Gastroesophageal Reflux Disease (GERD) and Associated Disorders

The Past, Present, and Future of Treatment

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CONTENTS

• Review of GERD impact
• Traditional Treatments
• Endoluminal Therapies
• Associated Disorders
• Thoughts for the Future
GERD Symptom Impact

- Most common digestive disorder
- Heartburn responsible for 4-5 million physician visits annually
- GERD Symptoms may affect more than 1/3 of population
- Omeprazole (Prilosec) - U.S. sales $4.2 billion in 2000
- Use of PPI’s in hospital increasing at rate of 30% per year
- Esophageal adenocarcinoma has the most rapidly rising prevalence of any cancer in U.S. and in Europe
Atypical GERD
Extraesophageal Symptoms

GERD may occur in as many as:

- 50% of patients with Non-Cardiac Chest Pain (NCCP)
- 78% of patients with chronic hoarseness
- 82% of patients with asthma and patients with chronic cough, dental erosions, exercise induced symptoms
Traditional Treatment Options

Medication
- Lifelong dependence
- Incomplete relief
- Tolerability
- Long-term safety
- Compliance
- Cost

Surgery
- General anesthesia
- Complications:
  - 0.07-1.0% mortality
  - 0.5-4.9% mortality for re-do
  - 5-10% dysphagia, recurrent hernia
- 2.8 days avg. hospitalization
- Up to 28 days recovery
- Learning curve 30% develop new symptoms
- Cost

Pathophysiology of GERD:

Effect of Surgical Therapy

- Hypotensive LES: Yes
- Transient LES relaxations: No Effect
  - tLESr’s responsible reflux in healthy subjects and most reflux episodes in GERD patients
- Anatomic changes at EG junction: Yes
  - Hiatal defect and hernia
## 24-Hour pH Studies post Laparoscopic Fundoplication

<table>
<thead>
<tr>
<th>Author</th>
<th># Patients pH Negative</th>
<th>Follow-up (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hinder</td>
<td>21/24 (87%)</td>
<td>3 -12</td>
</tr>
<tr>
<td>Hunter</td>
<td>49/54 (91%)</td>
<td>12</td>
</tr>
<tr>
<td>Watson</td>
<td>42/48 (87%)</td>
<td>3</td>
</tr>
<tr>
<td>Peters</td>
<td>26/28 (93%)</td>
<td>21</td>
</tr>
</tbody>
</table>
LARS: Pre and PostOp Bowel Symptoms

Post-Fundoplication
Long Term Results

- 5 year follow up data
- > 250 patients
- 75% resume PPI therapy
- 68% recurrent medically refractory GERD

Spechler, JAMA, 2000
Mucous cells in the gastric pits secrete mucus. In the deeper part of the gland, **parietal cells** secrete **hydrochloric acid**. G-cells, which are present predominantly only in the antrum of the stomach, secrete gastrin. ECL cells secrete histamine, and Chief cells secrete pepsinogen (an inactive form of the pepsin-digesting enzyme pepsin) intrinsic factor, needed for the absorption of vitamin B12, is also secreted by the gastric mucosa (most likely the parietal cells).
Pathophysiology of GERD: Effect of Drug Therapy

- **Hypotensive LES**  
  No Effect

- **Transient LES relaxations**  
  No Effect
  - tLESr’s account for virtually all reflux episodes in healthy subjects and most reflux episodes in GERD patients

- **Anatomic changes at EG junction**  (Hiatal Hernia)  
  No Effect
Chronic Heartburn Patients
Satisfied with Treatment

“How satisfied with your prescription heartburn medication are you, relative to the amount of symptom relief obtained?” (n=11,604)

Patients Totally Satisfied With Treatment (%)

<table>
<thead>
<tr>
<th></th>
<th>H₂RAs</th>
<th>PPIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>40%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>60%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>80%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>100%</td>
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</tbody>
</table>

45%* 58%*

*p<0.001

Why Endoluminal Approach?

- GERD = 14-20 million U.S. adults.

- PPI’s are highly effective for Acid Reflux
  - However, symptoms not relieved by PPI for 20+%
  - Approx. 10% of patients do not tolerate PPI’s
  - Compliance Issues
  - PPI and other antisecretory drugs may have limited benefits in treating non-acid reflux
  - *For NERD patients standard diagnostic processes is limited.

Endoluminal Therapy
Considerations for Adoption

- Compatibility of technique
- Long term data and durability
- Complications
- Treatment of GERD associated conditions
  - Variant anatomy
  - Motility considerations
  - Retreatment options
Endoscopic Options

- Endoscopic Valvuloplasty
  - Endocinch (BARD)
  - Plicator (NDO)/ Esophyx

- Endoscopic Implantation
  - Polymethylmethacrylate (PMMA) Microspheres
  - Enteryx (BOSTON SCIENTIFIC) Ethylene Vinyl Alcohol Copolymer
  - Gatekeeper (MEDTRONIC) Submucosal Hydrogel Prosthesis

- Endoscopic STRETTA
  - 14 minutes of Radiofrequency energy delivered to 2.5cm cuff of the submucosa at GE junction
Endocinch

- Like the Stretta procedure, EndoCinch endoluminal gastroplication surgery (ELGP) was approved by FDA in 2000 for the treatment of GERD
- Combines endoscopy with a suturing system and is typically performed by an experienced endoscopist
- Pair of video endoscopes, an esophageal overtube, and the EndoCinch Suturing System while the patient is under sedation
Endocinch

- A total of 70 patients treated with EndoCinch at a single referral centre
- 173 sutures were placed
- In summary, EndoCinch was shown to be safe but not as efficient as expected after 18 months of follow up
- Gross loss of plications was the putative mechanism for treatment failure in the majority of patients

I scheifcke, Gut. 2005 Jun; 54(6): 752–758
Two multicenter trials
149 patients were randomized between a circumferential and a linear plication configuration
All patients were dependent on anti-secretories and had proven reflux by 24-h pH monitoring
At 6-mo follow up, there was a 63% symptom score improvement with elimination of PPI therapy in 74% and normalization of pH in 30% patients
A pilot study on 7 patients also showed similar results but failed to show objective improvement of reflux
Endoscopic Full-Thickness Plication for GERD

- Performed under direct endoscopic visualization
- Restructures gastric cardia to create barrier to reflux
- Pre-tied suture secures full-thickness serosa to serosa tissue union
- 15-20 minute procedure

Pre-Plication

Post-Plication
Post-Plication Anatomy

Pre-Plication

Post-Plication
Endoscopic Full-Thickness Plication

1. Plicator and gastroscope retroflexed.
2. Arms opened, tissue retractor advanced to serosa.
3. Gastric wall retracted, arms closed.
4. Single, pre-tied implant is deployed, securing serosa-to-serosa plication.
5. Full-thickness plication restructures normal anti-reflux barrier.
Plicator™ System
## NDO Sham Adverse Events

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Count (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal discomfort</td>
<td>12 (25%)</td>
</tr>
<tr>
<td>Chest pain</td>
<td>8 (16%)</td>
</tr>
<tr>
<td>Sore throat</td>
<td>5 (10%)</td>
</tr>
<tr>
<td>Shoulder pain</td>
<td>4 (8%)</td>
</tr>
<tr>
<td>Epigastric pain</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Leukocytosis</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>(O_2) Desaturation</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Pneumoperitoneum</td>
<td>1 (2%)</td>
</tr>
</tbody>
</table>

- Majority of events resolved spontaneously; no late onset of any adverse events; no long-term patient injuries or deaths
NDO Sham
Patient Disposition (n=159)

159 Randomized

77 Plicator

71 Full or Partial Data

70 Full or Partial Data

106 Full or Partial Data
(4 incomplete med use)
(28 refused pH)

82 Sham

70 Full or Partial Data

70 Crossover

3-Mo Unblinding

6-Mo Follow-Up (Combined)

- All pts in active & crossover group received single plication
- No re-treatments performed

NDO Sham
Median GERD-HRQL Score

- 60% of patients achieved ≥ 50% HRQL score improvement
- 26 vs. 10 (p<0.001) median HRQL score improvement
- 6-mo scores comparable to baseline on PPI scores
NDO Sham Median Heartburn Score

- 4 point scale (0 = no Sx, 4 = daily Sx)
- 61% of patients reported HB scores ≤ 1 at 6-months
57% of subjects remained off daily PPI therapy out to 36 months.

The proportion of patients achieving ≥50% improvement in GERD-HRQL score was consistent from 12 months (59%) to 36 months (55%).

Endoscopic full-thickness plication can reduce GERD symptoms and medication use for at least 3 years post-treatment.
EsophyX

- Was evaluated in 2006
- Uninterrupted suture line at the base of LES and opposing gastroesophageal junction to the fundus
- Creating a neoesophageal valve of 2–6 cm (average 4 cm) and 230 in circumference (range 160–300) and restoring the angle of His
- However, serious complications such as esophageal perforation and postoperative bleeding were reported

Injection/Implantation Techniques

- Injection of bovine dermal collagen, Teflon, Plexiglas, and Polytef with no remarkable benefits
- Were removed from the market because of unsatisfactory benefit from symptoms control or objective measurement of antireflux properties and various degrees of complications

Wong RF, Gastrointestinal Endoscopy. 2005
Gatekeeper technique

- Implant hydrogel prosthesis
- Safe technique
- The help of endoscopic ultrasound
- No data available about the comparison to medical therapy
- Considered experimental
STRETTA®
The least invasive endoluminal approach

- Over 10,000 patients to date
- 6 Years of peer reviewed clinical data
- Non-invasive endoscopic treatment
- Can be performed under conscious sedation
- 14 min treatment/30-35 min procedure
- Out-patient procedure - 1 day back to work
- Safe: Low Complication rate < 0.07%
- Does not preclude any future treatment options
The Stretta Treatment Catheter

- Flexible, non-latex
- Soft bougie tip (20 French)
- 6 mm shaft (20 French)
- 65 cm operating length
- Balloon/basket (max 3 cm)
- 5.5 mm NiTi electrodes
- Temperature and impedance monitoring
- Irrigation and suction
Pre-fundoplication

Post-fundoplication

NISSEN

STRETTA
Stretta Mechanism of Action

1. Collagen contraction to strengthen the LES muscle and minimize sphincteric distensability

2. Neurolysis/Pacing of cardia afferent and efferent nerves that trigger transient LES relaxations

3. Neurohormonal (GABA) mediation to improve LES function
LES wall thickness after RF

- 50% mean increase in thickness of the GE junction \((p<0.0001)\)

Baseline control-untreated
5.2 mm ± 0.3

6 months post-treatment
7.8 mm ± 0.3

Results

83 consecutive patients: 65 men (78%) and 17 women (22%) have reached follow-up of 48 months. Complete, matched data sets for 80 patients (96.4%) are reported with assessments at baseline and 12, 36 and 48 month follow-up; three patients were lost to follow-up between three and four years. No serious complications were associated with the Stretta procedure. All results were statistically significant at all timepoints. GERD symptom scores improved from a mean score of 2.7 at baseline to 0.3 at 36 months and 0.6 at 48 months. 68.67% of patients showed complete resolution of symptoms with scores of 0 (p<0.001). The mean quality of life scores improved from 2.4 at baseline to 4.6 at 36 months, 4.3 at 48 months (p<0.001).

Use of anti-secretory medications in patients following Stretta was reduced from 100% of patients using prescription anti-secretory medication at baseline to 29.4% of patients at 12 months and 12.1% of patients at 36 months and 13.75% of patients at 48 months (p<0.001). No patient who was previously on PPI BID returned to this requirement following the Stretta procedure. 90.2% of patients on PPI or H2RA pre-procedure had reduced their medication to none at all. 88.75% of patients had complete elimination of the need for anti-secretory medications or a reduction in their medication usage (i.e. PPI BID to PPI) and significant improvement in both symptom score and QOL measures.

Conclusions

Our study demonstrates that Stretta represents a durable modality that can be offered to patients suffering from persistent GERD as a clinically viable treatment for the relief of symptoms and requirement for ongoing medical management or the potential need for an invasive surgical procedure.

<table>
<thead>
<tr>
<th>Count</th>
<th>Row %</th>
<th>Antacid PRN</th>
<th>PPI</th>
<th>Baseline</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPI</td>
<td>46</td>
<td>90.20</td>
<td>5</td>
<td>9.80</td>
<td>51</td>
</tr>
<tr>
<td>PPI BID</td>
<td>23</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>29</td>
</tr>
<tr>
<td>Post Stretta</td>
<td>79.31</td>
<td>69</td>
<td>20.69</td>
<td>11</td>
<td>80</td>
</tr>
</tbody>
</table>

At four years, 69 (or 86.25%) patients have reduced their meds to either antacid PRN or no meds at all.

Medications have been reported as follows:
Medications of PPI BID with or without H2RA
Medications of PPI and H2RA, either alone or in combination
Medications of antacid PRN or no medication (“None”)
13 Years of Clinical Studies
Safe, Effective + Durable

> 20,000 patients treated to date

10 Year outcome study published online – Feb 2014
• Surgical Endoscopy

35+ published peer-reviewed studies
• Consistency of reported results (US, EU, Japan, China)
• Uniform protocols and inter-trial consistency
• Use of validated clinical surveys

Level I Evidence
• 3 Randomized Sham Control trials
  • 158 total patients followed 3-12 months
  • Significant improvement in symptom scores or quality of life compared to Sham group
• 1 Randomized vs. PPI
SAGES CSR Guideline Gives Stretta Strongest Grade Recommendation

Clinical Spotlight Review – Endoluminal Treatments for Gastroesophageal Reflux Disease (GERD)

Clinical Spotlight Review published on: 02/2013 by the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES)

Conclusion

More than 30 peer reviewed studies, including 4 adequately powered randomized, controlled studies, a comprehensive meta-analysis and multiple prospective clinical trials have documented the safety and efficacy of the Stretta procedure. Durable treatment outcomes to at least 48 months also have been demonstrated in multiple studies, with significant reduction or elimination of medications used to treat the symptoms of GERD, as well as improvement in GERD QOL and symptom scores. Stretta may be recommended as an appropriate therapeutic option for patients with GERD who meet current indications and patient selection criteria and choose endoluminal therapy over laparoscopic fundoplication. Those criteria include:

- Adult patients (age >=18) with symptoms of heartburn, regurgitation, or both for >= 6 months who have been partially or completely responsive to antisecretory pharmacologic therapy.

The procedure has not been studied and should not be applied in treating patients with severe esophagitis, hiatus hernias > 2 cm, long segment Barrett esophagus, dysphagia, or those with a history of autoimmune disease, collagen vascular disease, and/or coagulation disorders. Further studies are needed to evaluate the role of Stretta in children if it is to be considered a therapeutic option.

Recommendation:
Stretta is considered appropriate therapy for patients being treated for GERD who are 18 years of age or older, who have had symptoms of heartburn, regurgitation, or both for 6 months or more, who have been partially or completely responsive to anti-secretory pharmacologic therapy, and who have declined laparoscopic fundoplication.

Quality of Evidence: (++++) GRADE Recommendation: Strong
# Patient Selection Criteria – GERD Treatments

<table>
<thead>
<tr>
<th>Medications (PPIs)</th>
<th>Middle Therapy RF Therapy – Stretta</th>
<th>Anti-Reflux Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>70% respond to meds</td>
<td>25-30% symptoms poorly controlled with meds</td>
<td>5% have anti-reflux surgery</td>
</tr>
<tr>
<td>- Mild GERD symptoms</td>
<td>- Mild to moderate GERD</td>
<td>- Severe GERD</td>
</tr>
<tr>
<td>- Functioning LES</td>
<td>- &lt;2 cm hiatal hernia</td>
<td>- Intolerant of long-term medications</td>
</tr>
<tr>
<td>- Highly motivated patient</td>
<td>- Partial response to meds</td>
<td>- Side effects</td>
</tr>
<tr>
<td>- Compliant to routine</td>
<td>- Non-compliant to PPIs routine</td>
<td>- Drug interactions</td>
</tr>
<tr>
<td>- Not requiring daily long-term use</td>
<td>- Intolerant of long-term medication use</td>
<td>- Post-Stretta with GERD symptoms</td>
</tr>
<tr>
<td>- Tolerant of medication</td>
<td>- Side effects</td>
<td>- Erosive esophagitis</td>
</tr>
<tr>
<td>- No side effects</td>
<td>- Drug interactions</td>
<td>- &gt;3 cm hiatal hernia (ARS)</td>
</tr>
<tr>
<td>- No drug interactions</td>
<td>- Post bariatric surgery with GERD symptoms</td>
<td>SPECIAL INDICATIONS</td>
</tr>
<tr>
<td></td>
<td>- Non-erosive reflux disease</td>
<td>- Transoral Fundoplication</td>
</tr>
<tr>
<td></td>
<td>- Post anti-reflux surgery with GERD symptoms</td>
<td>- &lt;2 cm hiatal hernia</td>
</tr>
<tr>
<td></td>
<td>- Extra-esophageal symptoms of GERD</td>
<td>- &lt;35 Body mass index</td>
</tr>
<tr>
<td>SPECIAL INDICATIONS</td>
<td>- Implanted Devices</td>
<td>SPECIAL CONSIDERATIONS</td>
</tr>
<tr>
<td>- Implanted Devices</td>
<td>- Magnetic implants are contraindicated for standard MRI</td>
<td></td>
</tr>
</tbody>
</table>
Final Thoughts

- Increasing incidence of GERD and associated medical conditions
- Increasing cost to society of medication, medical care
- Surgical treatment offers poor long term control of disease
- Endoluminal therapy currently represents the best documented potential treatment to help control both disease and costs
Thank you
“One’s age may be judged by the amount of pain one feels when presented with a new idea.”

- Balzac