ORIGINAL ARTICLE

Endoscopic or Surgical Myotomy in Patients with Idiopathic Achalasia

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ABSTRACT

BACKGROUND

Pneumatic dilation and laparoscopic Heller's myotomy (LHM) are established treatments for idiopathic achalasia. Peroral endoscopic myotomy (POEM) is a less invasive therapy with promising early study results.

METHODS

In a multicenter, randomized trial, we compared POEM with LHM plus Dor's fundoplication in patients with symptomatic achalasia. The primary end point was clinical success, defined as an Eckardt symptom score of 3 or less (range, 0 to 12, with higher scores indicating more severe symptoms of achalasia) without the use of additional treatments, at the 2-year follow-up; a noninferiority margin of –12.5 percentage points was used in the primary analysis. Secondary end points included adverse events, esophageal function, Gastrointestinal Quality of Life Index score (range, 0 to 144, with higher scores indicating better function), and gastroesophageal reflux.

RESULTS

A total of 221 patients were randomly assigned to undergo either POEM (112 patients) or LHM plus Dor's fundoplication (109 patients). Clinical success at the 2-year follow-up was observed in 83.0% of patients in the POEM group and 81.7% of patients in the LHM group (difference, 1.4 percentage points; 95% confidence interval [CI], –8.7 to 11.4; P=0.007 for noninferiority). Serious adverse events occurred in 2.7% of patients in the POEM group and 7.3% of patients in the LHM group. Improvement in esophageal function from baseline to 24 months, as assessed by measurement of the integrated relaxation pressure of the lower esophageal sphincter, did not differ significantly between the treatment groups (difference, –0.75 mm Hg; 95% CI, –2.26 to 0.76), nor did improvement in the score on the Gastrointestinal Quality of Life Index (difference, 0.14 points; 95% CI, –4.01 to 4.28). At 3 months, 57% of patients in the POEM group and 20% of patients in the LHM group had reflux esophagitis, as assessed by endoscopy; at 24 months, the corresponding percentages were 44% and 29%.

CONCLUSIONS

In this randomized trial, POEM was noninferior to LHM plus Dor's fundoplication in controlling symptoms of achalasia at 2 years. Gastroesophageal reflux was more common among patients who underwent POEM than among those who underwent LHM. (Funded by the European Clinical Research Infrastructure Network and others; ClinicalTrials.gov number, NCT01601678.)

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Achalasia is an esophageal motor disorder consisting of defective relaxation of the lower esophageal sphincter and disturbed esophageal peristalsis. The clinical symptoms associated with the condition include dysphagia, regurgitation, chest pain, and weight loss.[1] Current treatment options include endoscopic botulinum toxin injection, endoscopic pneumatic dilation, and surgical laparoscopic Heller's myotomy (LHM).[2] These therapies alleviate symptoms, mainly by reducing lower esophageal sphincter pressure and lowering the resistance to flow at the esophagogastric junction. On the basis of findings from randomized trials,[3,4] recent consensus statements and guidelines support both pneumatic dilation and LHM as effective primary therapies for achalasia without a clear preference for either method.[2,5]

Peroral endoscopic myotomy (POEM) is a purely endoscopic (scarless) method of myotomy[6] that has been used in clinical practice since 2010.[7] Since then, a multitude of studies, most of which were retrospective,[5,8-10] have shown the high clinical efficacy and safety of POEM. The aim of this randomized, noninferiority trial was to compare POEM with LHM plus Dor's fundoplication in patients with idiopathic achalasia.

Methods

Trial Design

This was a prospective, multicenter, randomized, open-label, noninferiority trial performed at eight centers in six European countries. The trial was approved by the institutional review board at each participating center. On-site data monitoring was provided by Clinical Trial Center North at the University Hospital Hamburg-Eppendorf and the European Clinical Research Infrastructure Network (ECRIN). Monitoring visits were performed (details are provided in Table S9 in the Supplementary Appendix, available with the full text of this article at NEJM.org). A safety board reviewed all adverse events. Various public foundations and Olympus Europa supported the trial. None of the sponsors had any role in the design of the trial or in the analysis or interpretation of the data. The authors vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol, available at NEJM.org.

Patients

Patients with symptomatic achalasia and a medical indication for surgical myotomy or pneumatic dilation were eligible for inclusion in the trial if they were 18 years of age or older, had an Eckardt symptom score[11] higher than 3 (a description of the scale is provided below), and had findings on preinterventional manometry that were consistent with the diagnosis of achalasia (classified as subtypes I to III).[12] Patients who had undergone previous surgery of the stomach or esophagus, including surgical therapy of achalasia, or who had received a diagnosis of secondary achalasia or other organic causes of dysphagia were excluded. Eligible patients who had previously undergone endoscopic treatment were not excluded. All patients provided written informed consent. Further details of the inclusion and exclusion criteria are provided in Tables S1 through S3 in the Supplementary Appendix.

Interventions

The patients at each center were randomly assigned in a 1:1 ratio to undergo either POEM or LHM plus Dor's fundoplication. Randomly permuted blocks of varying sizes, with separate blocks for each center, were used to balance group assignments according to center. A trial nurse who was unaffiliated with the research group and otherwise not involved with the trial performed the randomization.

POEM was performed as previously described by Inoue et al.[7] and involved the creation of an esophageal submucosal tunnel, which was extended 2 to 3 cm into the gastric cardia (Fig. 1). The length of myotomy was adjusted according to the achalasia subtype (i.e., 6 to 7 cm above the lower esophageal sphincter in type I and II and calibrated according to manometric extent in type III). The endoscopists had sufficient experience in therapeutic endoscopy, including esophageal interventions such as endoscopic mucosal resection and submucosal dissection (each had performed more than 50 procedures), and received formal POEM training that included the use of animal or endoscopic training models. The first 4 to 5 procedures were supervised by a tutor, and each endoscopist had to independently perform 8 to 10 run-in POEM procedures before the start of the trial. At each center, POEM was

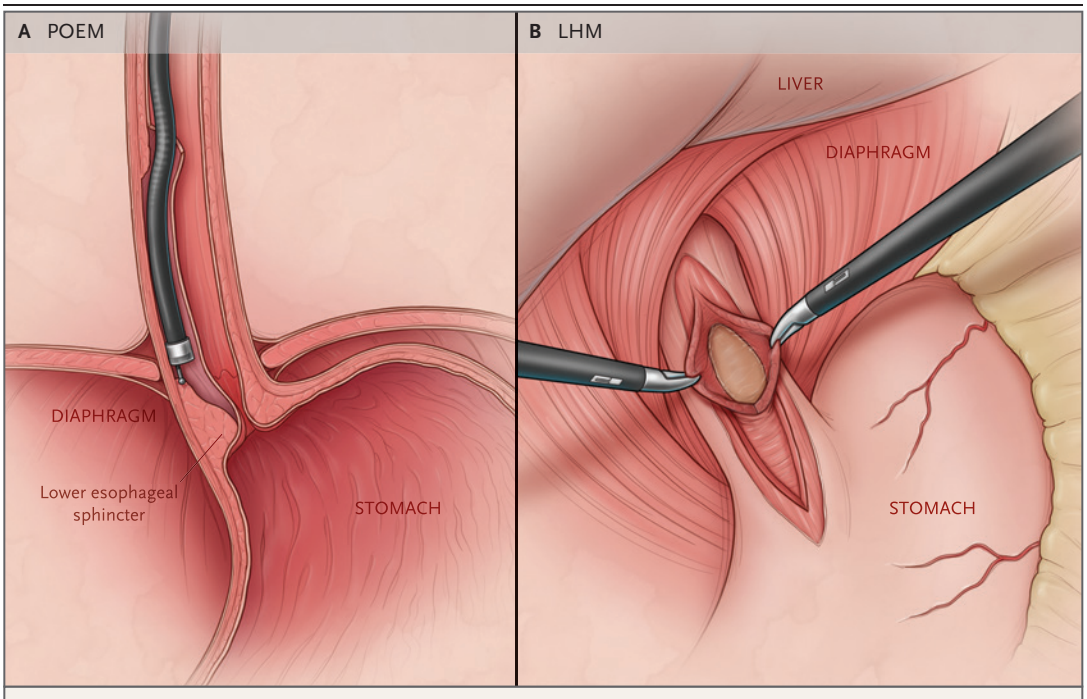

Figure 1. Alternative Methods of Treatment for Achalasia.

Panel A shows the peroral endoscopic myotomy (POEM) approach, in which transection of the muscular fibers of the lower esophageal sphincter is performed entirely with a standard endoscope. Panel B shows the surgical procedure by laparoscopic Heller's myotomy (LHM); a fundoplication is added to this procedure.

performed by one endoscopist (six centers) or two endoscopists (two centers).

LHM was performed according to current standards.[3] Surgical myotomy was performed by dividing the muscle fibers of the lower esophageal sphincter and extending the division to at least 6 cm into the esophageal side and at least 2 to 3 cm into the gastric cardia (Fig. 1). Anterior fundoplication with the use of the technique described by Dor was routinely performed. At each center, LHM was performed by one surgeon (five centers) or two surgeons (three centers); each surgeon had performed at least 20 LHM procedures. Further details of POEM and LHM plus Dor's fundoplication are provided in the protocol.

TRIAL FOLLOW-UP

Clinical data were collected at follow-up visits at 3, 6, 12, and 24 months. Patient-reported outcomes were assessed by means of telephone calls, mail, or follow-up appointments by dedicated trial personnel who were aware of the treatment-group assignments. Objective evaluation by means of endoscopy, manometry, and esophageal pH monitoring (at least 1 week after the discontinuation of a proton-pump inhibitor) was planned at 3 and 24 months (Table S4).

TRIAL END POINTS

The primary end point was clinical success, defined as an Eckardt symptom score of 3 or less without the use of additional treatments, at the 2-year follow-up. The Eckardt symptom score[11] is a validated questionnaire and is calculated as the sum of symptom scores of four components of achalasia including dysphagia, regurgitation, chest pain, and weight loss. Each component can be graded from 0 to 3 points. The maximum Eckardt symptom score is 12 points, with higher scores indicating more severe symptoms. A good outcome is classified as an Eckardt symptom score of 3 or less. All patients reported an Eckardt symptom score higher than 3 at baseline. The primary hypothesis was that POEM would be noninferior to LHM plus Dor's fundoplication with respect to the primary end point.

Prespecified secondary end points included

clinical measures regarding symptoms, Gastrointestinal Quality of Life Index score (range, 0 to 144, with higher scores indicating better function),[13] and gastroesophageal reflux.[14] Objective measures included the grading of endoscopic reflux lesions according to the Los Angeles Classification[15]; assessment of esophageal function, as measured by calculation of the integrated relaxation pressure of the lower esophageal sphincter by means of manometry; and 24-hour pH monitoring. Gastroesophageal reflux was considered abnormal if the acid exposure time (total percentage of time with pH <4) was greater than 4.5%.[3] Further details of these clinical measures are provided in Tables S5 through S7. Additional secondary end points included adverse events (i.e., complications such as bleeding, perforation or mucosal damage, ulcerations, prolonged pain that occurred during or immediately after the procedure) and serious adverse events (i.e., complications of the procedure that led to relevant additional interventional measures or reinterventions during or after the procedure, led to or prolonged inpatient hospitalization, or led to admission to the intensive care unit or death) (Table S8),[16-18] procedure time, length of myotomy, hospitalization time after intervention, laboratory data, and treatment failure. Additional procedural data, use of proton-pump inhibitors, and endoscopic findings at baseline were evaluated post hoc.

The statistical analysis plan (available with the protocol) specified that clinically relevant exploratory subgroup analyses would be performed. Exploratory subgroups were defined according to age (<40 or ≥40 years), sex, achalasia subtype (I, II, or III), and previous treatment for achalasia (yes or no). Secondary end points and post hoc outcomes are listed in Table S16.

STATISTICAL ANALYSIS

Sample size was calculated on the basis of a noninferiority design in which POEM was compared with LHM plus Dor's fundoplication. Available literature on treatments for achalasia showed a success rate of 86% (95% confidence interval [CI], 85 to 88) after LHM.[19] The clinical success rate of LHM plus Dor's fundoplication was observed to be 90% (95% CI, 84 to 96) at the 2-year follow-up in the European Achalasia Trial in 2011.[3] Assuming success rates of 90% for both POEM and LHM plus Dor's fundoplication, we estimated that each treatment group would require 99 patients who could be evaluated in order for the trial to have 80% power to detect noninferiority with the use of noninferiority margin of –12.5 percentage points with respect to the primary end point. Interventional gastroenterologists and surgeons involved in this trial considered a margin of –12.5 percentage points clinically acceptable. Feasibility was another factor, given the low incidence of achalasia (0.3 to 1.6 cases per 100,000 persons per year among adults[1]) and the willingness of patients to participate in trials comparing endoscopy with surgery. We initially aimed to enroll 220 patients to compensate for a 10% dropout rate. In August 2015, after 214 patients had undergone randomization, we increased the sample size to 240 because of a dropout rate that was higher than anticipated.

We performed analyses primarily in the modified intention-to-treat population, which included all patients who underwent randomization and the assigned treatment. The per-protocol population included all patients in the modified intention-to-treat population who completed follow-up without any major protocol deviation. We used multiple imputation to account for missing Eckardt symptom scores for patients who were lost to follow-up or withdrew from the trial during follow-up; predictive mean matching was used to account for the skewed distribution of Eckardt symptom scores (100 imputations with 1000 iterations each; five cases per match set). The following variables were used to impute missing Eckardt symptom scores: available Eckardt symptom scores (including baseline), achalasia subtype, previous treatment, body-mass index, age, and sex.

The primary analysis compared the percentages of patients in the POEM group who had clinical success at the 2-year follow-up with that in the LHM group. POEM was considered noninferior to LHM if the lower limit of the two-sided 95% confidence interval of the absolute between-group difference (POEM minus LHM) in the percentage of patients who had clinical success was above –12.5 percentage points. Several sensitivity analyses involving all patients in the modified intention-to-treat population were performed, including a complete-case analysis, a last-observation-carried-forward analysis, and

a maximum-likelihood analysis with an expectation-maximization algorithm. Identical analyses were applied to the per-protocol data set (see the Supplementary Appendix).

In exploratory subgroup analyses, we used logistic-regression models to evaluate interactions between subgroup variables and treatment group. Time courses of dichotomous and continuous variables were investigated with the use of mixed-effects regression models and generalized estimating equations, which were chosen on the basis of goodness of fit. Considering the distribution of the outcome variable, baseline levels, and repeated measurements per participant, we included age, sex, achalasia subtype, and previous treatment as covariates in these models. Post hoc analyses included calculation of the relative differences in the rate of clinical success, sensitivity analysis involving all patients who underwent randomization (tipping-point analysis in the intention-to-treat population), and an interaction test comparing Eckardt symptom scores over time.

Confidence intervals are not adjusted for multiple comparisons and cannot be used to draw inferences about effects. Analyses were conducted with the use of statistical software package R, version 3.5.1 (R Foundation for Statistical Computing), and SPSS software, version 22 (IBM).

RESULTS

PATIENTS

Between December 7, 2012, and October 9, 2015, a total of 241 patients were enrolled at eight European centers and underwent randomization after providing written informed consent (Fig. 2). Of the 241 patients enrolled, 20 were excluded from the trial, and 221 underwent the assigned treatment (112 in the POEM group and 109 in the LHM group [the modified intention-to-treat population]). In the modified intention-to-treat population, 4 patients were excluded from the POEM group and 6 patients (including 1 patient who had manometric findings at 3 and 24 months that were not consistent with achalasia) from the LHM group; thus, the per-protocol population comprised 108 patients in the POEM group and 103 patients in the LHM group. An overview of the distribution of patients across trial centers and of the patients who underwent treatment during the trial period but who did not consent to participate in the trial is provided in Table S9.

Demographic data, symptom scores, and Gastrointestinal Quality of Life Index scores at baseline were similar in the two treatment groups (Table 1). Overall, 108 of 112 patients (96.4%) in the POEM group and 104 of 109 patients (95.4%) in the LHM group had complete follow-up results with respect to the primary end point.

CLINICAL SUCCESS

In the modified intention-to-treat population, 93 of 112 patients (83.0%) in the POEM group and 89 of 109 patients (81.7%) in the LHM group had clinical success at the 2-year follow-up (the primary end point). Missing data on clinical success at 2 years were imputed for 4 patients in the POEM group and 5 patients in the LHM group. The percentage of patients who had clinical success at 3 months after the assigned intervention was 94.6% (95% CI, 88.2 to 97.8) in the POEM group and in 89.0% (95% CI, 81.2 to 93.9) in the LHM group. The percentages of patients who had clinical success over time are shown in Figure 3A. Similar results were obtained in the per-protocol population, with 82.4% of patients in the POEM group and 80.6% of patients in the LHM group having clinical success at 2 years (Table S10).

In the modified intention-to-treat population, the absolute between-group difference in the percentage of patients who had clinical success at the 2-year follow-up was 1.4 percentage points (95% CI, −8.7 to 11.4) in favor of POEM ($P=0.007$ for noninferiority). The lower boundary of the 95% confidence was above the prespecified noninferiority margin of −12.5 percentage points (Fig. 3B). In the per-protocol population, the corresponding between-group difference was 1.8 percentage points (95% CI, −8.7 to 12.3) in favor of POEM. These results were maintained in prespecified sensitivity analyses, and a post hoc tipping-point analysis in the intention-to-treat population (i.e., all patients who underwent randomization) showed that noninferiority would be supported in 88% of imputation scenarios (Fig. S2).

In an analysis of clinical success across time points, which was performed with the use of a mixed-effects logistic-regression model, the odds ratio for clinical success in the POEM group, as

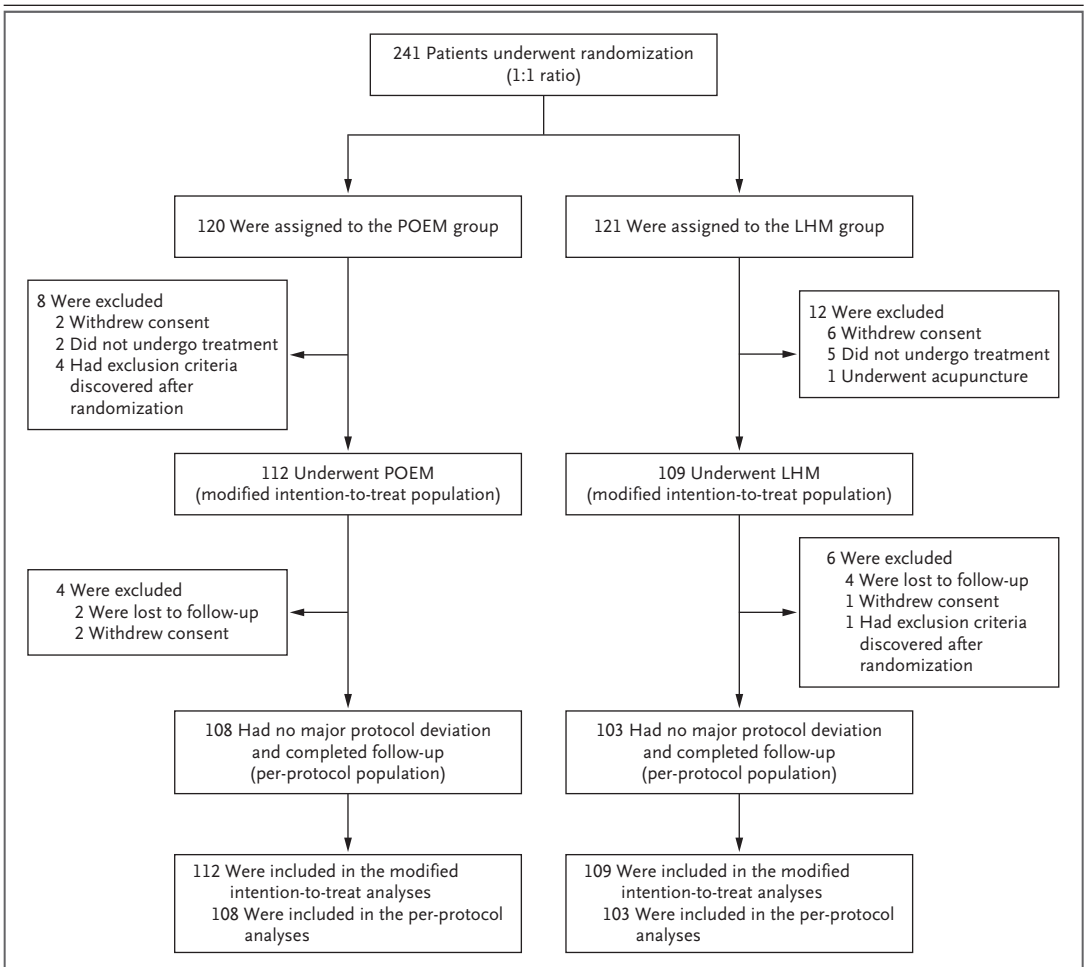

Figure 2. Enrollment, Randomization, and Follow-up.

Patients from eight European centers were randomly assigned to undergo either POEM (the POEM group) or LHM plus Dor's fundoplication (the LHM group). Analyses involved 221 patients in the modified intention-to-treat population, which included all patients who underwent randomization and the assigned treatment, and 211 in the per-protocol population, which included all patients in the modified intention-to-treat population who completed follow-up without any major protocol deviation. A comparison of patients who withdrew from the trial with those who were included in the primary analysis is provided in Table S15.

compared with the LHM group, was 1.28 (95% CI, 0.85 to 1.92). Exploratory subgroup analyses of the primary end point did not suggest evidence of any interaction on the basis of age, sex, achalasia subtype, and previous treatment (Fig. S3). The results in the modified intention-to-treat population, as summarized descriptively, showed that 10 of 12 patients (83%) with achalasia subtype III in the POEM group and 7 of 9 such patients (78%) in the LHM group had clinical success at 2 years after the assigned intervention. Among the patients who had not previously received any treatment for achalasia, 65 of 73 (89%) in the POEM group and 58 of 69 (84%) in the LHM group had clinical success at 2 years, and the corresponding proportions of patients who had clinical success at 2 years among those who had previously received any treatment (botulinum toxin injection, pneumatic dilation, or both) (Table 1) were 28 of 39 (72%) and 31 of 40 (78%).

To address the concern that lower-than-expected rates of clinical success may bias noninferiority analyses when only absolute differences were considered, a post hoc analysis of the

relative rate of clinical success revealed that the lower boundary of the 95% confidence interval of the odds of clinical success at the 2-year follow-up was 0.90 (odds ratio, 1.02; 95% CI, 0.90 to 1.15). This lower boundary was above the fixed ratio of 0.86 that corresponded with the prespecified noninferiority margin of the absolute between-group difference in the percentage of patients who had clinical success when a success rate of 90% was assumed and was thus consistent with noninferiority.

SECONDARY END POINTS

The between-group difference (POEM minus LHM) in the mean Eckardt symptom scores across time points was 0.16 points (95% CI, −0.04 to 0.36) in favor of POEM (Fig. S4). A total of 11 patients had persistent symptoms after undergoing the assigned intervention. A reintervention was performed in 2 of 3 patients in the POEM group in whom the initial intervention had failed and in all 8 patients in the LHM group in whom the initial intervention had failed. Recurrence of symptoms of achalasia was recorded in an additional 16 patients in the POEM group and 12 patients in the LHM group; in 1 patient in the POEM group, these symptoms occurred because of reflux, and a Dor's fundoplication was planned at the 2-year visit (Table S11).

Improvement in esophageal function, as assessed objectively by measurement of the integrated relaxation pressure of the lower esophageal sphincter with the use of high-resolution manometry, did not differ significantly between the treatment groups (difference, −0.75 mm Hg; 95% CI, −2.26 to 0.76). Similarly, improvement in Gastrointestinal Quality of Life Index scores between baseline and 24 months did not differ significantly between the groups (difference, 0.14 points; 95% CI, −4.01 to 4.28). Additional details are provided in Figures S5 and S6.

Procedure time was shorter in POEM group than in the LHM group by 13.81 minutes (95% CI, 6.26 to 21.36), but the length of hospital stay did not differ significantly between the groups (difference, 0.26 days; 95% CI, −0.12 to 0.63). Procedural data are provided in Table S12.

No deaths occurred during the trial. A serious adverse event occurred in 3 patients (2.7%) in the POEM group, and nine serious adverse events occurred in 8 patients (7.3%) in the LHM group (absolute between-group difference, 4.6 percentage points; 95% CI, −1.1 to 10.4). All serious and nonserious adverse events are listed in Table S13.

The development of gastroesophageal reflux disease was assessed clinically and by endoscopy and pH monitoring (Table 2 and Tables S14 and

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

Characteristic	POEM Group (N=112)	LHM Group (N=109)
Age — yr	48.6±14.9	48.6±14.6
Male sex — no. (%)	68 (60.7)	60 (55.0)
Body-mass index†	24.8±4.6	24.5±4.5
Esophageal function according to integrated relaxation pressure — mm Hg‡	26.8±11.4	26.0±10.9
Achalasia subtype — no. (%)		
I	15 (13.4)	21 (19.3)
II	85 (75.9)	78 (71.6)
III	12 (10.7)	9 (8.3)
Subtype unclassified	0	1 (0.9)
Previous therapy — no. (%)		
None	73 (65.2)	69 (63.3)
Endoscopic pneumatic dilation	27 (24.1)	31 (28.4)
Endoscopic botulinum toxin injection	7 (6.2)	8 (7.3)
Pneumatic dilation and botulinum toxin injection	5 (4.5)	1 (0.9)
Eckardt symptom score§	6.8±2.0	6.7±2.0
Gastrointestinal Quality of Life Index score¶	89.2±23.1	90.4±18.1

* Plus–minus values are means ±SD. Baseline characteristics were similar in the two treatment groups. Percentages may not total 100 because of rounding. LHM denotes laparoscopic Heller's myotomy, and POEM peroral endoscopic myotomy.

† The body-mass index is the weight in kilograms divided by the square of the height in meters.

‡ Esophageal function was assessed objectively by measurement of the integrated relaxation pressure of the lower esophageal sphincter at the esophagogastric junction with the use of high-resolution manometry.

§ The Eckardt symptom score is a validated questionnaire and is calculated as the sum of symptom scores of four components of achalasia including dysphagia, regurgitation, chest pain, and weight loss. Each component can be graded from 0 to 3 points. The maximum Eckardt symptom score is 12 points, with higher scores indicating more severe symptoms. A good outcome is classified as an Eckardt symptom score of 3 or less. All patients reported an Eckardt symptom score higher than 3 at baseline.

¶ The Gastrointestinal Quality of Life Index is a validated questionnaire and is calculated as the sum of subscores of 36 items regarding gastrointestinal function, emotion, physical function, social function, and medical treatment. Each subscore ranges from 0 to 4 points. The maximum Gastrointestinal Quality of Life Index score is 144 points, with higher scores indicating better function. Data were missing for two patients in the LHM group.

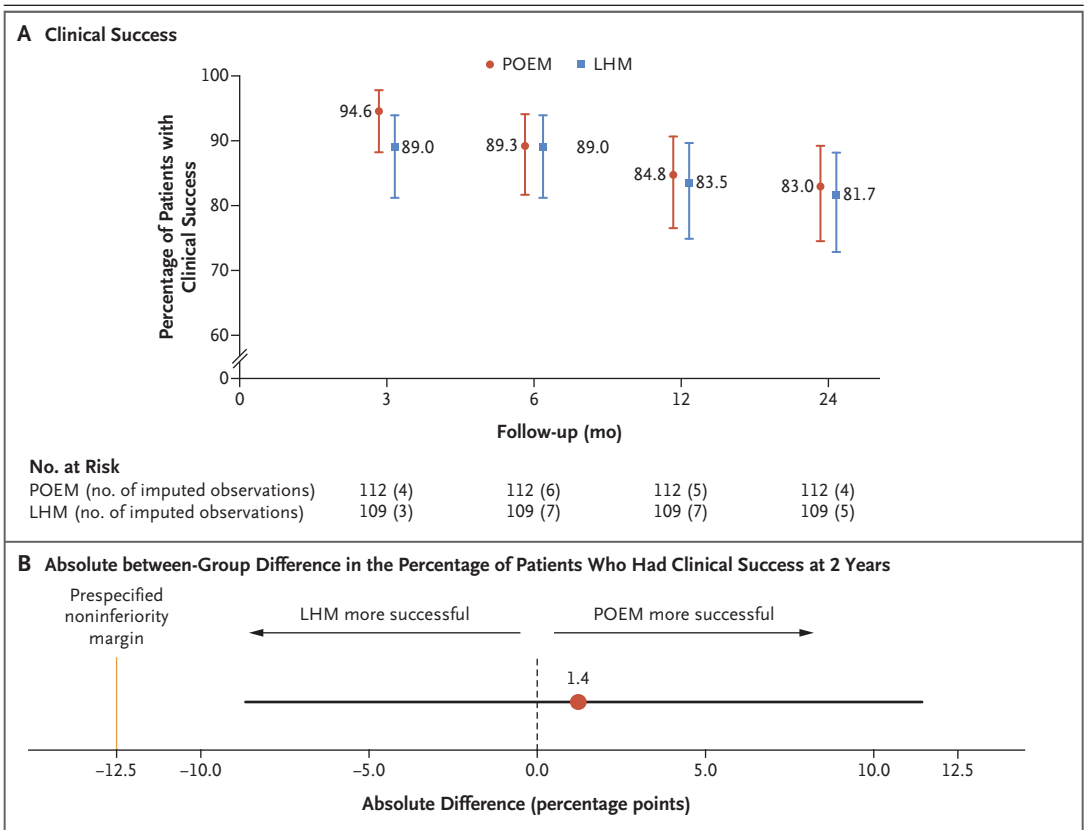

Figure 3. Rates of Clinical Success over Time and Results of the Primary Analysis.

Panel A shows the estimated percentage of patients in each treatment group (modified intention-to-treat population) who had clinical success, defined as an Eckardt symptom score of 3 or less (range, 0 to 12, with higher scores indicating more severe symptoms of achalasia) without the use of additional treatments, over the follow-up period. The primary end point was the percentage of patients who had clinical success at 2 years after the assigned intervention, which was 83.0% in the POEM group and 81.7% in the LHM group. The number of imputed observations at each time point is provided in parentheses. I bars indicate 95% confidence intervals. Panel B shows that the results of the primary analysis in the modified intention-to-treat population supported the hypothesis that POEM was noninferior to LHM. The absolute between-group difference in the percentage of patients who had clinical success at the 2-year follow-up was 1.4 percentage points (95% CI, −8.7 to 11.4) in favor of POEM (P=0.007 for noninferiority).

S15 and Fig. S7). Among 196 and 165 patients in the modified intention-to-treat population who underwent endoscopy at 3 months and 2 years, respectively, the incidence of reflux esophagitis (all grades) was higher in the POEM group than in the LHM group, both at 3 months (57% vs. 20%; odds ratio, 5.74; 95% CI, 2.99 to 11.00) and at 24 months (44% vs. 29%; odds ratio, 2.00; 95% CI, 1.03 to 3.85). As summarized descriptively, high-grade esophagitis (Los Angeles Classification grade C or D according to the Lyon Consensus[20]) was observed at 3 months in 6 of 100 patients (6%) in the POEM group and 3 of 96 patients (3%) in the LHM group and at 24 months in 4 of 87 patients (5%) in the POEM group and 5 of 78 patients (6%) in the LHM group. Esophageal pH monitoring showed similar proportions of patients with abnormal reflux at both time points (at 3 months, 41 of 93 [44%] in the LHM group and 27 of 82 [33%] in the LHM group, and at 24 months, 21 of 70 [30%] in the POEM group and 17 of 56 [30%] in the LHM group). A post hoc analysis of the use of proton-pump inhibitors showed that a higher percentage of patients in the POEM group than in the LHM group were receiving low-dose proton-pump inhibitors across time points after baseline (at baseline, 28 of 112 [25.0%] vs. 33 of

Table 2. Clinical and Objective Evaluation of Gastroesophageal Reflux Disease (a Secondary End Point) over Time.*

Measure	3 Months		2 Years	
	POEM Group (N = 112)	LHM Group (N = 109)	POEM Group (N = 112)	LHM Group (N = 109)
Clinical scores				
Mean DeMeester clinical score (95% CI)	0.9 (0.6–1.1)	0.5 (0.3–0.7)	1.2 (0.9–1.5)	1.0 (0.6–1.0)
Daily reflux symptoms — no./total no. (%)	5/108 (4.6)	2/105 (1.9)	7/107 (6.5)	2/103 (1.9)
Occasional reflux symptoms — no./total no. (%)	42/108 (38.9)	29/105 (27.6)	49/107 (45.8)	45/103 (43.7)
Daily proton-pump inhibitor use — no./total no. (%)	25/108 (23.1)	16/105 (15.2)	41/106 (38.7)	20/103 (19.4)
Occasional proton-pump inhibitor use — no./total no. (%)	8/108 (7.4)	13/105 (12.4)	15/106 (14.2)	8/103 (7.8)
LA Classification grade of reflux esophagitis — no./total no. (%)†				
Overall, grades A to D	57/100 (57)	19/96 (20)	38/87 (44)	23/78 (29)
Grade A	32/100 (32)	13/96 (14)	18/87 (21)	13/78 (17)
Grade B	19/100 (19)	3/96 (3)	16/87 (18)	5/78 (6)
Grade C	5/100 (5)	2/96 (2)	4/87 (5)	2/78 (3)
Grade D	1/100 (1)	1/96 (1)	0/87	3/78 (4)
Esophageal acid exposure‡				
Mean acid exposure time (95% CI) — %	7.1 (5.4–8.9)	6.7 (4.1–9.3)	5.7 (2.8–8.5)	5.4 (2.2–8.5)
Acid exposure time >4.5% — no./total no. (%)	41/93 (44)	27/82 (33)	21/70 (30)	17/56 (30)

* The 95% confidence intervals have not been adjusted for multiplicity and should not be used to draw inferences about effects.
† Los Angeles (LA) Classification grade was assessed on endoscopy: grade A indicates one or more mucosal breaks of 5 mm in length or less; grade B, one or more mucosal breaks of longer than 5 mm; grade C, mucosal breaks that extend between two or more mucosal folds (but involve <75% of the circumference of the esophagus); and grade D, mucosal breaks which involve at least 75% of the esophageal circumference.
‡ Esophageal acid exposure was assessed with the use of 24-hour pH monitoring; acid exposure time is the total percentage of time with a pH lower than 4.

109 [30.3%]; at 3 months, 33 of 108 [30.6%] vs. 29 of 105 [27.6%]; and at 24 months, 56 of 106 [52.8%] vs. 28 of 103 [27.2%]).

DISCUSSION

Our randomized trial prospectively compared the two different approaches to esophageal myotomy — POEM and LHM — in patients with idiopathic achalasia. Our results provide evidence for the noninferiority of POEM to LHM plus Dor's fundoplication in controlling symptoms of achalasia at 2 years but showed that gastroesophageal reflux was more common among patients who underwent POEM than among those who underwent LHM. This finding of noninferiority was corroborated by manometric data on esophageal function over time.

The rates of clinical success at 2 years for both approaches to esophageal myotomy were lower in our trial than in previous randomized trials of LHM or POEM.[3,21] A possible explanation may be the inclusion of patients who had previously received treatment (endoscopic pneumatic dilation or botulinum toxin injection) in our trial, whereas previous treatment for achalasia was an exclusion criterion in the other trials. In our trial, one third of patients in each treatment group at baseline had already been unsuccessfully treated. Although the descriptive differences in the proportions of patients who had clinical success at 2 years after LHM between those who had previously received treatment and those who had not are consistent with the findings in a previous trial,[22] the influence of having received previous treatment on the clinical success of POEM is less clear.[23,24]

Serious adverse events were reported in 3% of patients in the POEM group and 7% of patients in the LHM group; the trial was not powered to assess differences in infrequent adverse events. The percentage of patients who had minor ad-

verse events was similar in the treatment groups, although definitions of minor adverse events vary in the literature.[16] The need for additional surgery to treat adverse events after POEM has been reported,[25] including by our research group,[16,26] but in the current trial, there were no adverse events of POEM that required surgical repair. Treatment conversion from POEM to LHM was not needed in any patient in our trial, but we currently would not consider practicing POEM without a thoracic surgeon as an on-site back-up.

Gastroesophageal reflux has been a major concern with POEM, especially because, unlike LHM, no antireflux procedure is added to this procedure. Meta-analyses on this topic have shown that the incidence of gastroesophageal reflux is much higher after POEM than after LHM, ranging from a doubling[27] to an increase by a factor of nine,[9] but the meta-analyses were based mostly on retrospective case series. Our randomized trial showed that more cases of reflux esophagitis occurred among the patients in the POEM group than in the LHM group, with a larger between-group difference at 3 months than at 2 years. In addition, a higher percentage of patients in the POEM group than in the LHM group used proton-pump inhibitors during the follow-up period, even at 2 years. The results of pH monitoring did not differ significantly between the treatment groups at the 2-year follow-up, although not all patients agreed to undergo this test. The issue of gastroesophageal reflux after achalasia treatments should be examined further, especially regarding possible long-term consequences, such as development of Barrett's esophagus and its complications.[28,29]

Our trial has several limitations. Less than 50% of the eligible patients participated in the trial, mainly because of a lack of patient consent to undergo randomization. The surgeons were more experienced in performing LHM plus Dor's fundoplication than the endoscopists were in performing POEM. We did not analyze treatment effects on postoperative pain or on the use of pain medications; in general, the findings at the 2-year follow-up in this trial suggest that there was no between-group difference in improvements in patient-reported quality of life. Patients and trial personnel were aware of the treatment-group assignments because blinding was not possible. This was a potential source of bias given that the primary end point was based on patients' reports of symptoms; however, objective assessment by manometry corroborated the primary finding.

In conclusion, in this multicenter, randomized trial, the less invasive POEM approach was noninferior to LHM in controlling symptoms of achalasia but resulted in more cases of gastroesophageal reflux. Our results could assist in shared decision making in selecting the appropriate individual therapy for patients with primary achalasia.

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APPENDIX

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