Gastroesophageal reflux disease (GERD), also known as reflux esophagitis, is one of the most prevalent clinical conditions that arises from the gastrointestinal (GI) tract. GERD is a common clinical condition affecting 30 to 40 percent of the U.S. population, with an annual health-care expenditure of $12 billion for GERD (defined by typical symptoms, such as heartburn and regurgitation) and nearly $50 billion for those with suspected extra-esophageal reflux (chronic cough, asthma and throat symptoms presumed to be GERD-related). The cost of treating GERD continues to grow, both in terms of financial resources and in terms of the impact on the quality of life for many patients.

There are two principal factors involved in esophageal reflux: (i) the GI contents and (ii) the anti-reflux mechanism, which is comprised of the lower esophageal sphincter (LES) and the anatomic configuration of the gastroesophageal junction. Reflux occurs when the gradient between the LES pressure and the intra-gastric pressure is compromised as a result of a transient or sustained reduction in the former, or an elevation in the latter. Most patients with GERD have decreased LES pressures. However, some patients have normal LES pressures, but their sphincters relax inappropriately, thus resulting in reflux.

The goal of therapy is to control both the symptoms and mucosal damage. Treatment for GERD may include lifestyle changes (e.g., elevating the head of the bed, decreasing fat intake, quitting smoking, diet), pharmacological therapy (e.g., acid suppressants) or anti-reflux procedures. The majority of GERD patients have mucosal disease, and symptoms are controlled with medical therapy. Anti-reflux procedures may be an option for patients who have failed pharmacotherapy or for those who choose not to continue on medication therapy for the long-term. These procedures are designed to raise the pressure within the LES by wrapping a portion or all of the cardia of the stomach around the esophagus.

Recognizing that the AGA medical position statement on the management of GERD has not been updated since 2008, AGA convened a multi-disciplinary workgroup to develop a framework for selected services and procedures related to the diagnosis and treatment of GERD. The AGA Episode

Payment Framework for Gastroesophageal Reflux Disease\textsuperscript{4} addresses medical, as well as surgical, options for the management of GERD based on published specialty society guidelines, recent data and current practice. While most patients with GERD can be managed non-operatively with pharmacologic therapy, advancements in endoscopic and laparoscopic surgery have expanded the options for patients with GERD who are referred for surgical/endoscopic intervention. Surgical and endoscopic intervention should be entertained only after considerable initial evaluation and medical therapy by primary care and specialty physicians.

Over time, 20 to 40 percent of GERD patients do not experience adequate symptom relief with medical therapy and can be candidates for procedural intervention.\textsuperscript{5} For patients who have 1) failed medical management, 2) have complications of GERD, or 3) have extra-esophageal manifestations (asthma, hoarseness, cough, chest pain, aspiration), anti-reflux surgery may be an appropriate option.\textsuperscript{6} Increasingly, attention has been drawn to the side-effects of chronic PPI therapy, including dementia, bone loss, electrolyte abnormalities, and other side-effects including alopecia and edema. While anti-reflux surgery is a viable option to treat patients with severe GERD, fewer than 30,000 patients are treated surgically each year,\textsuperscript{7} representing a miniscule percentage of the three to six million daily GERD sufferers whose symptoms are not adequately controlled by medical therapy. The number of patients whose symptoms are not adequately controlled on medication, but who are not candidates for anti-reflux surgery is significant. The patients in this segment, referred to as the “treatment gap,” may be 1) aware of anti-reflux surgery, but have decided the potential benefits do not outweigh the risk of side-effects, or 2) have not been made aware of anti-reflux surgery due to the perception by practitioners that anti-reflux surgery presents potential undesired side-effects.\textsuperscript{8}

Due in part to the prevalence of GERD, there has been interest in minimally invasive transesophageal therapeutic alternatives to open or laparoscopic fundoplication in lieu of chronic medical therapy. Three types of procedures have been investigated: 1) radiofrequency (RF) energy to produce submucosal thermal lesions at the gastroesophageal junction; 2) submucosal injection or implantation of a prosthetic or bulking agent to enhance the volume of the lower esophageal sphincter; and 3) transoral esophagogastric fundoplication, where sutures or fasteners are placed in the lower esophageal sphincter to strengthen and lengthen the sphincter to decrease reflux, thus mechanically recreating the gastroesophageal valve. This statement focuses solely on the transoral fundoplication procedure.

The transoral fundoplication procedure that is currently performed in the U.S. is the result of several iterations of development. The original variation of the procedure performed predominantly in Europe was known as endoluminal fundoplication (ELF). This first generation procedure was developed to assess the feasibility of the approach, and was designed to demonstrate safety and efficacy. At that time, investigators were concerned with placing fasteners

through the distal esophagus and instead created gastro-gastric plications distal to the gastroesophageal junction. After experience was gained with the first generation procedure and devices, subsequent iterations of the technique were pursued to more closely replicate the principles and outcomes of traditional surgical fundoplication procedures.

The current transoral fundoplication procedure is performed from inside the patient’s stomach without incisions. This procedure delivers patient outcomes similar to those provided by conventional anti-reflux surgery (ARS) procedures and does not limit future treatment options. Following the principles of ARS, transoral fundoplication repairs the anti-reflux barrier by reducing a hiatal hernia (≤ 2 cm), and creating a valve 2 to 4 cm in length and greater than 270-degree circumferential wrap, thus restoring the dynamics of the angle of His. The device, along with a flexible endoscope, is introduced into the stomach under constant visualization. The endoscope and the device are retroflexed and a helical retractor is engaged into the tissue slightly distal to the Z-line. The fundus of the stomach is folded up and around the distal esophagus utilizing the tissue mold and chassis of the device. After locking all the tissue manipulating elements, an integrated suction apparatus is activated to gently grasp the distal esophagus and position it in the abdominal cavity distal to the diaphragm. H-shaped SerosaFuse polypropylene fasteners with strength equivalent to 3.0 sutures are then delivered through apposed layers of esophageal and fundus tissue to anchor the repair. Approximately 20 fasteners are implanted during the procedure to create fusion of the esophageal and fundus tissues and form the valve, resulting in a full-thickness, partial circumference, gastroesophageal fundoplication.9

The available literature on the current version of transoral fundoplication includes four randomized controlled trials (RCT), results from a multicenter registry and case series with longer term follow-up. Exclusion criteria common to the RCTs are BMI over 35, hiatal hernia greater than 2 cm, esophagitis LA grade C or D, Barrett’s esophagus greater than 2 cm, and esophageal ulcer.

The largest RCT with the lowest risk of bias is an industry-sponsored double-blind sham controlled multicenter study (RESPECT) that evaluated transoral fundoplication in patients whose symptoms were not well-controlled on proton pump inhibitors (PPIs).10 Out of 696 patients screened, 129 met inclusion and exclusion criteria and were randomized in a 2:1 ratio; 87 patients received transoral fundoplication combined with six months of placebo and 42 patients received sham surgery with six months of daily PPI therapy (sham/PPI). The primary outcome measure was the elimination of troublesome regurgitation, defined as mild symptoms for two or more days per week or moderate to severe symptoms more than one day per week. Crossover was allowed at three months in the case of treatment failure or at six months when the blind was broken. Failure at three months was observed in 36 percent of patients in the sham/PPI group compared with 11 percent in the transoral fundoplication/placebo group (p = 0.002). Self-reported regurgitation was eliminated in 22 percent more patients following transoral fundoplication compared to continued PPI therapy (67 percent vs. 45 percent, p = 0.023), while reductions in GERD symptoms scores were similar in the two groups. The objective measure of control of esophageal pH was significantly reduced after transoral fundoplication (mean percent time esophageal pH < 4 decreased from 9.3 percent to 6.3 percent, p < 0.001), but not sham surgery (from 8.6 percent to 8.9 percent). With follow-up out to 18 months, 71 percent of patients in the sham/PPI group crossed over to transoral fundoplication.

---

9 U.S. Food and Drug Administration (FDA), Center for Devices and Radiologic Health (CDRH). 510(k) summary. Endogastric Solutions EsophyX2 System with SerosaFuse Fastener and Accessories, Model 2.7.5. November 6, 2009b. K092400

compared with 28 percent of patients in the transoral fundoplication/placebo group who resumed PPI therapy (p < 0.001). Strengths of this study include the use of a sham surgery and placebo control to maintain double blinding, adequate power, objective as well as subjective outcome measures, and use of intent-to-treat analysis.

Håkansson, et al\textsuperscript{11} reported a double-blind sham-controlled randomized trial with 44 patients who had moderate to severe GERD symptoms without PPI therapy. This was a five-site, prospective, double-blind sham-controlled study of 44 patients, with 22 patients treated with the transoral fundoplication and 22 patients receiving a sham procedure consisting of an upper GI endoscopy under general anesthesia. Controls received a sham procedure. The primary outcome was the time in remission, which was longer following transoral fundoplication than sham (197 days vs. 107 days, p < 0.0001). At six months post-op 13/22 (59 percent) of transoral fundoplication patients were in clinical remission with complete cessation of PPIs, compared to 4/22 (18 percent) of the sham group. Sixty-nine percent of the transoral fundoplication group normalized esophageal acid exposure. Median GERD symptom scores (QOLRAD) in the transoral fundoplication group improved from 4.9 (1.96-6.44) at baseline to 6.4 (4.38-7) at six months, \textit{p}=0.0005. There was no appreciable change in the sham group, from 4.8 (1.80-6.44) at baseline to 5.2 (4.28-6.88) at six months.

Witteman, et al\textsuperscript{12} described the interim results of a non-blinded randomized controlled study involving 60 subjects assigned to either transoral fundoplication (n=40) or continuation of PPI therapy (n=20). Patients in this study had symptoms that were adequately controlled by PPIs, but did not want to be on lifelong PPI therapy. Control subjects were allowed to cross over to transoral fundoplication at the end of the six-month trial period, and all 20 subjects did undergo the fundoplication procedure. At the end of the initial six-month follow-up point, 37 transoral fundoplication subjects and 20 control subjects were available. Subjective GERD symptoms were improved to a greater extent in the transoral fundoplication group (p < 0.001), and satisfaction scores were higher (50 percent satisfied versus 0 percent). The fundoplication group had a significantly lower esophageal resting pressure vs. the control group (p=0.004), but no differences in total number of reflux episodes were detected (p=0.058). Cessation of PPI use was reported in 74 percent of fundoplication subjects and none of the controls.

Trad, et al\textsuperscript{13} reported the results of an RCT involving 63 subjects randomized to receive either transoral fundoplication (n=39) or high-dose PPIs (n=21). Subjects in the PPI group were treated for six months and then crossed over to fundoplication treatment. Both groups were followed for 12-months post fundoplication. At 12-months follow-up in the fundoplication-only group, global elimination of any atypical symptoms and regurgitation was achieved in 77 percent of subjects. Elimination of troublesome regurgitation was achieved in 95 percent of subjects. In the crossover group, daily PPI use decreased from 100 percent at the end of the PPI-use trial period to 10 percent six months after crossover treatment, and 71 percent of subjects had no PPI use at all. At

\textsuperscript{11} Håkansson B, Montgomery M, Cadière GB, et al. Randomized clinical trial: transoral incisionless fundoplication vs. sham intervention to control chronic GERD. \textit{Aliment Pharmacol Ther}. 2015 Dec;42(11-12):1261-70.


the end of the crossover evaluation period, endoscopic examination showed that healing of reflux esophagitis occurred in 85 percent vs. 38 percent of subjects at the end of the PPI treatment period.

In 2015, Trad\textsuperscript{14} published the results of the TEMPO trial, a multicenter RCT at seven U.S. community hospitals involving 66 subjects that compared transoral fundoplication (n=40) versus maximal dose PPI therapy (n=23) in partial responders to PPI therapy. At the six-month follow-up, troublesome regurgitation was eliminated in 97 percent of fundoplication patients versus 50 percent of PPI patients (relative risk [RR] = 1.9, p = 0.006), and 90 percent of patients in the fundoplication group had completely stopped taking PPI’s. All subjects underwent endoscopic evaluation at six-months follow-up and complete healing or reduction in reflux esophagitis at six months was achieved in 90 percent (18/20) of fundoplication subjects vs. 38 percent (5/13) of control subjects (p=0.018). The median total Reflux Symptom Index score in the fundoplication group decreased significantly from 23 (range, 0-43) on PPIs before procedure to three (range, 0-25) off PPIs at six-month follow-up (p<0.001).

In March 2016, Trad\textsuperscript{15} presented the three-year data from the TEMPO RCT with a crossover arm at the Society of Gastrointestinal Endoscopic Surgeons (SAGES) annual meeting. At three-year follow-up, elimination of troublesome regurgitation and all atypical symptoms was reported by 90 percent (37/41) and 88 percent (42/48) of patients, respectively. The mean Reflux Symptom Index score improved from 22.2 (9.2) on PPIs at screening to four (7.1) off PPIs three years post-transoral fundoplication, p < 0.0001. The mean total percent time pH <4 improved from 10.5 (3.5) to 7.8 (5.7), p=0.0283. Esophagitis was healed in 86 percent (19/22) of fundoplication patients. At the end of study, 71 percent (37/52) of patients had discontinued PPI therapy.

Testoni et al.\textsuperscript{16} reported a prospective study of 50 patients who were treated with transoral fundoplication and followed for up to six years (mean 53 months). Approximately three quarters of patients were completely responsive to a standard dose of PPI twice a day at baseline. All patients answered GERD questionnaires and underwent endoscopy, esophageal manometry and pH measurements at six, 12, and 24 months after transoral fundoplication. Beginning at three years after fundoplication, PPI consumption and GERD related symptoms (off medication) were obtained every year by telephone interview or office consultation. Thirty-three patients (66 percent) were available for follow-up at three years, and 14 patients (28 percent) were available for follow-up at six years. At one, two, three, four, five and six years, complete response (no PPI use) was observed in 51, 56, 53, 46, 32 and 36 percent of patients, respectively. Intention-to-treat analysis found the 52 percent of evaluable patients (n=33) had discontinued PPI use by 36 months. Factors predicting good outcomes were pre-procedure Hill’s grade I-II, no hiatal hernia or hernia 2 cm or less, effective esophageal motility, and number of fasteners deployed. Strengths of this study include the prospective assessment and length of follow-up.


\textsuperscript{15} Trad KS, Fox MA, Simoni G, et al. Transoral Fundoplication offers durable symptomatic control for chronic GERD: 3-year final report from the TEMPO randomized trial with a crossover arm. Flexible Endoscopy Session (Program Number SS07, Session Number SS08) March 17, 2016

Six-month,\textsuperscript{17} twelve-month\textsuperscript{18} and 24-month\textsuperscript{19} follow-up has been reported from a prospective multicenter registry of patients with chronic GERD who received transoral fundoplication using the EsophyX2 system with SerosaFuse fasteners. For the 100 consecutive patients who were treated in this community-based study, the median GERD symptom duration was nine years (range, one to 35 years), the median duration of PPI use was seven years (range, one to 20 years), and 92 percent of patients had incomplete symptom control despite maximal medical therapy. Of the 100 patients, 88 percent had objectively documented GERD at screening (abnormal pH test, esophagitis, Barrett esophagus or peptic strictures). Fasteners were successfully deployed in 89 percent of attempted deliveries, and a mean of 20 fasteners were used for fundoplication. Questionnaires were obtained from 96 of the 100 patients at 12-months and from 108 of 127 patients at 24 months. Results were found to be stable between six months and 12 months after the procedure. The median score on the GERD health-related quality of life questionnaire (GERD-HRQL) improved from 24 to two, the median reflux symptom index (RSI) was reduced from 20 to five, and the median gastroesophageal reflux symptom score (GERSS) was reduced from 26 to four. In the patients with an abnormal GERSS (>18) at screening, 88 percent normalized their score at 12 months and 65 percent had a normalized score at two years. Of 27 patients who underwent 12-month pH testing, 14 (52 percent) were normalized. Daily bothersome heartburn was eliminated in 66/85 (78 percent) and regurgitation symptoms were eliminated in 48/58 (83 percent). At two years, GERD-HRQL and regurgitation scores improved by 50 percent or greater in 66 percent and 70 percent of patients who had elevated pre-operative scores. Seventy-seven percent of patients were off of daily PPI therapy at 12 months. Daily PPI use remained fairly stable at two year follow-up (29 percent of patients).

In conclusion, the three-year plus evidence is sufficient to demonstrate sustainable improvement in health outcomes, symptom relief, decrease in PPI utilization and improvement in esophageal pH with transoral fundoplication. The selection criteria for transoral fundoplication includes GERD patients with BMI ≤ 35, hiatal hernia ≤ 2 cm, esophagitis LA grade A or B, Barrett's esophagus ≤ 2 cm, and absence of achalasia and esophageal ulcer. This option should be considered in patients not responding to PPI therapy (symptoms of regurgitation) who have documented objective evidence of GERD (pathologic acid exposure on pH testing (both off and on medication)) or esophagitis. Transoral fundoplication should be covered and reimbursed for appropriate patients who meet the selection criteria as described.