NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of endoluminal gastroplication for gastro-oesophageal reflux disease

Gastro-oesophageal reflux disease is when stomach acid and stomach contents flow back into the oesophagus because the ring of muscle around the top of the stomach is not working properly.

In this procedure a device with an endoscope (a thin, flexible tube with a camera on the end) is passed through the mouth and into the stomach. The device is used to wrap the upper portion of the stomach around the lower portion of the oesophagus and secure it, for example using multiple plastic fasteners. The aim is to prevent the stomach contents from flowing back into the oesophagus.

Contents

Abbreviations

Word or phrase	Abbreviation
Confidence interval	CI
Endoscopic full thickness plication	EFTP
Gastro-oesophageal reflux disease	GORD
Gastro-oesophageal reflux disease Health Related Quality of Life	GORD-HRQL
Gastro-oesophageal Reflux Symptom Score	GERSS
Health Technology Assessment	HTA
Intention to treat	ITT
Interquartile range	IQR
Proton pump inhibitor	PPI
Reflux Disease Questionnaire	RDQ
Reflux Symptom Index	RSI
Standard mean difference	SMD
Transoral incisionless fundoplication	TIF

Introduction

The National Institute for Health and Care Excellence (NICE) prepared this interventional procedure overview to help members of the interventional procedures advisory committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and professional opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in October 2022.

Procedure name

- Endoluminal gastroplication for gastro-oesophageal reflux disease

Professional societies

- Association of Upper Gastrointestinal Surgeons for Great Britain and Ireland (AUGIS)
- British Society of Gastroenterology (BSG).

Description of the procedure

Indications and current treatment

Gastro-oesophageal reflux disease (GORD) is a common condition caused by failure of the sphincter mechanism at the lower end of the oesophagus. Symptoms of GORD can be broadly grouped into those directly related to reflux episodes, such as heartburn, regurgitation and chest pain and nausea, and those symptoms caused by complications of reflux disease, including problems swallowing (dysphagia) and respiratory symptoms. Repeat episodes of GORD can damage the lining of the oesophagus and lead to oesophageal ulceration, oesophageal stricture, and Barrett's oesophagus.

NICE's clinical guideline on the investigation and management of gastro-oesophageal reflux disease and dyspepsia in adults makes recommendations for treatment The standard treatments for symptomatic GORD are lifestyle modification and drug therapy. Drug therapy includes acid-lowering agents such as H_2 receptor antagonists and proton pump inhibitors (PPIs). People with reflux symptoms that do not respond to medical treatment or who develop intolerance to medication may have anti-reflux surgery. Surgical or laparoscopic fundoplication surgery may be used, and minimally invasive treatments such as endoscopic radiofrequency ablation or endoscopic injection of bulking agents are available.

What the procedure involves

Different devices have been used for this procedure and exact details of the technique vary. The procedure is usually done with the patient under general anaesthesia. An endoscopic fastening device is inserted through the mouth and into the stomach, along with an endoscope for constant visualisation. The device is used to attach the fundus to the anterior and left lateral wall of the distal oesophagus slightly above the oesophagogastric junction. With 1 of the devices, polypropylene fasteners are delivered through apposed layers of oesophageal and fundus tissue to anchor the repair. About 20 fasteners are implanted during the procedure to create a full thickness, partial circumference, gastro-oesophageal fundoplication. The aim is to recreate a valve and form a barrier to reflux.

Endoluminal gastroplication for gastro-oesophageal reflux disease aims to reduce the morbidity associated with open or laparoscopic fundoplication.

Outcome measures

The Gastro-oesophageal Reflux Disease-Health Related Quality of Life (GORD-HRQL) is used to measure patient symptoms and impacts on daily life. Questions are scored 0 to 5 with higher scores indicating greater severity. Overall scores are obtained by summing the scores for each individual question; scores range from 0 to 50 or 0 to 75 depending on whether questions related to regurgitation are included.

The Gastro-oesophageal Reflux Symptom Score (GERSS) is used to assess the severity (scored 0 to 3 with 3 being the most severe) and frequency (scored 0 to 4 with 4 being daily) of heartburn, regurgitation, abdominal distension, dysphagia, and cough. To calculate total symptom scores, severity and frequency are multiplied for each symptom and are then summed, with overall scores ranging from 0 to 60.

The Reflux Symptom Index (RSI) is used to assess the severity of reflux and consists of 9 items each scored 0 to 5 (with 5 being the most severe).

The Reflux Disease Questionnaire (RDQ) is a 12-item self-reported questionnaire used to measuring the frequency and severity of upper gastrointestinal symptoms (heartburn, regurgitation, and epigastric pain) over a week; scores range from 0 to 5 for each item (with 5 being the most severe).

The DeMeester score is a 6-point global measure of acid exposure (defined as an oesophageal pH drop below 4) and ranges from 0 to 100, with a DeMeester score of greater than 14.72 indicating reflux.

Efficacy summary

Reduction in GORD symptoms

In a systematic review and meta-analysis of 1,475 people, the standard mean difference (SMD) between Gastro-oesophageal Reflux Symptom Score (GERSS) before and after all procedures (follow-up range 6 to 24 months) was 23.78 (95% CI 22.96 to 24.60; 6 studies, n=507; $p<0.001$; $I^2=98\%$), the SMD between the RSI before and after all procedures was 14.28 (95% CI 13.56 to 15.01; 8 studies, n=590; $p<0.001$; $I^2=95\%$), and the proportion of patients reporting resolution of hiatal hernia post-procedure was 91% (95% CI 83% to 98%; 12 studies; $p < 0.001$, I2=85.8%; McCarty 2018).

In an evidence synthesis of 580 people (done as part of a Health Technology Assessment [HTA]), of 3 studies reporting on heartburn, 1 study reported a statistically significant improvement between baseline and 6 months according to

both GORD-HRQL (scored 0 to 30 for heartburn with higher scores indicating greater severity) (17.69 to 3.74, p<0.001) and mean RDQ score across all heartburn items (scored 0 to 5 with higher scores indicating greater severity) (2.6 to 0.5, p<0.001). A second study reported a statistically significant improvement in mean RDQ across all heartburn related items from a mean of 2.99 at baseline to 0.45 at 6-month follow up (p<0.001) but no statistically significant difference between the intervention and control group (p=0.936; Grössmann 2021).

In an RCT of 70 people, the median percentage improvement in heartburn score according to GORD-HRQL in people assigned to endoscopic full thickness plication (EFTP) was 56% (IQR 38% to 100%) after 3 months, 75% (IQR 57% to 100%) after 6 months and 90% (IQR 67% to 100%) after 12 months. These median improvement end points were all statistically significant compared with sham treatment (p=0.001; Kalapala 2022).

In a case series of 50 people, the mean heartburn score (scored 0 to 30 with higher scores indicating increased severity) for people decreased from a mean of 18±9 at baseline to 8±7 at 2 years (n=45, p<0.01), 9±8 at 3 years (n=45, p<0.01), 4.5±4.6 at 5 years (n=34, p<0.01), 4.6±4.7 at 7 years (n=24, p<0.01), and 4.2±3 at 10-year follow up (n=12, p<0.01).

In the same study, the mean regurgitation score (scored 0 to 30 with higher scores indicating increased severity) decreased from a mean of 17±9 at baseline to 9±6 at 2 years (n=45, p<0.01), 10±6 at 3 years (n=45, p<0.01), 3.2±4.3 at 5 years (n=34, p<0.01), 3.3±4.4 at 7 years (n=24, p<0.01), and 3.2±4.4 at 10-year follow up (n=12, p<0.01; Testoni 2019).

In the evidence synthesis of 580 people from 3 studies, 1 study reported a statistically significant improvement between baseline and 6 months according to mean RDQ score across all regurgitation items (items (scored 0 to 5 with higher scores indicating greater severity) (2.94 to 0.19, p<0.001). A second study reported a statistically significant improvement in mean RDQ score across all regurgitation items from a 3.5 at baseline to 0.5 at 6-month follow up (p<0.001) but no statistically significant difference between the intervention and control group (p=0.072). A third study reported a statistically significant improvement in regurgitation between treatment groups (p=0.01) at 12 months according to a non-validated score. (Grössmann 2021).

In a crossover RCT of 63 people, the average regurgitation score according to the mean RDQ across regurgitation items (scored 0 to 5 with higher scores indicating greater severity) decreased from 3 on PPI and 3.7 off PPI at baseline to 0.6 at 1 year (n=60; p<0.001), 0.6 at 3 years (n=52; p<0.001), and 0.7 at 5 years (n=44; p<0.001). Elimination of troublesome regurgitation (according to the

RDQ) was 88% (n=48) at 1 year, 90% (n=41) at 3 years and 86% (95% CI 72 to 94%, n=43) at 5-year follow up (Trad 2018).

In an RCT of 70 people, the median percentage improvement in regurgitation score according to GORD-HRQL in people assigned to EFTP was 60% (IQR 48% to 92%) after 3 months, 96% (IQR 60% to 100%) after 6 months and 100% (IQR 90% to 100%) after 12 months. These median improvement endpoints were all statistically significant compared with sham treatment (p=0.001; Kalapala 2022).

In a case series of 151 people, median regurgitation score (scored 0 to 30 with higher scores indicating greater severity) also decreased from a baseline value of 15 (IQR 8 to 20) off PPIs and 11 (5 to 20) on PPIs to 0 (interquartile range [IQR] 0 to 4) at 4.92 years and 1 (IQR 0 to 3) at 5 to 9-year follow up for all patients.

In the same study, median dysphagia assessed by GORD-HRQL (scored 0 to 10 with higher scores indicating greater severity) decreased from a baseline median of 2 (IQR 0 to 4) to of 0 (IQR 0 to 2) at a median 4.92 year follow up ($p<0.0001$), median abdominal pain assessed by GORD-HRQL (scored 0 to 5 with 5 indicating greater severity) decreased from a baseline median of 2 (IQR 0 to 4) to 1 (IQR 0 to 2) at a median 4.92 year follow up ($p<0.001$; Bell 2021).

In the crossover RCT of 63 people, the average RSI score (scored 0 to 45 with higher scores indicating greater severity) decreased from 22.2 on PPI and 26 off PPI at baseline to 6.3 at 1 year (n=60; $p<0.001$), 4.3 at 3 years (n=52; $p<0.001$), and 6.8 at 5-year follow up (n=44; $p<0.001$). Elimination of troublesome atypical symptoms according to RSI was 82% (95% CI 70 to 90%, n=55) at 1 year, 82% (95% CI 75 to 95%, n=48) at 3 years and 80% (95% CI 64 to 89%, n=39) at 5-year follow up (Trad 2018).

In a case series of 46 people, the median RSI score at baseline in those completing 3-year follow up was 23.5 (95% CI 17 to 25.5) and decreased to 6 (95% CI 2.3 to 15, p=0.01) after 3 years. The proportion of people who had at least a 50% reduction in symptom score according to RSI in intention to treat (ITT) analysis was 70% (32/46) at 6 months, 70% (32/46) at 1 year, 62% (24/39) at 2 years and 60% (21/35) at 3 years (Testoni 2022).

Quality of life

In the systematic review and meta-analysis of 1,475 people, the SMD between GORD-HRQL before and after all procedures (follow up range 1.5 to 59 months) was 17.72 (95% CI 17.31 to 18.14; 25 studies, n=1236; $P < 0.001$; $I^2=94\%$).

In the case series of 50 people, the mean GORD-HRQL score (scored 0 to 50 with higher scores indicating increased severity) for patients off PPI decreased

from a mean of 46±19 at baseline to 18±13 at 2 years (n=45, p<0.01), 19±14 at 3 years (n=45, p<0.01), 10±7 at 5 years (n=34, p<0.001), 10±7.7 at 7 years (n=24, p<0.001), and 9.5±6.1 at 10-year follow up (n=12, p<0.001; Testoni 2019).

In the case series of 151 people, 64% of patients experienced a >50% reduction in GORD-HQRL scores at a median follow up of 4.92 years. The median GORD HRQL at 4.92 years decreased to 6 (IQR 3 to 16) from a baseline value of 21 (IQR 9.5 to 39) for patients off PPI. For patients on PPI, the median GORD HRQL decreased to 2 (IQR 0 to 7) from a baseline value of 14 (IQR 4-24). For all patients, the median GORD-HRQL between 5 and 9 year follow up was 5 (IQR 2 to 9) and 68% of patients followed up for at least 5 years reported a >50% reduction in GORD-HQRL scores (Bell 2021).

In the crossover RCT of 63 people, the average GORD-HRQL score (with higher score indicating greater severity) decreased from 26.4 on PPI and 32.8 off PPI to 6.9 at 1 year (n=60), 5.5 at 3 years (n=52), and 6.8 at 5 years (p<0.001 versus baseline for all values). Patient satisfaction with current health according to the GORD-HRQL increased from 2% at baseline to 75% (95% CI 63 to 84%, n=60; p<0.001) at 1 year, 83% (95% CI 70 to 91%, n=52; p<0.001) at 3 years, and 70% (95% CI 56 to 82%, n=44; p<0.001) at 5-year follow up (Trad 2018).

In the case series of 46 people, the median GORD-HRQL score at baseline in those completing 3-year follow up was 24 (95% CI 9.7 to 30.6) and decreased to 2.5 (95% CI 0.47 to 8.7, p=0.007) after 3 years. The proportion of people who had at least a 50% reduction in symptom score according to GORD-HRQL in ITT analysis was 67% (31/46) at 6 months, 65% (30/46) at 1 year, 64% (25/39) at 2 years and 60% (21/35) at 3 years (Testoni 2022).

In the RCT of 70 people, 66% (23/35) of patients assigned to endoscopic full thickness plication (EFTP) experienced at least a 50% improvement in GORD-HRQL after 3-month follow up (p<0.001 compared with sham). The median percentage improvement in GORD-HRQL in people assigned to have endoscopic full thickness plication was 69% (IQR 38% to 87%) after 3 months, 81% (IQR 61% to 100%) after 6 months and 92% (IQR 84% to 100%) after 12 months. These median improvement endpoints were all statistically significant compared with sham treatment (p=0.001; Kalapala 2022).

In a case series of 57 patients, median GORD-HRQL score increased from a median of 24 (IQR 15 to 28) to 7 (IQR 2 to 18) after a median 12-month follow up (n=36, p<0.01) and 10 (IQR 6 to 14) after a median 97 month follow up (n=23, p<0.01). Dissatisfaction with GORD symptom management also decreased from a baseline of 100% to 26% after a median follow up of 97 months (Chimikungara 2018).

Medication usage

In the systematic review and meta-analysis of 1,475 people, the mean proportion of people who reported stopping PPIs after the procedure (follow up range 1.5 to 59 months) was 89% (95% CI 82% to 95%; 28 studies, n=1,407; p<0.001, I^2=93.6%; McCarty 2018).

In the case series of 50 people, the proportion of people who halved PPI doses or stopped PPI altogether was 78% (39/50) at 2-year follow up, 76% (38/50) at 3 years, 60% (25/42) at 5 years, 65% (20/31) at 7 years and 73% (11/15) at 10 years in ITT analysis (Testoni 2019).

In the case series of 151 people, the proportion of people free of daily PPI use was 7% at baseline and increased to an estimated 73% at 0.5 years (n=94), 72% at 1 year (n=83), 71% at 2 years (n=78), 68% at 3 years (n=73), 69% at 4 years (n=65), 67% at 5 years (n=53), 69% at 6 years (n=42), 74% at 7 years (n=27), and 78% at 8 years (n=18; Bell 2021).

In a crossover RCT of 63 people, the percentage of people on daily PPI therapy decreased from 100% at baseline to 17% (n=60) at 1 year, 27% (n=52) at 3 years and 34% (95% CI 22 to 49%) at 5 years. At 5-year follow up, 46% (95% CI 32 to 60%) of people reported completely stopping PPI therapy (Trad 2018).

In the crossover RCT of 63 people, the median GORD-HRQL score at baseline in those completing 3-year follow up was 24 (95% CI 9.7 to 30.6) and decreased to 2.5 (95% CI 0.47 to 8.7, p=0.007) after 3 years. The proportion of people who had at least a 50% reduction in symptom score according to GORD-HRQL in ITT analysis was 67% (31/46) at 6 months, 65% (30/46) at 1 year, 64% (25/39) at 2 years and 60% (21/35) at 3 years (Trad 2018).

In the case series of 46 people, the proportion of people who stopped or at least halved PPI dose was 80% (37/46) at 6 months, 83% (38/46) at 1 year, 80% (31/39) at 2 years and 77% (27/35) at 3 years (Testoni 2022).

In the RCT of 70 people, the percentage of people off PPI at 12-month follow up was 63% (22/35) in the EFTP versus 11% (4/35) in the sham group (p<0.001; Kalapala 2022).

In the case series of 57 people, the percentage of people achieving PPI cessation was 47% after a median 12-month follow up (n=36) and 27% after a median 97-month follow up (n=23; Chimikungara 2018).

Oesophageal pH measurement and acid exposure

In the systematic review and meta-analysis of 1,475 people, the SMD between oesophageal acid exposure time before and after all procedures was 3.43 (95% CI 2.98 to 3.88; 15 studies, n=722; p<0.001; I^2 = 86%) with a follow up range from 1.5 to 36 months.

In the same study, the SMD between the mean number of reflux episodes in a 24-hour period before and after all procedures (follow up range 6 to 36 months) was 51.57 (95% CI 47.96 to 55.18; 13 studies, n=695; p<0.001; I^2 = 85%), and the SMD between DeMeester scores before and after all procedures ((follow up range 6 to 36 months) was 10.22 (95% CI 8.31 to 12.12; 11 studies, n=647; p<0.001; I^2 = 65%; McCarty 2018).

In the crossover RCT of 63 people, it was reported that 40% (16/40) achieved pH normalisation (defined as <5.3% of time with pH<4) at 3-year follow up (Trad 2018).

In the case series of 46 people, the number of acid refluxes decreased from a median baseline of 37 (IQR 24.5 to 54.2) to 24 (IQR 12.3 to 41.2) at 6-month follow up (p=0.0002) and 27.5 (IQR 13.4 to 46.6) at 1-year follow up (p=0.15). In the same study, the median percentage time with oesophageal pH < 4 decreased from 5.8% (IQR 1.5% to 8.3%) at baseline to 3.8% (1.3% to 5.1%) at 6-month follow up (p=0.006) and 4.2% (IQR 2.9% to 5%) at 1-year follow up (p=0.16; Testoni 2022).

In the RCT of 70 people, the median number of acid reflux episodes decreased from 51 (IQR 33 to 73) at baseline to 34 (IQR 16 to 63) at 3-month follow up (p=0.005); there was a further decrease to 32 (IQR 18 to 74) at 12-month follow up but this was not statistically significant (p=0.316; Kalapala 2022).

Need for reintervention

In the evidence synthesis of 580 people done as part of a HTA, 18 surgical reinterventions were reported across 2 RCTs; 14 in the intervention groups (11 endoscopic and 3 laparoscopic) and 4 in the control groups (all laparoscopic). In an observational study of 100 people also included in the HTA, 7 laparoscopic interventions and 1 endoscopic intervention was reported (Grössmann 2021).

In the systematic review and meta-analysis of 1,475 people, surgical revision or reintervention was reported in 7.5% (88/1176) of people. Most (89.5%) of these

revisions were done within 6 months of the initial procedure in studies where timing of re-treatment was reported (McCarty 2018).

In the case series of 50 people, 14% (7/49) of people were unresponsive to TIF and had surgical fundoplication during 10-year follow up (Testoni 2019).

In the case series of 151 people with median follow up of 4.92 years, 22% (33/151) of people had laparoscopic revisional surgery at a median of 14.7 months post-TIF (Bell 2021).

In the case series of 46 people, 1 person was unresponsive to transoral incisionless fundoplication (TIF) and had Nissen fundoplication within 6 months after the procedure (Testoni 2022).

In the case series of 57 people, 21% (12/57) of people had subsequent laparoscopic surgery after recurrent GORD at a median interval of 24 (IQR 10 to 36) months after TIF (Chimikungara 2018).

Safety summary

All events

In the systematic review and meta-analysis of 1,475 people, the overall rate of serious adverse events was 2% (95% CI 1% to 3%; 29 studies; $p<0.001$; $I^2=54.1\%$; McCarty 2018), with follow up from studies included in this measure ranging from 1.5 to 59 months (McCarty 2018).

In the evidence synthesis of 580 people, 1 study reported a greater percentage of people experiencing from moderate to severe adverse events in the intervention group than the control group with a follow up range of 3 to 12 months (Grössmann 2021).

Death

In a HTA of 580 people, death was reported in 1 study in 1 person in 11 months after the procedure (Grössmann 2021).

Perforation

In a case report outlining a case of oesophageal perforation after the procedure, the person subsequently developed mediastinitis, left sided pneumothorax, bilateral pleural effusions, and empyema. The person needed mechanical ventilation for 12 days and also developed acute renal injury; at the most recent follow up (time not reported) the patient had been hospitalised for 2 weeks because of the non-resolving right-sided empyema (Edriss 2014).

In a case report outlining a case of oesophageal perforation and oesophagopulmonary fistula after the procedure, the person was admitted to hospital multiple times over several weeks and went into early septic shock. After surgical treatment and drainage of a large parenchymal abscess cavity, the person was discharged with oral antibiotics and had no further complaints of reflux at 1 month follow up (Titus 2013).

In the case series of 151 people, oesophageal perforation was reported in 1% (2/151) of people, with 1 of the 2 people presenting with a mediastinal abscess. Both patients had laparoscopic surgery and recovered without further complications (Bell 2021).

In a case series of 46 people, 1 person reported oesophageal perforation and 1 person reported gastric fundus perforation (Testoni 2022).

Pneumothorax

In a case series of 50 people, pneumothorax happened in 4% (2/51) of procedures which was confirmed by X-ray immediately after the procedure and managed by immediate transthoracic drainage. Both people were discharged from hospital within 3 days (Testoni 2019).

Pleural effusion

In the RCT of 70 people, 1 person had moderate left sided pleural effusion accompanied by fever which needed a 5 day stay in hospital (Kalapala 2022)

Pain

In the evidence synthesis of 580 people, 1 study reported readmission of 1 person because of immediate postoperative pain (Grössmann 2021).

In the case series of 46 people, 7% (3/45) reported epigastric pain which presented 6 hours after initial procedure and needed major analgesics (Testoni 2022).

In the RCT of 70 people, left shoulder pain was reported in 23% (8/35) of patients who had EFTP and left sided chest pain was reported in 1 person (Kalapala 2022).

Bleeding

In the RCT of 70 people, intraoperative bleeding at the site of suture application was reported in 14% (5/35) of people who had EFTP (Kalapala 2022).

Other

In 1 included study in the evidence synthesis of 580 people for a HTA, 13% of people reported an extra hospital day because of pain, anxiety, nausea, or postoperative urinary retention (Grössmann 2021).

In a case series of 151 people, 1 person reported vomiting and was treated with antibiotics, 1 person with existing interstitial lung disease had hypoxaemia and was hospitalised for 5 days, and 1 person had a prolonged ileus and needed 3 days hospitalisation (Bell 2021).

Anecdotal and theoretical adverse events

In addition to safety outcomes reported in the literature, professional experts are asked about anecdotal adverse events (events that they have heard about) and about theoretical adverse events (events that they think might possibly occur, even if they have never happened).

For this procedure, professional experts listed the following anecdotal adverse events: oesophageal and pharyngeal perforation.

The evidence assessed

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to endoluminal gastroplication for gastro-oesophageal reflux disease. The following databases were searched, covering the period from their start to 14 October 2022: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the internet were also searched. No language restriction was applied to the searches (see the literature search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The inclusion criteria were applied to the abstracts identified by the literature search. If selection criteria could not be determined from the abstracts the full paper was retrieved.

Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded if no clinical outcomes were reported, or if the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients with gastro-oesophageal reflux disease
Intervention/test	Endoluminal gastroplication
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the IP overview

This IP overview is based on an estimated 2,000 people (after excluding definite patient overlap) from 2 systematic reviews (1 of which was done as part of a HTA), 2 RCTs, 4 case series, and 2 case reports.

Other studies that were considered to be relevant to the procedure but were not included in the main summary of the key evidence are listed in the appendix.

Summary of key evidence on endoluminal gastroplication for gastro-oesophageal reflux disease

Study 1 Grössmann (2021)

Study details

Study type	**Systematic review (undertaken as part of a HTA)**
Country	USA, Netherlands, Belgium, France, Sweden
Search period	Search date 2020: publications from previous 10 years (no start date reported)
Study population and number	N=580 patients across 8 studies with chronic GORD
Age and sex	Intervention groups: median age 51 to 55 years Comparison groups: median age 48 to 62 years
Patient selection criteria	Inclusion criteria: Studies with adult patients with chronic GORD (>6 months) with at least 1 typical reflux symptom despite PPI treatment; patients having endoscopic plication therapy (one of GORDx, EsophyX and MUSE); control groups of placebo, standard surgical treatment of GORD or PPI therapy; RCTs, prospective non-RCTs, or prospective single-arm studies & registries with n≥100 (safety only); publications from the last ten years.
Technique	Interventions: Patients were assigned to endoscopic plication using EsophyXZ (Gastric Solutions, Redmond, Wash, USA), Medigus Ultrasonic Surgical Endostapler (MUSE; Medigus Ltd, Omer, Israel) or GORDx (G-SURG GmbH, Seeon-Seebruck, Germany) Controls: Patients were assigned to PPI therapy, sham intervention or laparoscopic reflux surgery (depending on the study).
Follow up	3 months to 5 years
Conflict of interest/source of funding	None.

Analysis

Study design issues: The HTA Core Model Application for Rapid Relative Effectiveness Assessment (REA; 4.2) was the primary source for selecting assessment elements.

To identify primary studies containing information about efficacy and safety within the scope of the HTA, systematic literature searches were conducted using Medline, Embase, the Cochrane Library, CRD (DARE, NHS-EED, HTA) and HTA-INAHTA. To identify ongoing and unpublished studies, a search in 3 clinical trials registries (ClinicalTrials.gov; WHO-ICTRP; EU Clinical Trials) was also done and manufacturers of relevant devices contacted.

Two researchers independently screened entries, and in the case of disagreements, a third researcher was involved to resolve the differences. Risk of bias was assessed using the Cochrane Risk of Bias Tool for RCTs, the Risk of Bias In Non-randomised Studies of Interventions assessment tool (ROBINS-I) for non-randomised controlled studies (NRCTs) and the International Health Economics checklist for single-arm studies.

The quality of the body of evidence was assessed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methodology in which “high” = confidence that the true effect lies close to the estimate of the effect; “moderate” = moderate confidence in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different; “low” = confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect; and “very low” = Evidence either is unavailable or does not permit a conclusion.

The following outcomes were deemed “crucial” to obtain a recommendation: heartburn score, regurgitation score, health related quality of life, adverse events (including serious adverse events), death and surgical reintervention.

Study population issues: All studies included chronic GORD patients. All identified studies included chronic GORD patients with a history of daily PPI use over the last six months. Patients with a hiatal hernia of more than two centimetres were excluded from all trials except for two studies that also enrolled patients with hiatal hernias up to three centimetres.

Other issues: Some studies included in this HTA used former generations of the devices used in this study which are no longer available on the market.

There is patient overlap with the McCarty 2018 systematic review in the case of the following studies: Witteman (2015), all included Trad studies (as well as the Trad 2018 study included in Table 2), Håkansson (2015) and Hunter (2015).

Key efficacy findings

Number of patients analysed: 580

Symptom changes and quality of life

Outcomes	Impact (I=intervention, C=control)	No. of studies (patients on intervention vs control)	Certainty of the evidence (Importance)
Overall health-related quality of life, assessed with: GORD-HRQL, Quality Of Life in Reflux and Dyspepsia (QOLRAD), Gastrointestinal Quality of Life index (GIQLI) follow up: mean 6 months	1 study (GORD-HRQL) reported a statistically significant improvement between the study groups (p<0.001), 2 other studies reported improvements from baseline to 6-months post operating (GORD-HRQL: p<0.001 and QOLRAD: p=0.0005), 1 study (GIQLI) reported no statistically significant differences between study groups at baseline and after follow up Ranges of GORD-HRQL scores, I vs. C, baseline/6-months, mean (n=2): 26.25-26.5/5.23-12.4 vs. not reported GIQLI (n=1): no exact values available QOLRAD score, I vs. C, baseline/6-months, median (n=1): 4.9/6.4 vs. 4.8/5.2	4 RCTs (139 vs. 98)	VERY LOW [a,b,c] (Crucial)
Overall health-related quality of life (overall	No statistically significant improvement between study groups: GIQLI: p=0.66	1 RCT (30 vs. 30)	LOW [d,e] (Crucial)

HRQL) assessed with: GIQLI follow up: mean 12 months	GIQLI score, I vs. C, baseline/12-months, mean (n=1): 96.3/119.2 vs. 88.4/123.7		
Overall health-related quality of life (overall HRQL) assessed with: GORD-HRQL follow up: mean 6 months	Statistically significant improvements in the control group at 6-months follow up: GORD-HRQL: p=0.016 GORD-HRQL score, I vs. C, baseline/6-months, mean (n=1): 24.8/8.9 vs. 29.3/4.1	1 NRCT (11 vs. 16)	LOW [d,e] (Crucial)
Heartburn score assessed with: GORD-HRQL, RDQ follow up: mean 6 months	1 study reported a statistically significant improvement (RDQ: p<0.001; GORD-HRQL: p<0.001) from baseline to 6-months post operating, 1 study reported a statistically significant improvement (RDQ: p<0.001) from baseline to follow up, but no ss improvement between study groups (p=0.936) RDQ score, I vs. C, baseline/6-months, mean (n=1): 2.99/0.45 vs. NR RDQ score, I vs. C, baseline/6-months, median (n=1): 2.6/0.5 vs. 3.0/0.8 GORD-HRQL, I vs. C, baseline/6-months, mean (n=1): 17.69/3.74 vs. not reported	2 RCTs (127 vs. 65)	LOW [b,f] (Crucial)
Heartburn score assessed with: non validated score follow up: mean 12 months	Statistically significant improvement between treatment groups: non validated score: p=0.01 Non validated score, I vs. C, baseline/12-months, mean (n=1): 2.50/1.07 vs. 2.96/0.17	1 RCT (30 vs. 30)	LOW [d,e] (Crucial)
Regurgitation score assessed with: RDQ follow up: mean 6 months	1 study reported a statistically significant improvement (RDQ: p<0.001) from baseline to 6-months post operating, 1 study reported a statistically significant improvement (RDQ: p<0.001) from baseline to follow up, but no ss improvement between study groups (RDQ: p=0.072) RDQ score, I vs. C, baseline/6-months, mean (n=1): 2.94/0.19 vs. NR RDQ score, I vs. C, baseline/6-months, median (n=1): 3.5/0.5 vs. 3.8/0.8	2 RCTs (127 vs. 65)	LOW [b,f] (Crucial)
Regurgitation score assessed with: non validated regurgitation score Follow up: mean 12 months	ss improvement between treatment groups: non validated score: p<0.05 Non validated score, I vs. C, baseline/12-months, mean (n=1): 1.52/0.57 vs. 1.96/0.11	1 RCT (30 vs. 30)	LOW [d,e] (Crucial)

a = 3/4 high RoB, 1/4 moderate RoB,
b = different trends of improvements comparing treatment groups
c = different generation of devices
d = power calculations are lacking
e = high RoB

f = 1/2 high RoB, 1/2 moderate RoB

Key safety findings

Outcomes	Impact	No. of studies (patients on intervention vs control)	Certainty of the evidence (Importance)
Any adverse event (Any AEs) assessed with: number of patients follow up: range 3 to 12 months	1 study reported a ss improvement in bloating between study groups (p=0.009), but no ss difference between groups considering dysphagia (p=0.366), 1 study reported more percentages of patients suffering from moderate to severe AEs in the intervention group compared with the control group, 2 studies reported no ss differences between study groups	4 RCTs (186 vs. 120)	VERY LOW [b,c,g] (Crucial)
Any AEs assessed with: discharge time Follow up: mean 6 months	The mean discharge times for the control and the intervention groups were 1.2 and 3 days, respectively (p<0.05), except for one complicated patient in the intervention group who stayed 21 days.	1 NRCT (11 vs. 16)	LOW [d,e] (Crucial)
Any AEs assessed with: number of patients Follow up: range 6 to 24 months	Overall dysphagia, bloating and flatulence improved comparing baseline and 6-months follow up. After 12-month follow up de novo dysphagia (n=2), bloating (n=1), and flatulence (n=2) occurred. After 24-month follow up, de novo flatulence occurred in 2 patients.	1 observational study (n=100)	LOW [h] (Crucial)
Severe adverse events (SAEs) assessed with: number of patients Follow up: range 3 to 12 months	all 3 studies reported no ss differences between study groups	3 RCTs (99 vs. 75)	Moderate c,i (Crucial)
	no ss difference between treatment groups (p=0.219)	1 NRCT (11 vs. 16)	LOW d,e (Crucial)
SAEs assessed with: number of patients Follow up: mean 6 months	Extra hospital day due to pain, anxiety, nausea or postoperative urinary retention: 17 (13.4%) Additional 4 hospital days due to pulmonary issues: 1 (0.8%) Re-admission 2 days after the procedure due to immediate postoperative pain: 1 (0.8%)	1 observational study (n=100)	LOW [h] (Crucial)
Death assessed with: number of patients Follow up: range 3 to 12 months	1 patient who had undergone interventional procedure after crossover died, death occurred 11 months after the procedure	1 RCT (40 vs. 20)	LOW [d,e] (Crucial)
	No death was reported	1 observational study (n=100)	LOW [h] (Crucial)

Re-surgery assessed with: number of patients/re-surgeries Follow up: range 3 to 12 months	2 studies reported 18 re-surgeries 14 in the intervention group (11 endoscopic, 3 laparoscopic) and 4 in the control group (all laparoscopic)	2 RCTs (77 vs. 53)	LOW [c,e] (Crucial)
	8 re-surgeries (1 endoscopic, 7 laparoscopic)	1 observational study (n=100)	LOW [h] (Critical)

b = different trends of improvements comparing treatment groups
c = different generation of devices
d = power calculations are lacking
e = high RoB
g = 2/4 high RoB, 2/4 moderate RoB
h = Initially 100 patients were included in the study, however, in the 24-months follow up cohort 127 patients were analysed.
i = power calculations available in 2/3 RCTs

Study 2 McCarty (2018)

Study details

Study type	**Systematic review and meta-analysis**
Country	Not reported
Recruitment period	2001-2017
Study population and number	n=1475 patients with GORD across 32 studies
Age and sex	Mean age 50 years, 48% male
Patient selection criteria	Inclusion criteria: human subject studies investigating the use of TIF modality for the treatment of GORD; patients of any age in whom the presence of GORD was suspected based on clinical symptoms alone, pH monitoring, or a combination of the two. Exclusion criteria: Insufficient data; review articles; editorials; correspondence letters that did not report independent data; case series and reported studies with fewer than five patients.
Technique	TIF was done using the EsophyX device (EndoGastric Solutions, Redmond, Washington, USA) or the Medigus Ultrasonic Surgical Endostapler system (MUSE; Medigus Ltd., Omer, Israel).
Follow up	Mean 15.8 months (range 1.5-59 months)
Conflict of interest/source of funding	None.

Analysis

Study design issues: The primary aim of this study was to evaluate the feasibility, efficacy, and tolerability of TIF for the treatment of refractory GORD. Efficacy and safety of the procedure was measured by immediate technical success rate (the ability to do the procedure without issue) and serious adverse events reported during the follow up. Symptomatic improvement was measured by complete PPI therapy cessation post-procedure, and by validated pre- and post-procedure questionnaires to assess typical and atypical GORD symptoms. Partial cessation or decreased dose of PPI therapy was not considered to represent symptomatic improvement.

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement outline for reporting systematic reviews was followed. Two reviewers independently screened the titles and abstracts of retrieved articles according to predefined inclusion and exclusion criteria. Any differences were resolved by mutual agreement and in consultation with a third reviewer. In the case of studies with incomplete information, contact was attempted with the principal authors to obtain additional data.

Meta-analysis was done by calculating pooled proportions, and standardised mean difference between pre- and post-procedure characteristics. Fixed-effects models were applied to pre- and post-TIF data to determine effect size and corresponding 95%.

Study population issues: Data involving 2 separate devices that do TIF were included: 30 studies (n = 1390) with EsophyX and 2 studies (n = 85) with MUSE. Among studies that included the EsophyX device, 26 studies (n = 1232) used the TIF 2.0 protocol, 3 studies (n = 138) adopted the TIF 1.0 protocol, and one study used ELF (n = 20).

A total of 24 studies (n = 1208) reported BMI, with a mean BMI of 26.1±1.7 kg/m^2. Average GORD symptom duration for included patients was 8.2±2.1 years, with a mean duration of PPI therapy of 6.8±2.1 years. Hiatal hernia prior to TIF was reported in 65.6% (n=864) of patients in studies reporting this, and oesophagitis was present in 56.2% (n=672) of patients in studies reporting this. A total of 20 patients were reported to have undergone prior surgical treatment for GORD-associated symptoms (i. e. previous laparoscopic Nissen fundoplication).

Other issues: There is patient overlap with Testoni (2019), the Grossman 2021 (Study 1) systematic review in the case of the following studies: Witteman (2015), all included Trad studies (as well as the Trad 2018 study included in Table 2), Håkansson (2015) and Hunter (2015). It is also possible that the patient population in Bell (2021) study overlaps with earlier publications from the same author that are included in this systematic review.

Key efficacy findings

Number of patients analysed: 1,475 (n = 1390 EsophyX across 30 studies and n=85 MUSE across 2 studies)

Procedural success

Immediate procedural success rate (follow up range 1.5 to 59 months): 99% (95% CI 97% to 100%; 21 studies; P < 0.001, I^2=45.8%).

Need for revision or surgical intervention: 7.5% (88/1176; 21 studies) -TIF revision procedure n = 19; Dor fundoplication n = 1; Toupet fundoplication n = 1; and laparoscopic Nissen fundoplication n = 67).

The majority (89.5%) of revisions were done within 6 months of the initial TIF procedure in studies where timing of re-treatment procedure was reported (6 studies). After repeat endoscopic or surgical intervention, 77.8% (7/9) patients reported improvement in studies where symptomatic improvement after re-treatment was assessed (3 studies).

Symptom and quality of life changes

- GORD HRQL (all procedures, follow up range 1 to 59 months): SMD 17.72 (95% CI 17.31 to 18.14; 25 studies, n=1236; P < 0.001; I^2=94%).
- GORD HRQL (TIF 2.0): SMD 17.62 (95% CI 17.19 to 18.05; 15 studies, n=997; P < 0.001).
- GORD HRQL (MUSE): SMD 19.93 (95% CI 17.74 to 22.13; 2 studies, n=85; P < 0.001).
- GORD HRQL (TIF 1.0): SMD 16.58 (95% CI, 14.35 to 18.81; 3 studies, n=138 P; < 0.001).
- GORD HRQL (ELF): SMD 33.00 (95% CI 26.15 to 39; 1 study, n=40).
- Gastro-oesophageal Reflux Symptom Score (GERSS) (follow up range 6 to 24 months): SMD 23.78 (95% CI 22.96 to 24.60; 6 studies, n=507; P < 0.001; I^2=98%).
- Reflux Symptom Index (RSI) score (follow up 6 to 36 months): SMD 14.28 (95% CI 13.56 to 15.01; 8 studies, n=590; P < 0.001; I^2=95%).
- Resolution of hiatal hernia post-procedure (follow up 6 to 59 months): 91% (95% CI 83% to 98%; 12 studies; P < 0.001, I^2=85.8%).

Medication requirement

Cessation of proton pump inhibitor post-procedure (follow up 1.5 to 59 months): 89% (95% CI 82% to 95%; 28 studies, n=1407; P < 0.001, I^2=93.6%).

Oesophageal acid exposure

- Oesophageal acid exposure time (all procedures, follow up 1.5 to 36 months): SMD 3.43 (95% CI 2.98 to 3.88; 15 studies, n=722; P < 0.001; I^2 = 86%)
- Oesophageal acid exposure time (TIF 2.0): SMD 3.61 (95% CI 3.14 to 4.08, P < 0.001)
- Oesophageal acid exposure time (MUSE): SMD 3.97 (95% CI 1.236 to 6.59, P = 0.003)
- Oesophageal acid exposure time (TIF 1.0): SMD 1.90 (95% CI – 3.43 to 7.23, P = 0.49)
- Oesophageal acid exposure time (ELF): SMD 0.60 (95% CI – 1.23 to 2.43, P = 0.52)
- Mean number of reflux episodes in a 24-hour period (all procedures, follow up 6 to 36 months): SMD 51.57 (95% CI 47.96 to 55.18; 13 studies, n=695; P < 0.001; I^2 = 85%)
- Mean number of reflux episodes in a 24-hour period (TIF 2.0): SMD 53.18 (95% CI 49.49 to 56.87, P < 0.001)
- Mean number of reflux episodes in a 24-hour period (MUSE) SMD 70.4 (95% CI 21.84 to 118.96, P = 0.004)
- Mean number of reflux episodes in a 24-hour period (TIF 1.0): SMD 10.0 (95% CI -38.85 to 58.85; P = 0.69)
- Mean number of reflux episodes in a 24-hour period (ELF): SMD 7.30 (95% CI -12.85 to 27.45, P = 0.48)
- DeMeester scores pre- and post-procedure (all procedures, follow up 6 to 36 months): SMD 10.22 (95% CI 8.31 to 12.12; 11 studies, n=647; P < 0.001; I^2 = 65%)
- DeMeester scores pre- and post-procedure (TIF 2.0): SMD 10.42 (95% CI 8.47 to 12.36; P < 0.001)
- DeMeester scores pre- and post-procedure (TIF 1.0): SMD 5.01 (95% CI -4.83 to 14.86; P = 0.32)

Key safety findings

Rate of serious adverse events (follow up 1 to 59 months): 2% (95% CI 1% to 3%; 29 studies; P < 0.001; I^2=54.1%).

Study 3 Testoni (2019)

Study details

Study type	Case series
Country	Italy
Recruitment period	2007 to 2012
Study population and number	n=50 patients with symptomatic GORD
Age and sex	Mean age 45 ± 16 years, 70% male
Patient selection criteria	Inclusion criteria: Patients with symptomatic GORD. Exclusion criteria: Atypical symptoms of GORD; functional reflux; hiatal hernia longer than 3 cm, Barrett's oesophagus, oesophageal stricture, previous oesophageal, gastric or major abdominal surgery; other severe comorbidities (including collagen disease).
Technique	Fundoplication (TIF 2.0) was done by a single endoscopist using the EsophyX device.
Follow up	10 years
Conflict of interest/source of funding	None.

Analysis

Follow up issues: 98% (49/50) of patients were clinically evaluated at 2 and 3 years, 41/49 (83.7%) after 5 years, 30/49 (61.2%) after 7 years, and 14/49 (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.

Study design issues: The aim of this single centre observational prospective study was to evaluate the clinical efficacy of TIF at 2, 3, 5, 7, and 10 years. Clinical success was defined as complete discontinuation or halved consumption of PPI therapy, while clinical failure: defined as continuation of PPI dose as before procedure.

Intra- and inter-patient characteristics, GORD-HRLQ and GORD-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. Data was analysed on both an intention to treat (ITT) and per protocol (PP) basis (with patients who had surgical fundoplication on follow up included in the intention to treat analysis).

Study population issues: Mean study population BMI 22±3, mean GORD-HQOL score 20±13 for patients on PPI at time of enrolment compared with GORD-HQOL score 46±19 for patients off PPI for at least 14 days before enrolment. The mean heartburn score was 18±9 and regurgitation score was 17±9. Hiatal hernia was present in 56% (28/50) of patients and 22% (11/50) patients had oesophagitis.

Other issues: Previous version of study also included in McCarty (2018) systematic review.

Key efficacy findings

Number of patients analysed: 50 (51 procedures)

Technical and clinical success

Technical success: 49/50 patients (1 failure due to intraprocedural pneumothorax, 1 failure due to device malfunction with successful repeat procedure).

	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 had 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)

Change in symptoms

Follow up (per protocol)	Baseline (n=49)	2 years (n=45)	3 years (n=45)	5 years (n=34)	7 years (n=24)	10 years (n=12)
GORD-HRQL score (off PPI), mean±SD	46 ± 19	18 ± 13*	19 ± 14*	10 ± 7**	10 ± 7.7**	9.5 ± 6.1**
Heartburn score, mean ± SD	18±9	8±7*	9±8*	4.5 ± 4.6*	4.6 ±4.7*	4.2 ±3*
Regurgitation score, mean ± SD	17±9	9±6*	10± 6*	3.2 ± 4.3*	3.3 ±4.4*	3.2 ±4.4*

* = P value for outcome compared with baseline <0.01
** = P value for outcome compared with baseline <0.001

Medication usage

Medication outcome	2 years	3 years	5 years	7 years	10 years
Stopped PPI (PP analysis)	25/45 (55.6)	24/45 (53.3)	14/34 (41.2)	11/24 (45.8)	5/12 (41.7)
Stopped PPI (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)
Halved PPI (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)
Unchanged PPI (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)
Stopped or halved PPI (ITT analysis)	39/50 (78)	38/50 (76)	25/42 (59.5)	20/31 (64.5)	11/15 (73.3)

Key safety findings

Pneumothorax occurred in 3.9% (2/51) procedures; this was 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.

Study 4 Bell (2021)

Study details

Study type	**Case series**
Country	USA
Recruitment period	2008 to 2015
Study population and number	n=151 with GORD
Age and sex	Median age 62 years (range 30-91), 42% male
Patient selection criteria	Inclusion criteria: Patients ⩾18years of age who were able to provide informed consent and consented to TIF, and who had objective documentation of GORD. Exclusion criteria: Axial hernia height >2 cm; Los Angeles classification C or D oesophagitis; Barrett's oesophagus defined as visible columnar lined (⩾1cm) oesophagus demonstrating intestinal metaplasia on biopsy
Technique	TIF was done under general anaesthesia with complete muscle relaxation using the EsophyX2 (Endogastric Solutions, Inc., Redmond, WA, USA) device and a modified version of the TIF 2.0 technique.
Follow up	Median follow up 4.92 years (range 0.7 to 9.7 years)
Conflict of interest/source of funding	Research support for data collection provided by EndoGastric Solutions, Inc., Redmond, WA, USA.

Analysis

Follow up issues: Of the 151 patients who had TIF, 87% (131/151) were available for follow up. Five years or greater follow up was obtained on 51% (62) of the 120 total patients 5 years or more out from surgery (median follow up 6.8 years, range 5 to 9.7 years).

Study design issues: Single centre study analysis of prospectively collected data. The primary outcome measures were clinical response assessed by GORD-HRQL and regurgitation scores used in prior TIF studies, use of PPI, perioperative complications, and need for re-intervention.

Data were analysed using t tests for continuous data and Fisher's exact test for categorical data. A mixed effect model was used to assess the changes in treatment effect on quality-of-life measures (GORD-HRQL and regurgitation scores) in terms of testing mean differences, a p-value less than 0.05 was considered statistically significant. All mixed models were fitted in SAS software version 9.4 (SAS Institute, Inc., Cary, NC, USA). All other analyses were done using XLSTAT and JMP software.

Study population issues: The median BMI of participants was 26.6 (range 20-36.1) and the average duration of symptoms prior to TIF was 11.3 years (range 0.15–24.2). Daily PPI use prior to TIF was reported by 93% (140/151) of patients with 30% having taken 80mg/day. Seventy-eight per cent of patients reported moderate to severe ongoing GORD symptoms preoperatively despite PPI therapy. The median GORD-HQOL scores at baseline were 21 (IQR 9.5-39) off PPI and 14 (IQR 4-24) on PPI. Median regurgitation was 15 (8–20) off PPI and 11 (5–20) on PPI at baseline.

Other issues: Previous version of study also included in McCarty (2018) systematic review, but is it not possible to calculate the exact extent of overlap.

Key efficacy findings

Number of patients analysed: 151

Rate of reintervention

22% (33/151) of TIF patients had laparoscopic revisional surgery at a median of 14.7 months after surgery. All revisions were accomplished without perioperative complication and long-term quality of life outcomes were equivalent to those patients who did not undergo reoperation.

Symptom changes and quality of life

Outcome	
Median GORD HRQL at 4.92 years, all patients	4 (IQR 2-8)
Median GORD HRQL at 4.92 years, patients on PPI	6 (IQR 3-16)
Median GORD HRQL at 4.92 years, patients off PPI	2 (IQR 0-7)
Median GORD HRQL at 5-9 years	5 (IQR 2-9)
Successful (>50%) reductions in GORD-HRQL scores at 4.92 years	64%
Successful (>50%) reductions in GORD-HRQL scores in patients followed for >=5 years	68%
Median dysphagia (assessed by GORD HRQL) at 4.92 years (scored 0-10)	0 (IQR 0-2), p<0.0001 compared with baseline of 2 (IQR 0-4)
Median abdominal bloating (assessed by GORD HRQL) at 4.92 years (scored 0-5)	1 (IQR 0-2), p<0.001 compared with baseline of 2 (IQR 0-4)
Median regurgitation at 4.92 years	0 (IQR 0-4)
Median regurgitation at 5-9 years	1 (IQR-0-3)
Preservation of ability to vomit at 4.92 years (n=44)	95% (42/44)
Preservation of ability to belch at 4.92 years (n=44)	90% (57/63)

P value for GORD-HRQL score difference between patients on and off PPI therapy at 4.92 years follow up: p = 0.09.

GORD-HRQL by time points:

Time point	Estimated mean GORD-HQOL (SE)	Mean difference in GORD-HQOL compared with baseline (SE)	% of patients with >50% improvement in GORD-HRQL*	P-value for difference compared with baseline
Baseline	19.6 (0.9)	-	-	-
1 year (n=75)	7.5 (1.1)	–12.2 (1.3)	72	<0.0001
2 years (n=22)	7.1 (1.9)	–12.5 (2.0)	71	<0.0001
3 years (n=24)	9.7 (1.8)	–9.9 (1.9)	75	<0.0001
4 years (n=39)	10.1 (1.7)	–9.6 (1.8)	76	<0.0001
5 years (n=35)	6.4 (2.1)	–13.3 (2.2)	77	<0.0001
6 years (n=17)	5.9 (2.2)	–13.7 (2.2)	78	<0.0001
7 years (n=11)	3.5 (2.6)	–16.2 (2.7)	83	<0.0001
8 years (n=12)	8.8 (2.7)	–10.8 (2.7)	80	<0.0001
9 years (n=13)	6.1 (2.7)	–13.5 (2.7)	-	<0.0001

*Data estimated from bar charts

Pairwise comparison of HQRL:

Time point	Mean differences (SE)	p-value
2 years versus 1 year	–0.4 (2.1)	0.8640
3 years versus 2 years	2.6 (2.5)	0.3057
4 years versus 3 years	0.4 (2.4)	0.8762
5 years versus 4 years	–3.7 (2.7)	0.1635
6 years versus 5 years	–0.4 (3.0)	0.8862
7 years versus 6 years	–2.5 (3.4)	0.4695
8 years versus 7 years	5.3 (3.7)	0.1542
9 years versus 8 years	–2.7 (3.7)	0.4719

Regurgitation by time points:

Time point	Estimated mean (SE)	Mean differences (SE)	p-Value
Baseline (ref) (n=103)	13.7 (0.7)	-	-
1 year (n=75)	4.9 (0.8)	–8.8 (0.8)	<0.0001
2 years (n=22)	4.4 (1.3)	–9.2 (1.3)	<0.0001

3 years (n=24)	6.2 (1.2)	–7.4 (1.2)	<0.0001
4 years (n=39)	5.4 (1.3)	–8.3 (1.3)	<0.0001
5 years (n=35)	2.7 (0.7)	–11.0 (0.8)	<0.0001
6 years (n=17)	3.0 (1.4)	–10.7 (1.4)	<0.0001
7 years (n=11)	2.8 (1.7)	–10.9 (1.7)	<0.0001
8 years (n=12)	3.1 (1.7)	–10.6 (1.7)	<0.0001
9 years (n=13)	1.5 (1.7)	–12.2 (1.8)	<0.0001

Pairwise comparison of regurgitation:

Time point	Mean differences (SE)	P-value
2 years versus 1 year	–0.4 (1.3)	0.7557
3 years versus 2 years	1.8 (1.6)	0.2678
4 years versus 3 years	–0.8 (1.6)	0.5987
5 years versus 4 years	–2.7 (1.4)	0.0487
6 years versus 5 years	0.2 (1.4)	0.8641
7 years versus 6 years	–0.1 (2.1)	0.9477
8 years versus 7 years	0.2 (2.3)	0.9199
9 years versus 8 years	–1.6 (2.4)	0.5106

Medication usage

Time point	% of patients free of daily PPIs
Baseline (n=151)	7
0.5 years (n=94)	73
1 year (n=83)	72
2 years (n=78)	71
3 years (n=73)	68
4 years (n=65)	69
5 years (n=53)	67
6 years (n=42)	69
7 years (n=27)	74

8 years (n=18)	78

*Values estimated from bar charts

Key safety findings

List of complications

Complication	No. of patients	Comments
Oesophageal perforation	2	Patient 1: An immediate postoperative oesophagram demonstrating leak in patient with suspected oesophageal perforation led to suture repair of perforation, laparoscopic anterior fundoplication to cover the repair, and an uneventful postoperative course. Patient 2: Patient presented 7 days postoperatively with chest pain; CT scan was consistent with a mediastinal abscess oesophagram. Laparoscopic transhiatal drainage of the mediastinal abscess, takedown of the TIF, repair of oesophagus, and laparoscopic fundoplication resulted in an uneventful recovery
Vomiting	1	Elevated white blood cell count on postoperative day 1 – treated with antibiotics and recovered uneventfully
Hypoxaemia	1	Patient with existing interstitial lung disease was hospitalised for 5 days
Prolonged ileus	1	3 days hospitalisation

Study 5 Trad (2018)

Study details

Study type	RCT
Country	USA
Recruitment period	2012
Study population and number	n=63 patients with GORD (n=40 TIF vs. n=23 PPI)
Age and sex	Mean age 51.5 ± 10.3 years, 45% male
Patient selection criteria	Inclusion criteria: Patients with chronic GORD and daily troublesome regurgitation and/or atypical symptoms refractory to PPI therapy; pathological oesophageal acid exposure confirmed by 48-hour pH monitoring off PPI therapy (percentage time pH <4 greater than 5.3%); and history of PPI use for at least 6 months. Exclusion criteria: Patients with hiatal hernia >2 cm; Hill grade III or IV; oesophagitis of grade C or D (Los Angeles classification); Barrett's oesophagus >2 cm; BMI greater than 35 kg/m2; oesophageal motility disorders; previous gastric or oesophageal surgery.
Technique	Eligible patients were randomly assigned to receive either TIF 2.0 or maximum dose PPI therapy with a target allocation ratio of 2:1. After their 6-month evaluation, all patients in the PPI arm elected to undergo the TIF 2.0 procedure. All TIF 2.0 procedures were done using the EsophyX2 device (EndoGastric Solutions, Redmond, WA) under general endotracheal anaesthesia.
Follow up	5 years
Conflict of interest/source of funding	Multiple authors report receipt of speaking honoraria from EndoGastric Solutions. Study funded by (EndoGastric Solutions, Redmond, WA).

Analysis

Follow up issues: Of the randomised patients, 5% (3/63) were lost to follow up, 95% (60/63) completed 1 year follow up, 83% (52/63) completed the 3 year follow up and 70% (44/63) completed the 5-year follow up assessments.

Study design issues: Randomised multicentre open-label study with a crossover arm – patients in the PPI arm had TIF 2.0 6 months after initial randomisation.

Data were collected on elimination of troublesome symptoms, PPI use, reoperation, adverse events, and patient satisfaction. Troublesome symptoms were defined according to the Montreal consensus definition as mild symptoms occurring 2 or more days a week, or moderate to severe symptoms occurring more than 1 day a week.

Primary end points were elimination of troublesome regurgitation and elimination of all troublesome atypical symptoms at the 5-year follow up as evaluated by the RDQ (scored 0-24 with higher scores indicating greater severity) and Reflux Symptom Index (RSI; scored 0-45 with higher scores indicating greater severity).

Secondary endpoints were improvement in symptom scores (RDQ, RSI, GORD-HRQL), PPI use, reoperations, and satisfaction with current health condition. PPI use was self-reported by patients as complete cessation, occasional use (<3 days/wk.), or daily use rates. Patient satisfaction with their current health condition was reported as part of the GORD-HRQL (scored 0 to 50 with higher scores indicating greater severity), with 3 possible answers: satisfied, neutral, or dissatisfied.

Postoperative data at 1-, 3-, and 5-year intervals were compared with preoperative data using the repeated measures analysis of variance (ANOVA) followed by the post hoc Tukey-Kramer honestly significant difference multiple comparison procedure. In general, continuous variables were reported as means (SDs); categorical variables were reported as percentage, counts, and 95% CIs and were tested for significant difference using McNemar's test.

Patients who had a revisional procedure procedure) were included in the analyses and assigned the worst outcomes observed during the study from the timing of revisional surgery going forward. The statistical significance was prespecified by a p value of <0.05.

Study population issues: The mean BMI of the patient population was 28.5 ± 3.7, mean GORD symptom duration was 11.2 ± 9.8 years and mean PPI therapy duration was 8.6 ± 6.5 years. 1 patient had the short-segment variant of Barrett's oesophagus.

Other issues: Study also included in McCarty (2018) systematic review and Grossman (2021) systematic review as part of the HTA.

Key efficacy findings

Number of patients analysed: 60

Rate of reintervention

5% (3/60) of TIF patients had revisional intervention (1 Dor fundoplication between 1 and 2 years, 1 LNF between 2 and 3 years and a second LNF between 3 and 5 years).

Changes in symptoms and quality of life

Clinical outcome	Baseline (n=60)	1 year (n=60)	3 years (n=52)	5 years (n=44)
Elimination of troublesome regurgitation (as assessed by the RDQ)	-	88 (42/48)	90 (37/41)	86 (37/43) (95% CI 72 to 94%)
Average regurgitation score (according to RDQ)	On PPI: 3 Off PPI: 3.7 (p=0.0103)	0.6*	0.6*	0.7*
Elimination of troublesome atypical symptoms (according to RSI)	-	82 (45/55), (95% CI 70 to 90%)	88 (42/48), (95% CI 75 to 95%)	80 (31/39), (95% CI 64 to 89%)
Average RSI score	On PPI: 22.2 Off PPI: 26 (p=0.212)	6.3*	4.3*	6.3*
Average quality of life score according to GORD-HRQL	On PPI: 26.4 Off PPI: 32.8 (p=0.007)	6.9*	5.5*	6.8*
% Patient satisfaction with current health (according to GORD-HRQL)	2 (1/60)	75 (45/60) (95% CI 63 to 84%)*	83 (43/52) (95% CI 70 to 91%)*	70 (31/44) (95% CI 56 to 82%)*
% of patients achieving pH normalisation	-	-	40 (16/40)	-

* =p<0.001 vs. screening

Medication usage

Clinical outcome	Baseline (n=60)	1 year (n=60)	3 years (n=52)	5 years (n=44 for all patients, n=19 for patients with elevated levels of distal oesophageal acid exposure at 3 years*)
% of patients on daily PPI therapy -all patients	100 (63/63)	17 (10/60)	27 (14/52)	34 (15/44) (95% CI 22 to 49%)
% of patients on occasional PPI therapy – all patients	-	-	-	20 (9/44) (95% CI 11 to 35%)
% complete cessation of PPI therapy – all patients	-	-	-	46 (20/44) (95% CI 32 to 60%)
% of patients on daily PPI therapy – patients with elevated levels of distal oesophageal acid exposure at 3 years*	-	-	-	21% (4/19) (95% CI 8 to 44%)
% of patients on occasional PPI therapy –patients with elevated levels of distal oesophageal acid exposure at 3 years*	-	-	-	16 (3/19) (95% CI 5 to 38%)
% complete cessation of PPI therapy – patients with elevated levels of distal oesophageal acid exposure at 3 years*	-	-	-	63 (12/19)

* Defined as percentage total time of pH <4 greater than 5.3%, as measured by 48-hour pH testing

Key safety findings

No serious adverse events were reported, and no other complications associated with the TIF 2.0 procedure occurred in this study.

Study 6 Testoni (2022)

Study details

Study type	**Case series**
Country	Italy
Recruitment period	2015 to 2019
Study population and number	n=46 patients with GORD
Age and sex	Mean age 50 ±8 years, 54% male
Patient selection criteria	Inclusion criteria: Patients aged 18 to 70 years inclusive; chronic (at least 6 months) GORD-related symptoms, both oesophageal and extra-oesophageal, with complete or partial response to PPI therapy; endoscopic findings of GORD or Barrett's oesophagus<3 cm); evidence of non-erosive reflux disease (NERD) or hypersensitive oesophagus at functional tests; body mass index<40 kg/m2; seeking an alternative to medical or surgical treatment; availability for a long-term follow up. Exclusion criteria: functional pyrosis; hiatal hernia ≥2.5 cm and non-reducible hernia (assessed through barium swallow contrast X-ray) as contraindication to TIF with MUSE device; Barrett's oesophagus ≥3 cm; malignant upper GI neoplasia; previous GI or thoracic surgery; (oesophageal varices, stenosis, or diverticula; portal hypertension; scleroderma; BMI >40 kg/m2; bleeding disorders; (j) age<18 years and>75 years; GORD symptoms for less than 6 months; inability to give consent; unavailability to long-term follow up.
Technique	TIF was done using the Medigus Ultrasonic Surgical Endostapler (MUSE) device (Medigus, Omer, Israel) with patients under general anaesthesia.
Follow up	3 years
Conflict of interest/source of funding	None.

Analysis

Follow up issues: Two patients experienced post-procedural complications and 1 patient unresponsive to TIF were excluded from the follow-up analysis. Clinical follow up was available for 42 patients at 6 months and 1 year, 35 patients at 2 years, and 31 patients at 3 years. Follow up symptom assessment and endoscopy were done by physicians other than those who did TIF and who were unaware of the post-procedure outcomes.

Study design issues: Prospective single centre study that aimed to evaluate the effect of TIF done by a new-generation MUSE device. Primary endpoints were the percentage of patients who stopped or at least halved PPI consumption and the GORD-HRQL and RSI questionnaires scores (off-PPI), calculated both as median values and percentage of patients who experienced at least 50% reduction compared with before TIF. Secondary endpoints included safety outcomes, endoscopic findings assessing the presence and grade of oesophagitis, hiatal hernia and Hill's grade of the gastro-oesophageal valve compared with before TIF; HRM and 24-h pH-impedance findings compared with before TIF.

Statistical significance was assessed through separate paired samples two-tailed Wilcoxon signed-rank sum test. Both per protocol (PP set) and intention-to-treat (ITT set) analyses were done. The thresholds of statistical

significance were adjusted for multiple comparisons; the threshold value was 0.0125 for clinical parameters and 0.01 for functional parameters

Study population issues: The mean BMI of patients was 24±3.2 and mean duration of symptoms was 9±6 years. 67.4% (31/46) of patients complained of both oesophageal and extra-oesophageal symptoms. 22/46 patients (47.8%) required double-standard dose PPI therapy and 19/46 patients (41.3%) required single-standard dose PPI to control symptoms, while 5/46 patients (10.9%) assumed PPIs at halved standard dose or occasionally. At pre-TIF upper G.I. endoscopy, 2/46 patients (4.3%) had Barrett's oesophagus without dysplasia and 30/46 patients (65.2%) had a diagnosis of non-erosive reflux oesophagitis, confirmed by pathological 24-h pH-impedance recording.

Key efficacy findings

Number of patients analysed: 46

Technical success and rate of reintervention

TIF by MUSE™ was technically feasible in 45/46 patients (97.8%). In 1 patient it was impossible to pass the MUSE™ device through the cervical oesophagus because of a compression due to protrusion of a cervical vertebra.

One patient was unresponsive to TIF and had Nissen fundoplication within 6 months after the procedure.

Medication usage

PPI therapy, N (%)	6 months (PP, n=42)	6 months (ITT, n=46)	1 year (PP, n=42)	1 year (ITT, n=46)	2 years (PP, n=35)	2 years (ITT, n=39)	3 years (PP, n=31)	3 years (ITT, n=35)
Stopped	27/42 (64.3%)	27/46 (58.7%)	27/42 (64.3%)	27/46 (58.7%)	22/35 (62.9%)	22/39 (56.4%)	23/31 (74.2%)	23/35 (65.7%)
Dose at least halved	10/42 (23.8%)	10/46 (21.7%)	11/42 (26.2%)	11/46 (23.9%)	9/35 (25.7%)	9/39 (23.1%)	4/31 (12.9%)	4/35 (11.4%)
Stopped or dose at least halved	37/42 (88.1%)	37/46 (80.4%)	38/42 (90.5%)	38/46 (82.6%)	31/35 (88.6%)	31/39 (79.5%)	27/31 (87.1%)	27/35 (77.1%)
Dose unchanged	5/42 (11.9%)	5/46 (10.9%)	4/42 (9.5%)	4/46 (8.7%)	4/35 (11.4%)	4/39 (10.2%)	4/31 (12.9%)	4/35 (11.4%)

Symptom and quality of life changes

	Baseline - patients completing 1-year follow up (n=42)	**6 months (n=42)**	**P value at 6 months vs. baseline**	**1 year (n=42)**	**P value at 1 year vs. baseline**
Median GORD-HRQL score (95% CI)	22.0 (16.0–25.0)	9.0 (6.0–12.0)	< 0.0001	7.0 (3.3–10.0)	0.0001
Median RSI score (95% CI)	19.0 (17.0–24.2)	10.0 (3.0–12.0)	< 0.0001	5.5 (3.0–7.5)	0.0001

	Baseline - patients completing 2-year follow up (n=35)	**2 years (n=35)**	**P value at 2 years vs. baseline**	**Baseline - patients completing 3-year follow up (n=31)**	**3 years (n=31)**	**P value at 3 years vs. baseline**
Median GORD-HRQL score (95% CI)	23.5 (16.0–26.8)	8.5 (3.0–12.0)	0.0007	24.0 (9.7–30.6)	2.5 (0.47–8.7)	0.007
Median RSI score (95% CI)	17.0 (15.4–23.6)	7.0 (3.4–8.6)	0.0003	23.5 (17.0–25.5)	6.0 (2.3–15.0)	0.01

50% reduction of symptom score, n (%)	**6 months (PP, n=42)**	**6 months (ITT, n=46)**	**1 year (PP, n=42)**	**1 year (ITT, n=46)**	**2 years (PP, n=35)**	**2 years (ITT, n=39)**	**3 years (PP, n=31)**	**3 years (ITT, n=35)**
GORD-HRQL score	31/42 (73.8%)	31/46 (67.4%)	30/42 (71.5%)	30/46 (65.2%)	25/35 71.4%)	25/39 (64.1%)	21/31 67.7%)	21/35 (60%)
RSI score	32/42 (76.2%)	32/46 (69.6%)	32/42 (76.2%)	32/46 (69.6%)	24/35 (68.6%)	24/39 (61.5%)	21/31 (67.7%)	21/35 (60%)

Endoscopic findings

50% reduction of symptom score, n (%)	**Baseline (n=46)**	**6 months (PP, n=38)**	**6 months (ITT, n=46)**	**1 year (PP, n=31)**	**1 year (ITT, n=46)**
Grade A oesophagitis	14/46 (30.4)	7/38 (18.4%)	7/46 (15.2%)	6/31 (19.3%)	6/46 (13%)
Recurrent hiatal hernia	18/46 (39.1)	2/38 (5.3%)	2/46 (4.4%)	2/31 (6.5%)	2/46 (4.4%)
Hill's grade I	0	24/38 (63.2%)	24/46 (52.2%)	21/31 (67.7%)	21/46 (45.7%)
Hill's grade II	40/46 (87)	13/38 (34.2%)	13/46 (28.3%)	9/31 (29.0%)	9/46 (19.6%)
Hill's grade III	6/46 (13)	1/38 (2.6%)	1/46 (2.2%)	1/31 (3.3%)	1/46 (2.2%)

Oesophageal pH and acid reflux

Functional parameter, median (95% CI)	Baseline – patients with 6-month follow up (n=31)	6 months (n=31)	P value – 6 months vs. baseline	Baseline -patients with 1 year follow up	1 year	P value – 1 year vs. baseline
No. total refluxes	57.0 (38.3 to 79.4)	31.0 (24.5 to 54.1)	0.0002	41.5 (27.5 to 76.8)	40.5 (24.7 to 68.8)	0.37

No. acid refluxes	37.0 (24.5 to 54.2)	24.0 (12.3 to 41.2)	0.0002	31.5 (20.6 to 54.6)	27.5 (13.4 to 46.6)	0.15
No. weakly acid refluxes	11.0 (7.0 to 22.9)	8.5 (6.0 to 15.9)	0.22	7.5 (4.8 to 14.0)	10.0 (6.0 to 19.8)	0.23
No. alkaline refluxes	2.0 (1.0 to 3.4)	1.5 (0.0 to 2.7)	0.81	0.0 (0.0 to 1.5)	1.5 (1.0 to 2.5)	0.16
No. proximal refluxes	26.0 (12.8 to 37.8)	12.0 (5.8–20.3)	0.002	18.5 (11.0 to 34.5)	18.0 (7.2 to 30.5)	0.31
Longest reflux (min)	8.4 (3.6 to 11.9)	6.2 (5.0–15.0)	0.68	8.0 (3.4 to 11.0)	5.0 (4.0 to 12.0)	0.89
DeMeester score	21.1 (12.0 to 32.8)	20.0 (6.0 to 37.7)	0.53	17.8 (6.7 to 35.5)	16.4 (5.6 to 26.9)	0.46
% Total time oesophageal pH < 4	5.8 (1.5 to 8.3)	3.8 (1.3–5.1)	0.006	5.7 (3.2 to 7.1)	4.2 (2.9 to 5.0)	0.16

Key safety findings

Rate of complications

Complication	No. of patients	Comments
Oesophageal perforation	1	Occurred 48h after TIF
Gastric fundus perforation	1	Occurred 2 cm distally to the cardia as the consequence of an incorrect placement of stapler because of a difficult ultrasound-guided alignment.
Epigastric pain	3/45 (6.7%)	Presented 6h after procedure and required major analgesics

Study 7 Kalapala (2022)

Study details

Study type	RCT
Country	India
Recruitment period	2017 to 2019
Study population and number	n=70 patients with GORD (n=35 EFTP vs n=35 sham)
Age and sex	EFTP group: Median age 35 years (IQR 29-41), 71% male Sham group: Median age 37 (IQR 29-45), 71% male
Patient selection criteria	Inclusion criteria: Gastro-oesophageal flap valve grade I–III (Hill's classification); pathological oesophageal acid exposure (percentage time with oesophageal pH <4 in 24hours>4.2%); abnormal DeMeester score≥14.7 or total reflux episodes>73; lower oesophageal sphincter pressure (LESP) between 5 and 15mm Hg. Exclusion criteria: ASA physical status >II; previous oesophageal or gastric surgery; pregnancy; large hiatal hernia >3cm; Los Angeles grade C/D oesophagitis; para-oesophageal hernia; Barrett's oesophagus; presence of oesophageal dysmotility on HRM.
Technique	Patients were allocated to either the EFTP or the sham group in a ratio of 1:1 using block randomisation. On the day of procedure, all the patients had the assigned intervention (EFTP or sham) under general anaesthesia and endotracheal intubation after overnight fasting. All EFTP procedures were done using the GORDx device.
Follow up	12 months
Conflict of interest/source of funding	None

Analysis

Follow up issues: After randomisation and allotted intervention, patients were followed up and asked to visit hospital at 3, 6 and 12 months. There were no protocol deviations and all patients in both groups completed 12-month follow up including per-protocol hospital visits and response to telephone calls.

Study design issues: Single centre randomised sham-controlled trial that aimed to determine the efficacy and safety of EFTP (GORD-X) in patients with PPI-dependent GORD. The primary endpoint of the study was defined as reduction of 50% or more in GORD-HRQL total score from baseline at 3 months.

Secondary end points of the study included improvement in GORD-HRQL total score (scored 0-75 with higher scores indicating greater severity), improvement in GORD symptom scores at 3, 6 and 12 months, PPI usage, and oesophageal acid exposure and reflux episodes on 24-hour pH impedance monitoring at 3 and 12 months. Total reflux episodes determined by impedance were classified as acidic (pH <4) and non-acidic (pH >4) based on pH monitoring.

Wilcoxon signed rank test and Friedman's two-way analysis of variance by ranks were used for comparing single pairs and multiple related samples, respectively. The PPI dependency rate between the EFTP and the sham groups after intervention was compared in a Kaplan-Meier analysis using log-rank test. Cox proportional

hazards model was used to estimate the HR and 95% CIs. All tests of significance were two-tailed and a p value below 0.05 was considered statistically significant.

Study population issues: All patients were on PPI and the median (IQR) duration of PPI use was 2.5 (1.5–4.0) years. At the time of enrolment, 5/35 (14.2%) patients in the EFTP group and 3/35 (8.5%) in the sham group were on double dose PPI. The baseline demographics, endoscopic, manometric and reflux parameters did not differ significantly between the EFTP and the sham groups.

Other issues: If patients experienced reflux symptoms more than twice a week, PPI equivalent to 20mg rabeprazole or 40mg pantoprazole per day was prescribed over the phone and recorded. If the symptom control was inadequate at 4 weeks of starting PPI, the dose was doubled. Over the counter use of PPI was restricted but patients were allowed to use antacids on demand.

Key efficacy findings

Number of patients analysed: 70

Changes in symptoms and quality of life

Parameter	EFTP (n=35)	Sham (n=35)	P value
% of patients with ≥50% improvement in GORD-HRQL – 3 months (n)	65.7% (23/35)	2.9% (1/35)	<0.001
GORD-HRQL, Median percentage improvement (IQR)– 3 months	69.3 (38.0 to 87.2)	6.6 (2.1 to 13.9)	0.001
GORD-HRQL, Median percentage improvement (IQR)– 6 months	81.4 (60.9 to 100)	8.0 (2.2 to 21.6)	0.001
GORD-HRQL, Median percentage improvement (IQR)– 12 months	92.3 (84.4 to 100)	9.1 (4.8 to 36.0)	0.001
Heartburn symptom score, Median percentage improvement (IQR) – 3 months	55.6 (37.9 to 100)	7.4 (0 to 23.1)	0.001
Heartburn symptom score, Median percentage improvement (IQR)– 6 months	75.0 (56.5 to 100)	13 (0 to 37.5)	0.001
Heartburn symptom score, Median percentage improvement (IQR) – 12 months	89.7 (66.7 to 100)	15.4 (0 to 44.4)	0.001
Regurgitation symptom score, median percentage improvement (IQR)– 3 months	60 (47.6 to 92.3)	7.7 (0 to 13.3)	0.001
Regurgitation symptom score, median percentage improvement (IQR)– 6 months	96.2 (60 to 100)	6.9 (0 to 17.9)	0.001
Regurgitation symptom score, median percentage improvement (IQR)– 12 months	100 (90 to 100)	3.4 (−3.4 to 27.3)	0.001

Medication usage

Percentage of patients off PPI at 12 months: 62.8 % (22/35) in EFTP group and 11.4% (4/35) in sham group (p<0.001)

Estimated probability of PPI dependency in EFTP group at 12 months compared with sham (Kaplan-Meier): HR, 0.25; 95% CI 0.12 to 0.49; p<0.001

Oesophageal pH

Parameter, median value (IQR)	EFTP	P value (EFTP compared with baseline)	Sham	P value (sham compared with baseline)	P value: EFTP vs. sham
% time oesophageal pH <4 -Baseline	4.4 (2.0 to 8.7)	-	2.7 (1.3 to 5.9)		0.127
% time oesophageal pH <4 -3 months	3.6 (0.4 to 9.0)	0.422	3.5 (1.4 to 6.4)	0.915	0.833
% time oesophageal pH <4 -12 months	3.4 (0.6 to 5.5)	0.276	5.4 (2.0 to 9.0)	0.441	0.111
DeMeester Score – Baseline	15.1 (7.6 to 28.0)	-	12.2 (6.8 to 21.4)	-	0.447
DeMeester Score – 3 months	14.2 (1.7 to 29.3)	0.447	14.7 (6.2 to 20)	0.749	0.934
DeMeester Score – 12 months	21.5 (11.0 to 49.2)	0.231	20.1 (9.7 to 27.5)	0.343	0.504
Total reflux episodes - Baseline	90 (65 to 115)	-	92 (65 to 130)	-	0.733
Total reflux episodes – 3 months	66 (46 to 92)	0.005	85 (61 to 122)	0.055	0.072
Total reflux episodes -12 months	54.5 (33 to 100)	0.122	120 (69.5 to 129)	0.859	0.051
Acid reflux episodes - Baseline	51 (33 to 73)	-	40 (27 to 1)	-	0.106
Acid reflux episodes – 3 months	34 (16 to 63)	0.063	40 (30 to 62)	0.933	0.414
Acid reflux episodes -12 months	31.5 (17.5 to 73.5)	0.316	66 (47 to 69)	0.260	0.227
Non-acid reflux episodes - Baseline	34 (18 to 71)	-	49 (25 to 77)	-	0.264
Non-acid reflux episodes – 3 months	23 (12 to 42)	0.054	35 (21 to 70)	0.077	0.048
Non-acid reflux episodes – 12 months	11.5 (2.5 to 21.8)	0.038	50 (25.5 to 62.5)	0.214	0.005

Key safety findings

Rate of complications

Event	Frequency (ETFP)	Frequency (sham)	Length of hospital stay (days)	Severity
Fever, moderate left sided pleural effusion	1/35 (2.8%)	0	5	Moderate adverse event
Left sided chest pain	1/35 (2.8%)	0	3	Mild adverse event
Left shoulder pain	8/35 (22.8%)	0	1	Other incident*
Intraoperative bleeding at the site of suture application	5/35 (14.2%)	0	1	Other incident*

* Other incident – not classed as adverse event

Study 8 Chimikungara (2018)

Study details

Study type	Case series
Country	USA
Recruitment period	2007 to 2014
Study population and number	N=57 patients with GORD
Age and sex	Median age 46 years (IQR 37 to 59 years), 40% male
Patient selection criteria	Inclusion criteria: Patients with GORD as confirmed by oesophagogastroduodenoscopy, barium swallow test, and 48-h pH monitoring. Exclusion criteria: absence of pathologic reflux; hiatal hernia greater than 2 cm; LA grade C or D erosive oesophagitis; biopsy proven Barrett's oesophagus
Technique	Patients were placed in left lateral decubitus after undergoing general anaesthesia and TIF was done using the EsophyX device.
Follow up	Short term follow up: median 12 months (IQR 11-18 months) Long term follow up: median 97 months (IQR 55-109 months)
Conflict of interest/source of funding	None.

Analysis

Follow-up issues: After 12 months, 63% (36/57) of patients were analysed; 14/57 were lost to follow up, 2 died from causes unrelated to the procedure, and 5 had LARS within 1 year of TIF. At long-term follow up (median 97 months), 23/57 (40%) of patients were analysed; a further 6/57 were lost to follow up, and a further 7 had LARS.

Study design issues: Single centre retrospective study aiming to evaluate the long-term impact of TIF on disease-specific quality of life and antisecretory medication use.

The primary outcome measure of this study was the GORD-HRQL assessment of disease-specific quality of life. Secondary outcome measures included PPI use and satisfaction with the procedure. Data were analysed using t tests for continuous data, Fischer's exact test for categorical data, and the Wilcoxon matched pairs test for non-parametric data. A p value less than 0.05 was considered statistically significant.

Study population issues: Mean BMI at baseline was 28.8 ± 4.9 kg/m^2, and median GORD-HRQL score at baseline was 24 (IQR 15-28). The median DeMeester score was 30 (23–53). Twelve patients (21%) had endoscopic evidence of mild oesophagitis and twenty-six (46%) had endoscopic or radiographic evidence of a small hiatal hernia (1–2 cm). All patients were taking PPI therapy at least daily.

Key efficacy findings

Number of patients analysed: 57

Rate of reintervention

During the study period, 21% (12/57) of patients had subsequent LARS (11 laparoscopic Nissen fundoplication and 1 laparoscopic magnetic gastro-oesophageal junction reinforcement) for recurrent GORD symptoms at a median interval of 24 (IQR 10–36) months after TIF. There were no statistically significant differences in patient demographics, hiatal hernia presence, oesophagitis, or DeMeester score between those who had subsequent anti-reflux surgery and those who did not.

Change in symptoms and quality of life

Clinical outcome	Pre-op (n=57)	Short-term – median 12 months (n=36)	Long-term – median 97 months (n=23)
Median GORD-HRQL score (IQR)	24 (15-28)	7 (2-18) (p<0.01)	10 (6-14) (p<0.01)
Percentage of patients with daily PPI use	100 (57/57)	53 (19/36)	73 (16/23)
Percentage of patients achieving PPI cessation	-	47 (17/36)	27 (6/23)
Percentage dissatisfaction with GORD symptom management	100 (57/57)	-	26 (6/23)

Key safety findings

None reported.

Study 9 Edriss (2014)

Study details

Study type	Case report
Country	USA
Recruitment period	Not reported
Study population and number	n=1
Age and sex	48 year old male
Patient selection criteria	Not reported
Technique	Patient had TIF using the EsophyX device system (EndoGastric Solutions).
Follow up	Not reported
Conflict of interest/source of funding	None.

Analysis

Study design issues: This case report presented a case of TIF complicated by oesophageal perforation and developed mediastinitis, left pneumothorax, bilateral pleural effusions, and acute respiratory failure.

Key safety findings

The patient was diagnosed with GORD and hiatal hernia 15 years before presentation. His symptoms included chronic heartburn and night time cough that did not improve with lifestyle modification, histamine 2 blockers, and PPIs. Oesophageal 24-hour pH-impedance monitoring confirmed the diagnosis of GORD. He had TIF after failing conservative therapy.

A few hours after surgery, the patient developed midsternal chest pain. Physical examination revealed a mildly distressed state with rapid shallow breathing. His chest radiograph showed new small bilateral pleural effusions and bilateral lung opacities.

The next day, the patient had worsening chest pain, severe back pain, and shortness of breath. Physical examination revealed decreased breath sounds on the left side. The patient's respiratory status deteriorated, and he was intubated for mechanical ventilation. Another chest radiograph showed a large left-sided pleural effusion and bilateral pulmonary infiltrates consistent with consolidation and/or atelectasis.

Computed tomography of the chest showed moderate-to-large left-sided and moderate right-sided pleural effusions, a left-sided pneumothorax, and pneumomediastinum, findings consistent with distal oesophageal perforation. Computed tomography of the abdomen showed pneumoperitoneum.

The patient was started on vancomycin and ertapenem. A left-sided chest tube was inserted, and purulent, brown-greenish fluid was drained during the tube placement. Pleural fluid analysis showed an exudative effusion consistent with oesophageal perforation and empyema.

The patient had a fever for 5 days and leukocytosis despite the antibiotic coverage, chest tube placement, and nasogastric decompression. Blood cultures were negative on two occasions; pleural fluid cultures grew

coagulase-negative Staphylococcus nitric oxide synthase and diphtheroids. On postoperative day 8, a left-sided thoracotomy and decortication for non-resolving empyema was done. The patient needed mechanical ventilation for 12 days and also developed acute renal injury.

At his most recent follow-up visit, the patient had been hospitalised at another hospital for 2 weeks because of the non-resolving right-sided empyema and had had right thoracotomy with decortication.

The distal oesophageal perforation and left-sided pneumothorax were attributed to injury during application of the polypropylene H-fasteners.

Study 10 Titus (2013)

Study details

Study type	Case report
Country	USA
Recruitment period	Not reported
Study population and number	n=1
Age and sex	42 year old female
Patient selection criteria	Not reported
Technique	Patient had endoscopic reduction of the hiatal hernia and TIF with use of the EsophyX device
Follow up	1 month
Conflict of interest/source of funding	None.

Analysis

Study design issues: This case report presented a case of a distal oesophageal perforation and oesophagopulmonary fistula after treatment for GORD with the EsophyX device

Key safety findings

The patient presented to an outside institution with intractable reflux. Upper endoscopy showed a small, reducible hiatal hernia with no evidence of oesophagitis or Barrett oesophagus. She subsequently had endoscopic reduction of the hiatal hernia and TIF with use of the EsophyX device and was admitted for overnight observation.

The next morning, she was noted to have a cough, low-grade fever, and weakness. A chest radiogram showed left posterior basilar infiltrate and a small pleural effusion presumed to be a left lower lobe aspiration pneumonia. Intravenous antibiotics were begun, and she was discharged 3 days later, having a full liquid diet and oral ciprofloxacin. She had multiple readmissions over the next 3 weeks for similar signs and symptoms with worsening severity until an oesophagram and computed tomography scan of the chest demonstrated distal oesophageal perforation with transmediastinal fistulous connection to a large cavitary left lung lesion. Blood cultures were positive for methicillin-sensitive Staphylococcus aureus.

Upon transfer to a different hospital the patient was in early septic shock. Her symptoms included shortness of breath and productive cough. Oesophagram confirmed the leak at 5 cm above the GEJ. Esophagogastroduodenoscopy showed an H-fastener in an area of inflamed distal oesophagus at the level of the suspected leak. No clear perforation was encountered. Inspection of the hiatus on retroflexion showed multiple H-fasteners in place, with the fundoplication no longer intact.

The left side of the chest was explored through a seventh-interspace thoracotomy. Dense inflammatory adhesions from the left lower lobe to the diaphragm were taken down. A fibrosed fistulous tract was encountered and appeared to have obliterated. Insufflation through an endoscope confirmed fistula closure. Wide debridement of the fistulous phlegmon was done. The distal end of the fistula terminated in the left lower

lobe and led to a large parenchymal abscess cavity. The cavity was drained, debrided, and marsupialised. Four percutaneous drains were left within the thorax.

An oesophagram on postoperative day 4 showed no leak, and she had transition to oral antibiotics along with diet advancement. She was discharged on postoperative day 8 with a 4-week course of oral fluconazole, amoxicillin-clavulanate, and doxycycline. At 1-month follow up, she was tolerating soft foods with no further shortness of breath or cough, and no complaints of reflux.

Suspected cause of injury was an H-fastener placed too far proximally that had pulled through, lacerating the distal oesophagus.

Validity and generalisability of the studies

- Most of the evidence relates to the Esophyx device, with studies utilising the MUSE and GORDx devices also included in the key evidence.
- Follow up for studies ranged between 12 months and 10 years (but with high loss to follow up for studies with longer follow up periods).
- Some of the included studies have used previous versions of a device which are no longer available for use.

Existing assessments of this procedure

A 2021 systematic review undertaken as part of a Health Technology Assessment from the Austrian Institute for Health Technology Assessment assessing the efficacy and safety of this procedure has been included in the summary of key evidence (Grössmann 2021).

The final conclusion from this HTA was that "the inclusion in the catalogue of benefits is currently not recommended" for this procedure. The reasoning for this was that "the current evidence is not sufficient to prove that endoscopic plication is more effective and equally safe or equally effective and safer than laparoscopic surgery, PPI therapy and/or sham treatment in chronic GORD patients. Due to the methodological shortcomings of the available evidence no solid conclusions can be drawn neither for clinical effectiveness nor for the safety of endoscopic plication therapy. Hence, there is a need for high-quality studies showing consistent long-term effectiveness results as well as properly reported and detailed safety data."

A guideline from the European Society of Gastrointestinal Endoscopy (ESGE) on the endoscopic management of gastrointestinal motility disorders was published in 2019. The ESGE "recommends against the widespread clinical use of transoral incisionless fundoplication (TIF) as an alternative to proton pump inhibitor (PPI) therapy or anti reflux surgery in the treatment of gastro-oesophageal reflux disease (GORD), because of the lack of data on the long-term outcomes, the inferiority of TIF to fundoplication, and its modest efficacy in only highly selected patients. TIF may have a role for patients with mild GORD who are not willing to take PPIs or undergo anti reflux surgery." This was a strong recommendation based on a moderate quality of evidence (level of agreement 92.8%).

The ESGE also "recommends against the use of the Medigus ultrasonic surgical endostapler (MUSE) in clinical practice because of insufficient data showing its effectiveness and safety in patients with GORD. MUSE should be used in clinical trials only". This was a strong recommendation based on a low quality of evidence (level of agreement 100%) (Weusten 2020).

An expert panel recommendation on treatment for distinct GORD symptoms characterised by unresponsiveness to PPI therapy was published in the American Journal of Gastroenterology in 2018. The panel stated that TIF was "not judged appropriate in any scenario" due to "the lack of long-term data demonstrating sustained and consistent efficacy" (Yadlapati 2018).

A guideline from the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) concerning endoluminal treatments for GORD was published in 2013 and updated in 2017. The recommendation given said "Based on existing evidence, TIF can be done with an acceptable safety risk in appropriately selected patients. The procedure leads to better control of GORD symptoms compared with PPI treatment in the short term (6 months) but appears to lose effectiveness during longer term follow up and is associated with moderate patient satisfaction scores. Objective GORD measures improve similarly after TIF 2.0 compared with PPI. No comparative, controlled trials exist between TIF and surgical fundoplication, but preliminary evidence suggests that the latter can be used safely after TIF failure." This was a strong recommendation based on a moderate quality of evidence (Pearl 2017).

A guideline from the American Society for Gastrointestinal Endoscopy (ASGE) on the role of endoscopy in the management of GORD was published in 2015. The ASGE recommends that "endoscopic anti reflux therapy be considered for selected patients with uncomplicated GORD after careful discussion with the patient regarding potential adverse effects, benefits, and other available therapeutic options." This recommendation was based on a low quality of evidence (Muthusamy 2015).

Related NICE guidance

Below is a list of NICE guidance related to this procedure.

Interventional procedures

- Laparoscopic insertion of a magnetic titanium ring for gastro-oesophageal reflux disease. NICE interventional procedures guidance 585 (2017). Available from https://www.nice.org.uk/guidance/IPG585
- Electrical stimulation of the lower oesophageal sphincter for treating gastro-oesophageal reflux disease. NICE interventional procedures guidance 540 (2015). Available from https://www.nice.org.uk/guidance/IPG540

- Endoscopic radiofrequency ablation for gastro-oesophageal reflux disease. NICE interventional procedures guidance 461 (2013). Available from https://www.nice.org.uk/guidance/IPG461

- Endoscopic augmentation of the lower oesophageal sphincter using hydrogel implants for the treatment of gastro-oesophageal reflux disease. NICE interventional procedures guidance 222 (2007). Available from https://www.nice.org.uk/guidance/IPG222

- Endoscopic injection of bulking agents for gastro-oesophageal reflux disease. NICE interventional procedure guidance 55 (2004). Available from https://www.nice.org.uk/guidance/IPG55

NICE guidelines

- Gastro-oesophageal reflux disease and dyspepsia in adults: investigation and management. NICE clinical guideline CG184 (updated in 2019). Available from https://www.nice.org.uk/guidance/CG184
- Gastro-oesophageal reflux disease in children and young people: diagnosis and management. NICE guideline NG1 (2015). Available from https://www.nice.org.uk/guidance/NG1

Additional information considered by IPAC

Professional experts' opinions

Expert advice was sought from consultants who have been nominated or ratified by their professional Society or Royal College. The advice received is their individual opinion and is not intended to represent the view of the society. The advice provided by professional experts, in the form of the completed questionnaires, is normally published in full on the NICE website during public consultation, except in circumstances but not limited to, when comments are considered voluminous, or publication would be unlawful or inappropriate.

Three professional expert questionnaires for endoluminal gastroplication for gastro-oesophageal reflux disease were submitted and can be found on the NICE website.

Company engagement

A structured information request was sent to 3 companies who manufacture a potentially relevant device for use in this procedure. NICE received 0 completed submissions.

Issues for consideration by IPAC

- Ongoing trials and registries:

  - Observational Registry of Transoral Incisionless Fundoplication (TIF) for Gastro-oesophageal Reflux Disease (GORD) (NCT05066594); Observational registry; Italy; estimated enrolment n=100; estimated study completion date May 2029.

  - Transoral Incisionless Fundoplication Database Repository (TIF) (NCT04306380); case series; USA; estimated enrolment n=500; estimated study completion date December 2030.

  - Endoscopic Fundoplication with MUSE System (NCT03669874); cohort study; Italy; estimated enrolment n=80; estimated study completion date September 2026.

  -Multicentre Single-Blind RCT of cTIF Versus LNF For Treatment of GORD in Patients Requiring Hiatal Hernia Repair (NCT04795934); RCT; USA; estimated enrolment n=142; estimated study completion date December 2026.

References

1. Grössmann N, Wolf S, Wild C (2021). Endoscopic plication therapy in patients with gastroesophageal reflux disease (GERD). AIHTA Decision Support Document No. 127. Austrian Institute for Health Technology Assessment (AIHTA).
2. McCarty TR, Itidare M, Njei B et al. (2018). Efficacy of transoral incisionless fundoplication for refractory gastroesophageal reflux disease: a systematic review and meta-analysis. Endoscopy 50(7): 708–25.
3. Testoni PA, Testoni S, Distefano G et al. (2019). Transoral incisionless fundoplication with EsophyX for gastroesophageal reflux disease: Clinical efficacy is maintained up to 10 years. Endoscopy International Open 7(5): e647–54.
4. Bell RCW, Freeman K, Heidrick R et al. (2021). Transoral incisionless fundoplication demonstrates durability at up to 9 years. Therapeutic Advances in Gastroenterology 14: 17562848211004827.
5. Trad KS, Barnes WE, Prevou ER et al. (2018). The TEMPO Trial at 5 Years: Transoral Fundoplication (TIF 2.0) Is Safe, Durable, and Cost-effective. Surgical Innovation 25(2): 149–57.
6. Testoni SG, Cilona MB, Mazzoleni G et al. (2022). Transoral incisionless fundoplication with Medigus ultrasonic surgical endostapler (MUSE) for the treatment of gastro-oesophageal reflux disease: outcomes up to 3 years. Surgical Endoscopy 36(7): 5023-31.
7. Kalapala R, Karyampudi A, Nabi Z et al. (2022). Endoscopic full-thickness plication for the treatment of PPI-dependent GERD: Results from a randomised, sham-controlled trial. Gut 71(4): 686-94.
8. Chimukangara M, Jalilvand AD, Melvin WS et al. (2019). Long-term reported outcomes of transoral incisionless fundoplication: an 8-year cohort study. Surgical Endoscopy 33(4): 1304–9.
9. Edriss H, El-Bakush A, Nugent K. (2014). Oesophageal perforation and bilateral empyema following endoscopic EsophyX transoral incisionless fundoplication. Clinical endoscopy 47(6): 560-3.
10. Titus JM, Mason DP, Raymond DP et al. (2013). Oesophagopulmonary fistula and left lung abscess after transoral incisionless fundoplication. The Annals of Thoracic Surgery 96(2): 689–91.
11. Weusten BL, Barret M, Bredenoord AJ et al. (2020). Endoscopic management of gastrointestinal motility disorders - part 2: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. Endoscopy 52(7): 600–14.
12. Yadlapati R, Vaezi MF, Vela MF et al. (2018). Management options for patients with GERD and persistent symptoms on proton pump inhibitors:

recommendations from an expert panel. The American Journal of Gastroenterology 113(7): 980–6.

13. Pearl J, Pauli E, Dunkin B et al. (2017). SAGES endoluminal treatments for GERD. Surgical Endoscopy 31(10): 3783–90.

14. Muthusamy VR, Lightdale JR et al. (2015). The role of endoscopy in the management of GERD. Gastrointestinal Endoscopy 81(6): 1305–10.

Literature search strategy

Databases	Date searched	Version/files
MEDLINE (Ovid)	14/10/2022	1946 to October 13, 2022
MEDLINE In-Process (Ovid)	14/10/2022	1946 to October 13, 2022
MEDLINE Epubs ahead of print (Ovid)	14/10/2022	October 13, 2022
EMBASE (Ovid)	14/10/2022	1974 to 2022 October 13
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	14/10/2022	Issue 10 of 12, October 2022
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	14/10/2022	Issue 10 of 12, October 2022
International HTA database (INAHTA)	14/10/2022	n/a

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

Literature search strategy

Number	Search term
1	exp Gastro-oesophageal Reflux/
2	((Gastroesophag* or Gastro-oesophag* or Gastro oesophag* or Gastro-esophag* or Gastro esophag* or acid*) adj4 (Reflux* or junction*)).tw
3	(GORD* or Gord*).tw
4	Oesophageal Motility Disorders/
5	(Oesophageal* adj4 Motility* adj4 Disorder*).tw.
6	(Oesophageal* adj4 Dysmotility*).tw.
7	Heartburn/
8	(heartburn* or regurgitat*).tw.
9	pyros*.tw.
10	or/1-9 95631
11	Endoscopy/
12	Suture Techniques/
13	11 and 12

14	ELGP.tw.
15	(Endoluminal* or Endo-luminal*).tw.
16	Gastroplasty/
17	(Gastroplicat* or Gastro-plicat* or Gastroplast*).tw.
18	(Suture* adj4 (surg* or technic* or procedure* or method*)).tw.
19	(Endoscop* adj4 (suturin* or antireflux* or plication* or transoesophageal*)).tw.
20	or/14-19
21	Fundoplication/
22	fundoplicati*.tw.
23	21 or 22
24	(incisionless* or incision-less*).tw
25	23 and 24
26	TIF.tw.
27	20 or 25 or 26
28	10 and 27
29	EsophyX.tw.
30	EndoCinch.tw.
31	29 or 30
32	28 or 31
33	Animals/ not Humans/
34	32 not 33
35	limit 34 to ed=20210614- 20221031

Appendix

The following table outlines the studies that are considered potentially relevant to the IP overview but were not included in the summary of the key evidence. It is by no means an exhaustive list of potentially relevant studies.

Additional papers identified

Article	Number of patients/follow up	Direction of conclusions	Reasons for non-inclusion in summary of key evidence section
Antoniou SA, Koch OO, Kaindlstorfer A et al. (2012) Endoscopic full-thickness plication versus laparoscopic fundoplication: a prospective study on quality of life and symptom control. Surgical Endoscopy 26(4): 1063–8.	RCT n=60 (30 endoscopic plication vs. 30 lapraoscopic fundoplication) Follow up=12 months	Endoscopic plication and laparoscopic fundoplication resulted in significant symptom improvement with similar quality-of-life scores in a selected patient population with GORD, whereas operative treatment was more effective in the relief of heartburn and regurgitation at the expense of higher short-term dysphagia rates.	Studies with more patients or longer follow up are included.
Barnes WE, Hoddinott KM, Mundy S et al. (2011) Transoral incisionless fundoplication offers high patient satisfaction and relief of therapy-resistant typical and atypical symptoms of GORD in community practice. Surgical Innovation 18(2): 119–29.	Case series n=110 Follow up=median 7 months	At a median 7-month follow up (range 5-17), typical and atypical symptom scores were normalized in 75% to 80% of patients, proton pump inhibitors (PPIs) were completely discontinued by 93%, and 83% were satisfied with their current health condition. Endoscopy in 53 patients revealed Hill grade I tight valves in 89% of the cases, reduced hiatal hernia in 33/34 (97%), and healed reflux oesophagitis in 25/30 (83%). Based on global analysis, 72% of the patients were in remission, 20% improved	More recent studies are included.

		symptomatically, and only 8% had ongoing GORD. These results supported the safety and efficacy of TIF as well as encouraged its application as an alternative treatment of GORD refractory to PPIs.	
Bell RCW, Barnes WE, Carter BJ et al. (2014) Transoral incisionless fundoplication: 2-year results from the prospective multicenter U.S. study. The American Surgeon 80(11): 1093–1105.	Case series n=127 Follow up=2 years	GORD Health related Quality of Life and regurgitation scores improved by 50 per cent or greater in 63 of 96 (66%) and 62 of 88 (70%) patients who had elevated preoperative scores. The Reflux Symptom Index score normalized in 53 of 82 (65%) patients. Daily PPI use decreased from 91 to 29 per cent. In patients amenable to postoperative testing, oesophagitis healed in 12 of 16 (75%) and oesophageal acid exposure normalized in eight of 14 (57%). TIF safely achieved sustained symptomatic control over a 2-year period in two-thirds of patients with a virtual absence of de novo side effects.	Study included in Grössmann (2021) HTA and McCarty (2018) systematic review.
Bell RCW, Fox MA, Barnes WE et al. (2014) Univariate and multivariate analyses of preoperative factors influencing symptomatic outcomes of transoral fundoplication. Surgical Endoscopy 28(10): 2949–58.	Case series n=158 Follow up=median 22 months	Elevated preoperative QOL scores on PPIs and age ≥ 50 were most closely associated with successful outcome of TF in patients with persistent symptoms despite medical therapy.	Likely significant patient overlap with Bell (2014), which is included in Grössmann (2021) HTA and McCarty (2018) systematic review.

Bell RCW, Hufford RJ, Fearon J et al. (2013) Revision of failed traditional fundoplication using EsophyX transoral fundoplication. Surgical Endoscopy 27(3): 761–7.	Case series n=11 Follow up=median 14 months	Transoral revision of failed traditional fundoplication without herniation is technically feasible. It results in symptomatic and objective improvement of GORD without the risks of laparoscopic dissection for a majority of patients.	Studies with more patients or longer follow up are included.
Bell RCW, Mavrelis PG, Barnes WE et al. (2012) A prospective multicenter registry of patients with chronic gastro-oesophageal reflux disease receiving transoral incisionless fundoplication. Journal of the American College of Surgeons 215(6): 794–809.	Case series n=100 Follow up=6 months	Transoral incisionless fundoplication is safe and effective in multiple community-based settings in the treatment of medically refractory GORD, as demonstrated by an absence of complications, excellent symptom relief, and complete cessation of PPIs at 6-month follow up.	Studies with more patients or longer follow up are included.
Cadiere G, Rajan A, Germay O et al. (2008) Endoluminal fundoplication by a transoral device for the treatment of GORD: a feasibility study. Surgical Endoscopy and Other Interventional Techniques 22(2): 333–42.	Case series n=19 Follow up=1 year	The study demonstrated technical feasibility and safety of the ELF procedure using the EsophyXTM device. The study also demonstrated maintenance of the anatomical integrity of the ELF valves for 12 months and provided preliminary data on ELF efficacy in reducing the symptoms and medication use associated with GORD.	Studies with more patients or longer follow up are included.
Chen D, Barber C, McLoughlin P et al. (2009) Systematic review of endoscopic treatments for gastro-oesophageal reflux disease. British Journal of Surgery 96(2): 128–36.	Systematic review n=33 studies Follow up=range 3-26.2 months	At present there is insufficient evidence to determine the safety and efficacy of endoscopic procedures for gastro-oesophageal reflux disease, particularly in the long term.	A more recent systematic review (McCarty 2018) is included.

Chen S, Jarboe MD, Teitelbaum DH (2012) Effectiveness of a transluminal endoscopic fundoplication for the treatment of pediatric gastro-oesophageal reflux disease. Pediatric Surgery International 28(3): 229–34.	Case series n=11 Follow up=mean 8.2 months	The TIF procedure can complement the current surgically and medically available options for children with GORD, especially in complicated patients such as those with NI. However, complications including hemorrhage emphasize the potential risk of the procedure. Further studies with more patients and a longer follow up course must be conducted to better assess efficacy.	Studies with more patients or longer follow up are included.
Choi AY, Roccato MK, Samarasena JB et al. (2021) Novel Interdisciplinary Approach to GORD: Concomitant Laparoscopic Hiatal Hernia Repair with Transoral Incisionless Fundoplication. Journal of the American College of Surgeons 232(3): 309–18.	Case series n=60 Follow up=12 months	The results suggest that cTIF is safe and effective in reducing reflux symptoms in a large spectrum of GORD patients.	Studies with more patients or longer follow up are included.
Coronel MA, Bernardo WM, Moura DTH de et al. (2018) The efficacy of the different endoscopic treatments versus sham, pharmacologic or surgical methods for chronic gastro-oesophageal reflux disease: a systematic review and meta-analysis. Arquivos de Gastroenterologia 55(3): 296–305.	Systematic review n=1085 (16 studies) Follow up=range 3-12 months	This systematic review and meta-analysis shows a good short term efficacy in favor of endoscopic procedures when comparing them to a sham and pharmacological or surgical treatment. Data on long-term follow up is lacking and this should be explored in future studies.	Larger systematic review (McCarty 2018) included.
Ebright MI, Sridhar P, Litle VR et al. (2017) Endoscopic Fundoplication: Effectiveness for Controlling Symptoms of Gastro-oesophageal Reflux	Case series n=80 Follow up=mean 24 months	At a mean follow up of 24 months, TIF is effective. Although symptoms and satisfaction improved significantly, many patients continued to take PPIs. Future studies should focus on longer-term durability and	Studies with more patients or longer follow up are included.

Disease. Innovations 12(3): 180–5.		comparisons with laparoscopic techniques.	
Gerson L, Stouch B, Lobontiu A (2018) Transoral Incisionless Fundoplication (TIF 2.0): A Meta-Analysis of Three Randomized, Controlled Clinical Trials. Chirurgia (Bucur) 113(2): 173–84.	Meta analysis n=233 (3 studies) Follow up=3 years	In a meta-analysis of randomized controlled trials (RCTs), the TIF procedure data for patients with GORD refractory to PPIs produces significant changes, compared with sham or PPI therapy, in oesophageal pH, decreased PPI utilization, and improved quality of life.	Larger systematic review with meta-analysis (McCarty 2018) included.
Gisi C, Wang K, Khan F et al. (2021) Efficacy and patient satisfaction of single-session transoral incisionless fundoplication and laparoscopic hernia repair. Surgical Endoscopy 35(2): 921–7.	Case series n=33 Follow up=median 9 months	The majority of patients reported 75% or greater satisfaction with the procedure and had an improvement in GORD symptoms as well as decreased PPI use. There were no serious adverse events.	Studies with more patients or longer follow up are included.
Hakansson B, Montgomery M, Cadiere GB et al. (2015) Randomised clinical trial: transoral incisionless fundoplication vs. sham intervention to control chronic GORD. Alimentary Pharmacology & Therapeutics 42(1112): 1261–70.	RCT n=42 (22 patients TIF vs. 22 patients sham) Follow up=6 months	Transoral incisionless fundoplication (TIF2) is effective in chronic PPI-dependent GORD patients when followed up for 6 months.	Studies with more patients or longer follow up are included.
Hillman L, Yadlapati R, Whitsett M et al. (2017) Review of antireflux procedures for proton pump inhibitor nonresponsive gastro-oesophageal reflux disease. Diseases of the Esophagus : Official Journal of the	Systematic review n=45 studies (n=19 lapraroscopic fundoplicatio n, n=9 TIF, n=8 radiofrequen cy energy	Laparoscopic fundoplication remains the most proven therapeutic approach. Newer antireflux procedures such as magnetic sphincter augmentation and transoral incisionless fundoplication offer alternatives with varying degrees of success, durability, and side effect profiles that may better suit individual	No meta-analysis.

International Society for Diseases of the Esophagus 30(9): 1–14.	delivery, n=6 magnetic sphincter augmentation, n=3 other anti-reflux procedures Follow up=range 4 weeks-7.1 years	patients. Larger head-to-head comparison trials are needed to better characterize the difference in symptom response and side effect profiles.	
Huang X, Chen S, Zhao H et al. (2017) Efficacy of transoral incisionless fundoplication (TIF) for the treatment of GORD: a systematic review with meta-analysis. Surgical Endoscopy 31(3): 1032–44.	Systematic review and meta-analysis n=963 patients (18 studies) Follow up=range 3-72 months	TIF is an alternative intervention in controlling GORD-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.	Larger systematic review with (McCarty 2018) included.
Hunter JG, Dolan JP, Diggs BS et al. (2015) Efficacy of transoral fundoplication vs omeprazole for treatment of regurgitation in a randomized controlled trial. Gastroenterology 148(2): 324–33.	RCT n= 129 (87 TIF vs 42 omeprazole) Follow up=6 months	TIF was an effective treatment for patients with GORD symptoms, particularly in those with persistent regurgitation despite PPI therapy, based on evaluation 6 months after the procedure.	Studies with more patients or longer follow up are included.
Huynh P, Konda V, Sanguansataya S et al. (2021) Mind the Gap: Current Treatment Alternatives for GORD Patients Failing Medical Treatment and Not Ready for a Fundoplication. Surgical Laparoscopy, Endoscopy and Percutaneous Techniques 31(2): 264–76.	Systematic review n=83 articles (n=32 TIF, n=29 radiofrequency ablation, n=22 magnetic sphincter augmentation) Follow up=range 3 months-10 years	Variable freedom from PPI was reported at 1 year for RFA with a weighted mean of 62%, TIF with a weighted mean of 61%, MSA with a weighted mean of 85%, and fundoplications with a weighted mean of 84%. All procedures including PPIs improved quality-of-life scores but were not equal. Fundoplication had the best improvement followed by MSA, TIF, RFA, and PPI, respectively. DeMeester scores are variable after all procedures and PPIs. All MSA studies showed normalization	No meta-analysis.

		of pH, whereas only 4 of 17 RFA studies and 3 of 11 TIF studies reported normalization of pH.	
Ihde GM, Besancon K, Deljkich E (2011) Short-term safety and symptomatic outcomes of transoral incisionless fundoplication with or without hiatal hernia repair in patients with chronic gastro-oesophageal reflux disease. American Journal of Surgery 202(6): 740-7	Case series n=48 Follow up=median 6 months	The results support the safety and symptomatic improvement of TIF with or without laparoscopic hiatal hernia repair. The patients' symptoms were significantly improved, and PPI use was significantly reduced.	Studies with more patients or longer follow up are included.
Ihde GM, Pena C, Scitern C et al. (2019) pH Scores in Hiatal Repair with Transoral Incisionless Fundoplication. Journal of the Society of Laparoendoscopic Surgeons 23(1): e2018.00087	Case series n=97 Follow up=mean 296 days	Hiatal hernia repair combined with transoral incisionless fundoplication significantly improved outcomes in patients with gastro-oesophageal reflux disease in both subjective Gastro-oesophageal Reflux Disease Health Related Quality of Life and Reflux Symptom Index measurements as well as in objective pH scores	Mixed interventions
Janu P, Shughoury AB, Venkat K et al. (2019) Laparoscopic Hiatal Hernia Repair Followed by Transoral Incisionless Fundoplication With EsophyX Device (HH + TIF): Efficacy and Safety in Two Community Hospitals.	Case series n=99 Follow up=12 months	Hiatal hernia repair and TIF provides significant symptom control for heartburn and regurgitation with no long-term dysphagia or gas bloat normally associated with traditional antireflux procedures. Most patients reported durable symptom control and satisfaction with health condition at 12 months.	Mixed interventions

Surgical Innovation 26(6): 675–86.			
Kaindlstorfer A, Koch OO, Antoniou SA et al. (2013) A randomized trial on endoscopic full-thickness gastroplication versus laparoscopic antireflux surgery in GORD patients without hiatal hernias. Surgical Laparoscopy, Endoscopy & Percutaneous Techniques 23(2): 212–22.	RCT n=70 (n=37 endoscopic full-thickness gastroplication vs n=33 laparoscopic anti-reflux surgery (LARS)) Follow up=3 months	Improvements in the general subjective outcome parameters were similar after endoscopic full-thickness gastroplication compared with LARS despite a stronger reflux control provided by LARS. More effective relief of reflux-related symptoms favors LARS, and differences in side effect symptoms favor endoscopic full-thickness gastroplication.	Studies with more patients or longer follow up are included.
Kaindlstorfer A, Koch OO, Berger J et al. (2012) Full-thickness gastroplication for the treatment of gastro-oesophageal reflux disease: short-term results of a feasibility clinical trial. Surgical Laparoscopy, Endoscopy & Percutaneous Techniques 22(6): 503–8.	Case series n=41 Follow up=3 months	Endoscopic full-thickness plication is a safe and well-tolerated procedure that significantly improves quality of life and eliminates gastro-oesophageal reflux disease symptoms in the majority of patients, without side effects seen after laparoscopic fundoplication.	Studies with more patients or longer follow up are included.
Kim HJ, Kwon C-I, Kessler WR et al. (2016) Long-term follow up results of endoscopic treatment of gastro-oesophageal reflux disease with the MUSE TM endoscopic stapling device. Surgical	Case series n=37 Follow up=4 years	The MUSE stapling device appears to be safe and effective in improving symptom scores as well as reducing PPI use in patients with GORD. These results appeared to be equal to or better than those of the other devices for endoluminal GORD therapy. Future studies with larger patient series, sham control	Studies with more patients or longer follow up are included.

Endoscopy 30(8): 3402–8.		group, and greater number of staples are awaited.	
Koch OO, Kaindlstorfer A, Antoniou SA et al. (2013) Subjective and objective data on oesophageal manometry and impedance pH monitoring 1 year after endoscopic full-thickness plication for the treatment of GORD by using multiple plication implants. Gastrointestinal Endoscopy 77(1): 7–14.	Case series n=36 Follow up=12 months	Endoscopic plication is safe and improves objective and subjective parameters at 1-year followup, without side effects seen after laparoscopic fundoplication. Further studies on the clinical merit of this procedure in specific patient populations are warranted.	Studies with more patients or longer follow up are included.
Muls V, Eckardt AJ, Marchese M et al. (2013) Three-year results of a multicenter prospective study of transoral incisionless fundoplication. Surgical Innovation 20(4): 321–30.	Case series n=79 Follow up=3 years	The clinical outcomes at 3 years following TIF, patient satisfaction, healing of erosive oesophagitis, and cessation of PPI medication support long-term safety and durability of the TIF procedure for those with initial treatment success. Although complete normalization of pH studies occurred in a minority of patients, successful cases showed long-term durability.	Studies with more patients or longer follow up are included.
Narsule CK, Burch MA, Ebright MI et al. (2012) Endoscopic fundoplication for the treatment of gastro-oesophageal reflux disease: initial experience. The Journal of Thoracic and Cardiovascular Surgery 143(1): 228–34.	Case series n=46 Follow up=Mean 140 days	TIF is effective at short-term follow up and safe for patients with GORD. However, long-term follow up and randomised trials are required to assess the efficacy and durability of this approach compared with conventional surgical repair.	Studies with more patients or longer follow up are included.

Nguyen A, Vo T, Nguyen X-MT et al. (2011) Transoral incisionless fundoplication: initial experience in patients referred to an integrated academic institution. The American Surgeon 77(10): 1386–9.	Case series n=10 Follow up=Mean 9.2 months	Transoral incisionless fundoplication is technically safe in well-selected patients including those with prior oesophageal and gastric surgery.	Studies with more patients or longer follow up are included.
Peng L, Wan R, Chen S et al. (2022) Efficacy of endoscopic anterior fundoplication with a novel ultrasonic surgical endostapler for gastroesophageal reflux disease: Six-month results from a multicenter prospective trial. Endoscopic ultrasound; 2022 ahead of print.	Prospective case series N=54 transoral incisionless fundoplicatio n with the Medigus ultrasonic surgical endostapler (MUSE TM) for refractory GERD	A reduction of at least 50% in the GERD-HRQL score was observed in 77.8% (42/54) patients. Most patients 74.1% (40/54) discontinued PPIs and 11.1% (6/54) reported a >=50% dose reduction. The percentage of patients who had normalized acid exposure time after the procedure was 46.9% (23/49). The existence of hiatal hernia at baseline was negatively correlated with the curative effect. Mild pain was common and resolved within 48 h post-procedure. Serious complications were pneumoperitoneum (one case), mediastinal emphysema combined with pleural effusion (two cases).	Larger studies included in table 2.
Petersen RP, Filippa L, Wassenaar EB et al. (2012) Comprehensive evaluation of endoscopic fundoplication using the EsophyX TM device. Surgical Endoscopy 26(4): 1021–7.	Case series n=23 Follow up=6 months	Endoscopic fundoplication is associated with significant reduction in heartburn and abnormal acid exposure at 6 months, although the majority of patients did not experience normalization of their pH studies and remained on PPI therapy. The procedure has an acceptable safety profile, but the question remains as to whether it is effective enough to warrant a place in the armamentarium for the treatment of GORD.	Studies with more patients or longer follow up are included.

Richter JE, Kumar A, Lipka S et al. (2018) Efficacy of Laparoscopic Nissen Fundoplication vs Transoral Incisionless Fundoplication or Proton Pump Inhibitors in Patients With Gastro-oesophageal Reflux Disease: A Systematic Review and Network Meta-analysis. Gastroenterology 154(5): 1298-1308.	Systematic review and meta-analysis n=1145 patients (7 studies: n=2 TIF vs sham, n=2 TIF vs PPI, n=3 LNF vs PPI) Follow up=range 6 months-5 years	In this systematic review and network meta-analysis of trials of patients with GORD, LNF was found to have the greatest ability to improve physiologic parameters of GORD, including increased LES pressure and decreased percent time pH <4. Although TIF produced the largest increase in health-related quality of life, this could be due to the shorter follow up time of patients treated with TIF vs LNF or PPIs. TIF is a minimally invasive endoscopic procedure, yet based on evaluation of benefits vs risks, we do not recommend it as a long-term alternative to PPI or LNF treatment of GORD.	Larger systematic review (McCarty 2018) included.
Rinsma NF, Smeets FG, Bruls DW et al. (2014) Effect of transoral incisionless fundoplication on reflux mechanisms. Surgical Endoscopy 28(3): 941–49.	RCT n=78 (n=32 endoscopic fundoplicatio n and n=15 PPI therapy vs n=29 controls Follow up=6 months	Reduction in acid reflux by endoscopic fundoplication or PPI therapy leads to an increase in baseline impedance in GORD patients, likely to reflect recovery of mucosal integrity. The impact of non-acid reflux events on oesophageal mucosal integrity may be limited as no difference in the increase in baseline impedance was observed after both treatment options. The lack of association between impedance baseline and heartburn severity indicates that other factors may contribute to heartburn perception in GORD.	Results for endoscopic fundoplicati on and PPI therapy not reported separately.
Robertson JO, Jarboe MD. (2018) Long-Term Outcomes of Transoral Incisionless Fundoplication in a High-Risk Pediatric Population. Journal of Laparoendoscopic & Advanced Surgical Techniques. 28(1): 95–100.	Case series n=11 Follow up=Median 5.6 years	The recurrence rate was high, likely related to the fact that the population treated was extremely high risk. Recurrence was higher in patients with a prior fundoplication, perhaps identifying prior antireflux operations as a relative contraindication to TIF. Nevertheless, complications	Studies with more patients or longer follow up are included.

		were low, and a subset of patients did receive a durable benefit from the procedure.	
Snow GE, Dbouk M, Akst LM et al. (2021) Response of Laryngopharyngeal Symptoms to Transoral Incisionless Fundoplication in Patients with Refractory Proven Gastro-oesophageal Reflux. Annals of Otology, Rhinology and Laryngology 131(6):662-70	Case series n=49 Follow up=Median 10.5 months	In patients with objective evidence of GORD, TIF, or TIF with concomital hiatal hernia repair (cTIF) are safe and effective in controlling LPR symptoms as measured by normalization of RSI and improvement in patient satisfaction after TIF/cTIF.	Studies with more patients or longer follow up are included.
Stefanidis G, Viazis N, Kotsikoros N et al. (2017) Long-term benefit of transoral incisionless fundoplication using the esophyx device for the management of gastro-oesophageal reflux disease responsive to medical therapy. Diseases of the Esophagus : Official Journal of the International Society for Diseases of the Esophagus 30(3): 1–8.	Case series n=45 Follow up=12 months	After a median follow up period of 59 months (36–75) the median GORD-HRQL scores improved significantly from 27 (2–45) at baseline to 4 (0–26) ($P < 0.001$) in the 44 patients completing the study. Heartburn was eliminated in 12 out of the 21 patients included (57.1%), regurgitation was eliminated in 15 out of the 17 patients included (88.2%) and chest pain was eliminated in 5 patients out of the six patients included (83.3%). Overall, 32 patients out of the 44 patients (72.7%) that completed the study follow up reported elimination of their main symptom, without the need for PPI administration (no PPI usage). Furthermore, six more patients (13.6%), five with heartburn, and one with regurgitation reported half PPI dose taken for <50% of the preceding follow up period	Studies with more patients or longer follow up are included.

		(occasional PPI usage), while six more patients (four with heartburn, one with regurgitation, and one with chest pain) reported full or half PPI dose taken for more than 50% of the preceding follow up period (daily PPI usage). Creation of an esophagogastric fundoplication using the EsophyX device abolished reflux symptoms in 72.7% of PPI-responsive GORD patients at a median 59-month follow up.	
Svoboda P, Kantorova I, Kozumplik L et al. (2011) Our experience with transoral incisionless plication of gastro-oesophageal reflux disease: NOTES procedure. Hepato-Gastroenterology 58(109): 1208–13.	RCT n=52 (n=34 TIF vs n=18 Nissen laparoscopic fundoplicatio n) Follow up=12 months	It can be summarized that both NOTES TIF procedures with Esophyx and the Plicator are, after the initial learning curve, safe and effective methods for treatment of GORD, allowing substantial shortening of hospital stay. The effect of both procedures was sustained over 12 months. Longer follow up is necessary to verify efficacy for more years.	More recent studies are included.
Testoni PA, Testoni S, Mazzoleni G et al. (2015) Long-term efficacy of transoral incisionless fundoplication with Esophyx (Tif 2.0) and factors affecting outcomes in GORD patients followed for up to 6 years: a prospective single-	Case series n=50 Follow up=mean 52.7 months	TIF by the EsophyX achieved lasting elimination of daily dependence on PPI in 75–80 % of patients for up to 6 years. TIF seems an effective therapy for selected symptomatic GORD patients.	A later version of the same study with longer follow up (Testoni 2019) is included.

center study. Surgical Endoscopy 29(9): 2770–80.			
Testoni PA, Testoni S, Mazzoleni G et al. (2020) Transoral incisionless fundoplication with an ultrasonic surgical endostapler for the treatment of gastro-oesophageal reflux disease: 12-month outcomes. Endoscopy 52(6): 469–73.	Case series n=37 Follow up=12 months	TIF with MUSE significantly improved symptoms at 1-year follow up, allowing the consumption of PPIs to be stopped or halved in 90% of patients.	Studies with more patients or longer follow up are included.
Testoni PA, Vailati C, Testoni S et al. (2012) Transoral incisionless fundoplication (TIF 2.0) with EsophyX for gastro-oesophageal reflux disease: long-term results and findings affecting outcome. Surgical Endoscopy 26(5): 1425–35.	Case series n=42 Follow up=24 months	TIF using the EsophyX device allowed withdrawal or reduction of PPI in about 77% of patients at 6-month follow up and about 69% at 24 months. Larger number of fasteners deployed during TIF was predictive of positive outcome; pre-TIF ineffective oesophageal motility and hiatal hernia raised the risk of recurrence of GORD symptoms, but were not significant from a prospective point of view.	Studies with more patients or longer follow up are included.
Testoni S, Hassan C, Antonelli G et al. (2021) Long-term outcomes of transoral incisionless fundoplication for gastro-oesophageal reflux disease: Systematic-review and meta-analysis. Endoscopy International Open 9(2): e239–46.	Systematic review and meta-analysis n=418 patients (8 studies) Follow up=range 6 months-5 years	TIF appears to offer a long-term safe therapeutic option for selected patients with GORD who refuse life-long medical therapy or surgery, are intolerant to PPIs, or are at increased surgical risk.	Larger systematic review (McCarty 2018) included.

Toomey P, Teta A, Patel K et al. (2014) Transoral incisionless fundoplication: is it as safe and efficacious as a Nissen or Toupet fundoplication? The American Surgeon 80(9): 860–7.	Non-randomised comparative study n=60 (n=20 TIF vs.n= 20 Toupet fundoplication vs. n=20 Nissen fundoplication Follow up not reported	TIF leads to dramatic symptom resolution, similar when compared with Nissen or Toupet fundoplications. TIF promotes shorter operative times and lengths of stay. Patient satisfaction and effective palliation of symptoms show that TIF is safe and efficacious in comparison to Nissen and Toupet fundoplications and support its continued application and evaluation.	Larger studies or studies with longer follow up are included
Trad KS, Barnes WE, Simoni G et al. (2015) Transoral incisionless fundoplication effective in eliminating GORD symptoms in partial responders to proton pump inhibitor therapy at 6 months: the TEMPO Randomized Clinical Trial. Surgical Innovation 22(1): 26–40.	RCT (crossover) n=63 (n=40 TIF vs n=23 PPI) Follow up=6 months	At 6-month follow up, TIF was more effective than MSD PPI therapy in eliminating troublesome regurgitation and extraoesophageal symptoms of GORD.	A later version of the same study with longer follow up (Trad 2018) is included.
Trad KS, Fox MA, Simoni G et al. (2017) Transoral fundoplication offers durable symptom control for chronic GORD: 3-year report from the TEMPO randomized trial with a crossover arm. Surgical Endoscopy 31(6): 2498–2508.	RCT (crossover) n=63 (n=40 TIF vs n=23 PPI) Follow up=3 years	This study demonstrates that TIF can be used to achieve long-term control of chronic GORD symptoms, healing of oesophagitis, and improvement in EAE.	A later version of the same study with longer follow up (Trad 2018) is included.
Trad KS, Turgeon DG, Deljkich E. (2012). Long-term outcomes after transoral incisionless fundoplication in patients with GORD and LPR symptoms.	Case series n=28 Follow up=median 14 months	Results in 28 patients confirm the safety and effectiveness of TIF, documenting symptomatic improvement of GORD and LPR symptoms and clinically significant discontinuation of daily PPIs in 82% of patients.	Larger studies or studies with longer follow up are included

Surgical Endoscopy 26(3): 650–60.			
Trad KS, Turgeon DG, Simoni G et al. (2014) Efficacy of transoral fundoplication for treatment of chronic gastro-oesophageal reflux disease incompletely controlled with high-dose proton-pump inhibitors therapy: A randomized, multicenter, open label, crossover study. BMC Gastroenterology 14(1): 174.	RCT (crossover) n=63 (n=40 TIF vs n=23 PPI) Follow up=12 months	The results of this study indicate that in patients with incomplete symptom control on high-dose PPI therapy TIF may provide further elimination of symptoms and oesophagitis healing. In the original TIF group, the clinical outcomes of TIF remained stable between 6- and 12-month follow up.	A later version of the same study with longer follow up (Trad 2018) is included.
Weitzendorfer M, Spaun GO, Antoniou SA et al. (2017) Interim Report of a Prospective Trial on the Clinical Efficiency of a New Full-thickness Endoscopic Plication Device for Patients With GORD: Impact of Changed Suture Material. Surgical Laparoscopy, Endoscopy & Percutaneous Techniques 27(3): 163–9.	Case series n=28 Follow up=3 months	Endoscopic plication using the GORDx device may be effective in improving quality of life and GORD symptoms. Suture length between pledgets and suture material may have an impact on procedure outcomes.	Larger studies or studies with longer follow up are included
Weitzendorfer M, Spaun GO, Antoniou SA et al. (2018) Clinical feasibility of a new full-thickness endoscopic plication device (GORDx TM) for patients with GORD: results of a	Cohort study n=40 Follow up=3 months	Endoscopic plication with the GORDx™ device reduced distal acid exposure of the oesophagus, reflux-related symptoms, and improved GIQLI scores with minimal side effects in a selected cohort of patients and may be a safe	Larger studies or studies with longer follow up are included

prospective trial. Surgical Endoscopy 32(5): 2541–9.		alternative in the treatment of GORD.	
Wendling MR, Melvin WS, Perry KA. (2013) Impact of transoral incisionless fundoplication (TIF) on subjective and objective GORD indices: a systematic review of the published literature. Surgical Endoscopy 27(10): 3754–61.	Systematic review and meta-analysis n=559 procedures (15 studies) Follow up=range 3-25 months	TIF appears to provide symptomatic relief with reasonable levels of patient satisfaction at short-term follow up. A well-designed prospective clinical trial is needed to assess the effectiveness and durability of TIF as well as to identify the patient population that will benefit from this procedure.	Larger systematic review (McCarty 2018) included.
Wilson EB, Barnes WE, Mavrelis PG et al. (2014) The effects of transoral incisionless fundoplication on chronic GORD patients: 12-month prospective multicenter experience. Surgical Laparoscopy, Endoscopy & Percutaneous Techniques 24(1): 36–46.	Case series n=100 Follow up=12 months	TIF provided a safe and effective therapeutic option for carefully selected patients with chronic GORD.	Larger studies or studies with longer follow up are included
Witteman BPL, Conchillo JM, Rinsma NF et al. (2015) Randomized controlled trial of transoral incisionless fundoplication vs. proton pump inhibitors for treatment of gastro-oesophageal reflux disease. The American Journal of Gastroenterology 110(4): 531–42.	RCT n=60 (n=40 TIF vs n=20 PPI) Follow up=12 months	Although TIF resulted in an improved GORD-related quality of life and produced a short-term improvement of the antireflux barrier in a selected group of GORD patients, no long-term objective reflux control was achieved.	Larger studies or studies with longer follow up are included

Witteman BPL, Strijkers R, Vries E de et al. (2012) Transoral incisionless fundoplication for treatment of gastro-oesophageal reflux disease in clinical practice. Surgical Endoscopy 26(11): 3307–15.	Case series n=38 Follow up=median 36 months	Endoluminal fundoplication improved quality of life and reduced the need for PPIs in only a subgroup of patients at 3 years follow up. The number of patients requiring additional medication and revisional surgery was high.	Larger studies or studies with longer follow up are included.
Xie P, Yan J, Ye L et al. (2021) Efficacy of different endoscopic treatments in patients with gastro-oesophageal reflux disease: a systematic review and network meta-analysis. Surgical Endoscopy 35(4): 1500–1510.	Systematic review and meta-analysis n=516 (10 studies) Follow up=range 3-60 months	In terms of short-term reduction of the HRQL score and heartburn score in patients with GORD, TIF and Stretta may be comparable to each other, and both may be more effective than PPIs. TIF may increase the LES pressure in comparison with Stretta and PPIs. PPIs may reduce the percentage of time pH <4.0 when compared with TIF. This evidence should be interpreted with caution given the small number of included studies and inherent heterogeneity.	Larger systematic review (McCarty 2018) included.
Zacherl J, Roy-Shapira A, Bonavina L et al. (2015) Endoscopic anterior fundoplication with the Medigus Ultrasonic Surgical Endostapler (MUSE TM) for gastro-oesophageal reflux disease: 6-month results from a multi-center prospective trial. Surgical Endoscopy 29(1): 220–29.	Case series n=69 Follow up=6 months	The initial 6-month data reported in this study demonstrate safety and efficacy of this endoscopic plication device. Early experience with the device necessitated procedure and device changes to improve safety, with improved results in the later portion of the study.	Larger studies or studies with longer follow up are included.