

# Transoral incisionless fundoplication with EsophyX for gastroesophageal reflux disease: clinical efficacy is maintained up to 10 years



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## Bibliography

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## ABSTRACT

**Background** Transoral incisionless fundoplication with EsophyX is reported to be effective in patients with gastroesophageal reflux disease in short-medium term follow-up.

**Aim** To examine clinical outcomes up to 10 years.

**Methods** In total, 51 procedures were performed in 50 patients. All entered a yearly clinical follow-up schedule including gastroesophageal reflux disease health-related quality-of-life questionnaires, heartburn and regurgitation scores, and daily proton pump inhibitor consumption.

**Results** The procedure was successfully performed in 49/50 patients. Severe complications occurred in 2/51 procedures. The remaining 49 patients were re-evaluated at 2 and 3 years, 41 after 5 years, 30 after 7 years, and 14 after 10 years. Eight patients were lost to follow-up between 3 and 5 years. Seven patients who were unresponsive to endoscopic fundoplication underwent surgical fundoplication. The mean scores at 2 years were significantly lower than before the procedure and did not change substantially during the follow-up. The rates of patients who had stopped or halved antisecretive therapy 2, 3, 5, 7, and 10 years after the procedure were 86.7%, 84.4%, 73.5%, 83.3%, and 91.7%, respectively.

**Conclusions** Transoral incisionless fundoplication with EsophyX is an effective therapeutic option for symptomatic gastroesophageal reflux disease patients, with Hill grades I–II or hiatal hernia <2 cm, who refuse life-long medical therapy or surgery.

## Introduction

Transoral incisionless fundoplication (TIF) has become a widely used intervention to restore the valve at the gastroesophageal junction in selected cases suffering from gastroesophageal reflux disease (GERD). More than 20 000 procedures have been done so far, as reported by the manufacturer of EsophyX (Endo-Gastric Solutions, Redmond, WA, United States) – the most widely used device. TIF with the EsophyX device reconfigures the tissue to establish an omega-shaped, full-thickness gastroesophageal valve from inside the stomach. The procedure creates serosa-to-serosa plications which include the muscle layers and constructs valves 3–5 cm long, taking in 200–270° of the

circumference, and deploying multiple non-absorbable polypropylene fasteners through the two layers in a circumferential pattern around the gastroesophageal junction [1–4].

Data so far indicate that, in the majority of patients, the procedure achieves lasting improvement in GERD symptoms, with cessation or reduction in proton pump inhibitor (PPI) therapy and improvement in functional findings, measured by either pH or impedance monitoring.

The technique offers an acceptable alternative to surgery, mimicking partial anterior fundoplication, but less invasive and with no persistent side effects, in patients with proven pathological GERD with either a competent gastroesophageal valve or hiatal hernia not longer than 3 cm, who refuse, are in-

tolerant, or are unresponsive to PPI maintenance therapy. Laparoscopic fundoplication, although still considered to be the gold-standard approach for GERD refractory to medical treatment, does involve some risk of long-term adverse events such as dysphagia (5–12%), inability to vomit or belch, gas/bloat syndrome (19%), and excessive flatulence [5–7].

Several prospective observational studies and some comparative trials have proved the efficacy of TIF with EsophyX in obtaining a significant reduction in the acid exposure time (AET) assessed by esophageal 24-hour pH-impedance monitoring versus sham, and in controlling both typical and atypical GERD symptoms for up to 1 and 2 years, as reported in a recent meta-analysis [8]; however, only six have studied the outcomes at 3 [9–12] and 5 years [13, 14], and just one listed results at 5 to 6 years in a limited number of patients [11]. The relatively short follow-up in patients treated with TIF compared with surgery has raised concerns about the long-term efficacy of the procedure [15].

This study therefore examined the clinical efficacy of TIF at 2, 3, 5, 7, and 10 years in a series of patients who had undergone TIF 2.0 with the EsophyX device, performed by a single operator.

## Materials and methods

In total, 50 patients underwent TIF 2.0 for symptomatic GERD, according to the Rome III criteria [16], from January 2007 to December 2012, and were scheduled for yearly follow-up for up to 10 years in a single-center observational prospective study. Clinical outcomes at 2, 3, 5, 7, and 10 years after the intervention were the subject of the present study.

The indication for TIF in all but two patients was pathological gastroesophageal reflux (GER) with a positive correlation between symptoms and GER, documented by 24-hour pH-impedance. Two patients had 24-hour pH-impedance in the normal range but a positive correlation between symptoms and GER (hypersensitive esophagus). All but two of the patients were responsive or partially responsive to PPI. All patients complained of heartburn and/or regurgitation and had been on PPI maintenance therapy with a standard dose twice a day for at least 3 months before enrollment. For each patient, clinical and procedural data were stored in a computerized database in the endoscopy unit.

Patients with atypical symptoms of GERD, functional reflux, hiatal hernia longer than 3 cm, Barrett's esophagus, esophageal stricture, previous esophageal, gastric or major abdominal surgery, and other severe comorbidities (including collagen disease) were excluded from the study.

Fundoplication (TIF 2.0) was performed in all cases by a single endoscopist with in vivo experience in animal models and humans.

All patients gave written informed consent for the procedure and for data management for scientific purposes. Both the enrollment protocol and the long-term clinical assessment were approved by the Medical Ethics Committee of San Raffaele Scientific Institute of Milan. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki (6th revision,

2008) as reflected in a priori approval by the institution's human research committee.

## Study protocol

At enrollment, all patients completed the Gastroesophageal Reflux Disease Health-Related Quality-of-Life (GERD-HRQL) and Gastroesophageal Reflux Disease Quality-of-Life (GERD-QUAL) questionnaires while on a standard dose of PPI twice a day. PPI was then stopped for 14 days and the patients were asked to complete the two questionnaires once again. Heartburn and regurgitation scores were assessed separately. The GERD-HRQL is a validated 16-item questionnaire that measures the symptom severity of GERD patients [17]. Six items measure satisfaction with the degree of heartburn, two satisfaction with dysphagia/pain while swallowing, and one satisfaction with the impact of medication on daily life; one item measures overall satisfaction with the present condition, and six items measure satisfaction with regurgitation. Each item is scored from 0 to 5. Heartburn and regurgitation scores were extrapolated from the GERD-HRQL questionnaire and assessed separately. The GERD-QUAL is a validated 37-item questionnaire that measures the quality of life of GERD patients [18]; each item is scored from 1 to 5.

Patients then underwent:

- upper gastrointestinal endoscopy to determine the Hill grade and Jobe length of the gastroesophageal valve; the presence and size of hiatal hernia; the presence and severity of esophagitis according to the Los Angeles grading system [19];
- stationary esophageal manometry and 24-hour ambulatory pH-impedance monitoring performed off PPI (PPI therapy suspended at least 12 days previously); any drugs influencing gastrointestinal motility were discontinued 14 days before the functional investigation;
- scintigraphic recording of gastric emptying time.

GERD-HRQL and GERD-QUAL questionnaires, heartburn and regurgitation scores, daily PPI consumption, upper gastrointestinal endoscopy, esophageal manometry, and 24-hour ambulatory pH-impedance were repeated 6, 12, and 24 months after the TIF. Ambulatory pH-impedance was recorded when off PPI in patients who had still been taking them. GERD-QUAL was no longer assessed after 2 years.

GERD-HRQL, heartburn and regurgitation scores, and daily PPI consumption were investigated by telephone interview or office consultation 3, 5, 7, and 10 years after TIF.

All patients were contacted, including those unresponsive to TIF and who had undergone surgery. Two independent physicians unaware of the endoscopic procedures, initial post-interventional 2-year follow-up, and esophageal motility, conducted the long-term surveillance.

PPI consumption was considered "continued" when the daily drug dose was the same as before the procedure; "reduced" when any daily dose was taken for less than half the total number of days during follow-up; and "completely stopped" when not one dose of PPI was taken during the follow-up.

► **Table 1** Baseline clinical, functional and endoscopic characteristics of patients (n = 50) who underwent Transoral Incisionless Fundoplication 2.0 with EsophyX device.

Sex, n (%)	
▪ Male	35/50 (70)
▪ Female	15/50 (30)
Age, mean ± SD, years	45 ± 16
Body Mass Index, mean ± SD, kg/m <sup>2</sup>	22 ± 3
GERD-HRQL score, mean ± SD	
▪ On PPI	20 ± 13
▪ Off PPI <sup>1</sup>	46 ± 19
Heartburn score, mean ± SD	18 ± 9
Regurgitation score, mean ± SD	17 ± 9
Response to standard dose of PPI twice a day, n (%)	
▪ Completely responsive	36/50 (72)
▪ Partially responsive <sup>2</sup>	12/50 (24)
▪ Not responsive	2/50 (4)
Hiatal hernia, n (%)	28/50 (56)
▪ 1–2 cm long	26/28 (92.8)
▪ 2.5 cm long	1/28 (3.6)
▪ 3 cm long	1/28 (3.6)
Esophagitis (Los Angeles classification), n (%)	11/50 (22)
▪ Grade A	10/11 (90.9)
▪ Grade B	1/11 (9.1)
Hill's grade of gastroesophageal valve, n (%)	
▪ Grade I	3/50 (6)
▪ Grade II	34/50 (68)
▪ Grade III	12/50 (24)
▪ Grade IV	1/50 (2)
Jobe's length of gastroesophageal valve, mean ± SD, cm	0.98 ± 0.5
Ineffective esophageal motility, n (%)	18/50 (36)
Gastric emptying time abnormally long, n (%)	24/50 (48)
n, number; SD, standard deviation; GERD-HRQL, Gastro-Esophageal Reflux Disease-Health-Related Quality-of-Life; PPI, proton pump inhibitors.	
<sup>1</sup> Off PPI therapy: patients discontinued PPI for at least 14 days before enrollment. P < 0.01 off PPI vs on PPI.	
<sup>2</sup> Partially responsive: defined as a GERD-HRQL score > 12 on standard dose twice a day for at least 4 weeks.	

## Statistical analysis

Intra- and inter-patient characteristics, GERD-HRQL and GERD-QUAL total scores, heartburn and regurgitation scores, morphological and functional findings were compared by Wilcoxon's and Mann-Whitney tests or Fisher's exact test, as appropriate. A *P* value < 0.05 was considered to be statistically significant.

► **Table 2** Technical data for Transoral Incisionless Fundoplication 2.0 procedures (n = 51) with EsophyX device.

Technical success, n (%)	49/51 (96.1)
Technical failure, n (%)	2/51 (3.9)
▪ Intraprocedural pneumothorax	1/2 (50)
▪ Device malfunction (TIF 2.0 repeated with success)	1/2 (50)
Fasteners deployed to construct each valve, mean ± SD, n	12 ± 4
Post-TIF 2.0 hiatal hernia, n (%)	0
Hill's grade I for newly created valve, n (%)	49/51 (96.1)
Jobe's length of newly created valve, mean ± SD, cm <sup>1</sup>	2.7 ± 0.4
Post-procedure severe complications, n (%)	
▪ Pneumothorax	2 (3.9)
n, number; SD, standard deviation; TIF, transoral incisionless fundoplication.	
<sup>1</sup> <i>P</i> < 0.01 post-TIF 2.0 vs pre-TIF 2.0.	

cant. Data are presented as mean ± SD. Per-protocol and intention-to-treat analysis were performed; the latter include patients lost to follow-up.

## Results

The patients' main clinical and endoscopic characteristics are reported in ► **Table 1**. TIF 2.0 was successful in 49/50 patients. In two cases, the procedure was interrupted: in one case on account of pneumothorax, in the other for device malfunction. The latter procedure was repeated with success. In all, 51 TIF procedures were performed in 50 patients.

A mean of 12 ± 4 fasteners were deployed to construct each valve. Hiatal hernias were always reduced. In all cases, the Hill's grade of the newly created valve was I, and its mean length was statistically significantly greater than before the procedure (2.7 ± 0.4 vs. 0.98 ± 0.5 cm; *P* < 0.01).

Severe complications arose in two of the 51 procedures (3.9%), both pneumothorax. These were confirmed by X-ray immediately after the procedure, and managed by immediate transthoracic drainage. Both patients had rapid resolution of the pneumothorax and were discharged from hospital within 3 days. No persistent post-intervention side effects were reported.

Data are summarized in ► **Table 2**. Post-TIF endoscopic and functional findings have already been published [11], and are not the subject of the present clinical follow-up report.

All 49 patients were clinically evaluated at 2 and 3 years, 41 (83.7%) after 5 years, 30 (61.2%) after 7 years, and 14 (28.6%) after 10 years. Eight patients were lost to follow-up between 3 and 5 years; no other patients were lost during the subsequent follow-up.

Data on follow-up of patients and clinical efficacy of TIF assessed by GERD-HRQL, heartburn and regurgitation scores, and PPI consumption at 2, 3, 5, 7, and 10 years, according to

► **Table 3** Data on follow-up and PPI use in patients (n = 49) who underwent Transoral Incisionless Fundoplication 2.0 with EsophyX device and its clinical efficacy according to per-protocol analysis (excluding patients who underwent Nissen fundoplication and those lost to follow-up) and intention-to-treat analysis (including patients who underwent procedure-related complications and Nissen fundoplication and excluding those lost to follow-up).

	2 years	3 years	5 years	7 years	10 years
Patients on follow-up, n (%)	45/49 (91.8)	45/49 (91.8)	34/49 (69.4)	24/49 (49)	12/49 (24.5)
Patients who underwent surgical fundoplication on follow-up, n (%)	4/49 (8.2)	4/49 (8.2)	7/49 (14.3)	6/49 (12.2)	2/49 (4.1)
Patients lost to follow-up, n (%)	0	0	8/49 (16.3)	5/49 (10.2)	5/49 (10.2)
Clinical success, n (%) <sup>1</sup>					
▪ Per-protocol analysis	39/45 (86.7)	38/45 (84.4)	25/34 (73.5)	20/24 (83.3)	11/12 (91.7)
▪ Intention-to-treat analysis	39/50 (78)	38/50 (76)	25/42 (59.5)	20/31 (64.5)	11/15 (73.3)
Clinical failure, n (%) <sup>2</sup>					
▪ Per-protocol analysis	6/45 (13.3)	7/45 (15.6)	9/34 (26.5)	4/24 (16.7)	1/12 (8.3)
▪ Intention-to-treat analysis	6/50 (12)	7/50 (14)	9/42 (21.4)	4/31 (12.9)	1/15 (6.7)
Stopped PPI					
▪ PP analysis	25/45 (55.6)	24/45 (53.3)	14/34 (41.2)	11/24 (45.8)	5/12 (41.7)
▪ ITT analysis	25/50 (50)	24/50 (48)	14/42 (33.3)	11/31 (35.5)	5/15 (33.3)
Halved PPI					
▪ PP analysis	14/45 (31.1)	14/45 (31.1)	11/34 (32.3)	9/24 (37.5)	6/12 (50)
▪ ITT analysis	14/50 (28)	14/50 (28)	11/42 (26.1)	9/31 (29)	6/15 (40)
Unchanged PPI					
▪ PP analysis	6/45 (13.3)	7/45 (15.6)	9/34 (26.5)	4/24 (16.7)	1/12 (8.3)
▪ ITT analysis	6/50 (12)	6/50 (12)	9/42 (21.4)	4/31 (12.9)	2/15 (13.3)
Stopped or halved PPI					
▪ PP analysis	39/45 (86.7)	38/45 (84.4)	25/34 (73.5)	20/24 (83.3)	11/12 (91.7)
▪ ITT analysis	39/50 (78)	38/50 (76)	25/42 (59.5)	20/31 (64.5)	11/15 (73.3)

n, number; TIF, transoral incisionless fundoplication; Pts, patients; PPI, proton pump inhibitors; PP, per protocol; ITT, intention-to-treat.

<sup>1</sup> Clinical success: defined as complete discontinuation or halved consumption of PPI therapy.

<sup>2</sup> Clinical failure: defined as continuation of PPI dose as before procedure.

per-protocol and intention-to-treat analysis, are summarized in ► **Table 3**, ► **Table 4**. Seven patients unresponsive to TIF underwent Nissen fundoplication during the 10-year follow-up (14.3 %): four in the first year, three between 3 and 5 years after TIF. One of the first four patients was lost at the 7-year follow-up (not contactable). In the subsequent years, no further patients underwent surgery. All patients who required surgery within 12 months after TIF had preoperative Hill's grade III or more for the valve.

Over the 10-year follow-up, the GERD-HRQL scores when off PPI therapy, and heartburn and regurgitation scores remained significantly lower than the pre-TIF scores. The reduction was significant at 2 years and scores were similar at 3 years; between 3 and 5 years, there was a further slight reduction in the mean scores; at 7 and 10 years, scores did not change substantially from the 5-year picture. Mean and median GERD-HRQL heartburn and regurgitation scores appeared substantial-

ly unchanged between 2 and 10 years after the TIF procedure (► **Fig. 1**, ► **Table 4**).

The percentages of patients who had stopped or halved the PPI therapy 2, 3, 5, 7, and 10 years after TIF were 86.7%, 84.4%, 73.5%, 83.3%, and 91.7%, respectively; the rates remained substantially stable and similar to those at 2 years, with a tendency toward improvement at 10 years.

Considering only patients who completely stopped PPI therapy to be responders to TIF, there were 55.6%, 53.3%, 41.2%, 45.8%, and 41.7% full responders at 2, 3, 5, 7, and 10 years, respectively. The complete response rate after TIF had fallen by about 20% at 10 years compared to that at 2 years but the differences were not statistically significant ( $P > 0.05$ ) (► **Fig. 2a**, ► **Table 3**).

Intention-to-treat analysis of the effect of TIF on PPI use, including all 50 patients scheduled to undergo the procedure, showed that at 2, 3, 5, 7, and 10 years after TIF, respectively,

► **Table 4** Data on symptom scores during follow-up after Transoral Incisionless Fundoplication by EsophyX.

	Pre	2 years	P vs pre	3 years	P vs pre	5 years	P vs pre	7 years	P vs pre	10 years	P vs pre
No. of patients	49	45		45		34		24		12	
GERD-HRQL score (off PPI), mean ± SD	46 ± 19	18 ± 13	<0.01	19 ± 14	<0.01	10 ± 7	<0.001	10 ± 7.7	<0.001	9.5 ± 6.1	<0.001
Heartburn score, mean ± SD	18 ± 9	8 ± 7	<0.01	9 ± 8	<0.01	4.5 ± 4.6	<0.01	4.6 ± 4.7	<0.01	4.2 ± 3	<0.01
Regurgitation score, mean ± SD	17 ± 9	9 ± 6	<0.01	10 ± 6	<0.01	3.2 ± 4.3	<0.01	3.3 ± 4.4	<0.01	3.2 ± 4.4	<0.01

SD, standard deviation; GERD-HRQL, Gastro-Esophageal Reflux Disease-Health-Related Quality-of-Life; PPI, proton pump inhibitors.

78%, 76%, 59.5%, 64.5%, and 73.3% of patients had stopped or halved PPI therapy, and 50%, 48%, 33.3%, 35.5%, and 33.3% had completely discontinued it. The rate of patients who stopped or halved their dose of PPI did not change over time, while those who completely stopped PPI decreased by about 40% in the 10 years (► **Table 3**).

As regards procedure-related complications, for patients still taking the same dose of PPI as before TIF, and those who underwent surgical fundoplication, TIF was unsuccessful in 22%, 24%, 40.5%, 35.4%, and 26.7% of patients over the 2- to 10-year follow-up. However, the rate of unsuccessful TIF at 2 years was still the same at 10 years (► **Fig. 2b**).

Among the seven patients who underwent Nissen fundoplication, three showed a significant improvement in their GER-related symptoms, while four did not. The mean GERD-HRQL scores before and 1 year after surgery in responders were 36 ± 13 and 2.0 ± 2.6, respectively, compared to 57.5 ± 20.7 and 16.0 ± 2.7 in non-responders. At 2 years, only one of the four patients who had undergone surgery in the year after TIF completely stopped PPI therapy; at 5, 7, and 10 years, 57.1% of patients were still using PPI.

## Discussion

The present observational study is the first assessing the clinical efficacy of the TIF 2.0 procedure for symptomatic gastroesophageal reflux disease for up to 10 years. The study covers a prospective series of consecutive patients with documented pathological GERD, treated by a single endoscopist in a single center. GER-related symptoms were assessed 2, 3, 5, 7, and 10 years after TIF, using GERD-HRQL questionnaires, heartburn, and regurgitation scores. Daily PPI dependence was also recorded for up to 10 years. The study was carried out in a carefully selected group of patients with chronic GERD who were not satisfied with medical therapy. Partial results at 2 years have already been published [11], so this study reports clinical results from 2 years after the TIF 2.0 procedure.

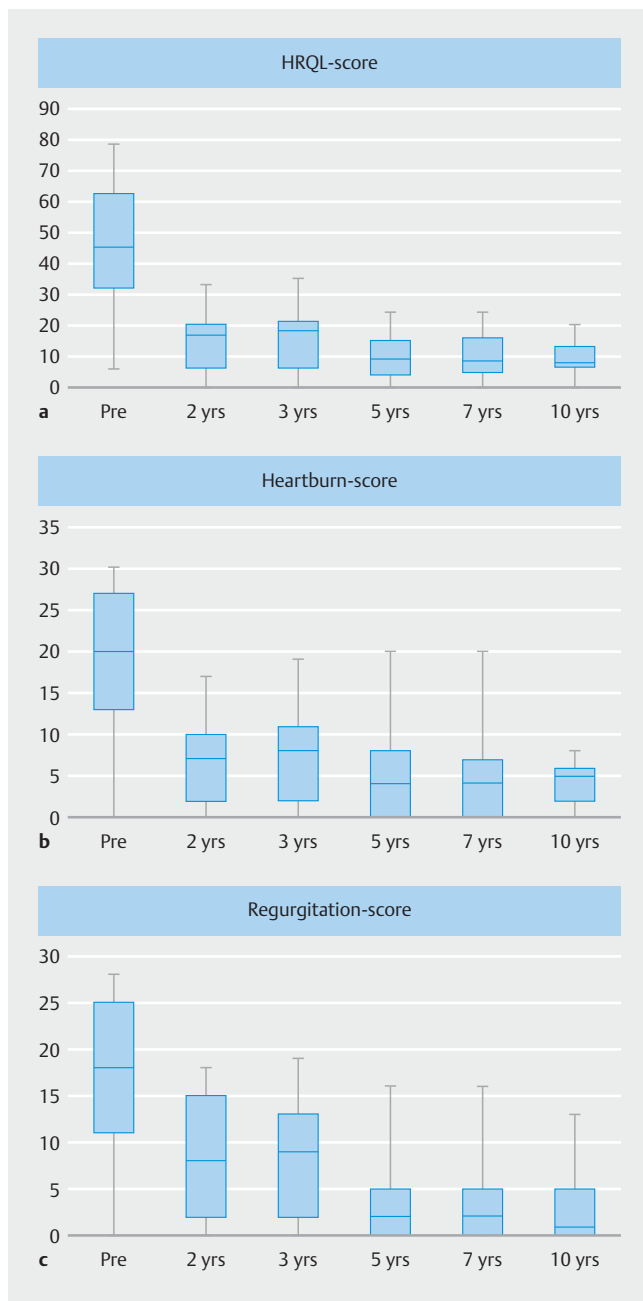
Our 2-year data agree with those reported in the only meta-analysis on TIF so far, which looked at the reports of five randomized control trials and 13 prospective observational studies (963 patients) published between 2007 and 2015 [8]. In that meta-analysis, the mean total satisfaction 6 months after TIF

ranged between 58% and 86% (mean 69.15%), and the total number of refluxes was significantly reduced, with outcomes comparable to that of surgery in the same period. Data on longer follow-up of patients who had undergone TIF were reported in the meta-analysis for three studies looking at 3-year outcomes in a limited number of cases [9–11]. The authors concluded that data on which to draw conclusions over the long term were lacking, but there was a tendency to restart PPI therapy in the majority of patients, though at lower doses than before TIF.

So far, four reports on 3-year outcomes have been published, with similar figures on symptom outcomes and PPI reduction or cessation. In the three studies examined in the meta-analysis, cessation of PPIs or halving their doses was reported in 74%, 74%, and 84% of patients, while complete cessation of PPIs was reported in 42%, 65%, and 53%. A more recent study on 3-year outcomes showed better results, with elimination of troublesome regurgitation and all atypical symptoms in, respectively, 90% and 88% of patients, significantly lower mean percentages of time with pH < 4, healing of esophagitis and discontinuation of PPI therapy in 86% and 71% of patients [12]. Two other studies published in 2017 and 2018 on 44 and 60 patients reported elimination of symptoms and cessation of PPI therapy in 72.7% and 66% of patients at a median 59-month follow-up and at 5 years, respectively [13, 14]. The total GERD health-related quality-of-life score improved decreasing from 22.2 to 6.8 at 5 years ( $P < 0.001$ ) [14].

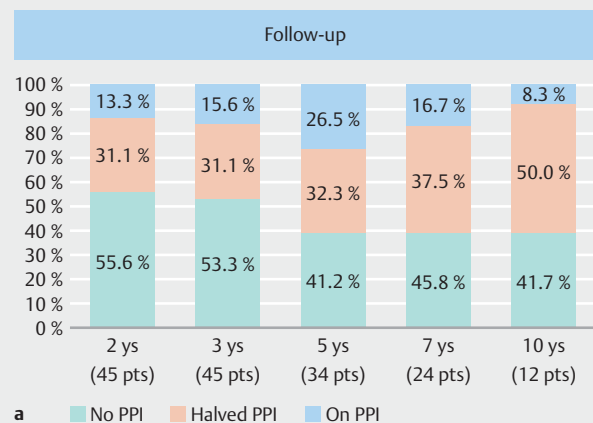
In the present study, symptomatic assessment with heartburn and regurgitation scores from the GERD-HRQL questionnaire gave significantly lower scores than before treatment over the follow-up period. Clinical evaluation indicated that 2-, 3-, 5-, 7- and 10-year results remained close to those at 2 years and stable up to 10 years.

Daily high-dosage PPI dependence was eliminated in 86.7%, 84.4%, 73.5%, 83.3%, and 91.7% at 2, 3, 5, 7, and 10 years, respectively; the rates remained similar to those at 2 years; this provides further evidence of the lasting effect of TIF on symptoms and PPI usage. At 10 years, the rate of patients who stopped PPI or halved the PPI dose was even higher – 91.7%; this improvement might possibly depend on the progressive scar-related fibrosis induced by the stitches over the years.

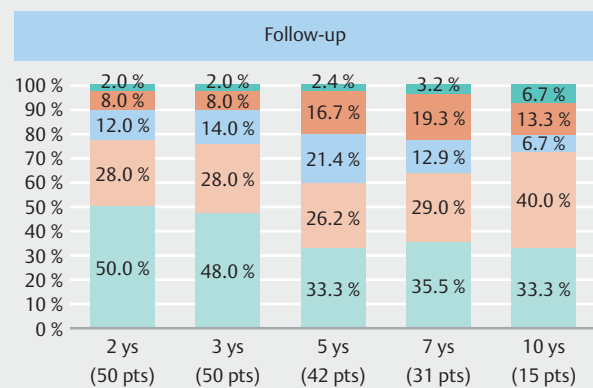


**Fig. 1** a Gastroesophageal reflux disease-Health-Related Quality-of-Life, b heartburn and c regurgitation scores when off proton pump inhibitor (PPI) therapy from baseline (T0) to 10-year follow-up. Data are reported as median and IQ range. HRQL, Health-Related Quality-of-Life.

Considering only patients who completely stopped PPI therapy to be responders to TIF, the proportion of full responders was less satisfactory, although still significant, with rates of 55.6%, 53.3%, 41.2%, 45.8%, and 41.7% at 2, 3, 5, 7, and 10 years, respectively. The complete response rate after TIF was slightly lower than at 2 years and was about 20% lower at 10 years; however, this reduction was not statistically significantly different ( $P>0.05$ ). Five-year outcomes in our study were less



**a** No PPI Halved PPI On PPI



**b** No PPI Halved PPI On PPI Nissen FP Complications

**Fig. 2** Symptomatic responses and proton pump inhibitor (PPI) use from 2- to 10-year follow-up according to **a** per-protocol analysis and **b** intention-to-treat analysis. Data are reported as proportions on the y axis.  $P>0.05$ , 3 years vs 2 years;  $P>0.05$ , 5 years vs 3 years;  $P>0.05$ , 7 years vs 5 years;  $P>0.05$ , 10 years vs 7 years. Pts, patients; Ys, years; PPI, proton pump inhibitors; FP, fundoplication.

favorable than in the other 5-year outcomes study recently published (41.2% vs. 72.7%) [13].

The limitation of the present study in the long-term follow-up is the limited number of patients clinically assessed at 7 and 10 years, without endoscopic and functional evaluations. Although only 24 and 12 patients had a 7- and 10-year post-TIF follow-up, the symptomatic curve over that period suggests that the results would not change much even with a larger number of cases.

Our results confirm that factors that negatively affect outcomes play a role only in the early postoperative period; patients who still respond 2 years after the operation enjoy a substantially unchanged response over the next few years.

In our published series [11], preoperative Hill grades III and IV and hiatal hernia larger than 2 cm at endoscopy, a small number of fasteners deployed (median  $10 \pm 2$ ), and the presence of severe ineffective esophageal motility at manometry were all associated with a higher rate of early unsuccessful results. Ineffective esophageal motility is a problem seen in a heteroge-

neous group with different manometric subsets and different symptom profiles, who might respond to the procedure in different ways [20].

The deployment of a larger number of fasteners (median 14 ± 2) raised the probability of being a responder about four-fold, as stated in another paper [4]. The adoption of the rotational technique to create the new valve gave a 50% increase in successful outcomes too, according to other studies [4, 21].

These factors may all play roles in the unsatisfactory outcomes in patients who failed TIF and required Nissen fundoplication. Four of the seven patients who underwent surgery after TIF (57.1%) still suffered GER symptoms. The low success rates after fundoplication in these selected patients with documented GERD, in whom functional heartburn was excluded, support the hypothesis that GERD-related symptoms might result from several different mechanisms, rather than just the impairment of the gastroesophageal junction. Although univariate and multivariate analysis showed that high preoperative GERD-HRQL scores, high PPI consumption, and age older than 50 years were the factors most closely associated with successful outcomes of transoral fundoplication [22], further data are still needed to clarify this point and help improve the selection of candidates for fundoplication, whether by TIF or laparoscopic surgery.

In our series, 2- and 3-year post-TIF results were similar to those with surgical posterior partial (Toupet) or anterior partial fundoplication, but inferior to those reported in patients operated by posterior total fundoplication (Nissen) [23, 24], though without any of the surgery-related persistent side effects. On the other hand, 5-year post-TIF results were substantially similar to those reported with Nissen fundoplication. A nationwide register-based follow-up study on the use of PPI after anti-reflux surgery reported that, at 5 years, 57.5% and 29.5% of patients still took PPI or were daily PPI-dependent [25]. Our 5-year results also indicated that 58.8% and 26.5% of patients were still taking PPI or were daily PPI-dependent. In the Cochrane meta-analysis on Nissen fundoplication, the pooled analysis of long-term results showed recurrence or persistence of heartburn and reflux symptoms in 41.2% and 24.6% of cases, respectively, with persistent side effects in 14% up to 23% of cases [24].

There are very few reports of 10-year outcomes after surgical fundoplication but, again, results are substantially comparable with our TIF findings [25–27]. In a systematic review of partial responders to PPI who had undergone laparoscopic fundoplication, 10 years after the operation, 35.8% reported heartburn and 29.1% regurgitation, with an 18.2% rate of acid-suppressive medication [26]. The nationwide register-based follow-up study on the use of PPI after antireflux surgery showed that, at 10 years, 72.4% and 41.1% of patients were taking PPI or were daily PPI-dependent [25]. In our patients the proportions were 58.3% and 8.3%.

TIF was associated with pneumothorax in 2 of the 51 cases (3.9%). In both, this was the result of pleural perforation caused by insertion of the needle close to the lesser gastric curve. This complication should therefore be borne in mind when attempting to create a very tight valve. One meta-analysis reported that

severe adverse events occurred in 19 out of 781 patients (2.4%) [8]; this figure is lower than the 14% indicated in the Cochrane meta-analysis on Nissen fundoplication [24]. However, persistent side effects were reported after laparoscopic fundoplication in 5–19% of cases [24], while there were none after TIF.

In conclusion, in this clinical follow-up study, TIF 2.0 with EsophyX achieved lasting elimination or 50% reduction of daily PPI consumption in 73.5–91.7% of cases 2 to 10 years after the intervention, with no troublesome persisting procedure-related side effects. PPI medication was completely stopped in about 56% of patients at 2 years and 42% at 10 years, with no changes over the years. Unsuccessful outcomes after TIF result in recurrence of GERD symptoms within 6–12 months after the intervention, and thereafter clinical results remain substantially stable up to 10 years. Moreover, 57% of patients with TIF failure who underwent surgical fundoplication were still dissatisfied after surgery.

We found that 2- to 3-year outcomes were substantially similar to those reported for anterior surgical fundoplication, but worse than for total fundoplication; 5- and 10-year outcomes were also very similar to those for Nissen fundoplication.

We believe that our clinical findings are sufficient to confirm that TIF appears to offer a safe therapeutic option, as effective as surgery in the long-term, for carefully selected symptomatic GERD patients, with Hill grade I or II of the valve or hiatal hernia not longer than 2 cm, who refuse life-long medical therapy or surgery, are intolerant to PPI, or have some risk of persistent post-surgical side effects.

## Competing interests

None

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