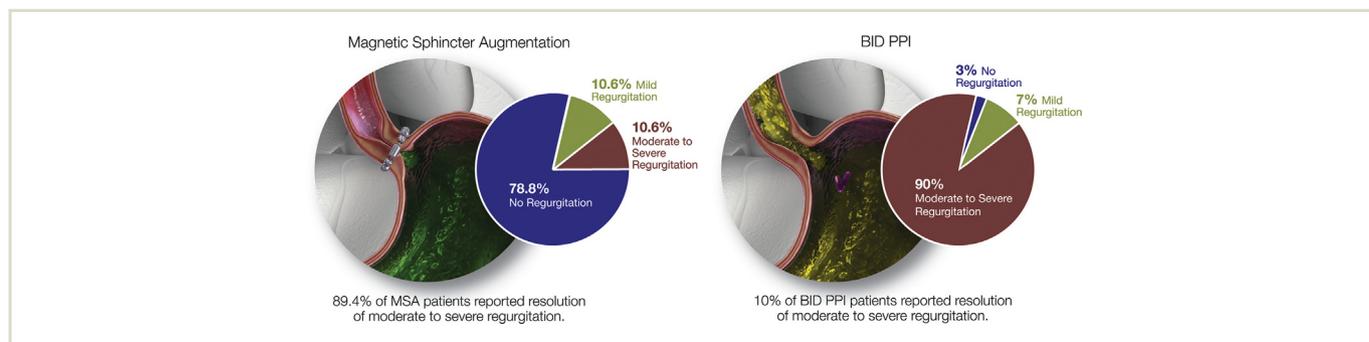


# Laparoscopic magnetic sphincter augmentation versus double-dose proton pump inhibitors for management of moderate-to-severe regurgitation in GERD: a randomized controlled trial

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## GRAPHICAL ABSTRACT



**Background and Aims:** GERD patients frequently complain of regurgitation of gastric contents. Medical therapy with proton-pump inhibitors (PPIs) is frequently ineffective in alleviating regurgitation symptoms, because PPIs do nothing to restore a weak lower esophageal sphincter. Our aim was to compare effectiveness of increased PPI dosing with laparoscopic magnetic sphincter augmentation (MSA) in patients with moderate-to-severe regurgitation despite once-daily PPI therapy.

**Methods:** One hundred fifty-two patients with GERD, aged  $\geq 21$  years with moderate-to-severe regurgitation despite 8 weeks of once-daily PPI therapy, were prospectively enrolled at 21 U.S. sites. Participants were randomized 2:1 to treatment with twice-daily (BID) PPIs ( $N = 102$ ) or to laparoscopic MSA ( $N = 50$ ). Standardized foregut symptom questionnaires and ambulatory esophageal reflux monitoring were performed at baseline and at 6 months. Relief of regurgitation, improvement in foregut questionnaire scores, decrease in esophageal acid exposure and reflux events, discontinuation of PPIs, and adverse events were the measures of efficacy.

**Results:** Per protocol, 89% (42/47) of treated patients with MSA reported relief of regurgitation compared with 10% (10/101) of the BID PPI group ( $P < .001$ ) at the 6-month primary endpoint. By intention-to-treat analysis, 84% (42/50) of patients in the MSA group and 10% (10/102) in the BID PPI group met this primary endpoint ( $P < .001$ ). Eighty-one percent (38/47) of patients with MSA versus 8% (7/87) of patients with BID PPI had  $\geq 50\%$  improvement in GERD–health-related quality of life scores ( $P < .001$ ), and 91% (43/47) remained off of PPI therapy. A normal number of reflux episodes and acid exposures was observed in 91% (40/44) and 89% (39/44) of MSA patients, respectively, compared with 58% (46/79) ( $P < .001$ ) and 75% (59/79) ( $P = .065$ ) of BID PPI patients at 6 months. No significant safety issues were observed. In MSA patients, 28% reported transient dysphagia; 4% reported ongoing dysphagia.

**Conclusion:** Patients with GERD with moderate-to-severe regurgitation, especially despite once-daily PPI treatment, should be considered for minimally invasive treatment with MSA rather than increased PPI therapy. (Clinical trial registration number: NCT02505945.) (Gastrointest Endosc 2018; ■:1-9.)

(footnotes appear on last page of article)

GERD is a chronic progressive disease of the esophagus, which affects approximately 20 million people in the United States.<sup>1</sup> The primary etiologic factor in GERD is a weakened lower esophageal sphincter (LES) and inability to maintain an adequate anatomic barrier between the stomach and esophagus.<sup>2,3</sup> Impaired LES function allows reflux of gastric contents into the esophagus and throat, which causes irritation and inflammation of the esophageal lining. The most common typical symptoms of GERD are heartburn and regurgitation. Regurgitation, the unpleasant sensation of gastric juice entering the esophagus, often accompanied by an acid taste in the mouth, is frequent or severe enough to affect quality of life in 13% of patients with GERD.<sup>4</sup>

Standard medical practice, endorsed by gastroenterology societies, is to recommend a proton-pump inhibitor (PPI) as first-line therapy for troublesome GERD-related symptoms or erosive esophagitis.<sup>5,6</sup> By decreasing gastric acid secretion, PPIs often are successful at alleviating heartburn and healing esophagitis. However, PPIs have no direct action on LES function and do little to prevent reflux of gastric contents into the esophagus.<sup>7</sup> PPI therapy consequently often fails to control regurgitation and in fact has a therapeutic gain of only 17% over placebo.<sup>8</sup> Perhaps because of a perceived lack of alternative treatments, it remains common practice to treat complaints of persistent regurgitation with increasing doses of PPIs, even when patients are refractory to once-daily PPIs.<sup>9</sup> Treating GERD surgically corrects the sphincter defects and significantly reduces the number of reflux events, rather than merely reducing the acidity of the refluxate.<sup>10</sup> It is therefore extremely effective at controlling regurgitation symptoms.

Augmentation of the LES can be performed with the LINX Reflux Management System (Torax Medical, Inc, Shoreview, Minn), which consists of a “bracelet” of magnetic beads that is placed around the distal esophagus by using laparoscopic surgery.<sup>11</sup> The magnets that make up the bracelet augment the LES by separating at a given pressure, hence the nomenclature *magnetic sphincter augmentation* (MSA). The strength of the magnets has been specifically designed to separate with the pressures generated during swallowing, allowing passage of liquid and solid boluses.<sup>12</sup> However, most gastroesophageal reflux events occur at a low pressure gradient that would be insufficient to open the augmented sphincter.<sup>13,14</sup> Unlike a traditional Nissen fundoplication, increases in intragastric pressure such as those that occur during belching and vomiting are sufficient to open the augmented LES and allow physiologic venting.<sup>15-17</sup> Single-arm studies have demonstrated MSA to be effective, safe, and durable in controlling typical GERD symptoms of heartburn and regurgitation.<sup>18-20</sup> We report herein the results of a prospective, randomized, controlled, multicenter study comparing MSA with twice-daily PPI therapy in a defined GERD population: those with moderate-to-severe regurgitation despite once-daily PPI therapy.

## METHODS

### Study design

This randomized, controlled, prospective, double-arm, crossover study enrolled 152 patients with moderate-to-severe regurgitation symptoms while they were being treated with once-daily PPIs and with objective confirmation of GERD, at 21 U.S. clinical sites between July 2015 and February 2017. Enrolled patients were randomly assigned 2:1 to the following treatment arms: Twice-daily PPI (BID PPI) therapy with omeprazole 20 mg (N = 102) or laparoscopic MSA (N = 50). Primary endpoint efficacy and safety assessments were performed at 6 months and are the subject of this report. At 6 months, eligible patients in the BID PPI arm could cross over to the MSA arm; both groups then underwent additional evaluation at 12 months, to be reported separately. 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](https://clinicaltrials.gov) identifier is NCT02505945. The study was sponsored by Torax Medical, Inc.

### Study patients

Patients were recruited primarily from 21 surgical clinics. Study inclusion criteria included patients aged at least 21 years, with moderate-to-severe regurgitation (based on a standardized survey, the Foregut Symptom Questionnaire [FSQ]<sup>21</sup>) while taking once-daily PPI therapy for at least 8 weeks and actively seeking alternative, surgical treatment for regurgitation symptoms. Additional criteria were body mass index <35, abnormal pH testing result (determined by DeMeester score or total percentage of time with pH <4), normal esophageal motility, hiatal hernia of  $\leq 3$  cm by endoscopy, absence of Barrett’s esophagus, or Los Angeles Classification grade C or D esophagitis.

### Study procedures

Screening included complete medical histories, physical examinations, GERD-related questionnaires, ambulatory esophageal pH monitoring while patients were off PPI treatment for at least 7 days, EGD, and esophageal manometry or barium esophagram. Screened patients meeting all inclusion criteria were enrolled in the study, completed baseline efficacy surveys, and were randomized to BID PPI or MSA treatment groups.

Baseline quality-of-life surveys included the FSQ, Reflux Disease Questionnaire (RDQ), and GERD–Health-Related Quality of Life (GERD-HRQL) questionnaire. Surveys were obtained with patients receiving PPI therapy, and after a 7-day washout period, surveys were obtained while patients were not being treated with PPIs. The FSQ evaluates the severity of regurgitation symptoms: none, mild (after straining or large meals), moderate (predictable

with position change, lying down, straining), and severe (constant). The GERD-HRQL consists of 10 questions—6 related to heartburn, 2 to dysphagia, 1 to bloating, and 1 to the impact of medications on daily life, scored 0 to 5 based on frequency and impact on quality of life.<sup>22</sup> The RDQ asks 12 questions addressing the symptom domains of heartburn, regurgitation, and dyspepsia by using a scale from 0 to 5 to rate the severity and frequency of 6 symptoms.<sup>23</sup> Endoscopy and 24-hour or 48-hour ambulatory esophageal pH monitoring were performed after the washout period while patients were not being treated with PPIs.

Patients assigned to the BID PPI arm were started on twice-daily omeprazole, 20 mg, 30 minutes before breakfast and 30 minutes before dinner. Patients assigned to the MSA group underwent laparoscopic MSA by a study investigator trained and experienced in MSA. Postoperatively, patients were instructed to eat a soft mechanical diet, including small bites of food regularly, to minimize capsular contracture around the MSA device, and patients were monitored by routine postoperative methods.

At 6 months, patients were administered the FSQ, RDQ, and GERD-HRQL questionnaires and underwent 24-hour impedance-pH testing. Per protocol, patients in the MSA group completed the questionnaires and underwent impedance-pH testing while not being treated with PPIs, whereas the BID PPI patients completed the questionnaires while being treated with BID PPIs. Impedance-pH test results were evaluated by a blinded, independent laboratory.

### Efficacy endpoints and outcomes

The primary endpoint was the percent of patients in both treatment arms who achieved elimination of moderate-to-severe regurgitation at 6 months, as reported on the FSQ. Secondary endpoints at 6 months included the following: (1) change from baseline scores (while on PPIs) in the GERD-HRQL questionnaire and RDQ, and percentage of patients achieving  $\geq 50\%$  decrease in GERD-HRQL score from baseline; (2) differences between treatment arms at 6 months in esophageal reflux parameters (number of reflux episodes and percentage of time with pH  $< 4$ ); and (3) PPI use at 6 months.

### Statistical analyses

Per the statistical plan in the protocol, all randomized patients who either started BID PPIs or completed the MSA procedure made up the analysis population for the primary efficacy endpoint. All other analyses were performed with data available at the follow-up visit. Intention-to-treat (ITT) analysis also was performed. Comparison of symptomatic outcomes between groups 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 ex-

pressed as mean ( $\pm$  standard deviation) or median (interquartile range [IQR]). Safety was assessed by the incidence of treatment-related adverse events. The sample size required for statistical significance was calculated a priori by using SAS version 9.3 (SAS, Cary, North Carolina, USA), with the assumptions that the success rate in the MSA group would be at least 70%, and the difference in success rates between the MSA and BID PPI groups would be at least 30%, with a power calculation of 85%. Given these assumptions, a minimum of 108 patients randomized and followed to 6 months was required for statistical significance. Additional participants were randomized (152 total) to ensure that a minimum of 50 participants was randomized to MSA and to ensure the sample size requirement of 108 participants, with final endpoint data, was met.

## RESULTS

### Patient disposition

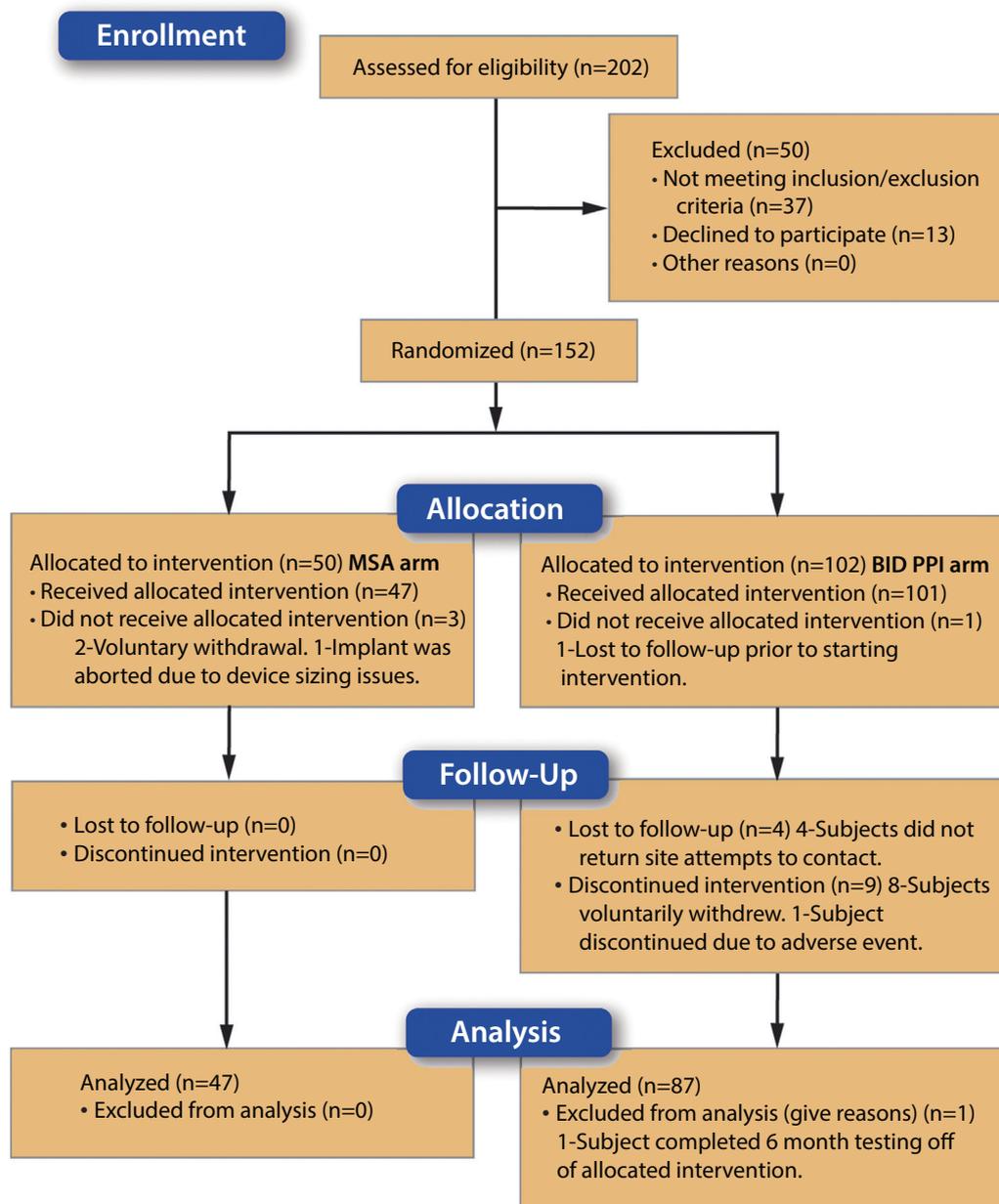
The study design and summary of patient disposition are shown in [Figure 1](#). Of 202 patients screened for eligibility, 152 met inclusion criteria, were enrolled in the study, and were randomized to MSA (N = 50) or BID PPI (N = 102). Three participants withdrew before undergoing the MSA procedure, and 1 participant failed to start BID PPI therapy. Demographic variables and baseline disease characteristics between both treatment arms were similar, with the exception of the DeMeester scores, which were significantly higher in the patients assigned to the MSA ([Table 1](#)). The median age (range) of all patients was 46 (21-76) years. The population was 58% male, 88% white, 5% Hispanic, 3% African American, 3% Asian, and 1% reported other. The average length of PPI use for all patients was 8.4 years.

### Efficacy

At the 6-month endpoint, all 47 patients (100%) in the MSA arm completed the surveys, and 44 of 47 (94%) completed impedance-pH testing. Thirteen patients in the BID PPI arm withdrew before the 6-month visit (PPI: 4 lost to follow-up and 9 voluntary [1 of 9 due to PPI-related adverse event]). Eighty-seven of 101 patients (86%) completed the surveys and 79 of 101 (78%) completed impedance-pH monitoring.

Based on the 6-month endpoint and FSQ results, 89% (42/47) of MSA patients achieved resolution of moderate-to-severe regurgitation compared with 10% (10/101) of patients in the BID PPI arm ([Fig. 2A](#);  $P < .001$ ). When analyzed by using ITT, 84% (42/50) of MSA and 10% (10/102) of BID PPI patients met the primary endpoint ( $P < .001$ ). The GERD-HRQL score in the MSA group decreased from 24 (baseline while being treated with PPIs) to 6 (6 months while not being treated with PPIs). In comparison, the BID PPI group mean GERD-HRQL score did not change markedly (25 at baseline taking

## Study Design and Patient Disposition



**Figure 1.** Study design and patient disposition. *MSA*, magnetic sphincter augmentation; *BID*, twice daily; *PPI*, proton pump inhibitor.

once-daily PPI to 24 at 6 months), demonstrating a significant difference between the 2 groups ( $P < .002$ ). The MSA group RDQ regurgitation score improved from a mean score of 4.2 at baseline to 1.6 at 6 months (1 = no symptoms, 6 = severe). The BID PPI arm score did not improve (4.4 at baseline and 4.3 at 6 months). Eighty-one percent (38/47) of patients in the MSA arm achieved a reduction of  $\geq 50\%$  from the baseline GERD-HRQL score (Fig. 2B), compared with 8% (7/87) of patients in the BID PPI arm ( $P < .001$ ). Satisfaction with current condition was 81% (38/47) in the MSA group, compared with 2% (2/87) in

the BID PPI arm (Fig. 2C). Ninety-one percent (43/47) of patients in the MSA arm discontinued PPI use at 6 months.

Figure 3 shows the severity of regurgitation among patients in both treatment arms at the 6-month endpoint, based on questionnaire scores. At baseline, 100% of patients reported moderate-to-severe regurgitation while taking once-daily PPIs. At the 6-month endpoint, 89% (42/47) of MSA patients had achieved relief from regurgitation (79% [37/47] reported no regurgitation, and 10.6% (5/47) reported mild regurgitation). In contrast, only 10% (10/101) of BID PPI patients reported relief of

TABLE 1. Patient demographics and baseline disease characteristics

Parameter	MSA (N = 50)	Omeprazole 20 mg BID (N = 102)
Age, median (range), y	46 (21-76)	46 (21-72)
Men, no. (%)	31/50 (62)	55/102 (54)
Women, no. (%)	19/50 (38)	47/102 (46)
BMI, mean ( $\pm$ SD), kg/m <sup>2</sup>	28 ( $\pm$ 4.3)	28 ( $\pm$ 4.1)
Esophagitis, no. (%)		
None	30/49 (61.2)	66/100 (66.0)
LA grade A	10/49 (20.4)	24/100 (24.0)
LA grade B	9/49 (18.4)	10/100 (10.0)
Hiatal hernia, no. (%)		
None	21/50 (42)	52/102 (51)
<3.0 cm	29/50 (58)	50/102 (49)
Total percentage of time with pH <4	11.5 (7.8-14.5)	9.3 (7.0-13.2)
DeMeester score, no.	40.3 (28.1-53.0) (47)	30.9 (24.3-39.5) (99)
RDQ regurgitation score		
While taking PPI	4.5 (3.3-5.3)	4.5 (3.8-5.3)
Not taking PPI	5.4 (4.5-5.8)	5.1 (4.3-5.8)
RDQ heartburn score		
While taking PPI	3.4 (2.3-4.5)	3.5 (2.5-5.0)
Not taking PPI	4.6 (3.3-5.5)	4.5 (3.5-5.5)
GERD-HRQL score while taking PPI, mean ( $\pm$ SD)	23.5 ( $\pm$ 10.1)	25.0 ( $\pm$ 9.6)
GERD-HRQL score not taking PPI, mean ( $\pm$ SD)	31.6 ( $\pm$ 10.4)	30.3 ( $\pm$ 8.5)

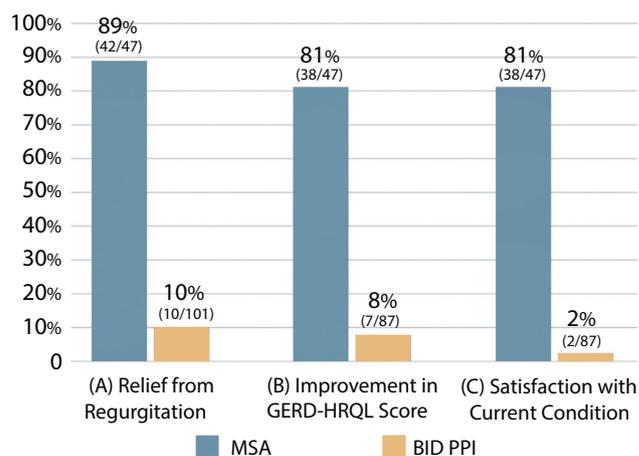
P values were not significant for any parameters except for DeMeester scores, which were .039.

Values are median (interquartile range [IQR]) unless otherwise noted.

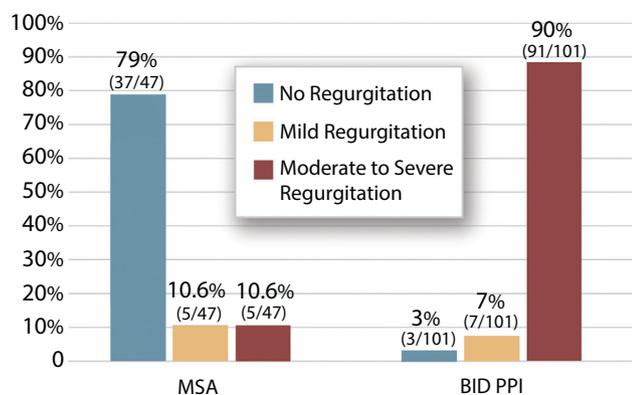
MSA, Magnetic sphincter augmentation; BID, twice daily; BMI, body mass index; SD, standard deviation; LA, Los Angeles Classification; RDQ, Reflux Disease Questionnaire; PPI, proton pump inhibitor; GERD-HRQL, GERD-health-related quality of life.

moderate-to-severe regurgitation at 6 months (3% reported no regurgitation and 7% mild regurgitation).

Impedance-pH testing measures both pH and the number of reflux events, regardless of acidity, and is considered a valuable technique for evaluating GERD in patients receiving PPI therapy.<sup>7</sup> The primary criteria for assessing reflux by using impedance-pH testing is the number of reflux events per 24 hours (Fig. 4).<sup>24</sup> By this measure, MSA controlled reflux significantly better than BID PPIs (22.5 IQR: [13.0-40.5] compared with 49.0 IQR:[31.0-76.78];  $P < .001$ ). Additionally, 91% (40/44) of patients in the MSA arm had a normal number of reflux episodes at 6 months versus 58% (46/79) in the BID PPI arm. Eighty-nine percent (39/44) of patients in the MSA arm had normal esophageal acid exposure by percentage of time with pH <4 as well as the DeMeester score, compared with 75% (59/79) and 71% (56/79) in the BID PPI arm, respectively. Mean esophageal acid exposure (percentage of time with pH <4) in the MSA group (2%) trended to being lower than in the BID PPI group (5%), but did not reach statistical significance ( $P = .065$ ). The mean



**Figure 2.** Results at 6-month endpoint. **A**, Percentage of patients achieving relief from regurgitation. **B**, Percentage of patients achieving  $\geq 50\%$  improvement (*decrease*) in GERD-health-related quality of life scores from baseline score on once-daily proton pump inhibitor therapy. **C**, Percentage of patient satisfaction with current condition. HRQL, health-related quality of life; MSA, magnetic sphincter augmentation; BID, twice daily; PPI, proton pump inhibitor.



**Figure 3.** Percentage of patients treated with magnetic sphincter augmentation or twice daily proton pump inhibitor therapy at the 6-month endpoint with no, mild, or moderate-to-severe regurgitation. MSA, magnetic sphincter augmentation; BID, twice daily; PPI, proton pump inhibitor.

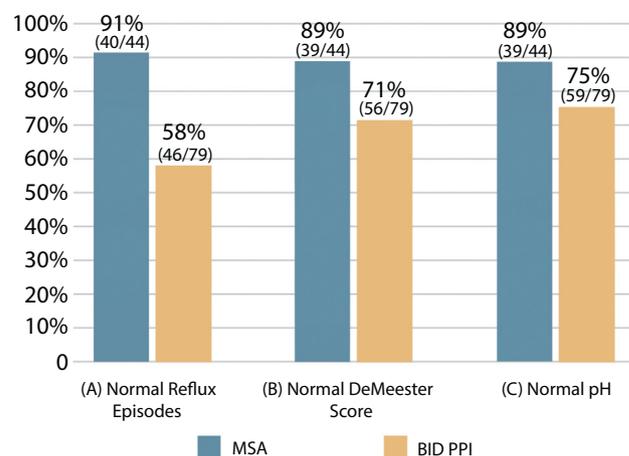
DeMeester score in MSA patients was 8 compared with 18 in the BID PPI arm ( $P = .059$ ).

### Safety

Fifteen patients (32%) in the MSA arm reported dysphagia, rated mild in 9 (19%), moderate in 4 (9%), and severe in 2 (4%). This was transient (minimal or resolved by 6 months) in 13 patients and was ongoing in 2 (4%). One rated moderate, and 1 rated severe. Healthcare utilization of patients with postoperative dysphagia is presented in Table 2. One patient complained of esophageal spasms shortly after the MSA procedure, which resolved after hospitalization. One patient required uneventful repair of a hiatal hernia that developed after an episode of severe vomiting some months after surgery; the MSA device was left in situ. No devices were explanted. Other adverse events in both groups were minor and did not fit any particular pattern; details are not reported.

### DISCUSSION

This is the first prospective, randomized, controlled study comparing MSA with BID PPI therapy in a population of patients with GERD with moderate-to-severe regurgitation despite once-daily PPI therapy. All patients had objectively confirmed GERD by ambulatory reflux monitoring and had clearly defined regurgitation symptoms. The results demonstrate the superiority of MSA compared with BID PPIs in controlling regurgitation in this population. Per protocol, 89% (42/47) of MSA patients achieved resolution of moderate-to-severe regurgitation at the 6-month primary endpoint. In stark contrast, only 10% (10/101) of patients in the medical therapy arm reported relief from moderate-to-severe regurgitation at the 6-month endpoint (per ITT, 84% [42/50] MSA versus 10% (10/102) BID PPI). Compared with entry symptoms while taking PPIs, 81% (38/47) of MSA patients



**Figure 4.** Results at 6-month endpoint. **A**, Percentage of patients with normal (<57) number of reflux episodes. **B**, Percentage of patients with normal DeMeester scores (<14.7). **C**, Percentage of patients with normal time with (<4.5%) pH <4. MSA, magnetic sphincter augmentation; BID, twice daily; PPI, proton pump inhibitor.

also reported a concomitant marked improvement in global GERD-HRQL at the 6-month endpoint compared with 8% (7/87) of patients taking BID PPIs. Ninety-one percent (43/47) of patients with the MSA device were able to stop using PPIs.

Quantitative 24-hour impedance-pH monitoring was used as a comparator. By permitting evaluation of reflux in patients, regardless of the acidity of the refluxate, impedance-pH testing allows objective comparison of patients taking acid-suppressive medication to patients having an anti-reflux procedure such as MSA.<sup>25,26</sup> In the present study, patients in the BID PPI arm continued to have a significant number of reflux episodes and/or abnormal esophageal acid exposure, concordant with ongoing regurgitation symptoms in the BID PPI arm. In contrast, 91% (40/44) of patients after the MSA procedure had a normal number of reflux events, and consequently 89% (39/44) demonstrated normal esophageal acid exposure. Non-acidic reflux can be the source of regurgitative symptoms, as demonstrated by persistent regurgitation in 90% (90/101) of patients taking BID PPIs, compared with only 11% (5/47) in MSA patients. This study demonstrates that control of reflux events (by MSA) is more important than neutralization of gastric pH (as occurs with PPI therapy) in controlling regurgitation symptoms.

Dysphagia, typically transient, was the most commonly reported side effect of MSA in this study and of other studies of the MSA procedure. Capsular formation, or scarring, around any implanted device is a normal physiologic event, and postoperative dysphagia is an anticipated event after MSA implantation. Minimizing long-term dysphagia involves keeping the scar tissue from contracting or becoming non-compliant. Distention of the distal esophageal lumen during swallowing of semi-solid boluses will expand the MSA device and improve capsular compliance. Postoperatively, patients are instructed to regularly eat semisolid food boluses

**TABLE 2. Healthcare utilization of MSA patients with postoperative dysphagia**

Intervention	n/N	%
None	9/15	60%
Medication (oral corticosteroids)	3/15	20%
Endoscopic dilation	3/15	20%
Surgical intervention (laparoscopic hiatal hernia repair)	1/15	6.7%

One patient had multiple healthcare utilizations.

MSA, Magnetic sphincter augmentation.

(eg, 1-2 tablespoons hourly while awake for the first 2-4 weeks), and this seems to play a significant role in lessening long-term dysphagia. In some cases, especially if the patient is at risk of becoming dehydrated or is regurgitating stuck food regularly, a short course of oral steroids can be administered. Although esophageal dilation by using fluoroscopy to observe magnet separation can be performed carefully, increased experience with MSA has led most surgeons to perform dilation less frequently. The percentage of short-term and long-term dysphagia reported in this study is equivalent to or less than that reported in other studies.<sup>18</sup> No patient in this study has required removal of the device because of unmanageable dysphagia.

Surgically reestablishing a barrier to gastric reflux addresses the etiology of GERD and controls regurgitation symptoms. Until recently, the only effective surgical procedure available for GERD was the Nissen fundoplication. It effectively prevents the reflux of gastric contents into the esophagus and eliminates regurgitation.<sup>27</sup> Nissen fundoplication has not been adopted widely because of side effects such as bloating, gas, difficulty belching, and inability to vomit. Nissen results have been variable, and it has been shown to lose efficacy over time, with a failure rate of 3% to 27% at 5 to 10 years.<sup>28-31</sup> Endoscopic procedures such as transoral fundoplication with the EsophyX (EndoGastric Solutions, Inc, Redmond, Wash, USA) device have demonstrated improvement in GERD symptoms, with minimal side effects.<sup>32</sup> Two studies of transoral fundoplication by using the EsophyX device found superior elimination of troublesome regurgitation in 67% to 97% of patients in the TIF group compared with 45% to 50% in the PPI-treated group at 6-month follow-up.<sup>33,34</sup> However, there are significant variations in objective improvement in esophageal reflux, symptomatic success, and durability.<sup>32,35,36</sup>

MSA has been demonstrated to improve typical GERD symptoms and gastric reflux into the esophagus in patients responsive to PPI therapy.<sup>18,37</sup> Consistent outcomes across multiple studies suggest that it is effective, lacks significant bloating side effects, and is a reproducible, durable procedure. In a propensity-matched cohort analysis, significant side effects of bloating and gas were absent in the MSA group compared with being present in 10% of the Nissen cohort.<sup>15</sup> Durability has been assessed out to 5 years,

and there has been little deterioration in success over time, with 85% or more of patients experiencing relief of typical GERD symptoms without requiring daily acid-suppressive medication.<sup>18,19,38</sup> The success of MSA in controlling regurgitation seen in this study is in line with previous MSA studies.<sup>19</sup>

Surgical treatment for refractory GERD often is overlooked or discounted for a variety of reasons: concern about durability, side effects, and the presumption that refractory GERD symptoms are not in fact because of GERD. However, with increasing reports about the safety of PPIs, persistent or increased dosing of PPIs without an anticipated successful endpoint has been concerning.<sup>39-41</sup> A low success rate of controlling regurgitation with increased doses of PPIs should not be surprising because PPIs merely change the composition of the refluxate and would not be expected to significantly reduce the number of reflux episodes or consistently reduce the volume of reflux.

Limitations of the current study include the inherent subjective nature of the questionnaires used as end points, although impedance-pH added some objective measure of the control of reflux. Also, there was potential referral bias insofar as recruitment began with patients presenting to a surgical clinic. Attempting to minimize this bias, we chose standardized measures of GERD symptoms such as the FSQ and GERD-HRQL that could be applied across a broader range of patients such as those seen in a medical clinic. A precise but practical definition of moderate-to-severe regurgitation was used to characterize better the patient population being studied. Another limitation might be the choice of 20 mg omeprazole BID as the control treatment, given that 40 mg BID PPI is commonly considered for refractory GERD symptoms.<sup>42</sup> The choice of 20 mg BID omeprazole dosing was chosen because (1) the U.S. Food and Drug Administration–recommended adult oral dose is 20 mg daily,<sup>43</sup> (2) a 20 mg BID dose of omeprazole appears to be more effective than 40 mg daily,<sup>44</sup> and (3) a dosage of 40 mg omeprazole BID has not been demonstrated to provide better gastric acid control than 20 mg BID.<sup>45</sup> We also chose not to monitor patient compliance or gastric acid control with the dosing because our intent was to mimic a real-world scenario in patients already familiar with taking PPIs. Despite these limitations, this prospective, randomized, controlled trial comparing control of regurgitation symptoms demonstrates the ability of MSA to control regurgitative symptoms while illustrating the lack of benefit achieved from increasing the dosage of PPI therapy to BID. In this population of GERD patients with regurgitation refractory to daily PPI therapy, MSA is far more effective at alleviating regurgitation and improving GERD-related quality of life than was increased dosing of PPIs.

## Conclusion

MSA provides significantly better control of moderate-to-severe regurgitation when compared with BID PPI

therapy. Patients with GERD and inadequately controlled regurgitation after initial dosing of acid-suppressive medication should be considered for minimally invasive surgical treatment with the MSA rather than treatment with increased doses of medication.

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*Abbreviations:* BID, twice daily; FSQ, Foregut Symptom Questionnaire; GERD-HRQL, GERD–health-related quality of life; ITT, intention-to-treat; LES, lower esophageal sphincter; MSA, magnetic sphincter augmentation; PPI, proton pump inhibitor; RDQ, Reflux Disease Questionnaire.

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**APPENDIX 1.**

Randomization was based on a prespecified randomization sequence of sealed envelopes generated by the biostatistician, by using each clinical site as a stratification parameter. Sites were blinded to the determinants for the randomization sequence (block size, stratification, etc). When a patient was enrolled, a Request for Randomization form was sent from the site to the sponsor team, who confirmed eligibility and selected the next sequentially assigned sealed envelope for that site.

**APPENDIX 2.**

Exclusion criteria: currently taking twice-daily PPIs; any contraindication, warning, or precaution related to LINX; medical history or condition contraindicating twice-daily PPIs; history of gastric or gastroesophageal surgery,

anti-reflux procedures, or gastroesophageal/gastric cancer; prior endoscopic anti-reflux intervention for GERD and/or previous endoscopic intervention for treatment of Barrett's esophagus; suspected or confirmed esophageal or gastric cancer; distal esophageal motility (average of sensors 3 and 4) <35 mmHg peristaltic amplitude on wet swallows or <70% (propulsive) peristaltic sequences; symptoms of dysphagia more than once per week within the previous 3 months; scleroderma; esophageal motility disorder such as, but not limited to, achalasia, nutcracker esophagus, or diffuse esophageal spasm or hypertensive LES; esophageal stricture or gross esophageal anatomic abnormalities (Schatzki's ring, obstructive lesions, etc); esophageal or gastric varices; any condition that may cause the patient to be non-compliant with or unable to meet the protocol requirements, limited life expectancy (ie, <3 years); pregnant or nursing or plans to become pregnant during the course of the study; suspected or known allergies to titanium, stainless steel, nickel, or ferrous materials.