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## Endoscopic anti-reflux therapy for gastroesophageal reflux disease

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### Abstract

Gastroesophageal reflux disease has an increasing incidence and prevalence worldwide. A significant proportion of patients have a suboptimal response to proton pump inhibitors or are unwilling to take lifelong medication due to concerns about long-term adverse effects. Endoscopic anti-reflux therapies offer a minimally invasive option for patients unwilling to undergo surgical treatment or take lifelong medication. The best candidates are those with a good response to proton pump inhibitors and without a significant sliding hiatal hernia. Transoral incisionless fundoplication and nonablative radiofrequency are the techniques with the largest body of evidence and that have been tested in several randomized clinical trials. Band-assisted ligation techniques, anti-reflux mucosectomy, anti-reflux mucosal ablation, and new plication devices have yielded promising results in recent noncontrolled studies. Nonetheless, the role of endoscopic procedures remains controversial due to limited long-term and comparative data, and no consensus exists in current clinical guidelines. This review provides an updated summary focused on the patient selection, technical details, clinical success, and safety of current and future endoscopic anti-reflux techniques.

**Key Words:** Treatment; Gastroesophageal reflux; Transoral incisionless fundoplication; Anti-reflux mucosectomy; Anti-reflux mucosal ablation; Stretta

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**Core Tip:** Gastroesophageal reflux disease is a common disorder that impacts quality of life. Endoscopic anti-reflux therapies are intended to offer an alternative for patients unwilling to undergo surgical treatment or take lifelong medication. Several techniques, such as transoral incisionless fundoplication, nonablation radiofrequency, plication methods, and anti-reflux mucosectomy, have shown encouraging results, but their role in the management of gastroesophageal reflux disease remains controversial. Careful patient selection and awareness of the advantages and disadvantages of each technique are essential to optimize outcomes. We herein provide an updated review of the technical aspects, clinical success, and safety of the principle endoscopic anti-reflux procedures.

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## INTRODUCTION

Gastroesophageal reflux disease (GERD) is a condition that develops when reflux of stomach contents causes troublesome symptoms or complications in the esophagus or beyond[1,2]. GERD is very frequent worldwide, with a prevalence ranging from 7.4% in Southern Asia to 19.6% in Central America, and it affects both sexes similarly[3]. The increment in aging and obesity, both predisposing factors for GERD, may increase its impact in the near future even further[4]. Many other factors also favor GERD exacerbation, including tobacco and certain drugs, such as calcium blockers and tricyclic antidepressants[5,6]. GERD negatively affects quality of life and imposes economic and productivity loss burdens[7].

Although the cause of GERD is still incompletely understood, several underlying predisposing pathophysiological mechanisms have been described. While low esophageal sphincter (LES) basal pressure may facilitate reflux after abdominal strain or during swallowing, a more pertinent mechanism is transient LES relaxation (TLESR), which can be associated with esophageal shortening[8,9]. Gastroesophageal junction (GEJ) disruption due to a hiatal hernia (HH) constitutes an additional factor because it contributes to LES incompetence and also displaces the acid pocket closer to the esophageal mucosa[10,11]. Altered visceral sensitivity has a bidirectional effect in GERD, magnifying symptoms in patients without mucosal injury and reducing symptom awareness in Barrett's esophagus patients[12]. Esophageal hypomotility, low saliva production, and other mechanisms such as certain breathing patterns may also contribute to GERD[13].

The management of GERD is multimodal. Lifestyle modifications such as weight loss, tobacco cessation, and, in selected cases, postural advice[14] have proven efficacy and may be sufficient in mild cases. Drug therapy occupies the next level, with proton pump inhibitors (PPIs) having a huge impact on GERD treatment due to high esophagitis healing rates, surpassing the performance of histamine receptor antagonists and exhibiting high cost-efficacy[15,16]. They are the cornerstone of medical GERD treatment. Anti-reflux surgery (ARS), namely laparoscopic fundoplication, is the last step in GERD management. Its objectives are as follows: (1) LES fixation to the hiatus and intraabdominal segment length augmentation; (2) LES basal pressure increase; and (3) hiatal repair. The latter aspect appears crucial because hiatal repair itself impacts the length and pressure of the LES more than fundoplication[17]. Randomized controlled trials (RCTs) have failed to demonstrate a clear long-term superiority of ARS over PPIs[18]. Consequently, ARS is reserved for patients who do not respond to PPIs, do not tolerate them due to adverse effects, or are unwilling to maintain them in the long term.

PPI refractoriness probably constitutes the most frequent indication for surgery, although it is a confusing term and thus deserves further consideration. The same concept frequently encompasses vastly different realities. Refractoriness can be partial or complete, a distinction that is clinically relevant. Recent and major trials have defined the grade of refractoriness needed to meet inclusion criteria[19]. Subsequently,

symptoms can persist for very different reasons, such as poor adherence to medical therapies, absence of a relationship with reflux (*e.g.*, functional heartburn), or objectively proven reflux persistence despite proper medical treatment. Therefore, guidelines advise a full diagnostic workup before surgery to demonstrate as consistently as possible that the symptoms, whether refractory or not, are objectively secondary to GERD[2,20-27].

In the last 30 years, effort has been made to design endoscopic anti-reflux therapies that serve as a valuable option for GERD management, either as an alternative to ARS or as bridge therapy between pharmacological treatment and surgery. They do not thus far allow hiatal repair and constrain candidate selection to individuals without a HH. In 1979, Angelchik[28] used a silicon prosthesis as the first endoscopic treatment for GERD. Since then, numerous other treatments have emerged, with many, such as GEJ injections of bulking agents and several plication techniques, disappearing because of low efficacy or unacceptable adverse effects[29-31]. Here, we present a comprehensive review of the endoscopic approaches for the treatment of GERD that have survived the test of time or have recently been designed (Table 1).

## INDICATIONS FOR ENDOSCOPIC ANTI-REFLUX THERAPY

Endoscopic therapies should be considered at least in the same scenarios as surgery and should offer some advantages over ARS. Specifically, endoscopic anti-reflux therapy should be considered in PPI nonresponders, in patients who have a contraindication to PPIs or have concerns regarding their long-term adverse effects, and in those who either do not qualify for ARS or refuse it. Ideally, endoscopic techniques should demonstrate noninferior efficacy, alongside a shorter operation time, lower complication rate, and lower secondary long-term morbidity. Finally, they should not preclude a future fundoplication in case of failure.

Laparoscopic fundoplication performed by skilled surgeons has a low short-term morbidity and mortality but can cause significant adverse effects in the medium term, such as dysphagia (in up to 24% of patients), gas-bloat syndrome, and incisional hernia, and revision surgeries are not infrequent[22]. It fails in 10%-15% of patients in the short term, and long-term studies have shown that more than 30% of patients are still on PPIs years after surgery[22,32]. This constitutes the scenario against which endoscopic therapies should be compared.

The guidelines of the main medical and surgical societies and expert consensus documents published in the last 10 years have addressed the endoscopic alternatives as well as the surgical option. Their recommendations and the level of evidence or consensus that they are based upon are summarized in Table 2[2,20-26,33-35]. Transoral incisionless fundoplication (TIF) and nonablative radiofrequency are considered appropriate in well-selected patients and situations according to recent guidelines.

## CURRENT ENDOSCOPIC THERAPIES

### *Transoral incisionless fundoplication*

The aim of TIF is to perform an endoscopic fundoplication by reestablishing the flap valve mechanism with a 3-cm high-pressure zone at the distal esophagus to durably restore LES function[36]. This procedure mirrors ARS by using an endoscopic suturing device with T-fasteners, the EsophyX<sup>®</sup> device (EndoGastric Solutions, Inc., Redmond, WA, United States)[37]. These devices have evolved from a longitudinally oriented gastrogastic plication to one with a greater degree of rotational movement, 200° to 300° in circumference and a 2-3-cm length wrap over the distal esophagus below the diaphragm to create full-thickness serosa-to-serosa esophagogastric plications. This easier to use and more automated device can deploy about 20 fasteners without the need for visualization of the stylet/fastener deployment. The objective of the technique is to restore the integrity of the angle of His by firing stabilizing T-fasteners, deployed 2 to 3 cm above the GEJ, with a 270° esophagogastric wrap, to mimic a Toupet surgical fundoplication. The EsophyX<sup>®</sup> device was approved in 2007 by the United States Food and Drug Administration as a single-use, two-operator device comprising a tip (tissue retractor, tissue mold and chassis, fasteners over a stylet, and the invaginator) and body (H-fasteners, helix retractor lock, vacuum connection, fastener pusher, helix retractor control, tissue mold knob, gastroscope point of insertion).

**Table 1 Comparison of current endoscopic therapies for gastroesophageal reflux disease**

	TIF	MUSE	Stretta®	GERDx™	ARMS/ARMA	Band ligation
Efficacy	++	+	+ -	+	+	+
Safety	+	+	++	+	+	+
Technical difficulty	++	++	+	++	+	+
Add-on device	+	+	+	+	-	-
RCT available	+	-	+	-	-	-
Maximum follow-up (yr)	10	5	10	0.25	3	1
Cost	++	++	++	++	+	+

++: Indicates the highest score; +: Indicates a moderate score or yes; -: Indicates uncertainty; TIF: Transoral incisionless fundoplication; MUSE: Medigus ultrasonic surgical endostapler; GERDx™: Endoscopic full-thickness plication device; ARMS: Anti-reflux mucosectomy; ARMA: Anti-reflux mucosal ablation; RCT: Randomized controlled trial.

Optimal candidates for TIF are patients who demonstrate LES incompetence (Hill grade II) without a concomitant HH. TIF 1.0 has been discontinued because TIF 2.0 achieves much better results[36]. The improved procedure has been evaluated in nine noncomparative studies[38-46] and in five RCTs[47-51] comprising 886 patients with moderate GERD without a large HH, Los Angeles grade C or D esophagitis, or Barrett's esophagus (Table 3). Clinical success rates ranged from a modest 50% at 12 mo to as high as 92% at 10 years. Severe adverse events (SAEs) have been reported in 2.4% of patients[52]. A recent network meta-analysis suggested that the TIF 2.0 procedure manages symptoms and allows PPI discontinuation at rates similar to those of ARS with an improved safety profile and fewer long-term adverse events[53]. A clinical response, defined by an improvement of at least 50% in GERD health-related quality of life (GERD-HRQL) score or remission of heartburn and regurgitation, was observed in 66% of patients treated with TIF. Moreover, TIF had the highest probability of improving GERD-HRQL (0.96), followed by ARS (0.66) and PPIs (0.042). In contrast, ARS had the highest probability of increasing the percent time at pH < 4 (0.99), followed by PPIs (0.64) and TIF (0.32)[53]. A review of the published evidence supports the belief that most selected patients undergoing TIF 2.0 experience a long-term elimination of GERD symptoms with no SAEs and that this procedure is a cost-effective alternative to ARS.

### **Medigus ultrasonic surgical endostapler**

The Medigus ultrasonic surgical endostapler (MUSE), or MUSE™ system (Medigus, Omer, Israel), combines microvisual, ultrasonic, and surgical stapling capabilities into one device, which enables a single endoscopist to perform a transoral anterior fundoplication. This flexible surgical endostapler resembles an endoscope with a rigid section holding a cartridge with five standard 4.8-mm titanium surgical staples. The distal tip contains an anvil for bending the staples, two small 21-gauge screws, and an ultrasonic transducer to measure the distance to the cartridge. This method is a three-step procedure: (1) The stapler is advanced into the stomach through an overtube and retroflex; (2) The system is retracted to 3 cm proximal to the GEJ for clamping when the tissue thickness is 1.4-1.6 mm, and the stapler is then fired; and (3) The procedure is repeated to add quintuplets of staples to create an anti-reflux barrier.

This endoscopic stapling system has been evaluated in four noncomparative studies [46,54-56] and in one two-arm case series study[57] including 209 patients with GERD without a HH larger than 3 cm (Table 3). Clinical success rates ranged from 69% to 92% with follow-up durations from 6 mo to 5 years. The risk of SAEs (empyema, hemorrhage, esophageal perforation) was 3.5%. Overall, data on the efficacy and safety of MUSE are scarce and evidence from RCTs is lacking.

### **Nonablative radiofrequency treatment (Stretta®)**

This endoscopic-guided method involves the application of radiofrequency energy to the muscle fibers of the LES and the gastric cardia, through the Stretta® system (Restech, Houston, TX, United States). The Stretta® catheter is introduced over the guidewire and positioned sequentially at three levels: 0.5 cm proximal to the GEJ, at the GEJ, and 0.5 cm below the GEJ. At each level, the balloon basket assembly is



**Table 2 Summary of guidelines and consensus recommendations and invasive gastroesophageal reflux disease therapies**

Society guidelines and year of publication	Indication for surgery	Strength of recommendation, level of evidence, and grade of consensus	Endoscopic anti-reflux therapy addressed	Guideline recommendation on endoscopic anti-reflux therapy	Strength of recommendation and level of evidence
ACG guidelines for diagnosis and management of GERD, 2013[2]	Option for long-term treatment	Quality: High. Strength: Strong	Radiofrequency, bulking agents, endoscopic suturing	Not recommended	Quality: Moderate. Strength: Conditional
	Generally not recommended in PPI-unresponsive patients	Quality: High. Strength: Strong			
	Refractory patients with objective evidence of ongoing reflux as the cause of symptoms	Quality: Low. Strength: Conditional			
EAES recommendations, 2014[22]	Good response but dependent on long-term PPI therapy, after optimal risk-benefit discussion	Grade: C. Consensus: 100%	Radiofrequency (Stretta®), bulking agent injection (Enteryx®), plication (EndoCinch®), full-thickness plication, EsophyX®	Not enough evidence available to recommend any as an alternative option to surgery	Grade of recommendation: B. Expert consensus: 100%
	Total or partial refractoriness despite adequate PPI therapy in terms of dosage and intake	Grade: A. Consensus: 100%			
	Well-selected NERD patients and those with hypersensitive esophagus	Grade: C. Consensus: 100%			
American Society of Gastrointestinal Endoscopy: The role of endoscopy in the management of GERD, 2015[95]	Not provided	Not provided	Radiofrequency (Stretta®) and transoral incisionless fundoplication	Consider in highly selected patients. No details on selection criteria	Low quality
Asia-Pacific consensus on refractory GERD management, 2016[23]	Refractory symptoms with objectively documented GERD	Quality: Moderate. Strength: Strong. Consensus: 100%	None	Not applicable	Not applicable
World Gastroenterology Organisation Global Guidelines, 2017[24]	Large hiatal hernia with volume-related reflux symptoms. Refractory esophagitis. Refractory symptoms documented as caused by GERD. Medication adverse effects	Not specified	Endoscopic therapies in general	Only in the context of clinical trials	Not specified
SAGES Guidelines on GERD surgical treatment, 2010, and on endoluminal anti-reflux treatments, 2017[21,34]	Appropriately selected GERD patients	Grade A	Transoral incisionless fundoplication	Control of symptoms in appropriately selected patients in the short term; appears to lose effectiveness	Quality: Moderate. Strength: Strong
			Radiofrequency	Control of symptoms in appropriately selected patients; long-term effect in appropriately selected patients	Quality: Moderate. Strength: Strong
USA expert panel (surgeons and advanced therapeutic endoscopists) recommendations on GERD management, 2020[25]	PPI responders (complete or partial)	Appropriate. Consensus: 87%-100%	Transoral incisionless fundoplication	PPI responders (complete or partial), no hernia, any other scenario	Appropriate. Consensus: 93%
	PPI nonresponder, no hernia, heartburn-hypersensitivity, or negative pH-impedance	Appropriateness uncertain		PPI responders (complete or partial) or nonresponders, significant hernia, any other scenario  PPI nonresponder, no hernia and acid breakthrough, hypersensitivity or	Not appropriate  Appropriate. Consensus: 80%-93%

study			negative pH-impedance study for heartburn		
	PPI nonresponder, any other scenario	Appropriate. Consensus: 80%-100%		PPI nonresponder, regurgitation, negative pH-impedance study	Appropriateness uncertain
ESGE guidelines on endoscopic management of gastrointestinal motility disorders, 2020 [35]	Not applicable	Not applicable	Radiofrequency	PPI responders (complete or partial) or nonresponders, no hernia, any scenario	Appropriateness uncertain
				PPI responders (complete or partial) or nonresponders, significant hernia	Not appropriate
			Transoral incisionless fundoplication	Possible role in mild GERD patients who are unwilling to take PPIs or undergo surgery. Against widespread use	Quality: Moderate. Strength: Strong. Consensus: 92.8%
			Medigus Ultrasonic Surgical Endostapler	Insufficient data. Use only in clinical trials	Quality: Low. Strength: Strong. Consensus: 100%
			Radiofrequency	Can be considered in selected patients only, without erosive esophagitis and hiatal hernia	Quality: Moderate. Strength: Weak. Consensus: 92.9%
ESNM/ASNM consensus paper on management of refractory GERD, 2020 [26]	Refractory GERD symptoms in patients with proven GERD	Consensus: 100%	Anti-reflux mucosectomy	Against routine use in clinical practice	Quality: Low. Strength: Strong. Consensus: 100%
			Transoral incisionless fundoplication	Short-term benefit in improving regurgitation in carefully selected patients	Consensus: 100%
			Radiofrequency	Variable symptom improvement, limited objective improvement in acid burden or manometric esophagogastric junction features	Consensus: 100%

ACG: American College of Gastroenterology; EAES: European Association of Endoscopic Surgery; SAGES: Society of the Americans Gastrointestinal and Endoscopic Surgeons; GERD: Gastroesophageal reflux disease; ESGE: European Society of Gastrointestinal Endoscopy; ESNM: European Society of Neurogastroenterology and Motility; ASNM: American Society of Neurogastroenterology and Motility; PPIs: Proton pump inhibitors; NERD: Nonerosive reflux disease.

inflated and then four nitinol needle electrodes (22-gauge, 5.5-mm) are extended into the muscular layer to deliver a radiofrequency current and induce a thermal reaction. Next, to deliver radiofrequency energy to four additional points, the catheter is rotated 45° clockwise[58]. The pathophysiological mechanism is not fully understood, but the thermal injury is thought to promote submucosal fibrosis and muscularis propria hypertrophy, which would decrease the frequency of TLESR and GEJ compliance while increasing LES and gastric yield pressures[58].

The Stretta® procedure has been evaluated in numerous cohort studies and in five RCTs, three with sham therapy and two with PPI use[59] (Tables 1 and 3). The RCT results did not show significant changes in esophageal acid exposure at 6 mo following Stretta®, compared with the PPI group[60]. Likewise, patients treated with Stretta® presented significant improvements in heartburn symptoms and quality of life in only the short term, compared with a sham procedure, with no long-term data[61-63]. A meta-analysis including 159 patients, limited to four RCTs, confirmed the absence of significant changes in patients with GERD[64]. More recently, a second meta-analysis that included both RCTs and 24 other cohort studies with 2468 evaluated patients[65] showed a significant postprocedural improvement in quality of life and in heartburn score but no improvement in basal LES pressure. The procedure is safe and well-tolerated, and SAEs are very rare. RCTs and cohort studies reported erosions, mucosal lacerations, gastroparesis, mediastinal inflammation, pneumonia,

**Table 3 Clinical success and safety of endoscopic therapies**

Technique	Study design and population	Clinical success, range	Major adverse events, range
Transoral incisionless fundoplication	No. of RCTs: 5; <i>n</i> = 343 No. of nonrandomized case series: 9; <i>n</i> = 543	50%–92%	0%–4.4%
Medigus ultrasonic surgical endostapler	No. of RCTs: 0 No. of nonrandomized case series: 5; <i>n</i> = 199	69%–92%	0%–9%
Nonablative radiofrequency (Stretta®)	No. of RCTs: 5; <i>n</i> = 173 No. of nonrandomized case series: 29; <i>n</i> = 2571	15%–100%	0%–1%
Endoscopic plication device (GERDx™)	No. of RCTs: 0 No. of nonrandomized case series: 1; <i>n</i> = 40	19 out of 40 patients were off PPIs	10%
Band ligation techniques	No. of RCTs: 1; <i>n</i> = 150 No. of nonrandomized case series: 2; <i>n</i> = 73	43%–54% <sup>1</sup>	0%
Anti-reflux mucosectomy	No. of RCTs: 0 No. of nonrandomized case series: 12; <i>n</i> = 331	58%–100%	0%–17%
Anti-reflux mucosal ablation	No. of RCTs: 0 No. of nonrandomized case series: 3; <i>n</i> = 130	58%–89%	0%–13%

<sup>1</sup>Clinical success not defined in the randomized controlled trial. There was a significant reduction in gastroesophageal reflux disease health-related quality of life score and 24-h pH-metry outcomes. RCT: Randomized controlled trial; PPIs: Proton pump inhibitors.

and pleural effusion[66].

### **Endoscopic plication device (GERDx™)**

The GERDx™ device (G-SURG GmbH, Seon-Seebruck, Germany) uses hydraulic elements for control and requires a slim gastroscope that works as a light source. It is the advanced single-use product of the company that has acquired the Plicator technology after withdrawal of the Plicator device (Ethicon Endo-Surgery, Somerville, NJ) from the market. The experience with GERDx™ is still minimal, with only two publications in this regard, one of which is an interim analysis by the same authors (Tables 1 and 3).

In a single-center, single-arm trial, Weitzendorfer *et al*[67,68] prospectively assessed the outcomes of 40 patients with refractory GERD treated with the GERDx™ device. Of the 40 patients, 7 underwent LARS before the 3-mo follow-up. The mean DeMeester score was reduced from 46.48 to 20.03 in the 30 patients who completed the follow-up. Of these 30 patients, 18 (60.0%) achieved normal DeMeester score levels. In addition, 3 (10.0%) stated that they were on daily PPI medication after the plication, with 8 (26.7%) taking on-demand medication and 19 (63.3%) off medication. Moderate SAEs were reported by 10% of the patients (a hematoma at the GEJ, a case of pneumonia, a suture passing through the left hepatic lobe, pleural empyema, a severe Mallory-Weiss tear). The single-study evidence, lack of a comparator arm, and the very short follow-up make this endoscopic treatment experimental at this time, necessitating new RCTs to corroborate improvements in quality of life and acid exposure and confirm procedural safety.

### **Anti-reflux mucosectomy and anti-reflux mucosal ablation**

Anti-reflux mucosectomy (ARMS) was first devised in a patient with a Barrett's esophagus-related lesion treated by endoscopic submucosal dissection. The resulting scar improved GERD symptoms and normalized the DeMeester score[69]. This observation led to the first case series, published by Inoue *et al*[69] in 2014. In ARMS, endoscopic resection of the gastric cardiac mucosa is performed to reduce the opening

of the GEJ. Initial ARMS cases were performed by endoscopic submucosal dissection, but subsequent reports indicated that cap- or band-assisted mucosal resection is faster, easier to perform, and equally effective[70-72]. ARMS has been suggested to suppress the backflow of gastric content and enhance the GEJ flap valve mechanism, but the underlying anti-reflux mechanism is poorly understood[72]. A RCT conducted in animals found that ARMS increased the pressure and volume required to induce fluid passage from the gastric cavity to the esophagus[73]. One clinical study revealed that ARMS increased the integrated relaxation pressure and LES resting pressure but decreased GEJ distensibility, which could hypothetically reduce the frequency of TLESR[72,74].

In 2020, Inoue *et al*[75] and Hernández Mondragón *et al*[76] proposed that ablation of the gastric cardiac mucosa by argon plasma coagulation (forced mode 100 W) or a coagulation current applied by an endoknive (spray coagulation 50 W, effect 2) can also induce scar formation and yield similar clinical outcomes. This approach, named anti-reflux mucosal ablation (ARMA), is intended to simplify the procedure, reduce the risk of perforation, and facilitate the retreatment of patients who have failed ARMS.

In addition to their technical simplicity, ARMS and ARMA do not require costly add-on devices and can be performed in a standard endoscopy room[72,76]. Key points during ARMS and ARMA are adequate submucosal injection to prevent perforation and the sparing of a rim of healthy mucosa to minimize the risk of GEJ stenosis. The procedure is not standardized, but most authors spare the esophageal mucosa and perform a gastric cardia 270°-320° treatment or mimic a “butterfly” shape by sparing 1 cm of normal mucosa along the greater and lesser curvature[72,75-77].

In total, 15 nonrandomized studies (12 on ARMS[69-72,74,77-83] and three on ARMA[75,76,84]) comprising 461 patients have evaluated the safety and effectiveness of these techniques (Tables 1 and 3). Follow-up ranged from 2 mo to a maximum of 3 years (in two studies[72,76]). Clinical success ranged from 58% to 100% at 2-6 mo[81, 83] and from 72% to 76% at 3 years[72,76]. Dysphagia was the most common adverse event, occurring in about 5% to 10% of the patients. In contrast to what occurs with dysphagia associated with ARS[85], ARMS- and ARMA-associated dysphagia can be easily treated by small-caliber balloon dilation and does not necessarily compromise clinical success[72,76]. Gastrointestinal perforation is the most feared complication and has been reported in four patients treated with ARMS[72,77,78] and in none treated with ARMA. Given the lack of RCT and long-term data, these techniques should be viewed as experimental and reserved for patients included in research protocols.

### Band ligation techniques

Three studies have assessed the outcomes of rubber band placement at the GEJ to reduce the width of the opening of the gastric cardia. Seleem *et al*[86] performed a RCT that included 150 patients with refractory GERD. The number of bands applied and the frequency of endoscopic sessions were determined according to the narrowing of the GEJ during banding. A maximum of four bands per session were allowed. Follow-up at 1 year showed a significant improvement in GERD-HRQL score and the number of reflux episodes. Mild dysphagia (25.3%) and epigastric pain (40%) were the most common adverse events, but no SAEs were recorded[86]. Hu *et al*[87] also reported favorable subjective and 24-h pH-metry outcomes in a case series of 13 patients and named the procedure “peroral endoscopic cardiac constriction”. The authors placed two single-band ligation devices (Fujinon, Tokyo, Japan) at the greater and lesser curvatures, close to the Z line. The first band was placed approximately 1.0 cm above the cardia along the lesser curvature, whereas the second band was delivered 1.0 cm above the greater curvature[87]. Finally, a clip was placed at the base of the bands to minimize the risk of band slippage. In 2020, another Chinese group reported favorable results with this technique in a nonrandomized study of 60 patients, with the approach now named “clip band ligation anti-reflux therapy (C-BLART)”[88] (Tables 1 and 3).

Because the above-mentioned RCT does not adhere to the Consolidated Standards of Reporting Trials quality requirements and the two case series were noncontrolled and included a limited number of patients, the technique should currently be viewed as experimental.

## FUTURE DIRECTIONS

The history of endoscopic therapies for GERD is replete with encouraging preclinical studies and case series that fail to clear the hurdle of long-term and well-designed



RCTs. The main underlying reasons are the complex and multifactorial pathophysiology of GERD and the often short-lived anatomical changes induced by endoscopic therapies. Moreover, many endoscopic techniques require expensive add-on devices and cumbersome technical steps that have limited their popularization. To complicate further this issue, patient selection has been heterogeneous, and we lack consensus regarding the definition of clinical success or the admissible thresholds of cost and adverse events. Future endoscopic therapies and GERD research should bear all of this in mind.

The first consideration is that only a subset of well-selected GERD patients are good candidates for endoscopic therapies because current techniques remain unable to fix the hiatus, enhance esophageal motility, or normalize LES competence. Artificial intelligence through knowledge-based clinical decision support systems could be of help in the future for improving patient selection. Combined approaches that consider more than one GERD mechanism have been proposed to address this issue, such as a combination of ARMS with a plication method[89] or of TIF with laparoscopic HH repair[90]. Second, technical feasibility is critical for introducing a procedure into clinical practice. The learning curve of anti-reflux endoscopic therapies has not been well-described, and scientific societies have not published curricula documents to guide training. Band ligation, ARMS, and, more recently, ARMA are at very early stages but represent an attractive option from this perspective. Our group is currently performing a double-blind RCT to assess the clinical success and safety of ARMA[91]. Third, patient-reported outcomes are increasingly being recognized by clinicians, regulatory agencies, and patients as highly valuable tools to assess the impact of new interventions. Thus, we believe that studies should place symptoms and GERD-related quality of life as primary endpoints. A “black or white” perspective for clinical success does not reflect the complexity of GERD patients, and partial but significant improvements should also be taken into account. This makes anti-reflux endoscopy not only an alternative to PPIs, but also a complementary tool that can reduce their consumption and partially improve quality of life. A > 50% drop in the GERD-HRQL score or in other validated clinical questionnaires has been used in recent RCTs and appears to be a reasonable approach[52,53]. In addition, more objective GERD parameters (24-h pH-impedance testing, endoscopic esophagitis) and sham/placebo arms are needed to support subjective improvements. Outcome definitions should be in line with recent international consensus[26,27,92,93]. RCTs should include long-term follow-up as part of the trial or as a post-RCT prospective observational phase to assess durability. Finally, endoscopic therapies seem cost-effective, but we need more comparative data with PPI and surgery[94].

## CONCLUSION

Endoscopic therapy for GERD aims to offer an alternative to PPIs and ARS in patients without significant diaphragmatic crura impairment. TIF, the technique with the largest body of evidence, has been proven to improve GERD symptoms and acid exposure time and reduce PPI consumption. Nonablative radiofrequency (Stretta®) is the method with the lowest rate of SAEs, but its efficacy has been called into question in recent meta-analyses. Band ligation techniques, ARMS, ARMA, and new plication devices have shown promising results in initial reports and RCTs are eagerly awaited. Careful patient selection, ongoing technical refinements, and RCTs with long-term data are the roadmap to unveil the potential of minimally invasive anti-reflux endoscopic techniques.

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