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Transoral incisionless fundoplication: current status

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Purpose of review
Transoral incisionless fundoplication (TIF) performed with the EsophyX device (Redmond, Washington, USA) is a totally endoscopic procedure with the objectives to mechanically repair a defective gastroesophageal valve and to reduce small hiatal hernias. The recent publication of randomized controlled trials and long-term follow-up data offers the opportunity to reevaluate this treatment modality and its role in the management of patients with chronic gastroesophageal reflux disease (GERD).

Recent findings
Randomized controlled trials have confirmed the ability of TIF to eliminate troublesome GERD symptoms, heal esophagitis, and improve distal esophageal acid exposure in appropriately selected patient populations. These studies establish TIF's superiority to conventional medical therapy, especially in clinical scenarios where proton-pump inhibitors fail to provide complete symptom relief across the spectrum of classic and atypical GERD manifestations, including regurgitation and laryngopharyngeal reflux. Long-term data indicate sustained positive outcomes and durability up to 6 years after procedure. These results were achieved with a low rate of serious adverse events and usually without introducing troublesome dysphagia, gas bloat, or flatulence.

Summary
Based on the most recent data, TIF appears to be a valuable treatment alternative for the management of appropriately selected patients with moderate to severe chronic GERD symptoms.

Keywords
atypical gastroesophageal reflux disease symptoms, EsophyX, gastroesophageal reflux disease, regurgitation, transoral incisionless fundoplication

INTRODUCTION

The first transoral incisionless fundoplication (TIF) procedure using the EsophyX device was performed in 2005. Since then, more than 17 000 procedures have been completed. The initial European experience and publications focused on the early iterations of this procedure (endoluminal fundoplication and TIF 1.0) and led to the 2007 Food and Drug Administration clearance of the EsophyX device in the United States [1,2]. During those early years on the US market, struggling to define its precise role in the management of gastroesophageal reflux disease (GERD) patients, the TIF procedure was met with a lack of enthusiasm from leading gastroenterological and surgical societies. This may be explained by the unfair comparison of TIF to the first generation of GERD endoluminal therapies (e.g., EndoCinch, Enteryx, Gatekeeper, and Endoscopic Plicator System, NDO Surgical, INC, Mansfield, Massachusetts, USA), which, with the exception of the Stretta procedure, are no longer available because of safety concerns or lack of effectiveness. Further, the absence of long-term data and randomized controlled trials (RCTs) at that time resulted in inconsistent coverage by third-party payers and limited adoption of TIF by physicians.

More recently, however, the TIF procedure performed with the EsophyX device has emerged as a viable alternative in the management of GERD patients with hiatal hernias 2 cm or less. In 2015, the publication of well designed, multicenter RCTs [3▪–5▪,6▪▪] confirmed its effectiveness and demonstrated its superiority over proton-pump inhibitors (PPIs) in selected patient populations with

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KEY POINTS

- The TIF procedure performed with the EsophyX device can be effective in treating regurgitation, heartburn, and laryngopharyngeal reflux refractory to optimal doses of PPIs in the appropriate patient population.
- TIF is associated with a low rate of serious complications, and studies have documented that TIF seldom results in postfundoplication syndromes, such as dysphagia, gas bloat, and flatulence.
- Ideal candidates for the TIF procedure are chronic GERD patients who have only mild to moderate deterioration of the gastroesophageal junction (absent or small hiatal hernia $\leq$2 cm, Hill grade I or II) and effective esophageal motility.

incomplete symptomatic response to maximal medical therapy. Furthermore, long-term studies from Europe [7▪▪] and the United States [8▪] have become available, pointing to sustained outcomes and durability up to 6 years after procedure. Concurrently, TIF has withstood the test of time with a solid safety profile. On the strength of this high-level clinical evidence from TIF studies, the American Medical Association assigned a new Current Procedural Terminology code for 'transoral esophagogastric fundoplasty', clearing the way for wider coverage and adoption.

The study reviews the most relevant literature published in the past 18 months, focusing on the currently performed version of the procedure (TIF 2.0, Fig. 1) [3▪] and addressing the critical issues of effectiveness, durability, safety, patient selection, and physiology.

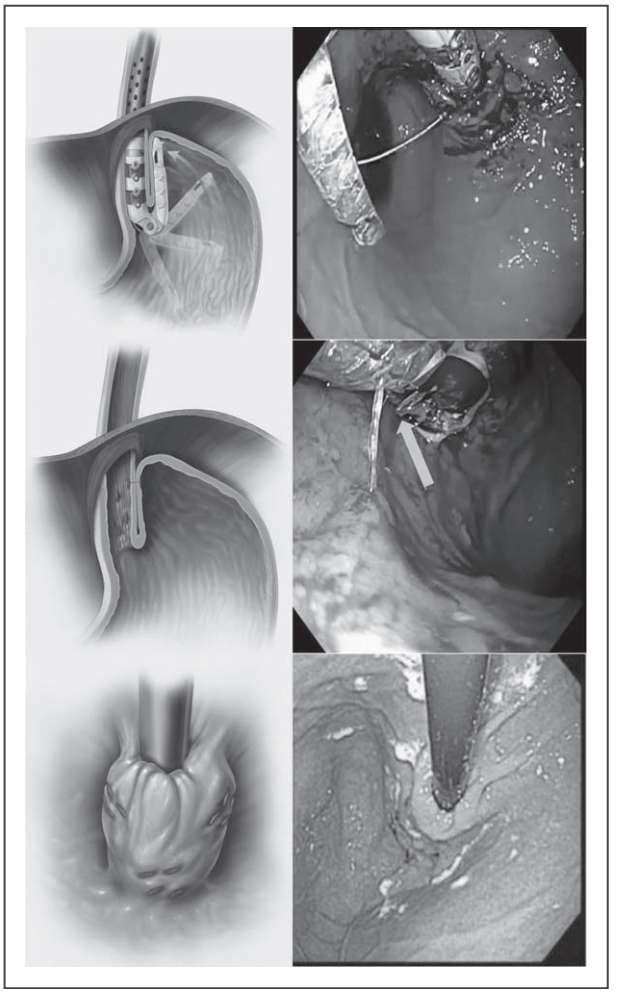

FIGURE 1. Transoral incisionless fundoplication creates a 270° anterior partial fundoplication.

EFFECTIVENESS

There are three therapy goals for chronic GERD: improved symptom control, healing of reflux esophagitis, and prevention of complications [9]. The four most recent randomized reports [3▪–5▪,6▪▪] provided the highest level of evidence and most comprehensive data on the ability of TIF to achieve these goals.

Typical gastroesophageal reflux disease symptoms

The Randomized EsophyX vs. Sham, Placebo-Controlled Transoral Fundoplication (RESPECT) trial [3▪] specifically evaluated the efficacy of TIF in eliminating troublesome regurgitation as defined by the Montreal consensus definition [9]. This double-blind study was carried out at eight academic and community centers in the United States. The patients were randomly assigned either to the TIF group (TIF and placebo pills) or to the control group (sham procedure and optimized dose of omeprazole). In selected patients with a hiatal hernia 2 cm or less, elimination of troublesome regurgitation was achieved in 67% of TIF/placebo patients vs. 45% sham/PPI patients at 6-month follow-up ($P < 0.023$). Further evidence was found in the TIF EsophyX vs Medical PPI Open Label (TEMPO) trial, an RCT with a crossover arm, where troublesome regurgitation was eliminated in 97 and 93% of TIF patients at 6 and 12-month follow-up respectively [4▪,5▪]. Although high-dose PPI therapy provided considerable improvements at 6-month follow-up in the control (crossover) group, an additional 67% of nonresponders to PPI therapy reported elimination of troublesome regurgitation 6 months following TIF. Thus, the ability of TIF to effectively eliminate regurgitation may have

Table 1. Mean quality of life scores before transoral incisionless fundoplication and at 6 and 12-month follow-up in patient's randomized to the transoral incisionless fundoplication group (TEMPO trial) [4▪,5▪]

Parameters	Baseline (before TIF on PPIs)	6 months (off PPIs)	12 months (off PPIs)	*P* value (6 months vs. baseline)	*P* value (12 months vs. baseline)	*P* value (6 vs. 12 months)
RDQ	2.91 (1.32)	0.35 (0.53)	0.50 (0.73)	<0.001	<0.001	0.772
Heartburn RDQ	2.99 (2.55)	0.45 (0.86)	0.63 (1.01)	<0.001	<0.001	0.776
GERD-HRQL	26.25 (10.51)	5.23 (7.14)	5.41 (6.80)	<0.001	<0.001	0.995
Heartburn GERD-HRQL	17.69 (7.51)	3.74 (5.51)	3.76 (4.50)	<0.001	<0.001	>0.999

GERD-HRQL, gastroesophageal reflux disease health-related quality of life; PPI, proton pump inhibitor; RDQ, Reflux Disease Questionnaire; TIF, transoral incisionless fundoplication.

important clinical implications in the treatment of this challenging patient population.

Elimination of troublesome heartburn has also been confirmed in the most recent RCTs. Using primarily the Reflux Disease Questionnaire (RDQ) to evaluate symptoms, Hunter *et al.* [3▪] reported that TIF provided better control of heartburn than sham procedure off medication, and that median heartburn scores significantly decreased from 2.6 to 0.5 in the TIF/placebo group 6-month after procedure. In the TEMPO study, sustained improvements in heartburn scores were reported in patients evaluated after TIF and off PPI therapy (Table 1) [4▪,5▪].

Atypical gastroesophageal reflux disease symptoms

Historically, patients presenting with atypical GERD symptoms, such as asthma, chronic cough, hoarseness, or chronic sore throat present a therapeutic challenge because of their unpredictable and frequently incomplete response to PPIs. Additionally, diagnosing GERD in patients exhibiting only extraesophageal manifestations is often challenging. In this setting, objective evidence, such as ambulatory pH monitoring (% total time pH < 4), impedance testing (symptom index and symptom association probability), and endoscopic findings of erosive esophagitis are required to establish the diagnosis with more certainty [10]. In the TEMPO trial, elimination of all troublesome atypical symptoms in patients with objective documentation of GERD was achieved in 62% of patients at 6 months and 82% of patients at 12-month follow-up [4▪,5▪]. The incremental response from 62 to 82% was not surprising; previous studies had already suggested that atypical symptoms tend to resolve at a slower pace than typical symptoms after antireflux surgery [11]. Based on these results, the TIF procedure appears to be a valuable alternative for well selected patients with significant atypical symptoms.

A European double-blind RCT (TIF vs. sham) was conducted in five centers using 'time to treatment failure' as the primary end point at 6 months. Using a composite outcome measure to evaluate individual therapeutic interventions, Lundell and colleagues found that significantly more TIF patients (59%) remained in clinical remission, compared with patients who underwent sham procedure (9%), $P < 0.0001$. The authors noted that the level of scientific proof supporting TIF efficacy and use surpasses anything currently available outside the area of traditional laparoscopic antireflux surgery [6▪▪].

DURABILITY

Lack of durability and poor long-term outcomes in the first generation of endoluminal therapies can largely explain their falling out of favor and ultimately being pulled off the market. Similar concerns have been raised in the early experience with TIF; however, review of the recent long-term follow-up data offers some reassurance.

In a cohort of patients with documented GERD treated by a single endoscopist, Testoni and colleagues [7▪▪] reported that symptomatic improvement, as measured by two GERD-specific quality of life questionnaires, is stable up to 6 years after TIF. Additionally, the percentage of patients who either stopped or halved their PPI therapy at 3-year follow-up seems nearly unchanged at 6 years (84%). Surprisingly, in the same study, complete discontinuation of PPIs dropped from 61% of patients at 6 months to 30% at 6 years, with the sharpest drop observed between 6 and 12 months after TIF. This confirms findings from previous studies [8▪,12▪] which suggest that most TIF failures occur within the first-year after procedure, underlining the consequences of poor patient selection. Furthermore, PPI use after an endoscopic procedure can often be explained by easy access to over-the-counter medications or patients' tendency to resume PPI use without objective documentation of GERD.

These factors suggest that PPI use after an endoscopic procedure might be an unreliable measure of success or failure. In fact, recent studies have demonstrated that PPIs may represent an acceptable adjunct to TIF procedures in patients whose GERD symptoms were uncontrolled on high-dose PPIs preoperatively [4▪,5▪].

Resolution of GERD symptoms also appears to be sustained in long-term follow-up studies. In the TEMPO trial, elimination of troublesome regurgitation was reported in 91% of patients at 3 years and resolution of atypical symptoms was supported by normalization of Reflux Symptom Index score in 87% of patients [abstract accepted for a podium presentation, the Society of American Gastrointestinal and Endoscopic Surgeon (SAGES) 2016 Annual Meeting]. Most importantly, resolution of both typical and atypical symptoms remained stable between the 1 and 3-year follow-up, indicating durability of TIF and confirming previously reported results in the large, prospective, multicenter US TIF registry [8▪].

SAFETY AND SIDE-EFFECTS

Consistently, and across all studies, low complication rates for TIF have been reported [3▪–5▪,6▪▪,7▪▪,8▪,12▪]. A 2013 systematic review of the published TIF literature found that the major complication rate was 3.2%, which is comparable with laparoscopic Nissen fundoplication [13]. In a database from the manufacturer of the EsophyX device, serious adverse events occurred in 0.41% of more than 17 000 TIF patients to date (Fig. 2), and there have been no reported mortalities following the procedure. In the RESPECT study, with the exception of brief postoperative epigastric pain, complications and adverse effects were no different between TIF/placebo and sham/PPI groups [3▪]. Authors of the TEMPO trial attribute the absence of any serious adverse events in their study to the experience of the investigators, each having performed more than 20 TIF procedures before study initiation [4▪,5▪]. Although improvements in the device and technique over the last few years have made the procedure more operator friendly, a rigorous, standardized training, and a strict educational curriculum for any new user is critical to preserving the safety profile of the TIF.

In addition to a strong safety profile, the very low incidence of new dysphagia, gas bloat, and excessive flatulence is perhaps one of the most attractive features of the TIF procedure. Postfundoplication syndromes were found to be virtually nonexistent in recent studies [3▪–5▪,6▪▪,7▪▪,8▪,12▪,13]. In fact, preexisting dysphagia, gas bloat, and flatulence were improved after TIF (92, 79, and 81%, respectively, at 6 months) [4▪]. Thus, it appears that TIF is well positioned to fill the 'therapy gap' between medical therapy and more invasive surgical procedures such as laparoscopic Nissen [3▪].

PATIENT SELECTION

Appropriate patient selection is critical for achieving good outcomes with any antireflux procedure. The presence of typical symptoms and a positive response to PPI therapy have traditionally been viewed as predictors of successful outcomes following laparoscopic antireflux surgery [14]. Although

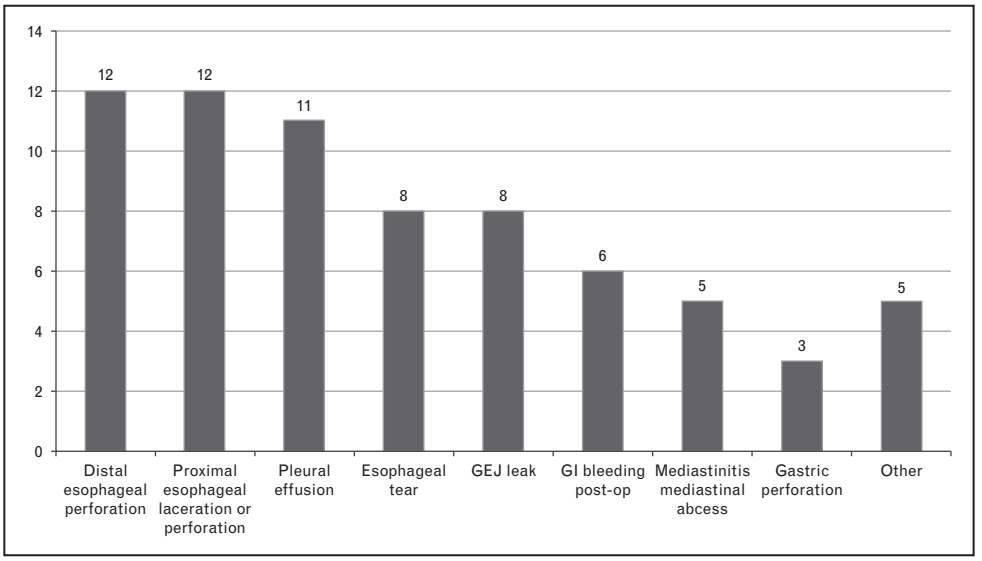

FIGURE 2. Serious adverse events after transoral incisionless fundoplication. Serious adverse events occurred in 0.41% of more than 17 000 patients to date (data provided by EndoGastric Solutions).

such patients are usually satisfied with continued medical management, many patients with partial or minimal response to PPI therapy will seek alternative treatments. In a prospective study of 158 patients with inadequate symptom control despite high-dose PPI therapy, those with typical symptoms (GERD-HRQL > 15) were more likely to have a successful TIF outcome [15▪]. For patients with more severe heartburn (GERD-HRQL score >30 on high-dose PPI therapy), preoperative counseling is key to setting realistic expectations regarding the likelihood of requiring adjunct acid suppression therapy to fully control GERD symptoms after the TIF [5▪].

Better TIF outcomes are also more likely if there is minimal anatomic deterioration of the gastroesophageal junction (GEJ) [7▪▪]. The Hill classification can be used to grade the endoscopic appearance of the gastroesophageal flap valve on a scale of I–IV, with higher values reflecting more severe disruption of the GEJ. The excellent clinical outcomes achieved in the TEMPO study [4▪,5▪] might be credited to restricting selection to patients with Hill grades I and II, while excluding patients with severe erosive esophagitis (Los Angeles grade C or D). In contrast, the somewhat lower rates of elimination of troublesome GERD symptoms observed in the RESPECT trial [3▪] can be attributed to the inclusion of patients with Hill grade III and more advanced disease.

In a single center, unblinded randomized trial by Witteman *et al.* [16▪], poor patient selection may have contributed to suboptimal outcomes. Despite sustained improvement in symptoms and quality of life scores in the TIF group at 12-month follow-up, the majority of TIF patients (61%) had resumed PPI therapy and there was no improvement of esophageal acid exposure from baseline. It is important to note that 41% of patients in the TIF arm of this study had Hill grade III or IV valve at entry, suggesting a large hiatal hernia. Furthermore, several of these TIF procedures were completed with as few as seven fasteners, whereas the most recent studies consistently used more than 20 fasteners on average. Incidentally, the number of fasteners deployed had previously been identified by Testoni *et al.* [7▪▪] as an important predictor of better outcomes.

Thus, based on the critical analysis of recent data, ideal candidates for the TIF procedure are chronic GERD patients with partial but inadequate symptom control on high-dose PPI therapy who have only mild to moderate deterioration of the GEJ (absent or small hiatal hernia ≤2 cm, Hill grade I or II), and effective esophageal motility.

OBJECTIVE OUTCOMES AND PHYSIOLOGY

TIF has been shown to achieve normalization of acid exposure in the distal esophagus in 45 [5▪] to 69% [6▪▪] of patients. The TEMPO randomized trial suggested that near equivalent rates of pH normalization are achieved when comparing TIF and maximal PPI therapy (52 vs. 54% of patients at 6-month follow-up) [4▪], a result in line with a report indicating that 50% of patients with complete reflux symptom control on twice daily PPI therapy had normalized acid exposure [17].

Healing of reflux esophagitis, a primary measure of success in evaluating GERD therapy, does not consistently correlate with rates of distal esophageal pH normalization [18]; this holds true with the TIF procedure. Healing of esophagitis was achieved in a majority of patients undergoing TIF across various studies, including the TIF US registry (75% at 24-month follow-up) [8▪], the RESPECT, and TEMPO randomized trials (77–100%) [3▪–5▪], well above the rates of pH normalization noted in these same studies. In the TEMPO trial, healing of reflux esophagitis rose from 38% in control patients on high-dose PPIs alone to 85% 6 months after crossover to TIF, whereas distal esophageal pH normalization, as evaluated by 48-h pH Bravo testing, fell from 52 to 33%, respectively at these same points. The reason underlying this disparity between rates of healing of esophagitis and rates of normalization of esophageal acid exposure is not clear. We speculate that a significant proportion of patients in this study may have suffered from nonacid reflux or experienced excessive proximal extent of reflux episodes [5▪], a theory that could be confirmed by impedance testing in future studies.

Although higher rates of pH normalization may be achieved with traditional antireflux laparoscopic surgery, such procedures have been associated with significant rates of postfundoplication syndromes such as dysphagia and gas bloat [10], likely side-effects attributable to supracompetent valves. One might argue that symptom control and healing of reflux esophagitis are more clinically relevant goals of GERD therapy than normalization of distal esophageal acid exposure. As had been observed in previous studies evaluating GERD therapies [17,19,20], recent TIF studies confirm the poor correlation between post-TIF symptom control and pH normalization [3▪,5▪].

In an attempt to explain the mechanism of action of TIF, recent physiologic studies point to a decrease in the number of postprandial transient lower esophageal sphincter relaxation episodes and to significant reduction in the distensibility of the GEJ [21▪]. One of the benefits of TIF

is the selective reduction of liquid-containing reflux episodes, whereas gas reflux events remain unaffected, accounting for the ability to vent gas following the TIF procedure and avoiding the gas bloat commonly associated with laparoscopic Nissen fundoplication.

CONCLUSION

The quality of high-level clinical evidence found in the recent literature supports the efficacy, safety, and durability of the TIF procedure performed with the EsophyX device and justifies its use as a therapeutic option for well selected patients with chronic GERD. The value of TIF has been demonstrated in select cases where PPIs fail to achieve complete symptomatic control. Ongoing studies focusing on the durability of TIF and comparing it to established treatments such as laparoscopic Nissen fundoplication are likely to further solidify its position in the armamentarium of antireflux therapies.

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Conflicts of interest

K.T. has received speaking honoraria from EndoGastric Solutions, manufacturer of the EsophyX device.

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- ■■ of outstanding interest

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The study attempts to explain the mechanism of action of TIF.