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Review

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Novel Surgical Treatments for Gastroesophageal Reflux Disease: Systematic Review of Magnetic Sphincter Augmentation and Electric Stimulation Therapy

Michal Stanak[a, c], Judit Erdos[a], Katharina Hawlik[a], Tudor Birsan[b]

Abstract

Electric stimulation therapy (EST) and magnetic sphincter augmentation (MSA) represent novel methods for the surgical treatment of gastroesophageal reflux disease (GERD). The aim of this review was to assess the effectiveness and safety of EST and magnetic sphincter augmentation device (MSAD) comapred to laparoscopic fundoplication (LF) and proton pump inhibitor therapy (in case of EST). We performed a systematic literature search without restrictions on publication dates in five electronic databases (MEDLINE, EMBASE, the Cochrane library, PubMed, and Centre for Reviews and Dissemination), complemented by hand search, search in trial registries, and documentation provided by the manufacturers. No study passed inclusion criteria for analyzing EST effectiveness. Concerning safety, lead erosion through the esophagus and trocar perforation of the small bowel occurred in 2.4% of patients (in one study). Only the registry study fulfilled inclusion criteria for effectiveness analysis of MSAD. The crucial outcome of GERD-health-related quality of life (HRQL) score improved from 20 to 3 points in MSAD patients, and from 23 to 3.5 points in LF patients. However, the LF patients were in a more severe stage of the disease. The results yield indefinite conclusions about the use of both MSAD and EST. Clinical effectiveness and safety of both MSAD and EST are not sufficiently proven and are yet to be supported by high quality evidence from randomized controlled trials.

Keywords: GERD; MSAD; EST; Magnetic; Electric; Esophagus; LES; Reflux

Introduction

Gastroesophageal reflux disease (GERD) is the most common upper gastrointestinal disease in the Western countries affecting around 15% of the population [1, 2], of which 10-20% are experiencing weekly symptoms [3]. Of the patients, 25-42% are refractory to a once-daily proton pump inhibitor (PPI) therapy, of which 25% would respond to an increase in PPI dosing to twice daily. However, 42% of GERD patients are dissatisfied with their PPI treatment outcomes [4].

Standard surgical treatment for GERD is laparoscopic fundoplication (LF), performed as a total or partial wrap of the fundus [5]. The most common is a loose (floppy) Nissen fundic wrap including a posterior hiatal hernia repair. However, the technical difficulty and the lack of a standardized fundoplication technique have a high impact on patient outcomes [1]. Furthermore, recovery time can be as long as 4 - 6 weeks and some practitioners recommend dietary restrictions to their patients for a variable period of time after surgery [6].

Magnetic sphincter augmentation (MSA) and electric stimulation therapy (EST) represent novel methods for the surgical treatment of GERD. The goal of both interventions is to reinforce the weak lower esophageal sphincter (LES), but the difference lies in the way it is achieved. The magnetic sphincter augmentation device (MSAD) is a ring of magnetic beads made of titanium that is laparoscopically placed around the lower esophagus just above the stomach. The MSAD aims to help the LES resisting opening to gastric pressures, preventing reflux from the stomach entering into the esophagus. Swallowing forces temporarily break the magnetic bond, allowing food and liquid to pass normally into the stomach. The magnetic attraction of the device closes the LES immediately after swallowing, restoring the body's natural barrier to reflux [7].

The EST comprises of a bipolar stimulation lead with two stitch electrodes, an implantable pulse generator, and an external programmer [8]. The pair of electrodes is placed in the anterior part of the lower esophagus and sutured in place using standard laparoscopic techniques [9]. The wires are then connected to a stimulator placed in the subcutaneous pocket in the left upper quadrant of the abdominal wall [9]. The EST delivers mild electrical signals to the LES throughout the day, aiming to restore normal function of the LES, preventing reflux from the stomach entering the esophagus.

As the incidence of GERD is increasing not only in the Western world, novel therapies that claim to eliminate the technical shortcomings of the standard surgical treatment LF are emerging to address the disease for the large proportion of

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[a]Ludwig Boltzmann Institute for Health Technology Assessment, Vienna, Austria
[b]St. John of God Hospital, Vienna, Austria
[c]Corresponding Author: Michal Stanak, Ludwig Boltzmann Institute for Health Technology Assessment, Garnisongasse 7/20, 1090 Vienna, Austria. Email: michal.stanak@hta.lbg.ac.at

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GERD patients refractory to standard medical therapy. As health care systems are facing the increasing demand for new therapies, the Austrian Federal Ministry of Health commissioned us to conduct a review on the effectiveness and safety of the two novel surgical interventions. To our knowledge, this is the first systematic review on MSAD and EST that takes into account only prospective evidence. Our aim was to review the literature on MSAD and EST in order to assess their effectiveness and safety compared to the established surgical alternative LF.

Methods

Search strategy

We performed a systematic literature search without any restrictions on the publication date in five electronic databases (MEDLINE, EMBASE, the Cochrane library, PubMed, and in the database of the Centre for Reviews and Dissemination), complemented by a hand search (reviewing the reference lists of included studies), and a search in trial registries (Clinicaltrials.gov, WHO-ICTRP, EU Clinical Trials). Full details of the search strategy (including syntaxes, parameters, and results) are available from the corresponding author upon request. As additional source of information, we considered documentation provided by the manufacturers.

Study selection

In a two-stage review process, two researchers independently screened abstracts and full-texts articles for eligibility based on the a priori defined inclusion criteria. Discrepancies were resolved by consensus or by consulting a third researcher.

Our inclusion criteria are listed as follows. 1) Sample characteristics: adult patients with chronic (> 6 months) GERD diagnosed based on 24 pH monitoring, esophagitis grade C or lower, typical symptoms of GERD (heartburn or regurgitation), and at least partial response to a therapeutic trial of PPIs. In the EST review, additional criteria included: LES end-expiratory pressure of 5 - 15 mm Hg and peristaltic contractions seen in ≥ 50% of swallows with a contraction amplitude of ≥ 30 mm Hg during baseline esophageal manometry. In both reviews, moderate to severe symptom chronic GERD and refractory GERD were considered. 2) Treatment characteristics: a) implantation of the MSAD using laparoscopic surgery. Product name: LINX® Reflux Management System; b) implantation of the EST device using laparoscopic surgery. Product name: EndoStim® LES Stimulator. 3) Publication related: studies comparing MSAD or EST with LF, the standard surgical treatment of GERD, and studies comparing EST with sham treatment or PPI therapy, reporting on at least one of the efficacy and safety outcomes described below in outcomes of interest. For the analysis of effectiveness, randomized controlled trial (RCTs) and non-RCTs were considered for inclusion while for the analysis of safety, prospective case series were included as well. We applied a language restriction and considered only English (and German for the assessment of MSAD) language articles.

Data extraction

One researcher extracted data and the other checked the data extraction. Data were recorded in a structured manner as follows: sample characteristics, study characteristics, primary outcome measures, and secondary outcome measures.

Outcomes of interest

The primary outcomes of interest comprise GERD-health-related quality of life (HRQL) score, adverse device effects (dysphagia, excessive bloating, nausea/vomiting, pain/discomfort, and inability to belch or vomit), and serious adverse device effects (device erosion, removal, migration, malfunction, and trocar perforation of the small bowel). Secondary outcomes included the single elements of the GERD-HRQL score, intermediate outcomes like heartburn, excessive bloating, daily regurgitation, extra-esophageal symptoms, and patient satisfaction, in case the study did not report on the GERD-HRQL score. Furthermore, intermediate outcomes like discontinuation of PPIs, deMeester pH score, re-hospitalization, re-operation, and hospital discharge were included.

Quality assessment

We assessed the quality and risk of bias of the included studies using the Institute of Health Economics' quality appraisal checklist for case series [10]. All studies that we included in the review were scored independently by two authors. Based on the data extraction tables, the data on each selected outcome category were synthesized across studies according to GRADE methodology [11].

Results

MSAD

Available evidence

In the systematic literature search for MSAD, we found 214 citations through electronic database search, 58 through hand search, and the manufacturer submitted 16 publications of which we identified one new publication. After removing duplicates, we screened 273 articles. There were 54 full-text articles assessed for eligibility, of which six were studies (five prospective case series and one prospective registry study) that met our inclusion criteria and were included in the qualitative analysis (Fig. 1: PRISMA tree MSAD).

Characteristics of included studies

Our analysis of the clinical effectiveness of the MSAD included 249 patients, of which 202 underwent the MSA procedure. For analysing safety of the MSAD, 356 patients from prospective

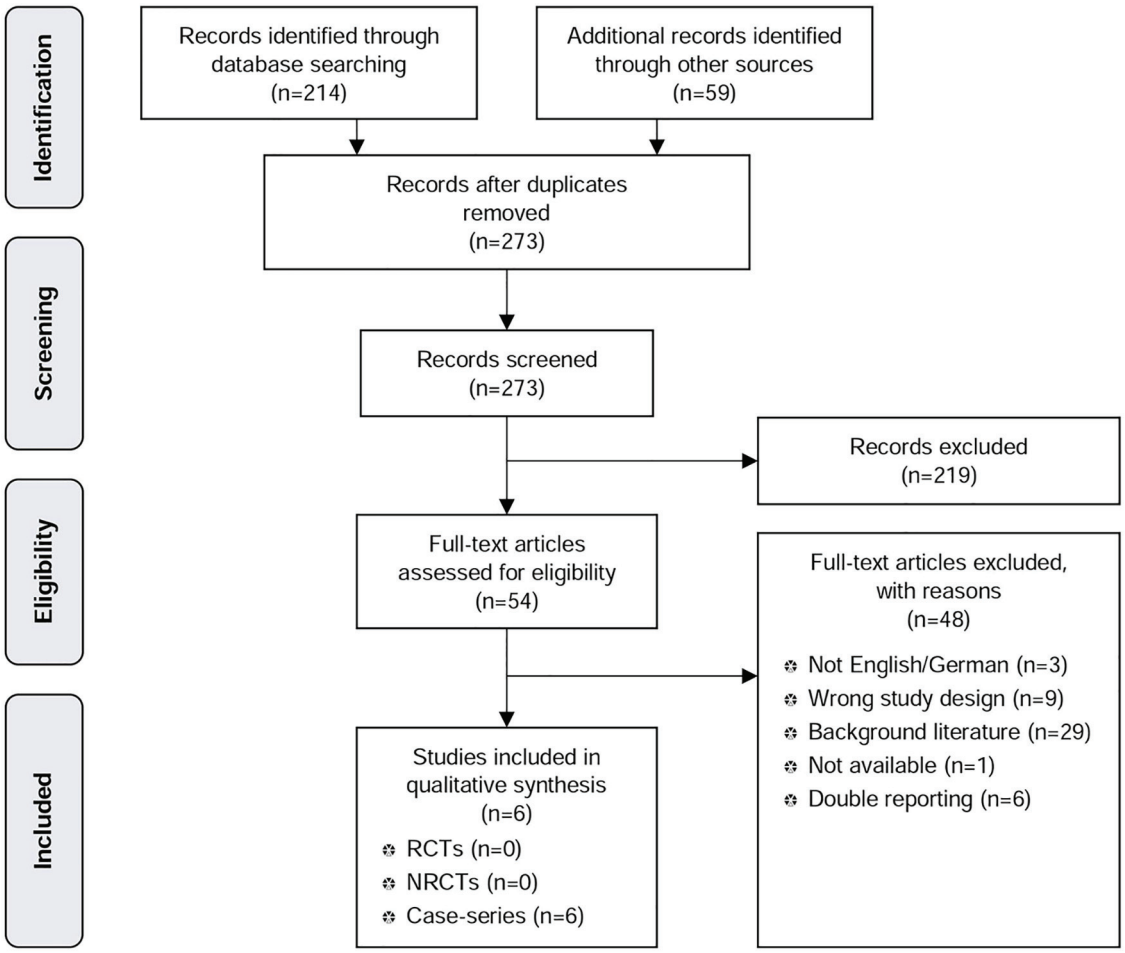

Figure 1. PRISMA tree MSAD.

case series and 202 from the registry study were included. The characteristics of each study are presented in Table 1 [12-21].

Patient characteristics of the included studies

In the MSAD prospective case series, patient characteristics were homogeneous in terms of Barrett's esophagus, motility disorder, hiatal hernia size, and body mass index (BMI). The inclusion criteria showed some heterogeneity in terms of age, length of GERD symptoms, PPI resistance and responsiveness, and confirmation of reflux by ambulatory esophageal pH monitoring.

In the controlled registry study, LF patients had a more severe disease in terms of hiatal hernia size, Barrett's esophagus, and esophagitis grade C and D. The mean BMI score, the number of years on PPIs as well as the number of years with GERD were similar [12]. The baseline characteristics are presented in Table 2 [12-20].

Effectiveness of MSAD

Only the registry study [12] fulfilled the inclusion criteria for the effectiveness analysis of the MSAD. The GERD-HRQL score improved from 20 to 3 points in MSAD patients, and from 23 to 3.5 points in LF patients. Heartburn improved from the baseline 30.8% to 3.5% at 1-year follow-up in the MSAD group, and from 40% to 8.5% in the LF group. Daily regurgitation dropped from 60% to 13% in LF patients, whereas in MSAD patients, it dropped from 58.2% to 3.1%. In terms of frequency of extra-esophageal symptoms, an improvement from 63.9% to 22.3% in the MSAD group and from 53.3% to 17.4% in the LF group was observed. Of MSAD patients, 81.8% discontinued PPI therapy compared to 63% of patients who underwent LF. Dysphagia was not reported, but post-operative excessive bloating appeared in 10% of MSAD patients, as opposed to 31.9% of LF patients. Of MSAD patients, 91.8% were satisfied at follow-up compared to 86.7% of LF patients.

Safety of MSAD

Only the registry study [12] allows for the comparison of dysphagia, excessive bloating, inability to belch or vomit, intraoperative complications, re-operation, and re-hospitalization rates between the two groups. Post-operative excessive bloat-

Table 1. Characteristics of the Included Prospective Case Series and Registry Studies of MSAD and EST

	MSAD prospective case series					MSAD prospective registry with control group	EST prospective case series		EST prospective registry
	Bonavina et al, 2013 [17]	**Schwameis et al, 2014 [15]**	**Smith et al, 2014 [16]**	**Reynolds et al, 2014 [14]**	**Ganz et al, 2015 [13]**	**Riegler et al, 2015 [12]**	**Kappelle et al, 2015 [18]**	**Rodriguez et al, 2015 [19]**	**Rodriguez et al, 2016 [20]**
Country	Italy	Austria	US	US	US, The Netherlands	Austria, Germany, Italy, UK	Chile, Colombia, India, Netherlands, Mexico, New Zealand, UK[a]	Chile	Chile
Sponsor	Torax Medical Inc.	Torax Medical Inc.	Torax Medical Inc.	Torax Medical Inc.	Torax Medical Inc.	Torax Medical Inc.	EndoStim Inc.	EndoStim Inc.	EndoStim Inc.
Study design	Single-center prospective case series	Single-center prospective case series	Single-center prospective case series	Two-center prospective case series	Multi-center prospective case series	Multi-center prospective registry with control group (NCT01624506)	Multi-center, prospective, international, open-label case series (NCT01574339)	Single-center, prospective, open-label case series (NCT01578642)	Single-center, prospective registry (NCT02441400)
Intervention	MSAD	MSAD	MSAD	MSAD	MSAD	MSAD	EST	EST	EST
Comparator	NA	NA	NA	NA	NA	LF	NA	NA	NA
Number of patients	100[b]	23	66	67	100	249 (202 vs. 47)	44[c]	26[d]	18[e]
Inclusion criteria	Patients > 18 years, GERD ≥ 6 months, PPI resistant GERD, reflux confirmed by ambulatory esophageal pH monitoring	At least partial response to PPIs, PPI resistant GERD	GERD, acceptable esophageal motility, clinical improvement on antisecretory medication with incomplete symptom control, medication intolerance, or side effects	Patients > 18 years, GERD > 6 months	Patients > 18 years < 75 years, GERD ≥ 6 months, at least partial response to PPIs, reflux confirmed by ambulatory esophageal pH monitoring	Advanced GERD with hiatal hernia > 3 cm, Barrett's esophagus, motility disorder, or esophagitis grade C or D Moderate GERD with abnormal esophageal pH, reflux symptoms despite PPI use	Patients 21 - 80 years, reflux symptoms, GERD-HRQL score ≥ 20 off PPIs and, an increase of ≥ 5 on PPIs, prior PPI use for 12 months, diagnosis based on 24-h pH monitoring result, LES end-expiratory 5 - 15 mm Hg, peristaltic contractions in ≥ 50% of swallows with contraction amplitude of ≥ 30 mm Hg esophageal manometry, excessive lower esophageal acid exposure as pH < 4.0 for ≥ 5% of the total time.	Patients 21 - 65 years, reflux symptoms ≥ 6 months, prior PPI use, GERD-HRQL score ≥ 20 off PPIs and, an increase of ≥ 10 on PPIs, ASA Physical Status Classification ≤ II, distal esophageal acid ex-posure during 24-h pH measurement pH of ≤ 4 for > 5% of total or > 3% of supine, time off, anti-secretory therapy, LES end-expiratory ≥ 5 mm Hg, esophageal body contraction amplitude of ≥ 30 mm Hg for ≥ 70% of swallows and ≥ 50% peristaltic contractions on manometry, esophagitis grade ≤ C.	NA
Exclusion criteria	Hiatal hernia > 3 cm, esophagitis grade B+, BMI > 35, Barrett's esophagus, motility disorder, gross esophageal anatomic abnormalities, allergy to the device's material (titanium, stainless steel, nickel, or ferrous materials)	Hiatal hernia > 3 cm, Barrett's esophagus, motility disorder, dysphagia, esophagitis grade C or D, allergy to the device's material	Hiatal hernia > 3 cm, advanced GERD, Barrett's esophagus, esophagitis grade B+	Hiatal hernia > 3 cm, motility disorder, esophagitis grade C or D, Barrett's esophagus, gross esophageal anatomic abnormalities, allergy to the device's material	Hiatal hernia ≥ 3 cm, esophagitis grade C or D, BMI > 35, Barrett's esophagus, motility disorder	Known conditions that make it unlikely to complete a 3-year follow-up	History of esophageal or gastric surgery, gastroparesis, multisystem disease, autoimmune or connective tissue disorder in past 2 years, Barrett's epithelium, any grade dysplasia, hiatal hernia > 3 cm, esophagitis grade D on upper endoscopy within 6 months, BMI > 35, T1DM or uncontrolled T2DM defined as HbA1c ≥ 9.5 in the previous 6 ms, or T2DM for ≥ 10 years, suspected or confirmed esophageal or gastric cancer, any malignancy in last 2 years, esophageal or gastric varices or dysphagia or esophageal peptic stricture, significant cardiac arrhythmia or cardiovascular disease, implanted electrical stimulator or chronic anticoagulant therapy, pregnant patients.	Non-GERD esophageal motility disorders or gastroparesis, multi-system diseases, Barrett's (> M2; > C1) esophagus, any grade of dysplasia, hiatal hernia ≥ 3 cm, BMI > 35, uncontrolled type 2 or history of type 2 or 1 diabetes mellitus for > 10 years, esophageal or gastric malignancy or varices, cardiac arrhythmia, ectopy, significant cardiovascular disease, implanted electro-medical device, pregnancy, esophageal or gastric surgery, anti-reflux surgery.	NA

Table 1. Characteristics of the Included Prospective Case Series and Registry Studies of MSAD and EST - *(continued)*

	MSAD prospective case series					MSAD prospective registry with control group	EST prospective case series		EST prospective registry
	Bonavina et al, 2013 [17]	Schwameis et al, 2014 [15]	Smith et al, 2014 [16]	Reynolds et al, 2014 [14]	Ganz et al, 2015 [13]	Riegler et al, 2015 [12]	Kappelle et al, 2015 [18]	Rodriguez et al, 2015 [19]	Rodriguez et al, 2016 [20]
Follow-up time	3 years (range 378 days - 6 years)	1 month	5.8 months (range 1 - 18.6 months)	5 months (range 3 - 14 months)	5 years	1	0.5 year	2 years	3 years
Loss to follow-up, n	5[f]	0	1	15	15	0	6.8[g]	19.2[h]	16.6[i]

[a]While the study refers to eight countries and 10 sites, www.clinicaltrials.gov lists seven countries and nine sites. [b]Patients 1 through 30 (30%) underwent the implantation procedure between March 2007 and May 2008 as part of a multi-center (US, IT) pilot study of 41 patients [21]. Patients 31 through 100 (70%) underwent the implantation procedure between December 2009 and February 2012 as part of a registry. Patients 1 - 30 from the multi-center study were recorded under NCT01057992 in Italy. [c]Baseline characteristics on 42 patients. [d]25 received intervention. [e]Baseline characteristics on 15 patients. [f]Out of the 41 patients of the pilot study [21], 11 patients were lost to follow-up. Out of the cohort of 100 patients (30 patients from the pilot study and 70 registry patients), five were lost to follow-up. [g]One loss to follow-up, one Toupet fundoplication due to hiatal hernia > 3 cm, and one trocar perforation of the intestine during implant procedure. [h]One loss to follow-up, one implant not attempted due to hiatal hernia > 3 cm, and three voluntary withdrawals. [i]One loss to follow-up, one implant not attempted due to hiatal hernia > 3 cm, and three voluntary withdrawals. ASA: American Society of Anesthesiologics; BMI: body mass index; EST: electric stimulation therapy; GERD: gastroesophageal reflux disease; LES: lower esophageal sphincter; LF: laparoscopic fundoplication; MSAD: magnetic sphincter augmentation device; NA: not available; PPIs: proton pump inhibitors.

ing was 10% in MSAD patients, compared to 31.9% in LF patients. No significant difference was observed between the two groups regarding intraoperative complication rates. Of MSAD patients, 1.6% experienced the inability to belch compared to 10.1% of LF patients, 8.7% experienced the inability to vomit compared to 56.6% of LF patients, and 7% of MSAD patients and 10.6% of LF patients experienced dysphagia at 1-year follow-up. Of MSAD patients, 4% were re-operated due to device removal compared to 6.4% in the LF group that were re-operated due to persistent GERD and herniation of the fundic wrap. Hospital re-admission rate was 5.4% for the MSAD group compared to 4.3% for the LF group.

Device removal, erosion, malfunction, and migration could be analyzed in both the registry and the case series because the effects directly attributable to the device can be analyzed without a control group, both in case of MSAD as well as EST. MSAD removal was reported in five studies. Two studies with short-term (up to 1 year) follow-up reported no device removals, three studies with long-term (1 - 5 years) follow-up indicated a device removal rate of 4% at 1-year follow-up, 3% at 3-year follow-up, and 7% at 5-year follow-up. Device erosion and migration was reported in three and two studies, respectively, but occurred in none. Device malfunctioning did not occur in the only study that recorded data on this outcome [13] (Table 3 [12-20]).

Evaluation of quality and strength of evidence

Overall, the quality of evidence for analyzing MSAD was very low. The reasons for downgrading were methodological limitations, inconsistency, and other modifying factors [14-16] (Table 4 [12-20]).

The overall risk of bias was high due to the unclear selection process [13, 16], non-consecutive recruitment of study participants [13, 17], multiple-reporting [12, 17], high loss to follow-up [13, 14], and entering the study at a similar point in the disease was either unclear [12, 14, 16] or clearly not fulfilled [13, 15, 17] (Table 5 [12-20]). All six studies were sponsored by the manufacturer Torax Medical Inc., and all of the effectiveness outcomes were patient reported, hence subject to a high risk of bias. The inclusion criteria in the registry study were different for the MSAD and LF patients, which undermines the validity of the studies.

EST

Available evidence

In the systematic literature search for EST, we found 365 citations through electronic database search, 22 additional citations were found through hand search, and the manufacturer submitted 28 publications, of which we identified 0 new publications. After removing duplicates, we screened 367 articles. Sixty-five full-text articles were assessed for eligibility, of which three were studies (two prospective case series and one prospective registry study) that met our inclusion criteria and

Table 2. Baseline Patient Characteristics of MSAD and EST Prospective Case Series and Registry Studies

	MSAD prospective case series					MSAD prospective registry with control group	EST prospective case series		EST prospective registry
	Bonavina et al, 2013 [17]	**Schwameis et al, 2014 [15]**	**Smith et al, 2014 [16]**	**Reynolds et al, 2014 [14]**	**Ganz et al, 2015 [13]**	**Riegler et al, 2015 [12]**	**Kappelle et al, 2015 [18]**	**Rodriguez et al, 2015 [19]**	**Rodriguez et al, 2016 [20]**
Age, years	Median 44.5 (range 23 - 77)	Median 43 (range 20 - 68)	Median 53.7 (range 18 - 86)	Median 53 (range 19 - 81)	Median 53 (range 18 - 75)	Mean 46.6 vs. 52.8 (P = 0.007)	Mean 49.6 (SD 12.4)	Mean 52 (SD 12)	Mean 56.1 (SD 9.7)
Sex, female vs. male	(26 vs. 74)	12 vs. 11	38 vs. 28	20 vs. 47	48 vs. 52	(77 vs. 125) vs. (19 vs. 28) (p=0.866)	18 vs. 24	11 vs. 14	7 vs. 8
Moderate GERD, %	NA	NA	NA	NA	NA	94 vs. 38.3	NA	NA	NA
BMI	Median 24 (range 17.3 - 33.0)	Median 26 (range 20 - 32)	Mean 26 (range 17.6 - 34.1)	NA	Median 28 (range 20 - 35)	Mean 25.7 vs. 26.1 (P = 0.611)	Mean 27.2 (2.4)	Mean 27.7 (SD 3.2)	Mean 27.4 (SD 3.2)
Hiatal hernia, none/< 2/≥ 2 cm, %	21/ 27/52	100/0[a]	67[b]	NA	NA	14.1/84.4/1.6 vs. 10.9/43.5/45.7[c]	39/22/39	88/8/4	93.3/0/6.7
Yrs of PPI use	Median 4	Median 1 (range 0 - 20)	NA	NA	Median 5	Mean 6.3 vs. 5.1 (P = 0.098)	NA	Mean 5.6 (SD 3.4)	Mean 5.9 (SD 3.3)
Yrs with GERD	Median 5.5	Median 4 (range 1 - 20)	NA	NA	Median 10 (range 1 - 40)	8.7 vs. 7.3 (P = 0.086)	NA	Mean 11.0 (SD 7.9)	Mean 12.2 (SD 9.1)
Barrett's esophagus, n	2	NA	3	NA	NA	8.7 vs. 7.3 (P = 0.086)	NA	NA	NA
Esophagitis, %									
Grade A and B	16	21.7	NA	NA	NA	41.4 vs. 44.7 (P = 0.212)	54	NA	93.3
Grade C and D	1	NA	NA	NA	NA	1 vs. 8.5 (P = 0.212)	5	NA	6.7

[a]100% no hernia or < 2 cm hernia. The mean hiatal hernia size was 1.34 cm (range 0 - 2 cm). [b]All hernias < 3 cm. [c]Different distinction: none/1 - 3 cm/> 3 cm. BMI: body mass index; EST: electric stimulation therapy; GERD: gastroesophageal reflux disease; MSAD: magnetic sphincter augmentation device; n: number; NA: not available; SD: standard deviation.

Table 3. Efficacy and Safety Outcomes From MSAD and EST Prospective Case Series and Registry Studies

	MSAD prospective case series					MSAD prospective registry with control group (I vs. C)	EST prospective case series		EST prospective registry
	Bonavina et al, 2013 [17]	Schwameis et al, 2014 [15]	Smith et al, 2014 [16]	Reynolds et al, 2014 [14]	Ganz et al, 2015 [13]	Riegler et al, 2015 [12]	Kappelle et al, 2015 [18]	Rodriguez et al, 2015 [19]	Rodriguez et al, 2016 [20]
Efficacy									
Median GERD HRQL score (pre-op./last follow-up)	Off PPIs 24/2	29/4 (P < 0.001)	26/6	NA/4 (0 - 26)	27/4 (P < 0.001)	20/3 vs. 23/3.5 (P = 0.177)	On PPIs 16.5/5.0 Off PPIs 31.0/5.0[a]	On PPIs 9/0[b]/1 Off PPIs 23.5/0/1	
Heartburn	% (pre-op./last follow-up)						% of days (pre-op./last follow-up)(IQR)		
	NA	95.7/22 (P < 0.001)	NA	NA	89/11.9 (P < 0.001)	30.8/3.5 vs. 40/8.5 (P = 0.229)	86 (64 -100)/17 (0 - 93)$_a$	92/7[c]/NA	
Regurgitation	Daily regurgitation, % (pre-op./last follow-up)						Median regurgitation % of days (pre-op./last follow-up) (IQR)		
	72/2	65/57 (P > 0.1)	NA	NA/44.2	57/1.2 (P < 0.001)	58.2/3.1 vs. 60/13 (P = 0.014)	79 (54 - 100)/0 (0 - 21)[a]	66/0[c]/NA	
Dysphagia, % (pre-op./last follow-up)	8/0	48/70 (P > 0.1)	NA	0.02/82.7[d]	5/6 (P = 0.739)	NA	NA	NA	NA
Excessive bloating, % (pre-op./last follow-up)	48/2	70/30 (P = 0.006)	NA	NA	52/8.3 (P < 0.001)	NA	NA	NA	NA
Extra-esophageal symptoms (asthma, chronic cough, laryngitis), % (pre-op./last follow-up)	52/16	57/17 (P = 0.039)	NA	NA	NA	63.9/22.3 vs. 53.3/17.4 (P = 0.552)	NA	NA	NA
Discontinuation of medication (PPIs), %	85	71.4[e]	83	76.9	84.7[f] (CI 95%, 81 - 95)	81.8 vs. 63 (P = 0.009)	NA	76	73
DeMeester pH score (pre-op./last follow-up)	Median 30.1/11.2	NA	Mean 32.3 (range 1.4 - 67)/NA	NA	Median 36.6 (16.3 - 83.8)/NA	NA	Median 35.1 (IQR 27.1 - 51.9)/17.5 (IQR 10.9 - 23.4)[g]	Median 36.6 (IQR 29.6 - 50.2)/16.1 (IQR 12.2 - 29.1)[h]/12.8 (IQR 7.2 - 18.8)	
Hospital discharge, %	96 (within 48 h)	52 (within 24 h), 82.6 (within 48 h)	25 (within 24 h)	51 (within 12 h), 100 (within 36 h)	NA	NA	NA	NA	NA
Patient satisfaction, % (pre-op./last follow-up)	5/87	0/74	NA/92[i]	NA	5/92.9[j] (P < 0.001)	91.8 vs. 86.7	7/54[k]	29/100/NA	
Esophagitis, % (pre-op./last follow-up)	NA	NA	NA	NA	NA	NA		NA	
None							41/51[l]		0/NA[m]
Grade A							323/181/31		60/NA
Grade B							5/0		33.3/NA
Grade C									6.7/NA
Safety									
Inability to belch, %	1	0	NA	NA	NA	1.6 vs. 10.1 (P = 0.007)	7.1[n]	0	0
Inability to vomit, %	1	0	NA	NA	NA	8.7 vs. 56.6 (P < 0.001)	4.8	NA	NA
Other non-serious ADEs, %	Mild odynophagia: 4, increased belching: 3	NA	NA[o]	Dehydration: 0.67, urinary retentions: 2	NA	Excessive bloating: 10 vs. 31.9 (P < 0.001)	Constipation, epigastric pain, fever, mesh repair hernia cicatricialis: 2.4 hiccups, impedance out of range: 4.8, weight loss/ anorexia: 11.9	Skin infection at pocket site, psychotic disturbance/nervous breakdown: 4, shoulder pain and a hypersensitive episode: 8	NA
Dysphagia, %	2	0.23	2.64	5.36	NA	7 vs. 10.6 (P = 0.373)	9.5	0	0
Pain/discomfort, %	NA	NA	NA	NA	NA	NA	45.2	20	0
Nausea/vomiting, %	NA	NA	NA	NA	NA	NA	7.1	12	0
Intraoperative complications, %	0	0	0	0	NA	1.49 vs. 2.13[p] (P = 1.00)	Trocar perforation of the small bowel during laparoscopy: 2.4	NA	NA
Reoperation rate, %	NA	NA	NA	NA	NA	4 vs. 6.4[r]	NA	NA	NA
Hospital readmission, %	NA	NA	NA	NA	NA	5.4 vs. 4.3	NA	NA	NA
Device erosion, %	0	NA	0	NA	0	NA	2.4	NA	NA
Device migration, %	0	NA	NA	NA	0	NA	NA	NA	NA
Device malfunction, %	NA	NA	NA	NA	0	NA	NA	NA	NA
Device removal, %	3	0	0	NA	7	4	NA	NA	NA

[a]42 patients at baseline, 41 at last follow-up. [b]24 patients at baseline, 21 at last follow-up. [c]18 patients' analysis. [d]55.8 described it as mild. A total of 44.2 described their dysphagia as severe. [e]Two patients (9.5%) were already off medication at baseline due to severe side-effects from PPIs. Two further patients were able to halve their daily PPI dosage. [f]At 5 years, 75.3% of patients reported complete cessation of PPIs, and 9.4% reported PPI use only as needed. [g]42 patients at baseline, 40 at last follow-up. [h]24 patients at baseline, 18 at last follow-up. [i]Patients who were satisfied or neutral about the intervention. [j]Defined through patient dissatisfaction where at baseline, 95% were dissatisfied and at 5 years, 7.1% were dissatisfied. [k]42 patients at baseline, 39 at last follow-up. [l]Out of 39 patients. [m]Data on 12 patients: six patients showed improvement by 1 grade, three patients have stable and three patients worsening esophagitis. [n]Includes both, post-operative bloating and belching. [o]A total of 8.58% of patients underwent 11.22% of contrast swallows, 4.62% of dilatations, 7.91% of esophagogastroduodenoscopy, 3.3% of pH testing and 0.66% of motility test mainly for diagnosis. Dilatations were done in 2.64% of patients for dysphagia. [p]An injury to the pleura in both groups, minor bleeding in two patients in the MSDA group. [r]Reoperations in the MSAD group were performed for device removal due to dysphagia, pain or persistent GERD, while in the LF group were for persistent GERD and herniation of the fundic wrap. ADE: adverse device effect; EST: electric stimulation therapy; GERD: gastroesophageal reflux disease; SADE: serious adverse device effect; HRQL: health-related quality of life; IQR: interquartile range; LF: laparoscopic fundoplication; MSAD: magnetic sphincter augmentation device; n: number; NA: not available; CI: confidence interval; PPIs: proton pump inhibitors; pre-op: pre-operation; SD: standard deviation.

were thus used for the qualitative analysis (Fig. 2: PRISMA tree EST).

Characteristics of included studies

No study passed the inclusion criteria for analyzing the EST effectiveness. For analyzing safety of the EST, a total of 70 patients were included. The characteristics of each study are presented in Table 1 [12-21].

Patient characteristics of the included studies

In the prospective case series and the registry study, patient characteristics showed homogeneity in terms of mean age and mean BMI, and heterogeneity in terms of hiatal hernia size. The baseline characteristics are presented in Table 2 [12-20].

Effectiveness of EST

No study fulfilled the study inclusion criteria for assessing clinical effectiveness of the EST. RCTs and non-RCTs were considered for inclusion, but could not be identified through the systematic literature search.

Safety of EST

Device related complications were reported in one study with 6 months follow-up [18]. Lead erosion through the esophagus occurred in 2.4% of patients and was followed by the device explantation. One procedure related complication, trocar perforation of the small bowel during laparoscopy, occurred also in 2.4% of patients. No other device related complications were reported. Table 3 shows the efficacy and safety outcomes [12-20].

Evaluation of quality and strength of evidence

The quality of evidence for analyzing EST was very low. This is due to the observational study design, heterogeneity of data, no P-values on pre-post comparison reported, and small sample size (Table 4) [12-20]. Furthermore, the patient group is not representative of the range of GERD patients requiring anti-reflux surgery due to the highly specific patient selection criteria [22].

The overall risk of bias was considered moderate because it was unclear if patients entered the study at a similar point in the disease, if patients were recruited consecutively, and conclusions concerning effectiveness were not supported by the results (Table 5) [12-20]. Internal validity of the trials conducted was undermined by the use of the concomitant therapy of PPIs in all trials. Occasional or regular use of PPIs was reported to be 12% and 24% in the case series [18, 19], and 27% in the registry study [20].

Discussion

The results of these systematic reviews yield indefinite conclusions about the use of both MSAD as well as EST for moderate to severe GERD patients in whom non-surgical treatment has failed due to incomplete symptom control despite maximum medication treatment or due to severe complications associated with PPI therapy. Both interventions are also an option for patients who opt for surgery despite successful medical management as the use of medications is life-long and non-curative, and for patients with GERD complications such as extra-esophageal symptoms (asthma, chronic cough, and laryngitis). Major advantages of MSAD and EST are that they are less invasive and reversible, their implantation is associated with a short learning curve for the surgeon, and they require a shorter hospital stay compared to LF. However, clinical effectiveness and safety of both MSAD and EST are not sufficiently proven by current clinical studies and so are yet to be supported by high quality evidence from RCTs.

Effectiveness and safety

Currently, there are no comparative data on the EST and only a single controlled registry trial on the MSAD [12]. However, within the registry trial, the differences in inclusion criteria between MSAD and LF patients are such that the comparative value of the study remains undermined (Table 2) [12-20]. Moreover, the fact that LF achieved an improvement in HRQL similar to MSAD despite the fact that patients in the LF group had a more severe disease possibly suggests the LF supremacy. Hence, our systematic review on MSAD [23] draws a different conclusion from systematic reviews and meta-analyses of Skubleny et al [24] as well as Chen et al [25]. Excluding the retrospective trials on methodological grounds [26] and recognizing the vast differences in patient inclusion criteria of the only remaining comparative study [12], we conclude that the effectiveness of MSAD is yet to be established. Also, data on long-term safety considerations such as durability of the devices and device removals need to be considered as well.

Mechanisms behind GERD

The mechanisms behind GERD need also to be analyzed because they have an impact on the effectiveness of interventions. Only the correct determination of GERD's pathophysiology will help in evaluating the efficacy of anti-reflux treatments. For instance, the LES residual pressure represents a surrogate outcome that the EST claims to improve, yet, the improvement was either reported not to be statistically significant (P = 0.8018) [18], or it was not reported at all in the remaining studies [19, 27]. Other mechanisms possibly having an influence on GERD may have an effect on transient LES relaxation, LES compliance, or the acid pocket [19]. Furthermore, as hiatal hernias make acid reflux more likely [28], it is possible that repairing of the hiatal hernia has an impact on the effectiveness of interventions and hence on GERD symp-

Table 4. Evidence Profile: Efficacy and Safety of MSAD and EST in GERD Patients

No. of studies/ patients	Study design	Estimate of effect	Study limitations	Inconsistency	Indirectness	Other modifying factors	Strength of evidence
Efficacy of MSAD							
Median GERD-HRQL score (pre-op./last follow-up) I vs. C							
1/249 [12]	Prospective registry with control group	20/3 vs. 23/3.5 (P = 0.177)	0	NA	0	0	Moderate
Efficacy of EST							
Due to the lack of a controlled group, no data on efficacy can be reported.							
Safety of MSAD							
Overall complication rate, % I vs. C							
1/249 [12]	Prospective registry with control group	NA	NA	NA	NA	NA	NA
Intraoperative complications, % I vs. C							
1/249 [12]	Prospective registry with control group	1.49 vs. 2.13 (P = 1.00)	0	NA	0	0	Moderate
Dysphagia, % I vs. C							
1/249 [12]	Prospective registry with control group	7 vs. 10.6 (P = 0.373)	0	NA	0	0	Moderate
Device removal, %							
5/336 [13-17]	Prospective case series + prospective registry with control group	0 - 7	-1	-1	0	-1	Very low
Safety of EST							
Adverse events (AEs)							
Post-operative bloating/belching							
3/67 [18-20]	Prospective case series + prospective registry	Not reported	-1[a]	-1[b]	0	-1[c]	Very low
Post-operative dysphagia							
3/67 [18-20]	Prospective case series + prospective registry	Not reported	-1	-1	0	-1	Very low
Nausea/vomiting							
3/67 [18-20]	Prospective case series + prospective registry	Not reported	-1	-1	0	-1	Very low
Pain/discomfort							
3/67 [18-20]	Prospective case series + prospective registry	Not reported	-1	-1	0	-1	Very low
Serious adverse events (SAEs)							
Trocar perforation of the small bowel							
1/42 [18]	Prospective case series	Not reported	-1	NA	0	-1	Very low
Device erosion lead through esophagus							
1/42 [18]	Prospective case series	Not reported	-1	NA	0	-1	Very low

[a]Unclear risk of bias due to unclear allocation concealment, no blinding, no control group. [b]Heterogeneous results, no P-value reported. [c]Small sample size. C: control; EST: electric stimulation therapy; GERD: gastroesophageal reflux disease; I: intervention; LF: laparoscopic fundoplication; MSAD: magnetic sphincter augmentation device; NA: not available; SEA: serious adverse event.

toms.

Ambiguity of alternatives

Proving the effectiveness of MSAD and EST seems to pose a challenge due to the ambiguity of comparators. On the one hand, LF is presented as a comparator, yet on the other hand, MSAD and EST claim to fill the "therapeutic gap between patients who are dissatisfied with PPI treatment and those who are reluctant to undergo Nissen fundoplication" [29]. In contrast to the LF, the target population of MSAD and EST seems to be represented by patients with a less severe disease. The exact patient group that would benefit most from the treat-

Table 5. Risk of Bias - Study Level

Study reference/ID	Bonavina et al, 2013 [17]	Schwameis et al, 2014 [15]	Smith et al, 2014 [16]	Reynolds et al, 2014 [14]	Ganz et al, 2015 [13]	Riegler et al, 2015 [12]	Kappelle et al, 2015 [18]	Rodriguez et al, 2015 [19]	Rodriguez et al, 2016 [20]
1. Is the hypothesis/aim/objective of the study stated clearly in the abstract, introduction, or methods section?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. Are the characteristics of the participants included in the study described?	Yes	Yes	Yes	Partially reported	Yes	Yes	Yes	Yes	Yes
3. Were the cases collected in more than one centre?	No	No	No	Yes	Yes	Yes	Yes	No	No
4. Are the eligibility criteria (inclusion and exclusion criteria) for entry into the study explicit and appropriate?	Yes	Yes	Yes	Yes	Yes	Partially reported[a]	Yes	Yes	Yes
5. Were participants recruited consecutively?	No[b]	Yes	Unclear[c]	Yes	Unclear[d]	Yes	Unclear[e]	Unclear[f]	Unclear[g]
6. Did participants enter the study at similar point in the disease?	No	No	Unclear	Unclear	No	Unclear	Unclear	Unclear[h]	Unclear
7. Was the intervention clearly described in the study?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
8. Were additional interventions (co-interventions) clearly reported in the study?	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
9. Are the outcome measures clearly defined in the introduction or methods section?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
10. Were relevant outcomes appropriately measured with objective and/or subjective methods?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
11. Were outcomes measured before and after intervention?	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
12. Were the statistical tests used to assess the relevant outcomes appropriate?	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
13. Was the length of follow-up reported?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
14. Was the loss to follow-up reported?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
15. Does the study provide estimates of the random variability in the data analysis of relevant outcomes?	No	Yes	No	No	Yes	Yes	Yes	Patrially reported	Yes
16. Are adverse events reported?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
17. Are the conclusions of the study supported by results?	Yes	Yes	Yes	No	Yes	No	Partially reported	Partially reported	Partially reported
18. Are both competing interest and source of support for the study reported?	Yes	No	No	No	Yes	Yes	Yes	Yes	Yes
Overall risk of bias	High	High	High	High	High	Low	Moderate	Moderate	Moderate

[a]Exclusion criteria are too vague (patients were excluded if they had known conditions that would make it unlikely for them to complete a 3-year follow-up). [b]Patients 1 through 30 (30%) underwent the implantation procedure as part of a multicenter pilot study of 41 patients (Magnetic Augmentation of the Lower Esophageal Sphincter: Results of a Feasibility Clinical Trial, Bonavina et al. 2008). Patients 31 through 100 (70%) underwent the implantation procedure as part of a registry. [c]150 patients were evaluated for device implant, 68 were implanted. The selection process is not detailed. [d]From the 257 patients that signed the consent 100 underwent device implant. The 157 who discontinued: 96 eligibility criteria not met, 36 consent withdrawn, 24 discontinuation when implant limit met and one discontinuation by investigator (Ganz 2013). [e]"Unclear": 110 patients screened and 66 specified screen failures. [f]"Unclear": 75 patients screened and 49 unspecified screen failures. [g]"Unclear": 21 patients at 24 months follow-up, 18 recruited for 5 years registry (3/21 elected not to join the 5 years observational registry). [h]"Unclear": only mean duration of PPI use and mean duration of GERD symptoms is reported.

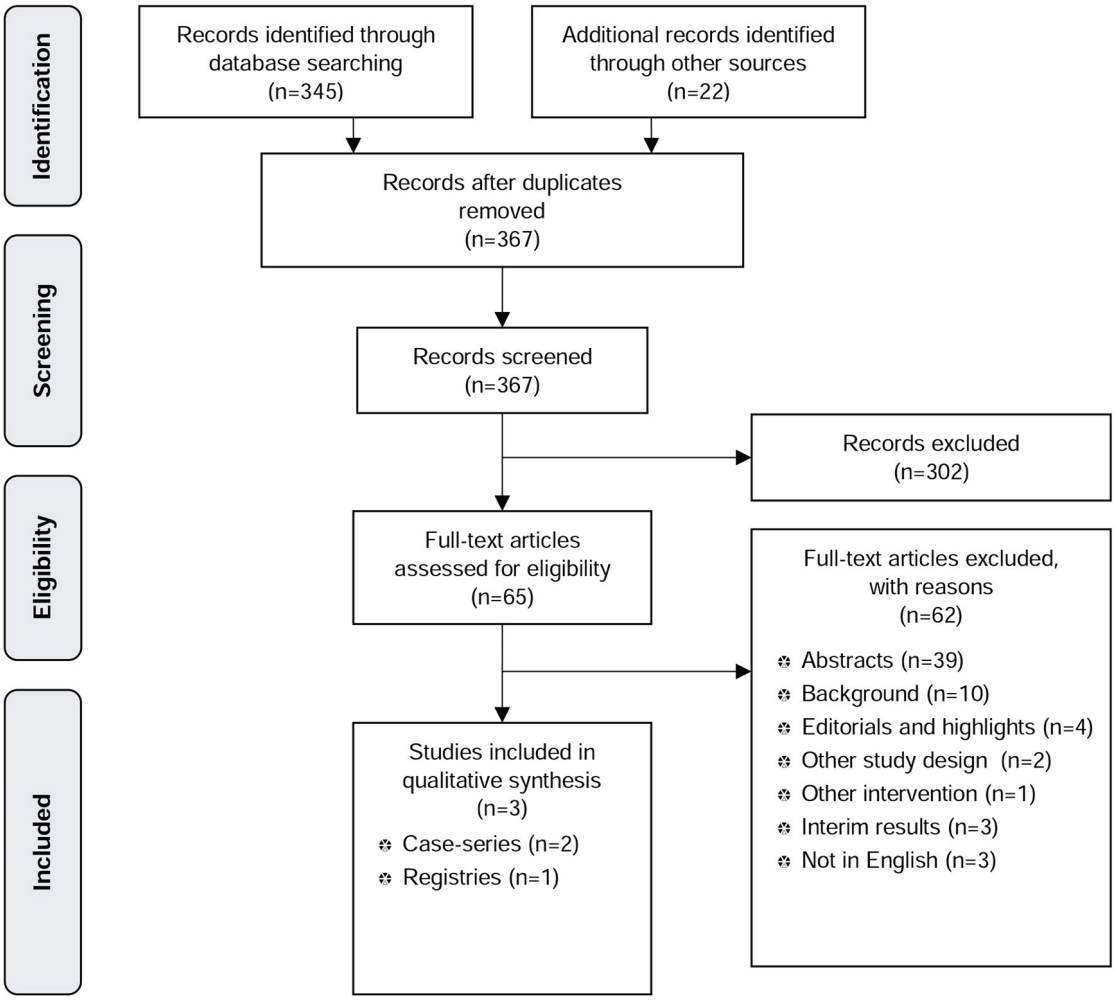

Figure 2. PRISMA tree EST.

ments thus needs to be more clearly defined. Hence, if there really is a therapeutic gap, it is unclear whether it is ethical to conduct an RCT between EST or MSAD, and LF as a comparator at all. Under these assumptions, a sham RCT would be needed to confirm the efficacy of EST. This could be done by implanting the EST device in both groups of patients at the same time, while activating the device straightaway in one group and postponing the activation in the control group. In case of MSAD, an RCT comparing MSAD with PPIs (in less severe cases) or MSAD with LF (in more severe cases) is still needed.

Limitations

The main limitation to be considered when interpreting these findings is that the MSAD literature search was done in 2016 and was not systematically updated since. However, the search was updated by hand search via searching the web and the clinical trial registries, which did not identify new prospective trials.

Conclusions

We conclude that the current evidence is not sufficient to prove that the two novel GERD treatments, EST and MSAD, are at least equally effective and as safe as the surgical comparator LF. The quality of the prospective evidence was low as there are only limited comparative data on the effectiveness of MSAD and no comparative data on EST. Both procedures have a relatively good safety-profile, making them a possible treatment option for moderate to severe GERD patients who either refuse further medical therapy or in whom non-surgical treatment has failed. The introduction of the two procedures into clinical practise outside controlled trials seems, however, premature. Controlled trials are essential to confirm safety benefits and establish effectiveness of these new interventions.

Disclosure

The Ludwig Boltzmann Institute for Health Technology As-

sessment conducted this study on behalf the Federal Ministry of Health, Austria.

Conflict of Interest

All authors declare that they have no conflict of interest.

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