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REVIEW

Efficacy of transoral incisionless fundoplication (TIF) for the treatment of GERD: a systematic review with meta-analysis

Xiaoquan Huang[1,2] · Shiyao Chen[1,2,3] · Hetong Zhao[4] · Xiaoqing Zeng[3] · Jingjing Lian[1,2] · Yujen Tseng[3] · Jie Chen[3]

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Abstract
Background The efficacy of transoral incisionless fundoplication (TIF) performed with the EsophyX device (Redmond, Washington, USA) and its long-term outcomes in gastresophageal reflux disease (GERD) are debated. We, therefore, performed a systematic review with meta-analysis of studies evaluating the role of TIF in GERD.
Methods A systematic search of EMBASE, SCOPUS, PubMed, and the Cochrane Library Central was performed. All original studies reporting outcomes in GERD patients who underwent TIF were identified. Only randomized controlled trials (RCTs) evaluating the efficacy of TIF, and prospective observational studies reporting outcomes after TIF were included.
Results A total of 18 studies (963 patients) published between 2007 and 2015 were identified, including five RCTs and 13 prospective observational studies. The pooled relative risk of response rate to TIF versus PPIs/sham was 2.44 (95 % CI 1.25–4.79, $p = 0.0009$) in RCTs in the intention-to-treat analysis. The total number of refluxes was reduced after TIF compared with the PPIs/sham group. The esophageal acid exposure time and acid reflux episodes after TIF were not significantly improved. Proton-pump inhibitors (PPIs) usage increased with time and most of the patients resumed PPIs treatment at reduced dosage during the long-term follow-up. The total satisfaction rate after TIF was about 69.15 % in 6 months. The incidence of severe adverse events consisting of gastrointestinal perforation and bleeding was 2.4 %.
Conclusions TIF is an alternative intervention in controlling GERD-related symptoms with comparable short-term patient satisfaction. Long-term results showed decreased efficacy with time. Patients often resume PPIs at reduced doses in the near future.

Keywords Meta-analysis · GERD · Transoral incisionless fundoplication · Esophagus · Endoscopy

Gastresophageal reflux disease (GERD) is a common condition affecting people worldwide [1], resulting in diminished quality of life and significant socioeconomic burden in modern civilization [2]. Typical symptoms of GERD include heartburn and regurgitation as well as other adverse events caused by the reflux of stomach contents into the esophagus [3]. Combinations of pharmacologic therapy and lifestyle modifications represent the first-line therapy for GERD. Although treatment with PPIs promotes healing of esophagitis and satisfactory control of symptoms, up to 50 % of these patients experience symptom relapse after a 3-year follow-up [4]. Further, PPIs are ineffective in approximately 25–42 % of patients [5], requiring higher doses of PPIs or surgical fundoplication. Although laparoscopic fundoplication is considered the gold-standard alternative for refractory GERD, which can eliminate reflux and life-long dependence on PPIs [6], it is invasive and associated with the risk of long-term adverse

✉ Shiyao Chen
Chen.shiyao@zs-hospital.sh.cn

1 Center of Evidence-Based Medicine, Zhongshan Hospital, Fudan University, Shanghai 200032, China

2 Endoscopy Center and Endoscopy Research Institute, Zhongshan Hospital, Fudan University, Shanghai 200032, China

3 Department of Gastroenterology, Zhongshan Hospital, Fudan University, Shanghai 200032, China

4 Department of Traditional Chinese Medicine, Changhai Hospital, Shanghai 200433, China

events such as dysphagia (5–12 %), inability to vomit or belch, gas/bloat syndrome (19 %) and excessive flatulence [7–9]. Minimally invasive therapies with fewer side effects are, therefore, desirable. Transoral incisionless fundoplication (TIF) is a relatively new endoscopic technique that restores the valve at the gastroesophageal (GE) junction via endoluminal fundoplication (ELF) using EsophyX^{TM} (EndoGastric Solutions, Inc., Redmond WA, United States). TIF 1.0 is a gastro-gastric stapling technique and later TIF 2.0 creating an esophagogastric plication [10]. The TIF procedure mimics traditional fundoplication surgery with less invasiveness and has become increasingly popular in recent years.

Reports showed that TIF was effective in reducing typical and atypical GERD symptoms, eliminating daily PPIs dependence, as well as normalizing distal esophageal pH. Other studies reported substantial failures rates and the long-term effects of TIF remain unclear. Wendling et al. [11] published a systematic review of the impact of TIF in 2013, but no randomized controlled trials of TIF were available at the time, including results with high-risk bias from the observational studies. Recently, several RCTs and long-term results of prospective observational studies were published. We, therefore, conducted this meta-analysis of these studies for the treatment of GERD.

Materials and methods

This systematic review has been registered in the PROSPERO International prospective register of systematic reviews (www.crd.york.ac.uk/PROSPERO; Register No. CRD42016032736) and complies with the criteria of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [12].

Search strategy

A systematic electronic search of EMBASE, SCOPUS, PubMed, and Cochrane Central Register of Controlled Trials using a combination of medical subject headings (MeSH) and free text from inception to February 20, 2016, was performed. No language or publication date limits were used. The abstract data were excluded and only complete studies that underwent the full and rigorous peer review were included. The following search terms were used, either as MeSH or free text input: (Transoral Incisionless Fundoplication OR EsophyX OR Transoral Fundoplication OR TIF) AND [Gastresophageal reflux (MeSH) OR GERD OR GORD OR gastroesophageal reflux]. We also searched Google Scholar for the gray literature. The reference lists from studies selected via electronic searches were manually searched for additional relevant trials. Two reviewers (XQ Huang and HT Zhao) performed this process independently, with results compared for congruence, and a senior investigator (SY Chen) was consulted when the two evaluators' opinions differed.

Selection criteria

To reduce the risks of bias, inclusion and exclusion criteria was defined prior to the literature search. Since RCTs represent the best evidence for interventional studies and prospective observational studies provide us with long-term results based on adequate sample size, both these studies were included. Studies were eligible for inclusion if they met the following criteria: (1) prospective studies (interventional designs (RCTs) or observational designs); (2) study subjects were patients with GERD requiring PPIs and TIF with/without PPIs; and (3) average follow-up duration was more than 90 days (3 months). If authors published overlapping reports, the most updated results were used to avoid double-counting. For long-term results of observational studies, we combined results from the same population. We excluded retrospective studies due to the high risk of bias. No restrictions with respect to patients' age, ethnic group, or sex were imposed. If a device other than EsophyX^{TM} was used, the study was excluded.

Data extraction

All data were extracted independently and crosschecked by three investigators (XQ Huang, SY Chen and HT Zhao) according to pre-specified inclusion criteria. Disagreements were resolved by discussion. The following data were extracted from each study: study design, study period, publication year, country, study sites, sample size, TIF technique (version 1.0 or 2.0), patient inclusion and exclusion criteria, number of fasteners to deploy, subjective outcomes (symptomatic relief after TIF), objective outcomes (esophageal 24-h acid exposure time, total number of refluxes (including acid reflux and non-acid reflux episodes) and acid reflux episodes after TIF and PPIs/sham in 24 h), severe adverse events, and patient satisfaction rate after TIF procedure.

When results were not directly reported, they were estimated from other data using published methodology [13, 14]. For instance, Kaplan–Meier curves were read by Engauge Digitizer version 5.2 (downloaded from http://digitizer.sourceforge.net). The data from graphs were digitized using the GetData Graph Digitizer version 2.26 (downloaded from http://www.getdata-graph-digitizer.com/).

Outcomes

Subjective outcomes included the overall response rate to TIF and patient satisfaction rate after TIF procedures. Responsiveness to TIF or control intervention was defined as an improvement of at least 50 % in the GERD health-related quality of life (GERD-HRQL) scores or remission of heartburn and regurgitation; complete cessation of PPIs usage was used if none of the outcomes above was obtained. Objective outcomes include the esophageal acid exposure time (% time pH < 4), 24-h total number of refluxes, 24-h acid reflux episodes and the number of patients with complete discontinuation or reduction in PPIs usage. Severe adverse events were recorded to evaluate the safety of TIF procedures as well.

Assessment of risk of bias

Quality assessment was performed independently by authors (XQ Huang, HT Zhao). The risk of bias was assessed following the instructions given in the Cochrane Handbook for Systematic Reviews of Interventions [15]. Random sequence generation, concealment of allocation, blinding of personnel and participants, incomplete outcome data, selective reporting, and other sources of bias were assessed to evaluate the methodological quality of RCTs. Any disagreements in data extraction were resolved by the senior author (SY Chen). For prospective observational studies, the IHE (Institute of Health Economics) quality appraisal tool for case series studies was used [16]. The quality assessment checklist includes seven domains with a total of eighteen items. Studies compliant with the items are indicated with an asterisk in Table 3. A study complying with 14 or more items ($\geq$70 %) was considered to be of acceptable quality.

Statistical analysis

To summarize the available evidence of subjective and objective outcomes in RCTs, we conducted meta-analyses for each evaluated TIF. A random-effects model was based on the DerSimonian and Laird approach pooling studies across all analyses considering possible heterogeneity [17]. Dichotomous outcomes were analyzed with relative risk (RR) along with 95 % confidence intervals (CIs) and continuous outcomes as the mean difference (MD, inverse variance methods) along with 95 % CIs using RevMan 5.3 software program (The Cochrane Collaboration, Oxford, Oxford shire, UK). RR and its respective 95 % CI were calculated as summary measures of the overall efficacy of TIF using intention-to-treat (ITT analysis) and later per-protocol analysis (PP analysis) as sensitivity analyses. A two-tailed $P < 0.05$ was considered statistically significant. Heterogeneity across studies was tested using inconsistency (I^2) and Chi-square (Cochrane Q) statistics [18]. Either Chi-square test $p < 0.10$ or $I^2 > 50$ % indicates substantial heterogeneity, which reflected the percentage of variability in effect estimates due to heterogeneity as opposed to chance alone. Sensitivity analyses were performed by excluding any single studies with clinical or methodological heterogeneous characteristics. Among prospective observational studies, only outcomes after TIF were analyzed; weighted averages were calculated for the percentage of patients responsive to TIF, esophageal acid exposure time, the ratio of patient cessation or reduction in PPIs usage, and satisfaction rate.

Microsoft Excel (Microsoft, Redmond, WA) and SPSS (SPSS, Chicago, IL) were used to produce descriptive statistics. For continuous variables, the mean and standard deviation (SD) were recorded from each study when available. For studies not reporting standard deviations or in which they were not calculated from the reported confidence intervals, median, standard errors, *P* values, figures and the reported mean of the study were used in the meta-analysis without undue bias. The estimates of standard deviation were performed according to the reported methods [15, 19].

Results

Studies

The flowchart identifies the process of manuscript enlistment (Fig. 1). Titles and abstracts of 725 papers were initially identified and reviewed, with 62 papers retrieved for full review. Of these, 42 papers were excluded for various reasons as presented in Fig. 1. Twenty studies were eligible containing five RCTs (two reports [20, 21] were based on the same RCT) and 13 prospective observational studies (two reports [22, 23] were based on the same trial).

A total of 18 studies (963 patients) published between 2007 and 2015 were identified, since the Esophy™ was approved by the FDA in 2007. Most of the studies excluded patients with large hiatal hernia exceed 2 or 3 cm and BMI $\geq$ 30 or 35 kg/m^2; two studies excluded large hiatal hernia (>5 cm); one excluded any patients with hiatal hernia; and one trial excluded patients with BMI > 40 kg/m^2. In these 18 studies, five observational studies used the TIF 1.0 technique while the remaining eight studies and all the five RCTs used the TIF 2.0 technique. The average number of fasteners deployed among 832 available TIF procedures was 18 $\pm$ 4 fasteners per patient.

The summary of included RCTs and prospective observational studies is displayed in Table 1 [20, 21, 24–27] and Table 2 [22, 23, 30–41].

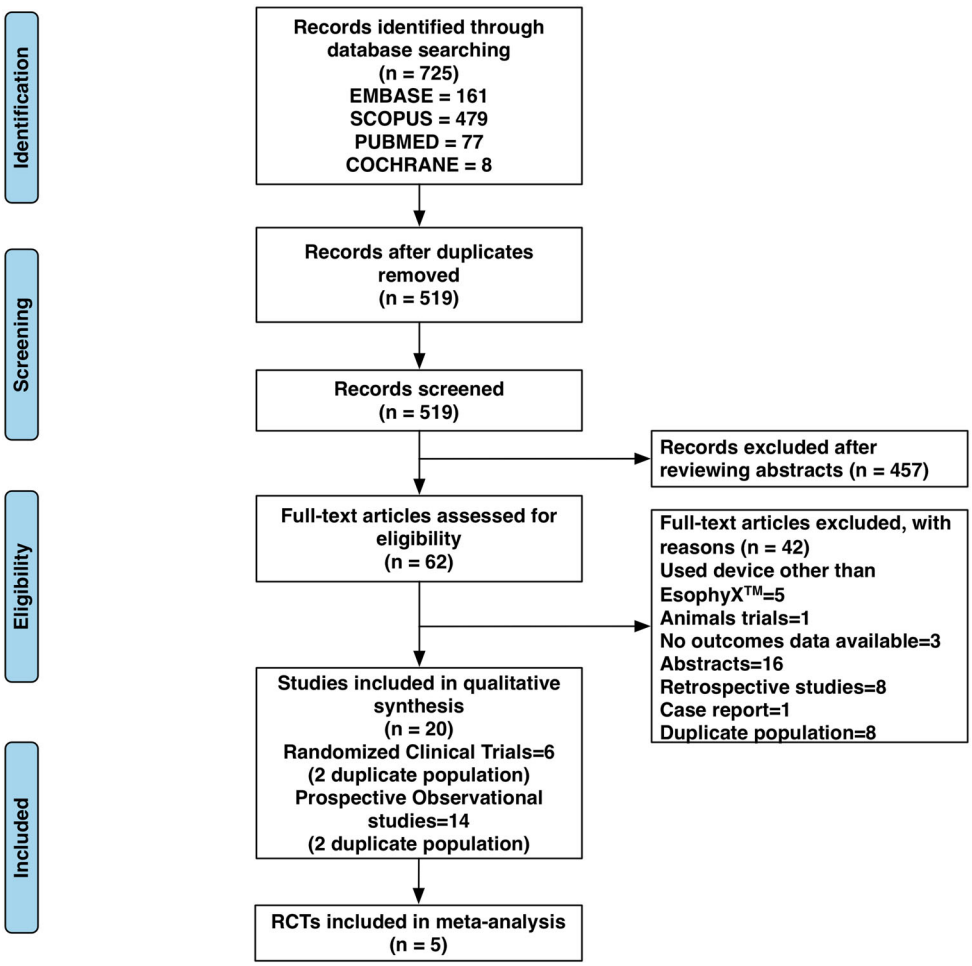

Fig. 1 Flow chart outlining the assessment of studies identified in the systematic review

Table 1 Characteristics of RCTs included

First author (ref)	Publication years	Study period	Country[a]	Study sites	TIF	Patients	Patients undergoing TIF	Fasteners	Severe adverse events
Hakansson [24]	2015	2011–2013	Sweden	5	2.0	44	22	21	0
Hunter [25]	2015	2011–2013	USA	8	2.0	129	87	23	0
Rinsma [27]	2015	2008–2012	Netherlands	1	2.0	47	32	NR	NR
Trad [20][b]	2015	2012	USA	7	2.0	63	39	21	0
Trad [21][b]	2014								
Witteman [26]	2015	2008–2011	Netherlands	1	2.0	60	40	18	3

NR not reported, *ref* reference

[a] According to the first author, if authors from several countries

[b] Two reports from the same trial

Risk of bias

All the five RCTs (six articles) were published between 2014 and 2015 and three of them were multi-centered. Trad [20, 21] published two reports of the TEMPO randomized clinical trial, and the preliminary six-month results were extracted from both articles for analysis.

Risk of bias was assessed, indicating the high quality of the trials with well-designed randomization and blindness. Sources of bias include detection and attrition bias. In

Table 2 Characteristics of prospective observational studies included

First author, publication year (ref)	Country[a]	TIF version	Patients	Fasteners (*n*)	Follow-up period (month)	Response to TIF (*n*)	Satisfaction rate (*n*)	Cessation of PPIs (*n*)	Reduction of PPIs (*n*)	Severe adverse events
Cadière[b] [22]	Belgium	2.0	19		12	53% (17)	82% (17)	82% (17)	NR	0
Cadière[b] [23]					24	64% (14)	86% (14)	71% (14)	7% (14)	
Cadière [30]	Belgium	2.0	86	14.25	6	77% (81)	65% (81)	69% (81)	14% (81)	3
					12	73% (79)		68% (79)	16% (79)	
Repici [31]	Italy	1.0	20	13	6	80% (20)	NR	55% (20)	NR	2
					12	73% (15)		47% (15)	NR	
Demyttenaere [32]	USA	1.0	26	NR	3	45% (22)	45% (22)	32% (22)	31% (22)	3
Testoni [33]	Italy	2.0	20	10	6	56% (18)	NR	55.6% (18)	22.2% (18)	0
Frazzoni [34]	Italy	1.0	10	NR	3	30% (10)	NR	NR	NR	NR
Petersen [35]	USA	2.0	23	NR	6	65% (17)	NR	0	58% (17)	0
Testoni [36]	Italy	2.0	42	12	6	60% (35)	NR	60% (35)	17.1% (35)	2
					12	47% (30)		46.7% (30)	23.3% (30)	
					24	42% (26)		42.3% (26)	26.9% (26)	
Witteman [37]	Netherlands	1.0	38	15.75	3	NR	70%(38)	NR	NR	2
					6	82% (38)		66% (38)	16% (38)	
					36	47% (19)		42% (19)	32% (19)	
Bell [38]	USA	2.0	100	20	6	75% (85)	63% (100)	80% (100)	9% (100)	0
Muls [39]	Belgium	1.0	86	NR	12	74% (54)	74% (54)	77% (54)	9% (54)	2
					36	80% (54)	70% (54)	65% (54)	9% (54)	
Wilson [40]	USA	2.0	100	NR	6	80%(96)	64% (96)	80% (96)	9% (35)	0
					12	73% (85)	58% (96)	46.7% (96)	3% (96)	
Testoni [41]	Italy	2.0	50	12	6	61% (49)	NR	61.2% (49)	22.5% (49)	2
					12	51% (49)		51.0% (49)	28.6% (49)	
					24	56% (41)		56.1% (41)	31.7% (41)	
					36	53% (32)		53.1% (32)	31.1% (32)	
					48	46% (24)		45.8% (24)	37.6% (24)	
					60	32% (19)		31.6% (19)	47.3% (19)	
					72	36% (14)		35.7% (14)	50.0% (14)	

NR not reported, *ref* reference

[a] According to the first author if authors from different countries

[b] Two reports from the same trial

addition, three of these five RCTs were sponsored by EndoGastric Solutions, Redmond, WA (Fig. 2).

Thirteen prospective observational studies (14 articles) were scored using the ICH quality appraisal tool for case series. Cadiere [22, 23] had two papers reporting the results from the same study in 2008 and 2009. All of these 13 studies had 14 or more yes responses (≥70 %) that were considered to be of acceptable quality (Table 3).

Subjective outcomes

Responsive rate to TIF

As shown in Fig. 3A, RR of treatment response was analyzed using the intention-to-treat (ITT) principle in four RCTs reporting remission of GERD-related symptoms [20, 24–26]. Among patients who underwent TIF, 124 of them (65.96 %) attained the standard of responsiveness in 6 months, compared with 30 patients (30.48 %) among those who did not undergo TIF. The pooled RR was significantly higher at 2.44 (95 % CI 1.25–4.79, $p = 0.009$) with an I^2 of 70 % and Chi-square of 10.07 in patients who underwent TIF compared with the controls. The per-protocol analysis was performed in sensitivity analyses (Fig. 3B). This RR was similar at 2.35 (95 % CI 1.30–4.26, $p = 0.005$) with an I^2 of 65 % and Chi-square value of 8.54.

Among patients who were responsive to TIF in prospective observational studies, the mean responsive rate weighted by sample size in 6 months and 1–6 years was shown, respectively (Fig. 4). Among these 13 trials, two provided results in 3 months ($n = 32$), nine in 6 months ($n = 439$), seven in 12 months ($n = 329$), three in 24 months ($n = 81$) and 36 months ($n = 105$), and only one showed results after 4, 5, and 6 years of follow-up ($n = 24$, 19, 14). This curve indicated GERD symptoms recurrence over time after TIF.

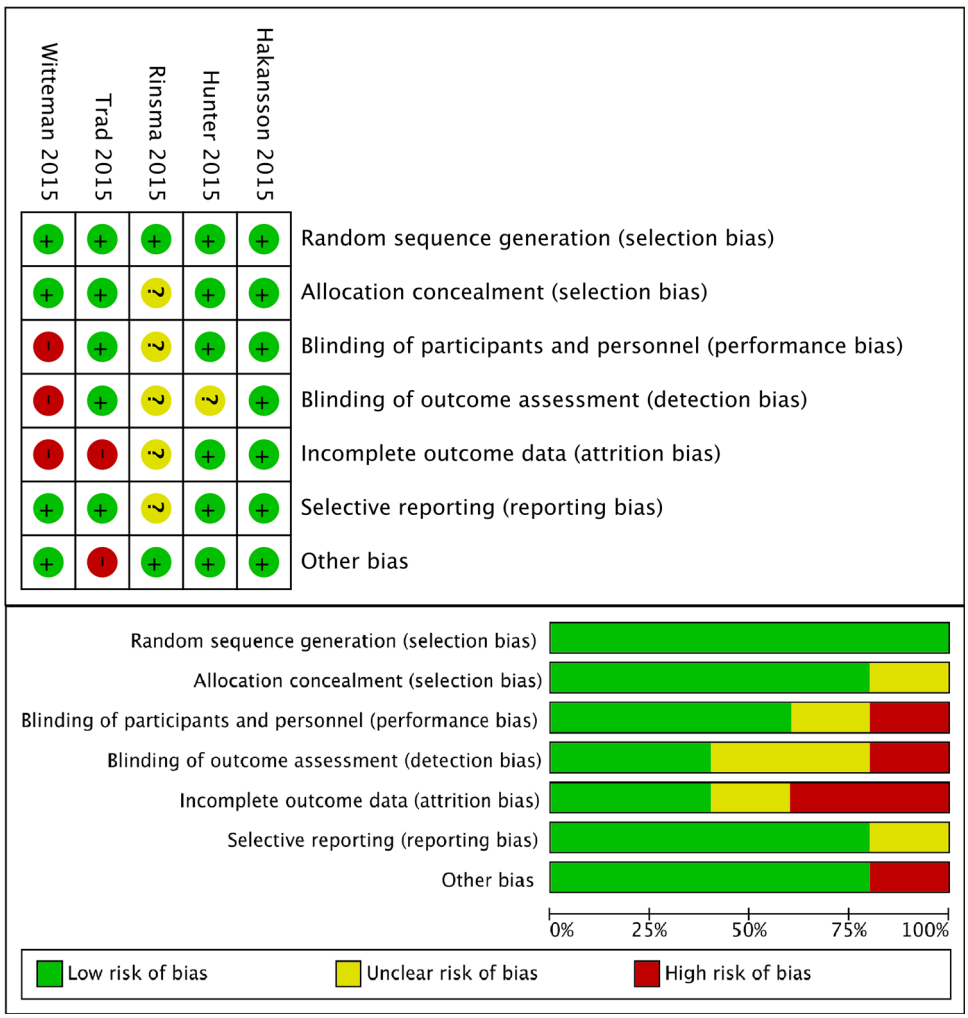

Fig. 2 Summary of risk of bias of included RCTs

Table 3 IHE quality assessment checklist for prospective observational studies

Study ID	Cadière [22]	Cadière [30]	Repici [31]	Demyttenaere [32]	Testoni [33]	Frazzoni [34]	Petersen [35]	Testoni [36]	Witteman [37]	Bell [38]	Muls [39]	Wilson [40]	Testoni [41]
Study objective													
Is the hypothesis/aim/objective of the study clearly stated in the abstract, introduction, or methods section?	*	*	*	*	*	*	*	*	*	*	*	*	*
Study population													
Are the characteristics of the participants included in the study described?	*	*	*	*	*	*	*	*	*	*	*	*	*
Were the cases collected in more than one center?		*								*	*	*	
Are the eligibility criteria (inclusion and exclusion criteria) to entry the study explicit and appropriate?	*	*	*	*	*	*	*			*	*	*	
Were participants recruited consecutively?			*	*	*		*	*		*		*	*
Did participants enter the study at a similar point in the disease?	*	*	*	*	*	*	*	*	*	*	*	*	*
Intervention and co-intervention													
Was the intervention clearly described in the study?	*	*	*	*	*	*	*	*	*	*	*	*	*
Were additional interventions (co-interventions) clearly reported in the study?	*	*	*		*			*	*			*	
Outcome measures													
Are the outcome measures clearly defined in the introduction or methods section?	*	*	*	*	*	*	*	*	*	*	*	*	*
Were relevant outcomes appropriately measured with objective and/or subjective methods?	*	*	*	*	*	*	*	*	*	*	*	*	*
Were outcomes measured before and after intervention?	*	*		*	*	*	*	*	*	*	*	*	*
Statistical analysis													
Were the statistical tests used to assess the relevant outcomes appropriate?	*	*	*	*	*	*	*	*	*	*	*	*	*
Results and conclusions													
Was the length of follow-up reported?	*	*	*	*	*	*	*	*	*	*	*	*	*
Was the loss to follow-up reported?	*	*	*	*	*	*	*	*	*	*	*	*	*
Does the study provide estimates of the random variability in the data analysis of relevant outcomes?		*	*	*	*	*	*	*	*	*	*	*	*

Table 3 continued

Study ID	Cadière [22]	Cadière [30]	Repici [31]	Demyttenaere [32]	Testoni [33]	Frazzoni [34]	Petersen [35]	Testoni [36]	Witteman [37]	Bell [38]	Muls [39]	Wilson [40]	Testoni [41]
Are adverse events reported?	*	*	*	*	*		*	*	*	*	*	*	*
Are the conclusions of the study supported by results?	*	*	*	*	*	*	*	*	*	*	*	*	*
Competing interests and sources of support													
Are both competing interest and source of support for the study reported?	*	*				*	*	*	*	*	*	*	*
Total score	15	17	15	15	16	14	16	16	15	17	16	18	15

Objective outcome

Acid exposure time

There were five RCTs comparing the esophageal acid exposure time with the control after TIF. The mean difference (MD) in the % acid exposure time between patients who treated with and without TIF was −0.34 (95 % CI −4.02 to 3.33, $I^2 = 87$ %, $p = 0.85$; Fig. 5A). Hakansson [24] and Hunter [25] reported comparisons between TIF and sham groups without PPIs. Therefore, subgroup analyses were performed. The results showed that TIF significantly reduced intraesophageal acid exposure time in GERD patients without PPIs therapy, the MD was −4.25 (95 % CI −7.87 to −0.63, $I^2 = 78$ %, $p = 0.02$; Fig. 5B). Thus, TIF procedure showed similar efficacy with respect to esophageal acid exposure time compared with PPIs and improved patients' acid exposure time compared with sham groups.

Changes in total number of refluxes

Three RCTs evaluated the total reflux episodes before and after TIF procedure [25–27]. A meta-analysis of the reduction of total reflux episodes was performed. Patients undergoing endoscopic fundoplication ($n = 150$) yielded significant reduction in reflux episodes compared with those who did not ($n = 73$), with a mean difference of −29.07 (95 % CI −39.17 to −18.98, $I^2 = 45$ %, $p < 0.00001$; Fig. 6).

Acid reflux episodes

Two RCTs [20, 27] reported the incidence of acid reflux episodes before and after TIF therapy. A meta-analysis of changes in acid reflux episodes was performed using a random-effects model. Patients undergoing endoscopic fundoplication ($n = 71$) showed no significant differences from those who received PPIs therapy ($n = 36$), with a mean difference of 10.43 (95 % CI −4.02 to 24.88, $I^2 = 0$ %, $p = 0.16$; Fig. 7).

PPIs usage

In 13 prospective observational studies, the tendency for resumption of PPIs in GERD patients who underwent TIF procedure is shown in Fig. 8. The mean of PPIs cessation or reduction ratio in GERD patients who underwent TIF were calculated in each follow-up period compensating for sample size. Although most of the patients resumed PPIs in the long-term follow-up, the doses were reduced compared with their previous dosage.

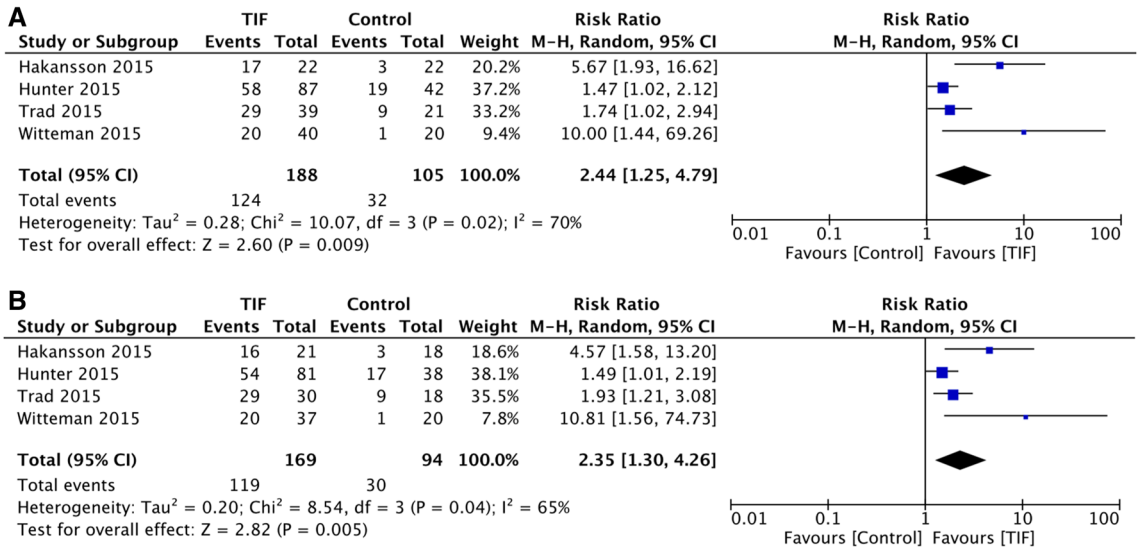

Fig. 3 **A** Meta-analysis of the response rate to TIF and PPIs/sham (ITT analysis). **B** Meta-analysis of the response rate to TIF and PPIs/sham (PP analysis)

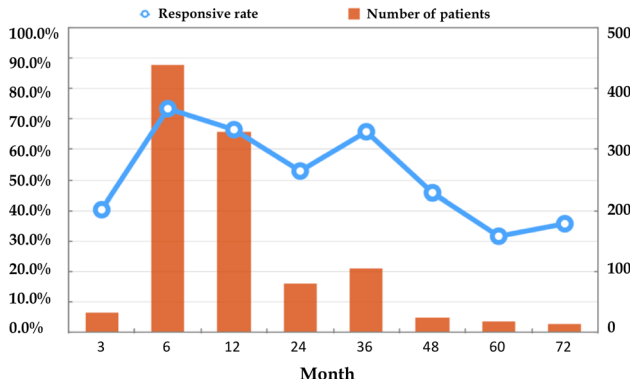

Fig. 4 Long-term efficacy of TIF in prospective observational studies

Satisfaction

The satisfaction data on TIF procedure were available in 10 observational studies. Satisfaction rates ranged from 45 to 86 % at a mean of 6 months, and the weighted average rate was 69.15 %.

Severe adverse events

There were 16 studies (4 RCTs and 12 prospective observational trials) reporting the occurrence of severe adverse events. As a whole, 19 severe adverse events occurred in a total of 781 patients who underwent TIF, considering the incidence rate of 2.4 %. Severe adverse events included seven perforations, five cases of post-TIF bleeding, four cases of pneumothorax, one requiring intravenous antibiotics, and one involving severe epigastric pain. One death was reported 20 months after the TIF procedure.

Discussion

A large population of GERD patients with poorly controlled symptoms following PPIs usage or daily dependence on PPIs is actively seeking an effective anti-reflux procedure. Long-term PPIs usage is expensive and has several well-known side effects. Laparoscopic nissen fundoplication is the surgical "golden standard" [6]. However, endoscopic treatments are less invasive. Endoscopic treatments for GERD include Stretta procedure, EndoCinch plication, medigus ultrasonic surgical EndoStapler, transoral incisionless fundoplication, and injection/implantation techniques [28]. Among these endoscopic interventions, TIF with EsophyX^{TM} device results in anatomical valve reconstruction, and represents the most promising therapy for GERD. Therefore, we only discussed EsophyX^{TM} for treatment of GERD in this meta-analysis. EsophyX^{TM} device is inserted orally within a thin, flexible tube with a surgeon operating the device and an assistant operating the gastroscope. The procedure typically takes less than an hour under general anesthesia. It allows the patient to return to work and normal activities within a few days after the TIF procedure. The initial TIF 1.0 technique creates a gastro-gastric plication using the fasteners centrally on the greater curvature at the squamocolumnar junction of the esophagus to the fundus of the stomach. Successively, the TIF 2.0 technique generates a physiological valve via fasteners placed on the far posterior and anterior sides of the lesser curvature with additional fasteners placed 1–3 cm proximal to the GE junction [29]. In 2007, the first European prospective, multicenter study on TIF was conducted by Cadière et al. [22], after which the

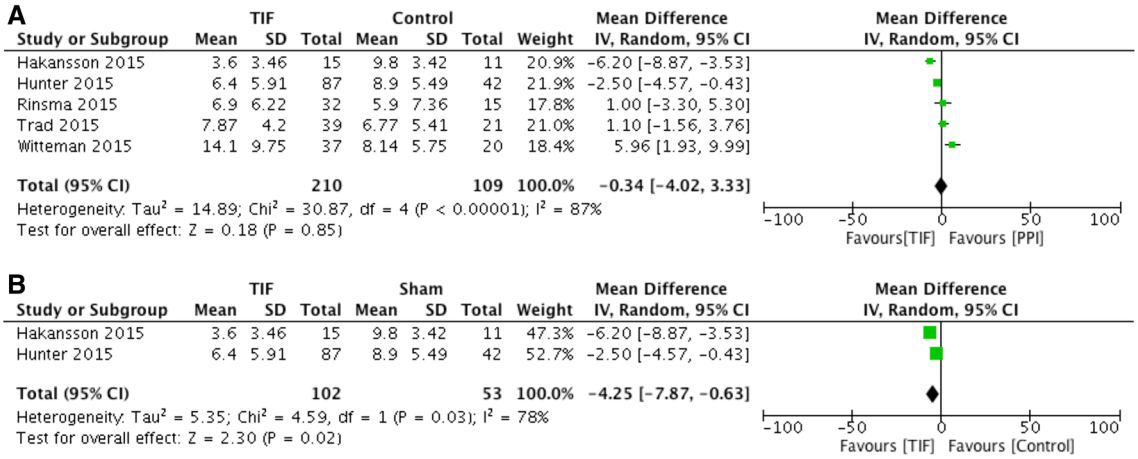

Fig. 5 **A** Meta-analysis of esophageal acid exposure time in TIF and PPIs/sham therapies. **B** Meta-analysis of esophageal acid exposure time in TIF and sham without PPIs

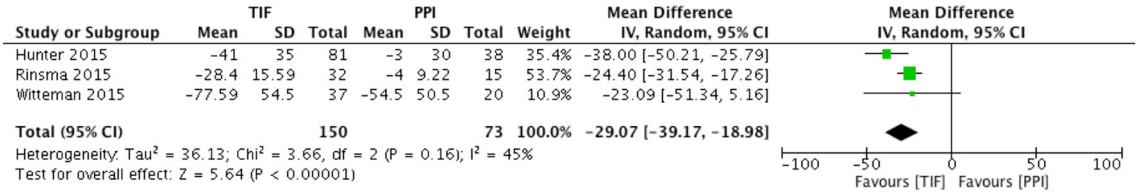

Fig. 6 Meta-analysis of changes in total reflux episodes among the TIF and PPIs/sham groups

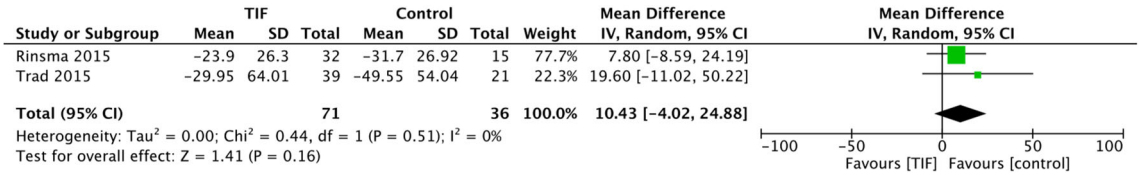

Fig. 7 Meta-analysis of changes in acid reflux episodes between TIF and PPIs/sham groups

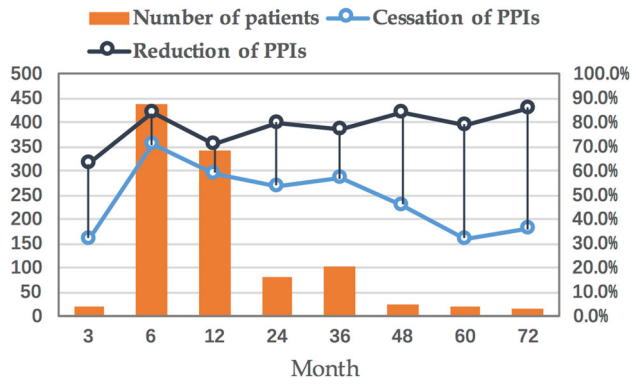

Fig. 8 Long-term outcomes of PPIs usage after TIF in prospective observational studies

approval of EsophyX™ device by the United States Food and Drug Administration (FDA) followed. Since then, multiple reports examining the short-term and long-term outcomes after TIF procedures were published. Wendling et al. [11] summarized the outcomes of 15 retrospective and prospective observational studies of TIF in 2013. Clinical evaluation of EsophyX™ is required to provide clear-cut recommendations.

This systematic review of 18 studies compared the short-term effects of TIF with PPIs/sham in the latest published RCTs and summarized the long-term efficacy and safety after the TIF procedure. However, data analysis was hampered by a lack of standardization in primary and secondary outcomes. Here, we used RR to evaluate the remission rate of GERD symptoms between endoscopic therapy and PPIs to reduce the risk of bias associated with subjective measuring systems.

Among these 18 studies, nearly all the enrolled patients required daily PPIs, failed to respond to PPIs, or were intolerant to PPIs before TIF. These GERD patients experience diminished quality of life with typical or

atypical GERD symptoms. Patients enrollment in these studies represents GERD patients in daily clinical practice. Selected patients with hiatal hernias less than 2 or 3 cm and BMI < 30 or 35 kg/m^2 were primarily included. The mean fasteners deployed were 18 per procedure that conformance to the goal of EsophyX to deploy all 20 fasteners as 10 plications sets [10].

In these five well-designed RCTs, TIF using EsophyX^{TM} showed beneficial effects on GERD patients in subjective outcomes. Both TIF and PPIs/sham group demonstrated comparable efficacy in reducing esophageal acid exposure time % and acid reflux episodes, without any statistical difference. The GERD develops from two essential factors: (a) the gastrointestinal contents and (b) the anti-reflux mechanism, which largely depends on the lower esophageal sphincter (LES) and the anatomic configuration of the GE junction. The mechanism of PPIs in treating GERD is mainly through inhibiting acid secretion; however, nonacid refluxes remain. It is similar to other fundoplication surgeries in that TIF increases the pressure within the LES, resulting in a reduction in total reflux episodes, including acid refluxes. Therefore, TIF has decreased acid reflux episodes when compared to PPIs and decreased acid exposure time when compared to the sham group. However, the long-term follow-up outcomes in the included prospective observational studies indicate decreased overall efficacy with time. PPIs usage led to dependence and even increased PPIs dosage with time. Similarly, the response rate to TIF decreased in our analyses of observational studies. Next generation of TIF and selected GERD patients are required to reach the similar efficacy of Nissen procedure.

Previous cost-effective study showed that EsophyX was more expensive and less efficacious than Nissen procedure according to the early results of TIF [42]. In the future, further studies of the cost-effectiveness of TIF for the treatment of GERD should include medications and economic endpoints for long-term follow-up before clinical application.

Limitations of our meta-analyses include the high degree of heterogeneity among included studies. We included RCTs comparing TIF with both sham and PPIs groups. These RCTs defined the treatment response differently, resulting in significant heterogeneity. However, it is acceptable clinically since our focus was on improvement in GERD symptoms regardless of PPIs usage.

Our study is the first systematic assessment of the efficacy and long-term outcomes of TIF for GERD. We have provided reliable results of TIF by pooling the results of RCTs and long-term prospective observational studies. The analyses of objective and subjective outcomes enable clinical decision making by physicians for treatment of patients with GERD.

In conclusion, pooled results of TIF 1.0 and 2.0 showed that TIF is an alternative intervention in controlling GERD-related symptoms for selected GERD patients, with severe adverse events occurred in 2.4 % of patients consisting of GI perforation and bleeding. However, its efficacy decreases with time. And the satisfaction rate measured in 6 months was 69.15 %. GERD patients who underwent TIF usually resume PPIs therapy at reduced doses in the near future.

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Compliance with ethical standards

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References

1. Bonavina L, Attwood S (2015) Laparoscopic alternatives to fundoplication for gastroesophageal reflux: the role of magnetic augmentation and electrical stimulation of the lower esophageal sphincter. Dis Esophagus Off J Int Soc Dis Esophagus ISDE. doi:10.1111/dote.12425
2. Bonatti H, Achem SR, Hinder RA (2008) Impact of changing epidemiology of gastroesophageal reflux disease on its diagnosis and treatment. J Gastrointest Surg Off J Soc Surg Aliment Tract 12:373–381. doi:10.1007/s11605-007-0294-9
3. Parekh PJ, Johnson DA (2015) Medical treatment versus surgery for treatment of gastroesophageal reflux disease. Tech Gastrointest Endosc 17:53–61. doi:10.1016/j.tgie.2015.02.003
4. Gerson LB, Boparai V, Ullah N, Triadafilopoulos G (2004) Oesophageal and gastric pH profiles in patients with gastro-oesophageal reflux disease and Barrett's oesophagus treated with proton pump inhibitors. Aliment Pharmacol Ther 20:637–643. doi:10.1111/j.1365-2036.2004.02127.x

5. Moraes-Filho JPP (2012) Refractory gastroesophageal reflux disease. Arq Gastroenterol 49:296–301. doi:10.1590/S0004-28032012000400012
6. Niebisch S, Peters JH (2012) Update on fundoplication for the treatment of GERD. Curr Gastroenterol Rep 14:189–196. doi:10.1007/s11894-012-0256-6
7. Herron DM, Swanström LL, Ramzi N, Hansen PD (1999) Factors predictive of dysphagia after laparoscopic Nissen fundoplication. Surg Endosc 13:1180–1183. doi:10.1007/PL00009616
8. Spechler SJ (1992) Comparison of medical and surgical therapy for complicated gastroesophageal reflux disease in veterans. The Department of Veterans Affairs Gastroesophageal Reflux Disease Study Group. N Engl J Med 326:786–792. doi:10.1056/NEJM199203193261202
9. Catarci M, Gentileschi P, Papi C, Carrara A, Marrese R, Gaspari AL, Grassi GB (2004) Evidence-based appraisal of antireflux fundoplication. Ann Surg 239:325–337
10. Bell RCW, Cadière G-B (2011) Transoral rotational esophagogastric fundoplication: technical, anatomical, and safety considerations. Surg Endosc 25:2387–2399. doi:10.1007/s00464-010-1528-6
11. Wendling MR, Melvin WS, Perry KA (2013) Impact of transoral incisionless fundoplication (TIF) on subjective and objective GERD indices: a systematic review of the published literature. Surg Endosc 27:3754–3761. doi:10.1007/s00464-013-2961-0
12. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol 62:1006–1012. doi:10.1016/j.jclinepi.2009.06.005
13. Parmar MK, Torri V, Stewart L (1998) Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. Stat Med 17:2815–2834
14. Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR (2007) Practical methods for incorporating summary time-to-event data into meta-analysis. Trials 8:16. doi:10.1186/1745-6215-8-16
15. Higgins J, Green S, Collaboration C (2008) Cochrane handbook for systematic reviews of interventions. Wiley, London
16. Moga C, Guo B, Schopflocher D, Harstall C (2012) Development of a quality appraisal tool for case series studies using a modified Delphi technique. Inst. Health Econ, Edmont
17. DerSimonian R, Laird N (1986) Meta-analysis in clinical trials. Control Clin Trials 7:177–188
18. Higgins JPT, Thompson SG, Deeks JJ, Altman DG (2003) Measuring inconsistency in meta-analyses. BMJ 327:557–560
19. Hozo SP, Djulbegovic B, Hozo I (2005) Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol 5:1–10. doi:10.1186/1471-2288-5-13
20. Trad KS, Barnes WE, Simoni G, Shughoury AB, Mavrelis PG, Raza M, Heise JA, Turgeon DG, Fox MA (2015) Transoral incisionless fundoplication effective in eliminating GERD symptoms in partial responders to proton pump inhibitor therapy at 6 months: the TEMPO randomized clinical trial. Surg Innov 22:26–40. doi:10.1177/1553350614526788
21. Trad KS, Simoni G, Barnes WE, Shughoury AB, Raza M, Heise JA, Turgeon DG, Fox MA, Mavrelis PG (2014) Efficacy of transoral fundoplication for treatment of chronic gastroesophageal reflux disease incompletely controlled with high-dose proton-pump inhibitors therapy: a randomized, multicenter, open label, crossover study. BMC Gastroenterol 14:174. doi:10.1186/1471-230X-14-174
22. Cadière GB, Rajan A, Germay O, Himpens J (2008) Endoluminal fundoplication by a transoral device for the treatment of GERD: a feasibility study. Surg Endosc 22:333–342. doi:10.1007/s00464-007-9618-9
23. Cadière G-B, Van Sante N, Graves JE, Gawlicka AK, Rajan A (2009) Two-year results of a feasibility study on antireflux transoral incisionless fundoplication using EsophyX. Surg Endosc 23:957–964. doi:10.1007/s00464-009-0384-8
24. Håkansson B, Montgomery M, Cadiere GB, Rajan A, Bruley des Varannes S, Lerhun M, Coron E, Tack J, Bischops R, Thorell A, Arnelo U, Lundell L (2015) Randomised clinical trial: transoral incisionless fundoplication vs. sham intervention to control chronic GERD. Aliment Pharmacol Ther 42:1261–1270. doi:10.1111/apt.13427
25. Hunter JG, Kahrilas PJ, Bell RCW, Wilson EB, Trad KS, Dolan JP, Perry KA, Oelschlager BK, Soper NJ, Snyder BE, Burch MA, Melvin WS, Reavis KM, Turgeon DG, Hungness ES, Diggs BS (2015) Efficacy of transoral fundoplication vs omeprazole for treatment of regurgitation in a randomized controlled trial. Gastroenterology 148(324–333):e5. doi:10.1053/j.gastro.2014.10.009
26. Witteman BPL, Conchillo JM, Rinsma NF, Betzel B, Peeters A, Koek GH, Stassen LPS, Bouvy ND (2015) Randomized controlled trial of transoral incisionless fundoplication vs. proton pump inhibitors for treatment of gastroesophageal reflux disease. Am J Gastroenterol 110:531–542. doi:10.1038/ajg.2015.28
27. Rinsma NF, Farré R, Bouvy ND, Masclee AM, Conchillo JM (2015) The effect of endoscopic fundoplication and proton pump inhibitors on baseline impedance and heartburn severity in GERD patients. Neurogastroenterol Motil Off J Eur Gastrointest Motil Soc 27:220–228. doi:10.1111/nmo.12468
28. Yew KC, Chuah S-K, Yew KC, Chuah S-K (2013) Antireflux endoluminal therapies: past and Present. Gastroenterol Res Pract Gastroenterol Res Pract 2013:e481417. doi:10.1155/2013/481417
29. Testoni PA, Vailati C (2012) Transoral incisionless fundoplication with EsophyX® for treatment of gastro-oesphageal reflux disease. Dig Liver Dis Off J Ital Soc Gastroenterol Ital Assoc Study Liver 44:631–635. doi:10.1016/j.dld.2012.03.019
30. Cadière G-B, Buset M, Muls V, Rajan A, Rösch T, Eckardt AJ, Weerts J, Bastens B, Costamagna G, Marchese M, Louis H, Mana F, Sermon F, Gawlicka AK, Daniel MA, Devière J (2008) Antireflux transoral incisionless fundoplication using EsophyX: 12-month results of a prospective multicenter study. World J Surg 32:1676–1688. doi:10.1007/s00268-008-9594-9
31. Repici A, Fumagalli U, Malesci A, Barbera R, Gambaro C, Rosati R (2010) Endoluminal fundoplication (ELF) for GERD using EsophyX: a 12-month follow-up in a single-center experience. J Gastrointest Surg 14:1–6. doi:10.1007/s11605-009-1077-2
32. Demyttenaere SV, Bergman S, Pham T, Anderson J, Dettorre R, Melvin WS, Mikami DJ (2010) Transoral incisionless fundoplication for gastroesophageal reflux disease in an unselected patient population. Surg Endosc 24:854–858. doi:10.1007/s00464-009-0676-z
33. Testoni PA, Corsetti M, Di Pietro S, Castellaneta AG, Vailati C, Masci E, Passaretti S (2010) Effect of transoral incisionless fundoplication on symptoms, PPI use, and pH-impedance refluxes of GERD patients. World J Surg 34:750–757. doi:10.1007/s00268-010-0394-7
34. Frazzoni M, Conigliaro R, Manta R, Melotti G (2011) Reflux parameters as modified by EsophyX or laparoscopic fundoplication in refractory GERD: EsophyX fundoplication in refractory GERD. Aliment Pharmacol Ther 34:67–75. doi:10.1111/j.1365-2036.2011.04677.x
35. Petersen RP, Filippa L, Wassenaar EB, Martin AV, Tatum R, Oelschlager BK (2012) Comprehensive evaluation of endoscopic fundoplication using the EsophyXTM device. Surg Endosc 26:1021–1027. doi:10.1007/s00464-011-1989-2
36. Testoni PA, Vailati C, Testoni S, Corsetti M (2012) Transoral incisionless fundoplication (TIF 2.0) with EsophyX for gastroesophageal reflux disease: long-term results and findings affecting outcome. Surg Endosc 26:1425–1435. doi:10.1007/s00464-011-2050-1
37. Witteman BPL, Strijkers R, de Vries E, Toemen L, Conchillo JM, Hameeteman W, Dagnelie PC, Koek GH, Bouvy ND (2012)

Transoral incisionless fundoplication for treatment of gastroesophageal reflux disease in clinical practice. Surg Endosc 26:3307–3315. doi:10.1007/s00464-012-2324-2

38. Bell RCW, Mavrelis PG, Barnes WE, Dargis D, Carter BJ, Hoddinott KM, Sewell RW, Trad KS, Gill BD, Ihde GM (2012) A prospective multicenter registry of patients with chronic gastroesophageal reflux disease receiving transoral incisionless fundoplication. J Am Coll Surg 215:794–809. doi:10.1016/j.jamcollsurg.2012.07.014
39. Muls V, Eckardt AJ, Marchese M, Bastens B, Buset M, Devière J, Louis H, Rajan A, Daniel MA, Costamagna G (2013) Three-year results of a multicenter prospective study of transoral incisionless fundoplication. Surg Innov 20:321–330
40. Wilson EB, Barnes WE, Mavrelis PG, Carter BJ, Bell RCW, Sewell RW, Ihde GM, Dargis D, Hoddinott KM, Shughoury AB, Gill BD, Fox MA, Turgeon DG, Freeman KD, Gunsberger T, Hausmann MG, Leblanc KA, Deljkich E, Trad KS (2014) The effects of transoral incisionless fundoplication on chronic GERD patients: 12-month prospective multicenter experience. Surg Laparosc Endosc Percutan Tech 24:36–46. doi:10.1097/SLE.0b013e3182a2b05c
41. Testoni PA, Testoni S, Mazzoleni G, Vailati C, Passaretti S (2015) Long-term efficacy of transoral incisionless fundoplication with Esophyx (Tif 2.0) and factors affecting outcomes in GERD patients followed for up to 6 years: a prospective single-center study. Surg Endosc 29:2770–2780. doi:10.1007/s00464-014-4008-6
42. Funk LM, Zhang JY, Drosdeck JM, Melvin WS, Walker JP, Perry KA (2015) Long-term cost-effectiveness of medical, endoscopic and surgical management of gastroesophageal reflux disease. Surgery 157:126–136. doi:10.1016/j.surg.2014.05.027