Laparoscopic Antireflux Surgery vs Esomeprazole Treatment for Chronic GERD

The LOTUS Randomized Clinical Trial

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Context Gastroesophageal reflux disease (GERD) is a chronic, relapsing disease with symptoms that have negative effects on daily life. Two treatment options are long-term medication or surgery.

Objective To evaluate optimized esomeprazole therapy vs standardized laparoscopic antireflux surgery (LARS) in patients with GERD.

Design, Setting, and Participants The LOTUS trial, a 5-year exploratory randomized, open, parallel-group trial conducted in academic hospitals in 11 European countries between October 2001 and April 2009 among 554 patients with well-established chronic GERD who initially responded to acid suppression. A total of 372 patients (esomeprazole, n=192; LARS, n=180) completed 5-year follow-up.

Interventions Two hundred sixty-six patients were randomly assigned to receive esomeprazole, 20 to 40 mg/d, allowing for dose adjustments; 288 were randomly assigned to undergo LARS, of whom 248 actually underwent the operation.

Main Outcome Measure Time to treatment failure (for LARS, defined as need for acid suppressive therapy; for esomeprazole, inadequate symptom control after dose adjustment), expressed as estimated remission rates and analyzed using the Kaplan-Meier method.

Results Estimated remission rates at 5 years were 92% (95% confidence interval [CI], 89%-96%) in the esomeprazole group and 85% (95% CI, 81%-90%) in the LARS group (log-rank $P=.048$). The difference between groups was no longer statistically significant following best-case scenario modeling of the effects of study dropout. The prevalence and severity of symptoms at 5 years in the esomeprazole and LARS groups, respectively, were 16% and 8% for heartburn ($P=.14$), 13% and 2% for acid regurgitation ($P<.001$), 5% and 11% for dysphagia ($P<.001$), 28% and 40% for bloating ($P<.001$), and 40% and 57% for flatulence ($P<.001$). Mortality during the study was low (4 deaths in the esomeprazole group and 1 death in the LARS group) and not attributed to treatment, and the percentages of patients reporting serious adverse events were similar in the esomeprazole group (24.1%) and in the LARS group (28.6%).

Conclusion This multicenter clinical trial demonstrated that with contemporary antireflux therapy for GERD, either by drug-induced acid suppression with esomeprazole or by LARS, most patients achieve and remain in remission at 5 years.

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GASTROESOPHAGEAL REFLUX disease (GERD) is a highly prevalent disorder caused by the reflux of gastric contents into the esophagus. It is a chronic, relapsing disease that negatively affects patients' health-related quality of life and reduces work productivity.[1-3] Consequently, a long-term management plan is required for each individual patient. Maintenance treatment with proton pump inhibitor (PPI) therapy may be an option, offering high rates of symptom resolution and healing of esophagitis.[4-6] However, some patients are reluctant to take long-term medication and may prefer to have antireflux surgery. A number of controlled studies have been undertaken comparing open antireflux surgery and laparoscopic antireflux surgery (LARS)[7] or open antireflux surgery and pharmaceutical treatment,[8,9] but few stud-

See also Patient Page.

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ies have compared pharmaceutical treatment with LARS, particularly over a longer term. Additionally, most of these comparisons included relatively small sample sizes and did not use optimized drug dosing or carefully controlled laparoscopic surgical techniques.[10-13]

The LOTUS (Long-Term Usage of Esomeprazole vs Surgery for Treatment of Chronic GERD) trial compared maintenance therapy provided by esomeprazole (dose-adjusted when required) with standardized LARS in patients who responded well to acid-suppressive therapy. Herein, we report the final results of the 5-year follow-up for the LOTUS trial.

METHODS

Study Design and Objectives

The LOTUS trial was an exploratory randomized, open, parallel-group, multicenter study conducted in 11 European countries between October 2001 and April 2009. The primary objective was to evaluate maintenance therapy with esomeprazole (in patients tested to be responsive to the medication) vs LARS performed by experts.

Patients were aged 18 to 70 years and had chronic symptomatic GERD. The diagnosis of GERD was established on the basis of typical clinical history and presence of esophageal mucosal breaks at endoscopy, classified by Los Angeles grade, and/or pathological pH-metry. Assessments included endoscopy with biopsy, 24-hour pH-metry and symptom response to esomeprazole. The participating centers had to be either academic units or affiliated with a university; each center participated in training sessions to ensure that operative procedures were conducted or supervised by a consultant surgeon who specialized in this type of laparoscopic upper gastrointestinal tract surgery; and surgical techniques were standardized[14] across centers. All patients had to be eligible for both LARS and pharmaceutical therapy and were randomized in blocks of 4 consecutive patient numbers to either treatment. Participants were not permitted to switch treatment groups if they requested the alternative treatment; patients had to leave the study to receive the alternative treatment. Protocol approval for this trial was obtained from local ethics committees. Written informed consent was obtained from all patients.

Because sustained resolution of reflux symptoms with esomeprazole treatment occurs in approximately 70% of patients with GERD,[15] a 3-month run-in period was required to verify the clinical response to esomeprazole, 40 mg/d, and only those who responded were randomized. Partial responders or patients refractory to treatment were excluded. This 3-month run-in period also allowed baseline assessments. Patients were required to have no more than Los Angeles grade B esophagitis at baseline and no more than mild heartburn or regurgitation at the end of 3 months of esomeprazole treatment to permit randomization. Symptom severity was classified as none, mild (awareness of symptoms but easily tolerated), moderate (discomfort sufficient to cause interference with normal activities), or severe (incapacitating, with inability to perform normal activities).

Responders were randomly assigned to undergo LARS or to receive esomeprazole, 20 mg once per day, increased stepwise to 40 mg once per day then 20 mg twice per day in case of incomplete control of heartburn and regurgitation. Full details of the protocol are described in the report of the interim 3-year results.[16] Patients visited the clinic 6 months after randomization and every 6 months thereafter. Follow-up endoscopy was planned at 1, 3, and 5 years. At endoscopy, the esophagus, cardia region, stomach, and duodenum were examined and biopsies were repeated.[17] Patients underwent pH-metry at baseline and again at 6 months and 5 years.[18]

Symptoms related to GERD were assessed at every visit, during which the investigator asked standardized questions about heartburn, acid regurgitation, epigastric pain, bloating, flatulence, diarrhea, and dysphagia severity. In addition, patients in the LARS group were asked about other gastrointestinal symptoms such as ability to vomit and ability to belch. Health-related quality of life and patient-reported symptoms were assessed by administering the validated Quality of Life in Reflux and Dyspepsia (QOLRAD) and Gastrointestinal Symptom Rating Scale (GSRS) questionnaires to patients at randomization and annually thereafter. Translations of the questionnaires into different languages were performed according to proposed guidelines and involved several independent translators.

During the follow-up period, patients in both treatment groups who experienced moderate to severe recurrent GERD symptoms for at least 3 consecutive days were instructed to contact the clinic. They were then questioned about their symptom control and need for other regular medication and were offered endoscopy.

Treatment End Points and Statistical Analyses

The main analysis was conducted using the intention-to-treat population comprising all randomized patients. Including patients randomized to undergo surgery but not operated on had little influence on the primary analysis because they were censored early.

The primary end point in this study, time to treatment failure, was defined as follows for the 2 study treatments.

In the esomeprazole group, the need for escalation in treatment for control of reflux disease was assessed at clinic visits by asking "Do you have sufficient control of your heartburn and acid regurgitation?" If the answer was no and the patient stated a need for other regular drug therapy, the dose of esomeprazole was increased to 40 mg once per day for 8 weeks and could be adjusted to 20 mg twice per day for a further 8 weeks if symptoms had not resolved. If this proved insufficient to control symptoms, the patient was classified as having had treatment failure.

The same questions were asked at clinic visits about symptom control in the LARS group, and if the answer was no and was backed up by a need for treatment with acid-suppressive drugs, the patient was classified as having had treatment failure. Patients were also classified as having had treatment failure if they had postoperative symptoms requiring medical action, perioperative death, postoperative death within 30 days of surgery, dysphagia requiring further treatment, or any other requirement to reoperate for symptom control. In the case of functional esophageal postoperative stenosis, 1 dilatation was allowed.

Time to treatment failure/censoring was defined as number of days between randomization and last visit for all participants within 5 years after randomization, regardless of reason for discontinuation or reason for visit. For patients who never returned for a visit, time of censoring was set as 0. As an exploratory analysis, the Kaplan-Meier method was used to estimate the proportion of patients in remission over time and, as specified in the study protocol, the log-rank test was used to test the statistical significance of the observed difference between the treatment groups. A per-protocol analysis was also performed on the primary end point and included all randomized patients except those with major protocol violations.[16]

In addition, to test the robustness of our main analysis, best- and worst-case outcomes scenarios were analyzed with censored patients considered to have had either treatment failures or treatment successes and after excluding censored patients.

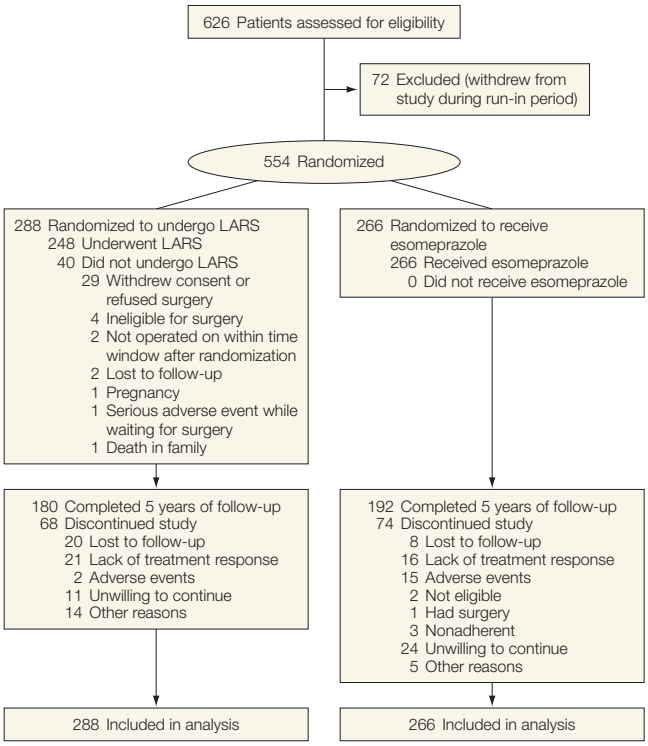
Secondary variables were presented descriptively and analyzed only for the intention-to-treat population, without any analysis of missing data. There were no adjustments for multiple comparisons because of the exploratory character of the study.

In a post hoc analysis, severity of GERD symptoms (none = 0; mild = 1; moderate = 2; and severe = 3) reported at 5 years was compared between treatments using a 2-sided Wilcoxon rank sum test. The safety population included all patients who received at least 1 dose of study drug and from whom postdose data were available.

This study was not designed as a superiority or equivalence trial but, rather, was an exploratory study to estimate the efficacy of LARS and PPI treatment in PPI responders. The sample size was determined by assuming that the true rate of treatment success (ie, patients who did not experience treatment failure within 5 years) would be at least 70% for both treatments. With 275 patients in each group, the true difference between the treatments was estimated not to differ from the observed difference by more than 8 percentage points with a probability of 95%. Thus, the sample size was derived to give a specific length of the confidence interval (CI) between the proportions of treatment success in the 2 treatment groups. The computation is based on the normal approximation for a continuity-corrected interval.[19] In an exploratory analysis, the log-rank test was used to test for the superiority of the observed difference between the treatment groups.

Statistical analyses were performed using SAS version 8.2 (SAS Institute Inc, Cary, North Carolina).

Figure 1. Patient Flow in the LOTUS Trial



LARS indicates laparoscopic antireflux surgery.

RESULTS

Study Population

A total of 626 patients completed enrollment for the study, of whom 554 were randomized, 288 to undergo LARS (40 of whom were not operated on) and 266 to receive esomeprazole. The reasons for the 40 patients who were not operated on were as follows: 29 withdrew consent or refused surgery; 4 were considered ineligible for surgery; 2 were not operated on within the time window after randomization; 2 were lost to follow-up; 1 was pregnant; 1 had a serious adverse event while waiting for surgery; and 1 had a death in the family. The demographic characteristics of

these 40 patients did not differ substantially from the other randomized patients in the study. The flow of patients included in the study and reasons for withdrawal at each stage are summarized in FIGURE 1. Of the 248 patients in the LARS group, 180 (73%) completed the 5-year follow-up visit and 68 discontinued the study before the 5-year visit, 33 of whom met the primary end point of treatment failure. In the esomeprazole group, 192 of the 266 patients (72%) completed 5-year follow-up and 74 discontinued, 19 of whom had treatment failure. Thus, the total discontinuation rate at 5 years for participants randomized to the LARS group (including the 40 who did not undergo surgery) was 108 of 288 (38%) and for participants randomized to the esomeprazole group was 74 of 266 (28%). In violation of the protocol, 1 participant in the esomeprazole was operated on by a surgeon who was not aware of the study at a time when the investigator was on vacation. This patient was withdrawn from the study subsequently.

Demographic characteristics and GERD disease history for participants in each treatment group are presented in TABLE 1. The 2 groups were well matched with regard to both demographics and history and current symptoms of GERD.

Table 1. Patient Demographics and Baseline Characteristics[a]

Characteristics	Laparoscopic Antireflux Surgery (n = 288)	Esomeprazole (n = 266)
Age, mean (SD), y	45 (10.9)	45 (11.5)
Male	199 (69)	199 (75)
Body mass index, mean (SD)[b]	27 (3.7)	27 (4.4)
Current smokers	81 (28)	58 (22)
Alcohol use	168 (58)	176 (66)
Previous upper gastrointestinal tract surgery	5 (1.7)	6 (2.3)
History of reflux symptoms, y		
<1	7 (2.4)	3 (1.1)
1-5	97 (34)	91 (34)
>5	184 (64)	172 (65)
Duration of verified reflux disease, y		
<1	84 (29)	80 (30)
1-5	146 (51)	135 (51)
>5	56 (19)	50 (19)
Heartburn severity		
None	102 (35)	92 (35)
Mild	72 (25)	61 (23)
Moderate	70 (24)	65 (24)
Severe	44 (15)	48 (18)
Regurgitation severity		
None	132 (46)	125 (47)
Mild	62 (22)	52 (20)
Moderate	70 (24)	66 (25)
Severe	24 (8)	23 (9)
Los Angeles grade of esophagitis		
No esophagitis	135 (47)	130 (49)
Grade A	79 (27)	56 (21)
Grade B	64 (22)	71 (27)
Grade C	10 (3.5)	10 (3.8)
Grade D	1 (0.3)	0
Abnormal 24-h esophageal pH	209 (73)	200 (75)
Endoscopic suspicion of esophageal metaplasia	32 (11.1)	28 (10.5)
Hiatal hernia	204 (71)	188 (71)
Helicobacter pylori–positive status	30 (10.4)	39 (14.3)

[a] Data are expressed as No. (%) of participants unless otherwise indicated.
[b] Body mass index is calculated as weight in kilograms divided by height in meters squared.

Treatment Efficacy

Time to Treatment Failure. Time to treatment failure, the primary efficacy variable, is presented as Kaplan-Meier plots for the intention-to-treat population in FIGURE 2. At 5 years, an estimated 85% (95% CI, 81%-90%) in the LARS group and an estimated 92% (95% CI, 89%-96%) in the esomeprazole group remained in remission (log-rank $P = .048$). There were 33 treatment failures in the LARS group (29 patients required other treatment to control reflux symptoms, 1 needed more than 1 dilatation, and 3 had postfundoplication adverse events including 1 gastric perforation and 2 with severe flatulence, bloating, and diarrhea) compared with 19 treatment failures in the esomeprazole group (all failures of symptom resolution). The results of the per-protocol analysis were similar: 85% (95% CI, 80%-90%) remission in the LARS group and 94% (95% CI, 91%-98%) remission in the esomeprazole group at 5 years (ie, 30 vs 12 treatment failures respectively; $P = .004$).

When best- and worst-case scenario case analyses were applied, the remission rates were 88.5% (95% CI, 84.1%-91.9%) in the LARS group and 92.9% (95% CI, 88.9%-95.5%) in the esomeprazole group, for a treatment difference of 4.3% (95% CI, –0.9% to 8.5%) when all censored patients were considered to have successful treatment. Corresponding rates when all censored cases were considered treatment failures were 61.5% (95% CI, 55.5%-67.1%) in the LARS group and 71.8% (95% CI, 65.9%-77.0%) in the esomeprazole group, for a treatment difference of 10.3% (95% CI, 2.2%-18.5%). When all censored patients were excluded from the analysis, the estimated remission rates were 84.3% (95% CI, 78.5%-88.8%) in the LARS group and 91.0% (95% CI, 86.0%-94.3% in the

esomeprazole group, for a mean treatment difference of 6.7% (95% CI, –0.1% to 13.4%).

The percentages of patients in the esomeprazole group who required an increased dose of esomeprazole to control their symptoms were similar for each year during the study; at 5 years, 23.1% of patients were receiving an increased dose (16.5% were taking 40 mg once per day and 6.6% were taking 20 mg twice per day).

GERD and Postoperative Symptoms. The prevalence and severity of GERD symptoms reported by patients at each clinic visit throughout the study is shown in FIGURE 3. The esomeprazole group showed similar levels of heartburn and regurgitation from baseline up to 5 years, while both symptoms decreased in the LARS group after randomization. At 5 years, acid regurgitation was significantly worse in the esomeprazole group than in the LARS group (13% vs 2%, respectively; $P<.001$), although there was no significant difference between the groups in the severity of heartburn (16% vs 8%; $P=.14$), epigastric pain (18% vs 18%; $P=.55$), or diarrhea (15% vs 16%; $P=.25$). At 5 years, dysphagia remained significantly more common in the LARS group than in the esomeprazole group (11% vs 5%, respectively; $P<.001$), as did bloating (40% vs 28%, respectively; $P<.001$) and flatulence (57% vs 40%, respectively; $P<.001$).

Endoscopic Findings. At 5 years, esophagitis of Los Angeles grades A, B, or C was observed in 12, 5, and 1 patients in the LARS group and in 16, 7, and 2 patients in the esomeprazole group, respectively. The percentage of patients in the esomeprazole group with hiatal hernia remained consistent over 5 years and was present in 62% at 5 years compared with 6% in the LARS group. The presence of stricture decreased in both treatment groups throughout the study, with 5 reported during the run-in period (3 in the esomeprazole group and 2 in the LARS group) and 2 after operation in the LARS group.

Endoscopic suspicion of esophageal metaplasia was present in 11.1% (32/288) of the LARS group and in 10.5% (28/266) of the esomeprazole group at entry, and its prevalence at 5 years remained stable in both study groups (13.6% [22/162] and 9.3% [17/183], respectively).

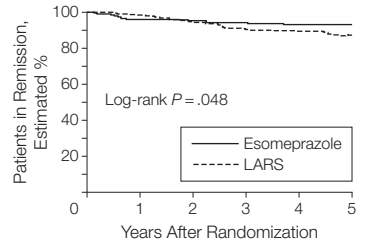
pH-Metry. Complete pH data were available for approximately 70% of the participants who were still in follow-up at 5 years. Baseline intraesophageal acid exposure was similar for the 2 treatment groups; the median percentage of time that pH was below 4 (upright plus recumbent) was 8.6% in the LARS group and 8.8% in the esomeprazole group. At 5 years, exposure time had decreased to 0.7% in the LARS group and to 1.9% in the esomeprazole group. The mean percentage of time with raised intragastric pH (>4) increased from 12.1% at baseline to 62.1% at 5 years in the esomeprazole group, while in the LARS group it remained fairly stable, decreasing slightly from 12.4% at baseline to 11.4% at 5 years.

Health-Related Quality of Life. QOLRAD scores on the food and drink and vitality dimensions as well as scores on the GSRS reflux dimension were the most abnormal at entry and the most sensitive to change with treatment. The mean scores for all dimensions improved in both groups and remained close to values observed in a healthy population (eTable 1; available online at http://www.jama.com).

Safety

There was no perioperative mortality and only 3% of patients had in-hospital morbidity. Serious adverse events were reported by 28.6% of patients who underwent LARS (n=248) and by 24.1% of the esomeprazole group (n=266) over 5 years (TABLE 2). Five patients had serious adverse events during the study that led to death either during the study (3 patients in the esomeprazole group, 1 of whom had pneumonia and 2 of whom had pancreatic carcinoma) or after the study (1 patient in the LARS group who had a malignant lung neoplasm and 1 patient in the esomeprazole group who had a fall that led to traumatic brain injury and femur and pelvic fracture). Further details of serious adverse events are shown in eTable 2. Laboratory variables monitored throughout the study are summarized in Table 2. Mean gastrin and chromogranin levels were elevated in patients treated with esomeprazole, as expected after long-term acid suppression. They appeared to stabilize after 3 years. No clinically relevant changes were noted in other laboratory variables.

Figure 2. Time to Treatment Failure



No. at risk

Esomeprazole	266	228	217	205	199	181
LARS	288	231	216	202	192	168

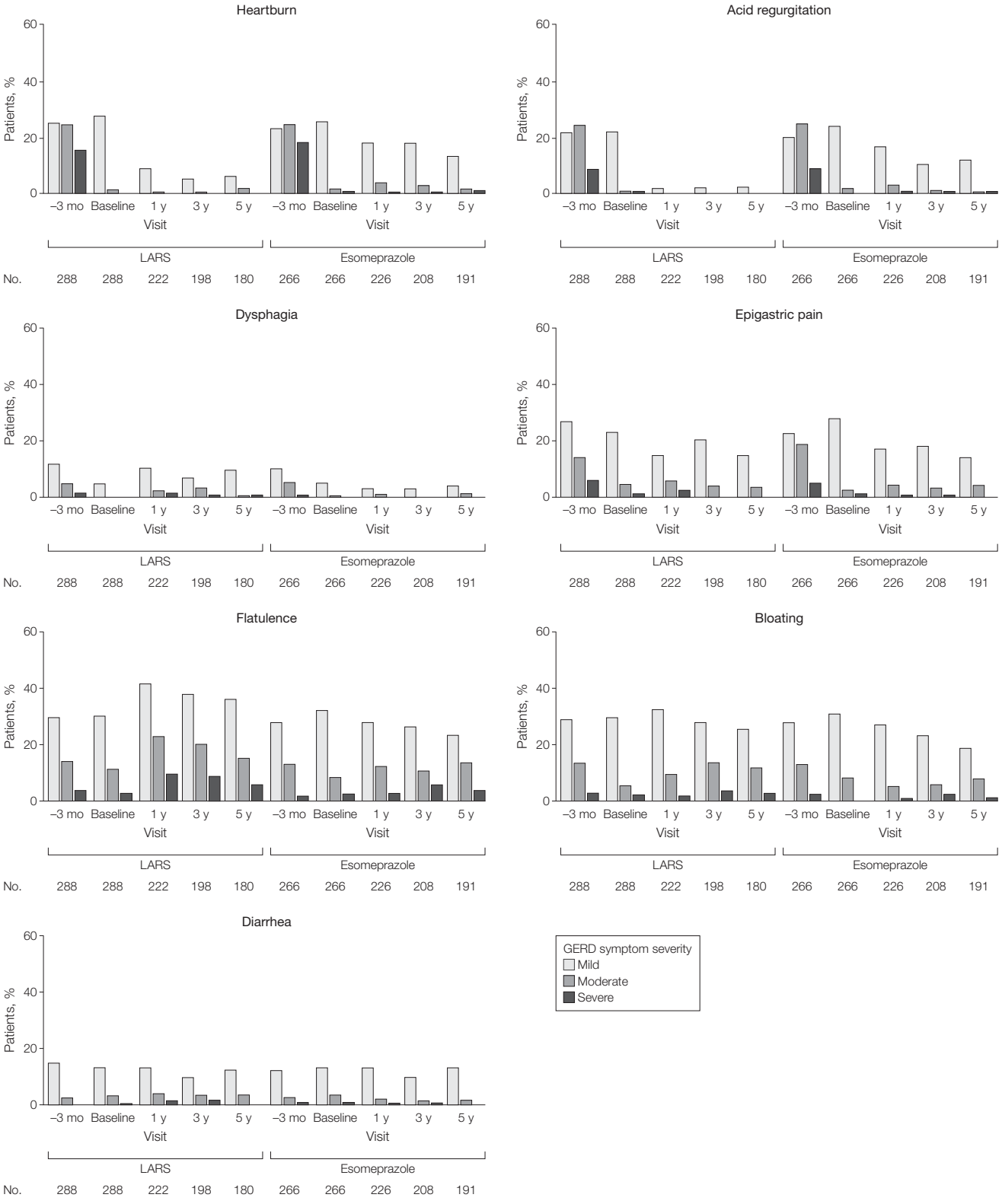
LARS indicates laparoscopic antireflux surgery.

COMMENT

This large, multicenter randomized trial demonstrated that with modern forms of antireflux therapy, either by drug-induced acid suppression or after LARS, most patients remain in remission for at least 5 years. In an exploratory analysis, the estimated remission rates at 5 years were higher in the esomeprazole group (92%; 95% CI, 89%-96%) than in the LARS group (85%; 95% CI, 81%-90%; log-rank $P=.048$). There was more regurgitation with esomeprazole than with LARS. In contrast, dysphagia, bloating, and flatulence were more common after LARS vs with esomeprazole. Both treatments were well tolerated, with no surgery-related mortality and similar safety profiles for both.[20]

The high remission rates reported in this trial are at variance with previous randomized studies comparing long-term medical therapy vs antireflux surgery. There may be several reasons for these apparent discrepancies. With respect to drug therapy, earlier trials used

Figure 3. Symptoms Reported by Each Treatment Group Throughout the Study as Mild, Moderate, or Severe



See definitions of mild, moderate, or severe symptoms in "Methods" section of text. GERD indicates gastroesophageal reflux disease; LARS, laparoscopic antireflux surgery.

drugs such as antacids, prokinetics, or histamine$_2$ receptor antagonists that are now known to be of limited efficacy. Proton pump inhibitors are more potent acid-suppressive agents, reducing the intensity of esophageal acid exposure. In the present study, patients were treated with esomeprazole, which suppresses gastric acidity more effectively than omeprazole and other PPIs.[21,22] Moreover, in our study, patients whose reflux symptoms were not adequately controlled by a standard maintenance regimen (ie, esomeprazole, 20 mg/d) were allowed to increase the dosage to 40 mg once per day and then to 20 mg twice per day. Dinnertime or split dosing can improve breakthrough nocturnal symptoms for some patients.[23] Dose escalation or split dosing applied in the LOTUS study may have contributed to the improved remission rate (92%) compared with that reported in the SOPRAN study at 5 years (57%),[9] in which patients received omeprazole and were not actively dose-titrated to the same extent. Most likely, LARS outcomes were better than reported in earlier studies because we recruited participating centers and surgeons with demonstrable expertise and standardized surgical technique, which has been shown to improve outcomes in other studies.[24,25] The outcome from this approach was manifested by the absence of mortality and the very low morbidity rate in the LARS group. Only 1 patient had dysphagia requiring more than 1 endoscopic dilatation. One recent meta-analysis suggested better outcomes for LARS compared with open surgery, but the need for reoperation may be more frequent after LARS.[7] In our experience, most patients (98%) did not experience long-term complications from LARS. The final endoscopic assessment did not show anatomical deterioration and hiatal repair was maintained, with only 5.6% of the LARS group having hiatal hernia after 5 years compared with 62.3% in the esomeprazole group, confirming similar observations from the SOPRAN study.[9] Our LARS group showed slight deterioration in symptom control between 3 years (estimated remission rate, 90%) and 5 years (estimated remission rate, 85%), while the esomeprazole group remained more stable. Better long-term symptom control in the esomeprazole group might have been related to dose escalation.

Long-term acid suppression has been associated with complications.[26-28] The serious adverse events reported in this study[20] (eTable 2) were similar between the LARS and esomeprazole groups, apart from slightly more cardiovascular complications in the esomeprazole group. However, there were no specific serious adverse events that were judged by the investigators to be attributable to acid-supressive therapy alone. Two hip fractures occurred during the study, 1 in the LARS group and 1 in the esomeprazole group that was caused by a serious fall that also resulted in femur fracture, brain trauma, and death. The few hip fractures we observed suggest that fractures are rare with PPI and that previous observational studies might have overestimated the risk of these events.[29]

Our trial has several limitations. First, we enrolled only PPI responders; our results do not generalize to patients who initially are partially or completely refractory to PPI therapy.[30] These poor responders are a heterogeneous group of patients with many underlying causes for their nonresponsiveness to treatment. The most common cause is the absence of actual reflux disease, with symptoms being caused by nonreflux conditions. Assessing the role of surgery in nonresponders requires specific investigations such as pH impedancemetry to better classify patients. The choice of long-term PPI maintenance therapy or LARS in patients who initially respond to acid suppression is relevant to clinical practice.

Second, 14% of participants randomized to receive surgery were not operated on for various reasons. Despite our efforts, we were unable to follow up this patient cohort, who did not differ from

Table 2. Safety Assessments

	Baseline		3-Year Follow-up		5-Year Follow-up	
	LARS	Esomeprazole	LARS	Esomeprazole	LARS	Esomeprazole
Serious adverse events[a]						
No. of patients with a serious adverse event	NA	NA	54	38	71	64
No. of patients with a fatal serious adverse event	NA	NA	0	1	1[b]	4[b]
Blood variables, mean						
Hemoglobin, g/L	149.4	149.5	149.4	150.4	149.0	150.0
Vitamin B_{12}, pmol/L	329.4	332.2	325.6	339.4	313.0	335.8
Serum gastrin, pg/mL	70.2	65.6	51.3	159.5	54.0	164.4
Chromogranin A, ng/mL	91.3	81.2	38.0	206.1	45.8	216.3
Alkaline phosphatase, u/L	71.7	71.8	69.1	71.6	67.9	68.3
Calcium, mmol/L	2.3	2.3	2.3	2.3	2.2	2.3
Vitamin D, nmol/L	49.5	50.1	53.6	57.9	50.2	50.6
Homocysteine, µmol/mL	11.7	11.5	11.2	11.5	13.2	12.5

Abbreviations: LARS, laparoscopic antireflux surgery; NA, not applicable.
[a] See also eTable 2. Total at 5 years is cumulative.
[b] One patient in each group died after the end of the study, but the serious adverse event started during the study.

participants at baseline but who declined surgery. For this reason, we performed a sensitivity analysis with best- and worst-case scenarios assuming that all participants not completing the study after randomization all either had treatment response or treatment failure. The results of this were similar to our overall findings. The number of participants randomized to receive surgery who did not undergo operation was considerably lower than the 38% of participants reported in the large UK REFLUX trial.[13] When treatment failures were excluded, the dropout rate during the 5-year duration was consistent with rates observed in other studies of chronic conditions and better than in other previous antireflux surgery clinical trials.[8,12,13]

Third, this study was not designed as a superiority or equivalence trial but, rather, as an exploratory study to estimate the efficacy of antireflux surgery and PPI treatment in PPI responders. At the time the study was designed, there were no good estimates for long-term treatment efficacy of esomeprazole (or other PPIs) in this patient population, and the 70% estimate of success with surgery was based on results with nonlaparoscopic procedures. We therefore selected a more pragmatic strategy for sample size determination by estimating the size of the CI for a given difference in efficacy. Nonetheless, we did prespecify that the treatment success rates in each group would be compared using log-rank tests for the superiority of the observed difference between the treatment groups.

In summary, most patients with GERD who are initially responsive to PPIs achieve and remain in remission at 5 years with contemporary antireflux therapy using either LARS or esomeprazole in a dose-escalating manner when required.

Author Contributions: Dr Lundell had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Drs Galmiche and Hatlebakk contributed equally to the article's content.
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Independent Statistical Analysis: Hans Wedel, PhD, emeritus professor in Epidemiology and Biostatistics at the Nordic School of Public Health, Gothenburg, Sweden, undertook an independent statistical analysis, of the data on behalf of AstraZeneca, for which he was reimbursed at standard rates. The results of his analyses are included in this article. His position as an academic faculty member working independent of AstraZeneca has been verified by the dean of the faculty, Anders Foldspang.
Online-Only Material: eTables 1 and 2 are available online at http://www.jama.com.
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