Electric stimulation therapy (EST) in patients with gastroesophageal reflux disease (GERD)

Systematic Review

Ludwig Boltzmann Institut
Health Technology Assessment

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All authors and the reviewers involved in the production of this report have declared they have no conflicts of interest in relation to the technology assessed according to the Uniform Requirements of Manuscripts Statement of Medical Journal Editors (www.icmje.org).

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Commissioned by the Austrian Ministry of Health, this report systematically assessed the intervention described herein as decision support for the inclusion in the catalogue of benefits.

CONTENT INFORMATION

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Content

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List of abbreviations

AEs .....adverse events
ACG.....American College of Gastroenterology
AWMF .....Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften
AVNRT .....Atrioventricular Nodal Re-entrant Tachycardia
BE.....Barrett's Esophagus
BMI .....body mass index
CE Mark ...Conformité Européene mark
CT.....controlled trial
DMC .....Data Monitoring Committee
DRG .....Diagnosis-Related Group
EST.....Electric Stimulation Therapy
ESTD .....Electric Stimulation Therapy Device
GERD .....Gastroesophageal Reflux Disease
GRADE .....Grading of Recommendations Assessment, Development and Evaluation
HRQL .....Health-related quality of life
H2RA .....H2-receptor antagonist
IPG .....implantable pulse generator
IQR.....inter-quartile range
LP .....Laparoscopic Fundoplication
LBI-HTA ...Ludwig Boltzmann Institute for Health Technology Assessment
MRI .....Magnetic Resonance Imaging
MSAD .....Magnetic Sphincter Augmentation Device
min .....minutes
mos .....months
NA .....not available
NERD .....Non-Erosive Reflux Disease
pts .....patients
pre-op. .....pre-operative
PPI.....Proton Pump Inhibitor
RCT.....randomized controlled trial
SAE.....serious adverse event
SD.....standard deviation
TIF .....Trans-oral Incisionless Fundoplication
yrs .....year

Summary

Introduction

Health Problem

Gastroesophageal reflux disease

Gastroesophageal reflux disease (GERD) is defined according to the Montreal consensus as a condition that develops when the reflux of stomach contents causes troublesome symptoms and/or complications, whereby troublesome means that they adversely affect an individual's well-being [1].

failure of the antireflux barrier, the lower esophageal sphincter (LES)

From a surgical perspective, GERD is the failure of the antireflux barrier, caused by a defective LES, a gastric emptying disorder, or failed esophageal peristalsis. The abnormalities result in a spectrum of disease ranging from symptoms only, such as heartburn, to esophageal tissue damage with or without subsequent complications including malignancy or airway disease [1].

Description of Technology

EST, a novel surgical treatment option for GERD

laparoscopic intervetion

electrical stimulation to reinforce the weak LES

Electric stimulation therapy (EST) represents a novel method for the surgical treatment of GERD. The EST comprises of three components: a bipolar stimulation lead with two stitch electrodes, an implantable pulse generator, and an external programmer [2]. The EST implant procedure is performed using standard laparoscopic techniques where a pair of electrodes is placed in the anterior part of the lower esophagus and sutured in place [3]. The wires are then connected to a stimulator placed in the subcutaneous pocket in left upper quadrant of the abdominal wall [3]. The goal of the intervention is to reinforce the weak lower esophageal sphincter (LES) by delivering mild electrical signals to the LES throughout the day. The stimulation aims to restore normal function of the LES, preventing reflux from the stomach entering the esophagus.

Methods

based on EUnetHTA Core Model, systematic literature search in 5 databases, GRADE

The EUnetHTA Core Model for Rapid Relative Effectiveness was the main source for selecting relevant assessment elements. We conducted a systematic literature search (without restriction on publication date) in bibliographic databases (Medline via Ovid, Embase, the Cochrane Library, PubMed, database of the Centre for Reviews and Dissemination) to anwer the research questions in the domains effectiveness and safety. Two researcher selected the relevant documents (in English) independently. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology was used for qualitatively summarising the results for the domain: „Safety".

Domain effectiveness

inclusion criteria for effectiveness

For analysing clinical effectiveness, prospective controlled studies were included. The crucial outcome to derive a recommendation was GERD HRQL score.

Domain safety

inclusion criteria for safety

For analysing safety, prospective controlled and uncontrolled studies were included. The crucial outcomes to derive a recommendation were: device erosion and trocar perforation of the small bowel during laparoscopy. Other relevant outcomes were post-operative bloating/belching, post-operative dysphagia, pain/discomfort, and nausea/vomiting.

Results

Available evidence

2 single arm prospective case series, 70 patients

A total of two single-arm prospective case series and one prospective registry were eligible for inclusion in the current report. Overall, safety was evaluated in the total of 70 patients.

Clinical effectiveness

no study fulfilled the study inclusion criteria

No study fulfilled the study inclusion criteria for assessing clinical effectiveness of the EST.

Safety

no direct comparison for EST and standard practice

In the absence of data from controlled studies, no comparisons can made between the EST and the surgical alternative treatment, laparoscopic fundoplication (LF). Device and procedure related complications were reported in one study with 6 months follow-up [4]. Lead erosion through esophagus occurred in 2.4% out of 42 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% out of 42 patients. No other device or procedure related complications were reported.

lead erosion in 2.4% patients (out of 42 patients)

postoperative AEs: constipation, pain, hiccups, inability to vomit, fever, post operative bloating and dysphagia

A number of short-term post-operative harms occurred. The following adverse events occurred in one study [4] (in % of patients): constipation 2.4%, epigastric pain 2.4%, hiccups 4.8%, inability to vomit 4.8%, and fever 2.4%. The following adverse events occurred in both case series [4, 5] (in % of patients): post-operative bloating/belching in 7.1% and 0%, post-operative dysphagia in 9.5% and 0%, nausea/vomiting in 7.1% and 12%, and pain/discomfort in 45.2% and 20%. No new adverse events occurred in the registry study.

Upcoming evidence

1 ongoing multicentre RCT

There is an ongoing study in the US and Europe that is a multicenter, randomized, double-blind, sham-controlled clinical trial (NCT02749071).

Reimbursement

currently not reimbursed

Currently, the use of EST for the treatment of GERD is not reimbursed by the Austrian health care system.

Discussion

quality evidence needed, high risk of bias

Overall, the quality of evidence was very low and the overall risk of bias was considered moderate. Internal validity of the trials conducted was undermined by the use of the concomitant therapy of Proton Pump Inhibitors (PPIs) in all trials.

advantages of the EST are lesser invasiveness, easier intervention, shorter hospital stay

Major advantages of the EST known to date are that it is less invasive and reversible, its implantation is associated with a short learning curve for the surgeon, it presumably allows a faster return to normal diet, and it requires a shorter hospital stay compared to LF.

target population are GERD patients not indicated for LF

The target population of the EST, however, seems to be less severe patients not indicated for LF and hence, a sham RCT is needed to confirm efficacy of the EST. Crucial outcome measures should include the device's ability to reduce the likelihood of developing GERD complications, like esophageal cancer, and the long-term safety considerations, like the durability of the device and device removals.

Conclusion

The current evidence is not sufficient to prove that the EST is at least equally effective and as safe as the comparator LF. There are no available comparative data on the two procedures or placebo controlled data on the EST and hence, no conclusions are made about the device effectiveness. Concerning safety, only device related complications were reported based upon data from prospective case series. These suggest a relatively safe profile of the EST that, however, needs to be confirmed by a high quality RCT, which will potentially influence the effect estimate considerably. Re-evaluation is recommended in 2022, as December 2021 is the estimated ongoing study (NCT02749071) completion date.

current evidence does not prove effectiveness of the EST and safety needs to be confirmed

reevaluation in 2022

The inclusion in the catalogue of benefits is currently not recommended.

inclusion not recommended

Zusammenfassung

Einleitung

Indikation und therapeutisches Ziel

gastroösophageale Refluxkrankheit (GERD): Prävalenz 15 %

Die gastroösophageale Refluxkrankheit (GERD) ist eine häufige Erkrankung in den Industrieländern der westlichen Welt mit einer Prävalenz von bis zu 15 % und einer zunehmenden Inzidenz. Aufgrund ihrer zunehmenden Häufigkeit beansprucht die Behandlung von GERD wachsende Ressourcen. Zu den beeinflussenden Faktoren für die Entstehung von GERD zählen falsche Ernährung (Fettleibigkeit, erhöhter Fettkonsum, Essen unmittelbar vor dem zu Bett gehen) und ein passiver Lebensstil (Bewegungsmangel).

Ernährung & Lebensstil

Symptome: Sodbrennen, Aufstoßen, Magenschmerzen Schweregrade: mild, moderat, schwer

Typische Symptome von GERD sind: Sodbrennen, Aufstoßen, Magenschmerzen. Zu den atypischen Symptomen zählen: chronischer Husten, Heiserkeit, Dysphagie, Schmerzen in der Brust, chronische Aspiration, Bronchitis, Sinusitis. Auf Basis der Häufigkeit und Schwere der Reflux-Symptome, wird von milder, moderater und schwerer GERD gesprochen, jedoch ohne explizite Definition über die Dauer der Erkrankung und die Art der Messung der verschiedenen Stadien.

progrediente Erkrankung

Der natürliche Verlauf der Erkrankung ist unklar. Traditionell wird die Krankheit als Spektrum beginnend mit nicht-erosivem Reflux (NERD), der sich zu GERD (erosive Ösophagitis, Stenose, Barrett-Ösophagus) entwickelt, beschrieben. Das Management von GERD wird durch die Schwere der Symptome bestimmt. Die Leitlinien der „American College of Gastroenterology“ (ACG) und der „Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften“ (AWMF) schlagen ein schrittweises Vorgehen vor

ACG & AWMF: schrittweises Vorgehen bei Interventionen

Gewichtsverlust,

Vermeidung von Mahlzeiten vor Zubettgehen,

H2RA Therapie,

8 Wochen PPI, PPI Erhaltungstherapie,

- Als erste Interventionen werden Veränderungen in der Ernährung und im Lebensstil vorgeschlagen,
- Gewichtsverlust für GERD-PatientInnen, die übergewichtig sind,
- Oberkörperhochlage und Vermeidung von Mahlzeiten 2-3 Stunden vor dem Zubettgehen für PatientInnen mit nächtlicher GERD,
- bei mild bis moderater Schwere der Symptome: ein H2-Rezeptor-Antagonist (H2RA) Therapie,
- wenn eine H2RA Therapie nicht ausreichend ist, und der/die PatientIn moderate bis schwere Symptome hat: Initiierung einer 8-wöchigen Therapie mit Protonenpumpeninhibitoren (PPI),
- bei anhaltenden GERD Symptomen ist eine PPI-Erhaltungstherapie (mit niedriger Dosierung) indiziert.

Operation: Therapie 2. Wahl

- Eine Operationsindikation ist gegeben, wenn zusätzlich zur langfristigen Behandlungsbedürftigkeit folgende Indikationskriterien erfüllt sind: intolerable Reflux-induzierte Restbeschwerden oder eine Unverträglichkeit gegenüber der PPI-Therapie besteht.

Beschreibung der Technologie

EST neue Technologie für chirurgische GERD Therapie

Die elektrische Stimulationstherapie (EST) stellt eine neuartige Methode zur chirurgischen Behandlung von GERD dar. Die EST besteht aus drei Komponenten: einer bipolaren Stimulationsleitung mit zwei Maschenelektroden, einem implantierbaren Impulsgenerator und einem externen Programmierer [2]. Die EST-Implantat-Prozedur wird unter Verwendung von Standard-laparoskopischen Techniken durchgeführt, bei denen ein Paar Elektroden in den vorderen Teil des unteren Ösophagus platziert und an der Stelle vernäht wird [3]. Die Drähte werden dann mit einem Stimulator verbunden, der in der subkutanen Tasche im linken oberen Quadranten der Bauchwand platziert ist [3]. Das Ziel der Intervention ist es, den schwachen unteren Ösophagussphinkter (LES) durch die Bereitstellung von milden elektrischen Signalen an die LES den ganzen Tag zu verstärken. Die Stimulation zielt darauf ab, die normale Funktion der LES, die Vermeidung von Reflux aus dem Magen in die Speiseröhre, wiederherzustellen.

laparaskopischer Eingriff

elektrische Stimulation um normale LES Funktion herzustellen

Methoden

Die Beantwortung der Forschungsfragen bezüglich Wirksamkeit und Sicherheit erfolgte anhand einer systematischen Literatursuche in folgenden Datenbanken:

Suche nach Publikationen in mehreren Datenbanken

- Medline via Ovid,
- Embase,
- the Cochrane Library,
- CRD (DARE, NHS-EED, HTA)

Kontakt mit Hersteller

Zusätzlich wurde eine Handsuche durchgeführt und der Hersteller kontaktiert. Die Studienauswahl erfolgte unabhängig durch beide AutorInnen (MS, KH). Der Erstautor (MS) extrahierte die Studiendaten und die Zweitautorin (KH) kontrollierte die Daten.

4-Augenprinzip bei Studienauswahl, Extraktion der Daten, Kontrolle

Die Daten der für die Entscheidung herangezogenen Endpunkte wurden aus den einzelnen Studien zusammengefasst und nach GRADE (Grading of Recommendations Assessment, Development and Evaluation) bewertet. Zusätzlich wurde das Bias-Risiko der Studien von beiden AutorInnen unabhängig voneinander bewertet.

GRADE & Risk of Bias Beurteilung

Klinische Wirksamkeit

Zur Bewertung der Wirksamkeit des LINX® Reflux Management Systems wurde der GERD HRQL score als *entscheidend* für eine Empfehlung erachtet. Weitere *wichtige* Endpunkte waren Sodbrennen, tägliches Aufstoßen, extra-ösophageale Symptome, Absetzen oder Reduktion von PPI-Medikamenten.

entscheidender Endpunkt zur Beurteilung der Wirksamkeit: GERD HRQL

Der GERD HRQL score misst die Veränderungen in typischen GERD-Symptomen nach einer chirurgischen oder medizinischen Behandlung. Der GERD HRQL score enthält Fragen zu Sodbrennen, Schwierigkeiten beim Schlucken, Blähungen und zur Medikamenteneinnahme. Die bestmögliche Punktzahl ist 0 (asymptomatisch), die schlechteste Punktzahl ist 50.

GERD HRQL score misst GERD-Symptome:

0-50 Punkte

Sicherheit

entscheidende Endpunkte zur Beurteilung der Sicherheitt: Prozedur- und Produkt-induzierte Komplikationen

Zur Bewertung der Sicherheit wurden die folgenden *entscheidenden* Endpunkte für eine Empfehlung herangezogen:

- Erosion des Produktes
- Trokarperformation im Zuge des laparaskopischen Eingriffes

Weitere *wichtige* Endpunkte waren:

- Post-operative übermäßige Blähungen und Aufstoßen
- Übelkeit und Erbrechen
- Schmerzen, Unwohlsein

Ergebnisse

Verfügbare Evidenz

2 prospektive, einarmige Fallserien, 1 Fallregister 70 Patienten

Insgesamt konnten zwei einarmige prospektive Fallserien und ein Fallregister identifiziert werden. Da keine der Studien die Einschlusskriterien für die Bewertung der Wirksamkeit erfüllte, konnten die Studien mit einer Gesamtzahl von 70 PatientInnen nur zur Bewertung der Sicherheit herangezogen werden.

Klinische Wirksamkeit

keine Studien zur Beurteilung der Wirksamkeit

Keine Studie erfüllte die Einschlusskriterien zur Beurteilung der klinischen Wirksamkeit.

Sicherheit

Erosion und Trokarperforation in 2.4 % der PatientInnen

Aufgrund fehlender kontrollierter Studien konnten keine Vergleiche zwischen EST und der derzeitigen Standardtherapie laparoskopische Fundoplikatio (LF) durchgeführt werden. Produkt- und prozessbedingte Komplikationen wurden in einer Studie mit einem Follow-up von 6 Monaten berichtet. Erosionen im Bereich der Speiseröhre traten in 2,4 % der 42 PatientInnen auf, woraufhin die Geräte explantiert wurden. Eine Trokarperforation der Dünndarmwand im Zuge der Laparoskopie trat in 2,4 % der 42 PatientInnen ein. Es wurden keine weiteren prozess- oder produktbezogenen Komplikationen beschrieben.

Postoperative AE: Blutungen, Verstopfung, Oberbauchschmerzen, Schluckauf, gestörter Würgereflex, Fieber

Des Weiteren wurde eine Reihe kurzfristiger postoperativer Schäden berichtet (Anzahl der PatientInnen in Prozent der jeweiligen Studie): Verstopfung 2,4 %, epigastrische Schmerzen 2,4 %, Schluckauf 4,8 %, Erbrechen und Fieber 2,4 %, postoperative Blähungen/Aufstoßen in 7,1 % und 0 %, postoperative Dysphagie in 9,5 % und 0 %, Übelkeit/Erbrechen in 7,1 % und 12 % und Schmerzen/Unwohlsein in 45,2 % und 20 %. Die Patientenregisterstudie berichtete keine zusätzlichen unerwünschten Ereignisse.

Laufende Studien

1 laufendes RCT

Derzeit gibt es eine laufende randomisierte, multizentrische doppel-blinde Studie in den USA und Europa, die die Intervention im Vergleich zu einer Scheinbehandlung untersucht (NCT02749071).

Kostenerstattung

derzeit nicht erstattet

EST wird in Österreich zurzeit nicht erstattet.

Diskussion

Qualität der Evidenz gering, Bias Risiko moderat

Insgesamt war die Qualität der Evidenz, aufgrund der Fehlenden Daten aus kontrollierten Studien, der Heterogenität der Ergebnisse, und der kleinen Stichprobengröße, sehr gering. Das Gesamtrisiko für Verzerrungen wurde als moderat eingestuft. Die hochspezifische PatientInnengruppe der Studien ist nicht repräsentativ für GERD-PatientInnen, die eine chirurgische Therapie benötigen.

Vorteile der EST wären geringe Invasivität, einfache Intervention

Die wesentlichen Vorteile der EST wären die Reversibilität und die niedrigere Invasivität des Verfahrens, die vermutlich eine schnellere Rückkehr zur normalen Diät erlaubt. Die Implantation des Produktes ist mit einer kurzen Lernkurve für ChirurgInnen assoziiert. Des Weiteren weist die Intervention einen kürzeren Krankenhausaufenthalt im Vergleich zur LF auf.

Zielpopulation: GERD PatientInnen ohne LF Indikation

Im Unterschied zur LF, die nur bei schweren GERD Fällen indiziert ist, scheint allerdings die Zielpopulation für EST auch moderatere GERD PatientInnen einzubeziehen, für die LF und chirurgische Verfahren primär nicht indiziert wären. Daher ist zur Beurteilung der Wirksamkeit ein Schein-RCT essentiell, in der das Gerät implantiert, bei der Kontrollgruppe aber vorerst nicht aktiviert wird.

Entscheidende Endpunkte für zukünftige Studien und die Bewertung der Wirksamkeit und Sicherheit sollten zusätzlich Langzeitfolgen beinhalten – wie zum Bespiel die Verminderung der Zahl an Speiseröhrenkrebserkrankungen und die Haltbarkeit des Produktes.

Empfehlung

Evidenz nicht ausreichend um Wirksamkeit und Sicherheit zu bewerten

Die vorhandene Evidenz lässt keine Rückschlüsse zu, ob EST mindestens gleich wirksam und genauso sicher ist wie der Komparator LF.

Es gibt keine kontrollierten Studien, um die Wirksamkeit von EST im Vergleich zu LF oder einer Scheinbehandlung zu bewerten. Des Weiteren konnten entscheidende Sicherheitsendpunkte nur auf Basis von Daten aus prospektiven Fallserien bewertet werden. Diese deuten darauf hin, dass EST ein relativ sicheres Verfahren ist. Jedoch ist eine Bestätigung dieser Ergebnisse durch ein RCT notwendig, da dies die Empfehlung stark beeinflussen könnte.

Re-Evaluierung 2022

Eine neuerliche Evaluierung wird für 2022 empfohlen, da im Dezember 2021 das laufende Schein-RCT fertig gestellt werden wird (NCT02749071).

Aufnahme nicht empfohlen

Auf Basis der derzeit verfügbaren Evidenz wird die Aufnahme von EST in den Leistungskatalog nicht empfohlen.

1 Scope

1.1 PICO question

PIKO-Frage

Is Electric Stimulation Therapy (EST) in comparison to the standard surgical treatments (Nissen fundoplication, partial or Toupet fundoplication) in patients with chronic gastroesophageal reflux disease (GERD) more effective or equally effective concerning improvement in GERD-Health-related quality of life (HRQL), and safer regarding the post-operative side effects and serious adverse events?

1.2 Inclusion criteria

Einschlusskriterien für relevante Studien

Inclusion criteria for relevant studies are summarized in Table 1-1.

Table 1-1: Inclusion criteria

Population	Adult patients with chronic (>6 months) GERD, diagnosis based on 24 pH monitoring, LES end-expiratory pressure of 5-15 mmHg, peristaltic contractions seen in ≥50% of swallows with a contraction amplitude of ≥30 mmHg during baseline esophageal manometry, typical symptoms of GERD (heartburn, or regurgitation), esophagitis grade C or lower (LA classification), and at least partial response to therapeutic medication with PPIs as 2nd line treatment. MeSH-term: Electric Stimulation Therapy, Electric Stimulation
Intervention	Electric stimulation therapy device (EST) inserted through laparoscopic surgery Product name: EndoStim® LES Stimulator MeSH-term: Gastroesophageal reflux, Gastrooesophageal reflux
Control	❁ Sham treatment (placebo) ❁ Standard surgical treatment of GERD: Nissen fundoplication, partial or Toupet fundoplication ❁ PPI therapy
Outcomes	
Efficacy	Clinical endpoint: ❁ GERD-Health-related quality of life (HRQoL) Intermediate outcomes: ❁ Heartburn ❁ Regurgitation ❁ Extra-esophageal symptoms ❁ Discontinuation of anti-reflux medication (PPIs) ❁ Improvement in LES pressure
Safety	Adverse events (AEs), serious adverse events (SAEs): ❁ Dysphagia ❁ Excessive bloating ❁ Inability to belch or vomit ❁ Operation related complications ❁ Device related complications (migration, erosion, malfunction, removal, removal) ❁ Re-hospitalisation ❁ Re-operation

Study design	
Efficacy	Randomised controlled trials (RCTs) Prospective non-randomised controlled trials (CTs)
Safety	Randomised controlled trials Prospective non-randomised controlled trials Prospective single-arm studies, registries

2 Methods

2.1 Research questions

Description of the technology	
Element ID	**Research question**
B0001	What is electric stimulation therapy (EST) and the alternative standard treatment option(s)?
B0002	What is the claimed benefit of the EST in relation to the alternative standard treatment option?
B0003	What is the phase of development and implementation of the EST and the alternative standard treatment option?
B0004	Who administers the EST and fundoplication and in what context and level of care are they provided?
B0008	What kind of special premises are needed to use the EST and the alternative standard treatment options?
B0009	What supplies are needed to use the EST and the alternative standard treatment option?
A0020	For which indications has the electric stimulation therapy device (ESTD) received marketing authorisation or CE marking?
A0021	What is the reimbursement status of the EST?

Health problem and Current Use	
Element ID	**Research question**
A0001	For which health conditions and for what purposes is the EST used?
A0002	What is the disease or health condition in the scope of this assessment?
A0003	What are the known risk factors for gastrooesophageal reflux disease (GERD)?
A0004	What is the natural course of GERD?
A0005	What is the burden of GERD for the patients with the disease or health condition?
A0006	What are the consequences of GERD for the society?
A0024	How is GERD currently diagnosed according to published guidelines and in practice?
A0025	How is GERD currently managed according to published guidelines and in practice?
A0007	What is the target population in this assessment?
A0023	How many people belong to the target population?
A0011	What is the expected annual utilisation of the EST?

Clinical Effectiveness	
Element ID	**Research question**
D0001	What is the expected beneficial effect of the EST on mortality?
D0005	How does the EST affect heartburn, regurgitation, and extraesophageal symptoms?
D0006	How does the EST affect the continuation with PPI therapy?
D0011	What is the effect of the EST on dysphagia and bloating?
D0016	How does the EST affect activities of daily living?
D0013	What is the effect of the EST on disease-specific quality of life?
D0017	Were patients satisfied with the EST?

Safety	
Element ID	**Research question**
C0008	How safe is the EST in comparison to LF?
C0002	Are there harms related to dosage or frequency of applying the technology?
C0004	How does the frequency or severity of harms change over time or in different settings?
C0005	What are the susceptible patient groups that are more likely to be harmed through the use of the technology?
C0007	Are EST and LF associated with user-dependent harms?
B0010	What kind of data/records and/or registry is needed to monitor the use of EST and LF?

2.2 Sources

Description of the technology

Quellen

- Handsearch in the POP, MDS, Syngerus, Ohtanen and CRD databases for Health Technology Assessments
- Background publications identified in database search: see Section 2.3
- Documentation provided by the manufacturers

Health problem and Current Use

- Handsearch in the POP, MDS, Syngerus, Ohtanen and CRD databases for Health Technology Assessments
- Background publications identified in database search: see Section 2.3
- Documentation provided by the manufacturers
- Erdös J, Stanak M. Magnetic Sphincter Augmentation Device (MSAD) in patients with gastroesophageal reflux disease (GERD). Decision Support Document No. 101; 2016. Vienna: Ludwig Boltzmann Institute for Health Technology Assessment.

2.3 Systematic literature search

systematische Literatursuche in 5 Datenbanken

The systematic literature search was conducted from January 2nd to February 3rd in the following databases:

- Medline via Ovid
- Embase
- The Cochrane Library
- CRD (DARE, NHS-EED, HTA)
- PubMed

At the time of the systematic literature search, no limitations to the study design were applied. In addition, handsearch of literature (web-search) was performed. After deduplication, overall 345 citations were included. The specific search strategy employed can be found in the Appendix.

EndoStim Inc., the manufacturer of EndoStim® LES Stimulator, submitted 28 publications of which 0 new citations were identified.

By hand-search, an additional 22 citations were found, resulting in overall 367 hits.

insgesamt 367 Publikationen identifiziert

2.4 Flow chart of study selection

Overall, 367 hits were identified. The references were screened by two independent researchers (MS, KH) and in case of disagreement, a third researcher was involved to solve the differences. The selection process is displayed in Figure 2-1.

Literaturauswahl

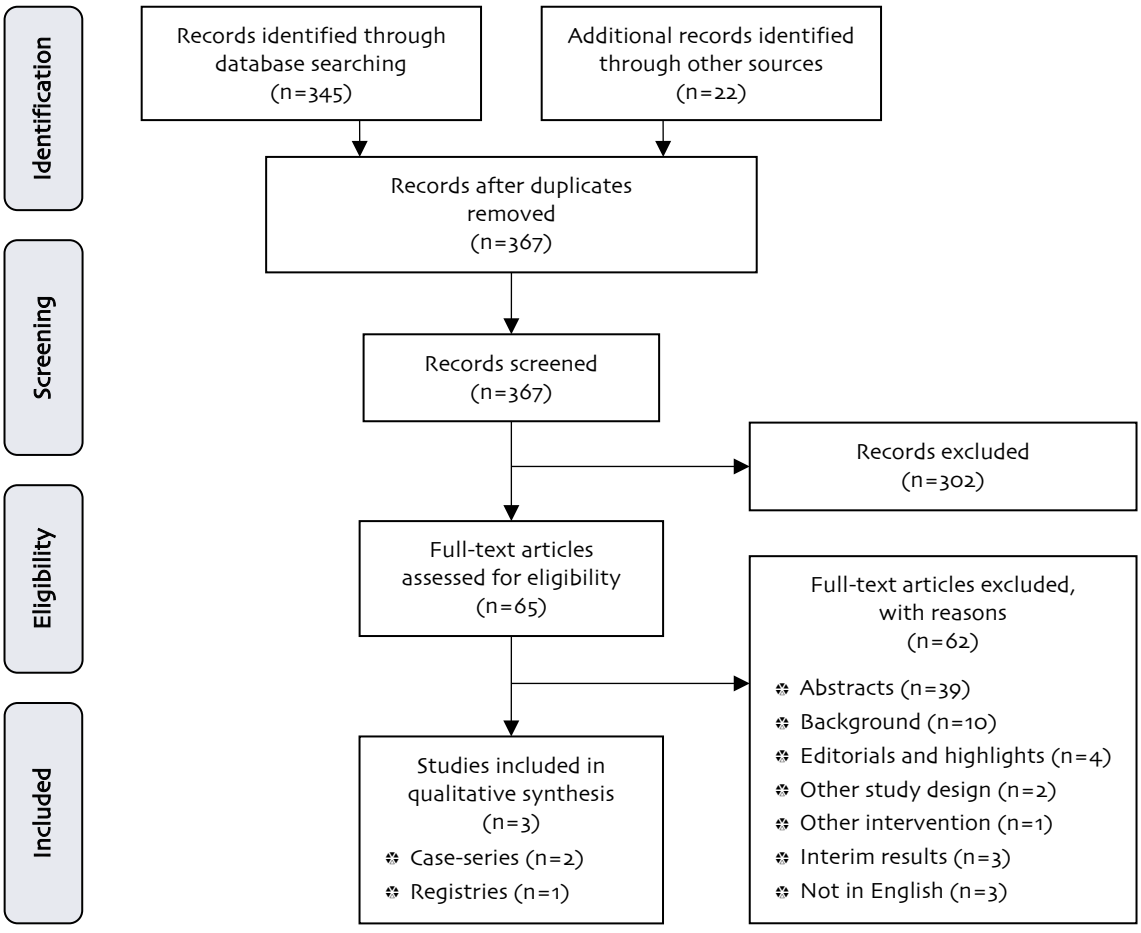


Figure 2-1: Flow chart of study selection (PRISMA Flow Diagram)

2.5 Analysis

Systematische Datenextraktion

The data retrieved from the selected studies were systematically extracted into a data-extraction-table (see Appendix Table A-1). No further data processing (e.g. indirect comparison) was applied. Two independent researchers (MS, KH) systematically assessed the quality of evidence (see Table 7-1) and the risk of bias using the checklists presented in the Appendix Table A-2).

2.6 Synthesis

Zusammenfassung der Ergebnisse mit GRADE

Based on the data-extraction-table (see Appendix Table A-1), data on each selected outcome category were synthesised across studies according to GRADE (Grading of Recommendations Assessment, Development and Evaluation) [6]. The research questions were answered in plain text format with reference to GRADE evidence tables (see Table 7-1).

3 Description and technical characteristics of technology

Features of the technology and comparators

B0001 – What is electric stimulation therapy (EST) and the alternative standard treatment option?

The EST comprises of three components: a bipolar stimulation lead with two stitch electrodes, an implantable pulse generator (IPG), and an external programmer (see Figure 3-1) [2]. The stimulation lead is 45 cm long and has sterile bipolar, stitch platinum-iridium electrodes at the end. The IPG is made of hermetically sealed titanium case construction (size 65x48x12 mm and weight 49 g), it is connected to the stimulation leads, and permanently implanted in a subcutaneous pocket in the left upper quadrant of the abdomen [2]. The IPG contains a medical grade lithium battery, microelectronics, communication coils, and an accelerometer for sensing patient posture [2]. The IPG is programmed by an external programmer via laptop PC software [2].

EST besteht aus 3 Komponenten: Stimulationsdraht mit 2 Elektroden, implantierbarer Pulsgenerator, externer Programmierer

The EST implant procedure is performed using standard laparoscopic techniques. A pair of electrodes are placed in the anterior part of the lower esophagus 1 cm apart and sutured in place [3]. Endoscopic visualization of the gastroesophageal junction is used to ensure that the wires do not enter the lumen [7]. The wires are then connected to a stimulator placed in the subcutaneous pocket in left upper quadrant of the abdominal wall [3]. It is recommended that the patient wears an elastic compression bandage over the pulse generator implantation site for 10-14 days in order to reduce the chances of seroma formation [8].

Implantation erfolgt mittels Standard laparaskopischem Eingriff

The stimulator may be switched on or off remotely, and the polarity of its current and pattern of stimulation can be modulated. Patients are not supposed to be aware of the stimulators activity [3]. The electrical stimulation is initiated 12 hours after the implant procedure. The current is applied intermittently through the day in specified time periods and can be personalized. Electrical stimulation is delivered using a 215-ls pulse at 20 Hz and 3-8 mA in 30 min sessions, 6-12 time per day [5, 8].

Durch die externe Programmierung kann der Stimulator an und ab geschalten werden, sowie die Polarität und Stromstärke adaptiert werden

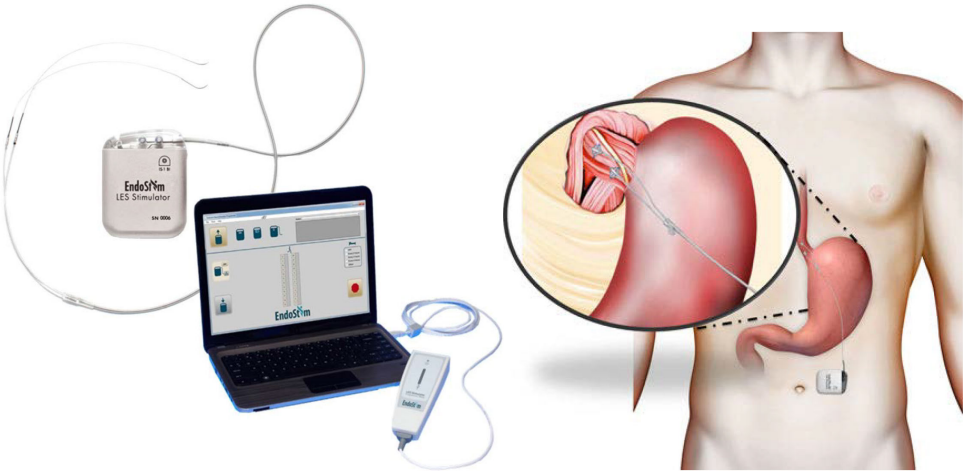


Figure 3-1: The EST device parts and the EST electrode position and IPG implant location [5, 7]

Marketed products

derzeit ist EndoStim® das einzige zugelassene Produkt

There is currently only one EST on the market, the EndoStim® LES Stimulator developed by EndoStim Inc. [3]. The EndoStim® device has two generations. The first-generation device, EndoStim I®, has a larger battery lasting approximately 10 years. The second-generation device, EndoStim II®, is 25% thinner and has 40% less volume [9]. EndoStim II® has a battery lasting approximately 7 years. Correspondence with EndoStim Inc. indicated that the therapy delivered as well as the lead and electrodes used are identical in both devices.

2 Generationen des Produktes sind am Markt

Hauptunterschied zw EndoStim I® und EndoStim II®: Kompatibilität mit MRT scannern

The main difference between EndoStim I® and EndoStim II® lies in their compatibility with Magnetic Resonance Imaging (MRI) scans. EndoStim II® announced the CE Mark approval for full body scans using 3.0 Tesla MRI machines in October 2015. Imaging of the head and extremities may also continue to be performed using both 1.5-Tesla and 3-Tesla systems [10]. In the United States, EndoStim II® seeks approval by the FDA and is currently allowed for investigational use only [11].

Current standard procedure

Chirurgische Standardmethode: Fundoplikatio

The current standard surgical treatment of GERD means wrapping the fundus of the stomach around the esophagus to create a new valve at the level of the esophagogastric junction, a technique called fundoplication. Options include Nissen fundoplication and partial or Toupet fundoplication.

Nissen Fundoplikatio: vollständige Manschette wird um Ösophagus gelegt

- Nissen fundoplication is currently the gold-standard and the most common surgical treatment with around 2000 procedures carried out in Austria per annum. It was first performed in 1955 by an open technique, but it is now typically carried out laparoscopically. High-quality evidence suggests the superiority of laparoscopy to open surgery concerning early outcomes (hospital stay, fewer complications) with no significant differences in late outcomes; although the reoperation rate is higher in the short-term [12, 13]. It is a complete or total wrap that encompasses 360° of the esophagus in a posterior fashion.

partielle Fundoplikatio: 270 Grad Manschette

- Partial fundoplication has two versions, but only one is recommended for the treatment of GERD, i.e Toupet fundoplication (posterior wrap), which covers roughly 270° of the posterior esophagus [13]. Partial fundoplication is associated with less post-operative dysphagia, fewer re-operations, and its effectiveness is similar to total fundoplication in terms of controlling GERD symptoms up to five years after surgery. However, there are concerns about the long-term effectiveness of partial fundoplication [12].

keine standardisierte Operationstechnik

Laparoscopic fundoplication (LF) is technically difficult and it may be performed differently by different surgeons, which has a high impact on patient outcomes. Although the most common is a loose (floppy) Nissen fundic wrap including a posterior hiatal hernia repair, the surgical technique has yet to be standardized to improve patient outcomes.

4-6 Wochen Rekonvaleszenz, zunächst nur flüssige Nahrung

The recovery time can be 4-6 weeks and patients may need to be on a pure liquid diet for one week after surgery before they can gradually start a soft food diet [14].

Hiatal hernia and its repair

Hiatushernie Reparatur in Antireflux Chirurgie

The esophagus passes through an opening in the diaphragm (the oesophageal hiatus) before it joins the stomach. If the stomach slips through the diaphragm into the chest, a condition called hiatal hernia develops. Hiatal hernia might be a cause of GERD [15], therefore, depending on its size, it is often repaired (posterior crural repair) at the time of anti-reflux surgery at the surgeons' discretion to ensure the success of the anti-reflux surgery. A sliding hernia of up to 3 cm can be effectively repaired by approximating the crura with interrupted stiches [16].

Hiatal hernia repair can be done in both interventions. Fundoplication allows for a concurrent hiatal hernia repair. LF is recommended for patients with hiatal hernia >2 cm or patients with their gastroesophageal junction in the chest [14].

B0002 – What is the claimed benefit of the EST in relation to the alternative standard treatment option?

Potentielle Vorteile: Weniger invasiver und kürzerer Eingriff, Reversibilität, einfachere Prozedur für Chirurgen

The claimed major benefits of the EST compared to LF are its lesser invasiveness and reversibility [17]. The laparoscopic insertion of the device requires little dissection and few steps, therefore, the operative time is shorter. The operation technique is less difficult, hence, its reproducibility is higher and the learning curve for the surgeon is also expected to be shorter [12, 18]. The EST procedure claims to be associated with fewer side-effects and a shorter hospital length of stay [4].

B0003 – What is the phase of development and implementation of the EST and the alternative standard treatment option?

Neue Technologie

Laufendes mulitzentrisches RCT soll Daten zur Wirksamkeit vorweisen

The EST was first implanted in a clinical setting in Chile in a single-centre, prospective, open-label case series (NCT01578642) in 25 patients [8]. Correspondence with the manufacturer suggests that device was first impanted in October 2010 and since then, 564 devices have been implanted. The EST is a novel technology that is in its emerging phase and hence, it is not part of the standard practice. Current clinical trials are investigating the use of the EST in other subgroups of GERD patients (after laparoscopic sleeve gastrectomy) that have been so far excluded from the use of the device [19]. Correspondence with EndoStim Inc. indicated that there is an ongoing study in the US and Europe that is a multicenter, randomized, double-blind, sham-controlled clinical trial (NCT02749071), including results of the previously interrupted European RCT (NCT02514616). This trial is supposed to serve as the basis for evaluation of efficacy of the EST for FDA approval. New versions of the device with substantial improvements are not expected in the near future.

verbesserte Versionen des Produktes sind nicht in Planung

chirurgische Standardmethode: Fundoplikatio

Fundoplication was first performed in 1955 and has become the standard surgical anti-reflux treatment. It has several modifications, of which two (Nissen and Toupet) are most commonly used and accepted in the clinical practice.

Administration, Investments, personnel and tools required to use the technology and the comparator(s)

B0004 – Who administers the EST and fundoplication and in what context and level of care are they provided?

B0008 – What kind of special premises are needed to use the EST and the alternative standard treatment options?

B0009 – What supplies are needed to use the EST and the alternative standard treatment option?

Fundoplikatio sollte nur in GERD-Zentren mit hoher PatientInnen-Frequenz durchgeführt werden

Both the EST and LF are performed under general anaesthesia by a foregut surgeon. The guidelines suggest that LF is to be done in high-volume centres by experienced foregut surgeons. Surgeons with little experience should have expert supervision during their early experience with the procedure to minimize morbidity and improve patient outcomes [12].

The premises, the operation team, and the supplies are similar; the only difference is the device itself.

Regulatory & reimbursement status

Indikation: chronische GERD PatientInnen mit anhaltenden Symptomen > 6 Monaten

A0020 – For which indications has the electric stimulation therapy device (ESTD) received marketing authorisation or CE marking?

The EndoStim® LES Stimulation System is intended for the treatment of patients with chronic GERD with symptom duration of 6 months or longer [9].

A0021 – What is the reimbursement status of the EST?

bislang nicht erstattet

Kosten: 8.240 € Materialkosten

Im Vergleich zu Fundoplikatio: Materialkosten, Erstausbildung von ChirurgInnen sind ein Zusatz, führt aber zu kürzeren OP-Zeiten

To our knowledge, the EST is only reimbursed in Germany. The costs associated with the EST operation include the price of the device (8.240 €), and the operation procedure (facilities, staff, anaesthesia, hospital stay). The information about the former was provided by the manufacturer.

In comparison to fundoplication, the material costs (device) and the initial training of surgical staff to undertake the implantation procedure are additional to the costs of the LF operation procedure; although the EST procedure might cost slightly less due to its shorter operation time. The EndoStim® device is reimbursed in the German DRG-System up to the amount of 12.508,49 €. In Austria, there are currently one centre where the EST is available.

4 Health Problem and Current Use

Overview of the disease or health condition

A0001 – For which health conditions and for what purposes is the EST used?

A0002 – What is the disease or health condition in the scope of this assessment?

The EST is used in patients with GERD, which is defined according to the Montreal consensus as a condition that develops when the reflux of stomach contents causes troublesome symptoms and/or complications. Symptoms are considered troublesome if they adversely affect an individual's well-being [1]. The EST is a second-line treatment for GERD patients in whom PPI medication failed to achieve complete symptom alleviation, symptoms recur despite initial successful medication, and for those who refuse to take life-long medication or suffer from side-effects of PPI therapy. The main aim of the EST is alleviation of symptoms by strengthening the weak LES, the anatomical cause of GERD. The EST is not curative, but long-term (life-long) use is essential to maintain the treatment effect.

GERD:
Reflux aus dem Magen in die Speiseröhre

EST:
2.Linie Behandlung nach Therapieversagen für chronische GERD-PatientInnen

From the surgical perspective, GERD is the failure of the anti-reflux barrier, which, when functioning improperly, allows abnormal reflux of gastric contents into the esophagus. It is a mechanical disorder caused by a defective LES, a gastric emptying disorder, or failed esophageal peristalsis. The abnormalities result in a spectrum of disease ranging from symptoms only, such as heartburn, to esophageal tissue damage with or without subsequent complications, including malignancy or airway disease [1].

Symptome:
Sodbrennen, Aufstoßen, Magenschmerzen

Reflux can be categorized based on symptoms or based on its nature.

Symptom based approach differentiates between typical and atypical symptoms:

- Typical symptoms: heartburn, regurgitation, epigastric pain.
- Atypical symptoms: chronic cough, hoarseness, globus, dysphagia, chest pain, chronic aspiration, bronchitis, sinusitis.

typische und atypische Symptome

Based on its nature, GERD can be acid or non-acid.

- Acid reflux with a pH<4.0
- Non-acid reflux with a pH>4.0

acid oder non-acid Refluxkrankheit

Non-acid reflux is poorly understood yet [14].

A generally accepted definition on the severity of GERD is lacking. Based on the frequency and severity of the experienced reflux symptoms, expressions used in the literature range from mild, through moderate, to severe GERD. However, there is no explicit definition clarifying the duration and measurement of the symptoms.

Schweregrade:
mild, moderat, schwer

A0003 – What are the known risk factors for gastrooesophageal reflux disease (GERD)?

There are anatomical and patient factors that can contribute to the development of reflux. The anatomical factors are related to the LES, the diaphragmatic crura, and the phrenoesophageal ligament. The patient factors include diet and lifestyle, as well as obesity. Eating refluxogenic foods, overeating,

anatomische Faktoren, Ernährung & Lebensstil

eating immediately before going to bed, increased fat consumption in the diet, and expanding proportion of obese individuals are significant risk factors for GERD. In obese patients, the intra-gastric pressure and the frequency of transient LES relaxations is chronically increased, which is thought to be the cause of GERD [14, 20].

A0004 – What is the natural course of GERD?

ungeklärter natürliche Verlauf

The natural history of the disease has not been well clarified yet. Currently, two concepts exist:

Spektrum beginnend mit nicht-erosivem Reflux (NERD), der sich zu GERD entwickelt

GERD Komplikationen: erosiver Ösophagitis, Stenose, Barrett-Ösophagus

- The traditional concept sees the disease as a spectrum that starts with non-erosive reflux disease (NERD) and might progress to complicated GERD (erosive esophagitis, stricture, Barrett's esophagus (BE)). This concept focuses on esophageal mucosal injury as the most significant clinical outcome in GERD. Patients with severe esophagitis are at high risk of developing a stricture and long-standing reflux symptoms are a major risk for developing BE. Patients with BE have an increased risk of esophageal adenocarcinoma with a 40 times greater incidence than in the general population [20].

neues Konzept: 3 individuelle Beschwerden (NERD, erosive Ösophagitis, Barrett-Ösophagus)

- The new concept considers GERD as a categorical disease with three distinct entities: NERD, erosive esophagitis, and BE. According to this concept, these are different disorders and the movement among them is limited. This concept focuses on mechanisms leading to symptom generation rather than mucosal injury. Some studies suggest that GERD is a chronic disease that is not progressive. However, other studies confirm that progression of NERD to erosive esophagitis is possible in 10% of GERD patients [20].

Both of these concepts assume that NERD might progress to GERD, it is debated though to what extent.

Effects of the disease or health condition on the individual and society

A0005 – What is the burden of GERD for the patients with the disease or health condition?

Lebensqualität

Quality of life is impacted through the experience of GERD symptoms such as heartburn, extra-esophageal manifestations (pulmonary or ear, nose, throat), or non-cardiac chest pain [21].

Lebensstil, Ernährung

lebenslange Medikation

Patients often complain about sleep disturbance. Their diet is also affected as the foremost treatment suggested is life-style and diet modification. Presumably, they also need to take life-long medication that may have serious side effects, be badly tolerated, alter the absorption of minerals and vitamins, have metabolic effects on bone density, pharmacokinetics or pharmacodynamics and related drug interactions and effects, or enhance the infection risk and hypersensitivity response with consequent organ damage [17].

A0006 – What are the consequences of GERD for the society?

zunehmende Häufigkeit, wachsende Ressourcennutzung

Due to its increasing incidence (approximately 5 per 1,000 person-years in the Western world [22]), GERD is leading to a growing utilisation of health resources (medical consultations, emergency room visits, hospitalization, and medication). Not only the doctor visits and diagnosis carry high financial expenses, but also the medication and the operation costs need to be considered in the long run [23].

The burden of disease on the individual affecting work productivity results in substantial societal burden and employer costs [17].

Current clinical management of the disease or health condition

A0024 – How is GERD currently diagnosed according to published guidelines and in practice?

ACG & AWMF: Richtlinien zur Diagnose der Refluxkrankheit

According to the American College of Gastroenterology (ACG) and the Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF) Guidelines [24, 25], the recommendations for the diagnosis of GERD (along with the level of evidence and the level of strength of the recommendation) are the following:

- A presumptive diagnosis of GERD can be established in the setting of **typical symptoms of heartburn and regurgitation**. Empirical medical therapy with PPIs is recommended in this setting (strong recommendation, moderate level of evidence).
- Patients with **non-cardiac chest pain** suspected due to GERD should have **diagnostic evaluation** before the institution of therapy (conditional recommendation, moderate level of evidence). A cardiac cause should be excluded in patients with chest pain before the commencement of a gastrointestinal evaluation (strong recommendation, low level of evidence).
- **Upper endoscopy** is recommended in the presence of alarm symptoms and for screening of patients at high risk for complications (strong recommendation, moderate level of evidence).
- **Ambulatory esophageal reflux monitoring** is indicated before the considerations of endoscopic or surgical therapy in patients with NERD, as part of the evaluation of those patients who are refractory to PPI therapy and in situations when the diagnosis of GERD is in question (strong recommendation, low level evidence). Ambulatory reflux monitoring is the only test that can assess reflux symptom association (strong recommendation, low level of evidence).

A0025 – How is GERD currently managed according to published guidelines and in practice?

ACG & AWMF: schrittweises Vorgehen bei Interventionen

The management of GERD is aligned with the severity of symptoms. The ACG and AWMF Guidelines [24, 25] suggest a stepwise approach that starts with lifestyle modifications including:

- **Weight loss** for GERD patients who are overweight or have had recent weight gain (conditional recommendation, moderate level of evidence). — Gewichtsverlust
- **Head of bed elevation** and **avoidance of meals 2-3 hours before bedtime** for patients with nocturnal GERD (conditional recommendation, low level of evidence). — Vermeidung von Mahlzeiten vor Zubettgehen

From *mild to moderate* severity symptoms, first a

- **H2-receptor antagonist (H2RA) therapy** is recommended. This can be used as a maintenance option in patients without erosive disease if patients experience heartburn relief (conditional recommendation, moderate level of evidence). — H2RA Therapie

If H2RA therapy is not sufficient and the patient has *moderate to severe* symptoms:

8 Wochen PPI

- An **8-week course of PPIs** is the therapy of choice for symptom relief and healing of erosive esophagitis. There are no major differences in efficacy between the different PPIs (strong recommendation, high level of evidence).

PPI mit niedriger Dosierung indiziert

- **PPI therapy** should be initiated at **once a day dosing** before the first meal of the day (strong recommendation, moderate level of evidence).
- For patients with **partial response to once daily PPI therapy**, tailored therapy with **adjustment of dose timing and/or twice daily dosing** should be considered (strong recommendation, low level of evidence). Switching to a different PPI may provide additional symptom relief (conditional recommendation, low level evidence).

PPI-Erhaltungstherapie

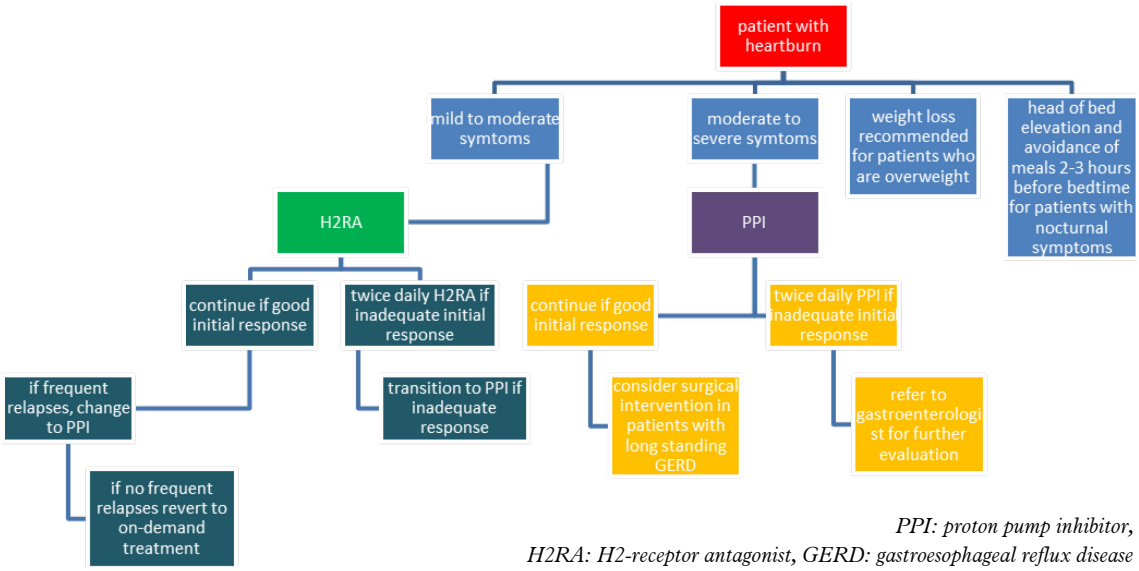
- **Maintenance of PPI therapy** should be administered for GERD patients who continue to have symptoms after PPI is discontinued and in patients with complications including erosive esophagitis and BE (strong recommendation, moderate level of evidence). For patients who require long-term PPI therapy, it should be administered in the lowest effective dose, including on demand or intermittent therapy (conditional recommendation, low level of evidence).
- **Non-responders to PPIs** should be referred for **evaluation** (conditional recommendation, low level of evidence).

Recommendations number 1-2 can only prevent approximately 20% of patients from a relapse. The relapse rate after discontinuation of the medication accounts for 90% [26].

refraktär GERD: kein standardisierter Management-Algorithmus

For patients with refractory GERD, there is no standardized management algorithm. The primary goal of the treatment is symptom reduction and eventual elimination [21].

The management of GERD is displayed in the following figure.



PPI: proton pump inhibitor, H2RA: H2-receptor antagonist, GERD: gastroesophageal reflux disease

Figure 4-1: Algorithmic approach to medical treatment of GERD [17]

Operation: Therapie 2.Wahl

Life-style modifications and medical treatment are the first-line therapy options. Surgical management is the second-line treatment. Before considering surgery, objective documentation of the gastroesophageal reflux is mandatory. Surgical therapy should be considered in patients who:

Indikationsstellung für OP: moderate/schwere GERD, PPI-Therapieversagen, PPI-Nebenwirkungen, GERD Komplikationen

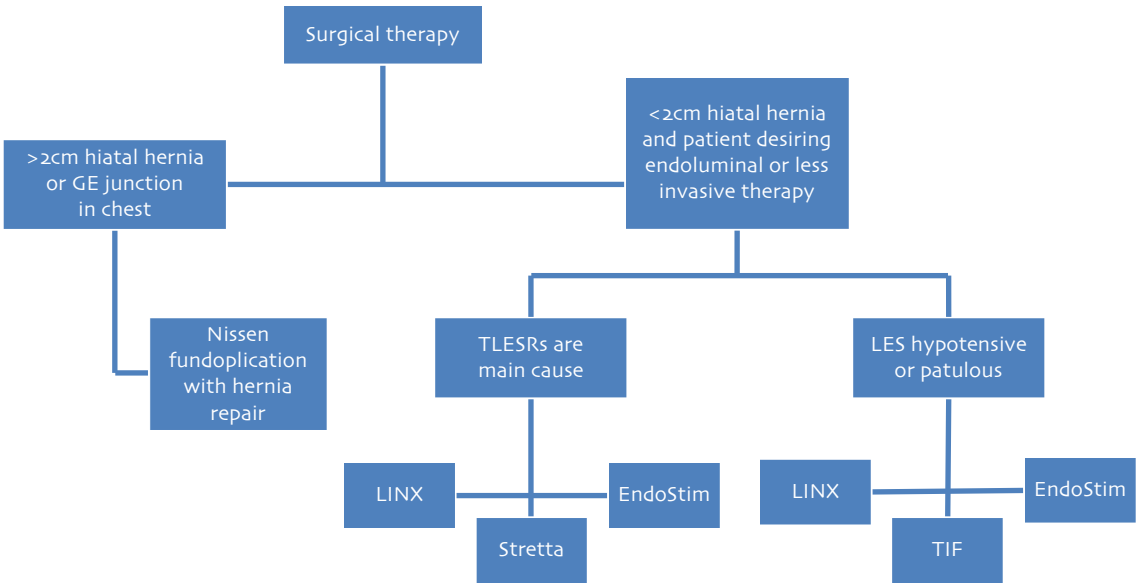
- have failed medical management (inadequate symptom control, severe regurgitation not controlled with acid suppression, or medication side effects);
- opt for surgery despite successful medical management (due to quality of life considerations, lifelong need for medication intake, price of medications, etc.);
- have complications with GERD (e.g. BE, peptic stricture);
- have extra-esophageal manifestations (asthma, hoarseness, cough, chest pain, aspiration).

The coexistence of Barrett's esophagus with gastroesophageal reflux symptoms is considered a clear indication for antireflux surgery. Surgical intervention for asymptomatic BE is, however, more controversial [1, 27].

It is important to note that there is no one best operation for all patients. Factors such as the degree of esophageal shortening, local expertise with laparoscopic techniques, prior operations and esophageal motility disorders, and the size of the hiatal hernia can influence the choice of operation [27].

Entscheidungsbaum in Antireflux Chirurgie

Choice of surgical procedure is displayed in the following figure:



TLESR: Transient lower esophageal sphincter relaxation; TIF: trans-oral incisionless fundoplication, LES: lower esophageal sphincter

Figure 4-2: Decision tree in anti-reflux surgical therapy, adapted [14]

Target population

A0007 – What is the target population in this assessment?

The target population in this assessment is adult patients with moderate to severe GERD, who are considered for surgical treatment due to incomplete symptom control despite maximum medication treatment or severe complications associated with PPI therapy.

A0023 – How many people belong to the target population?

Prävalenz 15 %
25-42 % der PatientInnen sind einmal pro Tag PPI-refraktär
42 % unzufrieden mit PPI-Therapie

The prevalence of GERD is around 15% [1, 24] and the incidence is increasing. It is the most common upper gastrointestinal disease in the Western countries with 10-20% of the population experiencing weekly symptoms [20]. 25-42% of patients are refractory to a once-daily PPI, 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 [21].

According to data from the Hauptverband, in 2014 in Austria, the Code LM030 (open fundoplication/hiatusplasty) was reimbursed 98 times, the LM040 (laparoscopic fundoplication/hiatusplasty) was refunded 1,723 times.

A0011 – What is the expected annual utilisation of the EST?

jährlich 100 Interventionen

The expected annual utilisation of EST, according to the Hauptverband, based on the previous years' experience, is 100 interventions per year in Austria.

5 Clinical effectiveness

5.1 Outcomes

The following outcomes were defined as *crucial* to derive a recommendation:

- GERD HRQL

QoL ist wichtigster Endpunkt für Empfehlung

Further outcomes considered were:

- Heartburn
- Regurgitation
- Discontinuation with medication (PPIs)
- Esophagitis

weitere relevante Endpunkte: Sodbrennen, Aufstoßen, Absetzen der PPI Medikation, Ösophagitis

GERD health-related quality of life score:

GERD HRQL score misst GERD-Symptome

Since, according to the traditional concept, GERD is a degenerative disease, the ultimate aim of the EST is to stop the process of degeneration by improving the function of the esophageal sphincter and thus improving the quality of life. Hence, GERD health-related quality of life (HRQL) score is considered a relevant primary outcome as the score represents a summation of patient-relevant items. It measures changes in typical GERD symptoms in response to a surgical or medical treatment and so includes questions about heartburn, difficulty with swallowing, bloating, and medication intake. The best possible score is 0 (i.e., asymptomatic in each item) and the worst possible scores is 50 (incapacitated in each item). It also reflects on patient satisfaction as it includes a question worded „How satisfied are you with your present condition?" This item is a numerical score and it is not reflected in the total GERD-HRQL score (21).

5.2 Included studies

Study characteristics and results of included studies are displayed in Table A-1 and Table A-2 and in the evidence profile in Table 7-1.

keine Studie erfüllte Einschlusskriterien

No study fulfilled the study inclusion criteria for assessing clinical effectiveness of the EST. RCTs and non-randomised CTs were considered for inclusion, but could not be identified through the systematic literature search (see Figure 2-1).

The systematic literature search (see Figure 2-1) did not identify any comparative trials matching our inclusion criteria for efficacy. The two prospective case series [4, 5] and one prospective registry study [28] are described in the results on safety.

5.3 Results

Mortality

keine Evidenz zu Mortalität und Morbidität

D0001 – What is the expected beneficial effect of the EST on mortality?

No evidence was found to answer the research question.

Morbidity

D0005 – How does the EST affect heartburn, regurgitation, and extraesophageal symptoms?

No evidence was found to answer the research question.

keine Evidenz zu Absetzen der PPI Medikation, Schluckstörungen und Blähungen

D0006 – How does the EST affect the continuation with PPI therapy?

No evidence was found to answer the research question.

Function

D0011 – What is the effect of the EST on dysphagia and bloating?

No evidence was found to answer the research question.

D0016 – How does the EST affect activities of daily living?

No evidence was found to answer the research question.

Health-related quality of life

keine Evidenz zu ADL GERD HRQL Patientenzufriedenheit

D0012 – What is the effect of the EST on disease-specific quality of life?

No evidence was found to answer the research question.

Patient satisfaction

D0017 – Were patients satisfied with the EST?

No evidence was found to answer the research question.

6 Safety

6.1 Outcomes

The following outcomes were defined as *crucial* to derive a recommendation:

- Device erosion
- Trocar perforation of the small bowel during laparoscopy

entscheidende Saftey Endpunkte:
Erosion des Produktes, Trokarperforation

Further outcomes considered were:

- Post-operative bloating/belching
- Post-operative dysphagia
- Nausea/vomiting
- Pain/discomfort

weitere Endpunkte:
postoperative Schluckstörungen, Übelkeit, Erbrechen, Schmerz

6.2 Included Studies

The study inclusion criteria for assessing safety differed from the ones for assessing clinical effectiveness. In addition to RCTs and non-randomised CTs, prospective studies without a control group (interventional single arm studies, case series, and registry studies) were considered for the assessment of safety. The systematic literature search (see Figure 2-1) identified two prospective case series [4, 5] and one prospective registry study [28], which matched our inclusion criteria. Study characteristics and results of included studies are shown in Table A-1 and Table A-2, and in the evidence profile in Table 7-1.

2 prospektive Fallserien, 1 prospektives Fallregister

Study characteristics

Overall, out of the total of 70 patients included in the studies, baseline characteristics data were reported on 67 patients, of which 29 were women and 38 were men. The registry study included 18 patients, but reported on 15 patients, of which 7 were women and 8 were men [28]. All three studies were sponsored by the manufacturer EndoStim Inc. Countries of recruitment were Colombia, India, Netherlands, Mexico, New Zealand, United Kingdom [4], and Chile [4, 5, 28]. Study recruitment times were October 2010 until January 2011 in the single center sace series [5], and April 2011 until July 2014 in the multi-centre case series [4], as stated by the manufacturer. Clinical follow-up time ranged from 6 months to 3 years. Loss to follow-up ranged from 6.8-19.2%. Model versions of the technology (generations of EndoStim®) were not reported in any of the studies. The multi-centre case series study included 44 patients [4], the single-centre case series included 26 [5], and the registry 18 patients [5, 28]. The registry study was a continuation of the single centre case series [5, 28].

insg. 70 PatientInnen
alle Studien finanziert durch den Hersteller

Follow- up:
6 Monate bis 3 Jahre

Patient characteristics

The mean age of patients varied between 49.6 [4]-56.1 [28]. The mean BMI ranged from 27.2-27.7 [4, 5]. There were differences in the presence of a hiatal hernia in the multi-centre [4] and the single centre study [5]: 39-88% of patients had no hiatal hernia, 8-22% of patients had hiatal hernia <2 cm, and

Durchschnittl. Alter:
zw 50 und 60 Jahren
Median BMI: 27

4-39% of patients with hiatal hernia >2 cm. The mean number of years that patients used PPIs was not stated in one study [4] and, in the remaining two studies, it was 5.6 [5] and 5.0 [28]. The mean number of years that patients experienced GERD symptoms prior to the study was not stated in one study [4] and, in the remaining two studies, it was 11 [5] and 12.2 [28].

Patient inclusion and exclusion criteria of the single centre case series and the single centre registry were the same at baseline, however, the inclusion criteria for the patients that continued in the registry were not reported.

gemeinsame Einschlusskriterien: vorangegangene GERD Symptomatik, PPI Medikation, Ösophagitis, usw.

The inclusion criteria shared by both case series were: previous reflux symptoms, prior PPI use, esophagitis grade ≤C, diagnosis based on 24-h pH monitoring result, LES end-expiratory pressure of 5–15 mmHg, peristaltic contractions in ≥50% of swallows (respectively in 70% of swallows[5]) with contraction amplitude of ≥30 mmHg oesophageal manometry, and excessive lower esophageal acid exposure as pH <4.0 for ≥5% of the total time [4, 5].

In contrast, the two case series showed also several differences. The age range varied from 21-80 [4] to 21-65 years [5]. Improvement in GERD-HRQL score ≥20 off PPIs and ≥10 on PPIs was an inclusion criterion in the single centre study [5], while in the multi-centre study, the increase of ≥5 on PPIs was sufficient [4]. ASA Physical Status Classification ≤II was an inclusion criterion in the single centre study [5].

Ausschlusskriterien der Studien

Both case series reported patient exclusion criteria that mainly referred to history of esophageal surgery, multisystem disease, Barrett's esophagus, any dysplasia, hiatal hernia ≥3 cm, BMI>35, history of diabetes mellitus, gastric malignancy, cardiac arrhythmia, cardiovascular disease, pregnancy, or implanted electro-medical devices [4, 5].

6.3 Results

Patient safety

C0008 – How safe is the EST in comparison to LF?

keine direkter Vergleich zw. EST und LF möglich da keine Daten von CTs vorhanden

In the absence of data from controlled studies, no comparisons can made between the EST and LF. Only device related complications can be considered for the analysis of safety because the effects directly attributable to the device can be analysed without a control group.

Erosionen in 2.4 % der PatientInnen

Device related complications were reported in one study with 6 months follow-up [4]. Lead erosion through 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.

C0002 – Are there harms related to dosage or frequency of applying the technology?

korrekte Implantation entscheidend

Safe use of the EST is sensitive to the proper implantation and functioning of the implanted electronic device. Correct delivery of the electrical stimulation, correct lead impedance (which was out of range in 4.8% of patients in one study [4]), and correct IPG implantation (where skin infections at pocket site occurred to 4% of patients [5]) are required.

C0004 – How does the frequency or severity of harms change over time or in different settings

A number of short term post-operative harms occurred. The following adverse events occurred in one study [4] (in % of patients): constipation 2.4%, epigastric pain 2.4%, hiccups 4.8%, inability to vomit 4.8%, and fever 2.4%. The following adverse events occurred in both case series [4, 5] (in % of patients): post-operative bloating/belching in 7.1% and 0%, post-operative dysphagia in 9.5% and 0%, nausea/vomiting in 7.1% and 12%, and pain/discomfort in 45.2% and 20%. No new adverse events occurred in the registry study.

postoperative AE: Blutungen, Verstopfung, Oberbauchschmerzen, Schluckauf, gestörter Würgereflex, Fieber

The only known data to report on the safety profile differences between generations of the EST is the difference between compatibility of the device generations with MRI, where EndoStim® II is approved for full body scans using 3.0 Tesla MRI, while EndoStim® I can only be used for imaging of the head and extremities using 1.5-Tesla [10].

There is no evidence that harms increase or decrease in different organizational settings.

C0005 – What are the susceptible patient groups that are more likely to be harmed through the use of the technology?

Patient groups that are most likely to be harmed through the use of the technology are patients with other comorbidities. Cardiac patients are susceptible to harm as the EST may interact with the patient's heart function or heart devices. Claimed to be unrelated to the EST, a SAE occurred in the multicentre study where a case of paroxysmal atrioventricular nodal re-entrant tachycardia (AVNRT) occurred several months after the start of the EST [4]. Furthermore, patients that are required to undergo magnet therapy are susceptible to harm as 4% of patients had the EST turned off by magnet therapy for arthritis [5]. Patients with psychological disorders are likely to be harmed as a case of psychotic disturbance/nervous breakdown occurred in 4% of patients in the single centre study [5]. Moreover, patients allergic to metals are susceptible to possible harm caused by the device as well as patients with eating disorders, as the case of weight loss/anorexia occurred in 11.9% of patients in the multi-centre study [4].

Komorbiditäten erhöhen das Risiko für AE, insb. Bei Kardialer Vorerkrankung

C0007 – Are the EST and LF associated with user-dependent harms?

The learning curve for the implantation procedure of the EST is claimed to be short and the esophagogastric junction left unaltered, making the EST reversible [29]. When placing the electrodes, the surgeon needs to avoid perforation of the esophageal lumen [2]. Furthermore, correct set up of the electrical stimulation by the gastroenterologist is crucial to minimize the risk of device malfunctioning.

kurze Lernkurve, reversible Intervention
Expertise nötig für Korrektes Set up, CAVE: Perforation

Investments and tools required

B0010 – What kind of data/records and/or registry is needed to monitor the use of EST and LF?

The existing registry study is missing some important information such as the device model type used, electrical set up of the device, reasons for deciding whether specific AEs and SAEs are related, possibly related, or unrelated to the intervention, and reporting on the outcomes of extraesophageal symptoms, hospital discharge, and improvement in esophagitis for all patients.

Daten zu Type des Medizinproduktes, set-up und AE, SAE fehlen

7 Quality of evidence

Qualität der Evidenz nach GRADE

The strength of evidence was rated according to GRADE (Grading of Recommendations Assessment, Development and Evaluation) scheme [1] for each endpoint individually. Each study was rated by two independent researchers. In case of disagreement a third researcher was involved to solve the difference. A more detailed list of criteria applied can be found in the recommendations of the GRADE Working Group [1].

GRADE uses four categories to rank the strength of evidence:

- *High* = We are very confident that the true effect lies close to that of the estimate of the effect;
- *Moderate* = We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different;
- *Low* = Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect;
- *Very low* = Evidence either is unavailable or does not permit a conclusion.

The ranking according to the GRADE scheme for the research question can be found in Table 7-1.

Stärke der Evidenz sehr niedrig

Overall the strength of evidence for the effectiveness and safety of the EST is very low. No evidence was available for the comparison of the EST and LF.

Table 7-1: Evidence profile: efficacy and safety of the EST in GERD patients

No of studies/patients	Study Design	Estimate of effect	Study limitations	Inconsistency	Indirectness	Other modifying factors	Strength of evidence
Efficacy							
Due to the lack of a controlled group, no data on efficacy can be reported.							
Safety							
Adverse events (AEs)							
Post-operative bloating/belching							
3/67 [4, 5, 28]	Prospective case series + prospective registry	Not reported	-1[1]	-1[2]	0	-1[3]	Very low
Post-operative dysphagia							
3/67 [4, 5, 28]	Prospective case series + prospective registry	Not reported	-1	-1	0	-1	Very low
Nausea/vomiting							
3/67 [4, 5, 28]	Prospective case series + prospective registry	Not reported	-1	-1	0	-1	Very low
Pain/discomfort							
3/67 [4, 5, 28]	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 [4]	Prospective case series	Not reported	-1	NA	0	-1	Very low
Device erosion lead through esophagus							
1/42 [4]	Prospective case series	Not reported	-1	NA	0	-1	Very low

Nomenclature for GRADE table:

Limitations: 0: no limitations or no serious limitations; -1: serious limitations

Inconsistency: NA: Not applicable (only one trial); 0: no important inconsistency; -1: important inconsistency

Indirectness: 0: direct, no uncertainty, -1: some uncertainty, -2 major uncertainty

Other modifying factors: publication bias likely (-1), imprecise data (-1), strong or very strong association (+1 or +2), dose-response gradient (+1), Plausible confounding (+1)

[1] Unclear risk of bias due to unclear allocation concealment, no blinding, no control group

[2] Heterogeneous results, no p-value reported

[3] Small sample size

8 Discussion

Because the Electric Stimulation Therapy is a new intervention that received the CE Mark in 2012 and currently seeks the FDA approval, there is scarce data on the clinical effectiveness and safety of the device. We could identify three prospective observational studies, two case series [4, 5] and one registry study [28], including the total of 70 patients.

neue Technologie, wenige Daten zur klinischen Wirksamkeit vorhanden: 70 Pts

Quality of evidence

Overall, the quality of evidence was very low due to the observational study design, heterogeneity of data, no p-values on pre-post comparison reported, and small sample size (see Table 7-1). Also, the highly specific patient group is not representative of the range of GERD patients requiring anti-reflux surgery due to the highly specific patient selection criteria [30]. The overall risk of bias was considered moderate because it was unclear if patients entered the study at similar point in the disease, if patients were recruited consecutively, and conclusions concerning effectiveness were not supported by the results (see Appendix Table A-2). 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 [4, 5], and 27% in the registry [28].

Qualität der Evidenz niedrig: nur Fallserien, zu kleine Stichproben

Moderates Biasrisiko

Interne Validität gering

Effectiveness data from observational studies

Large patient groups with non-acute diseases, such as the GERD patient group of this assessment, need the best evidence of controlled trials to prove effectiveness. The lack of RCTs and CTs restricted our analysis to single arm prospective studies as the best available evidence. Consequently, no conclusions on effectiveness of the EST can be made. Nonetheless, the observational data from the prospective trials show a possible effect concerning crucial outcomes. Both case series report improvement in GERD HRQL in on-PPI groups (improvement of 16.5-5 [4] and 9-0 [5]) and in off-PPI groups (improvement of 31-5 [4] and 23.5-0 [5]). The registry study reports slight deterioration by one point [29]. Improvement is also reported in the percentage of days with heartburn and regurgitation in both on-PPI and off-PPI groups and in median DeMeester pH score [7, 18, 29].

Wirksamkeit konnte nicht bewertet werden auf Grund fehlender RCTs,CTs

Beobactungsstudien berichten Verbesserung in QoL sowie

Improvement in discontinuation with medication (PPIs) was not reported in the multi-center study [18], but in in the remaining two studies, it was 76% [7] and 73% [29], respectively. The results were heterogeneous with reference to patient satisfaction, which improved from 7-54% in the multi-center study [18] and from 29-100% in the single center study [7]. Esophagitis improved slightly in the multi-center study [18], it was not reported in single centre [7], and insufficiently reported in the registry study [29][4].

in PPI-Therapieeinstellungen, Patientenzufriedenheit und Ösophagitis.

Safety data from observational studies

With 3-year follow-up data at hand, longer-term data is needed to prove the safety of the EST. Relations between the EST and cardiac issues related either to cardiac devices, or to the EST itself remain to be answered.

[4] Data reported on 66.6% of pts of which 50% showed improvement by 1 grade, 25% had stable and 25% worsening esophagitis

potentielle Interessenskonflikte nicht angegeben

In both the single center study and the registry study, the chair of the Data Monitoring Committee (DMC) was a consultant for EndoStim Inc. [5, 28] and because these two studies reported on less specific AEs and SAEs than the multi-center study [4], there might be a possibility of underreporting. The background of other committee members were not reported [4] and hence their independence cannot be evaluated.

Mechanisms behind GERD

Pathophysiologie der Erkrankung unklar

The mechanisms behind GERD are unclear and only the correct determination of its pathophysiology will help in evaluating the efficacy of anti-reflux treatments [32]. Various surrogate outcomes such as esophageal manometry, 24 pH monitoring, DeMeester score, or LES pressure attempt to quantify GERD. LES residual pressure, the main outcome that the EST claims to improve, was either reported with a statistically insignificant improvement ($p = 0.8018$) [4], or it was not reported in the remaining studies [5, 28]. Other mechanisms possibly having an influence on GERD may have effect on transient LES relaxations, LES compliance, or the acid pocket [5].

mehrere Surrogat Parameter zur Quantifizierung von GERD vorhanden

Hiatus Hernien Reparatur als potentieller Störfaktor

As hiatal hernias makes acid reflux more likely [15], it is possible that repairing of the hiatal hernia has an impact on the effectiveness of the intervention and hence on GERD symptoms. One study reported on the variable of impact of repairing hiatal hernia ≥2 [4]. Patients with an unrepaired hiatal hernia ≥2 cm or a significant hiatal defect compared to patients with repaired hernia of the same size showed a trend for less improvement in GERD HRQL, percentage of heartburn days and nights, and percentage of regurgitation days and nights [4].

Clinical trials

sham RCTs mit PatientInnen relevanten Endpunkten nötig

Quality RCTs need to be conducted to prove the EST efficacy. DeMeester suggests that an RCT against PPIs is needed [31], whereas Attwood argues that a comparison between surgical options (EST vs LF) is required as only those patients who are dissatisfied with PPIs will be willing to undergo surgery [32]. It is ambiguous what the appropriate comparator to the EST is. On the one hand, LF is the only established surgical alternative, yet on the other hand, the EST claims to fill the therapeutic gap between patients who are dissatisfied with the PPI treatment and those who are reluctant to undergo LF. The target population of the EST seems to be less severe patients not indicated for fundoplication, which changes the cut-off point of a surgical intervention to the less diseased. In the light of this ambiguity, ethicality of an RCT between the EST and LF is put into question. Hence, under these circumstances, a sham RCT is needed to confirm efficacy of the EST.

Zielpopoulation nicht klar definiert

laufendes sham RCT

Since July 2015, there was an EndoStim Inc. funded sham RCT ongoing in Belgium and France that was terminated due to a suspension of financial support in November 2015 (NCT02514616). Correspondence with EndoStim Inc., however, suggests that the trial was discontinued because a new multi-center trial with a similar design and a larger sample was started. The sites originally participating in NCT02514616 will join the larger FDA approval study (NCT02749071).

Other technologies

Konkurrierende aufstrebende Technologien: Radiofrequenz Ablation, Trans-orale Inzision der Fundoplicatio, Magnetischer Speiseröhrenring

There are some other emerging technologies aiming to fill the above mentioned therapeutic gap. These can be categorized into 3 groups:

1. radiofrequency ablation of the LES (Stretta System)
2. trans-oral incisionless fundoplication (TIF), i.e. suturing of the gastroesophageal junction
3. magnetic sphincter augmentation device (MSAD) [33, 34]

Evidenzlage zu allen Technologien derzeit niedrig

The first two alternatives provide a non-surgical approach, while the MSAD is a laparoscopically implanted ring of magnetic beads made of titanium that is placed around the lower esophagus [33]. Like the EST, MSAD is a reversible procedure with an acceptable safety profile that is lacking robust data on its effectiveness. The TIF seems to be safe and effective with 79-80% response rates, but with disappointing 2-year follow-up results. It is equally recommended only for patients with hiatal hernia <2 cm. The Stretta System is recommended by SAGES for non-complicated GERD and it is the only one that has undergone rigorous evaluation with randomized trials and positive effectiveness results [33, 34].

in Abwesenheit von klaren GERD Schweregraden: schwierig genaue Indikation für EST zu etablieren könnte ‚ungesundes' Verhalten fördern

Untreated chronic reflux might lead to secondary diseases, such as erosive esophagitis, esophageal stricture, Barrett's esophagus, or even esophageal cancer, therefore the effect of EST on these outcomes also needs to be analyzed. In the absence of clear severity scores supporting staging of well-defined indications however, there is a possible issue with the EST that instead of a change in the patient's dietary habits, particularly in the obese, the EST can facilitate unhealthy behaviour. In case the EST fulfils the mentioned therapeutic gap, it can be considered as the first line surgical treatment for prevention of esophageal cancer and, on the long run, as an option bringing savings to the health care system when contrasted to the costly PPI therapy. Moreover, long-term PPI therapy can have serious side-effects, such as decreased calcium absorption, osteoporosis, community acquired pneumonia, Clostridium difficile infection, small intestinal bacterial overgrowth, vitamin B12 deficiency, and drug interactions [35].

potentiell ökonomische wie gesundheitliche Vorteile durch Wegfall der PPI Medikation,

Studien mit größerer Fallzahl nötig

Major advantages of the EST known to date are that it is less invasive and reversible, its implantation is associated with a short learning curve for the surgeon, it presumably allows a faster return to normal diet, and it requires a short hospital stay compared to LF. Quality RCTs, in particular a sham RCT, with longer follow-up involving larger number of implanted patients should be conducted in order to prove efficacy of the EST.

9 Recommendation

In Table 9-1 the scheme for recommendations is displayed and the according choice is highlighted.

Table 9-1: Evidence based recommendations

	The **inclusion** in the catalogue of benefits is **recommended**.
	The **inclusion** in the catalogue of benefits is **recommended with restrictions**.
X	The inclusion in the catalogue of benefits is ***currently*** **not recommended.**
	The **inclusion in** the catalogue of benefits is **not recommended.**

Reasoning:

The current evidence is not sufficient to prove that the EST is at least equally effective and as safe as the comparator LF. There are no available comparative data on the two procedures or placebo controlled data on the EST and hence, no conclusions are made about the device effectiveness. Concerning safety, only device related complications were reported based upon data from prospective case series. These suggest a relatively safe profile of the EST that, however, needs to be confirmed by a high quality RCT, which will potentially influence the effect estimate considerably.

Evidenz unzureichend; derzeit nicht empfohlen

Currently, there is an ongoing sham-controlled RCT and hence the re-evaluation is recommended in 2022, as December 2021 is its estimated study completion date.

1 laufendes RCT, Re-Evaluierung 2022

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Appendix

Evidence tables of individual studies included for clinical effectiveness and safety

Table A-1: EST: Results from observational studies

	Kappelle [4, 36] (2015)	Rodriguez [5] (2015)	Rodriguez [28] (2016)
Country	Chile, Colombia, India, Netherlands, Mexico, New Zealand, United Kingdom[5]	Chile	
Sponsor	EndoStim Inc.	EndoStim Inc.	
Study design	Multi-centre, prospective, international, open-label case series (NCT01574339)	Single-centre, prospective. open-label case series (NCT01578642)	Single-centre, prospective registry (NCT02441400)
Intervention (I)	Electric stimulation therapy (EndoStim® LES Stimulator)	Electric stimulation therapy (EndoStim® LES Stimulator)	
Comparator (C)	none	none	
Number of pts (I vs. C)	44[6]	26[7]	18[8]
Inclusion criteria	Pts 21-80yrs, reflux symptoms, GERD-HRQL score ≥20 off PPIs &, an increase of ≥5 on PPIs, prior PPI use for 12 mos, diagnosis based on 24-h pH monitoring result, LES end-expiratory 5–15 mmHg, peristaltic contractions in ≥50% of swallows with contraction amplitude of ≥30 mmHg oesophageal manometry, excessive lower esophageal acid exposure as pH <4.0 for ≥5% of the total time.	Pts 21-65yrs, reflux symptoms ≥6mos, prior PPI use, GERD-HRQL score ≥20 off PPIs &, an increase of ≥10 on PPIs, ASA Physical Status Classification ≤ II, distal esophageal acid exposure during 24-hour pH measurement pH of ≤4 for>5% of total or>3% of supine, time off, anti-secretory therapy, LES end-expiratory ≥5mmHg, esophageal body contraction amplitude of ≥30 mmHg for ≥70% of swallows and ≥50% peristaltic contractions on manometry, esophagitis grade ≤C.	NA
Exclusion criteria	History of esophageal or gastric surgery, gastroparesis, multi-system disease, autoimmune or connective tissue disorder in past 2 yrs, Barrett's epithelium, any grade dysplasia, hiatal hernia >3 cm, esophagitis grade D on upper endoscopy within 6 mos, BMI>35, T1DM or uncontrolled T2DM defined as HbA1c ≥9.5 in the previous 6ms, or T2DM for ≥10 years, suspected or confirmed esophageal or gastric cancer, any malignancy in last 2 yrs, esophageal or gastric varices or dysphagia or oesophageal peptic stricture, significant cardiac arrhythmia or cardiovascular disease, implanted electrical stimulator or chronic anticoagulant therapy, pregnant pts.	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 yrs, 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

[5] While the study refers to 8 countries and 10 sites, www.clinicaltrials.gov lists 7 countries and 9 sites.

[6] Baseline characteristics on 42pts

[7] 25 received intervention

[8] Baseline characteristics on 15pts

	Kappelle [4, 36] (2015)	Rodriguez [5] (2015)	Rodriguez [28] (2016)
Primary outcome measure			
Baseline patient characteristics (I vs. C)			
Mean age, yrs (SD)	49.6 (12.4)	52 (12)	56.1 (9.7)
Sex, female vs. male	18 vs. 24	11 vs. 14	7 vs. 8
Mean BMI, (SD) ❁ Hiatal hernia ❁ none/<2 cm/>2 cm, % ❁ Mean yrs of PPI use (SD) ❁ Mean yrs with GERD (SD)	27.2 (2.4) 39/22/39 NA NA	27.7 (3.2) 88/8/4 5.6 (3.4) 11.0 (7.9)	27.4 (3.2) 93.3/0/6.7 5.9 (3.3) 12.2 (9.1)
Follow-up time, yrs	0.5	2	3
Loss to follow-up, %	6.8[9]	19.2[10]	16.6[11]
Outcomes			
Efficacy			
Improvement in median GERD HRQL score (pre-op./ last follow-up)[12] (IQR) ❁ on-PPI ❁ off-PPI	 16.5 (9.0–22.8)/5.0 (3.0–9.0)[13] 31.0 (26.2-36.8)/5.0 (3.0–9.0)	 9 (6–10)/0 (0–3)[14]/1 (0-2) 23.5 (21–25.3)/0 (0–3)/1 (0-2)	
Median heartburn % of days (pre-op./last follow-up) (IQR) ❁ days ❁ nights	 86 (64–100)/17 (0–93)[15] 64 (43–86)/0 (0–8)	 92/7[16]/NA 71/0/NA	

[9] 1 loss to follow-up, 1 Toupet fundoplication due to hiatal hernia >3 cm, 1 trocar perforation of the intestine during implant procedure

[10] 1 loss to follow-up, 1 implant not attempted due to hiatal hernia >3 cm, 3 voluntary withdrawals

[11] of the 21pts at 2 yr follow-up, 3 did not join 5 year observational registry, 3 losses to follow-up

[12] The total GERD-HRQL score represents a summation of 10 items (questions about heartburn, difficulty swallowing, bloating, satisfaction and medication take). The best possible score is 0 (i.e., asymptomatic in each item), and the worst possible scores is 50 (incapacitated in each item)

[13] 42 pts at baseline, 41 at last follow-up

[14] 24 pts at baseline, 21 at last follow-up

[15] 35 pts at baseline, 34 pts at last follow-up

[16] 18 pts' analysis

	Kappelle [4, 36] (2015)	Rodriguez [5] (2015)	Rodriguez [28] (2016)
Median regurgitation % of days (pre-op./last follow-up) (IQR)			
☘ days	79 (54–100)/0 (0–21)[17]	66/0[18]/NA	
☘ nights	50 (15–79)/0 (0–7)	31/0/NA	
Discontinuation with medication (PPIs), % at last follow-up	NA	76/73	
Median DeMeester pH score[19] (pre-op./last follow-up) (IQR)	35.1 (27.1–51.9)/17.5 (10.9–23.4)[20]	36.6 (29.6–50.2)/16.1 12.2–29.1[21]/12.8 (7.2–18.8)	
Patient satisfaction while on PPIs at baseline, % (pre-op./ last follow-up)	7/54[22]	29/100/NA	
Esophagitis, % (pre-op./last follow-up)			
☘ None	41/51[23]	NA/NA	0/NA[24]
☘ Grade A	31/31	NA/NA	60/NA
☘ Grade B	23/18	NA/NA	33.3/NA
☘ Grade C	5/0	NA/NA	6.7/NA
Safety			
Total number of AE	110 (in 32pts)	65 (in 19pts)	NA
Of which SAE	3 (2%)	2 (3%)	
AE related	52		
AE non-related	56		

[17] 35 pts at baseline, 34 pts at last follow-up

[18] 18 pts' analysis

[19] Global measure of esophageal acid exposure that quantifies gastroesophageal reflux. A DeMeester score > 14.72 indicates reflux.

[20] 42 pts at baseline, 40 at last follow-up

[21] 24 pts at baseline, 18 at last follow-up

[22] 42 pts at baseline, 39 at last follow-up

[23] out of 39 pts

[24] data on 12pts: 6pts showed improvement by 1 grade, 3pts has stable and 3pts worsening esophagitis

	Kappelle [4, 36] (2015)	Rodriguez [5] (2015)	Rodriguez [28] (2016)
Device/procedure-related mild AEs noted during the study, % of pts			
Post-operative bloating/belching	7.1	0	0
Constipation	2.4	NA	NA
Post-operative dysphagia	9.5	0	0
Epigastric pain	2.4	NA	NA
Hiccups	4.8	NA	NA
Nausea/vomiting	7.1	12	0
Inability to vomit	4.8	NA	NA
Weight loss/anorexia	11.9	NA	NA
Fever	2.4	NA	NA
Pain/discomfort	45.2	20	0
Impedance out of range	4.8	NA	NA
Mesh repair hernia cicatricialis	2.4	NA	NA
Skin infection at pocket site	NA	4	0
Psychotic disturbance/nervous breakdown	NA	4	0
Shoulder pain and a hypersensitive episode	NA	8	0
Device/procedure-related SAEs			
Intraoperative complications in % of pts			
✿ Trocar perforation of the small bowel during laparoscopy	2.4	NA	NA
Postoperative complications in % of pts			
✿ Device related complications (Lead erosion through esophagus, explantation)	2.4	NA	NA
✿ Reoperation rate	NA	NA	NA
✿ Hospital readmission	NA	NA	NA

MSAD – Magnetic Sphincter Augmentation Device, LP – Laparoscopic, LF – Laparoscopic Fundoplication, PPI – Proton Pump Inhibitor; Pts – patients; GERD HRQL – Gastroesophageal Reflux Disease Health-Related Quality of Life, BMI – Body Mass Index, yrs – year; mos – months; min – minutes; pre-op. – pre-operative; AEs – adverse events; SAEs – serious adverse events; NA – data not available

Risk of bias tables

Internal validity of the included studies was judged by two independent researchers. In case of disagreement a third researcher was involved to solve the differences. A more detailed description of the criteria used to assess the internal validity of the individual study designs can be found in the Internal Manual of the LBI-HTA [37] and in the Guidelines of EUnetHTA [38].

Table A-2: Risk of bias – study level

	Prospective case series		Prospective registry
Study reference/ID	**Kappelle [4, 36], 2015**	**Rodriguez [5], 2015**	**Rodriguez [28], 2016**
1. Is the hypothesis/aim/objective of the study stated clearly in the abstract, introduction, or methods section?	Yes	Yes	Yes
2. Are the characteristics of the participants included in the study described?	Yes	Yes	Yes
3. Were the cases collected in more than one centre?	Yes	No	No
4. Are the eligibility criteria (inclusion and exclusion criteria) for entry into the study explicit and appropriate?	Yes	Yes	Yes
5. Were participants recruited consecutively?	Unclear[25]	Unclear[26]	Unclear[27]
6. Did participants enter the study at similar point in the disease?	Unclear	Unclear[28]	Unclear
7. Was the intervention clearly described in the study?	Yes	Yes	Yes
8. Were additional interventions (co-interventions) clearly reported in the study?	Yes	Yes	Yes
9. Are the outcome measures clearly defined in the introduction or methods section?	Yes	Yes	Yes
10. Were relevant outcomes appropriately measured with objective and/or subjective methods?	Yes	Yes	Yes
11. Were outcomes measured before and after intervention?	Yes	Yes	Yes
12. Were the statistical tests used to assess the relevant outcomes appropriate?	Yes	Yes	Yes
13. Was the length of follow-up reported?	Yes	Yes	Yes
14. Was the loss to follow-up reported?	Yes	Yes	Yes
15. Does the study provide estimates of the random variability in the data analysis of relevant outcomes?	Yes	Patrially reported	Yes
16. Are adverse events reported?	Yes	Yes	Yes
17. Are the conclusions of the study supported by results?	Partially reported	Partially reported	Partially reported
18. Are both competing interest and source of support for the study reported?	Yes	Yes	Yes
	Moderate	Moderate	Moderate

[25] "Unclear": 110pts screened and 66 specified screen failures

[26] "Unclear": 75pts screened and 49 unspecified screen failures

[27] "Unclear": 21pts at 24mos follow-up, 18 recruited for 5 yr registry (3/21 elected not to join the 5 year observational registry)

[28] "Unclear": only mean duration of PPI use and mean duration of GERD symptoms is reported.

Applicability table

Table A-3: Summary table characterising the applicability of a body of studies

Domain	Description of applicability of evidence
Population	Study population represents a narrow spectrum of GERD patients as predifined by the manufacturer and hence for the most part, the target population does not differ from the enrolled population. The inclusion criteria predominantly do not reflect severe refractory GERD with hiatal hernias >3 cm, motility disorders, Barrett's easophagus or grade D esophagitis, but only mild to moderate GERD with incomplete symptom control by PPIs.
Intervention	Electric stimulation therapy device (EST) inserted through laparoscopic surgery. Product name: EndoStim® LES Stimulator
Comparators	Standard surgical treatment of GERD and Nissen fundoplication and partial, or Toupet fundoplication. However, there is a slight ambiguity as EST attempts to place itself into the „treatment gap" for which there is no comparator. It aims at patients who have persistant GERD, incomplete symptom control by PPIs, but whose condition is not severe enough to undergo any type of non-reversible fundoplication.
Outcomes	Effectiveness outcomes reported in the registry study are GERD HRQL, heartburn, regurgitation, discontinuation with PPI medication, DeMeester score, patient satisfaction, and esophagitis. Follow-up time was 0.5 to 3 yrs.The outcomes measured present the most important benefits. Safety outcomes that are most frequently reported in the three studies considered are post-operative bloating/belching, post-operative dysphagia, nausea/vomiting, pain/discomfort, device and procedure related side effects. Follow-up time ranged from 0.5 to 3 yrs and hence short-term safety profile of the EST on GERD may be assessed even though its comparative safety to LF cannot. The outcomes measured do present the most important health threats associated with the EST.
Setting	All of the studies included were either single-centre or multi-centre studies, with clinical centres based in Europe, South and Central America, Asia, New Zealand, and the United States. Clinical settings were not described in all of the studies, but it is likely that all patients received-standard care at university hospitals or transplant centres. Thus, it can be assumed that the results reflect a wide spectrum of clinical routines with regard to patient selection and treatment modalities and,therefore, the results are transferable to the Austrian setting. The surgeon's technical expertise likely determines the risk of local side effects. If introduced as a new treatment method in European hospitals, the treatment with EST will certainly be accompanied by a learning curve.

List of ongoing trials

Table A-4: List of ongoing trials of the EST

Identifier/ Trial name	Patient population	Intervention	Comparison	Primary Outcome	Primary completion date	Sponsor
NCT02441400 EndoStim Patient Registry (RESTORE)	Patients with GERD	EndoStim® LES Stimulator	Single arm, no comaprison group	Assessment of safety by incidence and severity of adverse events through 60-month (5 years) follow-up.	May 2019	EndoStim Inc.
LESS GERD Registry	Patients with GERD	EndoStim® LES Stimulator	Single arm, no comaprison group	NA	NA	EndoStim Inc.
NCT02749071 [29] An Investigation of the EndoStim® Lower Esophageal Sphincter (LES) Stimulation System for the Treatment of Reflux	Patients with GERD	EndoStim® LES Stimulator	Sham	Rate of (occurence) device and/or procedure-related serious adverse events in 12mos Percentage of subjects achieving pH success (pH<4 for mo more than 5.3% of time or at least 50% improvement in pH compared to baseline)	June 2017	EndoStim Inc.
NCT02514616 Electrical Stimulation Therapy (EST) of the Lower Esophageal Sphincter (GERD) (EST-SHAM-EUR)	Patients with GERD	EndoStim® LES Stimulator	Sham	Efficacy of EST on GERD symptoms (mean improvement in the GERD- health-related quality of life (HRQL) scores from baseline in control and treatment groups) at 14 weeks follow-up	November 2015	EndoStim Inc.
NCT02210975 An Investigation of Electrical Stimulation on Gastroesophageal Reflux Disease (GERD) in Patients After Sleeve Gastrectomy	Patients with GERD after Sleeve Gastrectomy	EndoStim® LES Stimulator	No comparitor	The incidence and severity of any complications that are associated with the investigational stimulation device throughout the follow-up period at 12 month follow-up Disease specific quality of life at 6 and 12 month follow-up	January 2016	EndoStim Inc.

[29] Terminated to become part of a larger trial NCT02749071

Literature search strategies

Search strategy for Cochrane

Search Name: Electrostimulation for GERD	
Search Date: 02/01/2017 18:03:53.310	
Description: (MEL2017 MS/KR)	
ID	Search
#1	MeSH descriptor: [Gastroesophageal Reflux] explode all trees
#2	„gastro*esophageal reflux" (Word variations have been searched)
#3	„gastro-esophageal reflux" (Word variations have been searched)
#4	GER:ti,ab,kw (Word variations have been searched)
#5	GERD:ti,ab,kw (Word variations have been searched)
#6	GORD:ti,ab,kw (Word variations have been searched)
#7	#1 or #2 or #3 or #4 or #5 or #6
#8	MeSH descriptor: [Electric Stimulation Therapy] explode all trees
#9	Electric* near Stimul*:ti,ab,kw (Word variations have been searched)
#10	MeSH descriptor: [Electric Stimulation] explode all trees
#11	electrostimul*:ti,ab,kw (Word variations have been searched)
#12	electro-stimul*:ti,ab,kw (Word variations have been searched)
#13	EST:ti,ab,kw (Word variations have been searched)
#14	EndoStim:ti,ab,kw (Word variations have been searched)
#15	LES near Stimul*:ti,ab,kw (Word variations have been searched)
#16	#8 or #9 or #10 or #11 or #12 or #13 or #14
#17	#7 and #16
Total: 23 Hits	

Search strategy for CRD

Search Name: Electrotherapy for GERD (MEL2017 MH/KR)	
Search Date: 02/01/2017	
ID	Search
#1	MeSH DESCRIPTOR Gastroesophageal Reflux EXPLODE ALL TREES
#2	(gastro*esophageal reflux)
#3	(gastro-esophageal reflux)
#4	(gastro-oesophageal reflux)
#5	(GER)
#6	(GERD)
#7	(GORD)
#8	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7
#9	MeSH DESCRIPTOR Electric Stimulation Therapy EXPLODE ALL TREES
#10	(Electric* NEAR Stimul*)
#11	MeSH DESCRIPTOR Electric Stimulation EXPLODE ALL TREES
#12	(electrostimul*)
#13	(electro-stimul*)
#14	(EST)
#15	(EndoStim)
#16	(LES NEAR Stimul*)
#17	#9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16
#18	#8 AND #17
Total: 2 Hits	

Search strategy for Embase

Search Name: Electrostimulation for GERD	
Search Date: 02/01/2017	
ID	Search
#23	'gastroesophageal reflux'/exp OR 'gastroesophageal reflux':ab,ti OR 'gastrooesophageal reflux':ab,ti OR 'gastro-esophageal reflux':ab,ti OR 'gastro-oesophageal reflux':ab,ti OR ger:ab,ti OR gerd:ab,ti OR gord:ab,ti AND ('electrotherapy'/mj OR (electric* NEAR/5 stimul*):ti,ab OR 'electrostimulation'/exp OR lectrostimul*:ti,ab OR 'electro stimul*':ti,ab OR est:ti,ab OR endostim:dn OR endostim*:ti,ab OR les:dn OR (les NEAR/1 stimul*):ti,ab)
Total: 264 Hits	

Search strategy for Medline

Search Name: Electrostimulation for GERD	
Search Date: 02/01/2017	
ID	Search
#1	1 exp Gastroesophageal Reflux/(26275)
#2	2 gastro?esophageal reflux.mp. (31464)
#3	3 gastro-?esophageal reflux.mp. (1502)
#4	4 GER.mp. (3394)
#5	5 GERD.mp. (7461)
#6	6 GORD.mp. (788)
#7	7 1 or 2 or 3 or 4 or 5 or 6 (34515)
#8	8 exp Electric Stimulation Therapy/(74443)
#9	9 (Electric* adj5 Stimul*).mp. (168133)
#10	10 exp Electric Stimulation/(132669)
#11	11 (therap* or treatment* or program*).mp. (6907194)
#12	12 10 and 11 (16907)
#13	13 electrostimul*.mp. (3382)
#14	14 electro-stimul*.mp. (309)
#15	15 EST.ti,ab. (11102)
#16	16 EndoStim.mp. (11)
#17	17 LES Stimul*.mp. (76)
#18	18 8 or 9 or 12 or 13 or 14 or 15 or 16 or 17 (230916)
#19	19 7 and 18 (150)
#20	20 remove duplicates from 19 (128)
Total: 128 Hits	

Search strategy for PubMed

Search Name: MELs 2017: Electric Stimulation Therapy for patients with GERD	
Search Date: 03/02/2017	
ID	Search
#1	((„Gastroesophageal Reflux"[Mesh] OR „gastroesophageal reflux" OR „gastrooesophageal reflux" OR „gastro-esophageal reflux" OR „gastro-oesophageal reflux" OR GER OR GERD OR GORD)) AND (Electric Stimulation Therapy OR (Electric Stimulation AND (therap* OR treatment* OR program* OR procedure* OR intervention* OR technolog*)) OR electrostimul* OR electro-stimul* OR EST[tiab] OR EndoStim OR „LES Stimulator")
Total: 99 Hits	

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