**Name of Journal:** *World Journal of Gastroenterology*

**Manuscript NO:** 67254

**Manuscript Type:** MINIREVIEWS

**Endoscopic anti-reflux therapy for gastroesophageal reflux disease**

Rodriguez de Santiago E *et al*. Endoscopic anti-reflux therapy

Enrique Rodríguez de Santiago, Eduardo Albéniz, Fermin Estremera-Arevalo, Carlos Teruel Sanchez-Vegazo, Vicente Lorenzo-Zúñiga

**Enrique Rodríguez de Santiago, Carlos Teruel Sanchez-Vegazo,** Department of Gastroenterology and Hepatology, Hospital Universitario Ramón y Cajal, Instituto Ramón y Cajal de Investigación Sanitaria (IRYCIS), Madrid 28034, Spain

**Eduardo Albéniz, Fermin Estremera-Arevalo,** Endoscopy Unit, Gastroenterology Department, Hospital Universitario de Navarra. Gastrointestinal Endoscopy Research Unit, Navarrabiomed Biomedical Research Center. Pamplona, Spain

**Vicente Lorenzo-Zúñiga,** Endoscopy Unit, Gastroenterology Department, Hospital Universitari i Politècnic La Fe, Instituto de Investigación Sanitaria La Fe (IIS La Fe), Valencia 46026, Spain

**Author contributions:** Rodriguez de Santiago E and Lorenzo-Zuñiga V designed the research study; all authors performed the literature review; Rodriguez de Santiago E drafted the first version of the manuscript; Estremera-Arevalo F, Lorenzo-Zuñiga V, Albeniz E, and Teruel Sanchez-Vegazo C critically reviewed the manuscript; all authors have read and approved the final manuscript.

**Corresponding author: Enrique Rodríguez de Santiago, MD, MHSc, PhD, Consultant Physician-Scientist,** Department of Gastroenterology and Hepatology, Hospital Universitario Ramón y Cajal, Instituto Ramón y Cajal de Investigación Sanitaria (IRYCIS), Ctra. de Colmenar Viejo km. 9100, Madrid 28034, Spain. enrodesan@gmail.com

**Received:** April 19, 2021

**Revised:** July 1, 2021

**Accepted:** August 31, 2021

**Published online:** October 21, 2021

**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

**©The** **Author(s) 2021.** Published by Baishideng Publishing Group Inc. All rights reserved.

**Citation:** Rodríguez de Santiago E, Albéniz E, Estremera-Arevalo F, Teruel Sanchez-Vegazo C, Lorenzo-Zúñiga V. Endoscopic anti-reflux therapy for gastroesophageal reflux disease. *World J Gastroenterol* 2021; 27(39): 6601-6614

URL: <https://www.wjgnet.com/1007-9327/full/v27/i39/6601.htm>

DOI: https://dx.doi.org/10.3748/wjg.v27.i39.6601

**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, nonablative 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.

**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 EsophyXâ device (EndoGastric Solutions, Inc., Redmond, WA, United States)[37]. These devices have evolved from a longitudinally oriented gastrogastric plication to one with a greater degree of rotational movement, 200º to 300º 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 EsophyXâ 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).

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 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 45º 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, and pleural effusion[66].

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

The GERDx™ device (G-SURG GmbH, Seeon-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, Sommerville, 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°-320º 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 cardial 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.

**REFERENCES**

1 **Vakil N**, van Zanten SV, Kahrilas P, Dent J, Jones R; Global Consensus Group. The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. *Am J Gastroenterol* 2006; **101**: 1900-1920; quiz 1943 [PMID: 16928254 DOI: 10.1111/j.1572-0241.2006.00630.x]

2 **Katz PO**, Gerson LB, Vela MF. Guidelines for the diagnosis and management of gastroesophageal reflux disease. *Am J Gastroenterol* 2013; **108**: 308-328; quiz 329 [PMID: 23419381 DOI: 10.1038/ajg.2012.444]

3 **Eusebi LH**, Ratnakumaran R, Yuan Y, Solaymani-Dodaran M, Bazzoli F, Ford AC. Global prevalence of, and risk factors for, gastro-oesophageal reflux symptoms: a meta-analysis. *Gut* 2018; **67**: 430-440 [PMID: 28232473 DOI: 10.1136/gutjnl-2016-313589]

4 **Diaz-Rubio M**, Moreno-Elola-Olaso C, Rey E, Locke GR 3rd, Rodriguez-Artalejo F. Symptoms of gastro-oesophageal reflux: prevalence, severity, duration and associated factors in a Spanish population. *Aliment Pharmacol Ther* 2004; **19**: 95-105 [PMID: 14687171 DOI: 10.1046/j.1365-2036.2003.01769.x]

5 **van Soest EM**, Dieleman JP, Siersema PD, Schoof L, Sturkenboom MC, Kuipers EJ. Tricyclic antidepressants and the risk of reflux esophagitis. *Am J Gastroenterol* 2007; **102**: 1870-1877 [PMID: 17511756 DOI: 10.1111/j.1572-0241.2007.01320.x]

6 **Boeckxstaens G**, El-Serag HB, Smout AJ, Kahrilas PJ. Republished: symptomatic reflux disease: the present, the past and the future. *Postgrad Med J* 2015; **91**: 46-54 [PMID: 25583739 DOI: 10.1136/postgradmedj-2013-306393rep]

7 **Gisbert JP**, Cooper A, Karagiannis D, Hatlebakk J, Agréus L, Jablonowski H, Nuevo J. Impact of gastroesophageal reflux disease on work absenteeism, presenteeism and productivity in daily life: a European observational study. *Health Qual Life Outcomes* 2009; **7**: 90 [PMID: 19835583 DOI: 10.1186/1477-7525-7-90]

8 **Holloway RH**, Dent J. Pathophysiology of gastroesophageal reflux. Lower esophageal sphincter dysfunction in gastroesophageal reflux disease. *Gastroenterol Clin North Am* 1990; **19**: 517-535 [PMID: 2228162 DOI: 10.1016/S0889-8553(21)00654-3]

9 **Iovino P**, Theron B, Prew S, Menon S, Trudgill N. The mechanisms associated with reflux episodes in ambulant subjects with gastro-esophageal reflux disease. *Neurogastroenterol Motil* 2021; **33**: e14023 [PMID: 33112052 DOI: 10.1111/nmo.14023]

10 **Ciriza-de-los-Ríos C**, Canga-Rodríguez-Valcárcel F, Castel-de-Lucas I, Lora-Pablos D, de-la-Cruz-Bértolo J, Castellano-Tortajada G. How useful is esophageal high resolution manometry in diagnosing gastroesophageal junction disruption: causes affecting this disruption and its relationship with manometric alterations and gastroesophageal reflux. *Rev Esp Enferm Dig* 2014; **106**: 22-29 [PMID: 24689712 DOI: 10.4321/s1130-01082014000100004]

11 **van Herwaarden MA**, Samsom M, Smout AJ. Excess gastroesophageal reflux in patients with hiatus hernia is caused by mechanisms other than transient LES relaxations. *Gastroenterology* 2000; **119**: 1439-1446 [PMID: 11113064 DOI: 10.1053/gast.2000.20191]

12 **Aziz Q**, Fass R, Gyawali CP, Miwa H, Pandolfino JE, Zerbib F. Functional Esophageal Disorders. *Gastroenterology* 2016 [PMID: 27144625 DOI: 10.1053/j.gastro.2016.02.012]

13 **Tack J**, Pandolfino JE. Pathophysiology of Gastroesophageal Reflux Disease. *Gastroenterology* 2018; **154**: 277-288 [PMID: 29037470 DOI: 10.1053/j.gastro.2017.09.047]

14 **Kaltenbach T**, Crockett S, Gerson LB. Are lifestyle measures effective in patients with gastroesophageal reflux disease? An evidence-based approach. *Arch Intern Med* 2006; **166**: 965-971 [PMID: 16682569 DOI: 10.1001/archinte.166.9.965]

15 **Dent J**, Hetzel DJ, MacKinnon MA, Reed WD, Narielvala FM. Evaluation of omeprazole in reflux oesophagitis. *Scand J Gastroenterol Suppl* 1989; **166**: 76-82; discussion 94 [PMID: 2690334 DOI: 10.3109/00365528909091249]

16 **Weijenborg PW**, Cremonini F, Smout AJ, Bredenoord AJ. PPI therapy is equally effective in well-defined non-erosive reflux disease and in reflux esophagitis: a meta-analysis. *Neurogastroenterol Motil* 2012; **24**: 747-757, e350 [PMID: 22309489 DOI: 10.1111/j.1365-2982.2012.01888.x]

17 **Louie BE**, Kapur S, Blitz M, Farivar AS, Vallières E, Aye RW. Length and pressure of the reconstructed lower esophageal sphincter is determined by both crural closure and Nissen fundoplication. *J Gastrointest Surg* 2013; **17**: 236-243 [PMID: 23188217 DOI: 10.1007/s11605-012-2074-4]

18 **Garg SK**, Gurusamy KS. Laparoscopic fundoplication surgery versus medical management for gastro-oesophageal reflux disease (GORD) in adults. *Cochrane Database Syst Rev* 2015: CD003243 [PMID: 26544951 DOI: 10.1002/14651858.CD003243.pub3]

19 **Spechler SJ**, Hunter JG, Jones KM, Lee R, Smith BR, Mashimo H, Sanchez VM, Dunbar KB, Pham TH, Murthy UK, Kim T, Jackson CS, Wallen JM, von Rosenvinge EC, Pearl JP, Laine L, Kim AW, Kaz AM, Tatum RP, Gellad ZF, Lagoo-Deenadayalan S, Rubenstein JH, Ghaferi AA, Lo WK, Fernando RS, Chan BS, Paski SC, Provenzale D, Castell DO, Lieberman D, Souza RF, Chey WD, Warren SR, Davis-Karim A, Melton SD, Genta RM, Serpi T, Biswas K, Huang GD. Randomized Trial of Medical versus Surgical Treatment for Refractory Heartburn. *N Engl J Med* 2019; **381**: 1513-1523 [PMID: 31618539 DOI: 10.1056/NEJMoa1811424]

20 **Kahrilas PJ**, Shaheen NJ, Vaezi MF, Hiltz SW, Black E, Modlin IM, Johnson SP, Allen J, Brill JV; American Gastroenterological Association. American Gastroenterological Association Medical Position Statement on the management of gastroesophageal reflux disease. *Gastroenterology* 2008; **135**: 1383-1391, 1391.e1-1391.e5 [PMID: 18789939 DOI: 10.1053/j.gastro.2008.08.045]

21 **Stefanidis D**, Hope WW, Kohn GP, Reardon PR, Richardson WS, Fanelli RD; SAGES Guidelines Committee. Guidelines for surgical treatment of gastroesophageal reflux disease. *Surg Endosc* 2010; **24**: 2647-2669 [PMID: 20725747 DOI: 10.1007/s00464-010-1267-8]

22 **Fuchs KH**, Babic B, Breithaupt W, Dallemagne B, Fingerhut A, Furnee E, Granderath F, Horvath P, Kardos P, Pointner R, Savarino E, Van Herwaarden-Lindeboom M, Zaninotto G; European Association of Endoscopic Surgery (EAES). EAES recommendations for the management of gastroesophageal reflux disease. *Surg Endosc* 2014; **28**: 1753-1773 [PMID: 24789125 DOI: 10.1007/s00464-014-3431-z]

23 **Fock KM**, Talley N, Goh KL, Sugano K, Katelaris P, Holtmann G, Pandolfino JE, Sharma P, Ang TL, Hongo M, Wu J, Chen M, Choi MG, Law NM, Sheu BS, Zhang J, Ho KY, Sollano J, Rani AA, Kositchaiwat C, Bhatia S. Asia-Pacific consensus on the management of gastro-oesophageal reflux disease: an update focusing on refractory reflux disease and Barrett's oesophagus. *Gut* 2016; **65**: 1402-1415 [PMID: 27261337 DOI: 10.1136/gutjnl-2016-311715]

24 **Hunt R**, Armstrong D, Katelaris P, Afihene M, Bane A, Bhatia S, Chen MH, Choi MG, Melo AC, Fock KM, Ford A, Hongo M, Khan A, Lazebnik L, Lindberg G, Lizarzabal M, Myint T, Moraes-Filho JP, Salis G, Lin JT, Vaidya R, Abdo A, LeMair A; Review Team:. World Gastroenterology Organisation Global Guidelines: GERD Global Perspective on Gastroesophageal Reflux Disease. *J Clin Gastroenterol* 2017; **51**: 467-478 [PMID: 28591069 DOI: 10.1097/MCG.0000000000000854]

25 **Gawron AJ**, Bell R, Abu Dayyeh BK, Buckley FP, Chang K, Dunst CM, Edmundowicz SA, Jobe B, Lipham JC, Lister D, Canto MI, Smith MS, Starpoli AA, Triadafilopoulos G, Watson TJ, Wilson E, Pandolfino JE, Kaizer A, Van De Voorde Z, Yadlapati R. Surgical and endoscopic management options for patients with GERD based on proton pump inhibitor symptom response: recommendations from an expert U.S. panel. *Gastrointest Endosc* 2020; **92**: 78-87.e2 [PMID: 32007519 DOI: 10.1016/j.gie.2020.01.037]

26 **Zerbib F**, Bredenoord AJ, Fass R, Kahrilas PJ, Roman S, Savarino E, Sifrim D, Vaezi M, Yadlapati R, Gyawali CP. ESNM/ANMS consensus paper: Diagnosis and management of refractory gastro-esophageal reflux disease. *Neurogastroenterol Motil* 2021; **33**: e14075 [PMID: 33368919 DOI: 10.1111/nmo.14075]

27 **Pauwels A**, Boecxstaens V, Andrews CN, Attwood SE, Berrisford R, Bisschops R, Boeckxstaens GE, Bor S, Bredenoord AJ, Cicala M, Corsetti M, Fornari F, Gyawali CP, Hatlebakk J, Johnson SB, Lerut T, Lundell L, Mattioli S, Miwa H, Nafteux P, Omari T, Pandolfino J, Penagini R, Rice TW, Roelandt P, Rommel N, Savarino V, Sifrim D, Suzuki H, Tutuian R, Vanuytsel T, Vela MF, Watson DI, Zerbib F, Tack J. How to select patients for antireflux surgery? The ICARUS guidelines (international consensus regarding preoperative examinations and clinical characteristics assessment to select adult patients for antireflux surgery). *Gut* 2019; **68**: 1928-1941 [PMID: 31375601 DOI: 10.1136/gutjnl-2019-318260]

28 **Angelchik JP**, Cohen R. A new surgical procedure for the treatment of gastroesophageal reflux and hiatal hernia. *Surg Gynecol Obstet* 1979; **148**: 246-248 [PMID: 154176]

29 **Yew KC**, Chuah SK. Antireflux endoluminal therapies: past and present. *Gastroenterol Res Pract* 2013; **2013**: 481417 [PMID: 23935608 DOI: 10.1155/2013/481417]

30 **Filipi CJ**, Lehman GA, Rothstein RI, Raijman I, Stiegmann GV, Waring JP, Hunter JG, Gostout CJ, Edmundowicz SA, Dunne DP, Watson PA, Cornet DA. Transoral, flexible endoscopic suturing for treatment of GERD: a multicenter trial. *Gastrointest Endosc* 2001; **53**: 416-422 [PMID: 11275879 DOI: 10.1067/mge.2001.113502]

31 **Fockens P**, Cohen L, Edmundowicz SA, Binmoeller K, Rothstein RI, Smith D, Lin E, Nickl N, Overholt B, Kahrilas PJ, Vakil N, Abdel Aziz Hassan AM, Lehman GA. Prospective randomized controlled trial of an injectable esophageal prosthesis *vs* a sham procedure for endoscopic treatment of gastroesophageal reflux disease. *Surg Endosc* 2010; **24**: 1387-1397 [PMID: 20198491 DOI: 10.1007/s00464-009-0784-9]

32 **Oor JE**, Roks DJ, Broeders JA, Hazebroek EJ, Gooszen HG. Seventeen-year Outcome of a Randomized Clinical Trial Comparing Laparoscopic and Conventional Nissen Fundoplication: A Plea for Patient Counseling and Clarification. *Ann Surg* 2017; **266**: 23-28 [PMID: 28294958 DOI: 10.1097/SLA.0000000000002106]

33 **Falk GW**, Fennerty MB, Rothstein RI. AGA Institute medical position statement on the use of endoscopic therapy for gastroesophageal reflux disease. *Gastroenterology* 2006; **131**: 1313-1314 [PMID: 17030198 DOI: 10.1053/j.gastro.2006.08.018]

34 **Pearl J**, Pauli E, Dunkin B, Stefanidis D. SAGES endoluminal treatments for GERD. *Surg Endosc* 2017; **31**: 3783-3790 [PMID: 28643067 DOI: 10.1007/s00464-017-5639-1]

35 **Weusten BLAM**, Barret M, Bredenoord AJ, Familiari P, Gonzalez JM, van Hooft JE, Lorenzo-Zúñiga V, Louis H, Martinek J, van Meer S, Neumann H, Pohl D, Prat F, von Renteln D, Savarino E, Sweis R, Tack J, Tutuian R, Ishaq S. Endoscopic management of gastrointestinal motility disorders - part 2: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. *Endoscopy* 2020; **52**: 600-614 [PMID: 32462649 DOI: 10.1055/a-1171-3174]

36 **Chang KJ**, Bell R. Transoral Incisionless Fundoplication. *Gastrointest Endosc Clin N Am* 2020; **30**: 267-289 [PMID: 32146946 DOI: 10.1016/j.giec.2019.12.008]

37 **Ihde GM**. The evolution of TIF: transoral incisionless fundoplication. *Therap Adv Gastroenterol* 2020; **13**: 1756284820924206 [PMID: 32499834 DOI: 10.1177/1756284820924206]

38 **Testoni PA**, Corsetti M, Di Pietro S, Castellaneta AG, Vailati C, Masci E, Passaretti S. Effect of transoral incisionless fundoplication on symptoms, PPI use, and ph-impedance refluxes of GERD patients. *World J Surg* 2010; **34**: 750-757 [PMID: 20091308 DOI: 10.1007/s00268-010-0394-7]

39 **Ihde GM**, Besancon K, Deljkich E. Short-term safety and symptomatic outcomes of transoral incisionless fundoplication with or without hiatal hernia repair in patients with chronic gastroesophageal reflux disease. *Am J Surg* 2011; **202**: 740-746; discussion 746-747 [PMID: 22014853 DOI: 10.1016/j.amjsurg.2011.06.035]

40 **Narsule CK**, Burch MA, Ebright MI, Hess DT, Rivas R Jr, Daly BD, Fernando HC. Endoscopic fundoplication for the treatment of gastroesophageal reflux disease: initial experience. *J Thorac Cardiovasc Surg* 2012; **143**: 228-234 [PMID: 22070927 DOI: 10.1016/j.jtcvs.2011.10.008]

41 **Bell RC**, Barnes WE, Carter BJ, Sewell RW, Mavrelis PG, Ihde GM, Hoddinott KM, Fox MA, Freeman KD, Gunsberger T, Hausmann MG, Dargis D, DaCosta Gill B, Wilson E, Trad KS. Transoral incisionless fundoplication: 2-year results from the prospective multicenter U.S. study. *Am Surg* 2014; **80**: 1093-1105 [PMID: 25347499 DOI: 10.1177/000313481408001124]

42 **Wilson EB**, Barnes WE, Mavrelis PG, Carter BJ, Bell RC, Sewell RW, Ihde GM, Dargis D, Hoddinott KM, Shughoury AB, Gill BD, Fox MA, Turgeon DG, Freeman KD, Gunsberger T, Hausmann MG, Leblanc KA, Deljkich E, Trad KS. The effects of transoral incisionless fundoplication on chronic GERD patients: 12-month prospective multicenter experience. *Surg Laparosc Endosc Percutan Tech* 2014; **24**: 36-46 [PMID: 24487156 DOI: 10.1097/SLE.0b013e3182a2b05c]

43 **Testoni PA**, Testoni S, Mazzoleni G, Vailati C, Passaretti S. Long-term efficacy of transoral incisionless fundoplication with Esophyx (Tif 2.0) and factors affecting outcomes in GERD patients followed for up to 6 years: a prospective single-center study. *Surg Endosc* 2015; **29**: 2770-2780 [PMID: 25480624 DOI: 10.1007/s00464-014-4008-6]

44 **Stefanidis G**, Viazis N, Kotsikoros N, Tsoukalas N, Lala E, Theocharis L, Fassaris A, Manolakopoulos S. Long-term benefit of transoral incisionless fundoplication using the esophyx device for the management of gastroesophageal reflux disease responsive to medical therapy. *Dis Esophagus* 2017; **30**: 1-8 [PMID: 27868281 DOI: 10.1111/dote.12525]

45 **Chimukangara M**, Jalilvand AD, Melvin WS, Perry KA. Long-term reported outcomes of transoral incisionless fundoplication: an 8-year cohort study. *Surg Endosc* 2019; **33**: 1304-1309 [PMID: 30167944 DOI: 10.1007/s00464-018-6403-x]

46 **Testoni PA**, Testoni S, Mazzoleni G, Pantaleo G, Cilona MB, Distefano G, Fanti L, Antonelli M, Passaretti S. Transoral incisionless fundoplication with an ultrasonic surgical endostapler for the treatment of gastroesophageal reflux disease: 12-month outcomes. *Endoscopy* 2020; **52**: 469-473 [PMID: 32187630 DOI: 10.1055/a-1124-3187]

47 **Rinsma NF**, Farré R, Bouvy ND, Masclee AA, Conchillo JM. The effect of endoscopic fundoplication and proton pump inhibitors on baseline impedance and heartburn severity in GERD patients. *Neurogastroenterol Motil* 2015; **27**: 220-228 [PMID: 25348594 DOI: 10.1111/nmo.12468]

48 **Witteman BP**, Conchillo JM, Rinsma NF, Betzel B, Peeters A, Koek GH, Stassen LP, Bouvy ND. Randomized controlled trial of transoral incisionless fundoplication vs. proton pump inhibitors for treatment of gastroesophageal reflux disease. *Am J Gastroenterol* 2015; **110**: 531-542 [PMID: 25823768 DOI: 10.1038/ajg.2015.28]

49 **Hunter JG**, Kahrilas PJ, Bell RC, Wilson EB, Trad KS, Dolan JP, Perry KA, Oelschlager BK, Soper NJ, Snyder BE, Burch MA, Melvin WS, Reavis KM, Turgeon DG, Hungness ES, Diggs BS. Efficacy of transoral fundoplication *vs* omeprazole for treatment of regurgitation in a randomized controlled trial. *Gastroenterology* 2015; **148**: 324-333.e5 [PMID: 25448925 DOI: 10.1053/j.gastro.2014.10.009]

50 **Håkansson B**, Montgomery M, Cadiere GB, Rajan A, Bruley des Varannes S, Lerhun M, Coron E, Tack J, Bischops R, Thorell A, Arnelo U, Lundell L. Randomised clinical trial: transoral incisionless fundoplication vs. sham intervention to control chronic GERD. *Aliment Pharmacol Ther* 2015; **42**: 1261-1270 [PMID: 26463242 DOI: 10.1111/apt.13427]

51 **Trad KS**, Barnes WE, Prevou ER, Simoni G, Steffen JA, Shughoury AB, Raza M, Heise JA, Fox MA, Mavrelis PG. The TEMPO Trial at 5 Years: Transoral Fundoplication (TIF 2.0) Is Safe, Durable, and Cost-effective. *Surg Innov* 2018; **25**: 149-157 [PMID: 29405886 DOI: 10.1177/1553350618755214]

52 **Huang X**, Chen S, Zhao H, Zeng X, Lian J, Tseng Y, Chen J. Efficacy of transoral incisionless fundoplication (TIF) for the treatment of GERD: a systematic review with meta-analysis. *Surg Endosc* 2017; **31**: 1032-1044 [PMID: 27495332 DOI: 10.1007/s00464-016-5111-7]

53 **Richter JE**, Kumar A, Lipka S, Miladinovic B, Velanovich V. Efficacy of Laparoscopic Nissen Fundoplication *vs* Transoral Incisionless Fundoplication or Proton Pump Inhibitors in Patients With Gastroesophageal Reflux Disease: A Systematic Review and Network Meta-analysis. *Gastroenterology* 2018; **154**: 1298-1308.e7 [PMID: 29305934 DOI: 10.1053/j.gastro.2017.12.021]

54 **Roy-Shapira A**, Bapaye A, Date S, Pujari R, Dorwat S. Trans-oral anterior fundoplication: 5-year follow-up of pilot study. *Surg Endosc* 2015; **29**: 3717-3721 [PMID: 25783833 DOI: 10.1007/s00464-015-4142-9]

55 **Kim HJ**, Kwon CI, Kessler WR, Selzer DJ, McNulty G, Bapaye A, Bonavina L, Lehman GA. Long-term follow-up results of endoscopic treatment of gastroesophageal reflux disease with the MUSE™ endoscopic stapling device. *Surg Endosc* 2016; **30**: 3402-3408 [PMID: 26537905 DOI: 10.1007/s00464-015-4622-y]

56 **Zacherl J**, Roy-Shapira A, Bonavina L, Bapaye A, Kiesslich R, Schoppmann SF, Kessler WR, Selzer DJ, Broderick RC, Lehman GA, Horgan S. Endoscopic anterior fundoplication with the Medigus Ultrasonic Surgical Endostapler (MUSE™) for gastroesophageal reflux disease: 6-month results from a multi-center prospective trial. *Surg Endosc* 2015; **29**: 220-229 [PMID: 25135443 DOI: 10.1007/s00464-014-3731-3]

57 **Danalioglu A**, Cipe G, Toydemir T, Kocaman O, Ince AT, Muslumanoglu M, Senturk H. Endoscopic stapling in comparison to laparoscopic fundoplication for the treatment of gastroesophageal reflux disease. *Dig Endosc* 2014; **26**: 37-42 [PMID: 23560891 DOI: 10.1111/den.12081]

58 **Sowa P**, Samarasena JB. Nonablative Radiofrequency Treatment for Gastroesophageal Reflux Disease (STRETTA). *Gastrointest Endosc Clin N Am* 2020; **30**: 253-265 [PMID: 32146945 DOI: 10.1016/j.giec.2019.12.006]

59 **Xie P**, Yan J, Ye L, Wang C, Li Y, Chen Y, Li G. Efficacy of different endoscopic treatments in patients with gastroesophageal reflux disease: a systematic review and network meta-analysis. *Surg Endosc* 2021; **35**: 1500-1510 [PMID: 33650003 DOI: 10.1007/s00464-021-08386-1]

60 **Coron E**, Sebille V, Cadiot G, Zerbib F, Ducrotte P, Ducrot F, Pouderoux P, Arts J, Le Rhun M, Piche T, Bruley des Varannes S, Galmiche JP; Consortium de Recherche Indépendant sur le Traitement et L'exploration du Reflux Gastro-oesophagien et de L'endobrachyoesophage (CRITERE). Clinical trial: Radiofrequency energy delivery in proton pump inhibitor-dependent gastro-oesophageal reflux disease patients. *Aliment Pharmacol Ther* 2008; **28**: 1147-1158 [PMID: 18616516 DOI: 10.1111/j.1365-2036.2008.03790.x]

61 **Corley DA**, Katz P, Wo JM, Stefan A, Patti M, Rothstein R, Edmundowicz S, Kline M, Mason R, Wolfe MM. Improvement of gastroesophageal reflux symptoms after radiofrequency energy: a randomized, sham-controlled trial. *Gastroenterology* 2003; **125**: 668-676 [PMID: 12949712 DOI: 10.1016/s0016-5085(03)01052-7]

62 **Aziz AM**, El-Khayat HR, Sadek A, Mattar SG, McNulty G, Kongkam P, Guda MF, Lehman GA. A prospective randomized trial of sham, single-dose Stretta, and double-dose Stretta for the treatment of gastroesophageal reflux disease. *Surg Endosc* 2010; **24**: 818-825 [PMID: 19730952 DOI: 10.1007/s00464-009-0671-4]

63 **Arts J**, Bisschops R, Blondeau K, Farré R, Vos R, Holvoet L, Caenepeel P, Lerut A, Tack J. A double-blind sham-controlled study of the effect of radiofrequency energy on symptoms and distensibility of the gastro-esophageal junction in GERD. *Am J Gastroenterol* 2012; **107**: 222-230 [PMID: 22108449 DOI: 10.1038/ajg.2011.395]

64 **Lipka S**, Kumar A, Richter JE. No evidence for efficacy of radiofrequency ablation for treatment of gastroesophageal reflux disease: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol* 2015; **13**: 1058-67.e1 [PMID: 25459556 DOI: 10.1016/j.cgh.2014.10.013]

65 **Fass R**, Cahn F, Scotti DJ, Gregory DA. Systematic review and meta-analysis of controlled and prospective cohort efficacy studies of endoscopic radiofrequency for treatment of gastroesophageal reflux disease. *Surg Endosc* 2017; **31**: 4865-4882 [PMID: 28233093 DOI: 10.1007/s00464-017-5431-2]

66 **Vaezi MF**, Shaheen NJ, Muthusamy VR. State of Evidence in Minimally Invasive Management of Gastroesophageal Reflux: Findings of a Scoping Review. *Gastroenterology* 2020; **159**: 1504-1525 [PMID: 32621903 DOI: 10.1053/j.gastro.2020.05.097]

67 **Weitzendorfer M**, Spaun GO, Antoniou SA, Tschoner A, Schredl P, Emmanuel K, Koch OO. Interim Report of a Prospective Trial on the Clinical Efficiency of a New Full-thickness Endoscopic Plication Device for Patients With GERD: Impact of Changed Suture Material. *Surg Laparosc Endosc Percutan Tech* 2017; **27**: 163-169 [PMID: 28383316 DOI: 10.1097/SLE.0000000000000396]

68 **Weitzendorfer M**, Spaun GO, Antoniou SA, Witzel K, Emmanuel K, Koch OO. Clinical feasibility of a new full-thickness endoscopic plication device (GERDx™) for patients with GERD: results of a prospective trial. *Surg Endosc* 2018; **32**: 2541-2549 [PMID: 29602998 DOI: 10.1007/s00464-018-6153-9]

69 **Inoue H**, Ito H, Ikeda H, Sato C, Sato H, Phalanusitthepha C, Hayee B, Eleftheriadis N, Kudo SE. Anti-reflux mucosectomy for gastroesophageal reflux disease in the absence of hiatus hernia: a pilot study. *Ann Gastroenterol* 2014; **27**: 346-351 [PMID: 25330784]

70 **Monino L**, Gonzalez JM, Vitton V, Barthet M. Antireflux mucosectomy band in treatment of refractory gastroesophageal reflux disease: a pilot study for safety, feasibility and symptom control. *Endosc Int Open* 2020; **8**: E147-E154 [PMID: 32010747 DOI: 10.1055/a-1038-4012]

71 **Debourdeau A**, Vitton V, Monino L, Barthet M, Gonzalez JM. Antireflux Mucosectomy Band (ARM-b) in Treatment of Refractory Gastroesophageal Reflux Disease After Bariatric Surgery. *Obes Surg* 2020; **30**: 4654-4658 [PMID: 32676843 DOI: 10.1007/s11695-020-04753-4]

72 **Sumi K**, Inoue H, Kobayashi Y, Iwaya Y, Abad MRA, Fujiyoshi Y, Shimamura Y, Ikeda H, Onimaru M. Endoscopic treatment of proton pump inhibitor-refractory gastroesophageal reflux disease with anti-reflux mucosectomy: Experience of 109 cases. *Dig Endosc* 2021; **33**: 347-354 [PMID: 32415898 DOI: 10.1111/den.13727]

73 **Li X**, Zhang W, Chen M, Wei S, Zhao X, Zhang G. A Prospective Randomized Trial to Assess the Antireflux Effect of Antireflux Mucosectomy in the Porcine Model. *Gastroenterol Res Pract* 2019; **2019**: 3286738 [PMID: 30944560 DOI: 10.1155/2019/3286738]

74 **Yoo IK**, Ko WJ, Kim HS, Kim HK, Kim JH, Kim WH, Hong SP, Yeniova AÖ, Cho JY. Anti-reflux mucosectomy using a cap-assisted endoscopic mucosal resection method for refractory gastroesophageal disease: a prospective feasibility study. *Surg Endosc* 2020; **34**: 1124-1131 [PMID: 31139995 DOI: 10.1007/s00464-019-06859-y]

75 **Inoue H**, Tanabe M, de Santiago ER, Abad MRA, Shimamura Y, Fujiyoshi Y, Ueno A, Sumi K, Tomida H, Iwaya Y, Ikeda H, Onimaru M. Anti-reflux mucosal ablation (ARMA) as a new treatment for gastroesophageal reflux refractory to proton pump inhibitors: a pilot study. *Endosc Int Open* 2020; **8**: E133-E138 [PMID: 32010745 DOI: 10.1055/a-1031-9436]

76 **Hernández Mondragón OV**, Zamarripa Mottú RA, García Contreras LF, Gutiérrez Aguilar RA, Solórzano Pineda OM, Blanco Velasco G, Murcio Perez E. Clinical feasibility of a new antireflux ablation therapy on gastroesophageal reflux disease (with video). *Gastrointest Endosc* 2020; **92**: 1190-1201 [PMID: 32343977 DOI: 10.1016/j.gie.2020.04.046]

77 **Wong HJ**, Su B, Attaar M, Kuchta K, Stearns S, Linn JG, Haggerty SP, Denham W, Ujiki MB. Anti-reflux mucosectomy (ARMS) results in improved recovery and similar reflux quality of life outcomes compared to laparoscopic Nissen fundoplication. *Surg Endosc* 2020 [PMID: 33237465 DOI: 10.1007/s00464-020-08144-9]

78 **Patil G**, Dalal A, Maydeo A. Feasibility and outcomes of anti-reflux mucosectomy for proton pump inhibitor dependent gastroesophageal reflux disease: First Indian study (with video). *Dig Endosc* 2020; **32**: 745-752 [PMID: 31834663 DOI: 10.1111/den.13606]

79 **Bapaye A**, Mahadik M, Pujari R, Bharadwaj T, Vare S, Date S, Dubale N, Bapaye J, Kulkarni A. Anti-reflux mucosectomy (ARMS) for refractory GERD-Initial clinical experience. *J Gastroenterol Hepatol* 2017; **32**: 255

80 **Vasilevskiy DI**, Bagnenko SF, Smirnov A, Lapshin AS, Dvoretskiy SU, Pryadko AS. Antireflux mucosectomy (Arms) in the treatment of patients with gerd and columnar-cell lined (barrett’s) esophagus. First experiences. *Surg Endosc* 2017; **31**: S405 [PMID: 28488176 DOI: 10.1007/s00464-017-5565-2]

81 **Shah R**, Maydeo AP, Dhir V. Anti reflux mucosectomy (ARMS) for refractory gastro esophageal reflux disease (GERD)-are we there yet? *United European Gastroenterol J* 2017; **5**: A354-A355 [DOI: 10.1177/2050640617725676]

82 **Ota K**, Takeuchi T, Harada S, Edogawa S, Kojima Y, Inoue T, Higuchi K. A novel endoscopic submucosal dissection technique for proton pump inhibitor-refractory gastroesophageal reflux disease. *Scand J Gastroenterol* 2014; **49**: 1409-1413 [PMID: 25384555 DOI: 10.3109/00365521.2014.978815]

83 **Ortega A**, Rosón P, Fern, ez F, Angeles Romero M, Angeles Perez Aisa M, Cotta J, Lozano M. Antireflux mucosectomy. preliminary results of a prospective study. *Endoscopy* 2019; **51**: S240-S241

84 **Mondragón OVH**, Pintor JC, Aguilar RAG, Garcia-Contreras L, Pineda OS, Mottú RAZ, Blanco-Velasco G, Murcio-Pérez E. Sa1247 Antireflux ablation therapy (ARAT), for reflux disease after poem procedure. early clinical experience. *Gastrointest Endosc* 2020; **91**: AB130

85 **Schuitenmaker JM**, van Hoeij FB, Schijven MP, Tack J, Conchillo JM, Hazebroek EJ, Smout AJPM, Bredenoord AJ. Pneumatic dilation for persistent dysphagia after antireflux surgery, a multicentre single-blind randomised sham-controlled clinical trial. *Gut* 2021 [PMID: 33452179 DOI: 10.1136/gutjnl-2020-322355]

86 **Seleem WM**, Hanafy AS, Mohamed SI. Endoscopic management of refractory gastroesophageal reflux disease. *Scand J Gastroenterol* 2018; **53**: 390-397 [PMID: 29488430 DOI: 10.1080/00365521.2018.1445775]

87 **Hu HQ**, Li HK, Xiong Y, Zhang XB, Zhi JL, Wang XX, Ling-Hu EQ. Peroral endoscopic cardial constriction in gastroesophageal reflux disease. *Medicine (Baltimore)* 2018; **97**: e0169 [PMID: 29642142 DOI: 10.1097/MD.0000000000010169]

88 **Liu S**, Chai N, Zhai Y, Zou J, Feng X, Li Z, Li L, Zhang X, Wang X, Wang S, Linghu EQ. New treatment method for refractory gastroesophageal reflux disease (GERD): C-BLART (clip band ligation anti-reflux therapy)-a short-term study. *Surg Endosc* 2020; **34**: 4516-4524 [PMID: 31728750 DOI: 10.1007/s00464-019-07238-3]

89 **Benias PC**, D'Souza L, Lan G, Gluckman C, Inamdar S, Trindade AJ, Miller LS, Carr-Locke DL. Initial experience with a novel resection and plication (RAP) method for acid reflux: a pilot study. *Endosc Int Open* 2018; **6**: E443-E449 [PMID: 29607397 DOI: 10.1055/s-0044-101453]

90 **Janu P**, Shughoury AB, Venkat K, Hurwich D, Galouzis T, Siatras J, Streeter D, Korman K, Mavrelis G, Mavrelis P. Laparoscopic Hiatal Hernia Repair Followed by Transoral Incisionless Fundoplication With EsophyX Device (HH + TIF): Efficacy and Safety in Two Community Hospitals. *Surg Innov* 2019; **26**: 675-686 [PMID: 31431138 DOI: 10.1177/1553350619869449]

91 **Fundacion para la Investigacion Biomedica del Hospital Universitario Ramon y Cajal**. Double-blind, Placebo-controlled Clinical Trial on the Efficacy of Antireflux Ablation of the Cardiac Mucosa for the Treatment of Gastroesophageal Reflux Disease. Available from: https://clinicaltrials.gov/ct2/show/NCT04711655

92 **Gyawali CP**, Kahrilas PJ, Savarino E, Zerbib F, Mion F, Smout AJPM, Vaezi M, Sifrim D, Fox MR, Vela MF, Tutuian R, Tack J, Bredenoord AJ, Pandolfino J, Roman S. Modern diagnosis of GERD: the Lyon Consensus. *Gut* 2018; **67**: 1351-1362 [PMID: 29437910 DOI: 10.1136/gutjnl-2017-314722]

93 **Yadlapati R**, Kahrilas PJ, Fox MR, Bredenoord AJ, Prakash Gyawali C, Roman S, Babaei A, Mittal RK, Rommel N, Savarino E, Sifrim D, Smout A, Vaezi MF, Zerbib F, Akiyama J, Bhatia S, Bor S, Carlson DA, Chen JW, Cisternas D, Cock C, Coss-Adame E, de Bortoli N, Defilippi C, Fass R, Ghoshal UC, Gonlachanvit S, Hani A, Hebbard GS, Wook Jung K, Katz P, Katzka DA, Khan A, Kohn GP, Lazarescu A, Lengliner J, Mittal SK, Omari T, Park MI, Penagini R, Pohl D, Richter JE, Serra J, Sweis R, Tack J, Tatum RP, Tutuian R, Vela MF, Wong RK, Wu JC, Xiao Y, Pandolfino JE. Esophageal motility disorders on high-resolution manometry: Chicago classification version 4.0©. *Neurogastroenterol Motil* 2021; **33**: e14058 [PMID: 33373111 DOI: 10.1111/nmo.14058]

94 **Funk LM**, Zhang JY, Drosdeck JM, Melvin WS, Walker JP, Perry KA. Long-term cost-effectiveness of medical, endoscopic and surgical management of gastroesophageal reflux disease. *Surgery* 2015; **157**: 126-136 [PMID: 25262216 DOI: 10.1016/j.surg.2014.05.027]

95 **ASGE Standards of Practice Committee**, Muthusamy VR, Lightdale JR, Acosta RD, Chandrasekhara V, Chathadi KV, Eloubeidi MA, Fanelli RD, Fonkalsrud L, Faulx AL, Khashab MA, Saltzman JR, Shaukat A, Wang A, Cash B, DeWitt JM. The role of endoscopy in the management of GERD. *Gastrointest Endosc* 2015; **81**: 1305-1310 [PMID: 25863867 DOI: 10.1016/j.gie.2015.02.021]

**Footnotes**

**Conflict-of-interest statement:** The authors declare no conflicts of interest for this article.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/Licenses/by-nc/4.0/

**Manuscript source:** Unsolicited manuscript

**Peer-review started:** April 19, 2021

**First decision:** June 23, 2021

**Article in press:** August 31, 2021

**Specialty type:** Gastroenterology and hepatology

**Country/Territory of origin:** Spain

**Peer-review report’s scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): B

Grade C (Good): 0

Grade D (Fair): 0

Grade E (Poor): 0

**P-Reviewer:** Singh A **S-Editor:** Gong ZM **L-Editor:** Filipodia **P-Editor:** Yuan YY

**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.

**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 responders (complete or partial) or nonresponders, significant hernia, any other scenario | Not appropriate |
| PPI nonresponder, no hernia and acid breakthrough, hypersensitivity or negative pH-impedance study for heartburn | Appropriate.  Consensus: 80%–93% |
| PPI nonresponder, no hernia, heartburn-hypersensitivity, or negative pH-impedance study | Appropriateness uncertain |
| PPI nonresponder, regurgitation, negative pH-impedance study | Appropriateness uncertain |
| PPI nonresponder, any other scenario | Appropriate.  Consensus: 80%-100% |
| 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 |
| ESGE guidelines on endoscopic management of gastrointestinal motility disorders, 2020[35] | Not applicable | Not applicable | 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% |
| Anti-reflux mucosectomy | Against routine use in clinical practice | Quality: Low.  Strength: Strong.  Consensus: 100% |
| ESNM/ASNM consensus paper on management of refractory GERD, 2020[26] | Refractory GERD symptoms in patients with proven GERD | 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.

**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; *n* = 343 | 50%–92% | 0%–4.4% |
| No. of nonrandomized case series: 9; *n* = 543 |
| Medigus ultrasonic surgical endostapler | No. of RCTs: 0 | 69%–92% | 0%–9% |
| No. of nonrandomized case series: 5; *n* = 199 |
| Nonablative radiofrequency (Stretta®) | No. of RCTs: 5; *n* = 173 | 15%–100% | 0%–1% |
| No. of nonrandomized case series: 29; *n* = 2571 |
| Endoscopic plication device (GERDx™) | No. of RCTs: 0 | 19 out of 40 patients were off PPIs | 10% |
| No. of nonrandomized case series: 1; *n* = 40 |
| Band ligation techniques | No. of RCTs: 1; *n* = 150 | 43%–54%1 | 0% |
| No. of nonrandomized case series: 2; *n* = 73 |
| Anti-reflux mucosectomy | No. of RCTs: 0 | 58%–100% | 0%–17% |
| No. of nonrandomized case series: 12; *n* = 331 |
| Anti-reflux mucosal ablation | No. of RCTs: 0 | 58%–89% | 0%–13% |
| No. of nonrandomized case series: 3; *n* = 130 |

1Clinical 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.



Published by **Baishideng Publishing Group Inc**

7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

**Telephone:** +1-925-3991568

**E-mail:** bpgoffice@wjgnet.com

**Help Desk:** https://www.f6publishing.com/helpdesk

https://www.wjgnet.com



**© 2021 Baishideng Publishing Group Inc. All rights reserved.**