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Efficacy of Transoral Fundoplication vs Omeprazole for Treatment of Regurgitation in a Randomized Controlled Trial

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BACKGROUND & AIMS: Transoral esophagogastric fundoplication (TF) can decrease or eliminate features of gastroesophageal reflux disease (GERD) in some patients whose symptoms persist despite proton pump inhibitor (PPI) therapy. We performed a prospective, sham-controlled trial to determine if TF reduced troublesome regurgitation to a greater extent than PPIs in patients with GERD. **METHODS:** We screened 696 patients with troublesome regurgitation despite daily PPI use with 3 validated GERD-specific symptom scales, on and off PPIs. Those with at least troublesome regurgitation (based on the Montreal definition) on PPIs underwent barium swallow, esophagogastroduodenoscopy, 48-hour esophageal pH monitoring (off PPIs), and high-resolution esophageal manometry analyses. Patients with GERD and hiatal hernias $\leq$2 cm were randomly assigned to groups that underwent TF and then received 6 months of placebo (n = 87), or sham surgery and 6 months of once- or twice-daily omeprazole (controls, n = 42). Patients were blinded to therapy during follow-up period and reassessed at 2, 12, and 26 weeks. At 6 months, patients underwent 48-hour esophageal pH monitoring and esophagogastroduodenoscopy. **RESULTS:** By intention-to-treat analysis, TF eliminated troublesome regurgitation in a larger proportion of patients (67%) than PPIs (45%) ($P = .023$). A larger proportion of controls had no response at 3 months (36%) than subjects that received TF (11%; $P = .004$). Control of esophageal pH improved after TF (mean 9.3% before and 6.3% after; $P < .001$), but not after sham surgery (mean 8.6% before and 8.9% after). Subjects from both groups who completed the protocol had similar reductions in GERD symptom scores. Severe complications were rare (3 subjects receiving TF and 1 receiving the sham surgery). **CONCLUSIONS:** TF was an effective treatment for patients with GERD symptoms, particularly in those with persistent regurgitation despite PPI therapy, based on evaluation 6 months after the procedure. Clinicaltrials.gov no: NCT01136980.

Keywords: TIF; EsophyX; Stomach; Esophagus.

Gastroesophageal reflux disease (GERD) remains one of the most common condition for which Americans take daily medication, and proton-pump inhibitor (PPI) use has more than doubled in the last decade.[1] Despite this, up to 40% of PPI-dependent GERD patients have troublesome symptoms of GERD, despite PPI therapy.[2,3] Although laparoscopic antireflux surgery has been suggested for this group of patients, fear of surgery, side effects, and recurrent symptoms have kept patient and referring physician interest to <10% of those otherwise qualifying for surgery.[4,5] Transoral endoscopic methods of treating GERD have been available for many years, but only one of these technologies allows the creation of a fundoplication, by folding the stomach anteriorly around the esophagus and securing it with multiple fasteners. Although this device has been in use for 9 years in Europe and 7 years in the United States, and has been proven effective in registry trials and one randomized controlled trial (RCT), comparison of effectiveness in patients with persistent symptoms on PPI has been absent.[6–8] Our aim was to determine whether or not transoral fundoplication (TF) was better than PPI treatment of troublesome GERD symptoms, particularly regurgitation, in a population of chronic PPI-dependent GERD patients.

Methods

Ethics Statement

This study was approved by the Institutional Review Board of each site and was conducted in accordance with the Good Clinical Practices and Declaration of Helsinki. All patients provided written informed consent form. All authors had access to the study data and reviewed and approved the final manuscript.

*Author share co-first authorship.

Abbreviations used in this paper: EGD, esophagogastroduodenoscopy; GERD, gastroesophageal reflux disease; ITT, intention to treat; PPI, proton pump inhibitor; RDQ, Reflux Disease Questionnaire; TF, transoral fundoplication.

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Study Design and Patients

The Randomized EsophyX vs Sham, Placebo-Controlled Transoral Fundoplication (RESPECT) trial was carried out at 8 academic and community medical centers across the United States. We recruited patients between the ages of 18 and 80 years with more than 6 months of GERD symptoms and troublesome regurgitation, despite a minimum PPI dose of 40 mg daily. Troublesome regurgitation was defined as mild symptoms for 2 or more days per week or moderate to severe symptoms more than 1 day per week, per Montreal consensus criteria.[3,9] Symptom assessment used the following 3 validated tools: the Reflux Disease Questionnaire (RDQ), the Gastroesophageal Reflux Symptom Score, and the GERD-Health Related Quality of Life on PPI and off PPI for at least 7 days. Abnormal amounts of gastroesophageal reflux off PPI for 7 days was confirmed by distal esophageal pH <4 for $>5.3\%$ of at least 1 of the 2 days that pH was measured with a Bravo (radiotelemetry) probe (Given Imaging, Yoqneam, Israel). High-resolution esophageal manometry confirmed the absence of esophageal motor dysfunction. Esophagogastroduodenoscopy (EGD) was performed to grade the appearance of the antireflux barrier (Hill grade), to confirm the absence of long segment Barrett's esophagus, and to grade esophagitis, if present. Cine-esophagography was performed to confirm the absence of hiatal hernia or a hiatal hernia ≤ 2 cm in length. Exclusion criteria included systemic disease not well controlled, obesity determined by body mass index >35, esophageal ulcer, stricture, Barrett's esophagus >2 cm in length, hiatal hernia >2 cm in length, Los Angeles grade C or D esophagitis, esophageal dysmotility, previous esophageal or gastric surgery, peptic ulcer disease, gastric outlet obstruction, gastroparesis, pregnancy or plans for pregnancy in the next 12 months, immunosuppression, portal hypertension, and coagulopathy. Patients were randomized 2:1 to either TF (study group) or sham surgery (control group). A computer-generated block-randomization method was used to assign patients to study or control group. After informed consent and administration of general anesthesia with endotracheal intubation, a sealed envelope, provided by an independent statistician, was opened by the operating team that indicated group allocation.

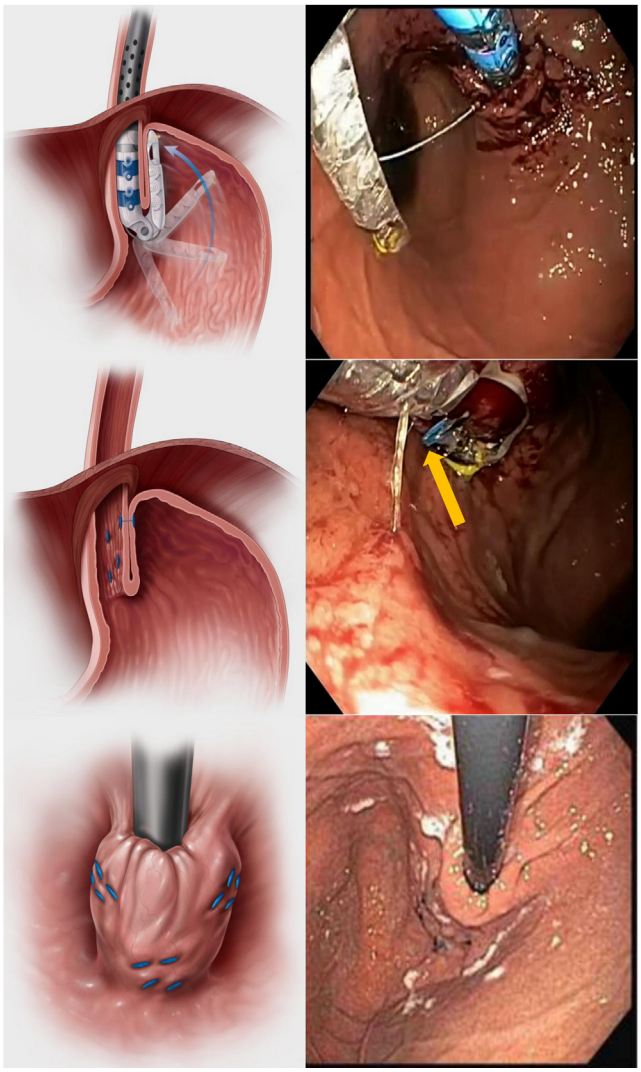

Figure 1. Transoral fundoplication creates a 3 cm flap valve, 180–270 degrees in circumference.

Operative Procedure

Patients allocated to the TF group underwent a standardized technique using the EsophyX-2 device (EndoGastric Solutions, Redmond, WA) as described previously.[10] The valve was created with a minimum of 13 fasteners, and was at least 1 cm long at either corner and 3 cm long in its mid-portion (Figure 1). Each participating surgeon submitted a video of a qualifying TF procedure that was reviewed and approved by Hunter and Bell before enrolling patients into the trial (Video 1). Patients in the control group had a sham procedure performed for 45–60 minutes, which included EGD for 30 minutes, and passage of a 50F Maloney dilator for 15 minutes, to simulate TF procedure and oropharyngeal irritation caused by TF.

Postoperative Care and Follow-Up

Patients were kept in the hospital overnight and were generally discharged the next day on omeprazole 40 mg for 14 days to help promote mucosal healing around fasteners if reflux control was incomplete. Thereafter, TF patients were switched to placebo, and sham patients were continued on omeprazole in an identical-appearing capsule. For the first 2 weeks postoperatively, patients were kept on a liquid diet. Soft foods were given from weeks 3 to 7, and a regular diet was reinstated 2 months after the operative procedure. Neither the patient nor their family was aware of allocation group until the 6-month point, or when they were declared failures and allowed to cross over to the other treatment arm. The perioperative caregivers (other than the operative team) were unaware of treatment allocation.

Follow-up occurred at weeks 2, 12, and 26 after TF or sham procedure. If troublesome symptoms of GERD recurred after 2 weeks, the medication dose was doubled (omeprazole 40 mg bid or placebo bid). If troublesome symptoms persisted at 3 months, despite bid medication use, the patient was declared a failure and the blind was broken. Once the blind was broken, failed TF patients were given PPI and sham patients were offered TF both for ethical reasons and to make study enrollment more attractive to potential participants (Figure 2).

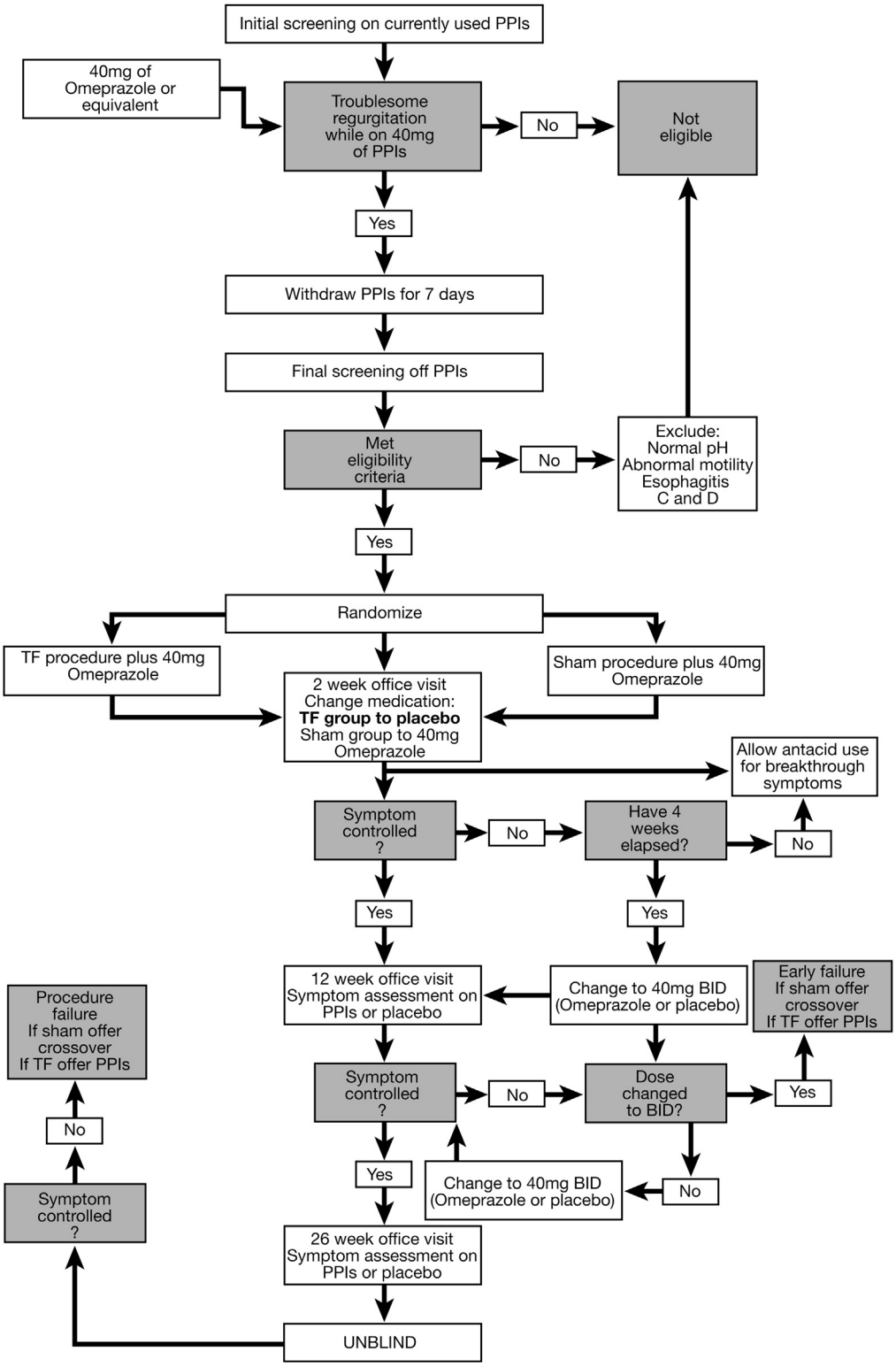

Figure 2. Study flow chart.

Six-month follow-up included repeating the 3 questionnaires on and off medication (PPI or placebo), 48-hour esophageal pH monitoring off medications (7 days), and EGD. After completion of these evaluation steps, the study was considered complete. Symptomatic sham patients were offered the opportunity to cross over to TF and TF patients with troublesome symptoms were offered PPIs.

Primary and Secondary End Points

The primary study end point was the elimination of troublesome regurgitation, per Montreal consensus definition, on placebo (TF group) and on PPI (control group). The Montreal consensus defines troublesome symptoms as mild symptoms occurring 2 or more days a week, or moderate to severe symptoms occurring more than 1 day a week.[2] The elimination

of troublesome regurgitation was evaluated with the RDQ. This instrument asks 12 questions addressing the symptom domains of heartburn, regurgitation, and dyspepsia using a scale from 0 to 5 to rate the severity and frequency of 6 symptoms.[11] A severity score of 2 or more and a frequency score of 3 or more for the regurgitation questions were required to meet the Montreal consensus criteria for troublesome regurgitation, a threshold supported by a recent analysis of the impact of regurgitation on quality of life.[9] Our primary hypothesis was that the proportion of transoral fundoplication/placebo patients who are relieved of troublesome regurgitation will be statistically significantly greater than those randomized to the sham/PPI group.

Secondary end points included early failure (defined as moderate to severe regurgitation at any time >12 weeks after surgery and after a doubling of medication, PPI, or placebo) and control of intraesophageal acid exposure. Other secondary outcomes assessed included improvement in various symptom scores (particularly heartburn), healing of esophagitis, common side effects associated with treatment (bloating and dysphagia), and significant adverse events.

Statistical Analysis

A sample size of 80 TF/placebo and 40 sham/PPI patients was necessary for an 85% power to detect a significant difference between the 2 treatment groups. Sample size was determined assuming a 30% greater elimination of troublesome regurgitation with TF as compared with PPI, based on previous reports.[12] The primary study end point of elimination of troublesome regurgitation was assessed using a χ^2 test. Binary secondary outcomes were also assessed with a χ^2 test, and continuous outcomes used a Wilcoxon matched pairs test for comparisons between screening and end-of-study values or a Mann-Whitney U test for comparisons between groups. Spearman ρ statistics was used to estimate correlation between postoperative pH parameters and symptom control as assessed by the quality of life symptom scores.

The primary end point was analyzed using the intent-to-treat population (ITT) and per protocol population. For the ITT analysis, a patient was declared a treatment failure if the 3-month and 6-month follow-up visits were not completed.[13] If a patient reported insufficient control of regurgitation on increased dose of medication at 3-month visit, and missed the 6-month visit, the patient was considered a treatment failure.

Results

Patient Population

Between June 2011 and September 2013, there were 3388 initial contacts made, mostly through web-based announcement of the trial. Six hundred and ninety-six patients were screened for eligibility and 567 were excluded. The most frequent reasons for exclusion were the presence of hiatal hernia >2 cm, absence of troublesome regurgitation, normal esophageal pH monitoring, and long segment Barrett's esophagus (Supplementary Figure 1). One hundred and twenty-nine patients were randomized, underwent sham surgery or TF, and were analyzed using the ITT population. Upon review of the entry criteria, 10 patients were excluded after treatment (6 in the TF arm and 4 in the sham arm), because they did not meet the entry criteria of troublesome regurgitation, as defined by Montreal criteria (8 patients), or did not have an abnormal pH study (2 patients). Of these 10 patients, 2 of 6 (33%) in the TF/placebo group and 2 of 4 (50%) in the sham/placebo group were declared early failures ($P > .999$). These patients did not receive 6-month follow-up with questionnaires and testing. Therefore, the PP analysis includes 81 TF/placebo and 38 sham/PPI patients. One patient in each group was lost to follow-up. The baseline and disease-related characteristics of the ITT study population are shown in Table 1.

Procedure

The mean operating time for TF was 49 minutes (range, 21–119 minutes). A mean of 23 fasteners was used (range, 13–37). As assessed by immediate post-procedure endoscopy, performance of 270-degree fundoplication (range, 200–340 degrees) resulted in the conversion of Hill grade 2 and 3 valves to Hill grade 1 in 79 of 82 (96%) patients. At discharge, epigastric pain was the only symptom that occurred more commonly in the TF than the sham group (34 of 83 vs 8 of 40; $P = .026$). Significant adverse events occurred in 7 patients in the TF/placebo group, and 1 in the sham/PPI group (Table 2). None of these events led to additional procedures, and all resolved without residual effect. Two patients with prolonged epigastric pain where treated with over-the-counter pain medication and did not report pain 4 weeks after TF.

Follow-Up and Early Failure (Intention to Treat)

At 3 months follow-up, 15 of 42 patients (36%) in the sham group met criteria for early failure, and 12 of 15 patients (80%) underwent crossover to TF. The 3 sham patients who had not crossed over completed the 6-month follow-up testing. In the TF/placebo group 10 of 87 patients (11%) met the criteria for early failure ($P = .002$) and all 10 returned to PPI treatment. Four of these 10 patients completed their 6-month follow-up testing. In total, 28 sham patients and 76 TF patients completed 6-month evaluation (Supplementary Figure 1).

Primary Outcomes

In the ITT analysis at 6-month follow-up, 58 of 87 (67%) TF/placebo patients reported the elimination of troublesome regurgitation vs 19 of 42 (45%) patients in the sham/PPI arm ($P = .023$).

The PP analysis revealed similar outcomes; 54 of 81 (67%) patients in the TF/placebo arm reported the elimination of troublesome regurgitation, and 17 of 38 (45%) patients in the sham/PPI arm reported elimination of troublesome regurgitation ($P = .028$).

Secondary Outcomes

As measured with the RDQ in those patients completing their 6-month follow up, TF provided equivalent improvement in symptom scores to sham/PPI on medication (Figure 3). TF provided greater reduction in heartburn and

Table 1. Demographics and Baseline Characteristics of the Study Patients

Variables	TF/placebo (n = 87)	Sham/PPI (n = 42)	*P* value
Female, n (%)[a]	40 (45.9)	26 (61.9)	.096
Age, *y*, median (range)	52 (22–74)	55 (22–73)	.513
50 y, n (%)[a]	35 (40.2)	13 (30.9)	.337
50–65 y, n (%)[a]	43 (49.4)	25 (59.5)	.348
>65 y, n (%)[a]	9 (10.3)	4 (9.6)	>.999
Body mass index, median (range)	27.1 (20.3–35.5)	27.8 (20.4–38.9)	.326
<25, n (%)	22 (25.3)	10 (24.3)	>.999
25–30, n (%)	45 (51.7)	19 (45.2)	.574
>30, n (%)	20 (23.0)	13 (30.5)	.391
GERD symptom duration, *y*, median (range)	10 (0.6–37)	10 (0.9–38)	.546
PPI therapy duration, *y*, median (range)	9 (1–30)	8 (1–23)	.541
Esophagitis (Los Angeles grade), n (%)[a]	17 (19.5)	6 (14.3)	.625
A[a]	10 (58.8)	3 (50.0)	>.999
B[a]	7 (41.2)	3 (50.0)	>.999
Hill grade, n (%)[a,b]	86 (98.8)	41 (97.6)	.547
I[a]	4 (4.6)	5 (12.2)	.147
II[a]	57 (66.3)	26 (63.4)	.842
III[a]	25 (29.1)	10 (24.4)	.674
Hiatal hernia, n (%)[a]	60 (69.8)	29 (69.0)	>.999
Axial length ≤1 cm[a]	33 (55.0)	18 (62.1)	.649
Axial length >1 cm and ≤2 cm[a]	27 (45.0)	11 (37.9)	.649
GTD, n (%)[a]			
≤1 cm	20 (33.9)[b]	13 (46.4)[b]	.345
>1 cm and ≤2 cm[a]	36 (61.0)[b]	15 (53.6)[b]	.642
>2 cm[a]	3 (5.1)[b]	0 (0)[b]	.548
RDQ score, median (range)			
On PPIs	2.8 (1.1–4.8)	3.3 (0.9–5.0)	.094
Off PPIs (n = 85 TIF; n = 40 sham)	3.3 (1.2–5.0)	3.6 (0.6–5.0)	.085
GERD-HRQL score, median (range)			
On PPIs	25 (0–41)	27 (7–45)	.108
Off PPIs (n = 85 TIF; n = 40 sham)	29 (3–47)	31 (9–50)	.450
GERSS, median (range)			
On PPIs	22 (3–54)	27 (8–56)	.052
Off PPIs (n = 85 TIF; n = 40 sham)	30 (5–60)	34 (9–60)	.185

NOTE. Esophagitis, Hill grade were evaluated with screening endoscopy. Hiatal hernia size was graded with videofluoroscopy. *P* values were calculated using Mann-Whitney *U* test unless indicated otherwise.
GERD-HRQL, Gastroesophageal Reflux Disease Health-Related Quality of Life; GERSS, Gastroesophageal Reflux Symptom Score; GTD, greatest transverse dimension; RDQ, Reflux Disease Questionnaire.
[a]Two-tailed Fisher's exact test.
[b]One patient in the transoral fundoplication (TF)/placebo groupo and one patient in the sham/PPI group have a missing data point.

Table 2. Significant Adverse Events

Randomization group	Significant adverse event	Maximum severity	Onset after procedure	Duration
Sham	Nausea	Severe	PPD 1	2 Days
TF	Temporary epigastric /abdominal pain	Severe	PPD 5	2 Weeks
	Chest pain	Severe	PPD 5	3 Days
	Musculoskeletal pain	Severe	PPD 1	1 Day
	Temporary epigastric /abdominal pain	Moderate	PPD 1	4 Weeks
	Dysphagia	Moderate	PPD 1	8 Days
	Dysphagia	Mild	PPD 1	1 Day
	Nausea	Mild	PPD 1	1 Day

NOTE. Per-protocol definition, the events reported were classified as serious adverse events as they required in-patient hospitalization or prolonged hospitalization. All reported serious adverse events resolved without residual effect.
PPD, post-procedure day; TF, transoral fundoplication.

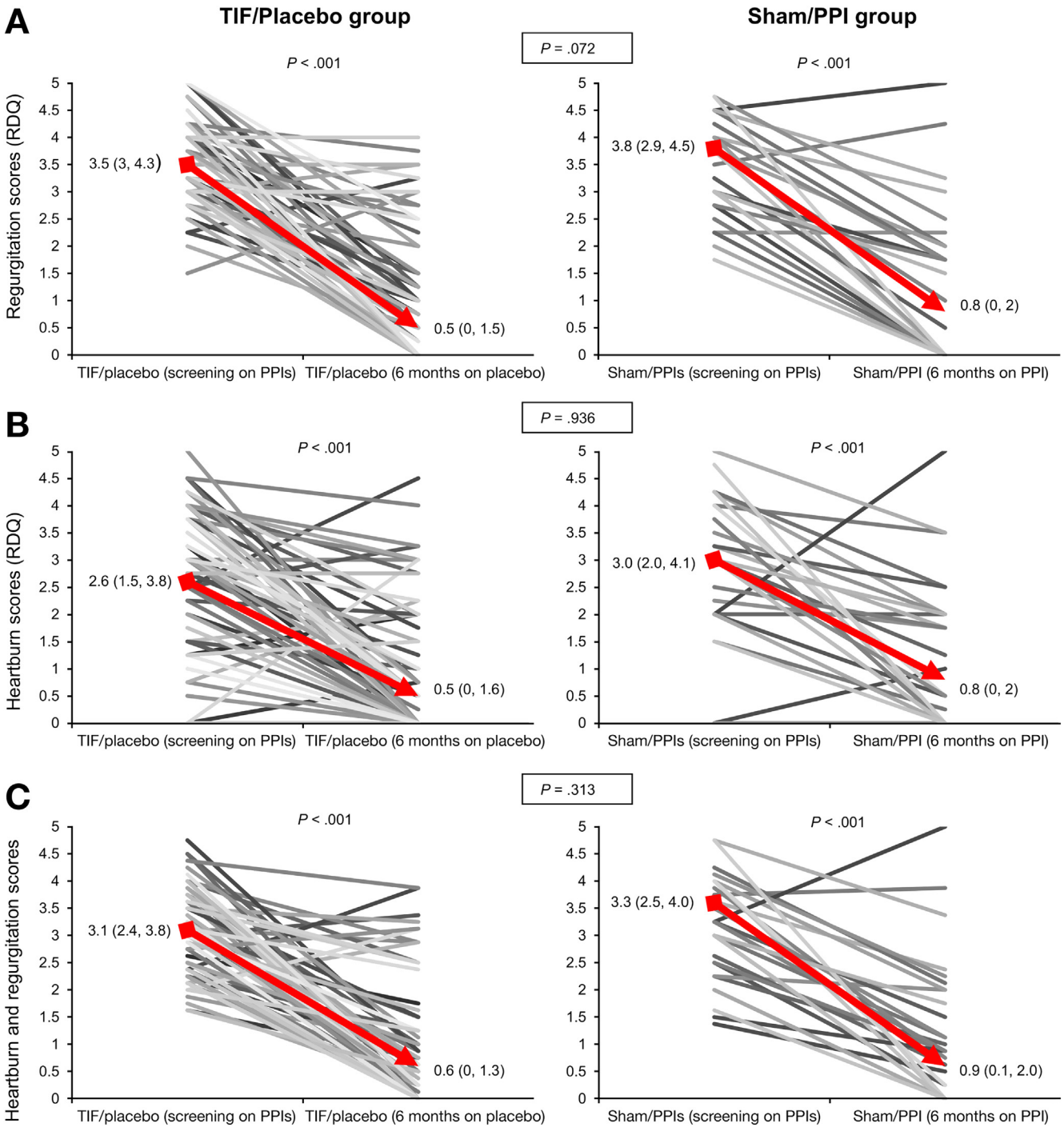

Figure 3. (*A*) Individual total regurgitation scores on placebo (TF group) and on PPI (sham group) in all patients undergoing symptomatic assessment before treatments and at 6-month follow-up. (*B*) Individual total heartburn scores on placebo (TF group) and on PPIs (sham group) in all patients undergoing symptomatic assessment before treatments and at 6-month follow-up. (*C*) Individual total composite heartburn and regurgitation scores on placebo (TF group) and on PPIs (sham group) in all patients undergoing symptomatic assessment before treatments and at 6-month follow-up. All scores were assessed using RDQ. *Red lines* represent improvement in the median (25%, 75% quartiles) scores. The *P* values in *boxes* represent comparisons between treatment groups.

regurgitation scores than the sham group off medication (Supplementary Figure 2).

TF was associated with significant decrease in intra-esophageal acid exposure in all parameters measured (Figure 4). Mean number of reflux episodes fell from 135 before TF to 94 after TF ($P < .001$). Mean percent total time pH <4 improved from 9.3 before TF to 6.4 after TF ($P < .001$). Mean DeMeester score fell from 33.6 before TF to 23.9 after TF ($P < .001$). Of these 3 measures, only the number of reflux episodes was normalized by the

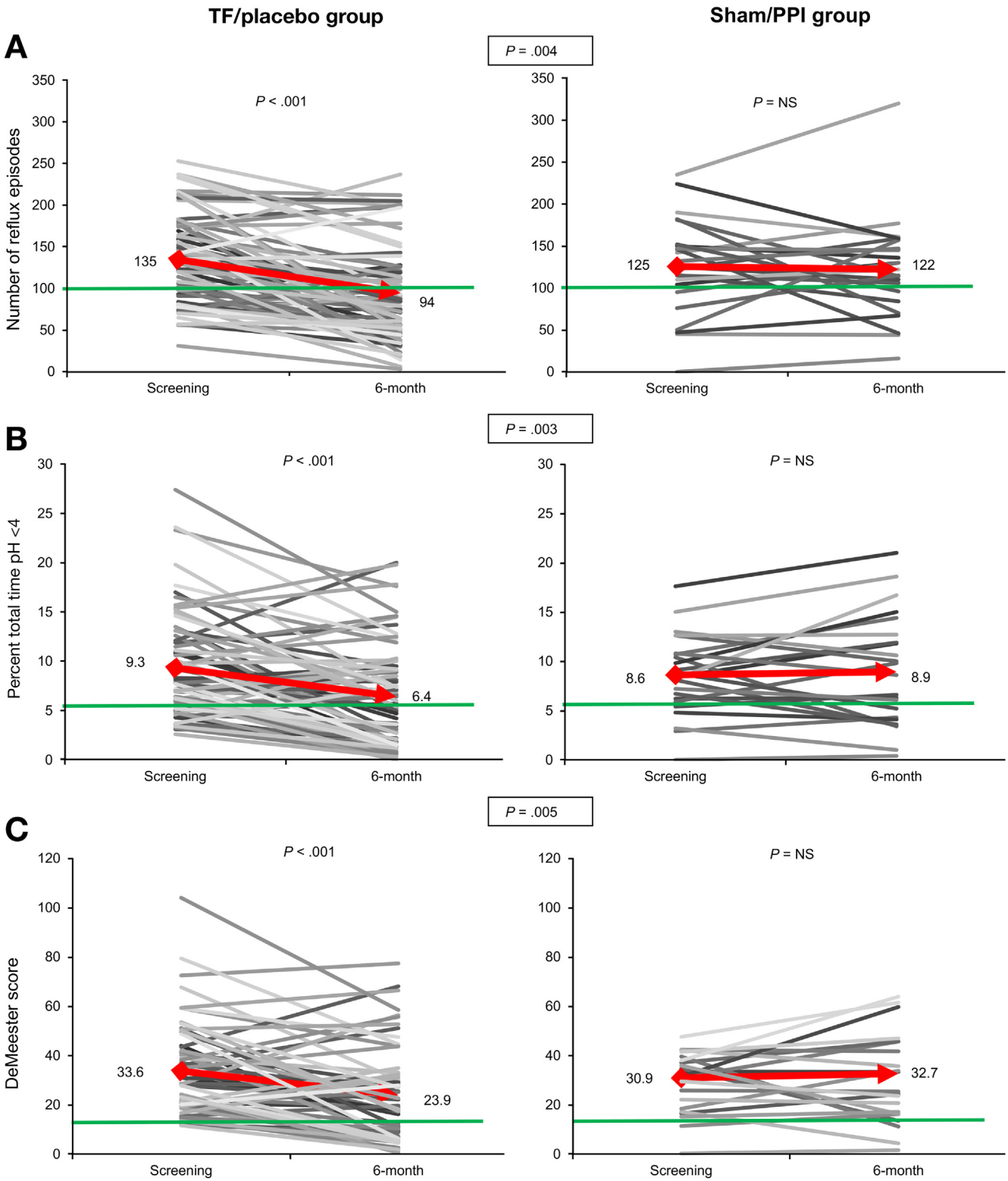

Figure 4. Total number of reflux episodes (*A*), percent time pH <4 (*B*), and DeMeester Score (*C*) were improved in TF/placebo group, but not in sham PPI group. The *red lines* represent change in mean scores. The *green lines* represent the cut-off for the normal values (reflux episodes = 100, percent total time pH <4 = 5.3% and DeMeester Score = 14.72). The *P* values in *boxes* represent comparisons between treatment groups.

performance of TF. After sham surgery, no improvement in pH control was detected, as measured with 48-hour pH testing off PPIs for 7 days. Mean number of reflux episodes were 125 before sham surgery and 122 after sham surgery (P = NS). Mean percent total time pH <4 was 8.6 before sham surgery and 8.9 after sham surgery (P = NS). Mean

DeMeester score was 30.9 before sham surgery and 32.7 after sham surgery (P = NS).

EGD revealed esophagitis in the minority of patients at baseline (17 in the TF group and 6 in the sham group). Of 17 patients in the transoral fundoplication/placebo group who had esophagitis on screening, 13 (76%) underwent endoscopy at 6 months. Reflux esophagitis was healed in 10 of 13 (77%); esophagitis improved from grade B to A in an additional 2 patients; in the last patient grade B esophagitis remained unchanged. In the sham/PPI group, of 6 patients with esophagitis on screening, 2 (50%) underwent endoscopy at 6 months. Esophagitis was healed in 1 patient (50%) improved from grade B to grade A in the other. At 6-month follow-up, de novo esophagitis was present in 4 TF/placebo patients (3 grade B and 1 grade A) and 5 sham/PPI patients (3 grade B and 2 grade A) (P = NS).

With the exception of postoperative epigastric pain, complications, and adverse effects were not different between TF and sham groups. On medication, bloating and dysphagia, as evaluated by Gastroesophageal Reflux Symptom Score, were improved after the procedure in both TF and sham groups (Supplementary Figure 3). One patient in the TF group and 2 patients in the sham group developed de novo dysphagia.

Including the early failures mentioned and follow-up out to 18 months, 30 of 42 patients (71%) in the sham/PPI arm have crossed over to TF. Including the early failures of TF mentioned, 24 of 87 (28%) in the TF/placebo group have resumed PPI ($P < .001$).

Discussion

A variety of endoscopic devices have been introduced to treat GERD over the past 2 decades. Most of these have been removed from the market because they were ineffective or unsafe. The only device available over the past 5 years that is capable of creating an antireflux valve endoscopically is the EsophyX device. Several case series and several registry reports have guided the evolution of the TF technique with this device.[7,12,14–16] As is common, early case series of this new surgical technique had mixed results, but as more experience was gained with the procedure, outcomes improved, and the number of related complications decreased.[6] One relevant trend observed was that procedures using fewer fasteners were associated with less favorable outcomes,[17] an observation that led us to use a mean of 23 fasteners in this series. A recent open-label randomized controlled trial comparing PPI treatment with TF demonstrated benefit for TF over PPI in control of troublesome GERD symptoms, with 54% of patients achieving normalization of intra-esophageal pH off PPI after TF. Similar pH normalization was achieved with high-dose PPI (on high-dose PPI), but GERD symptoms, particularly regurgitation and atypical symptoms, were better controlled with TF than with high-dose PPI.[8]

The Montreal definition of reflux is either mucosal damage or troublesome symptoms attributable to reflux. Consistent with this, we used the elimination of troublesome regurgitation (defined as that of sufficient magnitude to impair quality of life), rather than an improvement in regurgitation score as our primary end point. This approach has been recommended in previous published literature on assessing regurgitation in GERD management.[9,18] The primary end point in this study, elimination of troublesome regurgitation, was achieved in a greater proportion of patients treated with TF than with omeprazole: 67% vs 45%. That the reduction in composite symptom scores associated with treatment show no statistical difference between treatment groups at 6 month (Figure 3) is potentially confusing because these comparisons do not include data from the early failures, a group that was overrepresented in the sham/PPI treatment arm. Additionally, reduction in a symptom score is not measuring the same thing as the elimination of a troublesome symptom, and might yield different results, even if the populations queried were identical.

Secondary end points included response of other symptoms to TF, using well-validated questionnaires, and objective testing (48-hour esophageal pH monitoring and EGD). Evidence that TF was effective at improving GERD symptoms, heartburn, and regurgitation was well demonstrated with the improvement in 6-month RDQ scores as compared with baseline scores (Supplementary Figure 2). Improvement of intra-esophageal acid control was greater after TF than sham (Figure 4). Some studies evaluating TF,[15] PPI therapy,[19] and traditional laparoscopic fundoplication[20,21] demonstrated poor correlation between post-treatment pH parameters and symptom control, as evaluated with various disease-specific symptom scores. This study also found no significant correlation between objective and subjective outcomes in either treatment group (Supplementary Table 1). Although some studies have used pH normalization as a primary end point, the elimination of troublesome symptoms and the healing of reflux esophagitis are more clinically relevant goals of GERD treatment; symptom control might not require pH normalization. With traditional antireflux surgery, there has long been the concern that reflux control comes at the expense of new symptoms and side effects (primarily dysphagia and bloating). This did not appear to be the case in this study, as dysphagia and bloating scores were improved in both treatment groups, and new onset symptoms (dysphagia or bloating) were rare and evenly balanced between groups (Supplementary Figure 3).

Reflux esophagitis was healed in 77% of TF/placebo patients in this study, mirroring results from other recent reports from the United States.[7,15] However, these results must be interpreted from the perspective that this study was not designed to evaluate esophagitis healing and only a limited number of enrolled subjects had esophagitis at entry; 17 patients in the TF/placebo group and 6 patients in the sham/PPI group.

TF can fill the “therapeutic gap” that exists between PPI and laparoscopic fundoplication. Up to 40% of GERD patients have troublesome symptoms, despite adequately dosed PPI.[3] Although this group of patients might be treated with laparoscopic fundoplication or the LINX device,[22] the absence of hiatal hernia or advanced esophageal disease begs the question as to whether or not a less invasive and more calibrated treatment might be available to fill this gap. When comparing this trial with those using the LINX device,

in should be kept in mind that this trial was a prospective randomized trial, that patients in this study had less response to PPI therapy at baseline than in previously published case series of LINX use (Table 1), and that TF cannot effectively close a hiatal hernia, as is a part of the LINX procedure in many patients. Both interventions seem to have particular benefit in improving the symptom of regurgitation. Considering the virtual absence of dysphagia and bloating after TF, which can be problematic with LINX, it would appear that TF is an option for patients with troublesome regurgitation, as well as for patients with troublesome GERD symptoms who wish not to take PPI for a protracted period of time.

This study was not designed to evaluate the cost-effectiveness of TF compared with other treatments for chronic GERD. Currently, it is unclear if the benefit of TF would offset higher upfront cost of TF as compared with long-term PPI therapy. Higher upfront cost of TF can be offset by improvement in patients' quality of life and lower health care utilization in patients who do not fully respond to PPI therapy. Cost-effectiveness models can be developed from these and other data when longer term follow-up becomes available.

There are several limitations to this study. Our ITT analysis included 12 patients with limited follow-up data. Assessment of the primary end point at 6 months can be viewed as premature by some; however, we believed it likely that delaying the primary end point beyond 6 months would risk patients not entering or dropping out of the study prematurely. That 15 of 42 (36%) patients in the control group were early failures and 12 of these decided to cross over to TF is further evidence that they felt incompletely treated on escalating doses of PPI. Although there is a plan to follow both groups of patients beyond 6 months, the proof of efficacy was achieved in a 6-month window. Studies that have followed TF patients for more than 3 years have demonstrated little deterioration in the response measured shortly after operation.[16] Screening of interested patients eliminated about 81% of the patients who had GERD symptoms on PPI. The most frequent reason for exclusion was a hiatal hernia >2 cm, which eliminated 31% of those screened. TF has been shown to be capable of reducing hiatal hernias up to 2 cm in axial height, but patients with hiatal hernias >2 cm in height and troublesome GERD symptoms despite appropriate medical therapy should be considered for laparoscopic hiatal hernia repair with fundoplication.[23]

In this sham-controlled randomized controlled trial, transoral fundoplication was effective in eliminating troublesome GERD symptoms, especially regurgitation, with a low failure rate and good safety profile for 6 months. We believe TF has a role in treating GERD patients with small or absent hiatal hernia who suffer from troublesome regurgitation despite PPI therapy.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://dx.doi.org/10.1053/j.gastro.2014.10.009.

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Conflicts of interest
These authors disclose the following: John Hunter is a consultant for EndoGastric Solutions. Peter Kahrilas is a consultant for AstraZeneca, Pfizer, and Trimedyne; has been a consultant for GlaxoSmithKline; and has been on advisory boards for Torax Medical and Reckitt Benckiser. Reginald Bell has received research grant from EndoGastric Solutions. Erik Wilson is a consultant for Apollo, Gore Medical, and Ethicon. Karim Trad has acted as a speaker bureau member and has received speaking honoraria from EndoGastric Solutions. Brant Oelschlager is a consultant and has received a research grant from EndoGastric Solutions. Kevin Reavis is a consultant for EndoGastric Solutions. Eric Hungness received an honorarium as part of being Northwestern University faculty for a surgical training course with Baxter. The remaining authors disclose no conflicts.

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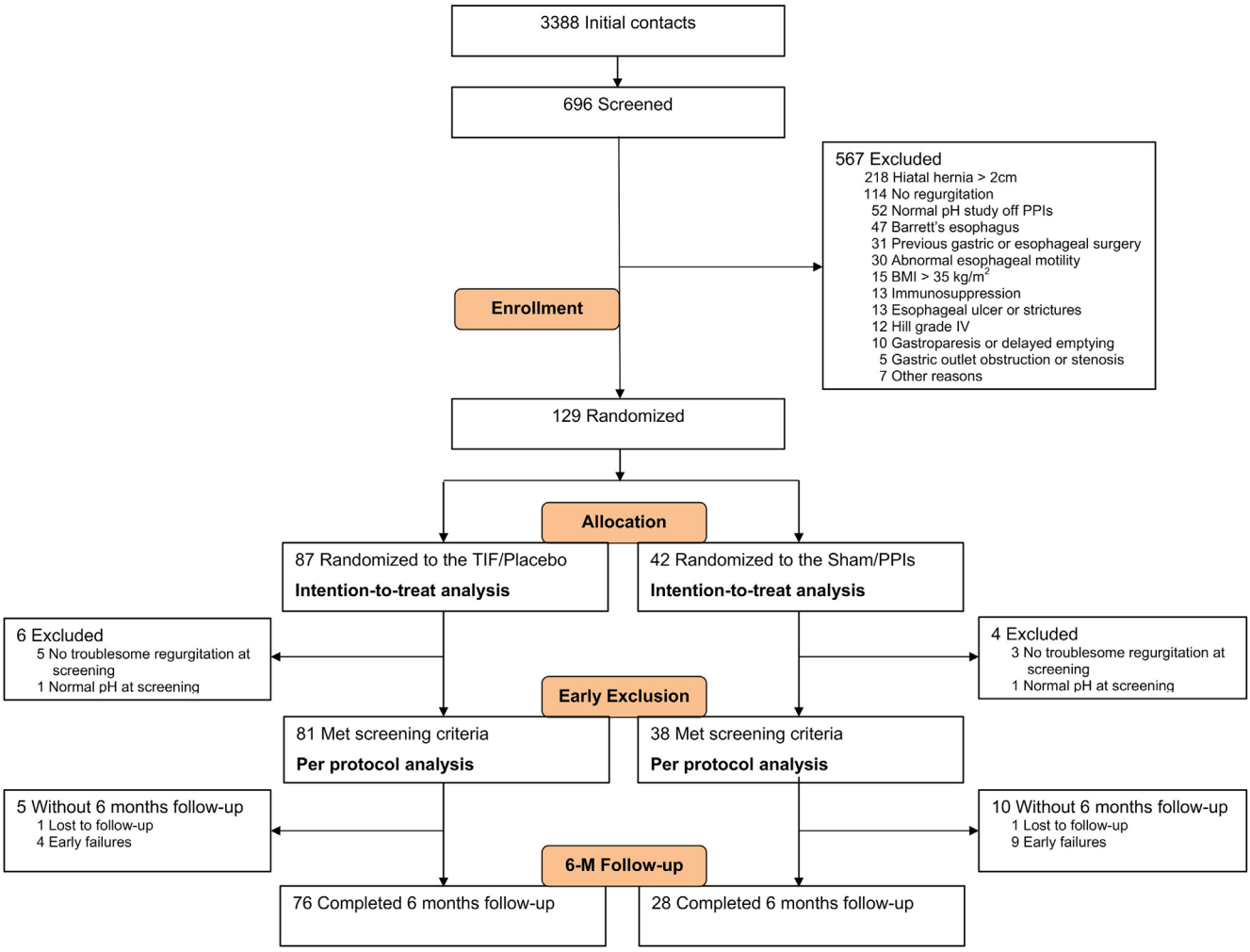
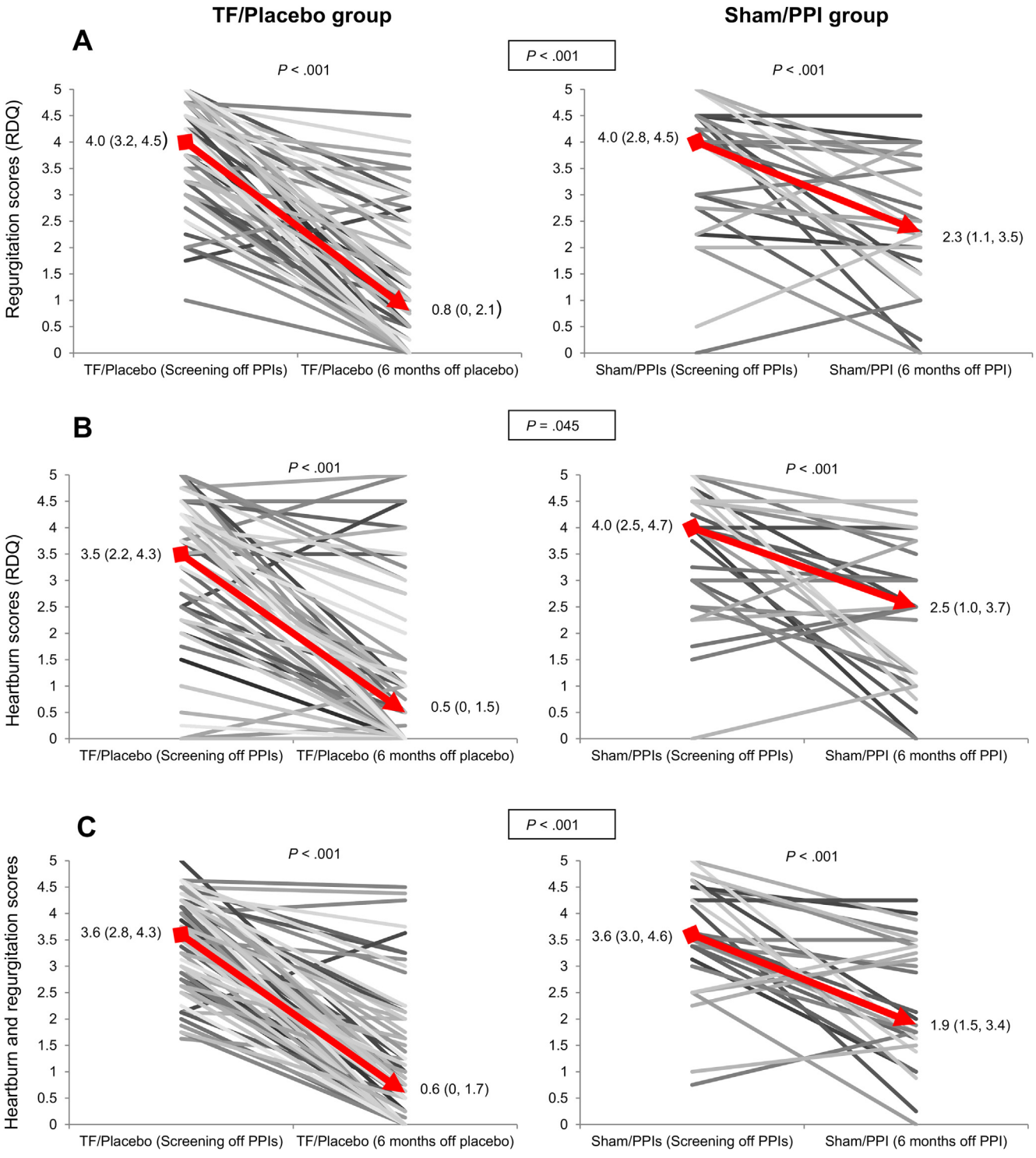
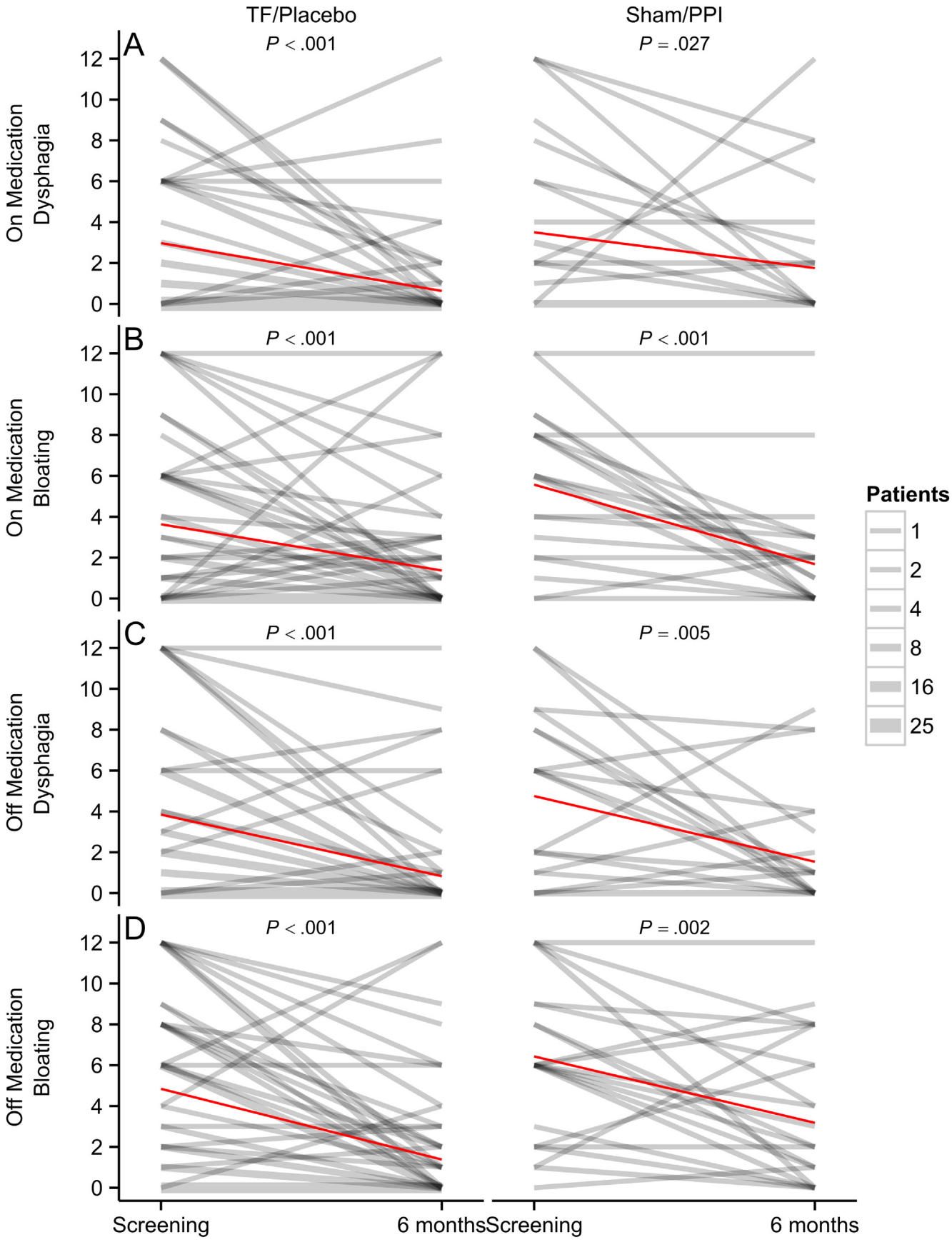


Supplementary Figure 1. CONSORT (Consolidated Standards of Reporting Trials) diagram.



Supplementary Figure 2. (*A*) Individual regurgitation scores off placebo (TF group) and off PPIs (sham group) undergoing symptomatic assessment before treatments and at 6-month follow-up. (*B*) Individual heartburn scores off placebo (TF group) and off PPIs (sham group) in all patients undergoing symptomatic assessment before treatments and at 6-month follow-up. (*C*) Individual composite heartburn and regurgitation scores off placebo (TF group) and off PPIs (sham group) in all patients undergoing symptomatic assessment before treatments and at 6-month follow-up. All scores were assessed using RDQ. *Red lines* represent improvement in the median (25%, 75% quartiles) scores. The *P* values in *boxes* represent comparisons between treatment groups.


TF/Placebo
Sham/PPI
A
P < .001
P = .027
On Medication Dysphagia
B
P < .001
P < .001
On Medication Bloating
C
P < .001
P = .005
Off Medication Dysphagia
D
P < .001
P = .002
Off Medication Bloating
0
2
4
6
8
10
12
Screening
6 months
Patients
1
2
4
8
16
25

Supplementary Figure 3. (*A*) Individual dysphagia scores on placebo (TF group) and on PPIs (sham group) in all patients undergoing symptomatic assessment before treatments and at 6-month follow-up. (*B*) Individual bloating scores on placebo (TF group) and on PPIs (sham group) in all patients undergoing symptomatic assessment before treatments and at 6-month follow-up. (*C*) Individual dysphagia scores off placebo (TF group) and off PPIs (sham group) in all patients undergoing symptomatic assessment before treatments and at 6-month follow-up. (*D*) Individual bloating scores off placebo (TF group) and off PPIs (sham group) in all patients undergoing symptomatic assessment before treatments and at 6-month follow-up. All scores were assessed using Gastroesophageal Reflux Symptom Score. Thickness of lines represents the number of patients with the same initial and final values. *Red lines* indicate the overall trend connecting the mean at screening and follow-up. *P* values are from Wilcoxon matched pairs tests.

Supplementary Table 1. Correlation Between pH Parameters and Symptom Scores in Both Treatment Groups

Parameters	Regurgitation	Heartburn	R&H	DMS	% Total time	NORE
TF group off placebo						
Regurgitation	1.00					
Heartburn	0.59 (<.001)	1.00				
R&H	0.91 (<.001)	0.85 (<.001)	1.00			
DMS	0.02 (.839)	0.14 (.249)	0.09 (.439)	1.00		
% Total time	0.01 (.889)	0.15 (.213)	0.09 (.433)	0.99 (<.001)	1.00	
NORE	0.03 (.771)	0.08 (.518)	0.07 (.556)	0.82 (<.001)	0.84 (<.001)	1.00
Sham group off Omeprazole						
Regurgitation	1.00					
Heartburn	0.50 (.009)	1.00				
R&H	0.83 (<.001)	0.86 (<.001)	1.00			
DMS	−0.08 (.695)	−0.09 (.639)	−0.12 (.552)	1.00		
% Total time	0.01 (.989)	−0.07 (.718)	−0.06 (.738)	0.98 (<.001)	1.00	
NORE	−0.03 (.869)	−0.04 (.831)	−0.08 (.696)	0.69 (<.001)	0.73 (<.001)	1.00

NOTE. Values are Spearman's ρ (P value).
DMS, DeMeester score; NORE, number of reflux episodes; R&H, regurgitation and heartburn composite score.
Symptom scores were assessed using RDQ.