Gastroesophageal Acid Reflux Control 5 Years After Antireflux Surgery, Compared With Long-term Esomeprazole Therapy

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BACKGROUND & AIMS: **We compared the ability of laparoscopic antireflux surgery (LARS) and esomeprazole to control esophageal acid exposure, over a 5-year period, in patients with chronic gastroesophageal reflux disease (GERD). We also studied whether intraesophageal and intragastric pH parameters off and on therapy were associated with long-term outcomes.**

METHODS: **We analyzed data from a prospective, randomized, open-label trial comparing the efficacy and safety of LARS vs esomeprazole (20 or 40 mg/d) over 5 years in patients with chronic GERD. Ambulatory intraesophageal and intragastric 24-hour pH monitoring data were compared between groups before LARS or the start of esomeprazole treatment, and 6 months and 5 years afterward. A secondary aim was to evaluate the association between baseline and 6-month pH parameters and esomeprazole dose escalation, reappearance of GERD symptoms, and treatment failure over 5 years in patients receiving LARS or esomeprazole.**

RESULTS: **In the LARS group (n = 116), the median 24-hour esophageal acid exposure was 8.6% at baseline and 0.7% after 6 months and 5 years ($P < .001$ vs baseline). In the esomeprazole group (n = 151), the median 24-hour esophageal acid exposure was 8.8% at baseline, 2.1% after 6 months, and 1.9% after 5 years ($P < .001$, therapy vs baseline, and LARS vs esomeprazole). Gastric acidity was stable in both groups. Patients who required a dose increase to 40 mg/d had more severe supine reflux at baseline, and decreased esophageal acid exposure ($P < .02$) and gastric acidity after dose escalation. Esophageal and intragastric pH parameters, off and on therapy, did not predict long-term symptom breakthrough.**

CONCLUSIONS: **In a prospective study of patients with chronic GERD, esophageal acid reflux was reduced greatly by LARS or esomeprazole therapy. However, patients receiving LARS had significantly greater reductions in 24-hour esophageal acid exposure after 6 months and 5 years. Esophageal and gastric pH, off and on therapy, did not predict long-term outcomes of patients. Abnormal supine acid exposure predicted esomeprazole dose escalation. ClinicalTrials.Gov identifier: NCT00251927 (available: http://clinicaltrials.gov/ct2/show/NCT00251927).**

Keywords: Clinical Trial; Proton Pump Inhibitor; Esophageal pH Monitoring; LOTUS Study.

Gastroesophageal reflux disease (GERD) is caused by the excessive exposure of esophageal mucosa to gastric acid.[1,2] Healing rates of reflux esophagitis (RE) relate to the level of control of esophageal acid exposure and reduction in gastric acidity.[3,4] Intragastric pH monitoring has been used to compare the effects of inhibitory agents on gastric acidity, on the basis that an effect on esophageal acid exposure translates into clinically relevant

Abbreviations used in this paper: **GERD, gastroesophageal reflux disease; LARS, laparoscopic antireflux surgery; LOTUS, Long-Term Usage of Esomeprazole vs Surgery for Treatment of Chronic Gastroesophageal Reflux Disease; PPI, proton pump inhibitor; RE, reflux esophagitis.**

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therapeutic gains.[5] The value of these pH parameters in a long-term clinical trial setting has not been assessed.

Proton pump inhibitors (PPIs) are the therapy of choice for patients with GERD.[6] In the long-term management of GERD, however, laparoscopic antireflux surgery (LARS) may be considered as an alternative. The results of the Long-Term Usage of Esomeprazole vs Surgery for Treatment of Chronic Gastroesophageal Reflux Disease (LOTUS) trial (ClinicalTrials.Gov identifier: NCT00251927) showed that LARS and individually adjusted doses of esomeprazole both achieved long-term control of chronic GERD.[7]

Several critical questions remain. Can PPI therapy control intraesophageal acid exposure over time? Can such therapy achieve the same level of acid reflux control as LARS and, if not, is the difference reflected in the level of symptom control achieved? Can intraesophageal and intragastric pH parameters off and on therapy predict long-term clinical outcome? The primary aim of this study was to compare 24-hour intraesophageal and intragastric pH parameters as objective measures of acid secretion and gastroesophageal reflux control. The secondary aim was to test the ability of these parameters to predict symptom control over 5 years, in patients randomized to LARS or esomeprazole.

Methods

This study was part of a prospective, randomized, open, parallel-group, multicenter trial (LOTUS) comparing the efficacy and safety of LARS with that of treatment with esomeprazole 20 or 40 mg/d (AstraZeneca R&D, Mölndal, Sweden) (as 22.3 or 44.5 mg of esomeprazole magnesium trihydrate, respectively) over 5 years in patients with chronic GERD.[7] pH monitoring was performed at baseline, 6 months, and 5 years, and the relationship with symptom severity during follow-up evaluation was compared with the need for esomeprazole dose escalation, as well as with treatment failures (which could occur at any time during follow-up evaluation). All authors had access to the study data and reviewed and approved the final manuscript.

Eligible patients had chronic GERD symptoms[1] and were considered suitable for, and willing to accept, both treatments. Exclusion criteria included the following: previous upper gastrointestinal surgery, Zollinger–Ellison syndrome, primary esophageal disorders, and other major comorbidities. The protocol was approved by the local ethics committees, and patients provided written informed consent.

Study Procedures

At enrollment, most patients were already on long-term PPI therapy. A 3-month run-in period was used to assess the clinical response to esomeprazole 40 mg once daily and responders were randomized to undergo LARS or to receive esomeprazole 20 mg once daily (increased stepwise to 40 mg once daily and then to 20 mg twice daily in the case of incomplete control of heartburn and regurgitation). After 8 weeks of run-in, esomeprazole was withdrawn for an investigational period of at least 7 days, whereupon baseline manometry and 24-hour pH monitoring, as well as endoscopy with biopsy specimens taken, were performed. RE was classified according to the Los Angeles classification.[8] Endoscopically suspected esophageal metaplasia was measured in axial extension and biopsy specimens were taken.[9]

After randomization, patients in the medical therapy arm started esomeprazole 20 mg once daily, whereas patients randomized to surgery took a dose of either esomeprazole 20 mg or 40 mg once daily while waiting for LARS, after which all acid-suppressive medication was withdrawn. At scheduled visits, all patients were asked "Do you have sufficient control of heartburn and acid regurgitation?" If a patient in the esomeprazole arm answered "no," the dose was increased to 40 mg once daily for 8 weeks and then, if necessary, to 20 mg twice daily for a further 8 weeks. If their response still was "no," the patient was defined as having a treatment failure. In the surgical arm, "treatment failure" occurred if the patient's response to this same question was "no" and they confirmed a need for medical therapy, or if there were postoperative symptoms needing medical therapy, dysphagia requiring repeated dilations, or perioperative or postoperative death occurred. Gastrointestinal symptoms over the preceding 3 days were recorded at each visit (including the day of pH measurement) and graded as none, mild, moderate, or severe.

Twenty-four–hour pH monitoring was repeated at 6 months and 5 years after randomization. Patients treated with medication were studied while on medication, whereas patients treated with surgery were always studied off acid-suppressive medication, even if symptoms had recurred.

Twenty-Four–Hour pH Monitoring Protocol

The esophageal electrode was placed 5 cm proximal to the lower esophageal sphincter. The results of pH monitoring were reported as the percentage of time of the total duration of the recording and of the time spent in upright and supine positions. Each recording was classified as normal or abnormal according to the reference values of each center; a recording was considered abnormal even if abnormal only when upright or supine. We also compared the number of periods with a pH less than 4.0 for longer than 5 minutes, and the duration of the longest reflux episode.

When possible, 2-channel intraesophageal and intragastric pH monitoring was performed, with the gastric pH electrode 15 cm distal to the esophageal pH electrode. Gastric acidity was assessed as the median 24-hour gastric pH and the percentage of time that the gastric

pH was greater than 4.0, as a proportion of the total duration of the recording. Most centers used Medtronic (Medtronic SA, Lausanne, Switzerland) or Orion II (Medical Measurement Systems BV, Enschede, The Netherlands) pH data storage units.

Statistical Analyses

Esophageal acid exposure data are not normally distributed.[10] Therefore, data from 24-hour pH monitoring were presented descriptively by medians and interquartile ranges, and comparisons between groups were performed using the Wilcoxon rank-sum test. The association between the severity of acid exposure at baseline and after 6 months on therapy and the subsequent breakthrough of reflux symptoms was assessed with the Spearman rank correlation. Baseline and 6-month pH data were compared for patients with or without treatment failure occurring during the subsequent course of the 5-year study period. Fractions were compared using the Fisher exact test.

Results

The number of patients randomized in the study was 554, and 372 patients completed the 5-year study period. Baseline pH recordings were available for 239 patients in the LARS group and 261 patients in the esomeprazole group. There were 267 patients with technically valid pH data at baseline, at the 6-month visit, and at the 5-year visit: 116 patients in the LARS group and 151 patients in the esomeprazole group. Baseline characteristics are detailed in Table 1.

Baseline Esophageal pH

At baseline, patients had been off study medication for a mean of 9.3 days. The median time with an esophageal pH less than 4.0 was 8.6% (range, 5.1%–16.1%) in the LARS group and 8.8% (range, 5.0%–13.4%) in the esomeprazole group (Figure 1*A*). Further details of baseline acid reflux variables are shown in Figure 1*B*–*D*. Patients later in need of an increased esomeprazole dose (40 mg/d) had a significantly higher percentage of time with a pH less than 4.0 in the supine position at baseline than patients who remained on 20 mg/d (median, 7.3% vs 1.7%; $P < .018$).

Intraesophageal pH After 6 Months and 5 Years on Therapy

Six months after randomization, the median proportion of time with an esophageal pH less than 4.0 was 0.7% (range, 0.2%–1.5%) in the LARS group and 2.1% (range, 1.0%–6.6%) in the esomeprazole group ($P < .001$) (Figure 1*A*). Acid exposure in the upright and supine positions after 6 months was 0.3% and 0.0%, respectively, in the LARS group, and 2.0% and 1.0%, respectively, in patients prescribed esomeprazole (both $P < .0001$). The median number of acid reflux episodes lasting more than 5 minutes at 6 months after randomization was 0 and 1 for patients treated with LARS and esomeprazole, respectively ($P < .0001$) (Figure 1*D*). In the esomeprazole arm, 138 patients received 20 mg/d and 13 patients were taking 40 mg/d at 6 months. The median proportion of time with an esophageal pH less than 4.0 over 24 hours was 2.0% in patients taking esomeprazole 20 mg/d and 3.6% ($P =$ NS) in patients who already had needed a dose escalation to 40 mg/d (Figure 2).

After 5 years, the median proportion of time with an esophageal pH less than 4.0 was similar to the 6-month recording in both groups (Figure 1*A*). This was also the case when acid reflux was subdivided into upright and supine reflux positions (Figure 1*B* and *C*). In the esomeprazole arm, 117 patients were taking 20 mg/d and 34 patients were taking 40 mg/d at 5 years. The median proportion of time with an esophageal pH less than 4.0 was not statistically different between patients whose symptoms were controlled throughout 5 years by taking esomeprazole 20 mg/d (2.2%) and patients taking 40 mg/d (1.9%) (Figure 2). Patients who increased their esomeprazole dosage between pH recordings experienced a significant reduction in the total time the esophageal pH was less than 4.0, from 4.2% to 1.7% ($P = .03$), and from 2.8% to 0.4% ($P = .051$) when assessed in the supine position.

After LARS, 90% and 89% of patients had normal esophageal acid exposure after 6 months and 5 years, respectively, compared with 66% and 72% on esomeprazole therapy ($P < .0001$).

Intragastric pH at Baseline, and After 6 Months and 5 Years on Therapy

Baseline intragastric pH recordings were available for 96 patients, after 6 months and 5 years. As seen in Figure 3, the proportion of time with a gastric pH greater than 4.0 showed only a small change between baseline, 6 months, and 5 years in the LARS group. In the esomeprazole group, corresponding values increased from 12.1% at baseline to approximately 60% after 6 months, and with no significant change after 5 years. Gastric acidity was similar in patients taking esomeprazole 20 mg/d and patients who had increased the dose to 40 mg/d (median pH, 4.7 and 5.0, respectively) (Figure 4). In the latter patients, the median gastric pH increased from 3.5 to 5.1 ($P =$ NS) (Supplementary Table 1).

pH Variables and Clinical Outcome Correlates

In the LARS arm, 8.5% of patients reported moderate-to-severe heartburn and 0.9% reported acid regurgitation of corresponding severity during the 3 days before

Table 1. Baseline Characteristics of Patients Investigated With pH Monitoring

	pH monitoring population			
	LARS (n = 116)	Esomeprazole (n = 151)	Total pH population (n = 267)	Total LOTUS study population (n = 554)
Sex, n (%)				
Male	82 (70.7)	127 (84.1)	209 (78.3)	398 (71.8)
Female	34 (29.3)	24 (15.9)	58 (21.7)	156 (28.2)
Age, *y*				
Mean (SD)	46.4 (10.6)	46.6 (11.0)	46.5 (10.8)	45.1 (11.2)
Median (range)	47 (21–69)	48 (23–69)	47 (21–69)	45 (18–72)
Ethnicity, n (%)				
Caucasian	115 (99.1)	150 (99.3)	265 (99.3)	552 (99.6)
Black	1 (0.9)	0	1 (0.4)	1 (0.2)
Oriental	0	1 (0.7)	1 (0.4)	1 (0.2)
Mean body mass index, kg/m^2	26.9	27.1	27.0	27.0
Current smoker, n (%)	30 (25.9)	31 (20.5)	61 (22.8)	139 (25.1)
Alcohol use, n (%)	68 (58.6)	113 (74.8)	181 (67.8)	344 (62.1)
Previous upper GI surgery, n (%)	1 (0.9)	2 (1.3)	3 (1.1)	11 (2.0)
Helicobacter pylori, n (%)	12 (10.3)	26 (17.2)	38 (14.2)	68 (12.3)
History of reflux symptoms, n (%)				
<1 y	2 (1.7)	3 (2.0)	5 (1.9)	10 (1.8)
1–5 y	34 (29.3)	46 (30.5)	80 (30.0)	188 (33.9)
>5 y	80 (69.0)	102 (67.5)	182 (68.2)	356 (64.3)
History of verified reflux disease, n (%)				
<1 y	34 (29.3)	48 (31.8)	82 (30.7)	164 (29.6)
1–5 y	63 (54.3)	76 (50.3)	139 (52.1)	281 (50.7)
>5 y	17 (14.7)	27 (17.9)	44 (16.5)	106 (19.1)
Unknown	2 (1.7)	0	2 (0.7)	3 (0.5)
Heartburn, n (%)				
None	46 (39.7)	63 (41.7)	109 (40.8)	194 (35.0)
Mild	26 (22.4)	33 (21.9)	59 (22.1)	133 (24.0)
Moderate	28 (24.1)	38 (25.2)	66 (24.7)	135 (24.4)
Severe	16 (13.8)	17 (11.3)	33 (12.4)	92 (16.6)
Acid regurgitation, n (%)				
None	58 (50.0)	80 (53.0)	138 (51.7)	257 (46.4)
Mild	22 (19.0)	35 (23.2)	57 (21.3)	114 (20.6)
Moderate	28 (24.1)	28 (18.5)	56 (21.0)	136 (24.5)
Severe	8 (6.9)	8 (5.3)	16 (6.0)	47 (8.5)
Los Angeles classification grade, n (%)				
A	36 (31.0)	36 (23.8)	72 (27.0)	135 (24.4)
B	28 (24.1)	42 (27.8)	70 (26.2)	135 (24.4)
C	5 (4.3)	8 (5.3)	13 (4.9)	20 (3.6)
D	1 (0.9)	0	1 (0.4)	1 (0.2)
No esophagitis	46 (39.7)	65 (43.0)	111 (41.6)	263 (47.5)
Hiatal hernia, n (%)	84 (72.4)	107 (70.9)	191 (71.5)	392 (70.8)
ESEM, n (%)	14 (12.1)	16 (10.6)	30 (11.2)	60 (10.8)
Esophageal acid exposure, % time pH < 4	8.6	8.8	8.7	8.5

ESEM, endoscopically suspected esophageal metaplasia; GI, gastrointestinal.

the 5-year visit, whereas in the esomeprazole arm, the corresponding numbers were 17.2% and 14.6%, respectively ($P = .047$, regurgitation, $P < .001$). Patients with mild-to-moderate heartburn (none had severe) at that time had a numerically higher percentage of time with acid exposure at 6 months than patients with no or mild heartburn (2.6% vs 1.9%; $P =$ NS). In total, 49 patients (among patients in the pH-metry cohort) experienced treatment failure during the 5 years of follow-up evaluation. Neither intraesophageal nor intragastric pH parameters at baseline were significantly different in patients with treatment failure from patients who remained in remission over the 5 years of follow-up evaluation (Figure 5).

Discussion

Comparisons between surgical and medical therapies are important when evaluating treatments for patients with chronic GERD; however, such comparisons seldom have been conducted in studies of adequate design and duration. We assessed data from a large randomized study comparing LARS and esomeprazole treatment in

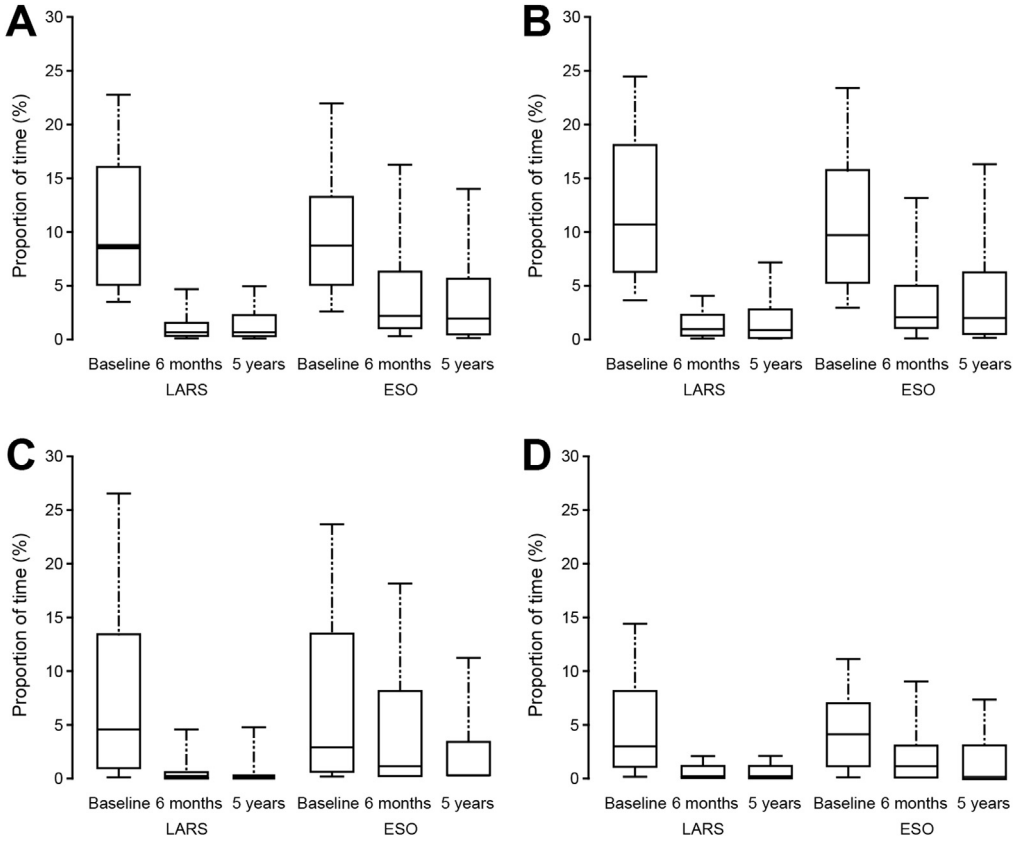

Figure 1. (*A*) Proportion of the total time with an esophageal pH less than 4.0. (*B*) Proportion of time in an upright position with an esophageal pH less than 4.0. (*C*) Proportion of time in a supine position with an esophageal pH less than 4.0. (*D*) Number of reflux episodes longer than 5 minutes in duration, in patients randomized to either LARS (n = 116) or esomeprazole (ESO) 20–40 mg/d (n = 151). The plots show the median value (*horizontal bar*), 25th and 75th quartiles (*box*), and 10th–90th percentile range (*whiskers*).

patients with GERD, with valid baseline, 6-month, and 5-year pH monitoring data available for 58% of patients.[7]

Long-term therapy with esomeprazole and LARS was effective in controlling esophageal acid exposure; significant reductions were observed in the proportion of time with an esophageal pH less than 4.0, as well as the number of long-lasting reflux episodes, with group median values suppressed to the normal range. LARS resulted in significantly less esophageal acid exposure during the total 24-hour period, as well as during the time spent in an upright or supine position than esomeprazole treatment.

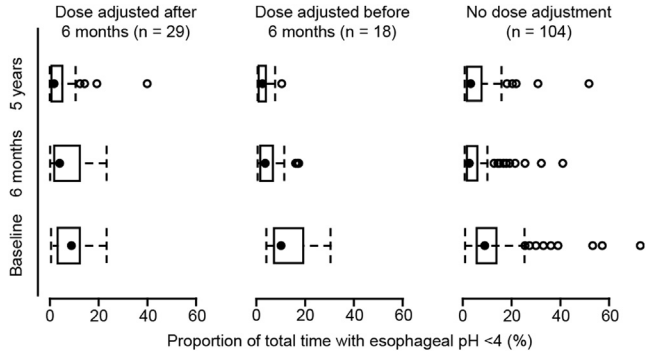

Figure 2. Proportion of the total time with an esophageal pH less than 4.0 at baseline, and at 6 months and 5 years after treatment allocation, in patients randomized to esomeprazole, with a dose adjustment before or after 6 months, or without a dose adjustment. The plots show the median value (*horizontal dotted line*), 25th and 75th quartiles (*box*), and 10th–90th percentile range (*whiskers*).

The reduction in acid exposure observed at 6 months was maintained at 5 years in both treatment groups; indeed, there were more patients with normal levels of acid exposure after 5 years than after 6 months, which may be explained by the adjustment of esomeprazole to a daily dose of 40 mg in some patients.

The greatest difference between the 2 treatment groups was observed in esophageal acid exposure when

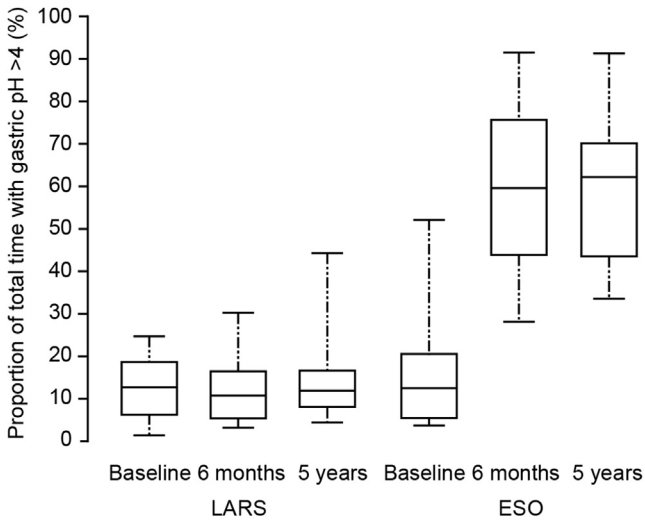

Figure 3. Proportion of the total time with a gastric pH greater than 4.0 in patients randomized to either LARS (n = 36) or esomeprazole (ESO) (n = 60). The plots show the median value (*horizontal bar*), 25th and 75th quartiles (*box*), and 10th–90th percentile range (*whiskers*).

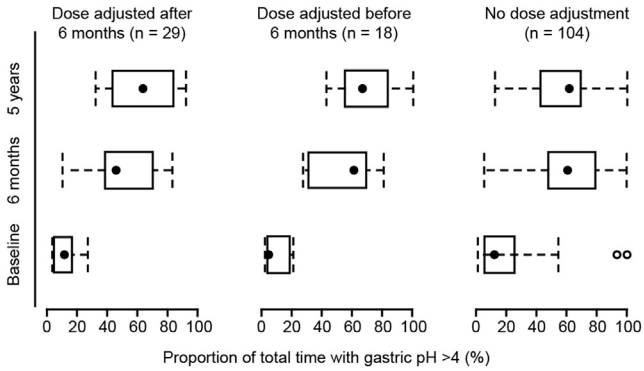

Figure 4. Proportion of the total time with a gastric pH greater than 4.0 at baseline, and at 6 months and 5 years after treatment allocation, in patients randomized to esomeprazole, with or without dose adjustment. The plots show the median value (*horizontal dotted line*), 25th and 75th quartiles (*box*), and 10th–90th percentile range (*whiskers*).

the patient was supine, suggesting that once-daily dosing of esomeprazole 20 mg, despite its significantly longer duration of action than other PPIs,[11] was inadequate to control gastric acidity overnight in a proportion of patients with supine reflux. Nocturnal gastric acid breakthrough[12] has been associated with long-lasting episodes of esophageal acid exposure, and has been implicated in PPI treatment failure.[12,13] We found only a weak

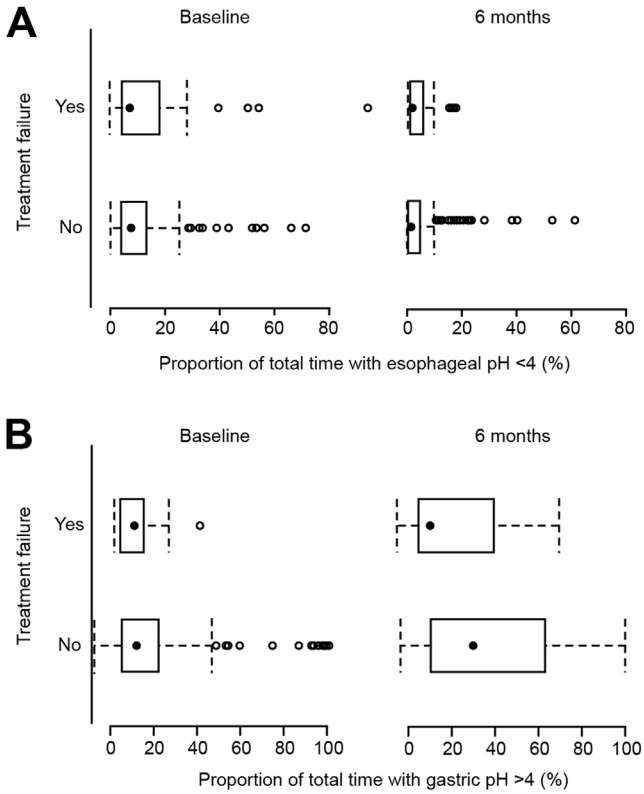

Figure 5. Proportion of the total time with (*A*) an esophageal pH less than 4.0 and (*B*) a gastric pH greater than 4.0 at baseline, and at 6 months after treatment allocation, in patients classed as having treatment failure or not. The plots show the median value (*horizontal bar*), 25th and 75th quartiles (*box*), and 10th–90th percentile range (*whiskers*).

association between esophageal acid exposure and gastric acidity, which probably is the result of most patients having predominantly daytime reflux.

Despite the wide variation that we observed in the esophageal acid exposure values at 6 months and 5 years, most patients had sufficient symptom control over time. A recent study reported that among patients with GERD rendered asymptomatic on PPI therapy, most patients continued to have abnormal esophageal acid exposure.[14] Patients with moderate–severe heartburn had higher acid exposure, a difference that was not statistically significant, perhaps owing to the low number of symptomatic patients. This suggests that an improvement (rather than a normalization) of esophageal pH could be a sufficient goal of therapy. The level of acid reflux control needed to alleviate symptoms and heal RE may differ among individuals owing to variations in factors such as mucosal sensitivity to acid, reflux pattern, volume and proximal extent of refluxate, and gastric emptying. It has been found that reflux symptom control after partial fundoplication is similar to that after a 360° fundoplication,[15] although acid reflux is eradicated only by the latter,[16,17] supporting the notion that it is unnecessary to reduce gastroesophageal reflux beyond a normal level in most patients.[18] Similarly, treatment with the potassium channel blocker AZD0865 resulted in significantly better control of gastric acidity and tended to reduce gastroesophageal reflux more than esomeprazole 20 mg/d, but provided no better symptom control.[19]

Previous studies have found an enhanced suppressive effect of esomeprazole 40 mg/d compared with 20 mg/d on intragastric acidity.[5] We found that those patients who needed an increase in dosage had a further significant reduction in esophageal acid exposure, as well as reduced gastric acidity (to a level similar to patients who did not require a dose increase). Heartburn and regurgitation were reduced to clinical remission. The need for the higher dose probably reflects individual differences in pharmacokinetics and also in acid reflux pattern, given that patients in need of increased esomeprazole doses had significantly more severe supine reflux at baseline than patients not requiring a dose increase.

It is likely that the longer duration of action of the higher esomeprazole dose, whether administered as a morning dose or as a split dose, reduces night-time reflux owing to nocturnal acid breakthrough.[11,20,21] From a pragmatic clinical perspective, however, it is doubtful whether ambulatory pH recordings have a role in identifying patients who are in need of dose adjustments at different stages of therapy.

The pharmacodynamic measurement of gastric acid control has been used as a proxy to assess the potential clinical efficacy of acid-suppressant medications.[5,11,22] An association has been shown between intragastric pH control and healing or prevention of relapse of healed RE.[4] However, the link between gastric pH and symptom control and clinical remission has not been well established.[23] Intragastric pH studies that have considered

outcomes did not assess a symptom relief end point,[3,4,24] suggesting that well-designed, long-term studies are needed to elucidate the link between GERD symptoms, acid-suppressive therapy, and 24-hour gastric pH profiles.

When we compared symptom control during esomeprazole therapy or after LARS, only weak associations were found with esophageal acid exposure and, in patients treated with esomeprazole, also with gastric acidity. This casts doubt on the relevance of intraesophageal and intragastric pH parameters for predicting clinical outcomes. It should be pointed out that the intragastric electrode was not positioned in relation to the "acid pocket" of the proximal stomach,[25] which is often the source of the refluxate. It is possible that even larger trials are required to determine whether pH parameters can predict the long-term course of GERD and therapy outcome. It seems pertinent at present to conclude that neither intraesophageal nor intragastric pH monitoring, at baseline or on therapy, can identify patients reliably who will experience treatment failure.

The proportion of time that the esophageal pH is less than 4.0 is the established parameter for diagnosing abnormal gastroesophageal acid reflux and residual acid reflux in treatment-resistant patients. Gerson et al[26] showed that more patients had normal esophageal acid exposure when taking PPIs if integrated esophageal acidity (taking account of the duration and acidity of reflux episodes) was analyzed. The use of this parameter might have reduced the reported difference in acid reflux control between our esomeprazole and LARS groups. Impedance pH-metry provides data on reflux irrespective of the pH of the refluxate, and weakly acidic reflux might explain residual symptoms in more patients. The low number of patients who failed therapy reduced our ability to analyze pH parameters as predictors of treatment failure.

In conclusion, both esomeprazole and LARS are effective in achieving and maintaining a reduction in distal esophageal acid exposure to a normal level. LARS nearly abolished gastroesophageal acid reflux, which probably explains the elimination of some remaining minor GERD symptoms. We found that neither intragastric nor intraesophageal pH parameters could predict the short- and long-term therapeutic outcome, which indicates that response to therapy in patients with GERD is individual and not related directly to normalization of acid reflux parameters alone.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at http://dx.doi.org/10.1016/j.cgh.2015.07.025.

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See the Appendix for a complete list of the Long-Term Usage of Esomeprazole vs Surgery for Treatment of Chronic Gastroesophageal Reflux Disease Study Group members.

Conflicts of interest
The authors disclose the following: Jan Hatlebakk is a member of the steering committee for Long-Term Usage of Esomeprazole vs Surgery for Treatment of Chronic Gastroesophageal Reflux Disease (LOTUS); Frank Zerbib has served as a consultant and/or speaker for Given Imaging, Shire, and Mederi Therapeutics; Stanislas Bruley des Varannes has served as a consultant and/or speaker for Given Imaging; Stephen Attwood is a member of the steering committee for LOTUS, a speaker for AstraZeneca, and was a previous speaker for Ethicon Endosurgery; Christian Ell receives research grants from AstraZeneca, Fujinon, ERBE, and Hitachi; Roberto Fiocca has received travel and related expenses for attending study-associated meetings and his institution received a grant from AstraZeneca for central histologic analyses; Jean-Paul Galmiche has served as a consultant for AstraZeneca, MKT, Shire, and Given Imaging; Stefan Eklund and Göran Långström are employees of AstraZeneca R&D (Mölndal, Sweden); Tore Lind is a consultant and former employee of AstraZeneca R&D (Mölndal, Sweden); and Lars Lundell is a member of the steering committee for LOTUS.

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Appendix

List of Principal Investigators at Each Center and Country Coordinators

Austria	Vienna	Universitätsklinik für Chirurgie	Johannes Miholic (country coordinator)
	Linz	Allgemeines Krankenhaus Linz	Rainer Hubmann Jan Danis (country coordinator)
Belgium	Leuven	UZ Gasthuisberg	Jan Tack Toni Lerut (country coordinator)
	Brussels	UCL Saint-Luc	Hubert Piessevaux
	Brussels (Anderlecht)	Hôpital Erasme–Clinique Universitaire Bruxelles	Jacques Devière
	Brussels	Centre Hospitalier Universitaire Saint-Pierre	Michel Buset
	Brussels	Clinique Saint-Jean	Cristiano Chioccioli
	Gent	UZ Gent	Danny De Looze
	Liège	Cliniques Saint-Joseph	Jean-Claude Demoulin
	Liège	Centre Hospitalier Universitaire Sart Tilman	Edouard Louis
	Haine-Saint-Paul	Centre Hospitalier Jolimont	Jean-Michel Ghilain Jean-Marc Maisin
Denmark	Århus	Århus Universitetshospital	Peter Funch-Jensen (country coordinator)
	Viborg	Regionshospitalet Viborg	Jørn Nielsen
	Herning	Regionshospitalet Herning	Lars Christensen
	Kolding	Kolding Sygehus	Henning Antonsen
	Odense	Odense Universitetshospital	Karsten Lauritsen
	Hillerød	Hillerød Hospital	Per Jess
	Glostrup	Glostrup Hospital	Lene Wallin
	Hvidovre	Hvidovre Hospital	Lars Naver
France	Nantes	Centre d'Investigation Clinique de Nantes	Jean-Paul Galmiche (country coordinator) Eric Letessier
	Bordeaux	Groupe Hospitalier Saint André	Frank Zerbib
	Grenoble	CHU de Grenoble	Bruno Bonaz Richard Bost
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Germany	Würzburg	Würzburg, Universitätsklinikum	Martin Fein Jörn Maroske
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	Hamburg	Israelitisches Krankenhaus Hamburg	Carsten Zornig
	Tübingen	Klinikum der Eberhard-Karls-Universität	Joachim Helmut Schneider
	München	München, Ludwig-Maximilians-Universität LMU, Chirurgie Poliklinikum	Thomas Hüttl
	Heidelberg	Universitätsklinikum Heidelberg	Markus Büchler
	Dresden	Universitätsklinikum Carl-Gustav-Carus an der TU Dresden	Ursula Wehrmann

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	Bochum	Schwerpunktpraxis Gastro-enterologie Praxis Kemen and Schmidt-Heinevetter	Solveig Kemen
	Herne	Internistische Praxisgemeinschaft	Dieterich Hüppe
Iceland	Reykjavik	Landspitali, University Hospital	Margrét Oddsdóttir (country coordinator) Bjarni Thjodleifsson (country coordinator)
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	Rozzano (Mi)	Istituto Clinico Humanitas	Riccardo Rosati
	Brescia	Spedali Civili di Brescia	Renzo Cestari
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Norway	Bergen	Helse Bergen HF Haukeland Universitetssykehus	Jan Hatlebakk (country coordinator)
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Supplementary Table 1. Time With pH Less Than 4.0 as a Proportion of Total Time, Time Upright, and Time Supine, and Median Gastric pH and Proportion of Time With pH Greater Than 4.0 in Patients Randomized to Treatment with Esomeprazole

	Group A, 20 mg/d for 6 months and 5 years (n = 115)	Group B, 40 mg/d for 6 months and 5 years (n = 11)	Group C, 20 mg/d for 6 months; 40 mg/d for 5 years (n = 23)
Proportion of total time with esophageal pH < 4.0, %			
Baseline	8.0	10.4	9.2
6 months	1.9	3.7	4.2
5 years	2.2	2.1	1.7
Proportion of time upright with esophageal pH < 4.0, %			
Baseline	9.8	11.3	8.7
6 months	1.8	2.8	2.5
5 years	2.0	2.9	1.3
Proportion of time supine with esophageal pH < 4.0, %			
Baseline	1.7	11.1	4.8
6 months	0.7	1.5	2.8
5 years	0.3	0.0	0.4
Median gastric pH[a]			
Baseline	1.6	1.3	1.5
6 months	4.8	4.9	3.5
5 years	4.6	4.7	5.1
Proportion of time with gastric pH > 4.0, %[b]			
Baseline	11.5	4.6	9.2
6 months	59.5	59.3	42.4
5 years	58.9	70.4	64.8

NOTE. Group A was in clinical remission throughout the study on esomeprazole 20 mg/d; group B needed an increase in esomeprazole dose from 20 to 40 mg/d before the 6-month pH monitoring; and group C had an increase in esomeprazole dose from 20 to 40 mg/d after the 6-month pH monitoring. Group median values are shown.

[a]Data were available for 65 patients.

[b]Data were available for 70 patients.