

AGA Institute Technical Review on the Use of Endoscopic Therapy for Gastroesophageal Reflux Disease

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Gastroesophageal reflux disease (GERD) is a common clinical problem. The prevalence of GERD was recently estimated to be 19 million cases per year in the United States, with an associated total cost of care of \$9.8 billion.¹ The single largest component of the cost of care of these patients is drug costs, estimated to be \$5.8 billion.

Gastroesophageal reflux occurs when the normal antireflux barrier between the stomach and the esophagus is impaired either transiently or permanently. Symptoms develop when the offensive factors in the gastroduodenal contents, which include acid, bile acids, and trypsin, overcome several lines of esophageal defense. As more components of esophageal defensive mechanisms are perturbed, the severity of reflux increases.

It is estimated that approximately 50% of patients with typical reflux symptoms in tertiary centers have erosive esophagitis, whereas nonerosive reflux disease is encountered in approximately 50%–70% of patients in community-based practices.² Despite the fact that GERD is rarely life-threatening, complications of GERD such as esophageal strictures, Barrett's esophagus, and esophageal adenocarcinoma may occur. Furthermore, GERD is a chronic disorder that impairs both quality of life and work productivity. Thus, the optimal therapeutic management of this disease is important.

The goals of treatment in GERD are to relieve symptoms, heal esophagitis if present, prevent recurrence of symptoms, and prevent complications. Both antisecretory medications and surgical therapy decrease symptoms and improve quality of life in GERD. Proton pump inhibitors (PPIs) are superior to H₂-receptor antagonists for symptom relief, acute healing of erosive esophagitis, and long-term treatment of esophagitis to prevent both endoscopic and symptomatic relapse.^{3,4} A number of concerns remain regarding the safety of long-term therapy with PPIs, including gastric mucosal atrophy (especially in *Helicobacter pylori*-infected patients), the appearance of fundic gland polyps, and pneumonia.⁵ Antireflux surgery, in skilled hands, also has excellent short-term outcomes regarding symptom relief.⁶ However, concerns remain regarding postoperative adverse events and the durability of the procedure.⁷

A variety of endoscopic techniques for the treatment of patients with GERD are currently available or under study as alternatives to antisecretory therapy or antireflux surgery. The appeal of this approach is to provide an option for patients who would prefer nonpharmacologic therapy but wish to avoid antireflux surgery. An ideal endoscopic antireflux technique should be effective, safe, and easy to apply, making it applicable to most endoscopists. Current techniques are less invasive than antireflux surgery, are performed in the outpatient setting, and include the delivery of radiofrequency energy to the gastroesophageal junction, injection or implantation of agents into the cardia or distal esophagus, and suture plication of the proximal stomach. Each of these endoscopic antireflux techniques is designed to alter the anatomy or physiology of the gastroesophageal junction to decrease gastroesophageal reflux.

This systematic review of all the currently available (or were expected to have become available) endoscopic antireflux devices is meant to evaluate the field as a whole and identify what is currently known regarding endoscopic antireflux therapies as well as areas of insufficient information.

Search Strategy

We performed a systematic review of the literature for all English-language articles dealing with endoscopic therapy for GERD in adults published between 1996 and August 2005. Search terms included the following: endoscopy, digestive system, and experimental gastroesophageal reflux; gastroesophageal reflux therapy and endoscopy; Medtronic; Bard; Boston Scientific; Ethicon; Stretta; Gatekeeper; Enteryx; EndoCinch; In-scope; Curon; and NDO. Searches were then combined in different orders to identify all relevant manuscripts. Databases searched included MEDLINE, EMBASE, the Cochrane Database of Systematic Reviews and Central Registry of Controlled Trials, the American College of Physicians Journal Club, DARE, and CCTR. The Food and Drug Administration's (FDA's) MAUDE database (<http://www.fda.gov>) was searched from 2000 to 2005 for adverse events reported with each of the techniques described in the following text. Following the initial broad search, we excluded articles in foreign languages and where initial review of the title and abstract did not show the article to be relevant. Additional references were obtained from the bibliographies of selected articles. Only full-length articles were considered. Studies published only in abstract form were excluded, with the exception of abstracts of randomized controlled trials from either Digestive Disease Week or the annual meetings of the American College of Gastroenterology since 1999.

Radiofrequency Energy

The delivery of temperature-controlled radiofrequency energy has previously been used for a variety of medical conditions such as benign prostatic hypertrophy, cardiac arrhythmias, and tumor ablation. Monopolar radiofrequency devices, such as the Stretta procedure, use an active electrode and a dispersive electrode (grounding pad). Radiofrequency current flows from the active electrode to the adjacent tissue, causing

Abbreviations used in this paper: CI, confidence interval; DMSO, dimethyl sulfoxide; FDA, Food and Drug Administration; EVOH, ethylene vinyl alcohol copolymer; GERD, gastroesophageal reflux disease; GERD-HRQL, gastroesophageal reflux disease health-related quality-of-life questionnaire; IQR, interquartile range; PPI, proton pump inhibitor; SF-36, Short Form Health Survey-36; QOLRAD, gastroesophageal reflux disease-specific quality-of-life survey scores.

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heating of tissue water molecules.⁸ In the Stretta procedure, radiofrequency energy is delivered in a controlled fashion with constant tissue temperature monitoring to a selected target temperature of 85°C. Once the tissue is heated to 65°C, collagen contraction occurs, resulting in tissue shrinkage.⁸

Technique

Radiofrequency energy delivery requires a special single-use catheter and radiofrequency energy generator (Stretta System; Curon Medical, Inc, Sunnyvale, CA). The radiofrequency generator contains one channel per needle for a total of 4 channels, an irrigation pump, and a temperature control feedback system to maintain a temperature of 85°C in the muscle layer when the needles are deployed. The generator delivers pure sine wave energy at the following settings: 465 kHz, 2–5 W/channel, and 80-V maximum at 100–800 Ω.⁸ When the catheter is positioned and the needles are deployed, radiofrequency energy is delivered to each electrode to achieve a temperature of 85°C while irrigation through the catheter keeps the mucosal temperature at <50°C.⁸ If the temperature at the base of the needle exceeds 50°C, the tip exceeds 100°C, or impedance exceeds 1000 Ω, the generator will automatically shut off to that needle.⁹

The single-use catheter consists of a balloon-basket assembly that inflates to a maximum of 3 cm in diameter, a soft guidewire tip, and 4 electrode delivery sheaths positioned in a radial fashion at 90° increments around the balloon, suction, and irrigation.^{8–10} Each of the 4 needles (25 gauge, 5.5 mm in length) is made of nickel-titanium and has a thermocouple (electrical thermometer) at its tip and base.

The procedure is typically performed using standard conscious sedation. However, the doses of meperidine and midazolam are typically 2 or more times higher than those used for colonoscopy or endoscopic ultrasonography.¹¹ The need for general anesthesia has also been reported in a subset of patients.¹² Before deploying the catheter, upper endoscopy is performed and the location of the squamocolumnar junction is determined. A guidewire is then passed into the duodenum and the endoscope removed. The catheter is inserted orally over the guidewire into the stomach and subsequently positioned, followed by connection to suction and irrigation lines. There is considerable variability among published studies regarding catheter positioning, and the technique has not been standardized from study to study. Typically, the catheter is first positioned 1–2 cm proximal to the endoscopically determined Z-line followed by removal of the guidewire. The catheter balloon is then inflated to a pressure of 2.5 psi, and the needles are deployed. Radiofrequency energy is delivered for 90–120 seconds, thereby heating the smooth muscle tissue; the needles are then retracted and the balloon deflated. The process is repeated at the same location after rotating the catheter 45°. After these 8 lesions are created, 8 additional lesions are created in an identical fashion at 0.5-cm intervals advancing to 1 cm below the Z-line. Published trials extend the lesions anywhere from 1 to 2 cm below the Z-line. Some studies also create cardia lesions by passing the assembly into the stomach, inflating the balloon to approximately 25 mL, and pulling the balloon back against the diaphragmatic impression for the first set of lesions and 22 mL for the second set of lesions. For the cardia lesions, the needles are again deployed, followed by creation of 2 additional sets of lesions by rotating the catheter 45° to the right and again to the left. A second set of

cardia lesions is created in an identical manner.⁹ Published procedure times vary from 46 to 69 minutes.^{11–16}

Mechanism of Action

The mechanism of action of radiofrequency ablation has been studied more extensively than that of any of the other endoscopic techniques. It is believed that radiofrequency energy delivery exerts its effect by 2 possible mechanisms: scarring at the gastroesophageal junction or neurolysis in that same region.¹⁷

Histologic data on the effect of radiofrequency ablation are available from 2 animal models. In a porcine model, radiofrequency energy was delivered at twice the recommended human duration (180 seconds) to 10 pigs at multiple sites extending from 2 cm above to 2 cm below the endoscopically determined gastroesophageal junction.¹⁸ There were no acute mucosal lesions noted. However, histopathologic review of specimens revealed focal circular muscle injury 2 hours after energy delivery but no apparent damage to the vagus nerve. Eight weeks after treatment, histologic studies revealed normal muscle appearance but occasional focal collagen deposition in the circular smooth muscle. In a canine model, intense treatment characterized by 12 lesions at each level extending from 5 mm proximal to 1.5 cm distal to the gastroesophageal junction resulted in marked thickening of the muscularis propria accompanied by fibrosis in the muscle layer when compared with control animals.¹⁹ The gastric cardia wall thickness was increased by 63% compared with control dogs 3 months after therapy. No histologic information on the effect of radiofrequency ablation on the gastroesophageal junction is available from human studies. However, wall thickness in 7 patients, as determined by endosonography, was unchanged 6 months after completing therapy.¹⁵

None of these observations seem to translate to any consistent effect on basal lower esophageal sphincter (LES) pressure in animals or humans.¹⁷ In the porcine model described previously, 20 pigs were studied after pharmacologically weakening the LES with injection of botulinum toxin.¹⁸ One week after botulinum toxin injection, 13 animals underwent radiofrequency energy treatment and 7 were not treated. LES pressure decreased from 15.4 ± 4.9 mm Hg to 11.8 ± 5.3 mm Hg 1 week after botulinum toxin injection in the radiofrequency ablation group but then increased insignificantly to 14.4 ± 3.8 mm Hg 8 weeks after therapy. In contrast, mean LES pressure decreased from 14.0 ± 3.6 mm Hg to 10.3 ± 3.2 mm Hg over the same period in the untreated animals. However, the difference in LES pressure between the 2 groups 8 weeks after treatment was not statistically significant ($P = .079$). That study also examined gastric yield pressure, that is, the intragastric pressure associated with the appearance of irrigation fluid in the esophagus after catheter irrigation of normal saline at a rate of 100 mL/min into the stomach of the animals after ligation of the pylorus. The mean gastric yield pressure was significantly greater in the treated group (43.4 ± 10.7 mm Hg) compared with the control group (24.9 ± 8.2 mm Hg) ($P = .0007$). However, the clinical and physiologic relevance of this change of yield pressure is uncertain.¹⁷ In humans, no increase in basal LES pressure has been noted.^{13–17}

The effect of radiofrequency ablation on transient LES relaxation has been studied in both animals and humans. A canine study by Kim et al assessed the effect of radiofrequency

energy delivery on transient LES relaxation in 11 animals before and 3 months after treatment.¹⁹ Energy was administered to the gastric cardia given at 5-mm increments starting at 5 mm above and 1.5 cm below the Z-line. Treatment was intense, with 12 lesions made at each of 5 levels. Treatment decreased the frequency of transient LES relaxation in 9 of 11 dogs tested from a median of 4 per hour (interquartile range [IQR], 3–6.8) to 3 per hour (IQR, 2–3) ($P = .004$) without changing the basal LES pressure. This was accompanied by a decrease in the rate of reflux events as well.

In humans, transient LES relaxation has been studied in depth by 2 investigators. DiBaise et al found no significant change from baseline to 6 months in either fasting transient LES relaxation or in transient LES relaxation induced by gastric distention in 18 patients.¹⁵ Integrity of vagal efferent function, as measured by pancreatic function response to sham feeding, was normal in 8 patients studied.¹⁵ In contrast, Tam et al demonstrated a 24% reduction in the rate of transient LES relaxation from a median of 6.8 per hour (IQR, 5.7–8.1) to 5.2 per hour (IQR, 4.2–5.8) ($P < .01$) during the 3-hour postprandial recording period in 20 patients 6 months after radiofrequency ablation.²⁰ Of note, their technique of radiofrequency ablation was again intense: 2 sets of lesions were created every 0.5 cm from 1.5 cm above to 1.5 cm below the squamocolumnar junction and an additional 6 sets of lesions were created at the gastric cardia.

Thus, what is the mechanism of action of radiofrequency ablation on frequency of transient LES relaxation? It is hypothesized that this technique can decrease transient LES relaxation either by a direct interference of afferent nerve signaling to the brain or by ablating mechanoreceptors in the cardia.²⁰ Alternatively, radiofrequency ablation may alter the mechanics of the gastric cardia due to induction of fibrosis and contraction, thereby resulting in less distention and thus decreasing the stimulus for transient LES relaxation.²⁰

Clinical Outcomes

Surveys. A multicenter survey of 558 patients who underwent radiofrequency ablation was obtained at a mean follow-up of 8 months posttreatment in both academic and community centers.²¹ Subjects reported that GERD symptom control, using a visual analogue scale, was 90% after radiofrequency ablation compared with 50% on medication and that treatment resulted in “satisfactory” symptom control in 77% compared with 26% at baseline while on medication. Antisecretory medications were no longer required by 51% of these patients at the time of follow-up. This study did not use a validated survey instrument and was administered to patients by a nurse or physician from each of the participating institutions.

Cohort studies. Triadafilopoulos et al described the initial US open-label results of radiofrequency ablation in 47 patients after 6 months.¹³ All patients studied had heartburn and/or regurgitation characterized by at least partial control with antisecretory medications, elevated acid exposure time, or DeMeester scores on 24-hour pH monitoring, Hertzog grade 2 esophagitis or greater, and hiatal hernias ≤ 2 cm. At 6 months, significant improvement was found by intent-to-treat analysis in heartburn symptoms, GERD health-related quality-of-life questionnaire (GERD-HRQL), and Short Form Health Survey-36 (SF-36) scores. Antisecretory therapy was completely

eliminated in 70% of patients, and PPIs were completely eliminated in 87%. Furthermore, significantly fewer patients had esophagitis at follow-up (25 vs 8) ($P = .005$) and median distal acid exposure time decreased from 11.7% to 4.8% ($P \leq .0001$). There was no change in LES pressure.

This study was subsequently extended to 118 patients, with 12-month follow-up available in 94 patients.¹⁴ Patients studied all had similar entry criteria as described previously. At 12 months, significant improvement was still found by intent-to-treat analysis in heartburn symptoms, GERD-HRQL scores, and SF-36 scores. Antisecretory therapy was completely eliminated in 40% of patients in contrast to 70% at 6 months, and PPIs were completely eliminated in 70% of treated individuals in contrast to 87% at 6 months. However, there was no longer any significant difference in the number of patients with esophagitis, and LES pressure actually decreased significantly at 6-month follow-up from a median of 15 mm Hg (IQR, 10.8–20.8) to 12.6 mm Hg (IQR, 9–18.5) ($P = .007$). The median distal acid exposure time decreased significantly from 10.2% (IQR, 6.1–14.7) at baseline to 6.4% (IQR, 3.7–12.2) at 6 months ($P = .0001$). Note, however, that the normal upper limit of acid exposure time for this study was 4%. A subsequent post-hoc analysis of this study found that responders to radiofrequency ablation, as measured by either GERD-HRQL, heartburn severity score, or no daily PPI use, had a significant decrease in distal esophageal acid exposure, whereas the nonresponders did not have any significant decrease in acid exposure.²²

Other investigators have reported several small single-center studies. One-year follow-up of 20 patients is available from Tam et al.²⁰ GERD-HRQL and SF-36 scores remained significantly improved in these patients at 1 year. This was accompanied by a significant decrease in median esophageal acid exposure time from 10.6% (IQR, 7.8–13.0) to 6.3% (IQR, 4.7–10.9) ($P < .05$), although only 4 of the 19 patients studied at that point had normalized acid exposure.

The Vanderbilt group reported 3-month follow-up on 13 of 25 treated patients and 6-month follow-up on 31 of 41 treated patients.^{12,23} GERD-specific quality-of-life survey scores (QOLRAD) and SF-12 physical and mental scores improved significantly in the 13 patients with 3-month follow-up and in the 31 patients with 6-month follow-up.^{12,23} Twenty of 31 patients (65%) with 6-month follow-up discontinued PPI therapy completely.¹² At 6 months posttherapy, 18 of 41 patients agreed to undergo pH monitoring, which demonstrated a significant improvement in acid exposure time from a mean of $8.4\% \pm 0.9\%$ before therapy to $4.4\% \pm 1.3\%$ ($P = .03$) after therapy, but the basal LES pressure was unchanged.

A study of 18 patients by DiBaise et al demonstrated a significant improvement in the GERD activity index and GERD-HRQL scores at 6 months.¹⁵ Seventeen of the 18 patients were able to completely stop all antisecretory medications despite no change in acid exposure time as measured by 24-hour pH monitoring after therapy.

Go et al reported on 50 patients undergoing radiofrequency ablation.²⁴ Follow-up data were available from 37 patients (74%) at a mean duration of 10 months. As in the previous studies, GERD-HRQL scores improved significantly. This study also examined a small subgroup of 10 patients who failed antireflux surgery, but radiofrequency ablation resulted in no improvement in GERD-HRQL scores for these patients. How-

Table 1. Systematic Review of Published Studies of Radiofrequency Ablation for Treatment of GERD

Author (reference no.), year	Intervention	Study design	No. of subjects	Length of study (mo)	Outcome measurements	Results	Comments
Richards et al, ²³ 2001	RFA	Cohort Single center	25	3	GERD QOLRAD (mean)	3.5 ± 0.4 → 5.5 ± 0.5	$P < .001$
					SF-12 physical (mean)	23.7 ± 3.0 → 31 ± 3.4	$P < .008$
					SF-12 mental (mean)	40.5 ± 2.9 → 47.7 ± 3.2	$P < .017$
							Only 13 patients available for 3-month follow-up
Triadafilopoulos et al, ¹³ 2001	RFA	Cohort Multicenter	47	6	Heartburn score (median)	4 → 1	$P \leq .0001$
					GERD-HRQL (median)	26 → 7	$P < .0001$
					SF-36 (mental) (median)	46.2 → 55.5	$P = .01$
					Medication use	100% → 30%	$P \leq .001$
					24-hour pH (median) (% time pH < 4)	11.7% → 4.8%	$P \leq .0001$
					Manometry	No difference	
					Esophagitis	53% → 17%	$P = .005$
Triadafilopoulos et al, ¹⁴ 2002	RFA	Cohort Multicenter	118	12	Heartburn score (median)	4 → 1	$P \leq .0001$
					GERD-HRQL (median)	27 → 9	$P \leq .0001$
					SF-36 physical (median)	40.9 → 53.1	$P \leq .0001$
					Medication use	100% → 60%	
					24-hour pH (median) (% time pH < 4)	10.2 → 6.4	$P = .0001$
					Manometry	No difference	(6-month data only)
					Esophagitis	31% → 25%	Not significant
DiBaise et al, ¹⁵ 2002	RFA	Cohort Single center	18	6	GERD activity index (median)	112.5 → 81.0	$P < .0001$
					GERD-HRQL (median)	21.5 → 11	$P < .0001$
					SF-36 (median)	Unchanged	
					Medication use	100% → 6%	
					24-hour pH (median) (% time pH < 4)	9.5% → 6.2%	Not significant
					Manometry	No difference	
					Esophagitis	No difference	
Wolfsen and Richards, ²¹ 2002	RFA	Survey Multicenter	558	8 (mean)	GERD symptom control baseline on medication vs after RFA by visual analogue scale	50% → 90%	$P < .0001$
					Satisfactory symptom control baseline on medication vs after RFA	26% → 77%	No statistical tests
					Antisecretory therapy	100% → 49%	No statistical tests
Houston et al, ¹² 2003	RFA	Cohort Single center	41	6	GERD QOLRAD (mean)	3.7 + 0.2 → 5.1 + 0.2	$P = .002$
					SF-12 physical (mean)	26.2 + 2.4 → 33.1 + 3.8	$P = .001$
					SF-12 mental	44.3 + 2.0 → 51.8 + 1.7	$P = .001$
					PPI use	100% → 35%	
					24-hour pH (mean) (% time pH < 4)	8.4 + 0.9% → 4.4 + 1.3%	$P = .03$
					LESP (mm Hg)	25.3 + 2.4 → 26.8 + 2.6	Not significant
							Limited follow-up at 6 months: 31/41 returned questionnaires and 18/41 had pH and manometry

Table 1. Continued

Author (reference no.), year	Intervention	Study design	No. of subjects	Length of study (mo)	Outcome measurements	Results	Comments
Tam et al, ²⁰ 2003	RFA	Cohort Single center	20	12	GERD-HRQL (median) SF-36 physical (median) 24-hour pH (median) (% time pH < 4) Antisecretory drug use	19.5 → 7 43 → 51.5 10.6% → 6.3% 100% → 35%	<i>P</i> < .05 <i>P</i> < .05 <i>P</i> < .05
Corley et al, ¹⁶ 2003	Stretta vs sham	Randomized controlled multicenter clinical trial	64	6	Change in heartburn score Change in GERD- HRQL score Change in SF-36 physical score Medication use 24-hour pH Esophagitis grade	−1.6 vs −0.6 −13 vs −3 7 vs 1 No difference No difference No difference	<i>P</i> = .01 <i>P</i> = .03 <i>P</i> = .05
Go et al, ²⁴ 2004	RFA	Cohort	50	Mean 10	GERD-HRQL	3.19 → 1.74	<i>P</i> = .012 Follow-up in only 74% of this mixed population, which included surgical failures

NOTE. Primary outcomes, when stated, appear in bold.

RFA, radiofrequency ablation; LES, lower esophageal sphincter pressure.

ever, this study was not powered adequately to address this question in the surgical failure patient group.

Controlled clinical trials. The only randomized, double-blind, controlled trial of radiofrequency ablation is the landmark study by Corley et al reported in 2003.¹⁶ In that study, 64 patients with GERD characterized by heartburn or acid regurgitation at least partially controlled by antisecretory therapy, abnormal acid exposure by 24-hour pH monitoring, small hiatal hernias (≤ 2 cm), and low-grade esophagitis (Hetzl-Dent grade II or less) were randomized to either active treatment or sham radiofrequency ablation. Sham patients who remained symptomatic at 6 months had the option of crossing over to open-label active therapy. At 5 months, the active arm was superior to sham treatment for all primary end points: mean heartburn score by a 6-point Likert scale (-1.6 [95% confidence interval [CI], -1.1 to -2.2] vs -0.6 [95% CI, -0.1 to -1.2]) ($P = .01$), mean GERD HRQL score (-13 [95% CI, -9 to -17] vs -3 [95% CI, -8 to 2]) ($P = .003$), and mean SF-36 physical score (7 [95% CI, 3 to 12] vs 1 [95% CI, -3 to 6]) ($P = .05$). However, there was no difference between treatment arms for any of the secondary outcome measures: daily PPI use, 24-hour pH, or esophagitis grade.

Results of a systematic review of published studies of radiofrequency ablation for treatment of GERD are summarized in Table 1.

Safety

Clinical trial adverse events. A variety of adverse events have been described after radiofrequency ablation, ranging from minor and self-limited to death. The most common side effect has been chest pain in 1.7%–100% of subjects. The largest reported series is the US multicenter open-label trial, where the complication rate was 8.6% (fever in 2, superficial

mucosal injury in 3, chest pain in 2, transient dysphagia in 1, submental swelling in 1, and sedation-related hypotension in 1).¹⁴ Other uncommon adverse events reported in clinical trials include nausea, vomiting, bleeding, and abdominal pain. Mediastinal inflammation was reported in one study,²⁰ as has been one case of self-limited gastroparesis.¹¹

Case reports. There have been no published case reports of adverse events.

FDA's MAUDE database of adverse events. The FDA's MAUDE database of adverse events was reviewed on August 30, 2005 (<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/search.cfm>). A total of 26 reports of adverse events were reported between 2000 and 2004. Of note, the number of reports has declined from a peak of 12 in 2000 to 1 in 2004. However, it should be noted that this reporting system is voluntary and it is unknown if this represents a true decrease in the incidence of adverse events or not. There were 3 deaths: one related to conscious sedation before the procedure in a morbidly obese individual, one due to esophageal leak and aspiration pneumonia, and one related to postprocedure aspiration pneumonia in a patient with Alzheimer's disease. There were also 3 additional cases of esophageal perforation, one of which required multiple surgical interventions. Also reported have been 2 cases of gastroparesis, 3 individuals with chest pain, 2 individuals with skin burns, and single cases of fever, atrial fibrillation, and pneumoperitoneum.

Endoscopic Injection Techniques

The concept of placement or implantation of inert material into the region of the gastroesophageal junction dates back more than 20 years to when O'Connor et al injected Teflon paste into the esophagogastric junction of dogs that had been

surgically altered to induce reflux.²⁵ Esophagitis was reversed in all 5 animals, and reflux volume improved after therapy. This same group of investigators subsequently reported their pilot experience of implanting cross-linked bovine dermal collagen into the gastroesophageal junction of 10 patients with GERD.²⁶ Improvement in both GERD symptoms and LES pressure was noted. However, the effect of this technique on subjective and objective measures was short-lived, because these measures returned to pretreatment levels by 1 year. Nevertheless, this technique appeared to be safe and well tolerated. Thus, the concept of endoscopic antireflux therapy using an implantable substance was born.

Since those early proof-of-concept studies, 4 implantable products have been described in humans: Plexiglas (polymethylmethacrylate) microspheres (Artes Medical Inc, San Diego, CA), polytetrafluoroethylene (Polytef; Mentor O & O Inc, Hingham, MA), a hydrogel prosthesis (Gatekeeper; Medtronic Inc, Minneapolis, MN), and an ethylene vinyl alcohol copolymer (EVOH) with tantalum dissolved in dimethyl sulfoxide (DMSO) (Enteryx; Boston Scientific Corp, Natick, MA).

The latter 2 devices either became commercially available in the United States (Enteryx in 2003) or were expected to become available in 2006 (Gatekeeper). Both of these devices have completed their US sham trial enrollment at the time of this report, but the final results from these trials have yet to be reported. Only these 2 devices will be reviewed in this report, and most of the available data pertain to the Enteryx device. However, note that Enteryx was withdrawn from the market by the manufacturer in September 2005 because of continuing reports of transmural injection and secondary complications related to incorrect device application. The development of the Gatekeeper device was suspended in late 2005 by the manufacturer due to concerns about the evolving market conditions related to endoscopic antireflux devices as well as anticipated regulatory concerns.

Enteryx

Technique. This is a combined endoscopic and radiologic technique, using the endoscopic image to select the appropriate injection site and to monitor for too shallow of an injection during implantation and fluoroscopy to monitor the depth of injection to avoid either intravascular injection or injection outside the gut wall.²⁷ The Enteryx kit contains the injectable solution comprised of 8% EVOH dissolved in DMSO along with a micronized tantalum powder that serves as a contrast for visualization under fluoroscopy. The solution is supplied in 10-mL glass vials and is accompanied by additional DMSO as well as DMSO-compatible injection catheters, syringes, and needles.

After priming the sclerotherapy-like catheter system with DMSO to prevent premature polymerization of the EVOH, a 4-mm, 23-gauge needle is introduced deep into the wall of the selected site. The exact details of injection site selection and technique vary in different studies. Some investigators inject 1–3 mm proximal to the squamocolumnar junction, whereas others inject at a site 1–2 mm distal to the squamocolumnar junction in a slightly caudal direction. Following agitation of the solution to suspend the tantalum component, the solution is drawn up into 1-mL syringes and the polymer is then injected slowly (1 mL/min) into the deep muscle layer under combined endoscopic and fluoroscopic guidance. The correct injection

depth is assumed based on the appearance of a bleb or ring seen fluoroscopically, with no bulging or discoloration of the mucosa seen endoscopically during injection. The latter would indicate a shallow submucosal injection. Between 1 and 2 mL is usually delivered at each injection site, typically in 4 quadrants, and the needle is left in place for an additional 20–60 seconds to ensure polymerization has occurred and to avoid backflow of a still-liquid polymer into the lumen of the gut, thus losing implant.^{27–29} If an “arc” pattern is formed under fluoroscopy, some investigators continue to inject up to 5 mL in one site.²⁷ It is believed that on contact of the solution with a physiologic space, the DMSO diffuses away, resulting in the precipitation or solidification of the hydrophobic copolymer and formation of a “spongy mass.” During the polymerization process, heat and pressure within the muscle layer often result in pain and need for additional sedation. Some investigators perform the procedure under deeper sedation using propofol or other deeper sedation techniques because of the prolonged pain and discomfort associated with the procedure.²⁸ Typically, a total of 6–8 mL is used during a single procedure.

Patients are often instructed to resume a soft diet for the first few days postprocedure and told to expect some chest discomfort related to the implantation procedure as well as a “garlic” odor related to the excretion of the DMSO.²⁷ Average procedure time in trials to date varies from 20 to 38 minutes, with a concomitant fluoroscopy time of 10–13 minutes.^{29–32}

Mechanism of action. The mechanism of action of Enteryx remains unclear, with limited physiologic information available to date. It is hypothesized that placement of Enteryx leads to an increased barrier to reflux.²⁷ Early work with Enteryx in a porcine model suggested that implantation of Enteryx into the region of the esophagogastric junction resulted in an initial inflammatory reaction accompanied by cellular necrosis.³³ Resolution of the acute inflammation was followed by a granulomatous reaction and ultimately the production of a circumscribed fibrous capsule that separated the normal tissue from the implant material. Implants resulted in no change in LES length or pressure. The yield pressure needed to equalize gastric and esophageal pressures during gastric distention with water was insignificantly increased in treated animals as compared with untreated ones. Nevertheless, the investigators suggested that this technique resulted in altered distensibility and geometry of the gastroesophageal junction. It is hypothesized that this change in distention of the cardia could potentially lead to fewer reflux events, either by affecting an increase in yield pressure that was noted in these experiments, preventing shortening of the LES during cardia distention, or perhaps by decreasing the number of transient LES relaxations, triggered by cardia distention. However, the effect of Enteryx on transient LES relaxation has not been reported to date.

Histologic data are available from one human study.³⁴ Thirty-four implants were placed in 9 patients before a planned esophagectomy. Pathologic evaluation of the esophagectomy specimens revealed that 30 of the 34 implants were correctly placed in the esophageal wall. However, 4 of the implants were either located subserosally or attached to the exterior of the gastroesophageal junction.

Clinical Outcomes

Pilot study. Deviere et al reported the initial results of an open-label pilot study of Enteryx in 2002.³⁰ Fifteen patients

with established GERD, with abnormal esophageal acid exposure by 24-hour pH monitoring, who required daily PPIs and with esophagitis (Savary-Miller grade 2 or less) underwent Enteryx injection 1–3 mm above the squamocolumnar junction. The primary end points included feasibility of the technique and effect of Enteryx injection on LES pressure. Secondary end points included effect of treatment on symptom scores, PPI use, and persistence of the implant in the esophageal wall.

Enteryx treatment resulted in a significant increase in LES resting pressure from a mean of 12.2 ± 0.9 mm Hg at baseline to 18.7 ± 1.5 mm Hg at 1 month and 16.7 ± 1.3 mm Hg at 6 months ($P = .001$). LES resting pressure increased in 12 of 15 patients. Thirteen of 15 patients had an improvement in heartburn score, as assessed by a nonvalidated 4-point scale, at 6 months, and only 4 of 15 were on PPI therapy at 6 months. After 4–12 months, 9 of 15 patients had $>50\%$ of the implant remaining, as determined by surface area of the radio-opaque material on plain radiographs. This pilot study then led to the series of studies described in the following text.

Cohort Studies

Johnson et al reported the 6-month results of an international, multicenter, open-label trial in 2003.²⁹ The primary end point of this study was the effect of Enteryx therapy on PPI use at 6 months, with success defined as either complete elimination of PPIs or a reduction of PPI dosage of $\geq 50\%$ compared with baseline. Secondary outcomes were GERD symptoms and quality of life using validated disease-specific and generic instruments (GERD-HRQL and SF-36), esophageal acid exposure, and esophageal manometric measures. Eighty-five PPI-dependent patients with GERD from 8 sites were enrolled over a 6-month period. Enteryx was placed 1–2 mm below the squamocolumnar junction, with an attempt made to inject into the deep muscle layer of the cardia. The goal was to achieve a total implant volume of 6–8 mL using 1–2 mL/injection, unless a “ring” was achieved at fluoroscopy. The implant injection rate was 1 mL/min or slower, and the needle was left in place for 1 minute after injection was complete to prevent back-diffusion of the liquid before polymerization could be achieved. PPI use was continued for an additional 10 days posttherapy. Follow-up assessment was made at 1, 3, and 6 months.

Eighty-four percent of patients achieved the primary end point of $\geq 50\%$ decrease in PPI dosage at 6 months, with 74% of subjects able to eliminate all PPIs at that time. Median GERD symptom scores improved from 24.0 (IQR, 22–31) to 4.0 (IQR, 0–11) ($P < .001$), and SF-36 quality-of-life scores improved significantly as well. Esophageal acid exposure improved from a median of 9.5% (IQR, 7–16) to 7% (IQR, 3–11) ($P < .001$) and normalized in 26 of 71 (37% by per-protocol analysis and 30.5% by intention-to-treat analysis) patients at 6 months. LES pressure was unchanged, but median LES length increased by 1 cm.

Subsequently, 12-month data from this same cohort became available.³⁵ Eight patients had withdrawn from the study after failing therapy. By intention-to-treat analysis, 76.5% of patients achieved the primary end point of $\geq 50\%$ decrease in PPI dosage (80% by per-protocol analysis), with 67% not taking any PPIs by intention-to-treat analysis. The treatment response remained stable between 6 and 12 months. Similar to the 6-month data from this cohort, symptom and quality-of-life scores remained improved. Esophageal pH improved by both per-protocol and intention-to-treat analysis, with 39% normalized at 12 months

(per protocol). LES pressure was again unchanged, but LES length was no longer increased at 12 months.

More recently, the 24-month follow-up of a subgroup (64 patients) of this original 85-patient cohort has been reported in conjunction with an additional 59 patients who were treated under the original protocol and had least 12 months of follow-up.³¹ Twelve-month per-protocol and intention-to-treat analyses and 24-month per-protocol analyses were reported. Of the 144 patients enrolled in this trial, only 118 could be evaluated at 12 months and complete data were available on even fewer patients. Sixty-four patients had data available for 24 months of follow-up.

Responders, as defined previously, were 78% (68% off all PPIs) by intention-to-treat analysis and 84% by per-protocol analysis at 12 months. At 24 months, the per-protocol response rate was 72%, with 67% of patients off all PPIs. As in the earlier studies, GERD symptom and quality-of-life scores improved. Esophageal acid exposure data available from 102 patients at 12 months decreased from a median of 10% (IQR, 7.0–18) at baseline to 6.4% (IQR, 3.0–13) ($P < .01$), with normalization achieved in 37% of evaluable patients. Enteryx resulted in no change in any parameter of esophageal manometry.

The most recent observational open-label data for Enteryx come from a multicenter European study of 93 PPI-dependent patients with GERD.³² The primary end point was PPI use, and treatment success was again defined as $\geq 50\%$ reduction in PPI dosage compared with baseline. Secondary end points included symptom and quality-of-life assessments using validated instruments, esophageal acid exposure, and LES pressure. The Enteryx implantation technique was similar to that described by Johnson et al previously, although the injection site for this study was at or below the squamocolumnar junction, which is somewhat different than the 1–2 mm below the squamocolumnar junction described.²⁹ The total volume injected was 6–8 mL, using injections of 1–2 mL in each quadrant. Follow-up occurred at 1, 3, 6, and 12 months postprocedure.

Seventeen patients discontinued the trial; 7 patients were lost to follow-up, and 10 patients withdrew from the study. By intention-to-treat analysis, 69% of patients were treatment responders and 52% were able to stop PPI therapy. In contrast, by per-protocol analysis, 86% were treatment responders and 65% were able to stop PPI therapy. Symptom and quality-of-life scores improved at 12 months, but there was no change in esophageal acid exposure time or LES pressure. Of 54 evaluable patients at 12 months, 52% had normalized esophageal acid exposure time.

Controlled clinical trials. There are now 2 completed sham-controlled trials of Enteryx as a treatment for GERD: a multicenter European trial that has been published as a peer-reviewed report³⁶ and a US multicenter trial with interim data analysis presented at Digestive Disease Week 2005.³⁷

The European trial was a multicenter, randomized (by concealed allocation), single-blind (patient) study conducted in 4 centers that enrolled 64 patients with GERD whose symptoms were controlled with PPIs but relapsed when PPIs were discontinued.³⁶ Thirty-two received Enteryx, and the other 32 received a sham procedure. Both groups were followed up for 3 months. Subsequently, the study allowed for re-treatment for patients who failed to respond to Enteryx or crossover to Enteryx therapy for sham failures. The primary outcome measure was as previously described in the open-label studies, $\geq 50\%$ reduction

in PPI use compared with baseline, and secondary outcomes included $\geq 50\%$ improvement in symptoms as measured by the GERD-HRQL and the proportion of patients requiring re-treatment. The method of treatment was as described previously by Johnson et al,²⁹ although again injection at or just below the squamocolumnar junction was described compared with the Johnson et al method of 1–2 mm below the squamocolumnar junction. The target volume of injection was 6–8 mL.

Between 12 and 23 patients were enrolled at each of the 4 sites, and 3 patients dropped out of the study at the 3-month visit. By intention-to-treat analysis, PPI use was reduced $\geq 50\%$ in 78% of Enteryx-treated patients versus 53% of sham-treated patients at 3 months ($P = .038$). Complete cessation of PPI use was seen in 68% of the Enteryx group and 41% of the sham group ($P < .001$). GERD symptoms improved by a median of 63% in the Enteryx group versus 25% in the sham group, and quality-of-life scores were improved in the Enteryx group but not the sham group. Nine Enteryx-treated patients were eligible for re-treatment versus 23 sham-treated patients. There was no difference in esophageal acid exposure between the 2 groups, although complete data were available for only 39 of the 64 patients. Outcomes at 6 months are not reported here because the study was then unblinded; the observations are by nature observational and no longer representative of the original randomized treatment scheme.

The US-predominant 16-center multicenter sham trial is only available as an abstract and includes per-protocol data from the first 62 patients that have at least 3 months of follow-up.³⁷ Similar to the European trial, these patients were PPI responders; however, unlike the European study, DMSO was sprayed into the gastric lumen in the sham arm in an attempt to maintain the single-blind nature of the study. The primary end point was also $\geq 50\%$ reduction in PPI use. However, the only data reported to this point are on esophageal acid exposure, GERD symptoms, and quality of life. Forty-seven percent of the sham-treated patients have crossed over to treatment with Enteryx versus 7% of Enteryx-treated patients ($P < .001$) being re-treated after the blind was broken at 3 months. Esophageal acid exposure improved by 4.3% in Enteryx-treated patients versus 0.5% in sham-treated patients ($P < .05$). pH success was achieved in 50% of Enteryx-treated patients versus 23% of sham-treated patients ($P < .05$), with normalization in 27% versus 15%, respectively. GERD symptom scores improved significantly more in the Enteryx-treated patients versus sham-treated patients ($P < .05$), and success was achieved in 83% of Enteryx-treated patients versus 54% of sham-treated patients ($P < .05$).

Results of a systematic review of published studies of Enteryx therapy for treatment of GERD are summarized in Table 2.

Safety

Clinical trial adverse events. A review of the clinical trials reported previously showed no serious adverse events requiring hospitalization or interventions. However, chest pain lasting days to weeks occurred in 53%–92% of patients, dysphagia in 20%–28% of patients lasting weeks to months, and transient fever in 12%–26% of patients.^{29–34} Adverse events in the European multicenter sham trial included chest pain in 69%, dysphagia in 28%, fever in 22%, bloating/flatulence in 3%, and

belching in 3% in the Enteryx arm versus 6%, 9%, 0%, 3%, and 0%, respectively, in the sham arm.³⁶

Case reports of adverse events. A number of serious adverse events following Enteryx treatment have been described in published case reports.^{38–40} Tintillier et al reported a case of esophageal abscess 4 days after injection of Enteryx.³⁸ Postprocedure, the patient developed a fever accompanied by abdominal discomfort. A barium esophagram revealed 2 “cavities” at the esophagogastric junction in communication with the esophageal lumen. At endoscopy, necrosis was noted in the lower esophagus with barium reflux from one of the cavities. The patient was treated with intravenous antibiotics but developed progressive renal failure and died suddenly during the fourth dialysis session. No autopsy was performed.

Noh et al reported a case of pneumomediastinum following Enteryx therapy.³⁹ One day after the procedure, the patient developed fever accompanied by pleuritic chest and abdominal pain resulting in hospitalization. Computed tomography revealed air in the mediastinum and bilateral pleural effusions, but an esophagram did not reveal an esophageal leak. The patient was treated successfully with antibiotics and discharged after 3 days.

Wong et al described 2 cases of mediastinal complications following Enteryx treatment.⁴⁰ The first patient developed severe chest pain within 24 hours and was hospitalized. Fever, bilateral pleural effusions, and a pericardial effusion developed. Treatment included intubation, antibiotics, chest tube drainage, and pericardial window and discharge after a 33-day hospitalization. At the time of surgery for creation of the pericardial window, exploration of the thorax revealed no evidence of migration of the Enteryx beyond the gastroesophageal junction but inflammation along the medial border of the esophagus with extension to the pericardium. The second case also involved the development of fever and chest and abdominal pain within 1 day of the procedure requiring hospitalization. Computed tomography of the chest revealed a pleural effusion and retention of Enteryx at the gastroesophageal junction. The patient was managed medically and discharged after 7 days.

FDA’s MAUDE database of adverse events. As of August 30, 2005, a search of the FDA’s MAUDE database of adverse events for Enteryx revealed 29 reports of serious adverse events between November 2003 and June 2005. There were 5 deaths, including one sudden death 3 days after an Enteryx procedure with no intervening symptoms believed not to be device related, one death from cardiovascular collapse following institution of dialysis for chronic renal failure 1 month or more after Enteryx treatment, 2 aortoenteric fistulas postprocedure with exsanguination (it is unclear if these are different cases or 2 reports of the same case), and one case of mediastinitis with sudden death. There were 16 hospitalizations for mediastinitis, pneumonitis, pleuritis, pericarditis, empyema, dysphagia, and chest pain, with some cases requiring pericardial windows or chest tube drainage. Polymer was found in one patient in the pleural space at the time of surgery. All cases appear to have resolved with medical and/or surgical therapy. The other cases were treated as outpatients, including 4 requiring endoscopy and dilation for dysphagia; one emergency department visit for chest pain, choking, and breathing problems; one patient with renal colic found to have embolization of Enteryx into the renal artery and aorta; and one patient with chest pain and shortness of breath. Enteryx was voluntarily withdrawn by the manufac-

Table 2. Systematic Review of Published Studies of Injectable Therapies for Treatment of GERD: Enteryx

Author (reference no.), year	Intervention	Study design	No. of subjects	Length of study (mo)	Outcome measurements	Results	Comments
Deviere et al, ³⁰ 2002	Enteryx	Cohort Single-center pilot study	15	6	Heartburn symptoms PPI use LESP (mean) (mm Hg)	87% of patients improved 100% → 27% 12.2 ± 0.9 → 16.7 ± 1.3	P = .001
Johnson et al, ²⁹ 2003	Enteryx	Cohort Multicenter	85	6	PPI use ≥50% PPI dose reduction GERD-HRQL (median) SF-36 physical (median) 24-hr pH (median) (% time pH < 4) LESP	100% → 26% 84% 24 → 4 44.8 → 50.8 9.5% → 7.0%	P < .001 P < .001 P < .001
Johnson et al, ³⁵ 2003	Enteryx	Cohort Multicenter	85	12	PPI use ≥50% PPI dose reduction GERD-HRQL (median) SF-36 physical (median) 24-hour pH (median) LESP	No difference 100% → 33% 76.5% Improved Improved Improved No difference	P < .001 P < .001 P = .002
Cohen et al, ³¹ 2005	Enteryx	Cohort Multicenter	64	24	PPI use ≥50% PPI dose reduction GERD-HRQL (median)	100% → 33% 72% Improved	Per protocol Per protocol These 64 patients are long-term follow-up from references 29 and 35. The 12- month results of 59 additional patients are not shown here.
Schumacher et al, ³² 2005	Enteryx	Cohort Multicenter	93	12	PPI use ≥50% PPI dose reduction GERD-HRQL (median) SF-36 physical (median) 24-hour pH (median) LESP	100% → 48% 60% Improved Improved No difference No difference	P < .0001 P < .0001
Deviere et al, ³⁶ 2005	Enteryx vs sham	Randomized controlled clinical trial Multicenter	64	3	≥50% reduction in PPI use Cessation of PPIs ≥50% improvement of GERD-HRQL SF-36 physical median improvement 24-hour pH (median)	78% vs 53% 68% vs 41% 67% vs 22% 14% vs 8%	P = .023 Enteryx vs sham P = .033 Enteryx vs sham P < .001 Enteryx vs sham P = .23
Lehman et al, ³⁷ 2005 ^a	Enteryx vs sham	Randomized controlled clinical trial Multicenter	62	3	GERD-HRQL success (score ≤11 or improvement of >9 points) 24-hour pH improvement pH success (pH ≤ 4 of ≤5% or ≥ 50% reduction in total time pH ≤4)	83% vs 54% 4.3% vs 0.5% 50% vs 23%	P < .05 Enteryx vs sham P < .05 Enteryx vs sham P < .05 Enteryx vs sham

NOTE. Primary outcomes, when stated, appear in bold.

LESP, lower esophageal sphincter pressure.

^aAbstract only.

Table 3. Systematic Review of Published Studies of Injectable Therapies for Treatment of GERD: Gatekeeper

Author (reference no.), year	Intervention	Study design	No. of subjects	Length of study (mo)	Outcome measurements	Results	Comments
Fockens et al, ⁴² 2004	Gatekeeper	Cohort Multicenter	68	6	GERD-HRQL (median) SF-36 physical (median) PPI use 24-hour pH (median) (% time pH < 4) Lower esophageal sphincter pressure (median) (mm Hg)	24.0 → 5 43.3 → 52.4 100% → 47% 9.1% → 6.1% 8.8 → 13.8	P < .05 P < .05 P < .01

NOTE. Primary outcome appears in bold.

turer based on the severity of these reports on September 22, 2005.

Gatekeeper

Technique. The Gatekeeper system includes the following components: a 16-mm overtube, a 2.4-mm prosthesis delivery system (1-mm-diameter needle, dilator, 2.4-mm-diameter sheath), a pushrod assembly, and the Gatekeeper prosthesis.⁴¹ The prosthesis consists of hydrogel mixed with tantalum for radio-opacity. The Gatekeeper procedure involves placement of 3–6 prostheses into the submucosal layer of the esophagus at the squamocolumnar junction under endoscopic guidance.⁴¹

Placement of the prosthesis is performed under direct endoscopic visualization.⁴¹ An initial endoscopy is performed, followed by placement of a guidewire (Savary type) and removal of the endoscope. The endoscope is then inserted into the Gatekeeper overtube, and the endoscope and overtube assembly are subsequently advanced under endoscopic visualization to the lower esophagus over the guidewire, such that markings on the overtube match the distance to the gastroesophageal junction. Suction is then applied via the endoscope, thereby pulling the esophageal wall into a shelf at the end of the overtube. An injection needle is then advanced using a dedicated “delivery sheath” of the overtube, and saline is injected into submucosal tissue captured through the slot present at the distal end of the overtube. A total of 3–6 mL of saline is injected to form a submucosal cushion, and the needle is then withdrawn. The prosthesis delivery system consisting of a 1-mm needle, dilator, and 2.4-mm sheath is then passed through the same channel and advanced into the saline-expanded submucosal space. The prosthesis is then placed into the sheath and advanced into the submucosal space using a push-rod assembly. The sheath is then withdrawn and the overtube rotated to deliver the next prosthesis at a different site. Maximal expansion of the prosthesis usually occurs within 24 hours, creating folds in the esophageal wall. The mean duration of this technique reported in the European multicenter trial was 26.6 minutes, during which an average of 4.3 prostheses were delivered to each patient.⁴² This device was believed to be reversible by “cutting” the mucosa over the prosthesis and mechanically removing the implant.

Mechanism of action. The mechanism of action for Gatekeeper has been studied in both animals and humans. Using a porcine model of LES weakening caused by injection of botulinum toxin, Easter et al found that placement of the

prosthesis resulted in an increase in LES pressure and gastric yield pressure in response to air insufflation into the stomach in the treated animals when compared with the untreated animals after 2 weeks, but no differences were noted at 2 and 6 months.⁴³ Pathologic evaluation of the esophagus in this porcine model revealed minimal fibrosis in the submucosa surrounding each prosthesis.⁴³ Novel work by Cicala et al in 9 patients with GERD showed that placement of hydrogel prosthesis resulted in a change in the intraesophageal distribution of acid 6 months after therapy.⁴⁴ These investigators found that while LES pressure and distal acid exposure time did not change in this small group of patients, the proximal extent of acid reflux, as measured by multichannel ambulatory pH monitoring, decreased significantly and was in the range of healthy subjects. These findings suggest that this technique may exert its effect by decreasing the aperture through which refluxate may flow, thus resulting in less proximal migration of the refluxate.⁴⁵

Clinical outcomes. Cohort studies. Fockens et al have reported the combined results from 2 European multicenter, prospective, open-label trials of Gatekeeper therapy in 68 patients with PPI-responsive GERD (Table 3).⁴² All patients had responded to PPI therapy before the procedure, and all had abnormal esophageal acid exposure by pH monitoring. The primary efficacy outcome in this trial was improvement in the GERD-HRQL score at 30 days. Secondary outcome measures were assessed at 3 and 6 months postprocedure and included improvement in GERD-HRQL and SF-36 scores, esophageal pH, and manometry as well as reduction in drug use. Seventy-seven procedures were performed in 68 patients at 9 centers over a 2-year period. Ten patients had a second procedure because of initial failure of the first procedure to control symptoms. On average, 4.3 prostheses were inserted per patient. It is important to note that follow-up data were incomplete for most outcomes and only per-protocol analysis was provided.

For the primary outcome at 1-month posttreatment, GERD-HRQL scores improved from a median of 24.0 (IQR, 16.5–30.0) at baseline to 8 (IQR, 2.0–14.0) ($P < .05$). For secondary outcomes, GERD-HRQL scores and the physical component of the SF-36 score remained improved at 3 and 6 months compared with baseline, but the mental subscale score of the SF-36 was not improved. Data on medication use were not collected systematically at all sites, and the data available were not considered reliable. Median acid exposure time was not improved at 3 months but was improved at 6 months (baseline, 9.1% [IQR,

6.0–14.3]; 3 months, 9.1% [IQR, 6.1–14.4]; 6 months, 6.1% [IQR, 2.9–10.2]) ($P < .05$). However, these data were only available from 45 of the 67 treated patients. Median LES pressure increased from 8.8 mm Hg (IQR, 6.0–13.8) at baseline to 10.5 mm Hg (IQR, 8.3–7.8) at 3 months and 13.8 mm Hg (IQR, 9.3–19.5) at 6 months ($P < .01$ for 6-month data) in 42 patients in whom it was measured.

Clinical trials. Fockens et al recently reported that enrollment of the US and European multicenter, sham-controlled trial of Gatekeeper has been completed.⁴⁶ However, no data related to this trial have been reported to date. Given the suspension of further development of this device and no plans to apply for FDA approval, further studies with this device are not expected.

Safety

Clinical trial adverse events. In the only trial reported to date with this therapy, approximately 15% of subjects reported an adverse event or complication at 1 month.⁴² Two patients required hospital admission (3%): one for intractable nausea requiring prostheses removal and one for a pharyngeal perforation. No deaths have been reported.

Case reports of adverse events. No case reports of adverse events or complications have been reported in the medical literature, although no use of the device outside of clinical trials has occurred in the United States because it has not yet been cleared or approved for use by the FDA.

FDA's MAUDE database of adverse events. No reports of adverse events have been reported to the FDA's MAUDE database, although no use of the device outside of clinical trials has occurred in the United States because it has not yet been cleared or approved for use by the FDA.

Endoscopic Suturing

The concept of endoscopic suturing was first described by Swain and Mills in 1986.⁴⁷ Subsequently, knot tying by endoscopy was found to be feasible.⁴⁸ Currently, there are 2 basic techniques designed to place sutures or "staples" at the cardia during upper endoscopy: superficial, mainly submucosal stitching devices and deep transmural plicating devices. Conceptually, both allow for the creation of pleats or plications of tissue just beneath the gastroesophageal junction. Three suturing devices have been described in humans: EndoCinch (Bard Endoscopic Technologies, Billerica, MA), Endoscopic Suturing Device (Wilson-Cook Medical Inc, Winston-Salem, NC), and NDO Plicator (NDO Surgical Inc, Mansfield, MA). Only the Bard and NDO devices have become commercially available in the United States. The Wilson-Cook Endoscopic Suturing Device was withdrawn from the marketplace in 2004. A fourth device, the Antireflux Device (Syntheon/ID, Miami, FL), is currently undergoing evaluation.

EndoCinch

Technique. The Bard EndoCinch device consists of several components, including a 9×32 -mm capsule suturing system, overtube, needle pusher, knot pusher, and suture cutter.⁴⁹ The technique requires 2 endoscopes. The sewing capsule is attached to the distal tip of a standard upper endoscope. This capsule has a hollow cavity into which a fold of surface tissue can be suctioned. A handle, which is mounted on the biopsy

port of a standard endoscope, drives the needle that runs through the biopsy channel to create a stitch. The handle controls the advance of the hollow-core needle, into which a 3.0 monofilament suture is back-loaded. A metal "t-tag" attached to the suture is captured into a chamber in the front of the mounted capsule after being driven forward by a stiff wire pushed through the hollow needle by the handle. Because the endoscope used for suturing has the sewing capsule mounted on its distal end, a second endoscope is used to fasten the ends of the suture material together after 2 stitches have been created with the sewing endoscope, as discussed in the following text.

The original device and technique required the use of a knot pusher and a guillotine catheter to perform extracorporeal knot tying and intragastric knot cutting. Revised versions now include a catheter with a small ring and peg to cinch the 2 ends of the suture while simultaneously cutting the suture material. This technical advance eliminated the need for hand-tying knots and substantially reduced the time needed to perform each plication (set of 2 stitches cinched together).⁵⁰

After standard upper endoscopy to review the anatomy and define landmarks, a guidewire is advanced through the endoscope into the distal stomach and the endoscope is removed while keeping the guidewire in position. An overtube is then loaded onto a 14-mm or 15-mm Savary-type dilator and advanced into position over the guidewire. The dilator and wire are subsequently removed from the patient, and the overtube remains as a conduit for subsequent instrument passage and exchanges. The endoscope with mounted sewing capsule is then placed into the overtube and advanced down the esophagus to the level of the squamocolumnar junction. The target for plication is usually within 1 cm of the squamocolumnar junction for the circumferential pattern of plication or within 3 cm for the linear or helical patterns.⁵⁰

Once the target area is identified for apposition of the sewing capsule to the gastric surface, suction is applied to the capsule via its accessory tubing, thereby drawing the adjacent tissue into the capsule chamber. After waiting 10 seconds, the handle is depressed, forcing complete penetration of a hollow needle loaded with a pledget attached suture ("t-tag") and needle through the suctioned tissue. Subsequent withdrawal of the handle leaves the tag captured in the front chamber of the sewing capsule. Release of suction and forward advancement of the endoscope releases the stitched tissue from the capsule lumen, and the endoscope is then withdrawn through the overtube. The same metal suture tag is reloaded into the hollow-core needle to place a second stitch at a location within 1–1.5 cm of the initial stitch. The second stitch is then placed in a similar manner and the endoscope subsequently removed. The suture ends are now extracorporeal.

The other endoscope is now needed to finish the plication. In the original technique, half-hitches were hand-tied and pushed to the surface of the stomach with a knot pusher.⁵⁰ Each subsequent half-hitch (5–6 total) required entry and removal of the endoscope via the overtube, and the final step involved removal of the pushing catheter and insertion of the guillotine catheter into the biopsy channel of the endoscope. After back-threading the suture ends through this cutting catheter and using the suture as a guide to the gastric surface, a quick back-tug on the catheter would cut the ends of the knot at the stomach surface. The total time to create one plication with this original method was approximately 15 minutes.⁵⁰ A new cinch-

ing/cutting catheter reduces the time to create a plication to about 5 minutes. The repetitive hand-tying steps and exchange of pushing and cutting catheters are replaced by the passage of a single cinching catheter back-loaded onto the suture material and guided to the gastric surface, where the cinching tag is placed and sutures are cut in one action.⁵⁰

Sedation required for this technique varies. For example, Chen et al reported that 59% of patients in the US multicenter trial received conscious (moderate) sedation, 27% had monitored (propofol) sedation, and 14% required general anesthesia.⁵¹ Limited information is available on procedure time. Median procedure time was 45 minutes (range, 25–100 minutes) in one study.⁵² Mean procedure times of 33 and 68 minutes were reported in 2 other studies.^{53,54}

Mechanism of action. Initial pilot work of endoscopic gastroplasty was performed in a canine model.⁵⁵ Esophageal manometry performed before and immediately after the procedures in 10 beagles demonstrated a significant increase in median LES pressure from 4.6 to 13.3 mm Hg ($P = .008$) and gastric yield pressure after air insufflation from 10 to 19 mm Hg ($P = .007$). However, repeated measures performed in one animal over 60 days showed a progressive decline in both LES and gastric yield pressures over time. A subsequent short-term study in a porcine model examined the effect of a gastroplication configuration of 2 stitches just below the cardioesophageal junction and 2 additional sutures 1 cm below that level on LES pressure and acid exposure.⁵⁶ One week after gastroplication, there was a modest increase in median LES pressure from 3 to 6 mm Hg ($P < .05$) and a decline in median acid exposure time from 9.3% to 0.2% ($P < .05$). Other animal studies have examined the optimal suture configuration.⁵⁷ Baboons were treated with either 3 sutures in a linear arrangement placed 1 cm apart on the lesser curvature with the most proximal suture just distal to the gastroesophageal junction or with 3 sutures at 120° intervals in a circular arrangement just distal to the gastroesophageal junction. Mean LES pressure was not increased with either configuration immediately postprocedure but was increased modestly at 6 months in the linear configuration only (5.39 to 7.64 mm Hg; $P < .008$). Gastric yield pressures were no different from that of control animals at 6 months for either configuration. Furthermore, suture retention at 6 months was highly variable; anywhere from 12% to 90% of sutures were retained at that time.⁵⁷ Histologic evaluation of the gastroplasty site in these animals demonstrated chronic inflammation of the proximal stomach. Pathologic evaluation of 23 suture sites was possible: 3 penetrated into the submucosa, 18 into the superficial muscularis, and 2 into the deep muscularis layers.

A number of studies have also examined the mechanism of action of gastroplication in humans. The most comprehensive study of the mechanism of action of gastroplication was performed by Tam et al.⁵⁸ Physiologic studies were performed at baseline and again at 6 months in 15 patients who underwent gastroplication using a configuration of 2 circumferentially placed plications 1 cm below the gastroesophageal junction. Gastroplication resulted in a significant increase in mean postprandial LES pressure from 4.3 ± 2.2 mm Hg to 6.2 ± 2.1 mm Hg ($P < .05$) without changing fasting basal LES pressure. Median transient LES relaxation frequency decreased from 2.7 per hour (IQR, 1.5–5.7) to 1.7 per hour (IQR, 0.5–3.3) ($P < .05$). Twenty-four-hour acid exposure time decreased significantly as

well at both 6 months and 12 months after therapy but normalized in only 27% of patients at 6 months. These findings were noted despite the fact that only one plication was visible in 6 of 15 patients at 6 months. Gastroplication has also been implicated in a decrease in acid sensitivity.⁵⁹ In a pilot study of 6 patients, all of whom had a positive Bernstein test before gastroplication, 4 patients no longer had any acid sensitivity 4 weeks after the gastroplication.

Endosonography after gastroplication has shown eccentric thickening of the smooth muscle layer adjacent to suture site in both humans and a porcine model.⁶⁰ Histologic examination from the porcine model indicated that the muscle thickening was limited to the circular muscle layer at the suture site.

Clinical outcomes. Cohort studies. The initial American multicenter trial of gastroplication involved 64 patients from 8 sites with symptomatic GERD, with or without erosive esophagitis (Savary–Miller grade 0–2), dependent on continued use of antisecretory drugs for symptom control, and documented acid reflux by pH monitoring.⁵⁴ For the purposes of this trial, treatment success was defined as a decrease in the heartburn severity score of 50%, using a nonvalidated scoring system, in addition to a reduction in the use of antireflux medications to <4 doses per month at 6 months. Patients were randomized to either linear or circumferential plication configurations. A total of 79 gastroplications were performed on the 64 patients, 52% linear and 48% circumferential, which included re-treatment in 15 individuals. Two plications were placed in 46 patients, whereas 3 plications were placed in 18 patients. For the study hypothesis (ie, decrease in heartburn severity score of 50%), success was achieved in 46.9% (95% CI, 34.7%–59.1%) by intent-to-treat analysis and 58.8% (95% CI, 45.3%–72.2%) by per-protocol analysis. For the other study hypothesis, PPIs were required by 86% at baseline; at 6-month follow-up, 62% of individuals took <4 doses of medication monthly. For the 51 patients in whom 6-month follow-up was available, heartburn frequency and severity as well as regurgitation all decreased significantly. SF-36 scores improved at 6 months in 2 of the subscales: social functioning and bodily pain. Mean acid exposure time decreased from 9.63% at baseline to 8.5% ($P < .011$) at 6 months in the 29 patients with follow-up. No changes were noted in LES pressure or grade of esophagitis, however. There was no difference in any outcomes related to linear versus circumferential placement of the stitches.

Short-term results are also available from a single-center study of 53 patients from Germany with symptomatic GERD, with or without erosive esophagitis, dependent on PPIs with at least partial symptom control, and documented acid reflux by pH monitoring.⁶¹ For the purposes of this trial, treatment success was defined as a decrease in the heartburn severity score of an undefined magnitude using a nonvalidated scoring system, patient satisfaction with the procedure, or reduction in antisecretory medication use by 50%. Each patient received a minimum of 2 plications, but the configuration was not given. Thirty-four of the 53 patients (64%) were defined as responders at 3 months. A decrease in PPI use by at least 50% was achieved in 39 of 53 patients (73.6%), and the median heartburn severity score improved from 70.1 (IQR, 49.9–83.5) to 15.4 (IQR, 3.5–40.3) at 3 months following intervention.

Schieffe et al subsequently increased the size of the Leipzig cohort described previously to 70 patients and extended follow-up to 18 months.⁶² Using the same combined end point as

described previously, the response rate at 18 months had declined to only 20%. Overall, there continued to be an improvement in the heartburn symptom score, which decreased from a median of 58.2 (IQR, 41.0–76.3) at baseline to 36.8 (IQR, 14.4–46.1) ($P = .001$) at 18 months. Only 6% of patients were completely off PPI therapy. In terms of objective measures, there was no significant change in esophagitis severity or LES pressure, although median LES length increased from 3.0 cm (IQR, 2.0–3.5) to 3.2 cm (IQR, 2.0–4.0) ($P < .05$). In the 54 patients who agreed to follow-up pH testing at 12 months, no significant reduction in distal esophageal acid exposure from baseline was detected, although 16 of 54 subjects (28%) normalized their pH studies. At 18 months following the EndoCinch procedure, the investigators reported finding all sutures in situ in only 12 of 70 subjects (17%), while no remaining sutures could be detected in 18 of 70 (26%).

One-year follow-up is available from a single-center Irish study of 22 patients who underwent the EndoCinch procedure consisting of 2 longitudinally placed plications at 1 and 2 cm below the squamocolumnar junction.⁵² The primary end point was not stated, and multiple outcomes were examined. The mean heartburn symptom score, as assessed by a nonvalidated questionnaire, was reduced from 19.22 at baseline to 7.5 at 12 months ($P < .0001$). The regurgitation score was reduced from a mean of 2.27 at baseline to 0.86 at 12 months ($P < .001$). QOLRAD quality-of-life assessments showed significant improvement compared with baseline reporting in all parameters. PPI use decreased from 100% at baseline to 36% at 12 months postprocedure. Acid exposure time and LES pressure were no different at 3 months postprocedure. Endoscopic assessment of the plications at 3 months found that all of the plications were intact in 17 patients (77%), one of the plications had vanished in 3 patients, and both plications had vanished in 2 patients.

One-year data are available from 36 PPI-dependent patients with GERD with abnormal 24-hour pH studies from a single center in Germany.⁶³ The technique here involved 2 or 3 gastric plications, and re-treatment was permitted in 5 patients. At 1 year, only 10% of the sutures were in their original position; 74% of the sutures were totally lost, and 16% had become loose. Heartburn symptoms were improved in 39% and were completely eliminated in 14%, although the metric used to assess symptoms was not given. PPI use was completely eliminated in 20% of patients, and esophageal pH studies improved in 66% of patients and normalized in 14% at 1 year.

Two-year follow-up data are now available for 85 patients from a US multicenter study.⁵¹ The study group here was different from other studies because patients with abnormalities such as hiatal hernia >2 cm, Barrett's esophagus, and failed prior antireflux surgery were allowed in addition to the usual entry criteria of chronic GERD symptoms responsive to antisecretory therapy and abnormal esophageal acid exposure. Patients were treated with 1–3 plications placed in either a linear or circumferential configuration. The primary end points were improvement in GERD symptom scores and elimination or $\geq 50\%$ reduction of PPI use. At 2-year follow-up, the median heartburn severity score decreased from 72 (IQR, 48–90) at baseline to 16 (IQR, 3.5–53) ($P < .0001$). Similarly, median regurgitation symptom score decreased from 2 (IQR, 1–3) to 1 (IQR, 0–1) ($P < .0001$). There were no or only occasional symptoms of heartburn or regurgitation in 51% and 77% of

patients, respectively, at 2 years. PPIs were completely stopped in 41% at 2 years.

Controlled clinical trials. Three sham-controlled clinical trials have been reported in abstract form only. The first study, by Rothstein et al, was a single institution study of 34 patients randomized to either EndoCinch gastroplication with 4 circumferential plications or sham plication.⁶⁴ The sham procedure in this study involved preparing the patients as for the “real” intervention, with comparable use of intravenous conscious sedation, passage and placement of an overtube, and exchange of endoscopes in a pattern to mimic the true EndoCinch procedure. Neither the patients nor the study coordinator were aware of the assignment, whereas the endoscopist and in-room assistants were. At 3-month follow-up, there were significant differences in heartburn frequency ($P = .049$), acid exposure time ($P = .013$), and discontinuation of daily acid suppressive medications between the 2 groups ($P = .012$). Acid exposure time normalized in only 2 of the treated subjects (12.5%). However, there were no differences in heartburn severity, regurgitation, LES pressure, quality-of-life scores, or SF-36 scores between the 2 groups.

A second single-center, sham-controlled study examined 47 patients with daily GERD symptoms, an abnormal 24-hour pH study, and hiatal hernias ≤ 3 cm.⁶⁵ Two or 3 longitudinal plications were placed in those randomized to active treatment. Relapse was defined quite differently in this study: PPI required for heartburn relief, more than 1 day of severe heartburn, 2 consecutive days with moderate symptoms, or 3 consecutive days with mild symptoms. Gastroplication was performed in 22 subjects, whereas 25 received a sham procedure. At 1 year, 19 of 22 gastroplication-treated patients and all 25 sham-treated patients experienced a relapse according to the criteria listed previously. Most of the relapses occurred within 1 month. Furthermore, there were no differences in esophageal acid exposure, medication use, or quality-of-life scores between the 2 groups at the conclusion of the study.

In contrast, preliminary data from a third randomized, sham-controlled trial of endoscopic gastroplication did show some improvements at 3 months.⁶⁶ This was a single-center study of 45 subjects with daily GERD symptoms, abnormal 24-hour pH monitoring, hiatal hernia ≤ 3 cm, and LA grade B esophagitis or less. The 15 patients in the treatment group received 3 plications (configuration not described), and these patients were compared with 17 in a sham group and 13 in an observation-alone group. At 3 months, the gastroplication group had a significant decrease from baseline in both heartburn severity score and PPI use but no difference in regurgitation score, quality-of-life measures, or acid exposure time compared with the control groups.

Clearly, these 3 clinical trials, albeit in abstract form, highlight the striking sham response rate and the need for randomized controlled trials of sufficient size to understand the true effectiveness of the endoscopic therapies for GERD. The outcomes at 3 months may be sufficient to determine a difference of the sham treatment from real procedure, while the longer-term follow-up at 1 year may reflect the inability of gastric suturing to be a durable therapy for GERD.

Use in alternate populations. Until recently, gastroplication was described only in patients with reflux characteristics as described previously, that is, symptomatic patients with abnormal esophageal acid exposure, low-grade esophagitis,

small hiatal hernia, no prior antireflux surgery, and no Barrett's esophagus. Recent observational studies have examined the impact of EndoCinch in other GERD patient groups.

A single-center study from Belgium examined the effect of endoscopic gastropliation in 20 patients refractory to high-dose PPI therapy.⁵³ All of these patients had abnormal esophageal acid exposure on pH monitoring. Primary and secondary end points were not defined. However, multiple outcomes were measured, including symptoms (combination of 14 different typical and atypical symptoms), use of antisecretory medications, and pH monitoring. Three plications were performed in each subject: 2 circumferential plications just below the gastroesophageal junction approximately 120° apart and a third plication 1 cm beneath the gastroesophageal junction. Of note, 11 patients were re-treated for persistent symptoms following the initial intervention. Mean symptom scores improved from 11.6 ± 1.3 at baseline to 7.1 ± 1.0 at 1 year ($P < .05$). Only 6 individuals (30%) were completely off PPIs at 1 year. Of the 4 patients with endoscopic esophagitis at baseline, 3 patients had the same grade at 12 months and one patient had complete healing. At 1 year, esophageal acid exposure improved from 17% ± 2.5% to 9.1% ± 1.4% ($P < .01$), but normalization of acid exposure was only accomplished in 6 patients (30%).

Liu et al examined gastropliation in a mixed group of 25 patients with classic symptoms of GERD that included 4 patients with Barrett's esophagus, 3 patients with hiatal hernias >3 cm, and 4 patients with prior antireflux surgery.⁶⁷ Importantly, 24-hour acid exposure was entirely normal in 9 patients and only borderline abnormal by DeMeester score in the remaining 16 patients. Gastropliation was performed 2 cm below the gastroesophageal junction with either 2 or 3 plications at the discretion of the endoscopist. The primary end points were improvement in heartburn symptom score and regurgitation frequency by a nonvalidated questionnaire. The secondary end point was medication use. Follow-up in this study varied from 6 to 21 months and was not standardized as per prior studies. In the 24 patients with available follow-up, heartburn scores decreased from 48 to 17 ($P < .001$) and regurgitation scores decreased from 1.8 to 0.7 ($P < .01$). PPI use decreased from 11.5 ± 4.2 doses per week to 5.3 ± 3.6 doses per week at an average of 12 months of follow-up, with 50% of patients completely off PPIs. Endoscopic follow-up in 10 patients revealed intact plications in 5 patients and loose or missing plications in the other 5 patients.

Gastropliation has also been studied in a limited number of patients after failed antireflux surgery and in children.^{68,69}

Comparison of endoscopic suturing with laparoscopic Nissen fundoplication. Several studies have compared endoscopic gastropliation with antireflux surgery. A case-control study examined symptoms by a validated questionnaire (GERD-HRQL) and patient satisfaction at 3 months postprocedure in 54 patients and found no difference in median postprocedure symptom scores between the 2 groups.⁷⁰ Patient satisfaction was higher in the surgery group (96%) compared with the gastropliation group (78%) ($P < .01$). However, the relevance of 6-week outcomes, given the long-term data described previously, is questionable. Another study of 87 consecutive patients referred from a single gastroenterologist for either gastropliation or laparoscopic antireflux surgery revealed less medication use in the surgery group at a mean follow-up of 8 months.⁷¹

Results of a systematic review of published studies of EndoCinch therapy for treatment of GERD are summarized in Table 4.

Safety. Clinical adverse events. A review of the clinical trials reported previously shows rare adverse events requiring hospitalization or interventions. One patient with fever and pain was found to have mediastinal air.⁵⁴ This was treated successfully with 3 days of intravenous antibiotics without surgery. There have been rare reports of bleeding that required transfusion or endoscopic intervention.^{51,52} There has also been one report of aspiration pneumonia requiring intravenous antibiotics.⁶⁷ Most events are transient. Adverse events in the initial US multicenter trial included pharyngitis in 31%, chest pain in 16%, vomiting in 14%, abdominal pain in 14%, hypoxia in 6%, bleeding in 3%, a mucosal tear from the overtube in 3%, and suture perforation in 2%.⁵⁴ Other studies describe pharyngitis/sore throat in 27%–57% and dysphagia in 1%–8%.^{51,52,58,63,67,71}

Case report of adverse event. There is one case report of a perforation at the gastroesophageal junction after gastropliation.⁷² This 29-year-old woman developed an acute abdomen several hours after placement of a single plication. Radiologic evaluation revealed extravasation of contrast in the intra-abdominal part of the esophagus. The patient was treated successfully with laparoscopic repair of the perforation in conjunction with a Nissen fundoplication. The patient's subsequent clinical course was unremarkable.

FDA's MAUDE database of adverse events. As of August 30, 2005, a search of the FDA's MAUDE database of adverse events for the EndoCinch revealed one report of a device malfunction and one report of an adverse event. The adverse event was a postprocedure bleed requiring blood transfusion and a 2-day hospital stay. At the time of the procedure, a hematoma was noted at the plication site.

Endoscopic Suturing Device

The Endoscopic Suturing Device was examined in one study.⁷³ Three-month results in 20 patients showed retention of only 12% of all plications with an accompanying poor clinical response. This device is no longer being marketed.

Endoscopic Full-Thickness Plication

Technique. The full-thickness Endoscopic Plication System passes 2 needles through tissue near the gastroesophageal junction to create a full-thickness serosa-to-serosa apposition of the proximal stomach.^{74,75} The first-generation plication system includes a reusable instrument with 2 working channels, one for a tissue retractor and one for passage of an endoscope, a single-use suture-based implant, an endoscopic tissue retractor, and a standard overtube. The second-generation system can be passed without an overtube and still accepts a small pediatric endoscope for viewing the operative field. The NDO instrument is reusable after reprocessing and deploys a single-use, preformed suture-based implant.

The NDO instrument has controls on the instrument handle that permit retroflexion of the distal end, opening and closing of the instrument arms, and placement of the implant. There are 2 instrument channels: one for insertion of the endoscope and one for insertion of a tissue retractor. The tissue retractor is a stainless steel corkscrew-shaped device designed to engage tissue from the area to be plicated. The implant, which consists of pretied suture material with polytetrafluoroethylene bolsters,

is loaded onto the arms of the instrument. The newer version of the system features single-use cartridges that are mounted onto the arms of the instrument.

Endoscopic plication is performed after an initial diagnostic endoscopy to view the landmarks. In the initial iteration of this device, a Savary guidewire is passed through the endoscope and an overtube is then advanced into the stomach over a Savary-type dilator.⁷⁶ The guidewire and dilator are subsequently removed, and the endoscopic plication instrument and endoscope assembly are passed into the stomach. The overtube is then retracted to a position just proximal to the gastroesophageal junction. The newer version of the instrument may be passed directly over a guidewire without the need for an overtube. The endoscope, passed through the hollow center of the NDO instrument, is subsequently advanced into the stomach and retroflexed to allow visualization, retroflexion, and proper positioning of the NDO instrument. After identifying a target area for plication, the instrument arms are widely opened, and the tissue retractor is advanced and inserted deeply in the target tissue, generally within 1 cm distal to the gastroesophageal junction. This catheter is designed to screw into tissue and catch the muscular structures at the gastroesophageal junction. There is tenting of the surface mucosa of the target tissue as the deeper layers are engaged by the tissue retractor. The full thickness of the gastric wall captured with the retractor is pulled toward the apex of the opened instrument arms. The instrument arms are then closed together and a pretied monofilament suture implant is deployed to fix the tissue in apposition just beneath the gastroesophageal junction. The instrument arms are then opened to release the plicated tissue; the tissue retraction device is disengaged from the gastric wall and withdrawn back into its channel. The instrument arms are subsequently closed again to allow removal of the NDO instrument in the straightened position. In initial trial results described in the following text, only one plication was performed. Average procedure time in the multicenter cohort study was 17.2 minutes.⁷⁶

Mechanism of action. Animal studies have confirmed that serosa-to-serosa tissue apposition can be attained without involvement of adjoining tissue.⁷⁵ The mechanism of action and optimal placement of full-thickness plication were studied in an ex vivo porcine stomach model in which ex vivo plications were performed in 1 of 4 quadrants within 1 cm of the gastroesophageal junction.⁷⁵ Gastric yield pressures increased approximately 8-fold.

Clinical outcomes. Pilot study. The initial pilot human study of the NDO plicator was conducted on 6 patients with GERD in India.⁷⁷ These individuals had symptomatic reflux partially responsive to acid suppression therapy and abnormal esophageal acid exposure time. The primary end points included safety, feasibility, and durability of the technique. Secondary end points included effect of treatment on symptom scores and quality of life. Plication was performed successfully in 6 of the 7 patients. One patient underwent Nissen fundoplication 6 months after successful plication due to persistence of symptoms. All 6 patients had an intact plication at 6 months. GERD-HRQL scores improved in all patients, and mean SF-36 quality-of-life scores also improved at 12 months.

Cohort study. Pleskow et al reported the 6-month results of a North American multicenter, open-label trial in 2004.⁷⁶ The primary end point of this study was the effect of plication on GERD symptoms as measured by the GERD-

HRQL at 3 months, with a goal of obtaining $\geq 50\%$ improvement. Secondary outcomes included reduction in the use of antisecretory drugs, quality of life using the SF-36, esophageal acid exposure, and esophageal manometry with corrections made for multiple comparisons. Sixty-four patients with symptomatic GERD and abnormal acid exposure who were responsive to antisecretory therapy were enrolled at 7 sites. Excluded from enrollment were individuals with a hiatal hernia >2 cm, high-grade esophagitis (Savary-Miller grade 3 or greater), and Barrett's esophagus. Follow-up assessment was performed at 1, 3, and 6 months after treatment.

GERD-HRQL scores improved from a mean of 20.2 at baseline when off all therapy to 7.9 ($P = .018$). By intent-to-treat analysis, 64% of patients achieved a reduction of $>50\%$ in GERD-HRQL scores. These findings were maintained at 6-month follow-up as well. For the secondary outcomes, SF-36 scores improved significantly; 65% of patients were able to discontinue all antisecretory medications at 6 months, and 74% completely discontinued PPI therapy. Esophageal acid exposure improved from a median of 10% (IQR, 6.4–15.6) to 8% (IQR, 4.5–13.1) and normalized in 30% of patients at 6 months. LES pressure was unchanged. Subsequently, 12-month data from this same cohort became available.⁷⁸ Mean GERD-HRQL scores at 12 months remained improved from 20.1 at baseline off all therapy to 9.8 ($P = .018$). By intent-to-treat analysis, 55% of patients achieved a reduction of $>50\%$ in GERD-HRQL scores and 68% of patients remained off PPIs.

Clinical trials. No sham-controlled study has yet been published, although a multicenter, international, randomized, controlled trial of 159 subjects has recently been completed.

Results of a systematic review of published studies of NDO plication therapy for treatment of GERD are summarized in Table 5.

Safety

Clinical adverse events. In the multicenter clinical trial, adverse events included pharyngitis (41%), abdominal pain (20%), chest pain (17%), dysphagia (11%), and nausea (6%).⁷⁶ However, serious adverse events were reported in 6 subjects. Two patients developed dyspnea during the procedure, which required endotracheal intubation accompanied by propofol to avoid the airway compromise caused by the esophageal overtube. One patient had a pneumothorax, which was treated conservatively. Two patients developed a pneumoperitoneum; one underwent a laparoscopic exploration, which did not show a perforation, and the other had an obvious gastric tear repaired endoscopically with endoclips and managed conservatively with antibiotics. The final adverse event was a mucosal abrasion in the fundus.

FDA's MAUDE database of adverse events. As of August 30, 2005, a search of the FDA's MAUDE database of adverse events for the NDO plicator showed 2 reports of serious adverse events in 2005. One patient developed an esophageal perforation after unsuccessful deployment of implant, necessitating thoracotomy to repair a full-thickness esophageal tear. A second patient reported abdominal pain and leukocytosis, which resolved after a brief hospitalization.

Syntheon Antireflux Device

This full-thickness plicator places a single titanium implant into the cardia of the stomach, creating a serosa-to-

Table 4. Systematic Review of Published Studies of Gastric Plication for the Treatment of GERD: EndoCinch

Author (reference no.), year	Intervention	Study design	No. of subjects	Length of study (mo)	Outcome measurements	Results	Comments
Filipi et al, ⁵⁴ 2001	EndoCinch	Cohort Single center	64	6	Decrease in heartburn severity score by 50%	46.9%	Nonvalidated questionnaire
					Heartburn score (mean)	62.7 ± 18.6 → 17.0 ± 20.2	P = .0001 Nonvalidated questionnaire
					SF-36	Improved in 2 subscales	
					Medication use	100% → 38% with > 4 doses/month	
					24-hr pH (mean) (% time pH < 4)	9.63 ± 6.8 → 8.50 ± 8.3	P = .011 6-month pH data in 29 patients
					LESP	No change	
					Mean esophagitis grade	No change	
Mahmood et al, ⁵² 2003	EndoCinch	Cohort Single center	26	12	Heartburn symptom score (mean)	19.22 → 7.5	P < .0001 Heartburn score assessed by nonvalidated instrument and standard deviation not provided
					Regurgitation score (mean)	2.27 → 0.86	P < .0001 Regurgitation score assessed by nonvalidated instrument and standard deviation not provided
					QOLRAD	Improved	
					PPI use	100% → 36%	P = .01
					24-hour pH at 3 months	No change	
					LES	No change	
Schiefke et al, ⁶¹ 2004	EndoCinch	Cohort Single center	53	3	Heartburn score (median)	70.1 → 15.4	Heartburn score assessed by nonvalidated instrument
					50% decrease in PPI use	74%	No statistical information given for response variables
Liu et al, ⁶⁷ 2004	EndoCinch	Cohort Single center	25	6–21 (mean, 12)	Heartburn symptom score	48 → 17	P < .001
					Regurgitation frequency score	1.8 → 0.7	P < .01
					Cessation of PPIs	50%	Heartburn and regurgitation frequency score assessed by nonvalidated instruments
							Mixed population included surgical failures, Barrett's esophagus, and larger hiatal hernias
Rothstein et al, ⁶⁴ 2004 ^a	EndoCinch vs sham	Randomized controlled clinical trial	34	3	Heartburn frequency	Plication superior to sham	P = .049
					Heartburn severity	No difference	
					Regurgitation	No difference	
					Quality of life	No difference	
					SF-36	No difference	
					Daily medication use	Plication superior to sham	P = .012
					24-hour pH	Plication superior to sham	P = .013
					LESP	No difference	
Arts et al, ⁵³ 2005	EndoCinch	Cohort Single center	20	12	Symptom score (mean)	11.6 ± 1.3 → 7.1 ± 1.0	P < .05
					Cessation of PPIs	30%	
					24-hour pH (mean) (% time pH < 4)	17.0 ± 2.5 → 9.1 ± 1.4%	P < .05 pH normalized in 30%
					Erosive esophagitis	3/4 no change	Symptom score assessed by nonvalidated instrument

Table 4. Continued

Author (reference no.), year	Intervention	Study design	No. of subjects	Length of study (mo)	Outcome measurements	Results	Comments
Abou-Rebyeh et al, ⁶³ 2005	EndoCinch	Cohort Single center	38	12	Heartburn symptoms improved Eliminate PPIs Normalize pH LESP	39% 20% 14% No change	GERD symptom assessment tool not given
Chen et al, ⁵⁴ 2005	EndoCinch	Cohort Multicenter	85	24	Heartburn symptom score (median) Regurgitation symptom score (median) PPI use (elimination or reduction)	72 → 16 2 → 1 69%	P < .0001 P < .0001 Mixed population with Barrett's esophagus, hiatal hernia > 2 cm, Grade 3 esophagitis (Savary–Miller), and prior antireflux surgery allowed
Park et al, ⁶⁸ 2005 ^a	EndoCinch vs sham	Randomized controlled clinical trial	47	12	Symptomatic relapse	No difference	Relapse defined: PPI required for heartburn relief, >1 day of severe heartburn, 2 consecutive days with moderate symptoms, or 3 consecutive days with mild symptoms.
Schwartz et al, ⁶⁶ 2005	EndoCinch vs sham vs observation	Randomized controlled clinical trial	45	3	Quality of life 24-hour pH Drug use Heartburn score	No difference No difference No difference Plication superior to sham or observation	P = .01
					Regurgitation score Quality of life PPI use	No difference No difference Plication superior to sham or observation	P < .001
					24-hour pH Manometry	No difference No difference	

NOTE. Primary outcomes, when stated, appear in bold.
LESP, lower esophageal sphincter pressure.

^aAbstract only.

serosa apposition and alteration of the anatomy of the proximal stomach similar to that from the NDO device. Unlike the NDO instrument, the Syntheon device is passed on a guidewire to the stomach and an upper endoscope inserted and passed along side and retroflexed to view the procedure in the cardia. A multicenter trial has recently been completed, and the results should be forthcoming in the near future.

Limitations of Data to Date

As this review demonstrates, other than 2 relatively small sham-controlled trials, most of the data on endoscopic therapy for GERD are derived from cohort studies or small case series. Other important design flaws that warrant further examination also characterize these studies. Evidence-based criteria for interpreting studies about therapy provide a framework to examine some of the limitations of the data to date.⁷⁹

Trial Design

Why the emphasis on randomized controlled clinical trials instead of observational studies? The randomized controlled clinical trial remains the gold standard when examining therapeutic interventions. First, randomization of patients distributes prognostic factors, both known and unknown, equally between the intervention and comparison groups.⁷⁹ Second,

patients in nonrandomized studies are more likely to demonstrate a magnified treatment effect versus that seen in randomized controlled trials.⁷⁹ Furthermore, the placebo response in the 2 fully published sham controlled studies was 30%–50% for the primary end points, further diminishing the effect magnitude of the treatment (an absolute difference of approximately 30% and a number needed to treat of 3 to gain one more responder to therapy).^{16,36}

Similarly, blinding of both patient and investigator is critical to decrease bias in clinical trials. Knowledge of the intervention received can affect the responses of the patient and often results in a biased assessment of outcomes, especially subjective ones.⁸⁰ Thus, nonblinded studies tend to show larger treatment effects than blinded trials.^{79,80} However, it must be recognized that complete blinding in sham studies of these devices will likely be impossible. For example, in the sham-controlled trials of both Enteryx and Stretta, chest pain was much more common in the active arm than in the sham arm, effectively unblinding the study for the investigator and/or patient. This limitation will likely persist despite careful attention to trial design, because it would be unethical to deliberately cause pain with no possible clinical benefit to the sham subject.

Another fundamental tenet of clinical trial design is the definition of primary and secondary end points. Clinical trials

Table 5. Systematic Review of Published Studies of Gastric Plication for the Treatment of GERD: Full-Thickness Plication

Author (reference no.), year	Intervention	Study design	No. of subjects	Length of study (mo)	Outcome measurements	Results	Comments
Chuttani et al, ⁷⁷ 2003	Full-thickness plication	Pilot	7	12	GERD-HRQL (mean) GI symptom rating scale (mean) SF-36 physical	18.8 ± 5.9 → 4.6 ± 5.6 6.8 ± 1.8 → 1.8 ± 1.4 34.6 ± 7.4 → 44.8 ± 5.9	No statistics given
Pleskow et al, ⁷⁶ 2004	Full-thickness plication	Cohort Multicenter	64	6	GERD-HRQL (median) GI symptom rating scale (median) SF-36 physical (median) PPI use 24-hour pH (median) (% time pH < 4) Lower esophageal sphincter pressure	19.0 → 5.0 2.0 → 1.0 50 → 55 92% → 26% 10% → 8% No change	P < .001 No statistics given <i>P</i> < .0001 <i>P</i> < .008
Pleskow et al, ⁷⁸ 2005	Full-thickness plication	Cohort	64	12	GERD-HRQL (median) GI symptom rating scale (median) SF-36 physical (median) PPI use	19.0 → 7.0 2.0 → 1.0 50 → 54 93% → 32	P < .001 <i>P</i> < .0001 <i>P</i> < .0001

NOTE. Primary outcomes, when stated, appear in bold.

are typically designed with a sample size of enough power to examine the primary end point, with secondary end points typically exploratory in nature.⁷⁹ Unfortunately, the majority of trials of endoscopic interventions are flawed in this regard. Few studies have clear definitions of primary and secondary end points and instead often list a series of end points together as the primary outcome. In fact, when multiple end points are studied, there is an increased probability of finding a “significant” difference by chance alone. End points measured in the trials noted previously were varied and included objective measures such as acid exposure by pH monitoring, LES pressure, and healing of esophagitis as well as subjective measures such as quality of life, GERD symptoms, and PPI use. While validated instruments such as the SF-36 and the GERD-HRQL have been used in some trials to more objectively assess symptom changes, other studies failed to use validated instruments, thereby calling into question the validity of those results. In the current era of validated scoring instruments and health services research, use of nonvalidated instruments is no longer appropriate or acceptable. The validity of measuring PPI consumption or percentage decrease in PPI consumption as a primary measure of treatment success is likewise not known.

Magnitude of Treatment Effect

Other than the 2 fully reported sham-controlled trials, all of the observational data to date do not allow us to determine the magnitude of the treatment effect, namely, how do various endoscopic interventions compare with standard medical therapy, surgical therapy, placebo, or each other. There are

little or no existing data to allow one to answer these questions. However, based on the sham trials to date, it appears the magnitude of the treatment effect is 30%–50% at best over sham (placebo), meaning the number needed to treat with these devices is 2–3 patients to achieve one clinical success.

Generalizability

Many of the reported series have used multiple centers and large numbers of investigators who generally enroll small numbers of subjects. There are certainly learning curve issues seen in the initial studies that may make the results less favorable in the hands of less experienced investigators, although the exact learning curve for any of the techniques remains unknown.

Finally, what patients were studied? Typically, patients enrolled in the trials discussed had “symptomatic” GERD responsive to PPIs, with small hiatal hernias (≤ 2 cm), abnormal acid exposure, and low-grade or absent esophagitis. This is the only group of individuals with GERD for which these limited observational and clinical trial data may be applied. These data do not allow us to generalize results to other patients, for example, those with high-grade esophagitis, larger hiatal hernias, atypical manifestations of GERD, failure of PPI therapy, and complications such as stricture, Barrett’s esophagus, or failed antireflux therapy.

Risk-Benefit Ratio

Are the benefits of endoscopic therapy worth the risks? The risks of standard therapies, namely, acid suppression and

surgical antireflux therapy, are already known, although the risks of decades of acid suppression with a PPI remain unclear. Risks of endoscopic intervention can be determined by reports of a limited number of patients in clinical trials, case reports, and voluntary postmarketing reports as described previously. The latter 2 methods are clearly flawed, because they do not represent a systematic assessment of adverse events.

Durability

GERD is a chronic disease, typically requiring lifelong therapy. Most studies of endoscopic intervention are short term and involve a small number of patients. Thus, the durability of these technologies beyond 1–2 years remains unclear.

Suggestions for Future Research

Endoscopic methods to treat GERD have been available for approximately 5 years. Given the existing data and limitations, it is now worth evaluating areas of unmet needs in this field before widespread clinical dissemination of these techniques. The following critical questions need to be addressed for new and existing technologies.

1. What is the mechanism of action of the technique? Such studies should be designed in consultation with experts in esophageal physiology and antireflux surgery. In particular, the effect of endoscopic interventions on proximal spread of the reflux column warrants further investigation.
2. How do existing and yet-to-be-developed techniques compare with standard medical or surgical therapy?
3. Are the techniques safe in the short-term and long-term? Clearly, more rigorous preclinical and clinical studies are warranted.
4. How durable are the techniques?
5. What are the optimal patient populations for intervention?
6. What technical skills are required, and how should they be taught?
7. What is the learning curve for each of these techniques?

Summary

The optimal endoscopic antireflux procedure should be effective, easy to apply, and safe. No existing device meets these criteria as currently designed and studied. A variety of endoscopic techniques for the treatment of GERD are currently available, including the delivery of radiofrequency energy to the gastroesophageal junction and suture plication of the proximal fundic folds, but there are no longer any devices that require injection of bulking agents or implantation of a bioprosthesis into the LES zone. Enteryx was voluntarily withdrawn from the market on September 22, 2005, and Gatekeeper was withdrawn in late 2005 before approval and is not expected to be marketed. Each of these techniques involves altering the anatomy of the gastroesophageal junction to decrease reflux. Only limited data are available on the mechanism of action of the various endoscopic techniques. Studies to date of endoscopic therapy have primarily enrolled PPI-dependent patients without severe esophagitis. Each of these techniques results in lessening of GERD symptoms and esophageal acid exposure, while concomitantly decreasing the need for antisecretory medications. Results of a sham-controlled trial of radiofrequency ablation demonstrated decreased heartburn in the active therapy group

compared with the sham group but no difference in acid exposure or need for medications in the 2 groups at 6 months. A sham-controlled trial of Enteryx showed decreased PPI use and improved symptoms in the active therapy arm but no difference in esophageal acid exposure between the 2 groups. To understand the role of these novel endoscopic therapies, sham-controlled trials will be required for every new endoscopic device and technique, as well as long-term follow-up of at least 3–5 years.

Most studies of endoscopic therapy have only limited follow-up information, and data suggest that some of these techniques, in their current iterations, are not durable. Short-term and long-term safety issues remain unresolved, but a number of life-threatening or fatal adverse events have been reported with these devices. The economics of all techniques for the patient, practitioner, and society are unknown. While newer devices and improvements in endoscopic antireflux techniques may yield better and more durable treatment outcomes, current data suggest that there are no definite indications for endoscopic therapy for GERD at this time. Both practitioners and patients need to be aware of the limitations in the evidence that exist with these devices at present.

One further issue that may be relevant to those awaiting further developments in the field of endoscopic antireflux devices is the withdrawal of Enteryx and the suspension of the Gatekeeper clinical development program. Most devices used in gastroenterology are cleared for clinical use by the FDA through what is known as a 510K process, wherein changes in the device and/or its application are relatively simple. However, devices such as Enteryx and Gatekeeper were either approved or in the process of approval via a premarket approval process. Changes to the devices or their application (label) after a premarket approval is granted are tedious and expensive and may require clinical trials supporting such changes. As such, manufacturers are likely to be reluctant to develop such products in the future. This may substantially alter endoscopic antireflux products developed and brought forward in coming years.

GARY W. FALK

*Department of Gastroenterology and Hepatology
Center for Swallowing and Esophageal Disorders
Cleveland Clinic
Cleveland, Ohio*

M. BRIAN FENNERTY

*Division of Gastroenterology and Hepatology
Oregon Health and Science University
Portland, Oregon*

RICHARD I. ROTHSTEIN

*Section of Gastroenterology and Hepatology
Dartmouth Medical School
Lebanon, New Hampshire*

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Address requests for reprints to: Chair, Clinical Practice and Economics Committee, AGA Institute National Office, c/o Membership Department, 4930 Del Ray Avenue, Bethesda, Maryland 20814. Fax: (301) 654-5920.

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