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Long-term maintenance effect of radiofrequency energy delivery for refractory GERD: a decade later

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Abstract
Background Patients with gastroesophageal reflux disease (GERD) often seek alternative therapy for inadequate symptom control, with over 40 % not responding to medical treatment. We evaluated the long-term safety, efficacy, and durability of response to radiofrequency treatment of the lower esophageal sphincter (Stretta).
Methods Using an intent-to-treat analysis, we prospectively assessed 217 patients with medically refractory GERD before and after Stretta. There was no concurrent control group in the study. Primary outcome measure was normalization of GERD-health-related quality of life (GERD-HRQL) in 70 % or greater of patients at 10 years. Secondary outcomes were 50 % reduction or elimination of proton pump inhibitors (PPIs) and 60 % or greater improvement in satisfaction at 10 years. Successful treatment was defined as achievement of secondary outcomes in a minimum of 50 % of patients. Complications and effect on existing comorbidities were evaluated. The results of a 10-year study are reported.
Results The primary outcome was achieved in 72 % of patients (95 % confidence interval 65–79). For secondary outcomes, a 50 % or greater reduction in PPI use occurred in 64 % of patients, (41 % eliminating PPIs entirely), and a 60 % or greater increase in satisfaction occurred in 54 % of patients. Both secondary endpoints were achieved. The most common side effect was short-term chest pain (50 %). Pre-existing Barrett's metaplasia regressed in 85 % of biopsied patients. No cases of esophageal cancer occurred.
Conclusions In this single-group evaluation of 217 patients before and after Stretta, GERD-HRQL scores, satisfaction, and PPI use significantly improved and results were immediate and durable at 10 years.

Keywords Stretta · GERD · Medication use · GERD-HRQL · Reflux · Radiofrequency energy · Barrett's

Gastroesophageal reflux disease (GERD) is the most common principal gastroenterological diagnosis in the US, associated with a wide range of symptoms, typically heartburn, acid regurgitation, and dysphagia, while severely impairing health-related quality of life (HRQL) [1, 2]. Until recently, it was thought that the predominant disease-causing mechanism of action was acid and/or bile penetration of the esophageal mucosa as the sole cause of heartburn manifestations [3, 4]. However, in recent years, research into mucosal receptors and their molecular response to stimulation, demonstrated both a direct and an indirect mechanism of action of acid and other caustic-sensing receptors causing release and activation of both neural and non-neural chemokine pathways leading directly to a decline in cell integrity, and the development of inflammation, pain, and compromised motility [5–9].

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Barrett's esophagus, an indicator of GERD, is the result of chronic esophageal reflux and afflicts an estimated 3.3 million Americans, requiring substantial endoscopic surveillance [10]. Esophageal adenocarcinoma is as prevalent in those with frequent heartburn as in those diagnosed with Barrett's esophagus, suggesting reflux itself is the cause of esophageal cancer, and not Barrett's specifically [11, 12]. Although proton pump inhibitors (PPIs) alleviate symptoms in many GERD patients, ~40 % demonstrate inadequate or a complete lack of symptom control [13, 14]. Long-term PPI use has been associated with a variety of adverse effects [15–19]. These include bone fractures, community-acquired pneumonia, mineral and vitamin deficiency, major adverse cardiovascular events, and others [15–19].

Fewer than two-thirds of heartburn sufferers are totally satisfied with their symptom relief, resulting in nearly 9 million yearly GERD-related office visits and significant loss of workplace productivity [2, 20, 21]. Surgical treatment for GERD correction may be associated with a significant decrease in long-term survival, as well as symptomatic recurrence requiring reintroduction of medication that can reach 62 % after 7 years post-operatively [22].

A number of minimally invasive, lower cost, and lower risk endoscopic procedures have been introduced since 1998, including Endocinch (Bard), Enteryx (Boston Scientific), Gatekeeper, Ndo Plicator (NDO), injection of sclerosants and collagen, and radiofrequency (RF) modulation of the lower esophageal sphincter (LES) or Stretta procedure [23–28], as well as three additional surgical technologies including Esophyx (EndoGastric Solutions), Linx titanium magnets (Torax), and implantable LES stimulators (EndoStim) [29–31].

Nearly all nonsurgical devices have been withdrawn from the market either due to ineffectiveness or complications [32–34], except for the Stretta device. The Stretta procedure delivers RF energy to the LES, resulting in an increase in basal LES pressure and overall improvement in the anti-reflux barrier [35], improving GERD symptoms by reducing LES compliance, contributing to a possible beneficial decrease in refluxate volume [36]. There is a significant decrease in intra-esophageal pH as well as both proximal and distal esophageal acid exposure [37]. Single, and more notably double-dose, Stretta therapy produces a more frequent normalization of GERD-HRQL, and a reduction in both the use of PPI medication and esophageal acid exposure [38].

This translates into significant improvement in GERD symptoms, patient satisfaction, and HRQL at short- and intermediate-term follow-up; however, longer-term durability, beyond 48 months, and effect on patient symptoms and medication requirements have not been established [39]. At 48 months, studies have demonstrated significant GERD improvement, and a sustained effect superior to that achieved with escalated PPI therapy above baseline dosing [40].

The aim of this study was to evaluate the efficacy of the Stretta procedure in patients with medically refractory GERD symptoms, 10 years after initial treatment, using an open-label design.

Methods

Study design

The study was designed as a 10-year, open-label, prospective trial in GERD patients with inadequate symptom control despite minimum twice-daily PPI therapy who underwent the Stretta procedure. The primary objective was assessment of GERD-HRQL using a validated questionnaire a decade after treatment with the Stretta procedure. This would allow the determination of the long-term maintenance effect of an intervention by the Stretta procedure.

Patients

From August 2000 to September 2004, a total of 217 patients underwent Stretta, 149 reaching the 10-year follow-up. Eligible patients had daily recurring symptoms of heartburn and regurgitation despite twice-daily PPI use. In the majority of patients, GERD was confirmed by upper endoscopy revealing erosive esophagitis (Los Angeles grade A or higher). If no erosive esophagitis was present, GERD was confirmed by abnormal esophageal acid exposure with ambulatory esophageal pH testing. Patients with erosive esophagitis were maintained on medical therapy until healed before undergoing the Stretta procedure. Most patients had normal esophago-gastric anatomy. A small subset of patients demonstrated failed Nissen fundoplication (NF) surgery (15) or large (>3 cm) hiatal hernia (5). Patients with short-segment Barrett's were included. Exclusion criteria were stenosis, stricture, or ulceration of the pylorus, pregnancy, poor surgical risk [American Society of Anesthesiologists (ASA) grade >III], achalasia, previous non-NF esophageal surgery, scleroderma-type collagen vascular disease, or severe uncontrolled medical illness.

This study was approved by the human subject study committee at the Heartburn and Reflux Study Center.

Study procedures

Prior to undergoing Stretta, patients completed the Velanovich reflux severity symptom assessment (GERD-HRQL

questionnaire) off and on medical anti-reflux therapy. GERD-HRQL scores range between 0 and 50, with scores <10 considered within normal range [41]. The GERD-HRQL is a short, disease-specific quality-of-life scale that is a better predictor of patient-perceived symptoms and satisfaction than the SF-36 [42]. Patients find the GERD-HRQL easy to understand, having few unanswered points when assessing the questionnaire [43], and it has proven to be reliable, valid, and practical for the assessment of symptom severity of GERD [44]. This validated questionnaire assesses current satisfaction and overall heartburn severity, specifically evaluating (i) heartburn lying down, standing, and post-meals; (ii) effect on diet; (iii) sleep impairment; (iv) difficulty swallowing; (v) painful swallowing; (vi) bloating/gassy feelings; and (vii) impact of medication need on daily activities. Responses are ranked 0–5; higher scores indicate more severe symptoms. Patient satisfaction is rated 0–5, with higher scores indicating greater satisfaction. Medication usage was assessed via standardized GERD medication scoring capturing type, dose, and frequency of use, scale 0–20, with lower scores indicative of as needed or no medication use. Questionnaires were obtained at baseline (off and on medication) then at 0.5, 1, 2, 3, 4, and 10 years after the Stretta procedure.

Subject localization challenges required utilizing various internet-based novel investigational methods including Internet searches of White Pages, 'people finders', public-domain government databases, and social media venues.

The Stretta procedure was performed by a single practitioner, with patients as outpatients at the Heartburn and Reflux Study Center in Baltimore, MD, USA. All received conscious sedation with a combination of midazolam and fentanyl. Using standard technique [28], a diagnostic upper endoscopy was performed to locate the gastroesophageal junction. Upon endoscope removal, a wire-guided flexible RF delivery catheter (a balloon-basket assembly with four treatment elements positioned radially around the balloon) is passed transorally then positioned within the gastroesophageal junction. After appropriate balloon inflation (<3 psi), the treatment elements are deployed 1–2 mm into the LES muscle, where energy is delivered in a series of thermal treatments at four levels in two positions (distal esophagus) and at two levels in three positions (gastric cardia). The monitoring of temperature and impedance at each treatment element ensured safe and precise RF delivery. As RF energy is applied during the procedure, chilled water is irrigated from the catheter down the esophageal mucosa to prevent ulceration or stricture. After completion of the procedure and catheter removal, the endoscopy is repeated to verify that there have been no complications such as bleeding or perforation and to document the appropriate site of treatment. All pre-Stretta medication is maintained for 6–8 weeks after the procedure to maintain baseline and allow time for complete procedural effect, and prevent potential complications.

At 0.5, 1, 2, 3, 4, and 10 years after the Stretta procedure, all patients in the 217-patient cohort were contacted. Unless patients were determined to be deceased or unwilling to participate, GERD-HRQL questionnaires, GERD medication assessment, and overall patient satisfaction were obtained through various modes of communication, primarily during in-office interviews as well as when necessary, via telephone interview, direct mail, and email.

Endpoints

The primary endpoint was defined as normalization of GERD-HRQL in 70 % or greater at 10 years, compared with baseline. Secondary endpoints measured separately were (i) 50 % or greater reduction or elimination of PPIs at 10 years and (ii) 60 % or greater improvements in satisfaction at 10 years, both compared with baseline. The definition of successful treatment for each secondary outcome was achievement of each outcome in a minimum of 50 % of patients. Adverse events and side effects were measured at all time points.

Statistical methods

Demographic characteristics and endpoint outcomes data (GERD, satisfaction, and medication scores) were summarized at each time point using means and standard deviations and evaluated using an intention-to-treat paradigm. Results were evaluated using a general mixed model analysis in order to determine whether there was significant difference (trend) between the eight time points off and on medication prior to the procedure, and 0.5, 1, 2, 3, 4, and 10 years ($N = 217$, all subjects with data regardless of how many time points were completed). For subjects who underwent two procedures, data from both procedures were concatenated to produce one single string of results, restarting the required 10-year interval for inclusion. In the event of a significant effect from this primary analysis, the data were sub-analyzed using a Bonferroni procedure to control for multiple comparisons among the time points and maintain a global 5 % significance level for these analyses. Since many patients did not complete the full 10 years of evaluation, the data were analyzed using all available data in the global repeated measures model and then in only those subjects who provided a 10-year assessment in order to determine if there were any type-one statistical errors due to any incomplete information on any given patient. All analyses were performed using NCSS 8 (Hintze version 2012; NCSS, LLC. Kaysville, UT, USA. www.ncss.com).

Table 1 Study population baseline characteristics

Characteristics	Complete cohort	Patient pool
Number of patients	217	99
Sex		
Male	88 (41)	41 (41)
Female	129 (59)	58 (59)
Age (years)		
Mean (SD)	50 (14)	50 (13.5)
Range	16–88	19–77
Weight (lbs)		
Mean (SD)	174 (40)	173 (42.5)
Range	96–342	96–342
Barrett's esophagus (%)	51 (22)	32 (32)
Erosive esophagitis (%)	0	0
Eosinophilic esophagitis (%)	0	0
PPI twice daily (%)	217 (100)	99 (100)
PPI twice daily + H_2 receptor antagonists (%)	83 (38)	44 (44)

Data are presented as *N* (%) unless otherwise indicated

PPI proton pump inhibitor, *SD* standard deviation

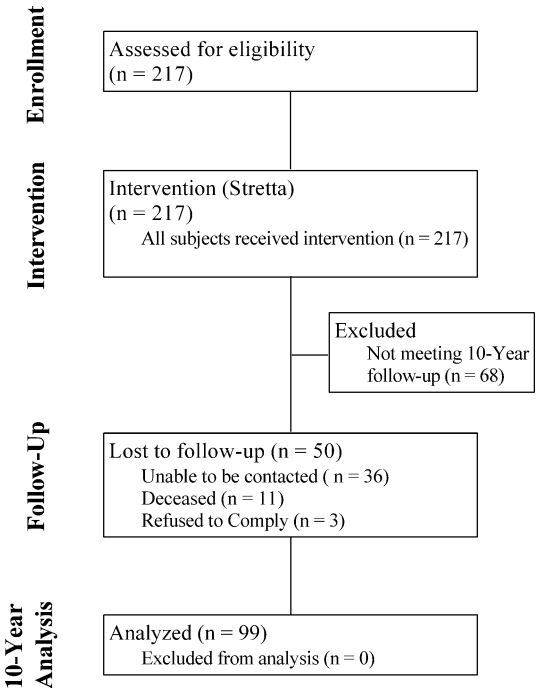


Fig. 1 Overview of cohort analysis

Results

Patient characteristics

The complete cohort group (CC) comprised 217 consecutive patients, 149 of whom reached their 10-year follow-up.

Table 2 Post-procedure symptoms

Treatment group	217	99
No symptoms	114 (53)	48 (48.5)
Patients with symptoms[a]	103 (47)	51 (51.5)
Abdominal pain	12 (10.2)	4 (8.3)
Chest discomfort	41 (34.7)	24 (50)
Diarrhea	2 (1.7)	0 (0)
Dyspepsia	37 (31.4)	12 (25)
Dysphagia	3 (2.5)	2 (4.2)
Fever (low grade)	1 (0.9)	0 (0)
Flatulence (increased)	13 (11.0)	2 (4.2)
Gas	2 (1.7)	1 (2.1)
Hiccups	1 (0.9)	0 (0)
Nausea	5 (4.2)	2 (4.2)
Odynophagia	1 (0.8)	1 (2.1)

Data are presented as *N* (%) unless otherwise indicated

[a] All symptoms were transient, lasting <2 weeks

All patient data were matched to baseline (Table 1). Of the 149 patients available for 10-year follow-up, 50 did not complete 10-year follow-up questionnaires or phone surveys (36 could not be contacted, 11 were deceased of natural causes or non-gastrointestinal-related disease, and three declined). A total of 99 remaining patients, who completed all time points at 10 years, represent the participant pool group (PP) (Fig. 1).

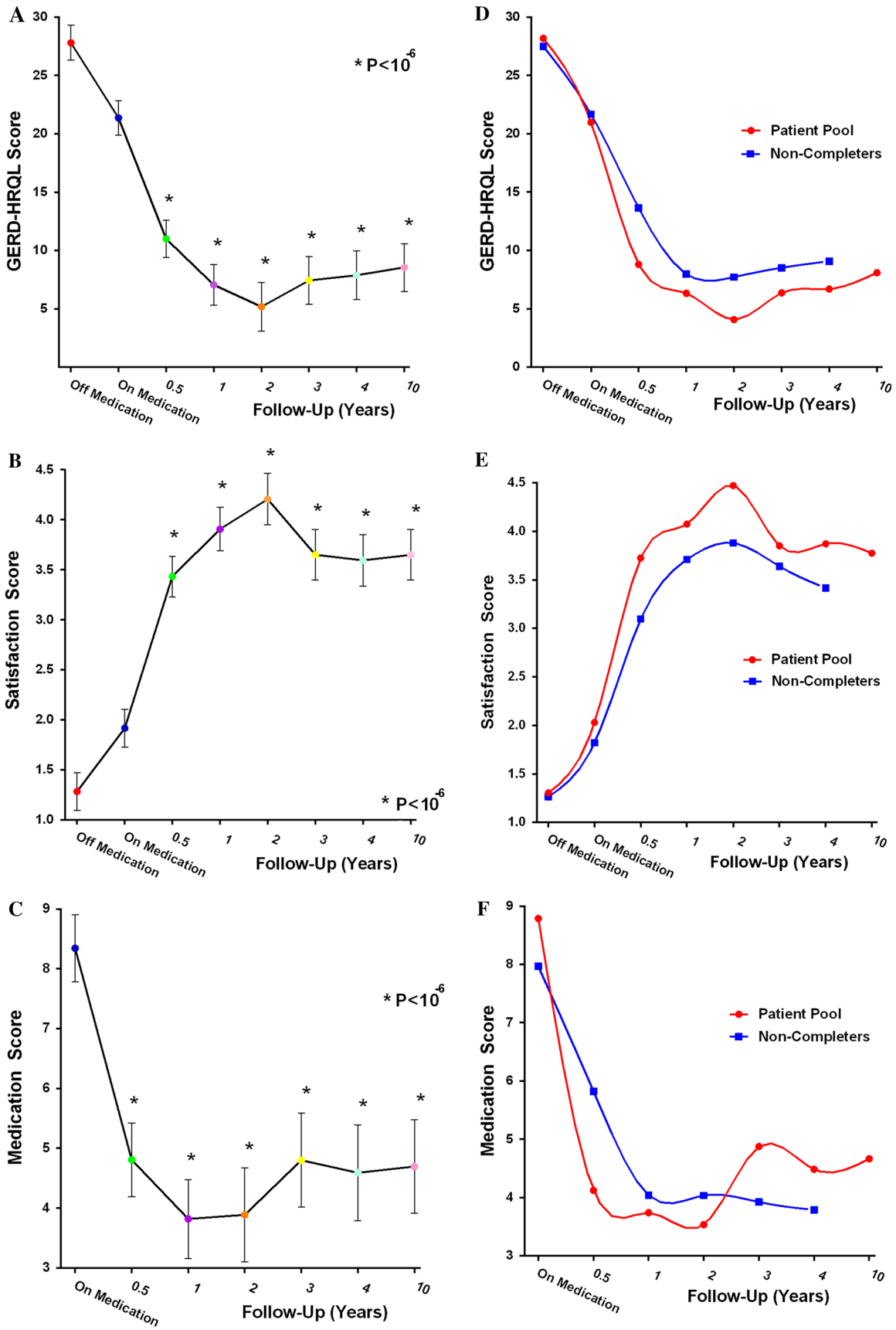
Of the 217-patient CC analysis, 68 had not yet reached the 10-year time point. The 118-patient non-completer group comprised 68 patients who had not reached the 10-year follow-up, in addition to the 50 patients who did not complete 10-year questionnaires.

Procedural information

Median procedure time was 25 min (range 19–45). No immediate adverse events occurred. A total of 217 Stretta devices were used without failure or malfunction. Patients were discharged within 60 min on a diet restricting nuts, chips, or pretzels for 24 h. Prior medication continued without dosing change.

Adverse events

Two episodes of minor proximal gastric bleeding were diagnosed by gastroscopy. The bleeding was self-limited, required no intervention or transfusion and resolved with the reinstitution of PPIs. No additional short-term adverse events occurred, and throughout the 10-year study period no long-term adverse events developed.


A
GERD-HRQL Score
* P<10-6
Off Medication
On Medication
0.5
1
2
3
4
10
Follow-Up (Years)
D
GERD-HRQL Score
Patient Pool
Non-Completers
Off Medication
On Medication
Follow-Up (Years)
B
Satisfaction Score
* P<10-6
Off Medication
On Medication
Follow-Up (Years)
E
Satisfaction Score
Patient Pool
Non-Completers
Off Medication
On Medication
Follow-Up (Years)
C
Medication Score
* P<10-6
On Medication
Follow-Up (Years)
F
Medication Score
Patient Pool
Non-Completers
On Medication
Follow-Up (Years)

◀**Fig. 2** Complete cohort ITT and comparative Bonferroni analysis: GERD-HRQL, satisfaction, and medication use over 10-year period. Post-procedure sample size at follow-up time points: 0.5 years ($N = 177$), 1 year ($N = 149$), 2 years ($N = 98$), 3 years ($N = 98$), 4 years ($N = 94$), and 10 years ($N = 99$). **A** CC mean GERD-HRQL assessment scores at baseline without and with PPIs compared with follow-up time points. There was a significant improvement after therapy for all six follow-up time points, with $p < 10^{-6}$ compared with baseline assessments both without and with PPIs. **B** CC mean patient satisfaction scores at baseline without and with PPIs compared with follow-up time points. There was a significant improvement after therapy for all six follow-up time points, with $p < 10^{-6}$ compared with baseline assessments both without and with PPIs. **C** CC mean medication score at baseline with PPIs compared with follow-up time points. There was a significant improvement after therapy for all six follow-up time points, with $p < 10^{-6}$ compared with baseline assessment with PPIs. **D–F** are respective comparative Bonferroni sub-analyses of patient pool and non-completers. Sub-analyses confirm that the results of each tested field (GERD-HRQL, satisfaction, and medication use) are the same regardless of whether all 217 (CC) or only 99 (PP) are considered, demonstrating no associated bias of non-completers and a strengthened consistent trend in both data sets over time. *Error bars* are indicative of 95 % CI. *CC* complete cohort group, *GERD-HRQL* gastroesophageal reflux disease-health-related quality of life, *ITT* intent-to-treat, *PP* participant pool, *PPI* proton pump inhibitor

Procedure-related symptoms

Minor transient side effects lasting under 2 weeks were experienced by 50 % of patients. The most common symptoms were chest discomfort (50 %), dyspepsia (25 %), and abdominal pain (8.3 %) in the PP group, and chest discomfort (34.7 %), dyspepsia (31.4 %), increased flatulence (11 %), and abdominal pain (10.2 %) in the CC group (Table 2).

Efficacy endpoints

The primary endpoint, normalization of GERD-HRQL in ≥70 % of patients, was achieved in 72 % of patients (71 of 99; 95 % confidence interval [CI] 66–77) at 10 years. The secondary endpoints were achieved as follows: (i) 50 % reduction or greater in PPI use compared with twice-daily PPI use at baseline was achieved in 64 % of patients (64 of 99; 95 % CI 58.5–69.5) as well as 41 % eliminating PPIs entirely (41 of 99; 95 % CI 35–46) at 10 years; and (ii) 60 % increase or greater in satisfaction compared with baseline without medication was achieved in 55 % of patients (54 of 99; 95 % CI 48–60) at 10 years.

GERD-HRQL, satisfaction, medication use summary

The post-Stretta effect was immediate at 6 months, and durable throughout long-term follow-up in regards to all tested fields (GERD-HRQL, satisfaction, and medication use). Based upon the Bonferroni test, results were the same whether analysis was performed on the CC (217) or the PP (99) group, demonstrating no bias associated with the non-Completers, and a strengthened consistent trend in both data sets over time (Fig. 2).

GERD-HRQL

In the CC group, there was significant decrease from baseline mean (off medication) of 27.81–8.55 ($p < 10^{-6}$) at 10-year follow-up. Statistical significance was shown from the second time point mean (on medication) of 21.36–8.55 ($p < 10^{-6}$) at 10 years (Fig. 2A, D).

Satisfaction

In the CC group, a significant increase was noted from baseline mean (off medication) of 1.28–3.65 ($p < 10^{-6}$) at 10-year follow-up. Additionally, statistical significance was shown from our second time point (on medication) mean of 1.92–3.65 ($p < 10^{-6}$) at 10 years (Fig. 2B, E).

Medication requirements

In the CC group, results demonstrated a significant decrease from baseline mean medication scores of 8.35–4.70 ($p < 10^{-6}$) at 10-year follow-up (Fig. 2C, F).

At baseline, 100 % of patients received twice-daily PPI therapy. At 10 years, 23 % (23 of 99) eliminated medical treatment entirely, and 41 % (41 of 99) of patients were off PPIs and taking no regular medical therapy. Of the remaining 59, 34 % (34 of 99) were taking a single dose of PPI and 25 % (24 of 99) were maintained on the equivalent of twice-daily PPI treatment.

Barrett's esophagus subset

In the cohort of 149 patients available for analysis at year 10, a total of 51 patients underwent repeat endoscopy at year 10 or later, without evidence of erosive esophagitis. Of this subset, 33 patients had prior Barrett's esophagus defined as positive metaplasia on four quadrant biopsies, and 18 patients did not have metaplasia. One of 33 Barrett's patients had low-grade dysplasia at study entry. At 10-year follow-up, only 5 of the 33 had any remaining metaplasia noted in biopsies. The one patient with low-grade dysplasia had no further dysplasia or metaplasia. In 18 patients without metaplasia, there was no change in esophageal histology.

Esophageal cancer

There were no reported cases of esophageal cancer in 217 patients. However, direct endoscopic confirmation was only possible in 51 patients at the time of data closure.

Miscellaneous

Of the 99 patients in the PP group, 12 were unsatisfied with initial results, and requested a second procedure. One underwent NF and 11 a Stretta procedure. Of the 11 who underwent a second Stretta, one was performed following collection of the 10-year data, and ten were performed 10 years prior to the 10-year data collection closure.

Discussion

This trial investigated the durability and safety of the Stretta procedure in patients with refractory GERD symptoms 10 years post-procedure. Stretta directly resulted in significant and sustained improvement 10 years post-procedure, with the normalization of GERD-HRQL scores in 72 % of patients. Patient medication use improved significantly, with 64 % of patients achieving a reduction of 50 % or higher in the medication taken, of whom 41 % were able to eliminate the use of PPIs entirely at 10 years following Stretta. This is in comparison with baseline twice-daily PPI therapy in all patients. These results are accompanied by a >60 % increase in satisfaction in 55 % of patients at the 10-year evaluation point. As such, both the primary and the secondary endpoints were exceeded in most participating subjects, validating the long-term usefulness of this endoscopic procedure.

Prior to release of these 10-year data, there have been more than 40 short-term Stretta studies, employing the same validated research tools, demonstrating short-term improvement of heartburn scores, medication usage, and satisfaction. In three studies looking at the then long-term data at 48 months, there were similar statistically significant, durable improvements noted in GERD-HRQL, quality of life, and satisfaction scores, with 72–86 % of patients successfully discontinuing daily medication use [40, 45, 46]. One possible explanation for the difference in the number of patients no longer receiving PPIs at 10 versus 4 years may be that, because GERD is a symptom-driven disorder, and once symptoms improve or resolve, patients rapidly lose the incentive to maintain lifestyle changes, leading to recurrence of symptoms [47].

In addition, in four adequately powered randomized controlled trials, three of which were sham-controlled [35, 36, 38], there was a statistically significant improvement in medication use, GERD-HRQL, and satisfaction scores in treatment groups but not sham procedure groups. At crossover, similar improvements occurred in the sham patients. No sham group patient was able to discontinue medical therapy, while 50–56 % of treated patients had discontinued PPI therapy at 1 year. Given these prior results, the 41 % discontinuation rate of PPIs at 10 years combined with 72 % normalization of GERD-HRQL scores confirms the sustainability of the response of the shorter-term trials.

The 10-year data have significance in the context of the reported results of other GERD treatments. Although PPIs have been considered the mainstay of GERD treatment, ~40 % of patients are refractory to anti-secretory drug treatment [13, 14], and the desirable clinical endpoint of complete symptom resolution is not possible to achieve in most patients [48]. Fewer than 60 % of patients taking PPIs are totally satisfied with symptom control compared with 72 % of Stretta patients who reported normalization of symptoms at 10 years.

The presented data also demonstrate that, at 10 years following Stretta, there are no adverse effects of treatment, confirming long-term safety. This is unlike reports in the recent literature of adverse effects with chronic PPI use, including vitamin B_{12} deficiency, iron deficiency, pneumonia susceptibility, enteric infections, bone fractures, hypergastrinemia, drug–drug interactions, rebound acid secretion, and major adverse cardiovascular events [15–19].

Until now, prior literature has documented a single comparison trial between NF and Stretta, and, in this short-term study, there was no significant difference in improvement in quality of life, or heartburn scores, with esophageal pH improved significantly in both groups, some patients returning to normal [49]. With the addition of the 10-year Stretta data, it is now possible to compare Stretta with the only 10-year long-term study of NF. In 62 % of NF patients at 7 years, there was significant recurrence of symptoms requiring regular anti-reflux medication, leaving only 38 % no longer receiving PPIs [22]. In contrast, 41 % of Stretta patients were off medication at 10 years. In addition, 10 years following the Stretta procedure, there has been no associated increase in morbidity or mortality in Stretta patients, contrary to that in the post-NF patient population [22]. The Stretta 10-year patient subset also included 11 patients who required a second Stretta procedure, all of which were performed without complications. This differs with the additional costs and complication rates [49] associated with the redo of failed NF, due to known anatomic failure rates of 3.6–7 % [50, 51].

The durability of the Stretta procedure to improve symptoms, satisfaction, and medication use as seen in the current 10-year data is likely due to the effect of the treatment on limiting reflux. The main mechanism of GERD is felt to be the inappropriate occurrence of transient relaxation of the LES, or transient LES relaxation (TLESR) [52], leading to reflux and regurgitation of caustic gastric contents. Traditionally, it has been felt that this allows direct penetration and damage of the surface esophageal

mucosa, with research now suggesting instead that it is a receptor-driven disease with transient receptor potential vanilloid 1 (TRPV1) receptors initiating a cascade of neural and non-neural pathways, resulting in direct stimulation of nerves responsible for the heartburn symptoms [7, 8, 53–55] or non-neurally mediated effects involving the release of platelet-activating factor (PAF), which can in turn disrupt motility [9], cause direct tissue destruction [56–60], or attract eosinophils, resulting in eosinophilic esophagitis [61].

Supporting the mechanism for the reduction in reflux are numerous studies that demonstrate that following the Stretta procedure there is a reduction in TLESRs [62], a reduction in tissue compliance without fibrosis [36], and an increase in smooth muscle fiber size, with more muscle fibers per muscle bundle that results in the lengthening and thickening of the sphincter, increasing physiological barrier function [63, 64].

The effect of these physiological changes is further borne out by studies that have demonstrated increased LES tone [36, 62, 65], reduced esophageal acid exposure with reported normalization of pH [37, 39, 49, 62], increased gastric yield pressure [66], and improvements in gastric emptying [67] and gastric motility [68]. Importantly, what has not been demonstrated is denervation or desensitization of the esophagus, with a number of studies refuting this conjecture [37, 49, 65, 68]. As noted by Kahrilas, there have been no human histopathological studies to date demonstrating neurolysis within the esophagus after Stretta [69]. Instead there is supporting evidence of the effects based on physiological data.

The 10-year data have also further confirmed that, in 11 of the study patients, as noted in the prior literature, patients who have partially responded may undergo repeat procedures to achieve a more maximal response [8, 40], and for the fifteen 10-year study patients for whom NF had failed, Stretta is effective in patients who experience recurrence of reflux symptoms, confirming prior publication of same [40, 49, 64].

Other potentially very important findings regarding Barrett's esophagus and esophageal cancer have been noted in the 10-year patient cohort. At the start of the trial, there were 33 Barrett's patients, including one with dysplasia. At the time of biopsy at 10-years post-Stretta, 28 of the 33 had no further dysplasia and/or metaplasia, and 5 of the 33 with remaining metaplasia showed no advancement of the disease. This suggests not only that there may be a protective effect of Stretta associated with improved reflux control, but that patients with non-high-grade dysplasia may safely undergo the procedure. With regard to esophageal cancer incidence in the 10-year cohort, of the patients available at the 10-year data cut off, there was no reported esophageal cancer, and 51 of the 99 patients had had recent confirming endoscopy, raising the question of whether a reduction in reflux associated with the Stretta procedure may help limit the development of esophageal cancer in the refluxing population.

Despite the myriad of options to control the causes and/or symptoms of GERD, ideal treatment would ensure long-term safety and durability without continued intervention. GERD is a symptom-driven disorder, and once symptoms improve or resolve, patients rapidly lose the incentive to maintain lifestyle changes, medication use, or alternative therapy, leading to recurrence of symptoms [47]. This raises the question of whether the ultimate goal in determining the success of any endoscopic or other therapy for GERD should be based upon motility parameters, pH normalization, and the abolition of reflux, as opposed to long-term improvement of symptoms, medication use, and quality of life [70]. These latter criteria seem particularly salient as no medical, endoscopic, or surgical treatment can completely control or reverse reflux. One randomized trial comparing Stretta with PPIs alone noted better quality of life as well as decreased PPI consumption, similar to Noar et al. [40], without reported changes in pH metry, further supporting this concept [71]. The Stretta procedure based on this long-term study is one modality that has been demonstrated to meet the need for more permanent and safe control of the underlying cause of reflux and the subsequent pathogenic alterations of the disease, symptomatic control, improvement in the quality of life, and reduction of dependence on medication.

Limitations of this study include the following: (i) this is a non-randomized, single-center, open-label prospective trial; (ii) there is no inclusion of long-term pH and motility data, and no NF comparison arm; (iii) due to the long study period, patient migration and associated difficulty in assessing GERD via validated questionnaires, it was difficult to collect complete 10-year data; (iv) the data presented are only 10-year data and perhaps 15- and 20-year data may be needed to show continued durability of response; (v) not all 10-year patients had undergone final endoscopic screening, which limits the ability to definitively conclude that the procedure may influence the rate of esophageal cancer or course of Barrett's esophagus; and (vi) the study does not directly address the potential cost benefits, which may merit further study.

Despite the limitations, this 10-year follow-up study adds new information to the available literature. It is the only study of long-term efficacy of the Stretta procedure. Even given the large amount of missing data at the 10-year collection point, the intent-to-treat analysis demonstrated significant and durable improvements beginning 6 months post-Stretta and extending to 10 years, with 72 % of patients normalizing GERD symptom scores, 41 % of patients able to remain off regular medication for GERD,

64 % of patients able to reduce medication use by 50 % or greater, and more than 60 % sustained improvement in satisfaction. Additionally, despite continued use of regular anti-reflux medication in 59 % of patients, there were significant improvements in satisfaction and control of GERD symptoms, which was uncontrolled at baseline.

In summary, the large cohort results document long-term durability, beneficial symptomatic effects, and elimination of medication usage resulting directly from the effects of the Stretta procedure in refractory GERD patients. Given current concerns about long-term PPI use, the long-term durability of the Stretta procedure suggest it is a viable treatment for the correction of GERD, resulting in reduction in medication use, and may positively impact disease progression.

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