Review Article

Stretta therapy in the management of gastroesophageal reflux disease (GERD)

Dalbir S. Sandhu, Ronnie Fass

The Esophageal and Swallowing Center, Division of Gastroenterology and Hepatology, MetroHealth Medical Center, Case Western Reserve University, Cleveland, OH, USA

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Correspondence to: Ronnie Fass, MD, FACG. Professor of Medicine, Head, Esophageal and Swallowing Center, Director, Division of Gastroenterology and Hepatology, MetroHealth Medical Center, Case Western Reserve University, 2500 MetroHealth Drive, Cleveland, OH 44109, USA. Email: ronnie.fass@gmail.com.

Abstract: Treatment of gastroesophageal reflux disease (GERD) includes medical, surgical, and endoscopic intervention. The growing concerns of patients and physicians alike about adverse effects of chronic proton pump inhibitor (PPI) therapy or anti-reflux surgery have positioned endoscopic therapy for GERD on par with other therapeutic interventions. Endoscopic radiofrequency (RF) ablation (Stretta) has been used for more than 15 years and it is the most studied and followed endoscopic procedure for GERD. The technique itself has improved over the years and has been shown to be effective, safe and durable. Several meta-analyses and cohort studies have cemented the efficacy of the technique in improving patients' health related quality of life, GERD symptoms, PPI consumption and esophageal acid exposure over more than 10 years follow up. Presently, endoscopic RF has been integrated into treatment guidelines of patients with GERD with diverse clinical scenarios.

Keywords: Heartburn; gastroesophageal reflux disease; endoscopy; esophagus; proton pump inhibitor (PPI); pH test

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Introduction

Gastroesophageal reflux disease (GERD) is a commonly encountered disorder worldwide characterized primarily by symptoms of heartburn and regurgitation due to gastroesophageal reflux. The other less common presentations are chest pain and discomfort, water brash, belching, epigastric pain, nausea, vomiting, cough, hoarseness, throat clearing, throat pain, and dysphagia. These symptoms can occur either solely or in combination with the cardinal symptoms (1).

Medical and surgical therapies have been the mainstay of treatment for GERD. However, the last two decades have seen a surge in endoscopic therapies as alternative options for GERD management. The majority of these endoscopic therapies such as NDO Plicator (NDO Surgical, Mansfield, MA, USA), endoscopic apposition device (EndoCinch, Bard Medical, Covington, GA, USA), Gatekeeper (Medtronic, Minneapolis, MN, USA), Plexiglas microspheres (Artes Medical, San Diego, CA, USA), injection devices (Enteryx, Boston Scientific, Natick, MA, USA) did not gain popularity due to lack of efficacy and concerns about safety. The only endoscopic therapies that are currently available and also approved by the United States Food and Drug Administration (FDA) are radiofrequency (RF) ablation (Stretta), transoral incisionless fundoplication (TIF) (EsophyX; EndoGastric Solutions, Redmond, WA, USA), and Medigus Ultrasonic Surgical Endostapler (MUSE™, Medigus, Omer, Israel).

The Stretta system (Mederi Therapeutics, Norwalk, CT, USA) involves the application of RF energy to the lower

esophageal sphincter (LES). RF energy has been used in the medical field for a long time primarily for ablation of cardiac arrhythmias. However, it was the pioneering work of Utley *et al.* who demonstrated an increase in LES pressure along with gastric yield pressure in porcine model and reduction of the rate of transient LES relaxations (TLESR) in canine models in response to RF application to the distal esophagus and proximal stomach (2). These findings in animal models were later confirmed in a multicenter trial that showed favorable short term outcomes of RFA to the distal esophagus in human subjects with GERD (3).

This review focuses on the current value of Stretta in the management of patients with GERD.

What is Stretta

The Stretta system delivers low power and low temperature RF energy to the LES and gastric cardia leading to remodeling of the smooth muscle by potentially increasing the thickness of the musculature as well as the size and amount of smooth muscle fibers in the treatment zone. This leads to strengthening of the esophagogastric barrier and possibly decreasing the rate of TLESR.

The Stretta system consists of the RF control module and the flexible Stretta catheter. The catheter has a 20 F soft bougie tip and a balloon, which opens a surrounding basket. On the widest area after balloon inflation, the catheter has four NiTi needle electrodes (5.5 mm), which can be extended into the lower esophageal muscle tissue. The catheter simultaneously aspirates and irrigates the esophageal lumen with water. The four-channel, thermocouple-controlled generator provides 60 to 300 Joules of RF energy to each needle, heating the surrounding muscle tissue to the target temperature between 65 and 85 ℃ while cooling the mucosa with its integrated irrigation system. During RF application, the system monitors the temperature and the impedance of the needle tips surrounding tissue.

How is Stretta procedure performed

The Stretta procedure is performed on an outpatient basis in the endoscopy unit with sedation protocol per the preference of the endoscopist. The preoperative preparation for Stretta is similar to an upper endoscopy with fasting for 12 hours prior to the procedure. After a diagnostic upper endoscopy, the location of the squamocolumnar junction (Z-line) is noted with subsequent per oral insertion of Stretta catheter. The tip of the catheter is placed 1–2 cm above the Z-line and suction is attached to the catheter with simultaneous infusion of cooled water through the inflow port of the catheter. The balloon is inflated and 4 nickel-titanium needle electrodes (22-gauge, 5.5 mm length) are deployed into the muscle of the gastroesophageal junction (GEJ) in the full position. The control module is set at 1.5 minutes delivery time, wattage 5 W, and target temperature of 85 ℃. RF energy and irrigation are done at the same time. After each treatment, the needles are retracted, the balloon is deflated, and the catheter is rotated 45 degrees with repetition of the treatment until a concentric ring is formed 1 cm above the Z-line. The catheter is then moved distally in increments of 5 mm to form a total of 4 levels of lesions with 2 lesion sets at each level. Pull-back lesion is created by advancing the catheter into the stomach, inflating the balloon fully to 25 cc, gently pulling the catheter against hiatus until it meets resistance. Few modifications have been utilized by different study groups such as creating lesion sets from 2 cm proximal to 2 cm distal to the Z-line by varying catheter's linear position with the creation of a total of 15–25 lesion sets.

Post procedure, patients are instructed to continue their anti-reflux medication for 3 weeks.

Coding

The most common ICD-10 diagnosis codes used for Stretta procedure is K21.0 (gastroesophageal reflux disease with esophagitis) and K21.9 (gastroesophageal reflux disease without esophagitis). The CPT code is 43257 (descriptor: esophagogastroduodenoscopy, flexible, transoral; with delivery of thermal energy to the muscle of LES and/or gastric cardia, for treatment of gastroesophageal reflux disease).

Mechanism of action

Our knowledge about mechanism of action of RF energy comes from its initial use for cardiac arrhythmia ablation. RF energy has been shown to cause ligament lengthening by leading to increased fibroblast growth factors activity, collagen deposition, and heat-induced collagen contraction. These changes in turn lead to wound healing, reduction in tissue compliance, and nerve pathway ablation (4). When RF energy is used for GERD, an increase in thickening of the GEJ musculature has been observed by both histologic and endosonography evaluations (2,5). Apart from the

mechanical effects secondary to increased thickening of the GE junction musculature, Stretta treatment has also been shown to decrease the frequency of TLESR. Utley *et al.* showed a 54% reduction in TLESR rate using a canine model. This effect is not fully understood and it is postulated that RF energy may disrupt the aberrant intramural vagal afferent nerve pathways within the gastric cardia, which have been shown to play an important role in generating TLESR (6).

Role of Stretta in GERD

Stretta received an initial approval in 2000 and an updated clearance on the RF generator in 2011 (7). In their guidelines, the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) recommended Stretta as an appropriate procedure for adult patients with GERD who wish to be off antisecretory therapy and refuse laparoscopic fundoplication (7). Numerous studies have demonstrated the positive impact of Stretta on GERD patients, improving both objective and subjective clinical endpoints (*Tables 1* and *2*).

The proper candidates for the Stretta procedure, are mentioned in *Tables 3* and *4*.

Richards *et al.* reported their initial experience with the Stretta procedure in 25 patients with GERD (32). Of the patients available for 3-month follow up, 62% (8/13) were off all antisecretory medication with the remaining 38% were able to reduce the amount considerably.

One of the earliest multicenter, prospective, nonrandomized study assessed long term (12-month) safety and efficacy of Stretta in GERD patients (35). Stretta was performed according to a standard protocol in 118 patients with chronic heartburn and/or regurgitation who needed daily antisecretory medication in addition to demonstrating abnormal esophageal acid exposure, a small sliding hiatal hernia (≤2 cm), and mild esophagitis (≤ grade B). At 12 months, significant improvement was noted in median heartburn score, GERD health-related quality of life (HRQL) score, patient's satisfaction, mental SF-36, and physical SF-36 with an acceptable 8.6% complication rate, none of which required therapeutic intervention. Most importantly, the study showed discontinuation of proton pump inhibitor (PPI) requirement from 88.1% to 30%. In addition, mean esophageal acid exposure significantly improved from 10% to 6%. A trend towards a reduction in the number of TLESRs was noted although the difference was not statistically significant.

A crossover, randomized controlled trial comparing Stretta to sham procedure recruited 64 patients with GERD to Stretta (35 patients) or to a sham procedure (29 patients) (12). A significant number of patients in the Stretta group demonstrated greater than 50% improvement in their GERD quality of life score compared to the sham procedure group (61% *vs.* 30%, P=0.03) at 6 months. Interestingly, these improvements in clinical endpoints persisted at 12 months after treatment. However, there were no significant differences in daily medication use after implementing a medication withdrawal protocol or in esophageal acid exposure time between the 2 arms. The procedure was noted to be safe and without adverse events.

Another randomized study recruited 36 patients into three groups, patients who underwent single treatment session with Stretta (n=12), patients who underwent a sham procedure (n=12) and patients who underwent a single treatment session with Stretta followed by repeat session if the GERD HRQL score did not improve by 75% as compared with baseline after 4 months (n=12) (10). At 12 months, the primary outcome of improved GERD HRQL and secondary outcomes of improved LES basal pressure, 24-h pH acid exposure time and PPI daily dose consumption were noted to significantly decrease in both Stretta groups (P=0.01). The double Stretta therapy was numerically but not significantly better than the single Stretta intervention for mean HRQL at 12 months.

Another prospective trial randomly allocated patients with PPI-dependent GERD to either the Stretta procedure or PPI regimen alone with the primary endpoint being the possibility for the patient to stop or to decrease PPI use at 6 months to less than 50% of the dose required at baseline to fully control symptoms (13). The study showed that 90% of the patients stopped or decreased PPI use compared to 50% in the PPI group (P=0.01). HRQL was not significantly different between the two groups. Also, no significant change in esophageal acid exposure was noted between baseline and 6-month values after RF treatment. This study concluded that even though RF allows reduction or discontinuation of PPI therapy in a subset of patients, the majority will continue to use a PPI.

More recently, a double-blind, randomized, cross-over study of Stretta versus sham treatment was conducted in 22 GERD patients, 11 in each arm. Barostat distensibility test of the EGJ before and after administration of sildenafil was the main outcome measure (9). Three months after the initial Stretta procedure, no changes were noted in esophageal acid exposure and LES basal pressure, although symptom score was significantly improved and EGJ

Table 1 Results of studies evaluating objective clinical endpoints of Stretta in GERD patients

Study	Study design	Number of patients	Follow up (months)	Objective clinical endpoints		
				Percentage of time pH <4 (pre and post) (%)	PPI usage (pre and post)	LES pressure (mmHg) (pre and post)
Arts *et al.* (8)	Cohort	13	6	11.6±1.6 *vs.* 46.8±7.2 (P<0.05)	100% on daily *vs.* 61% stopped/intermittent	17.3±3.0 *vs.* 18.2±2.0 (P=NS)
Arts *et al.* (9)	RCT	22	3	Non-significant	Non-significant	Non-significant
Aziz *et al.* (10)	RCT	36	12	9.4±3.4 *vs.* 6.7±2.8 (P<0.01)	P<0.01	11.6±3.2 *vs.* 16.2±4.5 (P<0.01)
Cipolletta *et al.* (11)	Cohort	32	12	11.7 *vs.* 8.4 (P=0.79)	32 *vs.* 6 (P=0.9)	16 *vs.* 22 (P=0.72)
Corley *et al.* (12)	RCT	35	6	9.5 *vs.* 9.9 (P=0.79)	30 *vs.* 13 (P=0.9)	13 *vs.* 16.2 (P=0.72)
Coron *et al.* (13)	RCT	23	12	12.2±7.1 *vs.* 11.4±6.3 (P=0.11)	0.01 (stopped or decreased) 0.11 (completely stopped)	13±8 *vs.* ?
DiBaise *et al.* (14)	Cohort	18	6	9.5 *vs.* 6.2 (P=NS) (distal esophagus total exposure)	P<0.001	13.6±1.3 *vs.* 12.7±1.8 (P=NS)
Dughera *et al.* (15)	Cohort	69	48	P=0.001	P<0.001	8.44 *vs.* 9.5 (P=NS)
Dughera *et al.* (16)	Cohort	86	96	P=NS	P=0.0001	P=NS
Dundon *et al.* (17)	Cohort	37	53	–	–	–
Gao *et al.* (18)	Cohort	505	12	–	–	–
Go *et al.* (19)	Cohort	50	3	–	–	–
Higuchi *et al.* (20)	Cohort	9	6	–	100% *vs.* 66.7% (P=0.009)	–
Houston *et al.* (21)	Cohort	41	6	8.4±0.9 *vs.* 4.4±1.3 (P=0.03)	37.8±4 *vs.* 5.8±1.6 mg/d (P=0.003)	25.3±2.4 *vs.* 26.8±2.6 (P=0.63)
Liang *et al.* (22)	Cohort	132	60	–	–	–
Liang *et al.* (23)	Cohort	85	36	–	–	–
Liu *et al.* (24)	Cohort	90	12	–	100% on PPI (baseline) *vs.* 21.1% on PPI (6 months) (P<0.05)	–
Lutfi *et al.* (25)	Cohort	86	26	7.8±2.6 *vs.* 5.1±3.3 (P=0.001)	–	–
Mansell *et al.* (26)	Cohort	29	4	–	79% *vs.* 17%	–
Mattar *et al.* (27)	Cohort	7	20	7±2 to 3±0 (P<0.05)	–	–
Meier *et al.* (28)	Cohort	60	12	16.7±12.8 to 8.8±6.6 (P=0.001)	–	14.8±9.1 to 16.7±10.0 (P=0.002)
Noar and Lotfi-Emran (29)	Cohort	109	48	–	100% *vs.* 25% (P<0.005)	–
Noar *et al.* (30)	Cohort	217	120	–	8.35 *vs.* 4.70 ($P<10^{-6}$)	–

Table 1 (*continued*)

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Study	Study design	Number of patients	Follow up (months)	Objective clinical endpoints		
				Percentage of time pH <4 (pre and post) (%)	PPI usage (pre and post)	LES pressure (mmHg) (pre and post)
Reymunde and Santiago (31)	Cohort	83	48	–	100% *vs.* 13.75% (P<0.001)	–
Richards *et al.* (32)	Cohort	65	6	8.2±0.9 to 4.4±0.5 (P<0.01)	89% were off or decreased usage	22.8±2.4 to 23.5±2.5 (P>0.05)
Tam *et al.* (33)	Cohort	20	12	10.6 *vs.* 6.3 (P<0.05)	100% *vs.* 35% at 12 months	5.2 *vs.* 8 (P<0.01)
Torquati *et al.* (34)	Cohort	82	27	6.4±1.5 to 3.1±1.4 (P=0.0001)	37.8±22.2 *vs.* 11.6±14.6 mg/d (P=0.001)	–
Triadafilopoulos *et al.* (35)	Cohort	118	12	10.2 to 6.4 (P=0.0001)	88.1% *vs.* 30% (PPI requirement)	15 *vs.* 12.6 (P=0.007)
Wolfsen and Richards (36)	Cohort	558	8	–	P<0.0001	–

RCT, randomized controlled trial; LES, lower esophageal sphincter; PPI, proton pump inhibitor.

compliance had significantly decreased in the Stretta group. Interestingly, administration of sildenafil restored EGJ compliance to pre-Stretta level arguing against EGJ fibrosis as the underlying mechanism of the Stretta procedure. Although, the authors performed endoscopy, esophageal manometry, 24-hour esophageal pH monitoring, and distensibility test of the GEJ both before the start of the study and after 3 months as part of reflux evaluation, no impedance monitoring was done, which unfortunately was one of the limitations of the study.

The majority of the Stretta studies were done in patients from Western countries. A group from Japan performed a small, open-label trial that showed similar results regarding the safety and efficacy of the Stretta procedure in Japanese patients (20). The authors reported a significant improvement in heartburn score (P=0.007) and decreased medication use (P=0.009) without any major adverse events.

Since these earlier studies, there have been more than 30 separate clinical trials and four systematic reviews that have evaluated the effect of Stretta in GERD. One of the earliest systematic review and meta-analysis included 18 studies with a total of 1,441 patients (37). The authors reported that the Stretta procedure provided significant improvement in heartburn score (P=0.001), GERD-HRQL (P=0.001) and in reflux and dyspepsia score (P=0.001). Esophageal acid exposure decreased from a pre-procedure Johnson-DeMeester score of 44.4 to 28.5 (P=0.007). This study concluded that Stretta is safe and effective in GERD patients. The procedure is well-tolerated and significantly reduced esophageal acid exposure although it did not consistently normalize esophageal pH.

A more recent systematic review and meta-analysis that was published included 2,468 unique Stretta procedures from a total of 28 studies (4 RCTS, 23 cohort studies, and 1 registry) (38). The mean follow-up time for the 28 studies was 25.4 (range, 14–36.7) months. The pooled results showed significant improvement in HRQL score by −14.6 (P<0.001), and heartburn standardized score by −1.53 (P<0.001) after the Stretta procedure. In addition, only 49% of the patients using PPI at baseline required PPI at follow up (P<0.001). The Stretta procedure also reduced the incidence of erosive esophagitis by 24% (P<0.001) and esophageal acid exposure by a mean of −3.01 (P<0.001). Although an increase in LES basal pressure was noted post Stretta therapy, the difference did not reach statistical significance. This study concluded that Stretta significantly improves subjective and objective clinical endpoints, except LES basal pressure.

A systematic review and meta-analysis by Lipka *et al.* that included only the 4 randomized controlled trials reported no evidence for efficacy of RF treatment in GERD patients (39). A total of 153 patients were analyzed from trials that compared Stretta with sham and 1 trial that compared Stretta with PPI. The primary outcome was

Table 2 Results of studies evaluating subjective clinical endpoints of Stretta in GERD patients

Study	Study design	Number of patients	Follow up (months)	Subjective clinical endpoints		
				Symptoms (mean/median heartburn) (before and after)	HRQL (mean/median)	Score used
Arts *et al.* (8)	Cohort	13	6	P<0.005	–	–
Arts *et al.* (9)	RCT	22	3	14.7±1.5 *vs.* 8.3±1.9 (P<0.005)	49.5±9.5 *vs.* 24±4.3 (P<0.05)	SF-36
Aziz *et al.* (10)	RCT	36	12	–	29.6±3.9 *vs.* 14.4±4.8 (P<0.01)	GERD-HRQL
Cipolletta *et al.* (11)	Cohort	32	12	3.4 *vs.* 1.6 (P=0.001)	28±7 *vs.* 16 (P=0.003)	GERD-HRQL (6-point Likert)
Corley *et al.* (12)	RCT	35	6	3.8 *vs.* 2.2 (P=0.01)	28 *vs.* 16 (P=0.003)	GERD-HRQL (6-point Likert)
Coron *et al.* (13)	RCT	23	12	1.6±0.7 *vs.* 2.1±1.0 (P=0.47)	49 *vs.* 48 (P=0.81)	SF-36 REFLUX-QUAL
DiBaise *et al.* (14)	Cohort	18	6	112.5 *vs.* 83.4 (P<0.001)	21.5 *vs.* 7 (P<0.001)	GERD-HRQL (5-point Likert)
Dughera *et al.* (15)	Cohort	69	48	P<0.001	P<0.003	GERD-HRQL (6-point Likert)
Dughera *et al.* (16)	Cohort	86	96	P<0.001	P<0.003	GERD-HRQL (6-point Likert)
Dundon *et al.* (17)	Cohort	37	53	3.66 *vs.* 2.43 (P=0.04)	1.83 *vs.* 1.92 (P>0.05)	GERD-HRQL (5-point Likert)
Gao *et al.* (18)	Cohort	505	12	5.31 *vs.* 1.79 (P=significant)	–	–
Go *et al.* (19)	Cohort	50	3	3.19 *vs.* 1.74 (P=0.0012)	3.92 *vs.* 1.63 (P=0.0001)	GERD-HRQL
Higuchi *et al.* (20)	Cohort	9	6	5.0±1.7 *vs.* 0.7±1.4 (P=0.007)	–	–
Houston *et al.* (21)	Cohort	41	6	–	3.7±0.2 *vs.* 5.1±0.2 (P=0.002) (QoLRAD score)	QOLRAD
Liang *et al.* (22)	Cohort	132	60	5.67±1.52 to 2.41±1.13 (P<0.001)	–	–
Liang *et al.* (23)	Cohort	85	36	P<0.001	–	–
Liu *et al.* (24)	Cohort	90	12	3.3 *vs.* 1.2 (P<0.05)	25.6 *vs.* 7.3 (P<0.01)	GERD-HRQL
Lutfi *et al.* (25)	Cohort	86	26	–	3.6±1.1 *vs.* 5±1.5 (P<0.001)	QOLRAD
Mansell *et al.* (26)	Cohort	29	4	4 *vs.* 1 (P<0.001)	32 *vs.* 9 (P<0.001)	–
Mattar *et al.* (27)	Cohort	7	20	0% *vs.* 83% (symptom resolution)	–	–
Meier *et al.* (28)	Cohort	60	12	–	19.2±9.0 to 6.6±7.3 (P<0.0001)	–
Noar and Lotfi-Emran (29)	Cohort	109	48	3.6 to 1.18 (P<0.001)	27.8 to 7.1 (P<0.001)	GERD-HRQL
Noar *et al.* (30)	Cohort	217	120	1.28 *vs.* 3.65 ($P<10^{-6}$) (satisfaction)	27.81 *vs.* 8.55 ($P<10^{-6}$)	GERD-HRQL
Reymunde and Santiago (31)	Cohort	83	48	–	2.4 *vs.* 4.3 (P<0.001)	QOLRAD
Richards *et al.* (32)	Cohort	65	6	–	3.9±0.2 to 5.7±0.2 (P<0.01)	QOLRAD
Tam *et al.* (33)	Cohort	20	12	–	19.5 *vs.* 7 (P<0.05)	GERD-HRQL
Torquati *et al.* (34)	Cohort	82	27	–	6.1±1.1 *vs.* 4.0±1.1 (P=0.0001)	QOLRAD
Triadafilopoulos *et al.* (35)	Cohort	118	12	4 to 1 (P=0.0001)	27 to 9 (P=0.0001)	GERD-HRQL
Wolfsen and Richards (36)	Cohort	558	8	86.8% *vs.* 75.3% (P<0.0001)	–	–

HRQL, health related quality of life; RCT, randomized controlled trial; QOLRAD, quality of life in reflux and dyspepsia.

Table 3 Potential candidates for the Stretta procedure

Side effects from medical therapy
Poor compliance with medical therapy
Desire to discontinue medical therapy
GERD symptoms not well controlled on medical therapy
GERD patients who are poor surgical candidates
Patients not interested in medical therapy or anti-reflux surgery
Preference for the Stretta procedure
Post bariatric surgery (limited data)
Prior anti-reflux surgery (limited data)

GERD, gastroesophageal reflux disease.

Table 4 Patient's candidacy criteria for the Stretta procedure

Typical GERD symptoms (heartburn and/or regurgitation)
Low grade erosive esophagitis (Los Angeles grade A and B)
Endoscopy negative with abnormal esophageal acid exposure
Small hiatal hernia (<3 cm)
LES pressure >5 mmHg
Response or partial response to PPI treatment

GERD, gastroesophageal reflux disease; LES, lower esophageal sphincter; PPI, proton pump inhibitor.

physiologic parameters of GERD, including normalization of esophageal pH values and augmentation of LES pressure. Secondary outcomes were HRQL and ability to stop PPI treatment. The study reported no significant changes in any of the aforementioned clinical endpoints. The mean % total time pH less than 4 was numerically lower after Stretta but it did not reach statistical significance. The study was limited by including only randomized controlled trials, which were short term and enrolled a very small number of patients. Inclusion of observational studies along with RCTs during meta-analysis improves longitudinal assessment of the long-term value of the intervention. It is also important to mention that even PPIs have not shown to normalize pH in up to 50% of symptomatic GERD patients (40) so pH normalization may not necessarily be a valid clinical endpoint to be used for evaluating Stretta's clinical efficacy.

Long-term effects of Stretta

The majority of studies using Stretta in GERD patients reported durability of symptom improvement for a period of 6–12 months. One of the earliest studies that showed long term efficacy of Stretta was reported by Reymunde *et al.* (31). The mean GERD QoL score was 2.4 at baseline, 4.6 after 3 years, and 4.3 after 4 years (P<0.001). The mean GERD symptom score was 2.7 at baseline, 0.3 after 3 years, and 0.6 after 4 years (P<0.001). Daily medication usage decreased from 100% at baseline to 13.6% after 4 years (P<0.001). Although, this was a single center, non-randomized study with lack of control arm and 24-hour pH measurements, it showed that Stretta was a safe and effective therapy with sustained improvement in GERD symptoms, QoL and PPI consumption after a 4-year period. Similar results were later reported by Noar *et al.* (29) and Dughera *et al.* (15) with both groups demonstrating safety, efficacy and durability of the Stretta procedure after a 4-year follow up period.

Later, Dughera *et al.* reported their results in 26 patients who underwent Stretta (16 females) after an eight-year follow up period (16). The primary end point of the study was to verify durability of the procedure with all patients undergoing clinical evaluation by an upper endoscopy, esophageal manometry and pH test. The study reported significant decrease in both heartburn and GERD HRQL scores at 8 years (P=0.003) as well as a significant increase of QoL scores at 4 years and then at 8 years (mental SF-36 and physical SF-36, P=0.001). After 8 years, 20 patients (76.9%, P=0.0001) were still completely off PPIs. Median LES resting pressure did not show significant change after 8 years and mean esophageal acid exposure significantly improved after 4 years (P=0.001) but returned to baseline after 8 years. The group substantiated the durable effect of the Stretta procedure in improving symptoms and quality of life after 8 years post treatment.

Thus far, the longest follow up results were provided by Noar *et al.* who reported their 10-year follow up of 217 patients with refractory GERD before and after Stretta using an intention to treat analysis (30). The primary outcome, which was normalization of GERD HRQL, was achieved in 72% of the patients and the secondary outcome of 50% or greater reduction in PPI use occurred in 64% of patients. A secondary outcome measure was patient satisfaction using Likert scale demonstrating a 60% or greater increase in satisfaction in 54% of patients. The most common side effect was short-term chest pain (50%). From a cohort of 149 patients available for analysis, a total of 51 patients underwent repeat endoscopy at year 10. Of those, 33 had prior Barrett's esophagus defined as metaplasia on four quadrant biopsies. At 10-year follow up, pre-existing

Barrett's metaplasia regressed in 85% of the biopsied patients (15% of the patients had metaplasia on biopsies) with no reported cases of esophageal cancer. This study demonstrated long-term safety and efficacy of the Stretta procedure.

Stretta compared to other therapies

The comparative trials reported above included sham and PPI as the comparator. However, more recently, a prospective observational study compared short-term and midterm outcomes of the Stretta procedure with laparoscopic Toupet fundoplication (LTF) (23). Of the 165 patients initially enrolled (80 to LTF and 85 to Stretta), 125 patients (65 LTF and 60 Stretta) completed the 3-year follow up study with significant improvement in symptom score in both groups after the procedures (P<0.5). However, as compared with LTF, the Stretta procedure had less effect on improving typical symptoms like heartburn, regurgitation and chest pain.

Stretta for GERD post-surgery

Laparoscopic sleeve gastrectomy (LSG) is one of the commonest bariatric procedures performed today in obese patients. Unfortunately, GERD is a common post-operative adverse event with one study showing new-onset of heartburn in 47.06% of the patients undergoing sleeve gastrectomy (41). A recent retrospective study evaluated the safety and efficacy of the Stretta procedure in 15 GERD patients, post-LSG. Pre-Stretta endoscopic reflux esophagitis was present in 26.7% of the patients with mean DeMeester score being 27.9±6. At 6 months post-Stretta treatment, 66.7% of the patients were not satisfied with the procedure and continued to have GERD symptoms although PPI treatment was discontinued in 20% of the patients. Two patients (13.3%) had undergone Roux-en-Y gastric bypass at 8 months post Stretta to relieve GERD related symptoms (42). This study, however had several limitations including retrospective design, small number of patients and lack of esophageal manometry and 24-hour pH monitoring in the post-Stretta period as the patients refused to undergo any further testing. The authors attributed this to the lack of satisfactory results with Stretta in their small cohort. Further studies are needed to evaluate the value of the Stretta procedure in post LSG patients who developed GERD.

Laparoscopic Nissen fundoplication (LNF) is the most common surgery done in patients with refractory GERD. However, over long term, several of these patients have recurring symptoms and the need for resumption of anti-secretory medication use. Noar *et al.* prospectively assessed patient reported outcomes in 18 refractory LNF patients and 81 standard refractory GERD patients who underwent Stretta after 10-year follow up (43). The refractory LNF patients demonstrated a significant median improvement in GERD-HRQL, satisfaction, and medication use at all follow-up time points (≥6 months to 10 years) as compared with baseline of both on- and off-medications (P<0.05). Importantly, at 10 years, median GERD-HRQL decreased from 36 to 7 (P<0.001), satisfaction increased from 1 to 4 (P<0.001), and medication score decreased from 7 to 6 (P=0.04). The study showed that in this small cohort of refractory LNF patients, Stretta provided sustained and durable improvement over 10 years.

Cost analysis

Unfortunately, not many studies have assessed the cost analysis of endoscopic anti-reflux therapies such as Stretta. One of the studies that applied a decision analysis model, by comparing the cost of endoluminal gastroplication *vs.* the Stretta procedure *vs.* PPI treatment demonstrated that endotherapy was the most economical strategy after 17 months in patients requiring twice daily use of PPI for symptom relief (44). Another recent study, employing a Markov model that was generated from the payer's perspective using a 6-month cycle and 30-year time horizon, compared long term cost-effectiveness of medical, endoscopic and surgical managements of GERD (45). In the base case analysis, which assumed a PPI cost of $234 over 6 months ($39 per month), Stretta and LNF were the most cost-effective strategies over a 30-year time period ($2,470.66 and $5,579.28 per quality adjusted life years gained, respectively). In this model, if PPIs exceeded $90 per month, medical therapy was no longer cost effective and procedural therapy should be considered for patients who require high dose PPI or expensive PPI.

Safety

To date, more than 17,000 Stretta procedures have been performed without serious side effects attributed to the procedure. Some of the rare adverse events that were reported included fever, superficial mucosal injury, chest pain requiring analgesics and transient dysphagia (35). Some

of the extremely rare complications that were described included esophageal perforation and death due to aspiration pneumonia (46). The esophageal perforation was attributed to poor patient selection or operator error.

Conclusions

Of the several available medical, endoscopic, and surgical therapies for GERD, Stretta therapy has established itself as an attractive option for patients who would like to avoid the dependence and risk of long-term medical therapy and complications or loss of efficacy overtime of surgery. The safety and efficacy of the Stretta procedure has been demonstrated in several thousand patients over the last 15 years. Although the results have been variable at times due to heterogeneity of the measured clinical endpoints such as decrease in esophageal acid exposure or increase in LES pressure, Stretta is a viable low cost and safe procedure for adult patients with GERD who require long term PPI treatment. Most importantly, Stretta does not preclude other therapies if needed and can be repeated when necessary.

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Footnote

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