

## RAPID COMMUNICATION

## Nonresorbable Copolymer Implantation for Gastroesophageal Reflux Disease: A Randomized Sham-Controlled Multicenter Trial

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**Background & Aims:** This aim was to determine whether endoscopic implantation of a biocompatible nonresorbable copolymer (Enteryx; Boston Scientific Corp, Natick, MA) is a more effective therapy for gastroesophageal reflux disease (GERD) than a sham procedure. **Methods:** In a randomized, single-blind, prospective, multicenter clinical trial, 64 patients with GERD were enrolled whose symptoms were well controlled by proton pump inhibitor (PPI) therapy and rapidly recurred after cessation of PPI therapy. Thirty-two patients were assigned to Enteryx implantation and 32 to a sham procedure consisting of standard upper endoscopy. Patients in both groups with unsatisfactory symptom relief after 3 months were eligible for re-treatment by Enteryx implantation. The primary study end point was  $\geq 50\%$  reduction in PPI use. Secondary end points included  $\geq 50\%$  improvement in GERD score and the proportion of patients not undergoing re-treatment procedure. Follow-up evaluations were performed at 3 and 6 months. **Results:** The percentage of Enteryx-treated patients achieving a  $\geq 50\%$  reduction in PPI use (81%) was greater than that of the sham group (53%), with a rate ratio of 1.52 (confidence interval [CI], 1.06–2.28;  $P = .023$ ). A higher proportion of the Enteryx (68%) than sham group (41%) ceased PPI use completely (rate ratio, 1.67; CI, 1.03–2.80;  $P = .033$ ). GERD health-related quality of life heartburn score improvement  $\geq 50\%$  was achieved by 67% of the Enteryx group versus 22% of the sham group (rate ratio, 3.05; CI, 1.55–6.33;  $P < .001$ ). More Enteryx-treated (81%) than sham-treated (19%) patients did not undergo re-treatment (rate ratio, 4.33; CI, 2.23–9.29;  $P < .001$ ). **Conclusions:** Enteryx implantation more effectively reduces PPI dependency and alleviates GERD symptoms than a sham procedure.

Minimally invasive endoluminal procedures for gastroesophageal reflux disease (GERD) are designed to provide long-lasting symptom relief and abolish or lessen medication dependency.<sup>1</sup> Several endoluminal modalities have now been introduced into clinical practice.<sup>2–6</sup> Among these are lower esophageal sphincter augmentation via endoscopic implantation of a biocompatible nonresorbable copolymer (Enteryx; Boston Scientific Corp, Natick, MA).<sup>7</sup> The copolymer is injected as a nonviscous liquid and rapidly forms a spongy solid in situ. By 3–6 months, the implant has been shown to undergo fibrous encapsulation in a porcine model.<sup>8</sup> The durability of the implant for at least 3 years has been demonstrated by spiral computed tomography in a small clinical study.<sup>9</sup> Lower esophageal sphincter augmentation with Enteryx is believed to derive its effectiveness by modifying the distensibility and compliance at the cardioesophageal junction.<sup>8</sup>

Clinical results of Enteryx implantation have been favorable.<sup>10,11</sup> In 2 prospective multicenter cohort trials involving 178 total patients followed up to 12 months, the procedure reduced use of proton pump inhibitors (PPIs) and alleviated symptoms in most patients, and no major complications were encountered.<sup>3,12</sup> A preliminary report has indicated continued benefit of the procedure through 24 months of follow-up.<sup>13</sup>

Thus far unknown is the extent to which the observed benefits may reflect a placebo response. In a meta-analysis of 22 drug trials in patients with erosive/ulcerative

Abbreviations used in this paper: CI, confidence interval; GERD, gastroesophageal reflux disease; HRQL, health-related quality of life; PPI, proton pump inhibitor; SF-36, 36-Item Short-Form Health Survey.

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esophagitis, 12% of patients receiving placebo had complete disappearance of symptoms compared with 32% of active drug recipients.<sup>14</sup> The proportion of heartburn-free days in the placebo group was 36%–46% as contrasted with 63%–66% of patients receiving 40 mg esomeprazole in 2 randomized, double-blind, multicenter trials.<sup>15</sup> In a sham-controlled trial of endoluminal radiofrequency energy treatment for GERD, 33% of the sham-treated patients were free of heartburn symptoms versus 61% of the active radiofrequency energy treatment group.<sup>16</sup> There is also the possibility that benefit may be overestimated in noncontrolled trials. The results of a randomized trial comparing Enteryx implantation with a sham procedure are described in this report.

## Patients and Methods

### Study Design

This multicenter, parallel-group, patient-blinded, randomized, controlled trial was conducted at 4 centers, 2 in Germany and one each in Belgium and Italy, under ethics committee approval from each center (Figure 1). Patients who had rendered their written informed consent were randomly allocated to Enteryx implantation or a sham procedure by means of a set of individually sealed opaque envelopes prepared at a centralized location. Randomized group assignments were generated by computer with a target ratio of 1:1. Patients were not apprised of their group assignments. They were informed that a second treatment would be offered after the 3-month follow-up visit if their symptoms continued. Patient recruitment commenced in November 2001, and follow-up data were collected through August 2004.

### End Points

The primary study end point was  $\geq 50\%$  reduction in PPI use compared with baseline. Secondary end points included  $\geq 50\%$  improvement in GERD health-related quality of life (HRQL) heartburn score<sup>17</sup> and the proportion of patients not undergoing a subsequent Enteryx procedure. Trial sample size was selected to attain 80% power in demonstrating a difference in response rate with respect to the primary end point based on the assumption of a 65% response rate in the Enteryx group and a 15% rate in the sham group.

### Eligibility

Nonpregnant patients 18 years of age or older with a history of heartburn, regurgitation, or both and American Society of Anesthesiologists Physical Status Classification I or II were eligible. Patients must also have demonstrated a satisfactory symptomatic response (GERD-HRQL heartburn score  $\leq 11$ ) to a previous course of PPI therapy  $\geq 3$  months. On PPI withdrawal for a minimum of 10 days, candidates must have experienced symptomatic relapse (GERD-HRQL heartburn score  $\geq 20$ ) and exhibited excessive lower esophageal acid exposure during prolonged pH-metry  $>12$  hours (pH  $\leq 4$  for  $\geq 5\%$  of total or  $\geq 3\%$  of supine time). Exclusion criteria

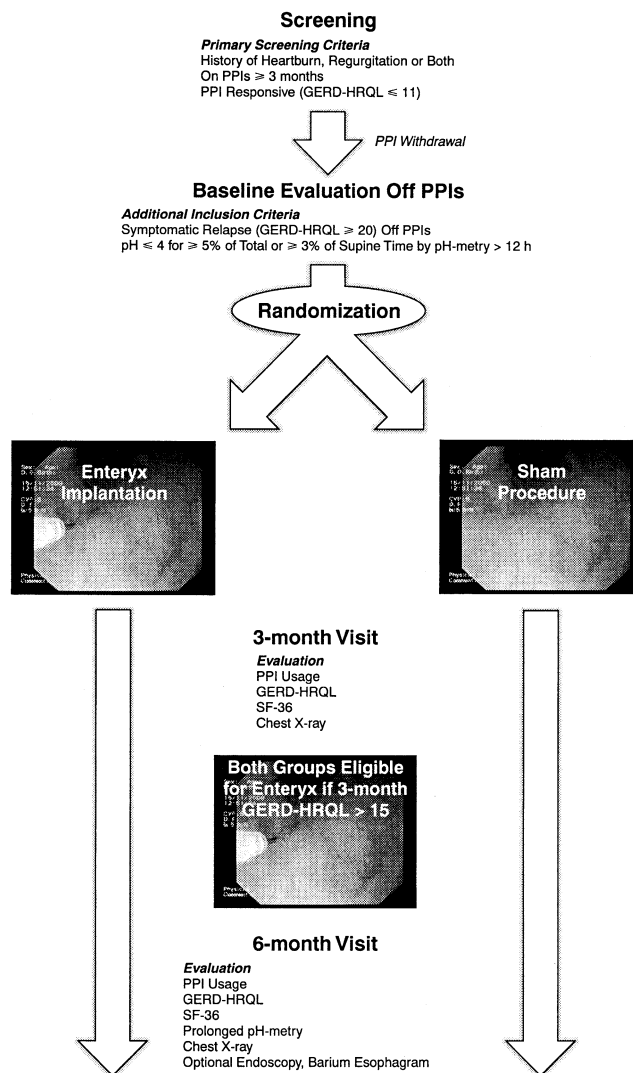


Figure 1. Trial design.

included the following: non-GERD esophageal motility disorders; diabetic gastroparesis; significant multisystem disease; prior gastric, esophageal, or GERD surgery; scleroderma, dermatomyositis, calcinosis-Raynaud's-esophagus-sclerodactyly syndrome, Sjögren's syndrome, or Sharp's syndrome; persistent esophagitis greater than or equal to grade III (Savary-Miller); Barrett's epithelium; hiatus hernia  $\geq 5$  cm; body mass index  $\geq 35$  kg/m<sup>2</sup>; autoimmune disorder requiring therapy in the preceding 2 years; suspected or confirmed esophageal or gastric cancer; esophageal or gastric varices; and anticoagulant use other than 300 mg aspirin or equivalent per day.

### Data Collection

Patient history was elicited at the screening visit, after which patients maintained a diary throughout the trial documenting their use of PPIs. GERD-HRQL and 36-item Short-Form Health Survey (SF-36)<sup>18</sup> questionnaires were completed at all visits (Figure 1). In order to exclude patients with motility disorders, dual manometry/pH-metry was performed at the baseline evaluation while patients were off PPI therapy.

Prolonged pH-metry (>12 hours) and barium esophagrams were part of the evaluation at baseline while patients were off PPI therapy; prolonged pH-metry was repeated at 6 months, while a barium esophagram was optional at this time point. Chest radiographs were obtained at the 3- and 6-month visits. The percentage of residual Enteryx implant material during follow-up as compared with the day of implantation was estimated by the investigators from radiograph images. Upper gastrointestinal endoscopy could be performed as an option at 6 months. A final follow-up evaluation will be conducted at 12 months.

### Study Procedure

PPI therapy was resumed  $\geq 3$  days before the study procedure. After an overnight fast, conscious sedation with midazolam or deep sedation with propofol was administered according to the standard practices of the study centers for upper gastrointestinal endoscopy. All patients received 1 mg glucagon and prophylactic antibiotics. Enteryx, which consists of ethylene vinyl alcohol in dimethyl sulfoxide with added radiopaque micronized tantalum powder, was injected either within the muscle layer or into the deep submucosal layer of the distal esophagus and cardia under both fluoroscopic and endoscopic guidance by methods previously described.<sup>3</sup> Introduced through the working channel of the endoscope, a 4-mm long, 23-gauge sclerotherapy-type needle was used to inject in an antegrade direction at or just below the squamocolumnar junction (Z-line). The target total volume of Enteryx injected was 6–8 mL.

The sham group underwent upper gastrointestinal endoscopy only, either with deep propofol-induced sedation or midazolam sedation for a minimum of 15 minutes. For those patients in the sham group receiving midazolam only, attending physicians and staff performed the same procedures used for Enteryx implantation except the actual injection of the copolymer solution. Patients received a 10-day supply of PPI medication and were instructed to discontinue their use of PPIs 10 days following the procedure. Thereafter, they were prescribed PPIs only if necessary and were asked to take only the minimum dosage required to alleviate their symptoms and to record such PPI use.

### Re-treatment

Both groups had undergone an Enteryx or sham “treatment” and were eligible for re-treatment if symptom control was unsatisfactory (GERD-HRQL heartburn score >15) at the 3-month visit. Enteryx implantation was the only form of re-treatment offered. Eligible patients were notified of their group assignment so that they could make an informed decision on proceeding with re-treatment, which could be scheduled after the 3-month visit. Before re-treatment, patients who had resumed PPI therapy were required to discontinue this therapy for at least 10 days and complete GERD-HRQL questionnaires.

### Statistical Analysis

Binary study end points were analyzed by calculation of rate ratios and exact confidence intervals (CIs) around the rate ratios. The rate ratio was defined as the proportion of total patients in the Enteryx group with the outcome of interest (eg,  $\geq 50\%$  reduction in PPI use) divided by the corresponding proportion in the sham group. A rate ratio of 1 indicates no between-group difference. When the rate ratio differs from 1 and the CI does not contain 1, a significant effect of group assignment can be inferred. Within-group changes in binary outcomes were assessed by exact McNemar test. Exact Clopper–Pearson CIs were calculated for binary proportions. Outcome predictors were evaluated by exact logistic regression.

Differences in continuous variables were determined by *t* test in the case of normally distributed data and by exact Mann–Whitney or Wilcoxon test otherwise. Median within-group changes versus baseline off PPIs were obtained by exact Hodges–Lehmann estimation. Absence of zero from the CI for the difference indicates statistical significance. Baseline PPI use was assessed by exact Wilcoxon–Mann–Whitney test for 2 ordered multinomials.

### Results

Twenty-three of the 64 study patients (36%) were enrolled at the Hôpital Erasme (Brussels, Belgium), 16 (25%) at the Policlinico Agostino Gemelli (Rome, Italy), 13 (20%) at the Evangelisches Krankenhaus Düsseldorf (Düsseldorf, Germany), and 12 (19%) at the Universitätsklinikum Charité (Berlin, Germany). Two patients in the sham group and one in the Enteryx group requested to be discontinued from the trial after the 3-month visit (Figure 2). There were no statistically significant between-group differences in baseline patient data (Table 1). In deviation from the protocol, 4 patients entered the trial despite GERD-HRQL heartburn scores >11 at the screening evaluation on PPIs and 5 additional patients entered the trial despite heartburn scores <20 at the baseline evaluation off PPIs. The deviant screening heartburn scores were 12 in 2 patients, 13 in one patient, and 16 in one patient, and the deviant baseline scores were 13 in one patient, 14 in 2 patients, and 19 in 2 patients.

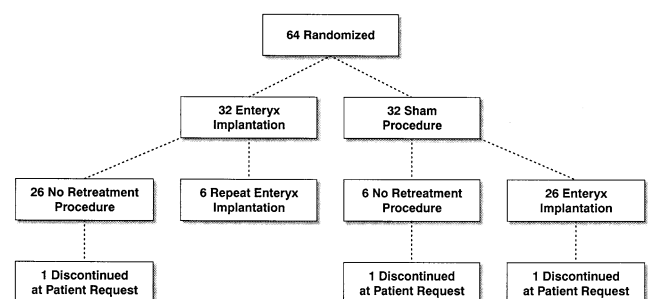


Figure 2. Disposition of study patients.

**Table 1.** Baseline Patient Data

Characteristic	Sham group (n = 32)	Enteryx group (n = 32)	P
Age (y), mean $\pm$ SD	48.6 $\pm$ 10.2	49.7 $\pm$ 14.2	.72
Body mass index ( $\text{kg}/\text{m}^2$ ), mean $\pm$ SD	25.9 $\pm$ 3.2	26.0 $\pm$ 3.41	.90
GERD-HRQL symptom score, <sup>a</sup> median (IQR)			
Heartburn	23.0 (21.3–30.0)	26.5 (22.3–31.5)	.38
Regurgitation	8.0 (0.3–13.8)	12.0 (7.3–14.0)	.07
SF-36 quality-of-life score <sup>a</sup> , median (IQR)			
Physical	40.5 (33.3–47.0)	39.6 (34.3–47.5)	.92
Mental	47.0 (33.0–56.8)	45.5 (36.3–53.8)	.98
Duration of acid reduction therapy (mo), median (IQR)	21.0 (12.0–45.0)	12.0 (5.8–26.2)	.05
Sex (%)			.60
Female	12 (38)	9 (28)	
Male	20 (62)	23 (72)	
GERD medication use (%)			
PPI			.06 <sup>b</sup>
Half standard dose	4 (13)	3 (9)	
Standard dose	25 (78)	19 (60)	
$\geq 2$ times standard dose	3 (9)	10 (31)	
Antacids and other <sup>c</sup>	3 (9)	7 (22)	.30

IQR, interquartile range.

<sup>a</sup>At baseline off PPI therapy.

<sup>b</sup>Indicates no significant between-group difference in PPI dose at baseline.

<sup>c</sup>Other: gastrointestinal motility drugs (n = 3); sucralfate (n = 1).

### Outcomes at 3 Months

As shown in Figure 3, the rate of  $\geq 50\%$  reduction in PPI use among Enteryx-treated patients (81%) was higher than that of the sham group (53%) at 3 months (rate ratio, 1.52; CI, 1.06–2.28). With exclusion of the 9 patients entering the trial in deviation from the protocol,  $\geq 50\%$  reduction in PPI use was achieved by 81% of the Enteryx group and 48% of the sham group (rate ratio, 1.69; CI, 1.11–2.84;  $P = .011$ ).

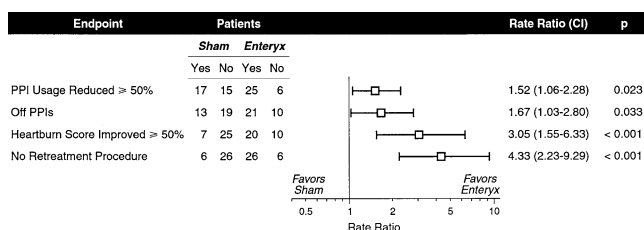
The PPI use result for 1 patient in the Enteryx group was not obtained at 3 months, although this patient remained in the study and was subsequently found to be completely off PPI therapy at 6 months. In an intent-to-treat analysis classifying this patient as a treatment failure at 3 months, 78% of the Enteryx group and 53% of the sham group achieved  $\geq 50\%$  reduction in PPI use (rate ratio, 1.47; CI, 1.02–2.22;  $P = .038$ ). The rate of complete PPI cessation at 3 months was also significantly higher in the Enteryx group (68%) than in the sham group (41%) (rate ratio, 1.67; CI, 1.03–2.80).

By 3 months, GERD-HRQL heartburn score in the Enteryx group had significantly improved by a median of 63% (CI, 47%–81%) compared with 25% (CI, 10%–39%) for the sham group. GERD-HRQL heartburn score improved  $\geq 50\%$  significantly more frequently in the Enteryx group (67%) compared with the sham group (22%) at 3 months (Figure 3). The rate of GERD-HRQL regurgitation score improvement  $\geq 50\%$  was also greater in the Enteryx group (63%) than in the sham group (31%) (rate ratio, 2.03; CI, 1.14–3.75).

SF-36 physical and mental scores improved significantly from baseline by a median of 14% (CI, 6%–31%) and 16% (CI, 6%–27%), respectively, at 3 months in the Enteryx group. No significant improvements from baseline were evident in the sham group for either physical score (median change, 8%; CI,  $-0.2\%$  to 18%) or mental score (median change, 3%; CI,  $-3\%$  to 14%). The percent changes from baseline to 3 months did not differ significantly between the groups for either SF-36 physical ( $P = .23$ ) or mental ( $P = .07$ ) score.

### Re-treatment

Nine Enteryx-treated patients were eligible for re-treatment at 3 months (GERD-HRQL heartburn score  $> 15$ ), of whom 6 (67%) actually underwent re-treatment (Figure 2). In the sham group, 20 of 23 eligible patients (87%) proceeded to Enteryx implantation as re-treatment. In deviation from the study protocol, 6 additional patients in the sham group underwent re-treatment despite failure to fulfill the heartburn score eligibility requirement. The rate of eligibility for re-



**Figure 3.** PPI use and heartburn score outcomes at 3 months and proportions of patients not proceeding to re-treatment. Error bars show exact CI.



treatment was lower in the Enteryx group than in the sham group (rate ratio, 0.42; CI, 0.22–0.73).

Significantly more Enteryx-treated (81%) than sham-treated (19%) patients did not undergo re-treatment (Figure 3). With exclusion of the 6 patients in the sham group who underwent re-treatment despite ineligibility, the proportion of the Enteryx group not proceeding to re-treatment remained higher than that of the sham group (rate ratio, 3.52; CI, 1.80–8.59;  $P < .001$ ). The time elapsed between the original procedure and the re-treatment procedure averaged  $136 \pm 38$  days for the Enteryx group and  $120 \pm 24$  days for the sham group ( $P = .20$ ).

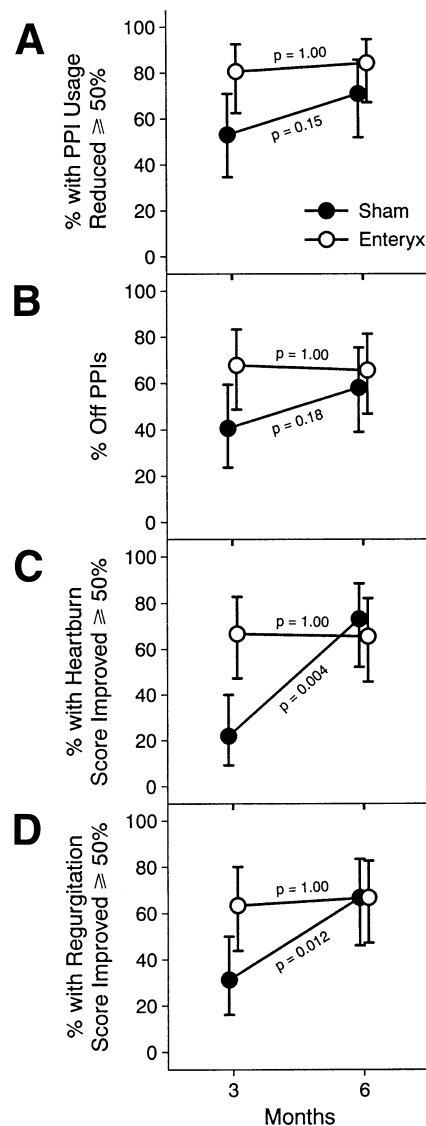
### Outcomes at 6 Months

In the Enteryx group, PPI use and symptoms remained stable at 6 months (Figure 4). Because 26 of the 32 patients in the sham group (81%) had undergone an Enteryx re-treatment procedure after 3 months, the major between-group differences observed at 3 months no longer persisted at 6 months.

Median heartburn score improvement at 6 months versus baseline off PPIs in the Enteryx group (63%; CI, 50%–75%) was unchanged from that at 3 months. By contrast, in the sham group, heartburn score improvement at 6 months (70%; CI, 52%–82%) was markedly higher than at 3 months due to the crossover of most patients in this group to Enteryx implantation. With exclusion of the 6 patients in the sham group who underwent re-treatment despite ineligibility, heartburn score for the sham group improved by a median of 71% (CI, 52%–82%) at 6 months.

At 6 months, significant median SF-36 physical and mental score improvements of 18% (CI, 5%–31%) and 12% (CI, 3%–22%), respectively, persisted in the Enteryx group. The sham group, which exhibited no significant improvements at 3 months, experienced significant median improvements at 6 months in SF-36 physical score of 22% (CI, 12%–33%) and mental score of 8% (CI, 0.1%–22%).

The PPI use and heartburn results at 6 months were not substantially affected by the contribution of 6 re-treated patients in the Enteryx group and 6 non-re-treated patients in the sham group. Thus, with these 12 patients excluded, reduction in PPI use  $\geq 50\%$  was attained at 6 months by 85% (CI, 65%–96%) of the Enteryx group and 77% (CI, 56%–91%) of the sham group, complete cessation of PPI use by 69% of the Enteryx group (CI, 48%–86%) and 62% (CI, 41%–80%) of the sham group, and heartburn score improvement  $\geq 50\%$  by 61% of the Enteryx group (CI, 39%–80%) and 73% (CI, 50%–89%) of the sham group. Corresponding values without the exclusions were 84%



**Figure 4.** Percentages of patients with (A) PPI use reduction  $\geq 50\%$ , (B) complete cessation of PPI use, and GERD-HRQL (C) heartburn and (D) regurgitation score improvement  $\geq 50\%$ . The majority of patients in the sham group (26 of 32) underwent an Enteryx procedure between the 3- and 6-month evaluations, so that between-group differences were no longer apparent at 6 months. For the 2 PPI use end points, all patients except 1 in the Enteryx group were evaluable at 3 months and all but 1 in the sham group at 6 months. For the 2 symptom end points, all patients except 2 in the Enteryx group were evaluable at 3 months. At 6 months, all but 3 patients in the Enteryx group and 6 patients in the sham group were evaluable with respect to heartburn score and all except 2 and 5 patients, respectively, with regard to regurgitation score. Depicted data are without exclusion of the 6 re-treated patients in the Enteryx group and 6 non-re-treated patients in the sham group. Error bars show exact CI. Indicated  $P$  values are for the significance of within-group change from 3 to 6 months by exact McNemar test. Median symptom scores at baseline off PPI therapy appear in Table 1.

of the Enteryx group (CI, 67%–95%) and 71% (CI, 52%–86%) of the sham group for reduction in PPI use  $\geq 50\%$ , 66% of the Enteryx group (CI, 47%–81%) and 58% (CI, 39%–75%) of the sham group for complete

**Table 2.** pH-metry

% Total time at pH < 4						
Group	n	Baseline		Final		<i>P</i>
		Median	IQR	Median	IQR	
Sham	16	14.0	7.1–22.8	12.7	7.0–21.3	.85
Enteryx	23	13.3	7.3–20.8	11.2	4.1–24.3	.94
Pooled	39	13.3	7.2–22.4	11.2	6.6–22.8	.87

IQR, interquartile range.

cessation of PPI use, and 66% (CI, 46%–82%) of the Enteryx group and 73% (CI, 52%–88%) of the sham group for heartburn score improvement  $\geq 50\%$ .

For the 6 re-treated patients in the Enteryx group, the rate of PPI use reduction  $\geq 50\%$  at 6 months was 83% (CI, 36%–100%) compared with 50% (CI, 12%–88%) at 3 months. Thus, although this was a small patient subgroup, the results were suggestive of incremental benefit resulting from the repeat Enteryx procedure.

### pH-metry

Prolonged pH-metry was not consistently performed at the same follow-up visit, and in some patients this diagnostic monitoring procedure was performed at more than one follow-up evaluation. In Table 2, the baseline percent total time at pH  $\leq 4$  is compared with results from the final pH-metry in the 39 patients with available data. There were no statistically significant between-group differences in esophageal acid exposure. Because of the incompleteness of the data and varied times of collection, the impact on pH in this study remains indeterminate. A correlation was not apparent between change in total time at pH  $\leq 4$  and either residual implant volume ( $P = .19$ ) or change in heartburn score ( $P = .61$ ).

### Residual Implant

At 3 months, after either an original implantation in the Enteryx group or a re-treatment procedure in

either group, the mean estimated residual implant volume was 67% (CI, 54%–79%). This finding remained essentially unchanged at 6 months (66%; CI, 56%–76%).

No residual implant could be detected in 2 patients in the Enteryx group. Both patients were completely off PPI therapy at 6 months. Neither had been re-treated.

### Outcome Predictors

Potential outcome predictors were screened in an exact multivariate logistic regression model with randomized group assignment as a covariate. No significant relationship could be detected between PPI dose reduction  $\geq 50\%$  at 3 months and specific PPI agent in use at baseline ( $P = .46$  for rabeprazole and  $P = 1.00$  for lansoprazole, pantoprazole, and esomeprazole, with omeprazole as the reference PPI), duration of prior PPI therapy ( $P = 1.00$ ), GERD-HRQL heartburn score at screening on PPIs ( $P = .64$ ), and GERD-HRQL heartburn score ( $P = .61$ ), esophageal acid exposure ( $P = 1.00$ ), Savary–Miller esophagitis grade ( $P = .47$ ), and presence of hiatal hernia ( $P = .62$ ) at baseline evaluation off PPIs.

### Adverse Events

Table 3 summarizes the most frequent procedure- or device-related adverse events from baseline through 3 months. Retrosternal, chest, or epigastric pain and dysphagia/odynophagia were the most common such adverse events in the Enteryx group during this period. These adverse events were infrequent in the sham group over this period. However, in reflection of the high proportion of patients in the sham group undergoing an Enteryx re-treatment procedure after 3 months, the cumulative incidence rates for these adverse events in the 2 groups were similar by 6 months.

One patient reported mild to moderate pain persisting for 6 months after Enteryx implantation, and upper gastrointestinal endoscopy revealed ulcerations and ex-

**Table 3.** Procedure- or Device-Related Adverse Events From Baseline to 3 Months

Adverse event type	Percentage of patients with adverse event							
	Sham group				Enteryx group			
	Mild	Moderate	Severe	Total	Mild	Moderate	Severe	Total
Retrosternal, chest, or epigastric pain	6.3	0.0	0.0	6.3	21.9	40.6	6.3	68.8
Dysphagia/odynophagia	9.4	0.0	0.0	9.4	3.1	15.6	9.4	28.1
Fever	0.0	0.0	0.0	0.0	9.4	12.5	0.0	21.9
Bloating/flatulence	3.1	0.0	0.0	3.1	3.1	0.0	0.0	3.1
Belching	0.0	0.0	0.0	0.0	3.1	0.0	0.0	3.1

NOTE. Adverse events were classified as mild if they were transient and easily tolerable without medical management or disruption of normal activities. Adverse events that did interfere with normal activities were categorized as moderate. Severe adverse events were defined as those resulting in incapacitation for work or normal activities and possibly requiring medical evaluation and/or treatment.

trusion of the Enteryx copolymer. Resolution of the ulceration, which may have been due to sloughing of the implanted material, was demonstrable on subsequent endoscopy.

## Discussion

This randomized trial provides evidence of an Enteryx implantation-specific decrease in PPI dependency, both in terms of  $\geq 50\%$  dose reduction and complete PPI cessation. In addition, symptom relief was significantly more pronounced in Enteryx-treated compared with sham-treated patients.

Heartburn score improvement  $\geq 50\%$  was documented in 67% of the Enteryx group at 3 months. Could this rate be due to resumption of PPI use rather than the Enteryx procedure itself? This was not the case. In the subgroup of Enteryx-treated patients completely off PPI therapy at 3 months, the rate of heartburn score improvement  $\geq 50\%$  at 3 months (80%; CI, 56%–94%) was actually higher than that of the entire Enteryx group. Conversely, the heartburn improvement rate among patients who did not completely cease PPI use (40%; CI, 12%–74%) was poorer, not better, than that of the Enteryx group as a whole.

Several endoluminal alternatives to Enteryx implantation have been investigated. In a randomized trial of 64 patients with GERD, radiofrequency energy improved heartburn symptoms more than did a sham procedure; however, there was no significant difference in medication use.<sup>16</sup> Endoscopic suturing decreased heartburn frequency and the extent of daily reliance on antisecretory medication compared with a sham procedure in a single-center randomized trial.<sup>19</sup> However, the frequency of complete antisecretory medication cessation did not differ between the groups. Acute pharyngitis has been described as a major complication of endoscopic suturing, affecting more than one half of patients undergoing this procedure.<sup>20</sup> In a multicenter trial of 64 medication-dependent patients with GERD undergoing endoscopic full-thickness plication, PPI use was eliminated by 74% of patients at 6 months and the median GERD-HRQL score improved 67%.<sup>6</sup> Lower esophageal sphincter augmentation by endoscopic placement of expandable polyacrylonitrile-based hydrogel prostheses has also been recently described, and significant symptom improvement and reduction in esophageal acid exposure were attained in a cohort study of 69 patients with GERD.<sup>5</sup>

In clinical trials thus far, life-threatening or other major complications attributable to Enteryx implantation have not been encountered.<sup>3,12</sup> Outside the context of clinical trials, however, recent reports of such complications have appeared.<sup>21,22</sup> Fatal hemorrhage apparently

due to an aortoesophageal fistula occurred in a woman 3 weeks after an Enteryx procedure. On postmortem examination, 2 ulcerations were noted approximately 1 cm above the squamocolumnar junction, and there was evidence that the Enteryx material had been injected transmurally into the superficial layer of the aorta. A second patient developed severe flank pain, and Enteryx material was evident in the aorta and renal arteries by computed tomography. Despite extensive ischemia of the kidney, renal function was preserved. Nevertheless, these cases underscore the importance of adhering closely to recommended techniques for Enteryx implantation. Specifically, Enteryx solution should only be injected in an antegrade direction into esophageal muscle under careful fluoroscopic guidance. Particular care should be taken to inject exclusively at or just below the squamocolumnar junction. Effective sedation is also essential, because transmural injection is unlikely in the absence of patient movement (for instance, due to belching). An agent such as propofol may be helpful in this regard.

A third case report involving pericardial effusion necessitating surgery has suggested an inflammatory response to injected Enteryx copolymer. This possibility will be addressed in a forthcoming update to the Enteryx Instructions for Use from the manufacturer. Additionally, it should be recognized that the incidence of serious complications appears to be small, because the reported cases have occurred in a total population of approximately 2600 patients treated with Enteryx implantation to date.

There was evidence of a substantial placebo effect. By 3 months, 53% of the sham group had reduced their PPI use  $\geq 50\%$  and 22% had experienced symptom improvement  $\geq 50\%$ . The symptom improvement in some patients in the sham group is consistent with evidence from a clinical trial of PPI-dependent patients with GERD in which a step-down therapy protocol rendered 39% of the patients asymptomatic off PPIs after 3 months.<sup>23</sup> In the randomized trial of endoluminal radiofrequency energy, daily PPI dependency declined markedly in the sham group from 72% of patients at baseline to 43% at 6 months.<sup>16</sup> Interestingly, more than twice as many sham patients in the present trial reduced their PPI use  $\geq 50\%$  than attained a symptomatic improvement of the same magnitude. Plausibly, because patients in the sham group were aware they would be offered re-treatment in the event of unsatisfactory symptom response, they may have been disinclined to resume their medication before the 3-month visit despite continuing symptoms.

Due to re-treatment, PPI use and symptom scores of the 2 randomized groups at 6 months tended to converge, so that persistence of the significant between-group differences demonstrable at 3 months could not be assessed. It should also be recognized that the re-treatment choices confronting eligible patients in the 2 groups differed qualitatively. The

patients in the sham group would receive a new treatment, whereas patients in the Enteryx group would be treated a second time by the same procedure.

Because the sham procedure entailed upper gastrointestinal endoscopy only, patients may have been able to discern their true group assignment despite blinding, for example, by the presence or absence of a characteristic odor from the dimethyl sulfoxide solvent of the Enteryx copolymer. If so, bias in responses to the study procedures could have been introduced. A second ongoing randomized trial of Enteryx implantation may in part elucidate this issue. In that trial, dimethyl sulfoxide will be administered to the sham group during upper gastrointestinal endoscopy, potentially improving the effectiveness of patient blinding.

Despite improved symptoms, significant within-group or overall reduction in acid exposure could not be detected. This result may reflect the previously reported poor correlation between GERD symptoms and pH monitoring data<sup>24–28</sup> and possibly insufficient statistical power of the present trial for evaluating the pH end point. A larger cohort of 85 patients enrolled at centers predominantly in North America achieved significant reduction in esophageal acid exposure following Enteryx implantation.<sup>3,12</sup> In a European cohort of 93 patients, a nonsignificant trend toward reduced supine time at pH  $\leq 4$  was observed with no difference in total time.<sup>12</sup> Further studies will be needed to resolve the disparities in pH results thus far. In the randomized trial of radiofrequency energy treatment, a reduction in esophageal acid exposure was not demonstrable, although symptomatic improvement was documented.<sup>16</sup> Reduced proximal reflux was detectable by dual pH-metry in a recently reported study of hydrogel prostheses, while no effect on acid exposure could be established by conventional pH-metry.<sup>29</sup>

The lack of detectable treatment effect on acid exposure in the present trial, although it contrasts with previous reports,<sup>3,12</sup> raises the possibility that Enteryx implantation might derive its effectiveness at least partly from esophageal desensitization, perhaps via neurolysis. However, evidence to support this proposition is lacking. In histopathologic examinations of excised tissue containing Enteryx implants from miniature pigs<sup>8</sup> and human subjects requiring esophagectomy because of underlying esophageal disease,<sup>7</sup> no evidence of neurolysis has been noted. In a study reported to the US Food and Drug Administration that was specifically designed to assess effects on neural tissue, 54 patients underwent embolization of brain arteriovenous malformations with the identical ethylene vinyl alcohol/dimethyl sulfoxide/tantalum material used in the Enteryx procedure (<http://www.fda.gov/ohrms/dockets/ac/03/briefing/3975b1-06-preclinical-2.doc>). Computed tomography, magnetic resonance imaging, and flat film skull radiographs failed to

show evidence of neurotoxicity attributable to the embolization material.

One additional advantage of Enteryx implantation is the feasibility of offering antireflux surgery to nonresponders.<sup>30</sup> Conversely, the procedure may be successfully performed as salvage therapy after failed endoscopic suturing.<sup>31</sup> Significant improvement in heartburn and regurgitation scores has also been reported after Enteryx implantation in patients with postgastrectomy biliary reflux.<sup>32</sup>

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