# Magnetic Sphincter Augmentation Superior to Proton Pump Inhibitors for Regurgitation in a 1-Year Randomized Trial

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**BACKGROUND & AIMS:** **Regurgitative gastroesophageal reflux disease (GERD) refractive to medical treatment is common and caused by mechanical failure of the anti-reflux barrier. We compared the effects of magnetic sphincter augmentation (MSA) with those of proton-pump inhibitors (PPIs) in a randomized trial.**

**METHODS:** **Patients with moderate to severe regurgitation (assessed by the foregut symptom questionnaire) despite once-daily PPI therapy (n = 152) were randomly assigned to groups given twice-daily PPIs (n = 102) or laparoscopic MSA (n = 50) at 20 sites, from July 2015 through February 2017. Patients answered questions from the foregut-specific reflux disease questionnaire and GERD health-related quality of life survey about regurgitation, heartburn, dysphagia, bloating, diarrhea, flatulence, and medication use, at baseline and 6 and 12 months after treatment. Six months after PPI therapy, MSA was offered to patients with persistent moderate to severe regurgitation and excess reflux episodes during impedance or pH testing on medication. Regurgitation, foregut scores, esophageal acid exposure, and adverse events were evaluated at 1 year.**

**RESULTS:** **Patients in the MSA group and those who crossed over to the MSA group after PPI therapy (n = 75) had similar outcomes. MSA resulted in control of regurgitation in 72/75 patients (96%); regurgitation control was independent of preoperative response to PPIs. Only 8/43 patients receiving PPIs (19%) reported control of regurgitation. Among the 75 patients who received MSA, 61 (81%) had improvements in GERD health-related quality of life improvement scores (greater than 50%) and 68 patients (91%) discontinued daily PPI use. Proportions of patients with dysphagia decreased from 15% to 7% ($P < .005$), bloating decreased from 55% to 25%, and esophageal acid exposure**

*Abbreviations used in this paper:* BID, twice daily; GERD, gastroesophageal reflux disease; HRQL, Health-Related Quality of Life; IQR, interquartile range; LES, lower esophageal sphincter; MSA, magnetic sphincter augmentation; PPI, proton pump inhibitor; RCT, randomized controlled trial; RDQ, Reflux Disease Questionnaire.



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**time decreased from 10.7% to 1.3% ($P < .001$) from study entry to 1-year after MSA (Combined $P < .001$). Seventy percent (48/69) of patients had pH normalization at study completion. MSA was not associated with any peri-operative events, device explants, erosions, or migrations.**

**CONCLUSIONS:** **In a prospective study, we found MSA to reduce regurgitation in 95% of patients with moderate to severe regurgitation despite once-daily PPI therapy. MSA is superior to twice-daily PPIs therapy in reducing regurgitation. Relief of regurgitation is sustained over 12 months. ClinicalTrials.gov no: NCT02505945**

*Key Words:* Surgery; Medical Treatment; LES; CALIBER Study.

**See editorial on page 1685.**

Medically refractory regurgitative gastroesophageal reflux disease (GERD) is common and reflects mechanical failure of the antireflux barrier, including the lower esophageal sphincter (LES).[1–5] PPIs do nothing to restore a weak LES[6,7] and are frequently ineffective in alleviating regurgitation despite the common misperception that medications are sufficient therapy. Ongoing, bothersome regurgitation despite PPIs persists in 13% of GERD patients even when heartburn is alleviated.[8] Sleep disturbance, loss of work hours, and increased over-the-counter medication use is associated with medically refractory regurgitation.[9]

Antireflux surgery is the most effective therapy to control medically refractory regurgitative symptoms.[10] Magnetic sphincter augmentation (MSA) using the LINX device (Torax Medical, acquired by Ethicon Endo-Surgery, Cincinnati, OH) is an alternative to fundoplication that uses magnetic attraction from inside a series of titanium beads to augment the weak LES and re-establish the body's natural barrier to reflux. Warren et al,[11] using high-resolution impedance manometry, found that MSA could restore a defective LES to normal without apparent deleterious effects on the esophageal body. Effective control of heartburn and ability to cease or decrease PPI use with MSA have been demonstrated in multiple observational studies.[12–27] As MSA functions more like a pressure-relief system (compared with the flap-valve of a fundoplication), patients with MSA have not suffered the bloating and inability to vent side-effects that have been the bane of fundoplication.[28]

The CALIBER (Randomized Controlled Trial of LINX versus Double-Dose Proton Pump Inhibitor Therapy for Reflux Disease) (NCT02505945) study compared the effectiveness of increased PPI dosing with laparoscopic MSA in patients with moderate-to-severe regurgitation despite once-daily PPI therapy. Six-month results demonstrated the superiority of MSA compared with twice-daily (BID) PPIs in controlling regurgitation in this population.[29] This paper presents 12-month follow-up of this randomized controlled trial (RCT), including data for MSA crossover patients.

## Materials and Methods

### *Study Design, Patient Population, and Study Procedures and Outcomes*

This randomized, controlled, prospective, double-arm, crossover study enrolled 152 patients at 21 US clinical sites between July 2015 and February 2017. Patients were required to have moderate-to-severe regurgitation symptoms (based on the Foregut Symptom Questionnaire)[30] while receiving once-daily PPIs for at least 8 weeks and actively seeking alternative, surgical treatment, and with objective confirmation of GERD. Patients were also required to have body mass index $<35$ kg/m$^2$, abnormal pH testing results (determined by DeMeester score or total percentage of time with pH $<4$), normal esophageal motility, hiatal hernia of $<3$ cm by endoscopy, and absence of Barrett's esophagus or Los Angeles Classification Grade C or D esophagitis. Patients were administered standardized quality of life surveys, the Reflux Disease Questionnaire (RDQ),[31] and the GERD–Health-Related Quality of Life (GERD-HRQL),[32] as well as specific questions regarding bloating, diarrhea, flatulence, and medication use at baseline and at 6- and 12-month follow-up.

Enrolled patients were randomly assigned 2:1 to either BID PPI therapy, following Food and Drug Administration–recommended dose strength, with omeprazole 20 mg BID ($n = 102$) or laparoscopic MSA (primary MSA cohort) ($n = 50$). At 6 months, treatment efficacy was determined by clinical evaluation as well as ambulatory transnasal 24-hour impedance or pH testing (on medication in the PPI cohort, off medication in the MSA cohort).[29] The second portion of the study allowed eligible patients in the BID PPI arm crossover to receive a laparoscopic MSA (MSA crossover cohort) if both moderate-severe regurgitation persisted and impedance pH testing demonstrated persistent excess reflux burden (defined as $\geq 57$ reflux episodes in a 24-hour period while on BID PPIs, regardless of acid exposure).[33] Those that did not qualify for crossover were placed on a reduced 20-mg daily dose of omeprazole (step-down cohort).

At 12 months, patients were assessed by the quality of life metrics and underwent esophagogastroduodenoscopy with telemetry capsule esophageal pH monitoring. Assessments were performed in the MSA patients off PPIs (if being taken) for 7 days, and on once-daily PPI in

the step-down PPI cohort. Any other GERD medications were stopped 7 days before testing, with the exception of antacids which were allowed until the morning of assessment. As it is often thought that some degree of response to PPI therapy is required for a good outcome from an antireflux procedure,[34] we additionally evaluated clinical outcomes based on the preoperative response of regurgitation and heartburn to PPIs.[35]

The study protocol and informed consent form were approved by the institutional review board for each site, and all patients provided voluntary, written, informed consent to participate in the study. The ClinicalTrials.gov identifier is NCT02505945, the study start date was June 2015, the primary completion date was October 2017, and actual study completion date was August 2018. The study was sponsored by Torax Medical, Inc (acquired by Ethicon Endo-Surgery). All authors had access to the study data and had reviewed and approved the final manuscript.

### *Statistical Analyses*

Comparison of symptomatic outcomes between cohorts were analyzed for statistical significance by using the Pearson chi-square test. Summary statistics were used for other efficacy measures. Categorical parameters were displayed by number and frequency; normal and abnormal continuous parameters were expressed as mean ± SD or median (interquartile range [IQR]).

## Results

### *Patient Disposition and Demographic and Clinical Characteristics*

Of 202 patients screened for eligibility, 152 met inclusion criteria, were enrolled in the study, and were randomized to the primary MSA (n = 50) or BID PPI (n = 102) cohorts (Figure 1). The median age of all enrolled patients was 46 (range, 21–76) years, and the population was 58% men. The average length of PPI use for all patients was 8.4 (range, 0.3–35) years. Demographic and clinical characteristics were similar for the 2 randomized treatment arms and were presented in the 6-month publication.[29] Baseline demographic and clinical characteristics of patients completing 12-month follow-up as well as by crossover eligibility are available in Tables 1 and 2.

Seventy-nine patients randomized to the BID PPI treatment arm completed 6-month impedance or pH testing per protocol (85 were completed, but 6 tests were deemed invalid, or the patient was not taking medication as assigned). Thirty-one of 79 (39%) patients met all crossover requirements and are included in this analysis as the MSA crossover arm (Supplementary Figure 1). Forty-eight of 79 (61%) patients did not qualify for crossover, were placed on a reduced dose of 20-mg omeprazole daily, and constitute the step-down arm. Two of the patients reported resolution of moderate-to-severe regurgitation and had >57 reflux episodes (both with normal esophageal acid exposure). Of the remaining 46 with ≤57 reflux episodes, 40 reported ongoing moderate-to-severe regurgitation and 6 did not. Per protocol, only number of reflux episodes was considered in crossover qualification. However, 20% (n = 11 of 44) of the step-down cohort in whom pH data was reported had abnormal DeMeester scores while on BID PPI (>14.7) and had ongoing moderate-to-severe regurgitation. None of preoperative demographics, symptoms, or objective data predicted likelihood of crossover on multiple regression analysis.

### What You Need to Know

#### Background

Regurgitative gastroesophageal reflux disease refractive to medical treatment is common and caused by mechanical failure of the antireflux barrier. We performed a trial to compare the effects of magnetic sphincter augmentation (MSA) with those of proton pump inhibitors (PPIs) in patients with regurgitation and gastroesophageal reflux disease.

#### Findings

In a randomized comparison study, we found that MSA controlled regurgitation in 96% of patients, whereas only 19% of patients receiving PPIs reported control of regurgitation.

#### Implications for patient care

MSA is superior to twice-daily PPIs therapy in reducing regurgitation. Relief of regurgitation is sustained over 12 months.

### *Safety*

No serious perioperative adverse events occurred in any arm of the study. Although 19 (39.6%) MSA patients and 10 (33.3%) MSA crossover patients reported instances of dysphagia, MSA patients reported less dysphagia at 6 and 12 months than at baseline (see Dysphagia).

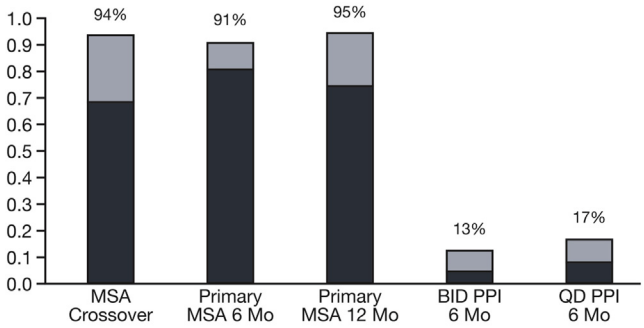


**Figure 1.** Percent of patients achieving relief of moderate-to-severe regurgitation by time after initiation of therapy. BID, twice daily; MSA, magnetic sphincter augmentation; PPI, proton pump inhibitor.

**Table 1.** Baseline Characteristics of Patients Completing 12-Month Follow-Up

| Visit | LINX system | Double-Dose PPIs | *P* value |
|---|---|---|---|
| Age at enrollment, *y* | 47.8 ± 13.1 (50) | 46.4 ± 13.7 (102) | $P_T = .575$ |
| Median (range) [IQR] | 46.2 (21.2–76.0) [37.6–60.2] | 46.2 (21.0–72.7) [36.1, 56.0] | $P_W = .651$ |
| Sex | | | .345 |
| Female | 38.0 (19/50) | 46.1 (47/102) | |
| Male | 62.0 (31/50) | 53.9 (55/102) | |
| BMI, $kg/m^2$ | 27.7 ± 4.3 (50) | 28.0 ± 4.1 (102) | $P_T = .642$ |
| Median (range) [IQR] | 27.6 (18.3–34.9) [24.8, 31.2] | 27.9 (19.9–35.8) [24.7, 31.0] | $P_W = .706$ |
| Hiatal hernia | 1.8 ± 0.7 (29) | 1.8 ± 0.7 (50) | $P_T = .866$ |
| Median (range) [IQR] | 2.0 (1.0–3.0) [1.0–2.0] | 2.0 (0.2–3.0) [1.0–2.0] | $P_W = .927$ |
| None | 42.0 (21/50) | 51.0 (52/102) | .298 |
| ≤3 *cm* | 58.0 (29/50) | 49.0 (50/102) | |
| >3 *cm* | 0.0 (0/50) | 0.0 (0/102) | |
| Esophagitis | | | .582 |
| None | 61.2 (30/49) | 66.0 (66/100) | |
| A | 20.4 (10/49) | 24.0 (24/100) | |
| B | 18.4 (9/49) | 10.0 (10/100) | |
| C | 0.0 (0/49) | 0.0 (0/100) | |
| D | 0.0 (0/49) | 0.0 (0/100) | |
| Manometry | | | |
| Distal amplitude | 77.8 ± 31.2 (32) | 89.1 ± 35.0 (69) | $P_T = .119$ |
| LES basal mean pressure | 22.6 ± 12.3 (43) | 23.3 ± 12.7 (93) | $P_T = .777$ |
| PPI use, *y* | 8.7 ± 6.8 (50) | 8.2 ± 6.5 (102) | $P_T = .638$ |
| Total % time pH <4 | 11.8 ± 5.2 (48) | 10.4 ± 5.0 (100) | $P_T = .132$ |
| DeMeester score | 41.4 ± 19.4 (48) | 35.6 ± 17.1 (99) | $P_T = .071$ |

Values are mean ± SD (n) or % (n/n).
BMI, body mass index; LES, lower esophageal sphincter; PPI, proton pump inhibitor.

### *Efficacy*

We report the individual results of the crossover MSA and the step-down cohorts. Additionally, as the primary MSA cohort was followed to study completion at 12 months, we report comparative data based on the final treatment received (PPIs vs MSA). For those in the medically treated arm, this comprises the 43 step-down patients receiving 20-mg omeprazole daily at 12 months. For the surgically treated arm, results consist of 6- and 12-month data from 44 primary MSA patients and 6-month postsurgery data (12 months from enrollment) from the 31 crossover patients (Supplementary Figure 1).

**Table 2.** Baseline Demographic and Clinical Characteristics by Crossover Eligibility

| Visit | Eligible (n = 31) | Not eligible (n = 50) |
|---|---|---|
| Age at enrollment, *y* | 44.2 ± 13.8 | 48.4 ± 13.4 |
| Female, % | 35.5 | 50.0 |
| BMI, $kg/m^2$ | 28.7 ± 4.0 | 27.7 ± 4.4 |
| Hiatal hernia | 2.0 (0.2 to 3.0) | 2.0 (1.0 to 3.0) |
| ≤3 *cm*, % | 35.5 | 50.0 |
| Esophagitis | | |
| None | 63.3 | 69.4 |
| A | 26.7 | 20.4 |
| B | 10.0 | 10.2 |
| Manometry | | |
| Distal amplitude, *mm Hg* | 88.5 (45.0 to 140.0) | 76.0 (41.0 to 235.0) |
| LES basal mean pressure, *mm Hg* | 20.2 (–11.3 to 43.6) | 25.2 (4.8 to 61.6) |
| PPI use, *y* | 5.8 (0.5, 35.0) | 8.0 (0.4 to 25.0) |

Values are mean ± SD, %, or median (range).
BMI, body mass index; LES, lower esophageal sphincter; PPI, proton pump inhibitor.

### *MSA Crossover Cohort at Study Completion (6 Months Postimplantation)*

Relief of moderate-to-severe regurgitation was 94% (n = 29 of 31) in the crossover with 68% (n = 21 of 31) reporting elimination of all regurgitation (Figure 1). The RDQ scores (ranked 0 [none] to 5 [severe]) reflect an average of severity and frequency of symptoms (scored 0–5) for 2 questions each on regurgitation, heartburn, and indigestion. After MSA implantation, median RDQ regurgitation scores improved from 4 (IQR, 3.25–4.75) off PPI and 3.5 (IQR, 2.5–4) on PPI at baseline to 0 (IQR, 0–1.125) ($P < .001$). Median GERD-HRQL (scored 0–50; >20 severe, <6 considered minimal) improved from 26 (IQR, 21–30) off PPI and 21 (IQR, 18–27) on PPI at baseline to 4 (IQR, 1–7) after MSA implantation ($P < .001$). Greater than 50% improvement in baseline GERD-HRQL on PPIs was reported in 80.6% (n = 25 of 31). Median RDQ heartburn scores improved from 3.5 (IQR, 2.25–4.5) off PPI, 2.38 (IQR, 1.5–3.6) on PPI to 0 (IQR,

0-0.5) ($P < .001$). Median DeMeester pH score improved to 6 (IQR, 2.2–17.6) postoperatively from 31.7 (IQR, 25.2–36.8) preoperatively ($P < .001$). A normal DeMeester score was observed in 70% (n = 21 of 30) 6 months postimplantation.

### *Step-Down PPI Cohort at Study Completion*

Relief of moderate-to-severe regurgitation in the step-down PPI cohort was 17% (n = 8 of 48) with 1 of 48 reporting complete regurgitation resolution. Median RDQ regurgitation score did not change significantly from baseline. Heartburn and GERD-HRQL scores also showed no significant change from baseline. Median DeMeester score tested on daily PPIs remained elevated at 16.7 (IQR, 1.9–164) and was normal in 54%.

### *Treatment Results Based on Final Treatment Arm (MSA or PPI)*

**Regurgitation.** At study completion, resolution of moderate-severe regurgitation was seen in 96% (n = 72 of 75) of MSA patients. Resolution of moderate-to-severe regurgitation 6 months postimplantation in the Total MSA cohort was 93% (n = 71 of 78) and at 12 months, 98% (n = 43 of 44) in the primary MSA cohort. The BID PPI cohort reported 11% resolution of moderate-severe regurgitation at 6 months, and 19% (n = 8 of 43) of patients in the step-down PPI arm met this endpoint at 12 months ($P < .001$ compared with MSA). Complete elimination of regurgitation was reported in 73% (n = 51 of 75) after MSA and 2% of step-down PPI patients, with the remainder reporting mild regurgitation ($P < .001$) (Figure 1).

Median RDQ scores for baseline regurgitation were 4 (IQR, 3.25–4.75) off PPI and 3.5 (IQR, 2.5–4) on PPI for the medication arm. At 6 and 12 months post-MSA implantation, median regurgitation scores improved to 0 (IQR, 0–1.125) and 0 (IQR, 0–0.5), respectively. No significant improvement occurred in PPI-treated patients.

**GERD-HRQL and heartburn.** The mean GERD-HRQL score at baseline was 30 ± 10 off PPIs and 24 ± 10 on daily PPIs. At 6 and 12 months after MSA implantation, the score improved significantly to 6 and 5, respectively ($P < .001$). Successful achievement of ≥50% change from baseline GERD-HRQL score on PPIs was seen in 81% (n = 61 of 75) of MSA patients at 6 months and 93% (41 of 44) at 12 months postimplant ($P < .001$). Identical improvements after MSA were seen in the heartburn component of the GERD-HRQL (6 of the 10 questions) at 12 months. No improvement in GERD-HRQL or related heartburn scores was seen in the medically treated cohort.

**Dysphagia.** Swallowing problems were evaluated using 2 GERD-HRQL questions: "Do you have difficulty swallowing" (dysphagia) and "Do you have painful swallowing" (odynophagia), scored on a scale from 0 (none) to 5 (severe). Mean dysphagia score values are graphically illustrated in Supplementary Figure 2. Difficulty swallowing that was scored ≥3 (bothersome every day or worse) was present in 27% of patients at baseline off PPIs and 15% of patients on PPIs. Following MSA, dysphagia scores ≥3 were reported by 11% (n = 8 of 75) of patients at 6 months postimplant and 7% (n = 3 of 44) of patients at 12 months postimplant ($P = .0184$). Similar findings were noted for odynophagia. No significant improvement was seen in medically treated patients.

**Bloating, flatulence, and diarrhea.** Abdominal bloating was assessed as none, occasional, frequent, or continuous. Baseline frequent or continuous bloating was present in 58% of patients off PPIs and 55% of patients on PPIs. After MSA this improved to 15% (n = 11 of 75) at 6 months and 27% (n = 12 of 44) at 12 months ($P = .0416$) postimplantation. No change was seen in the medically treated patients.

**Medication use.** MSA was associated with discontinuation of PPI in 91% (n = 68 of 75) of patients after implantation at study completion.

**Esophageal acid exposure after MSA.** At study completion, median total esophageal acid exposure in the combined primary and crossover MSA groups decreased from 10.7% (IQR, 7.7%–13.9%) to 1.3% (IQR, 0.4%–5.3%). At 12 months postimplantation, median total esophageal acid exposure time in the primary MSA group improved from 11.5% (IQR, 7.9%–14.8%) to 1.3% (IQR, 0.2%–5.3%) ($P < .001$), DeMeester Scores improved from 40.5 (IQR, 25.7–49.5) to 5.3 (IQR, 1.2–18.5) and normalized in 70% (n = 48 of 69). Results were similar 6 months postimplantation in the crossover MSA group. There were no statistically significant preoperative findings or variations in operative technique to account for variations in postoperative pH testing. The majority of patients with abnormal pH test post-LINX Torax Medical (acquired by Ethicon Endo-Surgery) were well controlled symptomatically. Figure 2 illustrates individual patient as well as the median DeMeester score at baseline and follow-up.

**Endoscopic evaluation.** Esophagitis in patients with confirmed abnormal esophageal acid exposure was present at baseline in 35% (n = 42 of 119) of the patients who completed 12-month evaluation (off PPI × 7 days), in 5 of 72 (7%) MSA patients at follow-up, and persisted in 8 of 47 (17%) patients maintained on single-dose PPI. No erosions or other device problems were seen on endoscopy at study completion.

**Effect of response to PPI at baseline on symptomatic outcomes.** Outcome in the MSA cohort was also analyzed based on whether regurgitation responded to PPIs or not. PPI nonresponders (defined as patients who reported less than one-half of a standard deviation improvement in RDQ regurgitation score between on and off PPIs at baseline) exhibited the same improvement in regurgitation after MSA as did responders (patients at

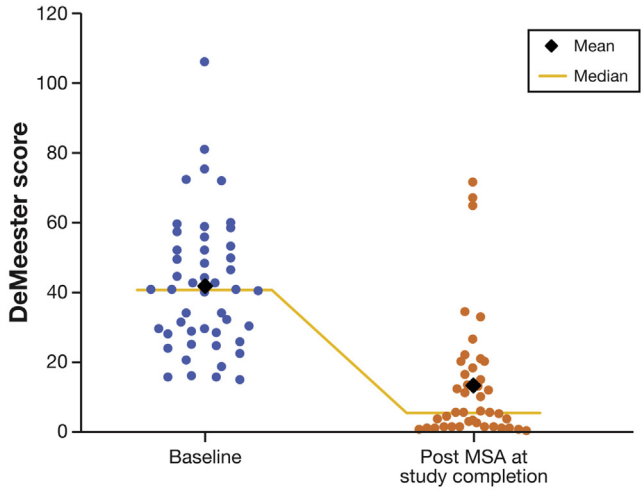


**Figure 2.** DeMeester pH scores for magnetic sphincter augmentation (MSA) for patients at baseline and study completion. Solid line indicates median scores, *black diamond* indicates mean score.

least one-half of a standard deviation improvement). The same results held using criteria of no or any improvement in score between on and off PPIs (Figure 3).

A similar baseline PPI responder or nonresponder analysis was performed using the average of the 6 questions of the GERD-HRQL that relate to heartburn as well as the 4 RDQ questions that relate to heartburn. The results of the analysis show that response, or lack of response to PPIs did not impact heartburn scores at 6 and 12 months (Table 2 and Figure 3).

## Discussion

This RCT directly compared acid-suppressive therapy to an antireflux procedure in patients with moderate-to-severe regurgitation and confirmed that mechanical restoration of the reflux barrier through MSA did control regurgitation better than did increasing doses of acid-suppressive medication. MSA was not associated with major surgical complications or increase in side effects such as abdominal bloating or dysphagia often seen with fundoplication.

Considerations and potential limitations in this study include the relatively limited duration of follow-up. Other studies of MSA have documented little decrease in efficacy between 1 and 5 years of follow-up, and additional long-term studies of MSA are ongoing. The current study compared medical and surgical therapy, and lacking evidence to suggest that medical therapy results improve over time, longer-term follow-up comparison of the 2 arms was deemed unnecessary. Another consideration was the use of transnasal impedance or pH testing at the 6-month endpoint but 48-hour telemetry capsule pH testing at the 12-month endpoint. Transnasal impedance or pH testing was the only method to evaluate ongoing nonacid regurgitation in the double-dose PPI cohort, as it measures both acidic and acid-neutralized reflux episodes and was appropriate to determine crossover eligibility. Telemetry capsule pH testing was utilized at 12 months when all patients were evaluated off PPIs and were undergoing follow-up endoscopy. Keeping these considerations in mind, we reached the following conclusions.

It is often stated, including in the American College of Gastroenterology guidelines,[34] that surgical therapy is not recommended for patients who do not respond to PPI therapy. However, the basis for these recommendations and the types of symptoms evaluated for response to PPI therapy is unclear. Three prospective cohort studies have compared the effectiveness of laparoscopic fundoplication between PPI responsive and nonresponsive populations and found significant symptom improvement with laparoscopic fundoplication in PPI nonresponders, though not quite as much as in PPI responders.[36] In this study, we evaluated patient outcomes after MSA based upon preoperative improvement (any response to PPI based on baseline quality-of-life surveys

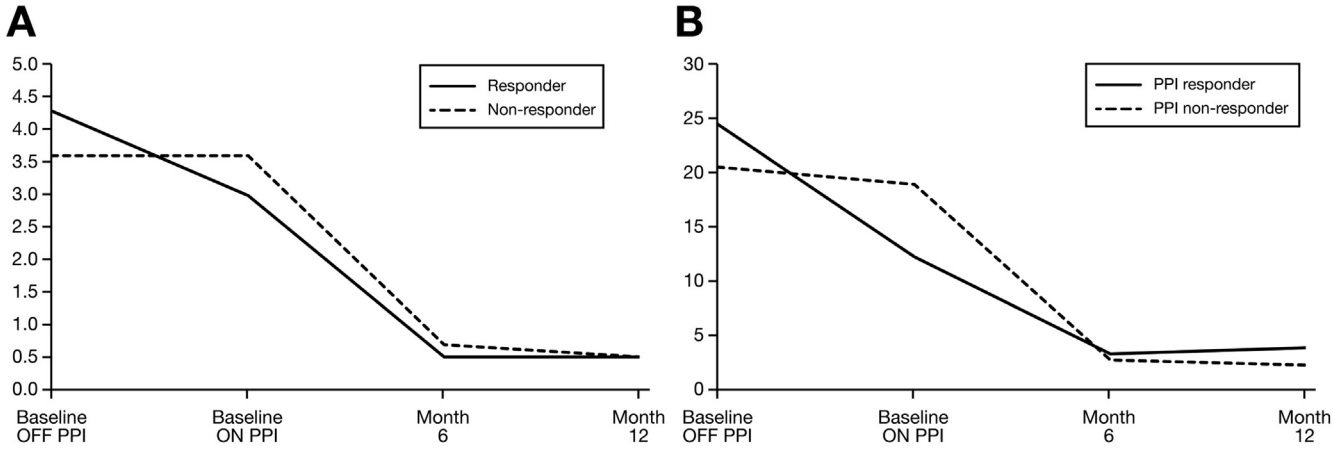


**Figure 3.** (*A*) Regurgitation and (*B*) heartburn scores for magnetic sphincter augmentation (MSA) patients by response to proton pump inhibitors (PPIs) at baseline. Responder is defined by having at least a half standard deviation change between on and off gastroesophageal reflux disease medication scores at baseline, compared with baseline, 6-month, and 12-month follow-up ($P < .001$) and nonresponders with responders at 6 and 12 months ($P > .28$) in all cases.

on and off PPIs) and response (at least a half of a standard deviation of improvement) in regard to symptoms of regurgitation and heartburn. Based on these parameters, we found no difference in outcomes after MSA whether patients demonstrated any baseline improvement in symptoms with PPIs. In patients with moderate-to-severe regurgitative symptoms despite once-daily PPIs and objective confirmation of abnormal esophageal acid exposure off PPI, both regurgitation and heartburn responded to MSA regardless of the response to PPIs.

Postoperative testing off PPIs performed at 6 months in the primary MSA group, and at study conclusion (12 months postimplantation in the primary MSA cohort and 6 months postimplantation in the MSA crossover cohort) it was found that median DeMeester scores improved from 33.4 (IQR 25.7–49.5) to 3.5 (IQR 1.9–11.9) 6 months postimplantation (both groups) and were 5 (IQR 1.2–18.5) at 12 months in the primary MSA group. Telemetry pH testing at 12 months was completely normal in 70% of patients undergoing MSA. This is in concert with other published studies of MSA and confirms objectively the high subjective response rate.[25]

Increased bloating and increased rectal gas issues are known side effects of laparoscopic fundoplication compared with PPIs.[37] Although this study did not compare MSA with Nissen fundoplication, patients reported a decrease in bloating and rectal issues after MSA compared with baseline PPI use. Continued ability to belch was reported in 99% (n = 74 of 75) of all patients who received MSA at 12 months.

That 61% of patients treated with BID PPIs did not qualify for crossover was greater than initial study design predictions. The crossover protocol did not allow for ongoing esophageal acid exposure, based on an a priori decision. If crossover criteria had included ongoing acid exposure as a marker, then 45% would not have qualified for crossover. As 87% of patients who did not qualify for crossover continued to have ongoing moderate-to-severe regurgitation, the value of impedance or pH testing on PPIs in this setting is unclear.

### *Conclusions*

The final results of this RCT found that MSA was superior to BID PPI therapy in patients with moderate-to-severe regurgitation despite daily PPI therapy. The response was sustained over 12 months. Regurgitation and associated heartburn symptoms responded to MSA even when completely nonresponsive to PPI therapy, in line with the mechanical, volume origin of regurgitative symptoms. Dysphagia improved by quality-of-life measures; bloating and gas were not significant after MSA.

MSA is an effective surgical treatment option for patients with medically refractory regurgitative GERD.

## Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2019.08.056.

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**Conflicts of interest**
These authors disclose the following: Reginald Bell, F. Paul Buckley III, Jon Gould, Leena Khaitan, Shanu Kothari, and John Lipham receive honoraria from Ethicon for teaching services. The remaining authors disclose no conflicts.

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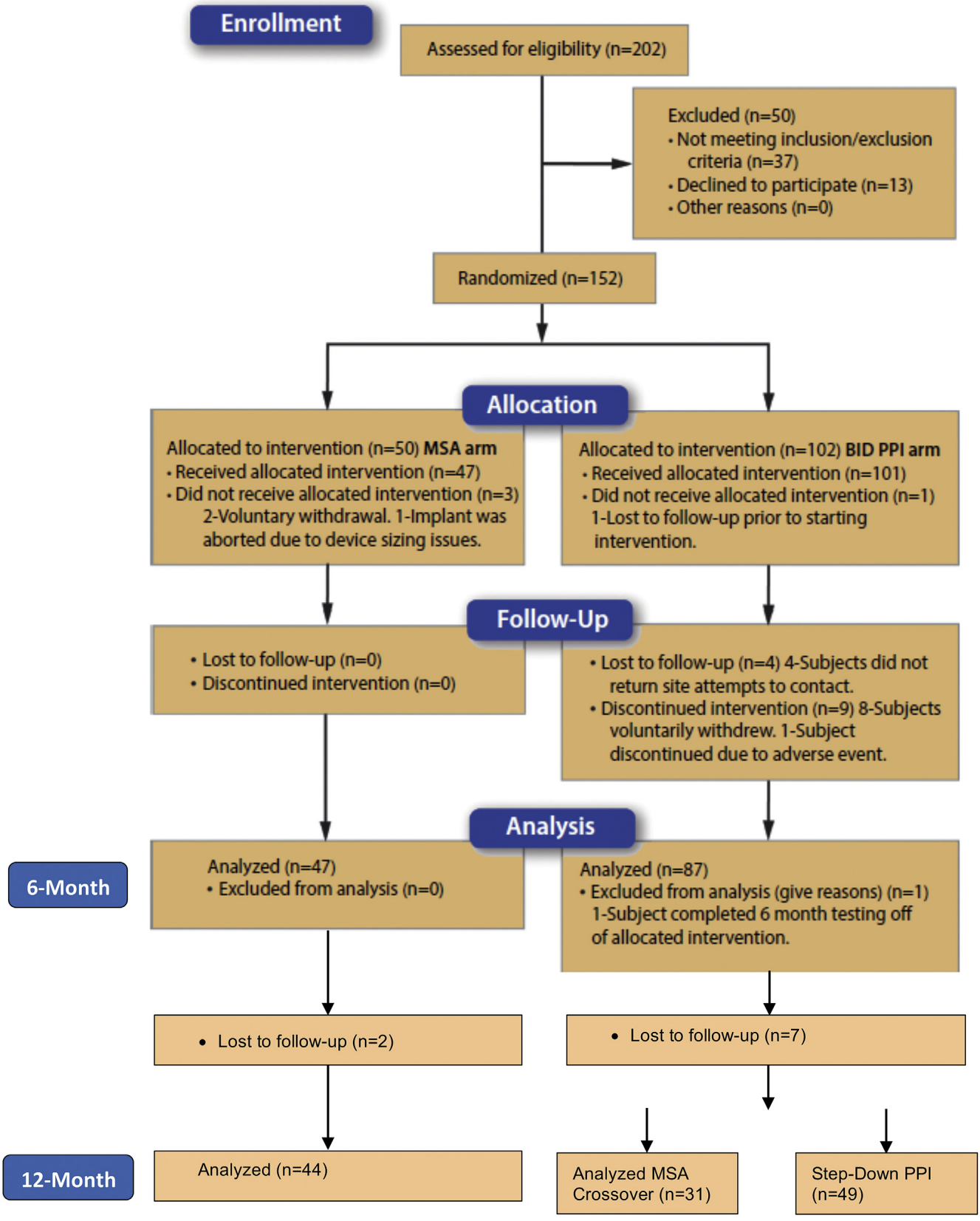
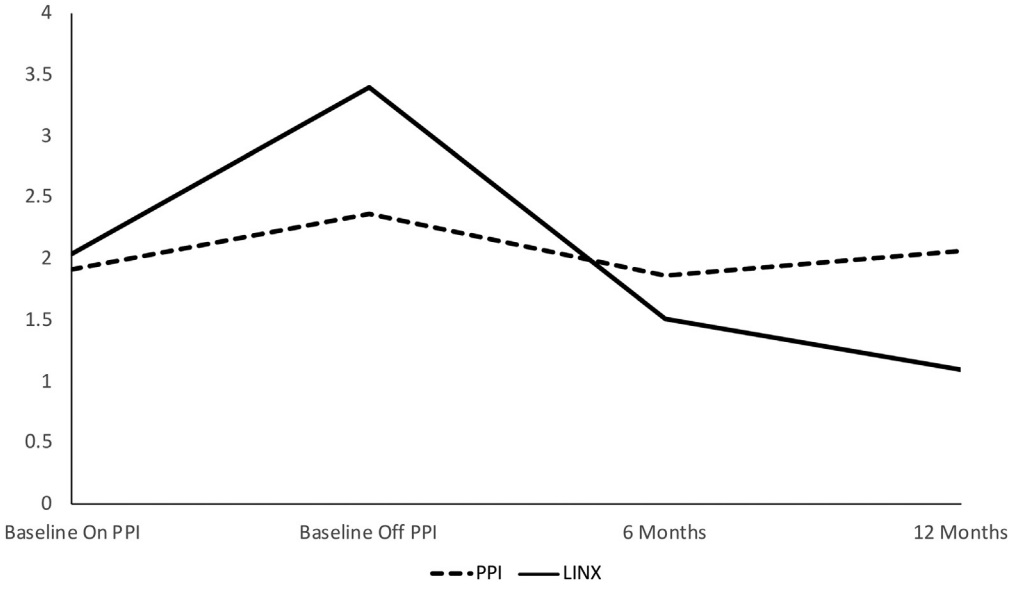



**Supplementary Figure 1.** Study design and patient disposition.




**Supplementary Figure 2.** Composite dysphagia score from GERD-HRQL by final treatment.