gastric emptying that may potentiate GERD (Kaynard and Flora, 2001).

GERD has varied presentations that may be divided into three categories: typical symptoms (heartburn and regurgitation); extraesophageal symptoms (chest pain, cough and reactive airway disease) and complications (ulcerations, strictures, Barrett's esophagus, cancer). Interestingly, symptoms do not reliably predict the presence of esophageal inflammation, and heartburn may be absent in patients with verified reflux esophagitis and other complications (DiPalma, 2001). Stricture formation occurs in about 10% of patients with esophagitis. Most strictures are located at the gastroesophageal junction and are manifested by the gradual development of solid food dysphagia over months to years (Katz, 2001). Strictures above the GE junction usually occur with Barrett's metaplasia. Barrett's esophagus is present in up to 10% of patients with chronic reflux (Lagergren et al, 1999). It is the result of chronic reflux induced injury to the esophageal squamous epithelium. The most serious complication of Barrett's

esophagus is esophageal adenocarcinoma. A recent Swedish study showed a strong relationship between symptomatic GERD and the development of esophageal adenocarcinoma (Lagergren et al, 1999). Patients who had reflux symptoms more than 3 times per week or had symptoms for more than 20 years had a 15 fold increased risk of developing cancer. The impact of treatment on ameliorating this risk is unknown.

Treatment of GERD

Medical treatment

Treatment of GERD is focused on providing symptomatic relief for the patient and on managing and/or preventing esophagitis and other typical or atypical complications. While effective therapy is available for most patients with GERD, 60% to 90% of symptomatic patients will need long term and potentially continuous treatment (Nostrant and Rabine, 2002). Lifestyle modifications should be suggested for all patients with GERD, and along with antacids and over-the-counter H2 blockers are usually sufficient for patients with mild symptomatic GERD (Howden and Chey, 2003). Elevating the head of the bed, weight loss, abstinence from smoking, avoidance of post-prandial recumbency, dietary modification and restriction of alcohol may all play a role in controlling reflux symptoms. Patients with more refractory symptoms generally require a "step up" approach with the addition of proton pump inhibitors if lifestyle modification and H2 blockers prove ineffective. While H2 receptor antagonists are up to 25% more effective than placebo in healing esophagitis than placebo, proton pump inhibitors lead to a therapeutic gain of 57% to 74% relief relative to placebo (Klinenberg-Knol et al, 1995). Patients with more debilitating symptoms usually require more intensive pharmacologic therapy, or antireflux surgery.

Surgical treatment

A variety of antireflux procedures have been described for the treatment of GERD. Nissen fundoplication (open or laparoscopic) seems to be superior to other procedures with symptomatic improvement occurring in 85%-90% of patients (Allgood and Bachmann, 2000). Fundoplication consists of the surgeon wrapping a portion of the gastric fundus around the distal esophagus to increase lower esophageal sphincter pressure. Complications of surgery include postoperative dysphagia (8-12%), abdominal bloating, diarrhea and a mortality rate of 0.3% to 0.5% (Waring, 2002).

The precise indications for the surgical treatment of patients with GERD remain controversial (Castell, 2001). The most frequent indication for antireflux surgery has been severe GERD unresponsive to optimal medical therapy. However, patients with continued symptoms despite optimal medical therapy may not in fact be suffering from GERD and will not benefit from surgery. Since surgery is generally considered to be equally effective to proton pump inhibitors, it is best considered as another option to long term therapy for GERD. Hence, younger patients with

chronic symptoms responsive to medical therapy but who would prefer not to be dependent on long term medical therapy may find antireflux surgery to be an attractive option.

Endoscopic treatment

The primary cause of acid reflux in most patients with GERD is thought to be due to increased transient lower esophageal sphincter (LES) relaxations. Therefore, most endoscopic treatments of GERD have concentrated on improving the antireflux barrier by decreasing gastroesophageal junction compliance and decreasing reflux episodes by decreasing the number of transient LES relaxations (Mahmood et al, 2002; Nostrant and Rabine, 2002). A variety of endoscopic procedures have been developed and tested in humans (Galmiche and des Varannes, 2003). To date, there are currently three FDA approved endoluminal methods for treatment of GERD: radiofrequency-energy delivery (Stretta, Curon Medical Inc, CA, USA), endoluminal suturing (Bard EndoCinch, Bard Interventional Products, Billerica, MA), and endoluminal injection of a biodegradable polymer (Enteryx, Enteric Medical Technology, Palo Alto, CA).

Stretta

The Stretta procedure is an endoscopic technique in which radiofrequency energy is delivered to the gastroesophageal junction by means of a flexible catheter. The catheter is comprised of a bougie tip, a balloon basket combination and 4-needle delivery sheaths positioned radially around the balloon. The catheter is passed through the mouth and positioned at the squamocolumnar junction, the region of the lower esophageal sphincter. The needles are deployed at a 45-degree angle through the mucosa into the smooth muscle into the longitudinal muscle layer of the esophagus or upper stomach (cardia). Sterile water is delivered to the base of each needle through the catheter to cool and preserve the overlying mucosa. (Torquati and Richards, 2002). Radiofrequency energy is delivered for 90 seconds via a 4-channel radiofrequency energy generator. The procedure is repeated for the final result of four rings in the distal LES and two in the gastric cardia. Currently, patients get 56 lesions placed over a period of 35 minutes. Heat induced collagen shrinkage is immediately evident after the Stretta procedure.

The procedure is thought to work by causing rings of tissue necrosis and collagen contraction with the subsequent wound healing process resulting in further reductions of lesion size and collagen deposition in the LES and upper stomach. This leads to mechanical alteration of the GE junction. It is also hypothesized that the radiofrequency energy disrupts the vagal nerve afferent pathways within the mesenteric plexus of the upper stomach, which have been implicated in transient LES sphincter relaxations (Utley et al, 2000). A third hypothesis is that the Stretta procedure works by desensitizing the esophagus.

The potential advantages of this procedure include the avoidance of complications of general anesthesia and surgery and the potential long-term side effects and adherence issues of long-term medication. It can be performed by a gastroenterologist on an outpatient basis with meperidine and midazolam anesthesia. There is mild discomfort due to catheter passage in 25% of cases; mild to moderate discomfort is also experienced with RF delivery in 50% to 70% of cases (Triadafilopoulos et al, 2001).

Bard EndoCinch

The Bard EndoCinch has multiple components and is placed into the patient via an overtube (of 19.7 mm diameter). The procedure is a multistep process in which an endoscopic sewing machine is mounted on a standard gastroscope; an endoscopic knotting device, overtube, and nylon thread are used to perform these operations. In the Bard method, the sewing machine is advanced to the GE junction and suction is applied which pulls a fold of tissue into the jaws of the device. The sewing machine is then applied; the knot is tied outside and pushed into place with a special device (Roy-Shapira et al, 2002). The suture ends are then tied to create a plication. During the procedure, typically 2-3 plications are created. Personnel required to perform the procedure include an endoscopist, a first assistant, an anesthetist and a circulating nurse. The patient receives a sedative or anesthetic (e.g. midazolam or propofol), antiemetic, motility inhibitor and throat anesthetic (Rothstein and Filipi, 2003)

Enterx

Enterix is an injectable solution containing 8% ethylene vinyl alcohol copolymer (EVOH) dissolved in dimethyl sulfoxide (DMSO) that has been approved for the treatment of GERD (Johnson et al, 2003). Enterix is injected through a sclerotherapy needle during upper endoscopy. A total of 6 ml is injected circumferentially into and along the muscle layer of the lower esophageal sphincter. The solution contains a radiocontrast agent to allow for visualization under fluoroscopy (Peters et al, 2003). Following injection, the DMSO diffuses resulting in solidification of the EVOH, which forms a spongy solid mass. The exact mechanism of action of Enterix is unknown, though it may act by firming up the LES. Adverse events associated with Enterix include retrosternal chest pain, dysphagia, fever, belching/bloating, and a garlic like taste following the procedure (Johnson et al, 2003).

TECHNOLOGY ASSESSMENT (TA)

TA Criterion 1: The technology must have final approval from the appropriate government regulatory bodies.

The Stretta System consists of a radiofrequency generator and a radiofrequency energy delivery catheter. On April 18, 2000, the CSM Stretta System (Curon [formerly Conway Stewart] Medical Inc., Sunnyvale, CA) received FDA 510k approval as a device substantially equivalent for the indications for use specified to devices marketed in

interstate commerce prior to May 28, 1976, the enactment date of the Medical Devices Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act. The device is indicated for "general use in the electrosurgical coagulation of tissue and intended for use specifically in the treatment of gastroesophageal reflux disease."

The Bard EndoCinch Interventional Endoscopic Suturing System (Bard Interventional Products, Billerica, MA) received FDA 510k approval on January 5, 2001 with class II (Special Controls) and allowance to begin marketing the device.

The Enteryx ProcedureKit (Enteric Medical Technologies, Inc., Foster City, CA) received FDA Pre-market Approval on April 22, 2003. The device is indicated for endoscopic injection into the region of the lower esophageal sphincter for the treatment of gastroesophageal reflux disease symptoms in patients responding to and requiring daily pharmacological therapy with proton pump inhibitors.

TA Criterion 1 is met for all three devices.

TA Criterion 2: The scientific evidence must permit conclusions concerning the effectiveness of the technology regarding health outcomes.

Stretta

To date, the publications on Stretta include one randomized, double-blinded, sham-controlled trial (Corley et al. 2003), two papers reporting on 6 and 12 month follow-up from the same multicenter case series (Triadafilopoulos et al. 2001, Triadafilopoulos et al. 2002), four papers describing single institution case series (Richards et al. 2001; DiBaise et al. 2001; Houston et al. 2002; Tam et al. 2003) and one case series describing results from a registry of patients who underwent Stretta™ at several different institutions (Wolfsen and Richards. 2002). One study presents results of a non-randomized comparison of Stretta™ and laparoscopic fundoplication from one center (Richards et al. 2003).

Outcomes assessed in the clinical trials of this procedure include: GERD symptoms; GERD health related quality of life (using the GERD-Health Related Quality of Life questionnaire) (Velanovich, 2000); general quality of life (using the Medical Outcomes Study SF-36) (McHorney et al. 1994); use of antireflux medications; esophageal motility (generally expressed as the frequency of transient lower esophageal sphincter relaxations); 24-hour ambulatory esophageal pH testing; the presence of esophagitis on EGD and overall patient satisfaction.

Bard EndoCinch

The published literature on the use of the Bard EndoCinch system for endoscopic suturing include one case series with 6 month follow-up (Filipi et al, 2001) and a one year follow up study (Mahmood et al, 2003). There are a number of other abstracts of this technique that have not yet been published in a peer reviewed journal. Outcomes assessed in the clinical trials of this technique are similar to those used for Stretta (see above).

Enteryx

To date, there is very limited published data regarding the use of Enteryx in the treatment of patients with GERD. Deviere et al, 2002, reports on the results of a small case series from two centers in Europe. Johnson et al, 2003, describe results from a prospective, multicenter, single arm study in the United States and Europe to evaluate the safety and efficacy of Enteryx for the treatment of GERD. Peters et al, 2003 and Louis and Deviere, 2003 report on aspects of the technique of implanting and visualizing Enteryx in humans.

Outcomes assessed in the clinical trials of this technique are similar to those used for Stretta (see above).

Level of evidence:

For Stretta, the levels of evidence are level 1, and level 5.

TA Criterion 2 is met for Stretta.

For Bard EndoCinch and Enteryx the available evidence is level 5 only.

TA criterion 2 is not met for Bard EndoCinch and Enteryx.

TA Criterion 3: The technology must improve net health outcomes.

Randomized-controlled trial

Corley et al, 2003 report on the first randomized, double-blinded, sham-controlled trial of radiofrequency energy (Stretta™) for the treatment of GERD. Participants were recruited from the medical practices and general population at 8 study sites. Inclusion criteria, among others, included: 1) GERD symptoms at least partially responsive to and requiring daily anti-acid medication, 2) 24-hour pH study demonstrating abnormal esophageal acid exposure, 3) normal esophageal peristalsis and sphincter relaxations, 4) EGD demonstrating no substantial esophageal ulcerations, 5) no Barrett's esophagus and 6) no significant hiatal hernia. Stretta was performed in the usual manner (described above) for a total of 22 sets of needle deployments. The sham procedure involved balloon inflation at each deployment position without needle deployment or energy delivery. Subjects discontinued their medications at day 22 post-procedure, but if symptoms returned a standardized step-up protocol was used until symptoms abated.

At six months, interested sham patients were allowed to crossover to open-label active treatment (consisting of a modified protocol that required fewer needle deployments).

The primary outcome measures were "heartburn" using a six point Likert scale, GERD health related quality of life and general quality of life. Secondary outcomes assessed at 0, 6, and 12 months included medication usage, esophageal acid exposure times (using 24-hour pH monitoring), the presence and grade of esophagitis on EGD and the LES pressure. Complications were assessed with a patient questionnaire.

A total of 64 patients were randomized (35 active treatment and 29 sham). Active treatment significantly improved heartburn scores, GERD-specific quality of life scores and general quality of life scores (SF-36 physical) compared with sham. Heartburn was assessed using a six-point Likert scale with 0=no symptoms up to 5=incapacitating symptoms. At six months, active patients had significantly decreased heartburn scores (mean decrease -1.6 to a score of 2.2) as compared with sham patients (mean decrease -0.6 to a score of 2.8). (A score of 2=symptoms noticeable and bothersome, but not every day; 3=symptoms bothersome every day). Active vs. sham patients had significantly increased quality of life scores (mean increase 7 vs. 1, mean scores 47 vs. 42), more were "responders" (greater than 50% improvement in GERD-HRQL score, 19 vs. 6, $p=0.03$) and more were without daily heartburn symptoms (19 vs. 7, $p=0.05$). These last two comparisons are essentially another way of measuring and reporting the improved heartburn scores mentioned above.

Secondary outcomes of the study were medication usage and esophageal acid exposure. At 6 months, they found no statistically significant differences in daily use of proton pump inhibitors (13 vs. 10) or in daily use of any medications. Additionally, they found no difference in median esophageal acid exposure times between active vs. sham treatments. In a subgroup analysis of patients with improved symptoms (responders), however, they found that symptom improvement was associated with decreased esophageal acid exposure, and patients who crossed over to treatment from sham showed a significant decrease in acid exposure at 12 months vs. baseline.

The authors' report finding no differences in LES pressure or esophagitis between the sham and active treatment groups. At 6 months, 20 of the 25 remaining sham patients crossed over to active treatment and these patients then significantly improved their GERD-HRQL scores.

There were no significant adverse events associated with Stretta. There were no post-procedure perforations, significant bleeding or deaths.

In sum, this well done RCT found that while patient's who underwent the Stretta procedure had significantly improved heartburn scores and quality of life scores as compared with the patients exposed to the sham procedure, they found no significant differences in esophageal acid exposure, and unlike in many of the uncontrolled case series, no

difference in medication use between the two groups. Notably, medication usage was significantly reduced in both the sham and active treatment groups, as has been found in other interventions that use medication withdrawal protocols for patients with GERD. Although the authors identify medication usage as a secondary outcome, this would appear to be inconsistent with what they identify to be the main purpose of Stretta™--as an alternative for patients who respond to medical therapy but whom desire an alternative to or cannot tolerate long-term medication use.

The authors point out several potential limitations of this study. First, they had a "moderate" dropout rate (by my calculation of between 19% to 25% depending on the outcome). However, they point out that in their "extreme case analysis" in which they treated missing active treatment patients as failures and missing sham patients as successes, they still found a significant improvement in GERD-HRQL. Second, the small size of the study and the large percentage of sham patients who discontinued their medication created the possibility of Type II error to detect differences in medication use. Third, improvement in esophageal acid exposure was shown only through the less reliable method of subgroup analyses.

Finally, they state that it is possible that subjects were able to guess their treatment assignments and therefore the results were biased in favor of the active treatment. In table 4, they do report that 4 patients in active treatment and none in the sham reported chest pain though the nature and extent of this complaint is not discussed. It is unfortunate that they did not survey the patients as to which treatment they believed they were exposed to as this would have clarified whether pain or other sensation associated with the radiofrequency treatment may have led to an elaborate placebo effect and contributed to the improved subjective measures which constitute their main findings.

Case Series

The other Stretta trials are all non-randomized case series and therefore it is difficult to draw conclusions from them regarding the effectiveness of Stretta for treating patients in usual clinical settings as compared with standard therapy. These trials will be discussed more briefly below. Triadafilopoulos et al, 2001, report on 6-month outcomes in 47 patients with GERD treated with Stretta. They found that compared to baseline, at 6 months there were statistically significant improvements in GERD symptom scores, heartburn scores, esophageal acid exposure time and SF 36 scores. At 6 months, 87% of patients no longer required proton pump inhibitors.

Triadafilopoulos et al, 2002 report on 118 patients with GERD and daily symptoms at least partially responsive to medication. Symptom and quality of life measures were evaluated blindly at 6 and 12 months. They found that median heartburn scores improved as did GERD-HRQL, quality of life as assessed by the SF-36. At baseline, 88.1% of patients were taking the equivalent of 40 mg of Omeprazole at baseline; at 12 months only 13% of patients were

taking proton pump inhibitors. In addition, 24-hour pH measures and manometry also improved. Overall, the procedure was well tolerated with the endoscopist rating of patient discomfort during the procedure of mild (47%), moderate (9%) or severe (2%).

Richards et al. (2001) describes results of 25 patients with chronic GERD on daily proton pump inhibitors. After treatment with Stretta, they report significant improvement on the SF-12 measures as well as GERD related quality of life scores. Mean daily proton pump inhibitor usage fell from an average of 43 mg to 6.4 mg at 3 months. DiBaise et al. (2002) reports on 18 patients with abnormal pH monitoring and manometry. They found improvements in GERD-HRQL scale at 6 months but no significant changes on pH monitoring or manometry. Houston et al. (2002) reports on results of Stretta for 41 patients with a long history of GERD. Thirty-three procedures were performed under conscious sedation and 8 under general anesthesia (3 secondary to inadequate pain control during RF delivery). They had 75% follow-up at 6 months and found that quality of life scores and SF-12 mental and physical scores improved at 6 months. Twenty of thirty-one patients were completely off PPI's at 6 months. One patient developed gastroparesis and ulcerative esophagitis on post-op day 12.

Tam et al. (2002) reports on a study from Australia in 20 patients that examined the impact of Stretta on esophageal LES function. They found that radiofrequency reduced the rate of post-prandial transient LES relaxations, and increased mean basal LES pressure as well as ambulatory acid exposure time at 12 months. At 12 months post-treatment, 13 patients (65%) were in "symptomatic remission".

Overall, these case series indicate that Stretta appears to be a relatively safe and well tolerated procedure when used in the context of a research study by trained endoscopists. In these case series, most patients demonstrate improvement in GERD related and overall quality of life scores. Results on other, perhaps more objective, measures such as esophageal acid exposure and manometry tend to be more equivocal. Overall, decisions about the safety and efficacy of this and other new technologies must be made on the basis of results from randomized trials, not case series.

Bard EndoCinch (Endoluminal Suturing)

Case Series

No randomized, controlled clinical trials of endoluminal suturing comparing outcomes with conventional antireflux therapies has been published. Filipi, (2001) published a multi-center case series of 64 patients with chronic GERD symptoms at least partially responsive to medications. Patients underwent symptom severity scoring, esophageal manometry, endoscopy and 24-hour pH probe monitoring before and after the suturing procedure. Patients were randomized to either linear or circumferential plication. The 64 patients underwent a total of 79 procedures, under

conscious sedation (69%), monitored anesthesia (14%) or general anesthesia (17%). In addition, a repeat procedure was performed on 11 of the 64 patients at 49-405 days after the original procedure. Ten patients withdrew before completion of the 6-month study for various reasons.

At 6 months, 51 patients reported improvements in heartburn severity and frequency and in regurgitation. The 24-hour pH probe monitoring showed improvement in the number of episodes below pH of 4. There was no significant difference in LES sphincter pressures at 6 months. Endoscopy showed no significant change in grade of esophagitis pre- and post-procedure, though there was a trend toward improvement. Results of SF-36 Quality of Life questionnaires showed significant improvement over baseline at 6 months on 2 subscales (pain and social functioning). At 6 months, 62% of patients were taking < 4 doses of antisecretory medications per month.

Adverse transient effects included pharyngitis in 31%, chest pain (16%), vomiting (14%), abdominal pain (14%) and gastric bleeding (3%).

Mahmood et al. (2003), report on results from a case series of 26 patients with persistent GERD symptoms and abnormal 24-hour pH monitoring. They used the Bard EndoCinch-I endoscopic suturing system to place the sutures on the lesser curvature and then formed the plication. They report that training in the use of the EndoCinch™ was obtained by attending the laboratory of Dr. Swain on 2 occasions and then practicing on live pig models 3 times. They performed the procedure on 26 patients; 4 were lost to follow-up. They report that all patients had significant improvement in heartburn scores, regurgitation frequency and quality of life assessments at one, three, six and 12 months. At 3 month follow-up, 24-hour pH values and manometry were improved and "there was no worsening" of esophagitis. At 12 months, PPI use decreased from 100% of patients to 36%. Immediately post procedure transient complaints occurred: sore throat (7 patients), vomiting (2), abdominal pain (3), chest soreness (5) and a few other complaints. Two patients had significant bleeds--one required 1 unit PRBC.

In sum, the published literature on Bard's EndoCinch is not sufficient to conclude that it is currently a safe and effective treatment for GERD. The complexity of the procedure makes it unlikely that it will be widely accepted in the foreseeable future (Roy-Shapira et al. 2002).

Enteryx

Case Series

Deviere et al. (2002), report on the results of a pilot study that enrolled 15 patients over one year. The diagnosis of GERD was established by pH monitoring (pH < 4 at least 4% of the time over 24 hours or at least 3% of the time during the night). Exclusions were similar to other studies with the addition of a BMI > 35. The implantation procedure was performed under both endoscopic and fluoroscopic guidance. Four quadrant injections were made

into the muscle of the cardia at the same level, 1-3 mm proximal to the squamocolumnar junction. The mean follow-up was 6.1 months. There were no clinically serious adverse events that were potentially life threatening or required surgical intervention. Heartburn severity rated on a scale from 1-4 improved from 3.40 to 1.87 ($p=0.006$); LES pressure increased from 12.2 mm Hg to 16.7 mm Hg ($p=0.038$). Four patients resumed use of PPI's by 3 months.

Johnson et al (2003), report on results from a prospective, multicenter single arm study evaluating the safety and efficacy of Enteryx. Eighty-five patients with heartburn symptoms responsive to PPI's were enrolled and had Enteryx solution injected along the muscle layer or deep sub-mucosal layer of the cardia. During the procedure, x-ray fluoroscopy was used to allow the physician to confirm intramural implant location. Ninety-two percent of patients experienced transient retrosternal chest pain; 84% reported that the pain resolved within 2 weeks. Seventeen patients reported mild or moderate dysphagia following the Enteryx procedure typically starting 4 days after the procedure. Approximately half resolved within 2 weeks and the remaining resolved within 12 weeks. Seventy four percent of patients were able to eliminate and 10% to reduce use of PPI's by 50% 6 months following the procedure. They report that patients experienced significant improvements in heartburn symptoms during the 6 months following treatment compared to baseline (when patients were off PPI's). In addition, SF-36 scores as well as esophageal acid exposure both improved at the 6-month follow-up. However, to achieve these results, nineteen patients underwent repeat implantation due to inadequate therapeutic response from initial therapy.

Two small case series do not provide adequate data upon which to evaluate the safety and efficacy of Enteryx in the treatment of GERD. The published literature on Enteryx is not sufficient to conclude that it is currently a safe and effective treatment for GERD.

TA Criterion 3 is not met for Stretta, Bard EndoCinch or Enteryx.

TA Criterion 4: The technology must be as beneficial as any established alternatives.

The established alternatives to endoscopic antireflux therapies for GERD include standard antisecretory medications, promotility agents, cholinergic agents and fundoplication surgery. H-2 receptor antagonist medications relieve symptomatic heartburn in approximately 60% of patients and heal esophagitis in 50%, and proton pump inhibitors relieve heartburn in 80% of patients and heal esophagitis in 90% (deVault et al. 1995). Laparoscopic fundoplication improves symptoms in 76-98% of patients and improves distal esophageal acid exposure time in 90% (Peters et al. 1995). One recent comprehensive review of medical and surgical management of patients with severe chronic GERD concluded that proton pump inhibitors are equivalent to surgery for both short and long term outcomes, but surgery is superior to H2 blockers (Walker et al. 1997). In another study of 5-year follow up of a randomized study comparing open fundoplication to medical therapy with omeprazole, Lundell et al (2001) found that surgical therapy

and medical therapy were equivalent in all important outcomes. No similar data exists comparing Stretta or other endoscopic anti-reflux therapy to medication or surgery.

There is one non-randomized study that compared outcomes of Stretta and laparoscopic fundoplication. Richards et al. (2003), prospectively evaluated all patients presenting for surgical evaluation (laparoscopic fundoplication) for GERD to Vanderbilt University Medical Center between August 2000 and March 2002. Patients were offered Stretta if they had documented GERD (as documented by a positive 24-hour pH study or biopsy proven esophagitis) and did not have a hiatal hernia larger than 2 cm, LES pressure less than 8 mm Hg or Barrett's esophagus. Sixty-five patients underwent the Stretta procedure (3 after failed fundoplication) and 75 underwent laparoscopic fundoplication (LF) (65 primary and 10 redo). Patients in the Stretta group were more likely to be younger (mean age of 46 vs. 49) and to have a larger average BMI (30.3 vs. 28.7). Preoperative esophageal acid exposure time was higher in the LF group while LES pressure was higher in the Stretta group. Six of 75 patients in the LF group had Barrett's esophagus. In the Stretta group, one complication occurred related to the procedure; a 22 year-old developed transient gastroparesis requiring decompression. In the LF group, there were 7 major complications (2 enterotomies, 1 pneumothorax, 1 slipped Nissen, 1 paraesophageal hernia and 2 incisional hernias).

At 6 months, GERD specific QOL scores and general health scores were significantly and similarly improved in both groups. Stretta patients had a mean follow-up of 7.3 months and LF patients 5.2 months. On follow-up, 58% of Stretta patients were off PPI's and 31% had reduced their dose; 97% of LF patients were off PPI's. Both groups expressed satisfaction with their procedure (89% Stretta and 96% LF)

The authors conclude that they envision a "new paradigm", in which the refractory GERD patient would be offered LF or Stretta based on size of the hiatal hernia, their LES pressure, and the presence of Barrett's esophagus and presence of aspiration related asthma and/or pneumonia. However-the data from this and other studies do not support this conclusion. First, this is not a randomized study, so any conclusions drawn from it should be interpreted cautiously. Second, the follow-up is too short to conclude that these are equally effective alternatives. Third, what is meant by "refractory" GERD is not entirely clear from the current literature. If it is defined as inability to wean off medications, then more patients after Stretta than surgery continue to be refractory. Corley et al. (2003) found that Stretta was not superior to sham in weaning patients off of medications. Fourth, acid production can usually be suppressed with adequate doses of PPI's alone; failure of a patient to respond to adequate PPI doses should raise the possibility that the diagnosis of GERD was not accurate in the first place. The failure of Stretta to improve 24-hour pH scores, to promote healing of esophageal ulcers and other measures of acid reflux (Corley et al. 2003) is concerning and lead us to conclude that this technology has not yet been shown to be equivalent to current standard of care.

In sum, the published literature does not support the conclusion that Stretta, Bard EndoCinch or Enteryx are as beneficial as the existing alternatives for the treatment of GERD.

TA criterion 4 is not met for Stretta, Bard EndoCinch or Enteryx.

TA Criterion 5: The improvement must be attainable outside of the investigational setting.

The published data are not sufficient to conclude that the efficacy and safety of Stretta, Bard EndoCinch and Enteryx have been established under conditions of usual medical practice.

TA criterion 5 is not met for Stretta, Bard EndoCinch and Enteryx.

RECOMMENDATIONS OF OTHERS

Blue Cross Blue Shield Association (BCBSA)

Endoscopic suturing, radiofrequency ablation, and implantation of inert polymers were addressed by a 2002 Technology Evaluation Center assessment. This assessment concluded that there was insufficient evidence in the published literature to permit scientific conclusions. The assessment also concluded that randomized studies are required to determine the effectiveness of these three treatment options in comparison to placebo, continued medical therapy, or surgery.

Centers for Medicare and Medicaid Services (CMS)

Information regarding a CMS opinion was not found. The CMS web site is silent regarding an opinion on the use of procedures specific to the treatment of Gastroesophageal Reflux Disease.

American Gastroenterological Association (AGA)

The AGA provided representation at the meeting and opinion in favor of the use of the Stretta procedure.

American Society of Gastrointestinal Endoscopy (ASGE)

The ASGE provided representation at the meeting and opinion in favor of the use of the Stretta procedure and Enteryx.

CONCLUSION

Heartburn is a daily symptom for 30 million adults in the United States. Effective therapy exists for the majority of patients with GERD, but long-term treatment is needed in 60% to 90% of this population. For the minority of patients whom fail medical therapy, surgical fundoplication improves symptoms, quality of life and acid reflux in 70% to 90% of patients, but carries a significant risk of symptoms such as solid-food dysphagia or gas-bloat syndrome (Nostrant and Rabine, 2002). An endoscopic technique that can successfully relieve symptoms and reduce acid reflux and presumably long-term complications in those patients refractory to medical treatment and that produces little post-operative complications would be of significant benefit to patients suffering with GERD. Unfortunately, there is insufficient data at this time to conclude that any of the three procedures reviewed in this report fulfill these criteria.

In the case of Enterx and Bard EndoCinch, the current literature does not include any randomized trial data, so it is not possible to fully evaluate the safety and efficacy of these procedures. In addition, with the Bard EndoCinch, questions remain about the safety of the procedure and the training required to perform it under conditions of routine clinical practice.

In contrast, Stretta has been rigorously evaluated with a randomized, double-blinded, sham-controlled trial (Corley et al. 2003). Based on the findings from this well-done trial, should Stretta be considered an option for patients who are intolerant of or desire an alternative to traditional medical or surgical therapies? The answer to this question remains "not yet" for the following reasons:

This trial did not enroll patients who were refractory to medical therapy, so it is not possible to conclude from this trial if Stretta will be helpful for patients with refractory symptoms on appropriate medical therapy. If Stretta should be considered as an alternative to surgical therapy is not addressed by this study and remains unknown.

The most significant finding of this study was that mean GERD-HRQL scores were significantly improved after treatment as compared with sham. The GERD-HRQL has been found to be superior to the SF-36 in the assessment of severity of symptoms and response to treatment for patients with GERD (Velanovich, 2000). This is a significant finding, though unexplainable as more objective measures of acid reflux did not improve. (This discrepancy between symptoms and objective findings has been demonstrated in other GERD treatment studies). However, if one compares mean HRQL scores of subjects in both the sham and active treatment arms on medications prior to treatment with the scores of subjects in the active treatment arm 6 months post-treatment, they are equivalent (all three scores are 16). Similar findings are evident for mean heartburn scores (a mean of 1.9 in the active treatment group at baseline on medication compared with a mean of 2.2 six months post treatment where a higher score equates with more symptoms) and the SF-36 score (see Table 1 and 2 in the paper and Appendix 1 of this report).

Therefore, the most we can conclude is that Stretta was successful in returning patients back to a similar level of symptoms they had at baseline on medications.

What about patients who simply desire not to take medications long term? In this study, Stretta was no better than sham procedure with a medication withdrawal protocol in decreasing medication usage over a relatively short-term follow-up. In addition, since Stretta did not improve esophageal acid exposure, esophageal erosions or LES pressure, all presumably risk factors for developing later complications from GERD, it does not seem advisable to recommend that patients discontinue a safe and effective treatment that has been proven to reduce acid exposure in favor of one that does not. Longer-term studies may demonstrate a potential downside of this inability to control acid reflux.

Patients with more severe GERD were excluded from the study. In clinical practice, these are the patients who are likely to be referred for this procedure, but for whom little efficacy or safety data exist.

Some commentators express concern that the potential long-term negative consequences of Stretta, such as stricture formation, remain unknown (Roy-Shapira, 2002). In addition, patients who are symptomatically improved but continue to experience acid reflux may be at increased risk of developing complications of reflux disease since they will not be motivated to seek evaluation

If Stretta is to be recommended as a competing strategy for patients with mild to moderate GERD, it must prove to be as safe, effective and durable as maintenance medical therapy with proton pump inhibitors. This still remains an open question.

TA criteria 2-5 are not met for Bard EndoCinch and Enteryx

TA criteria 3-5 are not met for Stretta.

RECOMMENDATION

It is recommended that Stretta, Bard EndoCinch and Enteryx for the treatment of GERD do not meet California Technology Assessment Forum criteria.

The California Technology Assessment Forum approved the recommendation as presented.

October 08, 2003

Appendix 1

	Sham Treatment n=29	Active Treatment n=35	p value
Mean Heartburn Scores			
off medications	3.6(±0.9)	3.8 (+/-0.9)	
post treatment	2.2(abs. change= 0.6)	2.2(abs.change= -1.6)	0.01
on medications	2(+/-1.6)	1.9(+/-1.5)	
Mean HRQL score			
off medications	25(+/-7)	28(+/-8)	
post treatment	21(abs. change= -3)	16(abs. change= -13)	
on medications	16(+ /-11)	16(+/-11)	0.003
Mean SF – 36 physical			
off medication	42(+/-11)	40(+/-7)	
post treatment	42	47(abs. change=7)	0.05
on medication	46(+/-11)	46(+/-8)	
Median 24 h-pH (%)			
off medication	9.9	9.5	
post treatment	10.7	9.9	
Esophageal erosion (#)			
pre-treatment	6	4	
post treatment	5	5	
Daily PPI use (#)			
pre-treatment	21(72%)	30(88%)	
post treatment	10(43%)	13(42%)	

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