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Ambulatory Reflux Monitoring Guides Proton Pump Inhibitor Discontinuation in Patients With Gastroesophageal Reflux Symptoms: A Clinical Trial

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BACKGROUND AND AIMS: Proton pump inhibitor (PPI) therapy fails to provide adequate symptom control in up to 50% of patients with gastroesophageal reflux symptoms. Although a proportion do not require ongoing PPI therapy, a diagnostic approach to identify candidates appropriate for PPI cessation is not available. This study aimed to examine the clinical utility of prolonged wireless reflux monitoring to predict the ability to discontinue PPIs. **METHODS:** This double-blinded clinical trial performed over 3 years at 2 centers enrolled adults with troublesome esophageal symptoms of heartburn, regurgitation, and/or chest pain and inadequate PPI response. Participants underwent prolonged wireless reflux monitoring (off PPIs for $\geq$7 days) and a 3-week PPI cessation intervention. Primary outcome was tolerance of PPI cessation (discontinued or resumed PPIs). Symptom burden was quantified using the Reflux Symptom Questionnaire electronic Diary (RESQ-eD). **RESULTS:** Of 128 enrolled, 100 participants met inclusion criteria (mean age, 48.6 years; 41 men). Thirty-four participants (34%) discontinued PPIs. The strongest predictor of PPI discontinuation was number of days with acid exposure time (AET) $>$ 4.0% (odds ratio, 1.82; $P < .001$). Participants with 0 days of AET $>$ 4.0% had a 10 times increased odds of discontinuing PPI than participants with 4 days of AET $>$ 4.0%. Reduction in symptom burden was greater among the discontinued versus resumed PPI group (RESQ-eD, –43.7% vs –5.3%; $P = .04$). **CONCLUSIONS:** Among patients with typical reflux symptoms, inadequate PPI response, and absence of severe esophagitis, acid exposure on reflux monitoring predicted the ability to discontinue PPIs without symptom escalation. Upfront reflux monitoring off acid suppression can limit unnecessary PPI use and guide personalized management. (ClinicalTrials.gov, Number: NCT03202537)

Keywords: Gastroesophageal Reflux Disease (GERD); Wireless pH Monitoring; Bravo; Functional Heartburn.

Gastroesophageal reflux disease (GERD) affects up to 30% of the adult US population and is among the most frequent gastrointestinal diagnoses in both primary care and subspecialty settings.[1–3] Clinically, GERD is suspected based on patient report of troublesome esophageal symptoms such as heartburn, regurgitation, and noncardiac chest pain.[2] Firstline management relies on empiric trials of acid suppression, namely proton pump inhibitor (PPI) therapy, and consequently PPIs are among the most widely prescribed class of medications worldwide.[2,3] However, up to 50% of patients do not derive adequate symptom relief with PPI therapy, incurring substantial healthcare burden, with annual drug costs for PPIs alone exceeding $12 billion and annual US healthcare expenditures of GERD accounting for up to $20 billion.[3–6] Since 2012 the American Board of Internal Medicine's Choosing Wisely campaign has sought to minimize unneeded PPI use for GERD symptoms.[7] Rising concerns regarding risks of long-term PPI use have further motivated patients and the medical community to reduce PPI use.[8,9] Unfortunately, validated approaches to identify appropriate candidates for PPI cessation are not available.

Prolonged wireless reflux monitoring is widely used to quantify esophageal acid exposure and to assess the associations between reflux episodes and patient-reported symptoms.[10] A large proportion of symptomatic patients with inadequate PPI response have normal levels of esophageal acid exposure on reflux monitoring.[3,4,11,12] However, the clinical utility of reflux monitoring to guide management, especially whether patients with normal reflux monitoring will tolerate cessation of PPI therapy, remains unknown. We hypothesize that prolonged reflux monitoring reliably identifies appropriate candidates for PPI cessation. In this prospective clinical trial, we aimed to examine the clinical utility of prolonged wireless reflux

Abbreviations used in this paper: **AET, acid exposure time; GERD, gastroesophageal reflux disease; PPI, proton pump inhibitor; RESQ-eD, Reflux Symptom Questionnaire electronic Diary.**

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WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

A large portion of patients with gastro-esophageal reflux symptoms derive inadequate relief with proton pump inhibitor (PPI) therapy. A diagnostic approach to identify candidates appropriate for PPI discontinuation is needed.

NEW FINDINGS

Thirty-four of 100 enrolled patients successfully discontinued PPI therapy over three weeks with overall reduction in symptom burden. The strongest predictor of PPI discontinuation was an acid exposure time of 4.0% on reflux monitoring.

LIMITATIONS

Not designed as a placebo controlled study.

IMPACT

Upfront prolonged wireless reflux monitoring off PPI can identify PPI non-responders that are able to tolerate PPI discontinuation, and thus, reduce health care burden and guide personalized management for this prevalent patient population.

monitoring to predict the ability to discontinue PPI therapy among a population of patients with gastroesophageal reflux symptoms and inadequate PPI response.

Methods

Study Design

This double-blind, single-arm, clinical trial was conducted over 3 years (May 2017 to May 2020) at 2 tertiary care centers (lead site, Northwestern University, Chicago, IL; second site, Washington University, St Louis, MO). The study was approved by the Institutional Review Board at participating sites and registered with clinicaltrials.gov (NCT03202537). This overarching trial (National Institutes of Health R01 DK092217-04) enrolled adults with gastroesophageal reflux symptoms and inadequate response to PPI therapy to assess the clinical utility of esophageal physiologic tools. The analysis presented in this article focused on performance of prolonged reflux monitoring to predict the ability to stop PPI therapy for 3 weeks.

Study Population

Adult patients with troublesome symptoms of heartburn, regurgitation, and noncardiac chest pain, defined as at least 2 episodes per week according to the Montreal definition, who remained symptomatic despite a compliant trial of single-dose PPI therapy for at least 8 weeks were eligible for enrollment. Patients may have also experienced concurrent extra-esophageal symptoms such as cough, globus, sore throat, or dysphonia; however, patients with isolated extraesophageal symptoms were not included. Exclusion criteria included active severe erosive esophagitis (Los Angeles C or D), long-segment Barrett's esophagus ($\geq$3 cm in length), prior foregut surgery, signs or symptoms of heart disease, pregnancy, manometric evidence of a major motility disorder according to Chicago classification version 3.0,[13] or >15 eosinophils per high-power field on esophageal biopsies obtained for endoscopic signs of eosinophilic esophagitis. Patients with insufficient pH monitoring time captured (at least 14 hours per day for $\geq$3 days) were also excluded. All participants provided written informed consent.

Study Protocol and Intervention

The study intervention was PPI cessation for 3 weeks. After remaining off PPI therapy for 1 week, participants underwent 96-hour wireless reflux monitoring. Subsequently, participants were instructed to refrain from resuming PPI therapy for an additional 2 weeks unless esophageal symptoms escalated to the extent that maximal over-the-counter antacid use did not provide adequate symptom control. Participants and study investigators were blind to the results of reflux testing during the intervention.

Wireless pH monitoring. During a sedated upper gastrointestinal endoscopy, the wireless pH delivery catheter system (Bravo; Medtronic, Minneapolis, MN) was introduced transorally, and the pH capsule was positioned 6 cm proximal to the endoscopically identified squamocolumnar junction, corresponding to 5 cm above the proximal border of the lower esophageal sphincter. Once the system was in the appropriate position, the external portable vacuum pump was switched on to apply suction to the well of the capsule and suck in adjacent esophageal mucosa. After 30 seconds, the plastic safety guard was removed and the activation button was depressed. Participants were instructed to remain within 3 feet of the pager-sized receiver at all times, continue usual activities, remain off PPIs, and log symptoms and meals in a written and electronic diary. Participants returned the wireless pH study receiver 96 hours later.

Esophageal physiologic tests. As part of the study protocol, participants also underwent high-resolution impedance esophageal manometry and 24-hour multichannel intraluminal impedance pH monitoring on PPIs, either at the time of enrollment before PPI cessation or at a later date after the PPI cessation trial per patient and/or site preference.

Patient-reported symptoms. At enrollment participants completed the GerdQ instrument, a 6-item validated questionnaire evaluating reflux symptoms with a 7-day recall period with scores ranging from 0 to 18, where higher scores indicate more severe symptoms.[14,15] Participants also completed the Reflux Symptom Questionnaire electronic Diary (RESQ-eD) during the daytime and nighttime at 4 time points during the study: on PPIs at time of enrollment and off PPIs at weeks 1, 2, and 3. The RESQ-eD is a validated electronic symptom diary for use in patients with symptoms of GERD and inadequate response to PPIs developed in line with US Food and Drug Administration guidance on patient-reported outcomes that measures symptom intensity ranging from 0 to 5 for 13 symptoms in the morning and before bedtime, with a 7-day recall period, where higher scores indicate higher symptom burden.[16] The study coordinator contacted participants weekly for 4 weeks to monitor symptoms, collect questionnaire scores, and determine whether PPI therapy was resumed.

Data Source and Measurement

Data for all participants were electronically collected in a uniform deidentified dataset through Research Electronic Data Capture hosted at the lead study site with multisite access for the secondary participating center. Data collected for

participants were demographics, endoscopic findings (presence and degree of erosive esophagitis, hiatal hernia size), eosinophil count on esophageal biopsy, questionnaire scores, and PPI use. Reflux monitoring data analyzed by a blinded external investigator using manufacturer software (AccuView Reflux Software; Medtronic) were monitoring time, total and daily acid exposure time (AET; percentage of time esophageal acid exposure was below a pH of 4.0), DeMeester score, number of reflux events, longest reflux event, symptoms reported, symptom index (proportion of symptoms associated with a reflux episode; optimal threshold $>$ 50%), and symptom association probability (a statistical calculation expressing the probability that symptom events and reflux episodes were associated; $\geq$95% considered positive).[10] All authors had access to the study data and reviewed and approved the final manuscript.

Outcomes

The primary outcome was status of PPI use during the study intervention, categorized as discontinued PPIs or resumed PPIs. Secondary outcomes were change in symptoms during the study intervention measured by absolute and percentage of change in RESQ-eD score and presence of objective GERD on reflux monitoring.

Sample Size

The target sample size for this analysis was 100 participants. Anticipating successful PPI discontinuation in approximately 70% of participants with 0 days of positive AET compared with 40% of participants with $\geq$1 day of positive AET, a sample size of 84 was calculated to provide a Type I error rate of 0.05 and power of 80%.

Data Analysis

All data are summarized as count (percent) or mean (SD) for categorical or continuous variables, respectively. The primary analysis aimed to assess the potential utility of various demographic, clinical, and physiologic measures on reflux monitoring to predict the outcome of PPI cessation. Univariate logistic regression models were fit with summaries including the odds ratio (OR) with its confidence interval (CI) and *P* value and c-statistic. The c-statistic represents the area under the receiver operating characteristic curve corresponding to the logistic regression model. AET as measured over the course of 4 days of reflux monitoring was also classified by number of days with acid exposure above 4.0%, 5.0%, or 6.0% to examine if an optimal combination could identify those likely to discontinue PPIs. Two-sample *t* tests assuming unequal variances were used to compare means between PPI cessation groups. A secondary analysis assessed the predictor of symptom severity measured by RESQ-eD at baseline and change throughout the study with the outcome of GERD or no GERD using univariate logistic regression models. All figures and analyses were conducted using R v3.6.0 (Developer R Core Team; License GNU GPLv3.60; Vienna, Austria).

Results

Baseline Characteristics

Of 142 patients screened, 128 met eligibility and provided informed consent, of which 100 participants met inclusion criteria, completed the study, and are included in the analysis (Figure 1). Among the included participants, 41% were men with a mean age of 48.6 years (SD, 14.9) and mean body mass index of 27.1 kg/m^2 (SD, 5.5). Participants reported a mean GerdQ score of 8.6 (SD, 4.2) at intake. On upper endoscopy 30 participants had erosive esophagitis (16 Los Angeles A and 14 Los Angeles B esophagitis) and 27 participants had a hiatal hernia. Mean reflux monitoring time was 3.4 days (SD, 0.3) with a mean total esophageal AET of 5.8% (SD, 3.8%) and mean DeMeester score of 21.6 (SD, 13.6) (Table 1).

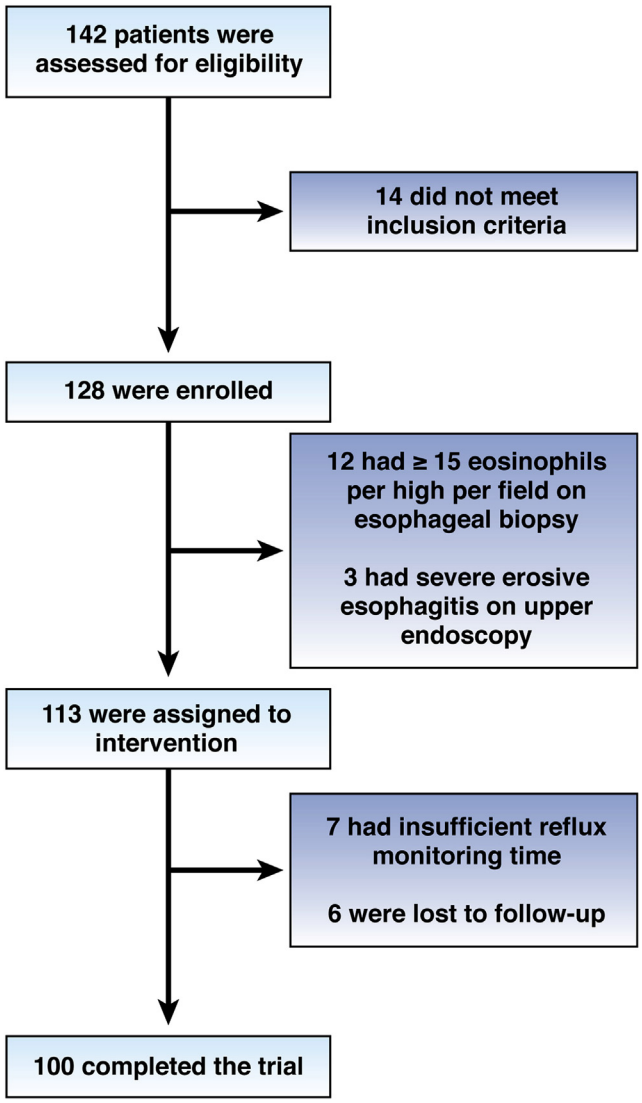

Figure 1. Enrollment and inclusion of patients.

Outcome of PPI Cessation

Thirty-four participants (34%) discontinued PPIs and 66 resumed PPIs. Compared with the discontinued PPI group, participants who resumed PPIs reported higher mean baseline RESQ-eD scores (17.8 [SD, 11.7] vs 12.0 [SD, 9.6]; $P = .02$) and GerdQ scores (9.3 [SD, 4.6] vs 7.2 [SD, 3.0]; $P = .01$).

Table 1. Baseline Characteristics and Factors Associated With Outcome of PPI Cessation Intervention

Predictor	All Subjects (n = 100)	PPI Discontinued (n = 34)	PPI Resumed (n = 66)	OR (95% CI)	*P* value
Age, y	48.6 (14.9)	47.7 (14.3)	49.0 (15.3)	1.01 (0.98–1.04)	.68
Male, n (%)	41 (41)	13 (38.2)	28 (42.4)	1.19 (0.51–2.82)	.69
Body mass index, kg/m^2	27.1 (5.48)	27.4 (4.7)	27.0 (5.9)	0.99 (0.92–1.07)	.79
Hiatal hernia, n (%)	27 (27)	10 (29.4)	17 (25.8)	0.83 (0.33–2.14)	.70
Esophagitis, n (%)					
Los Angeles A	16 (16)	4 (11.8)	12 (18.2)	Reference	
Los Angeles B	14 (14)	5 (14.7)	9 (13.6)	0.60 (0.12–2.90)	.53
None	70 (70)	25 (73.5)	45 (68.2)	0.60 (0.15–1.93)	.42
Baseline symptoms					
Index RESQ-eD score	19.1 (11.8)	12.0 (9.6)	17.8 (11.7)	1.06 (1.01–1.11)	.02
Index GerdQ score	8.6 (4.23)	7.2 (3.0)	9.3 (4.6)	1.19 (1.04–1.39)	.02
Heartburn, n (%)	68 (68)	22 (64.7)	46 (69.7)	1.25 (0.51–3.01)	.61
Regurgitation, n (%)	38 (38)	10 (29.4)	28 (42.4)	1.77 (0.74–4.42)	.21
Chest pain, n (%)	38 (38)	16 (47.1)	22 (33.3)	0.56 (0.24–1.31)	.18
Wireless pH monitoring					
AET total, %	5.8 (3.8)	4.3 (3.6)	6.6 (3.6)	1.21 (1.07–1.39)	.01
DeMeester score	21.6 (13.6)	16.2 (12.6)	24.3 (13.4)	1.05 (1.02–1.10)	.01
DeMeester score > 14.2, n (%)	67 (67)	17 (50)	50 (76)	3.12 (1.31–7.63)	.01
No. of reflux events	127 (80.2)	104.3 (80.6)	138.2 (78.1)	1.01 (1.00–1.01)	.05
Longest reflux event, min	32.0 (24.8)	22.7 (16.8)	36.9 (26.9)	1.03 (1.01–1.06)	.01
Lowest daily AET	3.0 (2.72)	2.0 (2.4)	3.5 (2.8)	1.28 (1.07–1.57)	.01
Highest daily AET	9.82 (6.48)	7.4 (5.4)	11.1 (6.6)	1.12 (1.04–1.22)	.01
No. of days AET > 4.0%	2.2 (1.5)	1.4 (1.4)	2.7 (1.3)	1.82 (1.34–2.56)	<.01
No. of days AET > 5.0%	1.9 (1.5)	1.2 (1.4)	2.3 (1.4)	1.73 (1.27–2.44)	<.01
No. of days AET > 6.0%	1.7 (1.4)	1.1 (1.3)	2.0 (1.4)	1.65 (1.20–2.37)	<.01
AET > 4 for 1+ days, n (%)	82 (82)	22 (65)	60 (91)	5.45 (1.88–17.37)	<.01
AET > 4 for 2+ days, n (%)	66 (66)	14 (41)	52 (79)	5.31 (2.19–13.44)	<.01
AET > 4 for 3+ days, n (%)	46 (46)	8 (24)	38 (58)	4.41 (1.80–11.78)	<.01
AET > 4 for 4+ days, n (%)	30 (30)	5 (15)	25 (38)	3.54 (1.29–11.45)	.02
Symptom index for heartburn	19.1 (24.3)	12.6 (22.9)	22.5 (24.5)	1.02 (1.00–1.04)	.06
Symptom index for regurgitation	11.1 (24.1)	8.7 (24.8)	12.4 (23.9)	1.01 (0.99–1.03)	.47
Symptom index for chest pain	6.0 (17.9)	4.3 (17.5)	6.8 (18.1)	1.01 (0.98–1.04)	.52
SAP for heartburn	44.8 (47.4)	30.2 (44.9)	52.3 (47.2)	1.01 (1.00–1.02)	.03
SAP for regurgitation	20.8 (35.2)	13.6 (33.2)	24.5 (40.8)	1.01 (1.00–1.02)	.18
SAP for chest pain	14.0 (31.7)	10.8 (26.7)	15.7 (34.0)	1.01 (0.99–1.02)	.47
SAP > 95% for heartburn, regurgitation, or chest pain, n (%)	46 (46)	11 (32)	35 (53)	2.36 (1.01–5.77)	.052
Change in RESQeD score from baseline					
Absolute change wk 1	1.11 (8.04)	2.14 (8.78)	–0.58 (6.43)	1.05 (0.99–1.12)	.142
Absolute change wk 2	–2.35 (8.97)	–1.41 (9.9)	–3.9 (7.07)	1.03 (0.98–1.09)	.231
Absolute change wk 3	–4.52 (10.1)	–3.21 (10.8)	–6.69 (8.58)	1.04 (0.99–1.09)	.150
Percent change wk 1	15.2 (67.4)	24.7 (75.7)	–0.45 (48.0)	1.01 (1.00–1.02)	.106
Percent change wk 2	–5.71 (73.3)	4.09 (75.3)	–21.7 (68.3)	1.01 (1.00–1.01)	.135
Percent change wk 3	–19.8 (78.8)	–5.31 (86.4)	–43.7 (58.1)	1.01 (1.002–1.02)	.039

NOTE. Values are mean (SD) unless otherwise defined. SAT, symptom association probability.

Primary Analysis: Association Between Reflux Monitoring and Outcome of PPI Cessation

All reflux monitoring data were associated with outcome of PPI cessation. Total AET was significantly higher in the resumed PPI group compared with the discontinued PPI group (6.6% [SD, 3.6%] vs 4.3% [SD, 3.6%]; $P < .01$). The strongest predictor of PPI discontinuation was number of days with AET > 4.0% in which every additional day with AET > 4.0% was associated with a 1.8 increased odds of PPI resumption (OR, 1.82; 95% CI, 1.34–2.56; $P < .01$) with an area under the receiver operating characteristic curve of 0.73 (95% CI, 0.62–0.83) (Figure 2). For instance, the odds of discontinuing PPIs for participants with zero days of an AET > 4.0% was 10 times greater than participants with

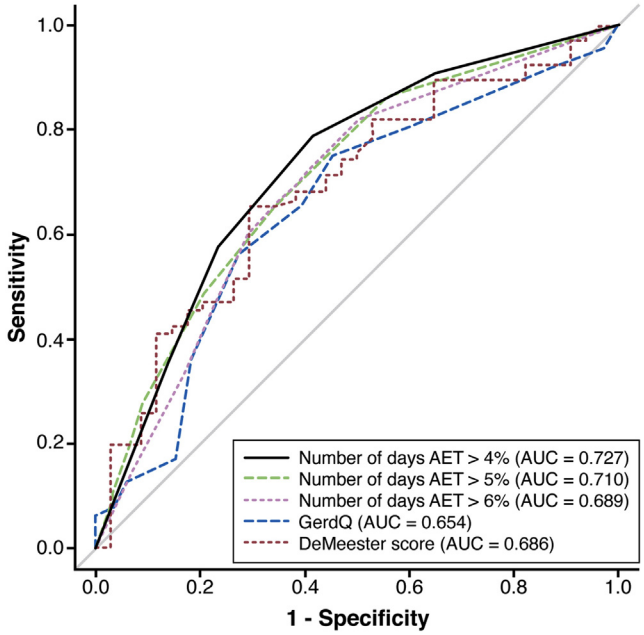

Figure 2. Receiver operating characteristics for outcome of PPI cessation intervention. AUC, area under the curve.

AET > 4.0% across all 4 days (OR, 10.0; 95% CI, 2.70–43.32; $P < .01$) (Figure 3). An AET > 4.0% for 2 or more days maximized the prognostic performance (OR, 5.31; 95% CI, 2.19–13.44; $P < .001$) with an area under the receiver operating characteristic curve of 0.69, 79% sensitivity, and 59% specificity for the ability to discontinue PPI therapy. As such, in subsequent analyses below, objective GERD is defined as AET > 4.0% for 2 or more days.

Figure 4 examines the relationship between outcome of PPI cessation (resumed or discontinued PPIs) and results of reflux monitoring (objective GERD or no GERD). Overall, 71% of results on reflux monitoring were concordant with outcome (resumed PPI/objective GERD or discontinued PPIs/no GERD). Among 29 discordant cases, 14 participants without GERD resumed PPIs and 15 participants with objective GERD discontinued PPIs, 7 (47%) of which had erosive esophagitis. Among the 14 participants with Los Angeles B esophagitis, 13 (93%) had objective GERD (Supplementary Table 1).

Symptom Severity During Study Intervention

From baseline to the end of the intervention, the mean RESQ-eD score decreased by 19.8% (SD, 78.8%). The RESQ-eD decreased for all participant subgroups except those that resumed PPIs and had objective GERD (Figure 5). Reduction in RESQ-eD was greater among participants with objective GERD compared with no GERD (–42.1% [SD, 49.3%] vs –7.0% [SD, 89.6%]; $P = .03$).

Discussion

Inadequate symptom relief with PPI therapy among patients experiencing gastroesophageal reflux symptoms is a common occurrence and contributes a substantial healthcare burden in terms of inappropriate PPI use, delay in appropriate management, and healthcare costs. This is the first blinded prospective clinical trial to use relevant

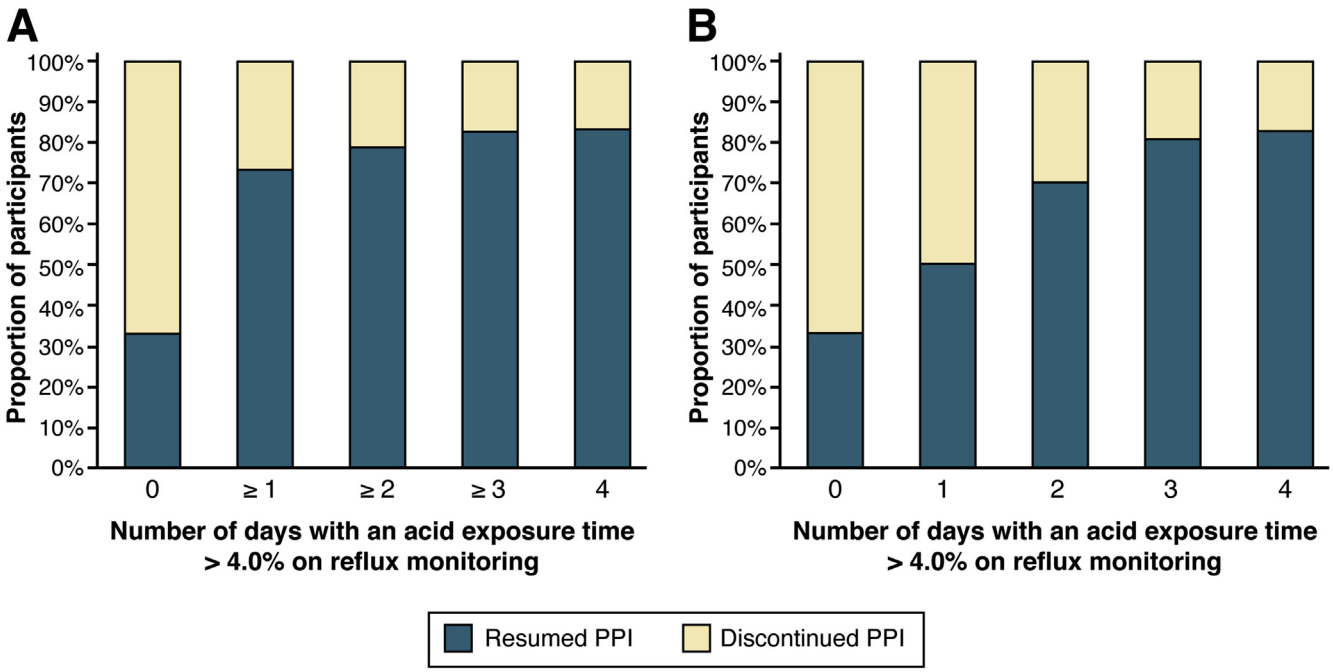

Figure 3. Ability to discontinue PPI based on number of days with elevated acid exposure. The proportion of patients that resumed PPI therapy (*blue shading*) increases as the number of days with a positive acid exposure time (defined as > 4.0%) increases. Panel (*A*) depicts the proportion of participants either resuming or discontinuing PPI therapy based on having 0 days positive or a minimum of 1, 2, 3 or 4 days positive. Overall the proportion of participants resuming PPI therapy plateaus around 80% for those with at least 2 or more days positive. Panel (*B*) depicts the proportion of participants either resuming or discontinuing PPI therapy based on the absolute number of days positive (0, 1, 2, 3 or 4 days).

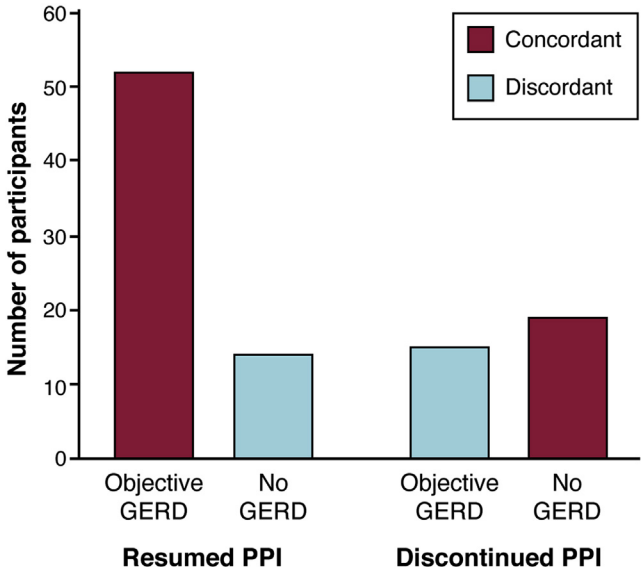

Figure 4. Agreement between reflux monitoring and outcome of PPI cessation.

clinical outcomes, including the ability to discontinue PPI therapy and symptom severity off PPIs, to determine the utility of prolonged wireless reflux monitoring. Our results establish that prolonged reflux monitoring off PPIs is clinically useful to guide the management of patients with inadequate PPI response. Of 100 participants, 34% tolerated PPI cessation throughout the study. An AET $>$ 4.0% on reflux monitoring was an important physiomarker in predicting the ability to discontinue PPIs. Patients with negative wireless reflux monitoring, defined as 0 days with AET $>$ 4.0%, had 10 times the odds of tolerating PPI discontinuation compared with those with all 4 days positive. Overall, the threshold of 2 or more days of AET $>$ 4.0% was most predictive of the ability to refrain from PPI resumption. Patients who discontinued PPIs also reported greater reduction in symptom burden compared with those who resumed PPIs; however, symptom scores alone did not predict which patients were able to discontinue their PPI therapy. Results from this study support the upfront use of prolonged wireless reflux monitoring to provide a personalized approach to the management of patients with inadequate PPI response.

Importantly, this study validates esophageal acid exposure as a reliable physiomarker of GERD and is the first to demonstrate the prognostic ability of acid exposure to predict response to PPI cessation.[4,17] The high negative predictive value of reflux monitoring observed in this study could translate to PPI discontinuation in over one-third of symptomatic patients with inadequate response to PPIs. This shift in management could have tremendous implications for patient care and healthcare utilization. Prior cost models estimate considerable cost saving with upfront prolonged wireless reflux monitoring compared with empiric PPI therapy, ranging between $1048 and $15,853 per patient.[18,19] As such, findings from this study could conservatively translate to a cost saving of $35,632 per 100 symptomatic patients with inadequate PPI response. Although the concept of upfront reflux monitoring for inadequate PPI response is endorsed by the American College of Gastroenterology and American Gastroenterological Association, guidelines are based on very low level of evidence and expert opinion, and clinical practice frequently differs from societal recommendations.[20–22] Our study is the first trial to demonstrate the clinical utility of upfront measurement of acid exposure to guide PPI management for the population with an inadequate PPI response.

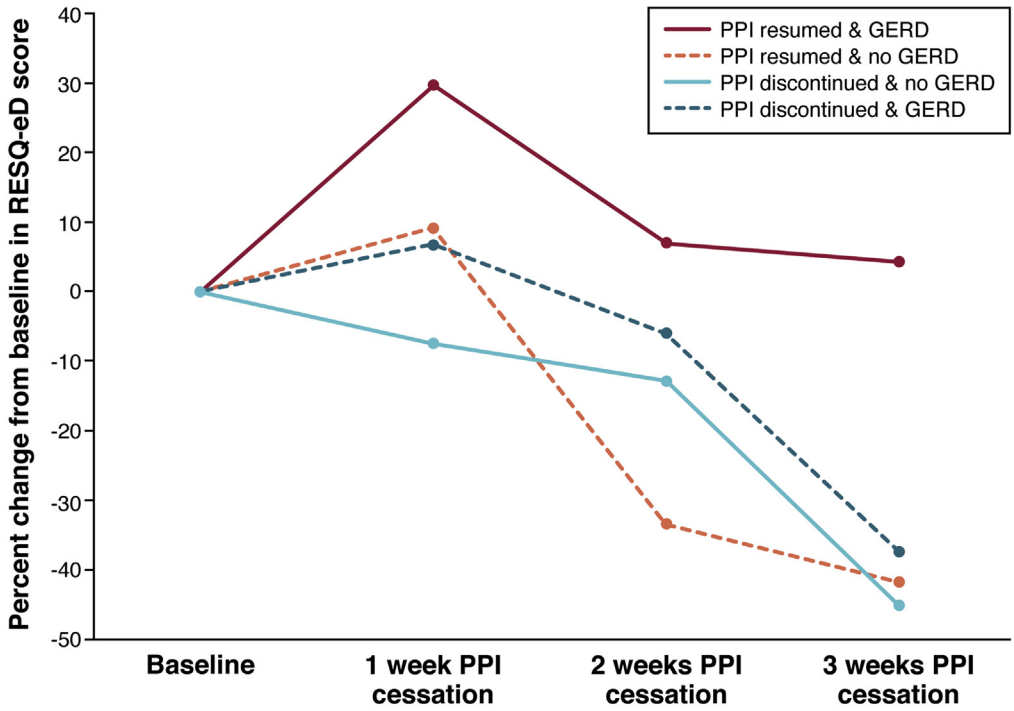

Figure 5. Patient-reported RESQ-eD scores throughout PPI cessation intervention.

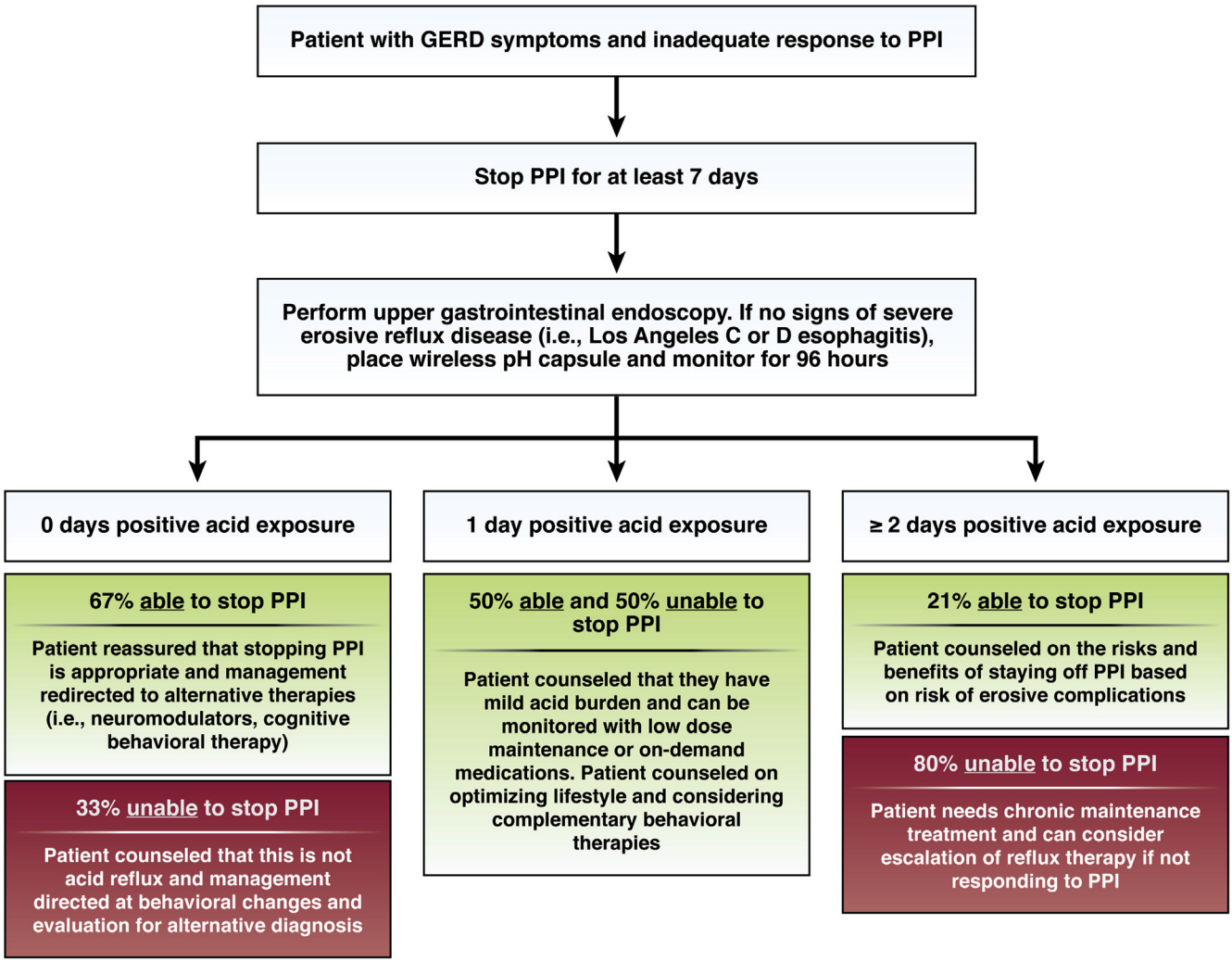

Figure 6. Conceptual paradigm of diagnostic evaluation and management for patients with GERD symptoms and inadequate symptom response to PPI therapy.

Further, this study highlights the shortcomings of directing antireflux management based on patient-reported symptoms or tolerance of PPI cessation alone. In this study, outcome of PPI cessation was incongruent with objective acid exposure in 29% of cases. Among 15 patients with elevated acid exposure who discontinued PPI therapy, 47% had erosive esophagitis on endoscopy. It is plausible that fear of long-term PPI use drove PPI discontinuation in this group of patients with erosive reflux disease.[8] Nonetheless, it is well established that maintenance PPI therapy in erosive reflux disease reduces the risk of progression to Barrett's esophagus and esophageal adenocarcinoma.[20,23–25] Hence, reliance on patient-reported symptoms or tolerance of PPI cessation alone without objective reflux monitoring data could result in deleterious outcomes. Further, although not considered conclusive for GERD in the Lyon consensus, this study highlights that Los Angeles B esophagitis is suggestive of objective pathologic GERD.

Figure 6 conceptualizes the implications of these results for the care paradigm of symptomatic patients with inadequate response to PPI therapy. Upfront prolonged reflux monitoring allows for phenotyping the patient and using a personalized management approach.[26] Patients with normal acid exposure over 4 days can be reassured on the appropriateness of PPI cessation with evaluation redirected toward alternative etiologies. Most patients will be able to stop PPIs without exacerbation of symptoms. In some cases, functional heartburn or reflux hypersensitivity may drive persistent symptoms, for which a growing body of literature and experiences support the efficacy of psychological interventions (ie, hypnotherapy, cognitive behavioral therapy) and pharmacologic neuromodulation.[4,11,12,27–32] On the other hand, most patients with 2 or more days of elevated acid exposure will require ongoing acid suppression and possibly escalation of antireflux management.[33] Patients with mild elevation in acid exposure may demonstrate varying ability to stop PPI therapy. This group should be counseled that acid exposure is mild with therapeutic focus on lifestyle optimization, particularly weight management, complemented by behavioral or pharmacologic treatment as needed. For those unable to tolerate PPI cessation, on-demand or titration to the lowest effective dose of PPI is reasonable.[20,34,35] This conceptual model is based on clinical experience coupled with results from this study, and

outcomes of a phenotype-guided personalized management approach to GERD requires evaluation in a future phenotype stratified clinical trial. Further, predictors of PPI requirement should similarly be studied in a population with extraesophageal symptoms such as dysphonia, sore throat, and cough because the patient population in our current study was limited to patients experiencing typical symptoms of reflux.

This study design attempted to address limitations inherent to this study. Given the potential of rebound gastric acid secretion within 7 days of PPI cessation, the duration of PPI cessation intervention was 21 days because symptoms typically return 1 week after discontinuing PPIs, and erosive esophagitis changes and inflammation present 2 weeks after discontinuing PPI therapy in erosive esophagitis healed while on PPIs.[36] This potential is also minimized because 75% of patients had been off PPI therapy for at least 10 days before their endoscopy. Lack of a placebo arm in this single-arm trial may introduce response bias among participants; however, this study aimed to determine symptom response during PPI cessation without knowledge of acid exposure as opposed to whether acid exposure could predict symptoms on acid suppression. Blinding the participant and study investigators to reflux monitoring data and the external analyst to outcome minimized potential biases. Multiple measures were evaluated statistically, which increases the potential of a Type I error rate. Although the study was conducted at tertiary care referral centers, the results should be generalizable to healthcare settings that manage patients with symptoms of GERD. The clinician should be aware of practical limitations inherent to wireless and catheter-based reflux monitoring, including the potential for misplacement of the wireless capsule and that exclusion of meals to avoid intrameal acid exposure relies on patient-reported mealtimes. Further, unlike catheter-based impedance pH monitoring, wireless reflux monitoring does not capture weakly or nonacidic reflux events, which risks the potential for a negative wireless reflux monitoring study for a patient with nonacidic volume-predominant GERD pathology.

In conclusion, this prospective double-blind clinical trial of 100 patients with inadequate PPI response highlights the strong association between acid exposure data measured on prolonged wireless reflux monitoring and a patient's ability to successfully stop PPI therapy without symptom exacerbation. This study is the first of its kind to provide high-level evidence in support of early reflux monitoring off acid suppression to phenotype the patient with inadequate PPI response and personalize care accordingly. A phenotype-guided care approach for patients with suspected GERD and inadequate PPI response has tremendous implications for health-related quality of life and resource utilization associated with GERD.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2020.09.013.

References

1. Peery AF, Crockett SD, Barritt AS, et al. Burden of gastrointestinal, liver, and pancreatic diseases in the United States. Gastroenterology 2015;149:1731–1741.
2. Vakil N, van Zanten SV, Kahrilas P, et al. The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. Am J Gastroenterol 2006;101:1900–1920; quiz 1943.
3. Delshad SD, Almario CV, Chey WD, et al. Prevalence of gastroesophageal reflux disease and proton pump inhibitor-refractory symptoms. Gastroenterology 2020;158:1250–1261.
4. Spechler SJ, Hunter JG, Jones KM, et al. Randomized trial of medical versus surgical treatment for refractory heartburn. N Engl J Med 2019;381:1513–1523.
5. Kahrilas PJ, Boeckxstaens G, Smout AJ. Management of the patient with incomplete response to PPI therapy. Best Pract Res Clin Gastroenterol 2013;27:401–414.
6. Shaheen NJ, Hansen RA, Morgan DR, et al. The burden of gastrointestinal and liver diseases, 2006. Am J Gastroenterol 2006;101:2128–2138.
7. Foundation A. American Gastroenterological Association—treating GERD. Choosing Wisely 2012:2020; Available at: https://www.choosingwisely.org/clinician-lists/american-gastroenterological-association-treating-gerd/. Accessed June 20, 2020.
8. Kurlander JE, Kennedy JK, Rubenstein JH, et al. Patients' perceptions of proton pump inhibitor risks and attempts at discontinuation: a national survey. Am J Gastroenterol 2019;114:244–249.
9. Kurlander JE, Rubenstein JH, Richardson CR, et al. Physicians' perceptions of proton pump inhibitor risks and recommendations to discontinue: a national survey. Am J Gastroenterol 2020;115:689–696.
10. Gyawali CP, Kahrilas PJ, Savarino E, et al. Modern diagnosis of GERD: the Lyon consensus. Gut 2018;67:1351–1362.
11. Abdallah J, George N, Yamasaki T, et al. Most patients with gastroesophageal reflux disease who failed proton pump inhibitor therapy also have functional esophageal disorders. Clin Gastroenterol Hepatol 2019;17:1073–1080.
12. Yadlapati R, Tye M, Keefer L, et al. Psychosocial distress and quality of life impairment are associated with symptom severity in PPI non-responders with normal impedance-pH profiles. Am J Gastroenterol 2018;113:31–38.
13. Kahrilas PJ, Bredenoord AJ, Fox M, et al. The Chicago classification of esophageal motility disorders, v3.0. Neurogastroenterol Motil 2015;27:160–174.
14. Dent J, Vakil N, Jones R, et al. Accuracy of the diagnosis of GORD by questionnaire, physicians and a trial of proton pump inhibitor treatment: the Diamond Study. Gut 2010;59:714–721.
15. Jonasson C, Wernersson B, Hoff DA, et al. Validation of the GerdQ questionnaire for the diagnosis of gastro-oesophageal reflux disease. Aliment Pharmacol Ther 2013;37:564–572.
16. Vakil N, Bjorck K, Denison H, et al. Validation of the reflux symptom questionnaire electronic diary in partial responders to proton pump inhibitor therapy. Clin Transl Gastroenterol 2012;3:e7.

17. Patel A, Sayuk GS, Gyawali CP. Parameters on esophageal pH-impedance monitoring that predict outcomes of patients with gastroesophageal reflux disease. Clin Gastroenterol Hepatol 2015;13:884–891.
18. Afaneh C, Zoghbi V, Finnerty BM, et al. BRAVO esophageal pH monitoring: more cost-effective than empiric medical therapy for suspected gastroesophageal reflux. Surg Endosc 2016;30:3454–3460.
19. Lee WC, Yeh YC, Lacy BE, et al. Timely confirmation of gastro-esophageal reflux disease via pH monitoring: estimating budget impact on managed care organizations. Curr Med Res Opin 2008;24:1317–1327.
20. Katz PO, Gerson LB, Vela MF. Guidelines for the diagnosis and management of gastroesophageal reflux disease. Am J Gastroenterol 2013;108:308–328; quiz 329.
21. Kahrilas PJ, Shaheen NJ, Vaezi MF, et al. American Gastroenterological Association medical position statement on the management of gastroesophageal reflux disease. Gastroenterology 2008;135:1383–1391.
22. Gyawali CP, Carlson DC, Chen JW, et al. Esophageal physiologic testing american college of gastroenterology clinical guideline. Am J Gastroenterol 2020;115:1412–1428.
23. Singh S, Garg SK, Singh PP, et al. Acid-suppressive medications and risk of oesophageal adenocarcinoma in patients with Barrett's oesophagus: a systematic review and meta-analysis. Gut 2014;63:1229–1237.
24. Kahrilas PJ, Boeckxstaens G. Failure of reflux inhibitors in clinical trials: bad drugs or wrong patients? Gut 2012;61:1501–1509.
25. Shaheen NJ, Falk GW, Iyer PG, et al. ACG clinical guideline: diagnosis and management of Barrett's esophagus. Am J Gastroenterol 2016;111:30–50; quiz 51.
26. Yadlapati R, Pandolfino JE. Personalized approach in the work-up and management of gastroesophageal reflux disease. Gastrointest Endosc Clin North Am 2020;30:227–238.
27. Riehl ME, Chen JW. The proton pump inhibitor nonresponder: a behavioral approach to improvement and wellness. Curr Gastroenterol Rep 2018;20:34.
28. Dickman R, Maradey-Romero C, Fass R. The role of pain modulators in esophageal disorders—no pain no gain. Neurogastroenterol Motil 2014;26:603–610.
29. Cannon RO 3rd, Quyyumi AA, Mincemoyer R, et al. Imipramine in patients with chest pain despite normal coronary angiograms. N Engl J Med 1994;330:1411–1417.
30. You LQ, Liu J, Jia L, et al. Effect of low-dose amitriptyline on globus pharyngeus and its side effects. World J Gastroenterol 2013;19:7455–7460.
31. Roman S, Keefer L, Imam H, et al. Majority of symptoms in esophageal reflux PPI non-responders are not related to reflux. Neurogastroenterol Motil 2015;27:1667–1674.
32. Riehl ME, Kinsinger S, Kahrilas PJ, et al. Role of a health psychologist in the management of functional esophageal complaints. Dis Esophagus 2015;28:428–436.
33. Gawron AJ, Bell R, Abu Dayyeh BK, et al. Surgical and endoscopic management options for patients with GERD based on proton pump inhibitor symptom response: recommendations from an expert U.S. panel. Gastrointest Endosc 2020;92:78–87.
34. Gyawali CP, Fass R. Management of gastroesophageal reflux disease. Gastroenterology 2018;154:302–318.
35. Yadlapati R, Pandolfino JE, Alexeeva O, et al. The Reflux Improvement and Monitoring (TRIM) program is associated with symptom improvement and weight reduction for patients with obesity and gastroesophageal reflux disease. Am J Gastroenterol 2018;113:23–30.
36. Dunbar KB, Agoston AT, Odze RD, et al. Association of acute gastroesophageal reflux disease with esophageal histologic changes. JAMA 2016;315:2104–2112.

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Conflicts of interest
These authors disclose the following: Rena Yadlapati is a consultant for Medtronic, Ironwood Pharmaceuticals, and Diversatek; receives research support from Ironwood Pharmaceuticals; and is on the advisory board for Phatom Pharmaceuticals. C. Prakash Gyawali is a consultant for Medtronic, Diversatek, Ironwood, Iso-Thrive, and Quintiles. Dustin A Carlson is a consultant for Medtronic. Peter J. Kahrilas receives research support from and is on the advisory board for Ironwood Pharmaceuticals. Michael F. Vaezi is a consultant for Ironwood Pharmaceuticals, Diversatek, Phathom Pharmaceuticals, and Daewood and holds a patent on mucosal integrity by Vanderbilt University. John E. Pandolfino is a consultant for Medtronic, Ironwood Pharmaceuticals, and Diversatek; receives research support from Ironwood Pharmaceuticals and Takeda; is on the advisory board for Medtronic and Diversatek; and has stock options in Crospon Inc. The remaining authors disclose no conflicts.

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Supplementary Table 1. Clinical and Reflux Monitoring Data for Subgroups

	PPI Resumed		PPI Discontinued	
	Objective GERD	Normal	Objective GERD	Normal
	(n = 52)	(n = 14)	(n = 15)	(n = 19)
Male, n (%)	23 (44.2)	5 (35.7)	8 (53.3)	5 (26.3)
Age, y	48.6 (14.8)	50.5 (17.4)	51.3 (14.7)	45.0 (13.8)
Body mass index, kg/m^2	28.1 (5.92)	23.2 (3.79)	29.0 (5.4)	26.1 (3.84)
Hiatal hernia, n (%)	15 (28.8)	2 (14.3)	5 (33.3)	5 (26.4)
Esophagitis, n (%)				
Los Angeles A	12 (23.1)	0 (0.0)	2 (13.3)	2 (10.5)
Los Angeles B	8 (15.4)	1 (7.1)	5 (33.3)	0 (0.0)
None	32 (61.5)	13 (92.9)	8 (53.3)	17 (89.5)
Symptoms				
Index RESQ-eD score	23.6 (12.3)	11.8 (8.05)	18.7 (12.7)	12.9 (7.72)
Index GerdQ score	9.92 (4.72)	6.92 (3.25)	7.93 (3.02)	6.68 (2.94)
Heartburn, n (%)	38 (73.1)	8 (57.1)	12 (80.0)	10 (52.6)
Regurgitation, n (%)	23 (44.2)	5 (35.7)	3 (20.0)	7 (36.8)
Chest pain, n (%)	17 (32.7)	5 (35.7)	6 (40.0)	10 (52.6)
Wireless pH monitoring				
AET total, %	7.68 (3.2)	2.6 (2.12)	7.27 (3.5)	1.97 (1.1)
Positive symptom-reflux association, n (%)	23 (44.2)	4 (28.6)	5 (33.3)	4 (21.1)
Percentage of change in RESQ-eD from study initiation to completion	4.27 (92.3)	–37.5 (54.6)	–41.8 (73.4)	–45.1 (47.0)

NOTE. Values are mean (SD) unless otherwise defined.