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Randomized Trial of Medical versus Surgical Treatment for Refractory Heartburn

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ABSTRACT

BACKGROUND

Heartburn that persists despite proton-pump inhibitor (PPI) treatment is a frequent clinical problem with multiple potential causes. Treatments for PPI-refractory heartburn are of unproven efficacy and focus on controlling gastroesophageal reflux with reflux-reducing medication (e.g., baclofen) or antireflux surgery or on dampening visceral hypersensitivity with neuromodulators (e.g., desipramine).

METHODS

Patients who were referred to Veterans Affairs (VA) gastroenterology clinics for PPI-refractory heartburn received 20 mg of omeprazole twice daily for 2 weeks, and those with persistent heartburn underwent endoscopy, esophageal biopsy, esophageal manometry, and multichannel intraluminal impedance–pH monitoring. If patients were found to have reflux-related heartburn, we randomly assigned them to receive surgical treatment (laparoscopic Nissen fundoplication), active medical treatment (omeprazole plus baclofen, with desipramine added depending on symptoms), or control medical treatment (omeprazole plus placebo). The primary outcome was treatment success, defined as a decrease of 50% or more in the Gastroesophageal Reflux Disease (GERD)–Health Related Quality of Life score (range, 0 to 50, with higher scores indicating worse symptoms) at 1 year.

RESULTS

A total of 366 patients (mean age, 48.5 years; 280 men) were enrolled. Prerandomization procedures excluded 288 patients: 42 had relief of their heartburn during the 2-week omeprazole trial, 70 did not complete trial procedures, 54 were excluded for other reasons, 23 had non-GERD esophageal disorders, and 99 had functional heartburn (not due to GERD or other histopathologic, motility, or structural abnormality). The remaining 78 patients underwent randomization. The incidence of treatment success with surgery (18 of 27 patients, 67%) was significantly superior to that with active medical treatment (7 of 25 patients, 28%; P=0.007) or control medical treatment (3 of 26 patients, 12%; P<0.001). The difference in the incidence of treatment success between the active medical group and the control medical group was 16 percentage points (95% confidence interval, −5 to 38; P=0.17).

CONCLUSIONS

Among patients referred to VA gastroenterology clinics for PPI-refractory heartburn, systematic workup revealed truly PPI-refractory and reflux-related heartburn in a minority of patients. For that highly selected subgroup, surgery was superior to medical treatment. (Funded by the Department of Veterans Affairs Cooperative Studies Program; ClinicalTrials.gov number, NCT01265550.)

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In the United States, approximately 20% of adults regularly have symptoms of gastroesophageal reflux disease (GERD),[1] and annual costs for managing GERD exceed $12 billion.[2] Patients with heartburn, the cardinal symptom of GERD, report reduced work productivity and significant impairments in health-related quality of life.[3,4] Proton-pump inhibitors (PPIs) are highly effective for healing reflux esophagitis[5] but less effective for eliminating GERD symptoms, which persist in some 30% of patients treated with PPIs.[6] Only 58% of patients taking prescription PPIs for chronic heartburn report complete satisfaction with this treatment,[7] and "PPI-refractory GERD" is the most common reason for GERD-related referrals to gastroenterologists.[8]

Five major mechanisms might underlie PPI-refractory heartburn[9]: first, abnormal acid reflux persists despite PPI therapy; second, there is reflux hypersensitivity, in which esophageal exposure to acid is normal but "physiologic" reflux episodes (acidic or nonacidic) evoke heartburn[10]; third, heartburn is caused by esophageal disorders other than GERD (e.g., achalasia); fourth, heartburn is caused by extraesophageal disorders (e.g., heart disease); or fifth, heartburn is functional (i.e., not due to GERD or any other identifiable histopathologic, motility, or structural abnormality).[10] The frequency with which these mechanisms underlie PPI-refractory heartburn is not clear, and distinguishing among them requires systematic evaluation that includes endoscopy with esophageal biopsy, esophageal manometry, and esophageal multichannel intraluminal impedance (MII)–pH monitoring. MII-pH monitoring measures reflux episodes (acidic according to pH, and nonacidic according to MII) and their association with heartburn episodes.

For patients with PPI-refractory heartburn that is reflux-related (due to persistently abnormal acid reflux or reflux hypersensitivity), there are no medical treatment options of established long-term benefit. PPIs are often continued despite inadequate symptom relief.[11] Other options include reflux-reducing medications, such as baclofen,[12] or neuromodulators (e.g., tricyclic antidepressants) that dampen visceral hypersensitivity.[13] However, baclofen and neuromodulators often have unacceptable side effects, and studies of their efficacy for PPI-refractory heartburn are few and of short duration.[12-14] Recommendations for medical management of this condition are largely opinion-based.[6,15-17]

In principle, antireflux surgery (fundoplication), which creates a barrier to reflux of all gastric material (acidic and nonacidic), should relieve PPI-refractory heartburn that is reflux-related. In practice, however, patients with "GERD symptoms" that are unresponsive to PPIs often do not have a response to surgery either.[18] This might result from preoperative failure to document that the symptoms are truly reflux-related. Alternatively, for patients with reflux hypersensitivity, surgical reduction of reflux might not relieve symptoms generated by a hypersensitive esophagus.

Systematic evaluation including esophageal MII-pH monitoring may distinguish PPI-refractory patients with non-GERD disorders (who will not benefit from fundoplication) from those with persistently abnormal acid reflux or reflux hypersensitivity (who might have a response to surgery).[19] MII-pH monitoring is a relatively recent innovation, however, and experts disagree on its clinical usefulness.[20] Surgeons are reluctant to rely on it to select patients for fundoplication, generally preferring traditional esophageal pH monitoring for that purpose.[21] We hypothesized that if non-GERD and functional disorders were excluded by systematic workup, then antireflux surgery would be superior to medical therapy for patients with PPI-unresponsive heartburn that MII-pH monitoring identifies as being reflux-related.

METHODS

TRIAL OVERSIGHT

This trial was approved by the Veterans Affairs (VA) central institutional review board. All the patients provided written informed consent. The authors vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol, available with the full text of this article at NEJM.org.

TRIAL DESIGN

Prerandomization Trial Procedures

All patients who were referred to VA gastroenterology clinics for heartburn refractory to PPIs were screened (Fig. 1). Eligible patients completed the GERD–Health Related Quality of Life (GERD-HRQL) questionnaire, which measures

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severity of heartburn and other GERD symptoms (scores range from 0 to 50, with higher scores indicating worse symptoms).[22] Irrespective of PPI type and dose that patients were taking at trial entry, all received a 2-week trial of omeprazole at a dose of 20 mg twice daily, with instructions to take omeprazole 30 minutes before breakfast and dinner, and GERD-HRQL scoring was repeated (this score was considered the baseline score).

Patients with an improvement (decrease) of less than 50% in the GERD-HRQL score completed questionnaires (Veterans RAND 36-Item Health Survey [VR-36] measuring health-related quality of life [scores range from 0 to 100, with higher scores indicating better function], Patient Health Questionnaire 9 [PHQ-9] measuring depression [scores range from 0 to 27, with higher scores indicating worse depression], and the Generalized Anxiety Disorder 7-Item Questionnaire [GAD-7] measuring anxiety [scores range from 0 to 21, with higher scores indicating worse anxiety]) and underwent endoscopy with esophageal biopsy, esophageal manometry, and MII-pH monitoring while receiving 20 mg of omeprazole twice daily. Patients with severe reflux esophagitis, non-GERD endoscopic abnormalities, eosinophilic esophagitis, achalasia, or absent contractility were excluded.

Trial participation required trial surgeon approval and a positive symptom association probability (SAP >95%, indicating a significant [$P<0.05$] association between heartburn and reflux episodes [acidic, nonacidic, or all]), abnormal acid reflux (esophageal pH <4 for ≥4.2% of the 24-hour monitoring period), or both. The sequence of trial procedures varied owing to logistic and patient convenience issues, and further testing was not performed if any test ruled out reflux-related, PPI-refractory heartburn. Initial slow recruitment of patients resulted in intratrial changes to the protocol, including revised power calculations. (For details on prerandomization trial procedures, randomization, intratrial changes to the protocol, and the statistical analysis, see the Supplementary Appendix, available at NEJM.org.)

Randomization

Patients were assigned to receive active medical, control medical, or surgical treatment with the use of an adaptive-randomization procedure that stratified patients according to MII-pH results (positive SAP alone, abnormal acid reflux alone, or both positive SAP and abnormal acid reflux) and with the use of a "biased coin" procedure to balance treatment assignments.[23] Randomization status (determined by the adaptive-randomization and biased-coin procedures) was programmed centrally on a secured server, which ensured concealment of treatment assignments.

Medical Treatment Groups

Investigators and patients were unaware of whether medical treatment was active or placebo. At all clinic visits, patients were queried about missed medication doses, and medication counts were performed. Patients in both groups received active omeprazole at a dose of 20 mg twice daily throughout the trial. Baclofen, desipramine, or identical-appearing placebos were added sequentially. All patients received baclofen (or baclofen placebo), with the dose gradually increased to 20 mg three times daily, for the trial duration unless unacceptable side effects occurred or less than 50% improvement in the GERD-HRQL score was found on any quarterly clinic visit, in which case baclofen (or baclofen placebo) was discontinued. After discontinuation, patients with contraindications to desipramine were declared to have treatment failure. Patients without contraindications to desipramine received desipramine (or desipramine placebo), with the dose gradually increased to 100 mg at bedtime, for the trial duration unless unacceptable side effects occurred or less than 50% improvement in the GERD-HRQL score was found on any quarterly clinic visit, at which time patients were declared to have treatment failure.

Surgical Treatment Group

Surgical treatment was laparoscopic Nissen fundoplication. Heartburn medications were prohibited after fundoplication. Patients with less than 50% improvement from the baseline GERD-HRQL score at any quarterly clinic visit or with heartburn severe enough to result in medication were declared to have treatment failure.

Follow-up

Patients who had undergone randomization were seen at quarterly clinic visits for GERD-HRQL scoring and medication adjustments and at 1 year for GERD-HRQL scoring.

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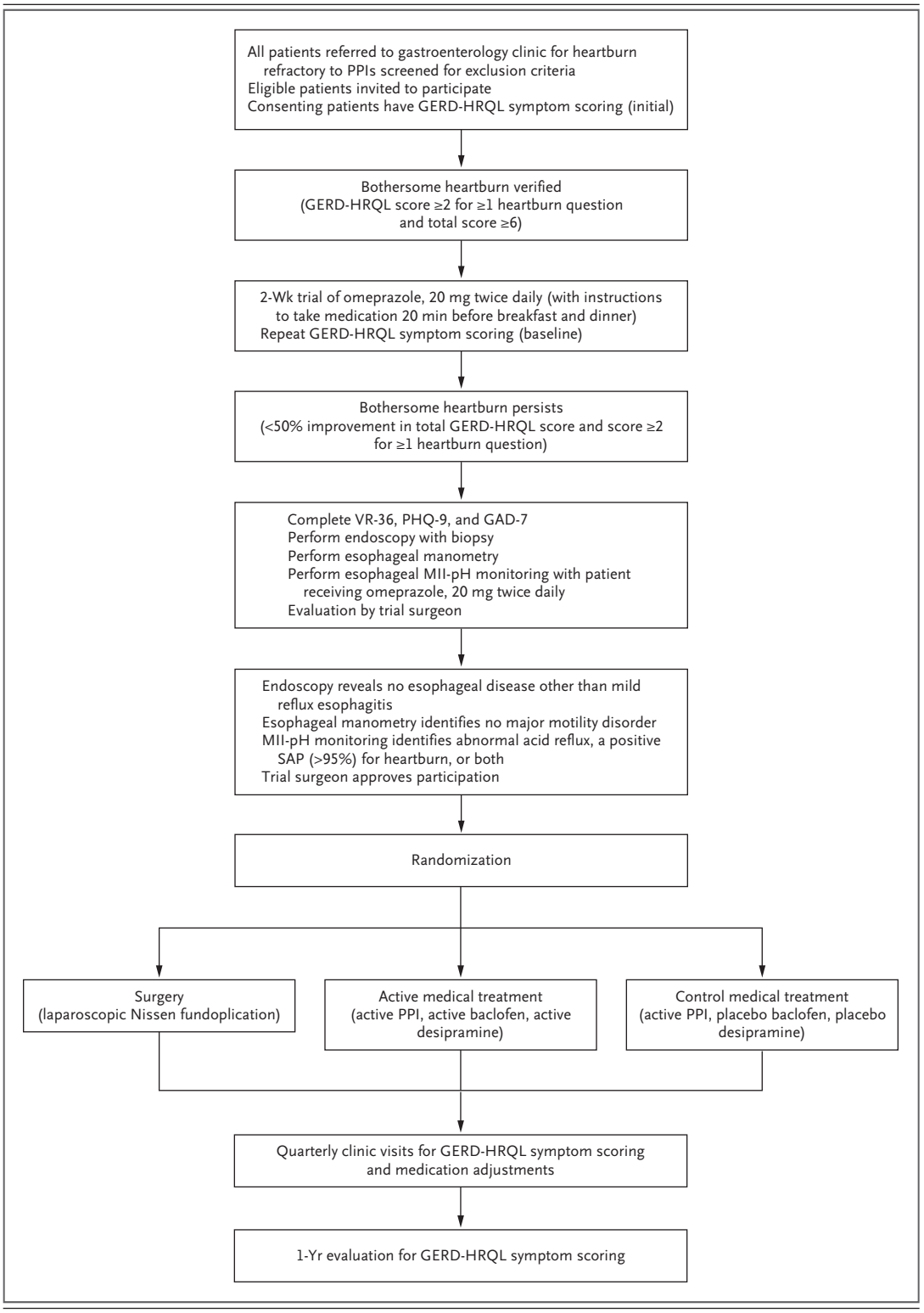

STATISTICAL ANALYSIS

The primary outcome was treatment success, defined as an improvement (decrease) of 50% or more in the GERD-HRQL score from baseline to 12 months, a definition used in other prospective trials of antireflux procedures.[24] In the surgery group, patients were considered to have treatment failure if they did not have an improve-

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Figure 1 (facing page). Trial Design.

From August 29, 2012, through December 2, 2015, medical records of all consecutive patients who were referred to gastroenterology clinics at participating Veterans Affairs (VA) medical centers for heartburn refractory to proton-pump inhibitors (PPIs) (on the basis of the referring physician's assessment) were screened for preliminary exclusion criteria (see the Supplementary Appendix), and those with no identified exclusions were invited to participate in the trial with the understanding that they would enter the randomized trial of medical or surgical treatment if trial procedures documented reflux-related heartburn. The sequence in which trial procedures were performed varied as a result of logistic and patient convenience issues. Further testing was not performed if any test excluded reflux-related, PPI-refractory heartburn (e.g., if endoscopy established an alternative diagnosis, such as eosinophilic esophagitis, then manometry and multichannel intraluminal impedance [MII]–pH monitoring were not performed if they had not already been performed). Total scores on the Gastroesophageal Reflux Disease–Health Related Quality of Life (GERD-HRQL) scale range from 0 to 50, with higher scores indicating worse symptoms. Scores on individual heartburn questions range from 0 to 5, with higher scores indicating worse symptoms. Symptom association probability (SAP) values of more than 95% indicate significant ($P<0.05$) associations between periods of reflux episodes and periods of heartburn symptoms. GAD-7 denotes the Generalized Anxiety Disorder 7-Item Questionnaire (which measures anxiety), PHQ-9 Patient Health Questionnaire 9 (which measures depression), and VR-36 the Veterans RAND 36-Item Health Survey (which measures health-related quality of life).

ment of 50% or more in the GERD-HRQL score or if they had used medication for heartburn symptoms at any of the quarterly assessments during the 12-month follow-up period; in the medical treatment groups, patients were considered to have treatment failure if they did not have an improvement of 50% or more in the GERD-HRQL score at any assessment after dose adjustment was completed (see above). Prespecified secondary outcomes included the frequency with which non-GERD disorders underlay PPI-refractory heartburn and the frequency of anxiety and depression in these patients. This article does not include all analyses and outcomes that were prespecified in the protocol and does not include any analyses or outcome measures that were not prespecified in the protocol.

Analyses were performed on an intention-to-treat basis. Fisher's exact test of two proportions was used to compare treatment success in three pairwise comparisons: surgery versus active medical treatment, surgery versus control medical treatment, and active medical treatment versus control medical treatment. To keep the overall type I error at 0.05 for the null hypothesis, the alpha level for each of the three comparisons was adjusted with the use of the Hochberg method.[25] Comparisons between groups that were excluded from the trial and randomly assigned patients (Table 1) and comparisons among treatment groups (Table 2) used chi-square analyses for categorical variables and the Kruskal–Wallis test for continuous measures. All reported P values are two-sided and unadjusted. We used SAS software, version 9.4 (SAS Institute), for all analyses.

RESULTS

PRERANDOMIZATION PROCEDURE EXCLUSIONS

Patients were recruited from August 29, 2012, through December 2, 2015; follow-up ended December 31, 2016. A total of 366 patients (280 men; mean [±SD] age, 48.5±12.2 years) were enrolled and began the prerandomization evaluation; 288 were excluded during prerandomization trial procedures (Fig. 2). A total of 70 patients were unwilling or unable to complete prerandomization procedures (Table S1 in the Supplementary Appendix); 54 were excluded for miscellaneous reasons; 42 were excluded because heartburn was relieved during the 2-week omeprazole trial; 23 were found to have non-GERD organic disorders (9 had eosinophilic esophagitis, 7 had other endoscopic or histologic abnormalities [2 had severe reflux esophagitis, 1 candida esophagitis, 2 gastric ulcer, and 2 unspecified abnormalities], and 7 had manometric abnormalities [2 had achalasia, 2 esophago-gastric junction outflow obstruction, and 3 severe ineffective esophageal motility]); and 99 had functional heartburn (MII-pH monitoring showed normal esophageal acid exposure and an SAP of ≤95%, which indicated no significant association between reflux episodes and heartburn). Thus, only 78 patients were eligible for randomization because they completed the full evaluation and were determined to have reflux-related, PPI-unresponsive heartburn documented by MII-pH monitoring. A revised power calculation called for 108 randomly assigned patients, but enrollment was capped at 78 solely because of funding limitations.

Baseline characteristics (age, sex, race, and GERD-HRQL scores) were generally similar in

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Table 1. Demographic and Clinical Characteristics of the Patients.*

Characteristic	Patients with Functional Heartburn (N=99)	Patients with Reflux-Related, PPI-Refractory Heartburn Who Underwent Randomization (N=78)
Sex — no. (%)		
Male	76 (77)	64 (82)
Female	23 (23)	14 (18)
Race — no. (%)†		
White	69 (70)	54 (69)
Black	17 (17)	9 (12)
Other or mixed	13 (13)	15 (19)
Age	50.5±12.2	45.4±11.8
GERD-HRQL score‡		
Initial	23.9±7.9	25.5±8.1
Baseline	21.4±7.7	23.9±8.2
VR-36§		
Physical component	36.1±9.9	37.6±9.7
Mental component	40.0±13.5	43.3±12.8
Physical functioning	56.3±27.6	63.1.0±25.6
Role limitations due to physical health	36.2±39.3	39.7±38.1
Role limitations due to emotional problems	46.2±49.9	56.7±46.0
Vitality	34.9±19.0	41.4±20.5
Mental health index	57.8±22.8	63.6±22.5
Social functioning	49.6±30.2	55.6±26.2
Pain index	40.1±22.1	43.9±21.7
General health	45.9±21.3	51.8±20.9
PHQ-9 score¶	10.4±6.4	9.2±7.2
GAD-7 score‖	8.2±6.3	7.5±6.9

* Plus–minus values are means ±SD. There were no significant differences between the two populations for any characteristic except age (P=0.003), baseline score on the Gastroesophageal Reflux Disease–Health Related Quality of Life (GERD-HRQL) index (P=0.04), and score for vitality on the Veterans RAND 36-Item Health Survey (VR-36) (P=0.04). PPI denotes proton-pump inhibitor.

† Race was determined by patient report.

‡ Scores on the GERD-HRQL index range from 0 to 50, with higher scores indicating worse symptoms. The baseline score was assessed after a 2-week trial of omeprazole at a dose of 20 mg twice daily, with instructions to take omeprazole 30 minutes before breakfast and dinner.

§ The VR-36 measures health-related quality of life on multiple dimensions. Scores range from 0 to 100 for all dimensions, except role limitations due to physical health (range, −7 to 110) and role limitations due to emotional problems (range, −2 to 114), with higher scores indicating better function. The number of patients with functional heartburn who had missing data was as follows: for physical component, two; for mental component, two; for role limitations due to physical health, one; for role limitations due to emotional problems, two; and for pain index, one.

¶ Scores on Patient Health Questionnaire 9 (PHQ-9) range from 0 to 27, with higher scores indicating worse depression. Data were missing for two patients with functional heartburn.

‖ Scores on the Generalized Anxiety Disorder 7-Item Questionnaire (GAD-7) range from 0 to 21, with higher scores indicating worse anxiety.

patients who received a diagnosis of reflux-related, PPI-refractory heartburn and subsequently underwent randomization and in patients who did not undergo randomization because they had functional heartburn, had a response to PPI treatment, or dropped out before completing evaluation (Table S2). Baseline demographic characteristics and scores on quality of life (GERD-HRQL and VR-36), depression (PHQ-9), and anxiety (GAD-7) were similar in patients

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Table 2. Demographic Features, GERD-HRQL Scores, and Multichannel Intraluminal Impedance (MII)–pH Monitoring Results, According to Treatment Group.*

Variable	Surgery (N=27)	Active Medical Treatment (N=25)	Control Medical Treatment (N=26)
Sex — no. (%)			
Male	23 (85)	18 (72)	23 (88)
Female	4 (15)	7 (28)	3 (12)
Race — no. (%)			
White	17 (63)	20 (80)	17 (65)
Black	2 (7)	2 (8)	5 (19)
Other or mixed	8 (30)	3 (12)	4 (15)
Mean age (95% CI) — yr	44.9 (40.2–49.5)	43.9 (38.9–49.0)	47.2 (42.5–52.0)
Mean GERD-HRQL score at baseline (95% CI)	25.8 (22.5–29.1)	21.0 (18.6–23.4)	24.7 (20.9–28.5)
Mean results of MII-pH monitoring (95% CI)†			
Total % of time with pH <4‡	6.1 (3.4–8.8)	7.7 (2.6–12.7)	8.8 (2.2–15.5)
DeMeester score§	20.5 (11.8–29.2)	27.6 (10.5–44.7)	21.5 (11.9–31.2)
Total nonacidic reflux events¶	38.9 (26.4–51.4)	50.6 (27.2–74.0)	47.8 (35.6–60.1)
Heartburn SAP‖	92.2 (84.2–100)	89.2 (79.6–98.7)	86.5 (73.3–99.6)
MII-pH monitoring randomization criteria — no. (%)†			
SAP of >95% alone**	14 (52)	12 (48)	11 (42)
Abnormal acid reflux alone	6 (22)	5 (20)	4 (15)
Abnormal acid reflux and SAP of >95%	7 (26)	7 (28)	11 (42)

* There were no significant differences among the randomized groups for any feature included in this table. Symptom association probability (SAP) values of more than 95% indicate significant ($P<0.05$) associations between periods of reflux episodes and periods of heartburn symptoms. Percentages may not total 100 because of rounding. CI denotes confidence interval.
† Data for MII-pH monitoring were missing for one patient in the active medical group.
‡ A value of 4.2% or higher for the total percentage of time with an esophageal pH of less than 4 indicates abnormal acid reflux.
§ DeMeester scores of more than 14.7 indicate abnormal acid reflux.
¶ Reflux events with a pH of more than 4 were considered nonacidic. Shown is the total number of nonacidic reflux events recorded during the 24-hour monitoring period, irrespective of whether they were associated with heartburn.
‖ Heartburn SAP values are those for all reflux events (acidic and nonacidic).
** An SAP of 95% alone indicates reflux hypersensitivity.

who received a diagnosis of functional heartburn and those who received a diagnosis of reflux-related, PPI-refractory heartburn and subsequently underwent randomization (Table 1).

RANDOMLY ASSIGNED PATIENTS

A total of 78 patients (64 men; mean age, 45.4±11.8 years; 54 white, 9 black, 14 other race, and 1 unknown race) with reflux-related, PPI-unresponsive heartburn were randomly assigned to receive surgical treatment (27 patients), active medical treatment (25), or control medical treatment (26). MII-pH monitoring showed an SAP of more than 95% alone (reflux hypersensitivity) in 37 patients, abnormal acid reflux alone in 15, and both an SAP of more than 95% and abnormal acid reflux in 25 (data were missing for 1 patient) (Table 2). There were no significant differences among treatment groups in demographic and clinical features or in the distribution of MII-pH monitoring results (i.e., groups had similar percentages of patients with an SAP of >95% alone, abnormal acid reflux alone, and an SAP of >95% and abnormal acid reflux).

After trial completion, review of primary data collection forms revealed discrepancies in eligibility criteria data for 5 randomly assigned patients, which raised uncertainty about whether these patients met all eligibility criteria. Analyses that excluded these 5 patients were similar to our primary analyses (see the Supplementary Appendix).

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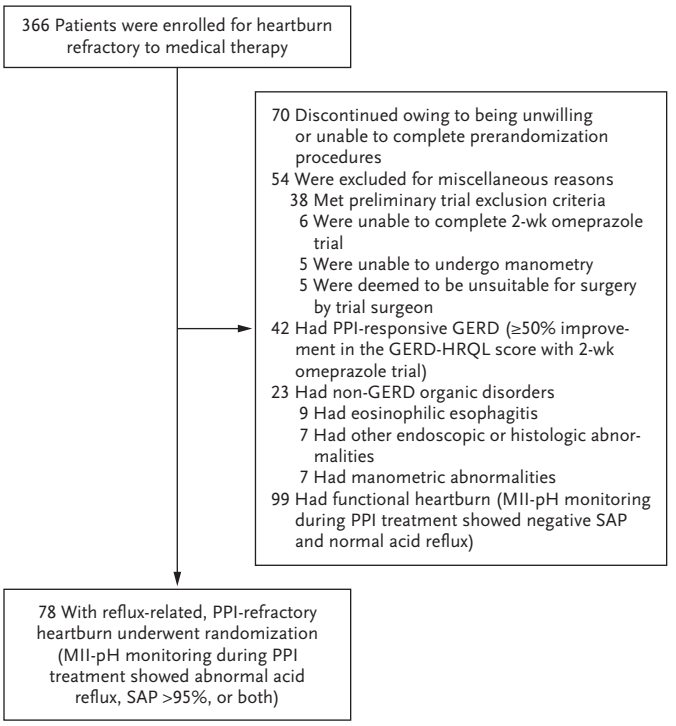

Figure 2. Patient Exclusions.

The medical records of consecutive patients who were referred to gastroenterology clinics at participating VA medical centers for heartburn refractory to PPIs were screened for preliminary exclusion criteria, and patients with no identified exclusions were invited to participate in the trial with the understanding that they would enter the randomized trial of medical or surgical treatment if trial procedures documented reflux-related heartburn. These 366 patients accepted those terms and provided written informed consent. Data on how many patients declined to provide written informed consent are not available. Of the 38 patients who met preliminary trial exclusion criteria after enrollment, 6 had coexisting conditions because of which the patient was considered by the local trial investigator to be unable to participate, 6 had non-GERD disorders that can cause heartburn sensation, 4 had a "heartburn" description did not meet the trial definition, 4 had laboratory exclusions, 3 had previous upper gastrointestinal surgery, 3 were ruled to be not suitable for the trial or were enrolled in another trial, 2 had an initial GERD-HRQL score that conferred ineligibility, 2 had contraindications to trial medications, 2 had morbid obesity, 2 were using forbidden medications, 1 had schizophrenia, 1 had a paraesophageal hernia, 1 was older than 70 years of age, and 1 had a seizure disorder. A total of 5 patients who were randomly assigned to the surgery group did not undergo surgery (2 declined, 1 was lost to follow-up before surgery, 1 moved from the area before surgery, and 1 had a change in medical status that precluded surgery). One patient who was assigned to receive active medical treatment was lost to follow-up before receiving medical treatment. All patients who were assigned to receive control medical treatment were treated as assigned.

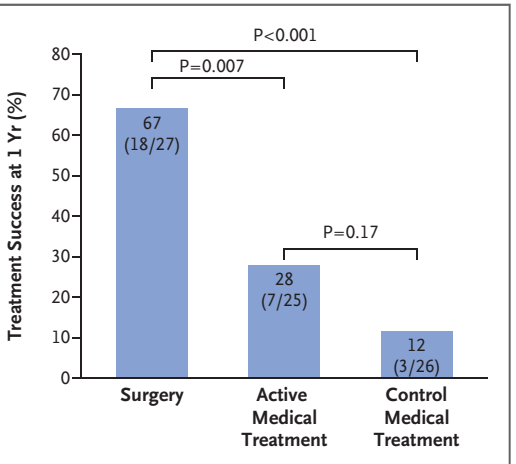

Figure 3. Treatment Success at 1 Year (Intention-to-Treat Analyses).

Treatment success was defined as an improvement (decrease) of 50% or more in the GERD-HRQL score from baseline.

OUTCOMES

At 12 months, treatment success (≥50% improvement in the GERD-HRQL score) occurred in 18 of 27 patients (67%) in the surgery group, 7 of 25 (28%) in the active medical group, and 3 of 26 (12%) in the control medical group (Fig. 3 and Fig. S1A and S1B). The incidence of treatment success with surgery was significantly superior to that with active medical treatment (P=0.007; Hochberg-adjusted significance threshold, 0.025) or control medical treatment (P<0.001; Hochberg-adjusted significance threshold, 0.017). The difference in the incidence of treatment success between the active medical group and the control medical group was 16 percentage points (95% confidence interval [CI], −5 to 38; P=0.17). The relative risk of treatment success was 2.38 (95% CI, 1.20 to 4.71) for surgery versus active medical treatment, 5.78 (95% CI, 1.93 to 17.31) for surgery versus control medical treatment, and 2.43 (95% CI, 0.71 to 8.35) for active medical treatment versus control medical treatment (unadjusted comparisons). A prespecified subgroup analysis assessed the incidence of treatment success with surgery among patients with reflux hypersensitivity (SAP of >95% alone) and patients with abnormal acid reflux (acid reflux alone or with an SAP of >95%). The incidence of success in the surgery group was 71% among the 14 patients with reflux hypersensitivity and 62% among the 13 with abnormal acid reflux.

There were five serious adverse events in 4 patients in the surgery group, four serious adverse events in 4 patients in the active medical group, and five serious adverse events in 3 patients in the control medical group (Table S3).

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One surgical patient had a herniated Nissen fundoplication that resulted in repeat surgery complicated by postoperative pneumonia; recovery was complete, and repeat surgery successfully controlled heartburn. There were no deaths.

DISCUSSION

Among 366 patients enrolled in our trial of medical and surgical treatments for PPI-refractory heartburn, systematic evaluation revealed that GERD underlay truly PPI-refractory heartburn in only a minority of patients. In 42 patients referred because of "PPI-refractory" heartburn, heartburn was relieved during a standardized, 2-week trial of omeprazole twice daily. A systematic evaluation showed that GERD was not the likely cause of heartburn for an additional 122 patients — 99 received a diagnosis of functional heartburn and 23 received a diagnosis of a non-GERD organic disorder. Only 78 patients completed the full assessment and were found to have GERD that was truly unresponsive to twice-daily PPIs. In that highly selected group, the incidence of treatment success with laparoscopic Nissen fundoplication at 1 year (67%) was significantly superior to that with active medical treatment (28%) or control medical treatment (12%).

In our trial, a substantial minority of patients who were referred to gastroenterology clinics with "PPI-refractory" heartburn got relief when prescribed omeprazole twice daily with explicit instruction on how to take it properly. There are two likely explanations as to why some previously PPI-refractory patients had a response to this standardized PPI trial. First, trial patients were given explicit instructions to take omeprazole 30 minutes before meals. This is important because PPIs bind only to gastric proton pumps that are actively secreting acid. Fewer than 10% of those pumps are active during fasting, whereas approximately 70% are active when stimulated by meals.[26] Consequently, PPIs are most effective when taken before meals. Second, patients taking PPIs other than omeprazole at trial entry were switched to omeprazole. Relative potencies of different PPIs vary widely,[27] and individual patients can exhibit considerable variability in response to different PPIs.[28]

This trial highlights the critical importance of systematic evaluation, similar to that recommended by Gyawali and Fass,[17] for managing the care of patients with PPI-refractory heartburn. Many patients would not complete this rigorous evaluation, and among those who did, the cause of heartburn in most of them was not GERD. Furthermore, no demographic or clinical characteristics distinguished patients with reflux-related heartburn from those with functional heartburn, those whose heartburn responded to omeprazole taken properly, and those who would not complete diagnostic evaluation. Although coexisting psychological conditions are common in patients with functional gastrointestinal disorders,[29,30] we found no significant differences in PHQ-9 depression and GAD-7 anxiety scores between patients who received a diagnosis of functional heartburn and those who received a diagnosis of reflux-related, PPI-refractory heartburn, with both groups having mean scores in the "moderate" range (i.e., 7 to 10)[31] (Table 1).

Our finding that reflux hypersensitivity can respond to fundoplication is noteworthy because reflux hypersensitivity is considered a functional disorder, which might not be expected to improve with a procedure that eliminates reflux without altering abnormal esophageal pain perception.[10] Furthermore, we identified hypersensitivity to nonacidic reflux by SAP values on esophageal MII monitoring, a newer technology whose usefulness in selecting patients for fundoplication has been questioned,[21,32] as has the validity of the SAP in general.[33,34] For our surgical patients, the incidence of treatment success was 71% among the 14 with reflux hypersensitivity and 62% among the 13 with abnormal acid reflux. In support of our findings, observational studies have noted that patients chosen for fundoplication on the basis of MII results can do well.[35-37] However, the overall 1-year incidence of treatment success among our surgical patients with PPI-refractory heartburn (67% in an intention-to-treat analysis) is considerably lower than the more than 90% incidence of success with fundoplication that is commonly described in observational studies involving patients with typical, PPI-responsive GERD.[38] The reasons for this are not entirely clear, but patients considering surgery for reflux-related, PPI-refractory heartburn should be advised that surgery was successful in only approximately 2 of 3 cases in our trial.

PPIs are inactivated through the hepatic cytochrome P450 isoenzyme CYP2C19, and *CYP2C19* mutations can influence PPI inactivation rates and clinical efficacy.[39] We did not test for these mutations, because this seldom is done in clini-

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cal practice and because we documented PPI acid-control efficacy by MII-pH monitoring.

Limitations of our trial include its relatively small sample size and predominance of white men (reflecting the veteran patient population). With no sham-surgery group, we cannot determine the contribution of the placebo effect to the incidence of treatment success with surgery. Furthermore, because MII-pH monitoring was performed only while patients were taking PPIs, we cannot determine how many would have abnormal acid reflux when not taking these drugs.

Another limitation involves the intratrial protocol amendments required to enable trial completion. Overly restrictive entry criteria that limit trial enrollment, generalizability, and completion are a common problem in trials involving patients with functional gastrointestinal disorders.[40,41] We found early trial recruitment inadequate because most patients with PPI-refractory GERD who were referred to our gastroenterology clinics had contraindications to desipramine (e.g., concomitant use of other antidepressants). Consequently, we amended the protocol to allow the entry of patients with contraindications to desipramine. We also amended power calculations to detect only large differences between medical and surgical treatments, reasoning that physicians would not recommend surgery unless it were considerably more effective than medical therapy. Our findings document the considerable superiority of antireflux surgery over feasible medical therapy for patients with reflux-related heartburn that is resistant to PPIs. Although the incidence of treatment success did not differ significantly between active medical treatment and control medical treatment (28% and 12%, respectively), our amended trial was insufficiently powered to rule out an important benefit of medical therapy (the 95% confidence interval around the 16-percentage-point difference was −5 to 38).

In conclusion, for patients referred to our clinics for heartburn unrelieved by PPIs, systematic workup revealed that heartburn was both truly PPI-refractory and reflux-related in a minority of patients. In that highly selected group, laparoscopic Nissen fundoplication was significantly superior to medical therapy. We conclude that systematic workup including esophageal MII-pH monitoring can identify a subgroup of patients with PPI-refractory heartburn, including those with reflux hypersensitivity, who can have a response to antireflux surgery.

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APPENDIX

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