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Lower Esophageal Sphincter Devices for Laparoscopic Surgery in Patients with Gastroesophageal Reflux Disease (GERD)

Systematic Review

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Systematic Review

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List of abbreviations

ACG ..... American College of Gastroenterology
AEs ..... Adverse events/Adverse Ereignisse
AWMF ..... Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften
BE ..... Barrett's oesophagus
BMI ..... Body mass index
CE Mark ..... Conformité Européene mark
CG ..... Control group
CRD ..... Centre for Review and Dissemination
CT ..... Controlled trial
DARE ..... The Database of Abstracts of Reviews of Effects
EST ..... Electrical stimulation therapy/Elektrostimulationstherapie

GERD ..... Gastroesophageal reflux disease/Gastroösophageale Refluxkrankheit
GERD-HRQL..... GERD-Health Related Quality of Life Questionnaire
GI..... Gastrointestinal
GRADE..... Grading of Recommendations Assessment, Development and Evaluation
H2RAs..... Histamine 2 receptor antagonist
HRQoL ..... Health-related quality of life
HTA ..... Health Technology Assessment
IG..... Intervention group/Interventionsgruppe
IHE..... International Health Economics
INAHTA ..... International Network of Agencies for Health Technology Assessment
IPG ..... Implantable pulse generator
IQR..... Inter-quartile range
KG ..... Kontrollgruppe
KH..... Krankenhaus
Krit ..... Kriterium/Kriterien
LA..... Los Angeles
LBI HTA..... Ludwig Boltzmann Institute for HTA
LES..... Lower esophageal sphincter
LQ ..... Lebensqualität
MedUni..... Medical University Vienna/Medizinische Universität Wien
MSA ..... Magnetic sphincter augmentation/Magnetische Sphinkter-Augmentation
MRI ..... Magnetic resonance imaging
NERD ..... Non-erosive reflux disease
NRCTs ..... Non-randomised controlled studies
NA ..... Not applicable/Not available
NR ..... Not reported
Pts..... Patients
Pat. ..... Patient*innen
PPI..... Proton pump inhibitor
prosp..... Prospective/Prospektiv
QoL ..... Quality of life
RCTs ..... Randomised controlled studies
RDQ ..... Reflux Disease Questionnaire
RoB..... Risk of bias
RefluxStop™ ..... RS
SADEs..... Serious adverse device effects/Schwerwiegende adverse gerätebezogene Effekte
SAEs ..... Serious adverse events/Schwerwiegende adverse Ereignisse
SD..... Standard deviation
SNRIs..... Serotonin-norepinephrine reuptake inhibitors
SoF ..... Summary of findings
stat.sign ..... Statistical significant/statistisch signifikant
SSRIs..... Selective serotonin reuptake inhibitors
TLESR ..... Transient lower esophageal sphincter relaxation
US..... United States
vollst ..... Vollständig
vs..... Versus

Executive Summary

Introduction

Health Problem

Gastroesophageal reflux disease (GERD) is a condition that develops when the reflux of stomach contents causes troublesome symptoms and/or complications such as heartburn, extra-oesophageal manifestations, or non-cardiac chest pain adversely affects an individual's quality of life (QoL). GERD is the most common upper gastrointestinal disease in high-income countries with 10-20% of the population experiencing weekly symptoms. Approximately 42% of GERD patients are dissatisfied with their PPI treatment outcomes or fail medical management, since PPIs do not address the underlying incompetency of the lower esophageal sphincter (LES). These patient groups are potential candidates for surgical therapy.

GERD: contents from the stomach flow into the esophagus (mostly accompanied by symptoms)

prevalence: 10%-20%

Description of Technology

Minimal-invasive laparoscopic approaches for the surgical treatment of GERD have been developed over the last 30 years. These novel technologies that are used as a second-line treatment for chronic GERD patients have the main aim to reduce the lifelong use of PPI medication or to replace the surgical gold standard laparoscopic fundoplication, and to offer a gap therapy for these patients.

laparoscopic procedures to reinforce the lower esophageal sphincter as 2nd-line therapy

The focus of this report is on three different implantable devices: magnetic sphincter augmentation (**MSA**) with a magnetic ring implant (LINX® Reflux Management System from Ethicon, Johnson & Johnson/Torax Medical), a non-active implant made of medical silicone (RefluxStop™ [**RS**] from Implantica Trading AG) and electrostimulation therapy (**EST**) with an implantable pace-maker for the LES (EndoStim® from EndoStim® Inc.). These devices for reinforcing the native LES claim to be less invasive as well as safer compared to laparoscopic fundoplication such as Nissen or Toupet fundoplication and should result in shorter periods of hospitalization.

3 different implantable devices: magnetic sphincter augmentation (MSA), RefluxStop™ (RS), electrical stimulation therapy (EST)

Research question

Is implantation of a device reinforcing the lower esophageal sphincter through laparoscopy in comparison to standard of care in patients with chronic GERD more effective and equally safe or equally effective and safer concerning improvements in health-related quality of life (HRQoL) as well as post-operative side effects and serious adverse events (SAEs)?

research question

Methods

To answer the research question on the effectiveness and safety outcomes, a systematic literature search was conducted in four databases. In addition, a manual search was performed and information provided by the manufacturer was considered. The study selection, data extraction, and assessment of the methodological quality of the studies were performed independently by two researchers.

systematic literature search in 4 databases

Domain effectiveness

The following clinical effectiveness outcomes were defined as *crucial* to derive a recommendation: HRQoL, heartburn and regurgitation score.

***crucial* outcomes for effectiveness …**

Domain safety

… and safety

The following safety outcomes were defined as *crucial* to derive a recommendation: any adverse events (AEs), SAEs, death.

Results

Available evidence

in total 7 studies for all 3 devices

MSA: 4 studies
RS: 1 study
EST: 2 studies

no study to evaluate effectiveness for RS & EST

A total of seven studies met the predefined inclusion criteria for all three devices: four studies (one randomised controlled trial [RCT], two single-arm studies, and one registry-based study) investigated the **MSA**, one prospective single-arm study analysed the **RS** device, and two prospective single-arm studies for the **EST** were included. For the inclusion of prospective single-arm studies, a cut-off of at least 100 (**MSA**) and 30 (**RS, EST**) patients was defined. The analysis of effectiveness was limited to controlled trials. Therefore, comparative evidence data from a total of 152 patients were only available for the **MSA**. Additionally, a total of 656 patients were available for the safety analysis of **MSA** from observational studies. The study for **RS** with 50 patients and two studies for **EST** with a total of 81 patients met the inclusion criteria for the analysis of safety-related endpoints.

Clinical effectiveness

MSA: improvements in HRQoL, regurgitation & heartburn in comparison to PPI control group

To assess the clinical effectiveness, only the RCT for the **MSA** was considered. Concerning the a priori defined *crucial* clinical effectiveness outcomes, improvements in the mean GERD-HRQL score and reduction of the GERD-HRQL score ≥50% from baseline for a majority of **MSA** patients (81% and 93%) vs no improvement for PPI patients after six and 12 months were observed (p-value=NR). Furthermore, a statistical significant difference in the elimination of (moderate-to-severe) regurgitation for MSA was observed compared to PPI ($p<0.001$). Improvements were also observed in the other regurgitation score and the heartburn component of the GERD-HRQL after six and 12 months, respectively (p-value=NR).

Safety

no substantial cases of de novo/excessive dysphagia for any of the 3 devices

(a few cases of excessive bloating or problems with belching)

Since no RCT or NRCT was identified that compared surgical methods or LES devices with each other, no procedure- or device-related safety comparisons could be made. However, a total of seven studies (**MSA**: 4, **RS**: 1, **EST**: 2) reported on AEs and SAEs for all three devices. No substantial cases of de novo or excessive dysphagia – common AEs after surgery – were observed for any of the three devices. Only a small number of patients undergoing laparoscopic MSA in the three prospective single-arm studies suffered from postoperative dysphagia, excessive bloating, or were unable to belch and vomit. Excessive bloating was reduced for the **RS** device and **EST**.

MSA: no AEs & SADEs, 1 SAE in RCT & 8 intraoperative complications

RS: no ADEs, 8 non-device AEs & 7 SAEs

EST: 59 AEs & 8 SAEs

No AEs and serious adverse device effects (SADEs) were reported in the RCT for **MSA**. One procedure-related SAE occurred in one patient in the RCT, and eight patients experienced intraoperative complications in the prospective, registry-based study during implantation of the **MSA** device. No adverse device-related effects (ADEs) were reported for the **RS** device, but eight procedure-related and other non-device-related AEs occurred in eight patients, and seven procedure-related SAEs occurred in five of 47 patients. For **EST**, 59 procedure- and device-related AEs and eight device- and procedure-related SAEs were reported in eight of 79 patients.

While four patients underwent reoperation in the **MSA**-RCT and the rate of device explantation ranged from 2.4% to 7% in the prospective single-arm studies examining the **MSA** device, no **RS** device was explanted. In contrast, devices were explanted in all six patients undergoing **EST** who experienced SAEs. Deaths were not reported for any of the devices.

re-surgery rates/explantation

Upcoming evidence

Through the clinical trial search, no registered ongoing or planned randomised controlled trial comparing any of the three devices with LF could be identified. Four observational studies (one comparing **MSA** with LF) were identified. However, whether the trials add to the current evidence is questionable. According to the manufacturer of the **RS** device, results of a five-year data collection are expected to be available by mid- to end-2022 and further clinical trials are also being planned. A RCT comparing **EST** to sham treatment and an observational study were discontinued as the company was no longer operating at that time.

no registered ongoing RCTs identified

Reimbursement

All three devices are currently not included in the catalogue of benefits. The costs associated with the **MSA** include the price of the device, the sizing tool (€ 4,240/€ 100), and the operation procedure. The costs associated with the **EST** operation include the price of the device (€ 8.240), and the operation procedure. Price or cost data on the **RS** device are not publicly available. In comparison to LF, the material costs and the initial training of surgical staff to undertake the implantation procedures are additional to the costs of the operation procedure, although the procedures under investigation might cost slightly less due to the shorter operation time.

devices are currently not reimbursed in Austria

Discussion and conclusion

Overall, no clear conclusion can be made whether LES devices in laparoscopic surgery lead to substantially superior outcomes than the (investigated) comparators, since no robust clinical comparative data are available. **MSA** seems to improve HRQoL and symptom scores over time, but only an improvement compared to PPI medication was identified. No RCT directly comparing **MSA, RS** or **EST** with the gold standard LF has been published to date. Therefore, no differences in the safety profile to surgical comparators could be identified. Furthermore, long-term safety data is lacking. LF, especially Nissen or Toupet fundoplication, is regarded as gold standard among the surgical antireflux procedures in order to improve the function of the LES. High-quality RCTs and NRCTs are needed due to the lack of long-term follow-up data (>2-3 years) with larger samples (n>100) and lack of adequate comparators.

no robust clinical comparative data available → no solid conclusions possible

high-quality evidence is needed (larger sample, longer follow-up, adequate comparators etc.)

Recommendation

Due to the methodological shortcomings of the available evidence and the lack of controlled evidence, especially between different surgical approaches, the inclusion of either of the three investigated devices in the catalogue of benefits is currently not recommended.

inclusion is currently not recommended

Zusammenfassung

Einleitung

Indikation und therapeutisches Ziel

GERD: Reflux aus dem Magen in die Speiseröhre (meist begleitet von Symptomen)

Prävalenz: 10 %-20 %

~42 % der GERD-Patient*innen mit PPI unzufrieden

Die gastroösophageale Refluxkrankheit (GERD) ist charakterisiert durch den Rückfluss von Mageninhalt in die Speiseröhre. Dieser Reflux wird oft von unangenehmen Symptomen und/oder Komplikationen begleitet. GERD wird als unangenehm wahrgenommen, wenn Symptome wie Sodbrennen, extraösophageale Manifestationen oder nicht-kardiale Brustschmerzen die Lebensqualität (QoL) einer Person beeinträchtigen. GERD ist die häufigste Erkrankung des oberen Magen-Darm-Trakts in Ländern mit hohem Einkommen, wobei 10 %-20 % der Bevölkerung wöchentlich unter Symptomen leiden. Zwischen 10 % und 40 % dieser Patient*innen sind refraktär gegenüber einer einmal täglichen Medikation mit Protonenpumpeninhibitoren (PPI). Darüber hinaus sind 42 % der GERD-Patient*innen mit den Ergebnissen ihrer PPI-Behandlung meist unzufrieden und somit potenzielle Kandidat*innen für eine chirurgische Therapie.

zunehmende Häufigkeit → steigender Ressourcenbedarf & gesellschaftliche Kosten

Aufgrund der zunehmenden Inzidenz führt GERD unter anderem zu einer steigenden Inanspruchnahme von Ressourcen im Gesundheitswesen (z. B. Arztbesuche, Krankenhausaufenthalte, Medikamente etc.). Auf gesellschaftlicher Ebene kann die Krankheitslast die Arbeitsproduktivität beeinträchtigen, was wiederum zu erheblichen gesellschaftlichen Belastungen und Kosten führt.

Beschreibung der Technologie

minimal-invasive laparoskopische Verfahren zur Unterstützung des unteren Ösophagussphinkters (UÖS) als Zweitlinientherapie

Ziel: Reduktion der Einnahme von PPI & „Lückentherapie“

In den letzten 30 Jahren wurden optionale minimal-invasive laparoskopische Ansätze für die chirurgische Behandlung von GERD entwickelt. Diese neuartigen Technologien werden als Zweitlinienbehandlung für chronische GERD-Patient*innen eingesetzt. Dazu zählen vor allem Patient*innen, bei denen aufgrund der Inkompetenz des unteren Ösophagussphinkters (UÖS) eine medikamentöse Behandlung mit PPI nicht anschlägt. Ebenso kommt eine Implantation eines solchen Geräts im Zuge eines laparoskopischen Eingriffs möglicherweise auch für all jene Patient*innen in Frage, die eine lebenslange medikamentöse Behandlung ablehnen, unter Nebenwirkungen der PPI-Therapie leiden und damit unzufrieden sind oder mögliche erhebliche Nebenwirkungen der laparoskopischen Fundoplikation (LF) vermeiden wollen. Somit ist das Hauptziel dieser Verfahren, sowohl die lebenslange Einnahme von PPI-Medikamenten zu reduzieren, als auch den chirurgischen Goldstandard der LF zu vermeiden bzw. eine „Lückentherapie“ für betroffene Patient*innen anzubieten. Die dabei eingesetzten Medizinprodukte dienen der Verstärkung des nativen unteren Ösophagussphinkters und sollen – im Vergleich zur LF wie der Nissen- oder Toupet-Fundoplikatio – weniger invasiv und sicherer sein sowie zu kürzeren Krankenhausaufenthalten führen.

3 implantierbare Medizinprodukte am Markt: Magnetische Sphinkter-Augmentation (MSA), RefluxStop™ (RS), Elektrostimulationstherapie (EST)

Der Fokus des vorliegenden Berichts liegt auf drei unterschiedlichen implantierbaren Produkten bzw. Verfahren, wovon drei Geräte auf dem Markt erhältlich sind: die Magnetische Sphinkter-Augmentation (**MSA**) mit einem magnetischen Ringimplantat (LINX® Reflux Management System von Ethicon, Johnson & Johnson/Torax Medical), ein nicht-aktives Implantat aus medizinischem Silikon (RefluxStop™ [**RS**] von Implantica Trading AG) und die Elektrostimulationstherapie (**EST**) mit einem implantierbaren Schrittmacher für den UÖS (EndoStim® von EndoStim® Inc.).

Fragestellung

Forschungsfrage

Ist die Implantation eines Medizinprodukts zur Verstärkung des unteren Ösophagussphinkters durch Laparoskopie im Vergleich zur Standardbehandlung (z. B. PPI-Medikation oder LF) bei Patient*innen mit chronischem GERD effektiver und gleich sicher oder gleich effektiv und sicherer in Bezug auf die Verbesserung der gesundheitsbezogenen Lebensqualität (HRQoL), postoperativer Nebenwirkungen und schwerwiegender unerwünschter Ereignisse (SAEs)?

Methoden

systematische Literatursuche in 4 Datenbanken

Die Beantwortung der Forschungsfragen bezüglich der Wirksamkeit und Sicherheit von implantierbaren Medizinprodukten zur Verstärkung des unteren Ösophagussphinkters durch Laparoskopie erfolgte anhand einer systematischen Literatursuche in folgenden Datenbanken:

- Medline via Ovid
- Embase
- The Cochrane Library
- HTA-INAHTA

Bewertung der Evidenzqualität nach dem GRADE-Schema

Zusätzlich wurde eine Handsuche durchgeführt und die Hersteller kontaktiert. Die Studienauswahl erfolgte unabhängig durch zwei Autor*innen (CS, JE). Studiendaten wurden von einem Autor (CS) extrahiert und von der zweiten Autorin (JE) kontrolliert. Die Bewertung der Qualität der Evidenz nach GRADE (Grading of Recommendations Assessment, Development and Evaluation) wurde von zwei Autor*innen (CS, JE) vorgenommen. Zusätzlich wurde das Verzerrungsrisiko der Studien bewertet.

Klinische Wirksamkeit

***entscheidende* Endpunkte für die Wirksamkeit …**

Zur Bewertung der klinischen Effektivität von implantierbaren Geräten zur Verstärkung des unteren Ösophagussphinkters durch Laparoskopie wurden die folgenden Endpunkte als *entscheidend* für eine Empfehlung eingestuft: HRQoL, Sodbrennen- und Regurgitationscore.

Sicherheit

… und Sicherheit

Zur Bewertung der Sicherheit von implantierbaren Geräten zur Verstärkung des unteren Ösophagussphinkters durch Laparoskopie wurden die folgenden *entscheidenden* Endpunkte für eine Empfehlung herangezogen: unerwünschte Nebenwirkungen (AEs), SAEs und Todesfälle.

Ergebnisse

Verfügbare Evidenz

insgesamt 7 Studien für alle 3 Verfahren eingeschlossen;

MSA: 1 Cross-Over-RCT mit PPI-Komparator & 3 einarmige Beobachtungsstudien; RS: 1 prosp. einarmige Studie;

Insgesamt erfüllten sieben Studien (in neun Publikationen) für alle drei Geräte die vordefinierten Einschlusskriterien. Vier Studien, eine randomisierte kontrollierte Studie (RCT) veröffentlicht in zwei Publikationen, zwei einarmige Studien und eine registerbasierte Studie (in zwei Publikationen) untersuchten die MSA. Für die Bewertung von RS wurde eine prospektive einarmige Studie und für die Bewertung des EST-Geräts wurden zwei prospektive einarmige Studien eingeschlossen. Für den Einschluss von prospektiven einarmigen Studien wurde ein Cut-off von mindestens 100 (MSA) bzw. 30 (RS, EST) Patient*innen definiert. Die Analyse der Wirksamkeit beschränkte sich auf kontrollierte Studien. Insgesamt konnte nur für die MSA eine Studie zur

EST: 2 prosp. einarmige Studien

keine Studie zur Bewertung der Wirksamkeit für RS & EST

Untersuchung der klinischen Wirksamkeit identifiziert werden, wodurch die Daten von insgesamt 152 Patient*innen (Interventionsgruppe [IG]: 50 versus Kontrollgruppe [KG]: 102) ausgewertet werden konnten. Für die Sicherheitsanalyse der **MSA** wurden zusätzlich zwei prospektive einarmige Studien und eine registerbasierte Studie mit insgesamt 656 Patient* innen miteinbezogen. Bei der systematischen Literaturrecherche zur Bewertung der klinischen Wirksamkeit von **RS** und der **EST** wurden keine Studien identifiziert, die die Einschlusskriterien erfüllten. Allerdings erfüllten eine Studie für **RS** mit 50 Patient*innen und zwei Studien für die **EST** mit insgesamt 81 Patient*innen die Einschlusskriterien für die Analyse sicherheitsrelevanter Endpunkte.

Einschluss: BMI ≤35 kg/m²

Ausschluss: Hiatushernie >3 cm, Ösophagitis LA Grad C&D (Ausnahme 1 Studie – Anzahl Pat. aber minimal: 1.6 % bzw. 1 %)

Studienpopulation recht homogen (Ausnahme 1 Studie für die EST)

Alle identifizierten Studien für jedes der drei Geräte schlossen chronische und refraktäre GERD-Patient*innen ein, wobei die meisten Studien berichteten, dass ein großer Anteil der Patient*innen in der Vergangenheit täglich PPI eingenommen hatte. In allen Studien kamen nur Patient*innen mit einem BMI ≤35kg/m^2 in Frage. Darüber hinaus wurden Patient*innen mit einer Hiatushernie von mehr als drei Zentimetern und Patient*innen, die eine Ösophagitis vom Los Angeles (LA) Grad C und D aufwiesen, in allen Studien (mit Ausnahme von zwei) ausgeschlossen: Eine Studie, die die **EST** untersuchte, berichtete nicht näher über die Ein- und Ausschlusskriterien, und die prospektive, registerbasierte Studie für die **MSA** schloss auch einen minimalen Anteil an Patient*innen (1,6 %) mit einer Hiatushernie von mehr als drei Zentimetern und Patient*innen mit Ösophagitis LA Grad C oder D (1 %) ein. Insgesamt schien die Studienpopulation in den und quer über die Studien, recht homogen zu sein, mit Ausnahme einer Studie, in der das **EST**-Gerät untersucht wurde.

Klinische Wirksamkeit

Wirksamkeitsdaten nur für MSA verfügbar

2 Vergleichsszenarien: vollständige MSA-Kohorte (inkl. Cross-Over) vs PPI-Kohorte nach 6 Monaten & primäre MSA-Kohorte vs PPI-Kohorte nach 12 Monaten

Die einzige Studie, die für die Ableitung einer Empfehlung in Bezug auf entscheidende Wirksamkeitsergebnisse für die laparoskopische **MSA** in Frage kam, war ein Cross-Over-RCT. Es lagen zwei Veröffentlichungen mit unterschiedlichen Nachbeobachtungszeiträumen (sechs und 12 Monate) vor, in denen **MSA** mit einer PPI-KG verglichen wurde. Geeignete Patient*innen im PPI-Arm konnten nach sechs Monaten eine **MSA** erhalten. In dieser Studie wurden Vergleichsdaten nach der letzten Nachuntersuchung jeder Kohorte auf der Grundlage der zuletzt erhaltenen Behandlung berichtet: „vollständige“ (vollst.) **MSA**-Kohorte (mit Cross-Over) vs PPI-KG nach sechs Monaten und „primäre“ **MSA**-Kohorte (ohne Cross-Over) vs PPI-KG nach 12 Monaten.

GERD-HRQL für HRQoL & Sodbrennen

FSQ & RDQ für Regurgitation

Die Studie verwendete den krankheitsspezifischen GERD-HRQL-Fragebogen zur Messung der gesundheitsbezogenen Lebensqualität (HRQoL). Zur Messung der Regurgitationssymptome (Beseitigung der mittelschweren bis schweren Regurgitationssymptome) wurden der Foregut Symptom Questionnaire (FSQ), ein nicht validierter Fragebogen, und der Reflux Disease Questionnaire (RDQ) verwendet. Zur Messung der Sodbrennen-Symptome wurde die Sodbrennen-Komponente des GERD-HRQL-Fragebogens ausgewertet.

Verbesserungen in GERD-HRQL-Score ≥50 % von Baseline für MSA-Pat. vs keine Verbesserung für PPI-Pat. (beide Vergleichsszenarien)

Bei beiden Vergleichen verringerte sich der mittlere GERD-HRQL-Score (Verbesserung der Lebensqualität) der Patient*innen, während in der PPI-Kohorten nach sechs Monaten und 12 Monaten keine Verbesserungen eintraten. Während ein Großteil der Patient*innen in den MSA-Kohorten (81 % bzw. 93 %) eine Verringerung des GERD-HRQL-Scores um ≥50 % nach sechs bzw. 12 Monaten gegenüber dem Ausgangswert zeigten, wies kein*e Patient*in in den PPI-Kohorten nach sechs bzw. 12 Monaten eine Verringerung des GERD-HRQL-Scores um ≥50 % gegenüber dem Ausgangswert auf.

Die Studie zeigte einen statistisch signifikanten Unterschied in der Beseitigung der mittelschweren bis schweren Regurgitation in der vollst. MSA-Kohorte im Vergleich zur PPI-Kohorte bei der 6-monatigen Nachuntersuchung ($p<0.001$). Während 51 von 75 Patient*innen in der vollst. MSA-Kohorte eine vollständige Beseitigung der Regurgitation aufwiesen, hatte nur ein Patient in der PPI-Kohorte keine Regurgitationssymptome nach sechs Monaten ($p<0{,}001$). Der mit dem RDQ bewertete Regurgitationscore zeigte bei der vollst. MSA-Kohorte nach sechs Monaten eine Verringerung (Verbesserung) des mittleren Scores im Vergleich zur PPI-Kohorte, die nach sechs Monaten keine signifikante Verbesserung aufwies. In der primären MSA-Kohorte ging der Wert ebenfalls zurück, während in der PPI-Kohorte nach 12 Monaten keine signifikante Verbesserung zu verzeichnen war (p-Werte = keine Angabe). Die Autor*innen berichteten, dass in der primären MSA-Kohorte nach 12 Monaten Verbesserungen in der Sodbrennen-Komponente des GERD-HRQL zu beobachten waren, während in der PPI-Kohorte keine Verbesserungen auftraten.

stat.sign. Unterschied in Beseitigung mittelschwerer bis schwerer Regurgitation im Vergleich zu PPI

Verbesserung auch im RDQ-Score & Sodbrennen via GERD-HRQL

Sicherheit

Da keine RCTs identifiziert wurden, die chirurgische Verfahren oder Medizinprodukte für die Unterstützung des UÖS miteinander vergleichen, konnten keine verfahrens- oder gerätebezogenen Sicherheitsvergleiche angestellt werden. Allerdings berichteten insgesamt sieben Studien (**MSA**: 4, **RS**: 1, **EST**: 2) für alle drei Geräte über AEs und SAEs.

keine verfahrens- & gerätebezogenen Sicherheitsvergleiche

Im RCT wurde bei der großen Mehrheit der **MSA**-Patient*innen nach 12 Monaten keine wesentliche de novo oder übermäßige Dysphagie – häufige unerwünschte Ereignisse nach Operationen (OP) – beobachtet. Die Dysphagie nahm sogar postoperativ gegenüber dem Ausgangswert ab. Eine geringe Anzahl von Patient*innen, die sich in den drei prospektiven einarmigen Studien einer laparoskopischen **MSA** unterzogen hatten, litten unter postoperativer Dysphagie, übermäßigen Blähungen oder waren nicht in der Lage, aufzustoßen und zu erbrechen. Im Falle von **RS** kamen auch keine neuen Fälle von Dysphagie vor und die übermäßigen Blähungen nahmen im Laufe des Follow-Ups ab. Bei den Patient*innen, die ein **EST**-Gerät implantiert bekamen, nahmen exzessive Blähungen, Ösophagitis und Dysphagie im Vergleich zum Ausgangswert bei der 24-monatigen Nachbeobachtung insgesamt ab.

keine übermäßige Dysphagie bei allen 3 Geräten

kleiner Anteil der Pat. mit übermäßigen Blähungen oder Problemen beim Aufstoßen

Im RCT für **MSA** wurden keine AEs und schwerwiegenden unerwünschten gerätebezogenen Effekte (SADEs) berichtet, und kein Gerät wurde explantiert. Ein verfahrensbedingtes SAE (Speiseröhrenspasmus kurz nach der OP) trat bei einem Patienten im RCT auf, und acht Patient*innen erlitten intraoperative Komplikationen in der prospektiven, registerbasierten Studie bei der Implantierung des **MSA**-Geräts. In der **RS**-Studie wurden ebenfalls keine unerwünschten gerätebezogenen Effekte (ADEs) berichtet, allerdings traten acht verfahrensbezogene und andere nicht gerätebezogene AEs bei acht Patient*innen und sieben verfahrensbezogene SAEs bei fünf von 47 Patient*innen während der 12-monatigen Nachbeobachtungszeit auf. In den Studien zum **EST**-Gerät wurden 59 verfahrens- und gerätebedingte AEs und acht geräte- und verfahrensbedingte SAEs bei acht von 79 Patient*innen berichtet.

MSA: keine AEs & SADEs, 1 SAE im RCT & 8 Pat. intraoperative Komplikationen in prosp. einarmigen Studien

RS: keine ADEs, 8 nicht-gerätebezogene AEs & 7 SAEs

EST: 59 AEs & 8 SAEs

Während vier Patient*innen im **MSA**-RCT erneut operiert wurden und die Rate der Geräteentfernungen in den prospektiven einarmigen **MSA**-Studien zwischen 2,4 % und 7 % lag, wurde in der **RS**-Studie kein Gerät explantiert. Im Gegensatz dazu wurden bei allen sechs Patient*innen, die sich einer **EST** unterzogen und bei denen SAEs auftraten, die Geräte explantiert. Todesfälle wurden für keines der Geräte berichtet.

MSA: 4 Re-OPs bzw. Rate 2,4 %-7 %;
RS: 0 Re-OPs;
EST: 6 Explantationen

Laufende Studien

bisher kein Vergleich MSA vs LF in RCTs & wenig robuste Langzeitdaten

RS & EST auch keine RCTs

Systematische Übersichten und Meta-Analysen von Beobachtungsstudien haben zwar gezeigt, dass die **MSA** eine gleichwertige Kontrolle wie die LF bietet, gemessen an der Notwendigkeit einer postoperativen PPI-Therapie und dem GERD-HRQL, bei einem akzeptablen Sicherheitsprofil. Es wurden jedoch bisher keine RCTs veröffentlicht, die die **MSA** direkt mit dem chirurgischen Goldstandard LF vergleicht. Darüber hinaus gibt es nur wenig robuste Langzeitdaten zur Sicherheit und zum Auftreten von ADEs und SADEs. Für das **RS**-Implantat und die **EST** gibt es auch keine Studien, die Vergleiche mit LF oder PPI anstellen. In Ermangelung an RCTs, in denen diese drei Verfahren mit dem derzeitigen Goldstandard oder miteinander verglichen werden, ist es derzeit schwierig, eine Empfehlung abzugeben.

keine laufenden registrierten RCTs identifiziert

Bei der Suche nach klinischen Studien konnte keine laufende registrierte oder geplante kontrollierte Studie identifiziert werden, die eines der drei Geräte mit LF vergleicht. Für **MSA** wurden vier Beobachtungsstudien mit einem LF-Vergleich identifiziert. Es ist jedoch fraglich, ob diese Studien zur aktuellen Evidenz beitragen. Nach Angaben des Herstellers von **RS** (Implantica Trading AG) werden die Ergebnisse einer fünfjährigen Datenerhebung voraussichtlich Mitte bis Ende 2022 vorliegen. Darüber hinaus sind auch weitere internationale klinische Studien in Planung. Eine randomisierte kontrollierte Studie, in der die **EST** mit einer Scheinbehandlung verglichen wurde und eine Beobachtungsstudie wurden am 18. Oktober 2019 eingestellt, da das Unternehmen zu diesem Zeitpunkt nicht mehr tätig war.

Kostenerstattung

alle 3 Verfahren in Österreich derzeit nicht erstattungsfähig

Aktuell sind die **MSA**, die Implantation des **RS**-Devices und die **EST** nicht im österreichischen Leistungskatalog enthalten. Die mit der laparoskopischen **MSA** verbundenen Kosten umfassen den Preis des Geräts und des Sizing-Tools (€ 4.240 bzw. € 100) sowie das Operationsverfahren (Einrichtungen, Personal, Anästhesie, Krankenhausaufenthalt). Die **EST** wurde in Deutschland bis zur Insolvenz von EndoStim® Inc. erstattet. Der aktuelle Erstattungsstatus ist unklar. Die mit der **EST** verbundenen Kosten umfassten den Preis des Geräts (€ 8.240) und das Operationsverfahren (Einrichtungen, Personal, Anästhesie, Krankenhausaufenthalt). Preis- oder Kostendaten für das **RS**-Implantat sind nicht öffentlich verfügbar. Im Vergleich zur Fundoplikatio fallen zusätzlich zu den Kosten des Operationsverfahrens noch die Materialkosten und die anfängliche Schulung des chirurgischen Personals an. Aufgrund der kürzeren Operationszeit könnten die Verfahren aber etwas weniger kosten.

Diskussion und Fazit

für große Pat.-Gruppen ist die beste Evidenz erforderlich

Insgesamt konnte für zwei der drei Medizinprodukte, **RS** und **EST**, keine vergleichende Evidenz gefunden werden. **MSA** scheint die HRQoL, Sodbrennen- sowie Regurgitationssymptome im Laufe der Zeit zu verbessern, aber es wurde ausschließlich eine Verbesserung im Vergleich zur PPI-Medikation festgestellt. Für große Patient*innengruppen mit nicht akuten Erkrankungen wie GERD ist die beste Evidenz in Form von randomisierten kontrollierten Studien mit adäquaten Komparatoren nötig, um die Wirksamkeit nachzuweisen und mögliche sicherheitsrelevante Bedenken auszuschließen.

aktuell keine klare Aussage zur Wirksamkeit & Sicherheit möglich

qualitativ hochwertige Studien mit längerer Nachbeobachtungszeit & mehr Pat. notwendig

Zusammenfassend kann keine eindeutige Aussage darüber getroffen werden, ob die drei untersuchten Medizinprodukte zur Unterstützung des UÖS in der laparoskopischen Chirurgie zu wesentlich besseren Ergebnissen führen als die untersuchten Komparatoren und die aktuelle Standardversorgung, da keine belastbaren klinischen Vergleichsdaten vorliegen. Die LF, insbesondere die Fundoplikatio nach Nissen und Toupet, gilt als Goldstandard unter den chirurgischen Anti-Reflux-Verfahren zur Verbesserung der Funktion des UÖS. Bislang wurde keine randomisierte Studie veröffentlicht, die die **MSA**, das **RS**-Implantat oder die **EST** direkt mit dem Goldstandard LF vergleicht. Darüber hinaus gibt es nur begrenzte Langzeitdaten zur Sicherheit, z. B. zum Auftreten von gerätebedingten Erosionen, und es konnten keine Unterschiede im Sicherheitsprofil der drei Medizinprodukte im Vergleich zu chirurgischen Komparatoren festgestellt werden. Aus diesen Gründen wird in Zukunft qualitativ höherwertige Evidenz, z. B. RCTs und/oder NRCTs mit einer größeren Anzahl von Patient*innen (n>100) und längeren Nachbeobachtungszeiten (>2-3 Jahre) erforderlich sein, um die derzeit unsichere Evidenzlage zu klären und die derzeitigen Erkenntnisse über das Sicherheitsprofil zu ergänzen.

Empfehlung

Aufnahme in Leistungskatalog vorerst nicht empfohlen

Aufgrund von methodischen Defiziten und Ermangelung an robusten Daten reicht die derzeitige Evidenz nicht aus, um zu beweisen, dass die **magnetische Sphinkter-Augmentation** mit dem LINX® Reflux Management System zur Stärkung des UÖS in der laparoskopischen Chirurgie wirksamer und ebenso sicher oder ebenso wirksam und sicher ist wie die laparoskopische Fundoplikatio oder PPI bei chronischen GERD-Patient*innen. Die derzeitige Evidenz für **RefluxStop™** und die **Elektrostimulationstherapie** mit dem EndoStim®-Device reicht ebenfalls nicht aus, um zu beweisen, dass die Geräte wirksamer und gleich sicher oder gleich wirksam und sicherer sind als Standardbehandlungen wie die laparoskopische Fundoplikatio oder PPI bei chronischen GERD-Patient*innen. Aus diesem Grund werden die drei untersuchten implantierbaren Medizinprodukte zur Verstärkung des unteren Ösophagussphinkters durch Laparoskopie vorerst nicht für die Aufnahme in den österreichischen Krankenhausleistungskatalog empfohlen.

1 Background

1.1 Overview of the disease, health condition and target population[1]

GERD: Reflux aus dem Magen in die Speiseröhre

Surgical management is considered in patients with moderate-to-severe gastroesophageal reflux disease (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 [1-4]. Symptoms are considered troublesome if they adversely affect an individual's wellbeing.

laparoskopische Operationsverfahren: 2. Linien-Behandlung für chronische GERD-Pat. trotz PPI-Therapie oder bei Pat. mit PPI-Nebenwirkungen

Anti-reflux surgery, including endoscopic or laparoscopic procedures, is a second-line treatment for GERD patients …

- in whom GERD is incompletely controlled by optimal medical therapy with proton pump inhibitors (PPI) and lifestyle modifications,
- in whom GERD symptoms recur despite initial successful medication, and
- who refuse to take life-long medication or suffer from side-effects of PPI therapy [5, 6].[2,3]

GERD aus chirurgischer Perspektive: Schwäche des unteren Ösophagussphinkters (UÖS)

From a surgical perspective, GERD is the failure of the anti-reflux barrier. GERD is a mechanical disorder caused by a defective lower esophageal sphincter (LES), gastric emptying disorder, or failed esophageal peristalsis. When the anti-reflux barrier functions improperly, abnormal reflux of gastric contents gets into the esophagus. Depending on the nature of the condition, GERD can be generally acidic or non-acidic:

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

Symptome: Sodbrennen, Aufstoßen, Magenschmerzen

The abnormalities result in a spectrum of disease ranging from gastrointestinal symptoms such as heartburn, acid regurgitation, to esophageal tissue damage with or without subsequent complications, including malignancy or airway disease [6]. The exact mechanism by which non-acid reflux episodes produce symptoms remains uncertain [7].

laparoskopische Operation (OP) nur bei objektiver Evidenz von Reflux empfohlen

Furthermore, surgery may be indicated for extra-esophageal GERD symptoms such as chronic cough, laryngeal disease, or asthma, but only when there is solid objective evidence to attribute such symptoms to the reflux [5]. For patients without objective evidence of reflux and patients who fail to meet objective criteria such as hypotensive lower esophageal sphincter, surgery is not recommended as evidence for this population is contradictory [3, 5].[2]

Risikofaktoren: anatomische Faktoren, Ernährung & Lebensstil

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 (e.g. tobacco smoking), as well as obesity [8]. Eating reflux-

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[1] This section addresses the following assessment HTA CORE MODEL DOMAIN: CUR

[2] **A0002** – What is the disease or health condition in the scope of this assessment?

[3] **A0001** – For which health conditions and for what purposes are LES devices in laparoscopic surgery used? &
A0007 – What is the target population in this assessment?

ogenic foods, overeating, eating immediately before going to bed, increased fat consumption in the diet, and expanding proportion of obese individuals are significant risk factors for GERD [6]. Factors that may contribute to the association of obesity and GERD include increased intra-abdominal pressure, a higher prevalence of hiatal hernia, a higher gradient of abdominal to thoracic pressure, increased levels of oestrogen, and increased production of bile and pancreatic enzymes [8].[4]

ungeklärter natürlicher Verlauf

The natural history of the disease has not been well clarified yet. Currently, two concepts exist[5]:

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

GERD Komplikationen: erosive Ösophagitis, Stenose, Barrett-Ösophagus (BE)

- The traditional concept considers 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 40 times greater incidence than in the general population [9].

neues Konzept: 3 individuelle Beschwerden (NERD, erosive Ösophagitis, BE)

- 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 the progression of NERD to erosive esophagitis is possible in 10% of GERD patients [9].

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

Belastung für Pat.: Lebensqualität, Lebensstil, Ernährung & lebenslange Medikation mit potentiellen schwerwiegenden Nebenwirkungen

The major burden for GERD patients is the impact on quality of life (QoL) through the experience of GERD symptoms such as heartburn, extra-esophageal manifestations (pulmonary or ear, nose, throat), or non-cardiac chest pain [10]. Moreover, patients often complain about sleep disturbance. 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 [11]. For example, high-quality studies have found that PPIs increase the risk of intestinal infections caused by various germs, because the pH value is raised unphysiologically by medication [3][6].

globale Prävalenz ~14 % (häufigste Erkrankung des oberen Magen-Darm-Trakts in Ländern mit hohem Einkommen);

10 %-40 % PPI-refraktär, 42 % potentielle Kandidat*innen für OP

The global pooled prevalence of GERD is estimated to be about 14% [12, 13]. However, prevalence of GERD around the world varies substantially depending on the specific country or region [14]. Whereas prevalence estimates in Europe suggest a range of 8.8%-25.9%, the range of GERD prevalence estimates in East Asia is 2.5%-7.8% [15]. Apart from estimates of local or global prevalence numbers, GERD is the most common upper gastrointestinal (GI) disease in high-income countries with 10%-20% of the population experiencing weekly symptoms [8, 9, 15]. Between 10%-40% of these patients are refractory to a once-daily PPI, of which 25% would respond to an increase in

[4] **A0003** – What are the known risk factors for GERD?

[5] **A0004** – What is the natural course of GERD?

[6] **A0005** – What is the burden of disease for GERD patients?

PPI dosing to twice daily [4, 10, 16]. However, 42% of GERD patients are dissatisfied with their PPI treatment outcomes and are potential candidates for surgical therapy [10][7].

zunehmende Häufigkeit, steigende Ressourcennutzung & gesellschaftliche Kosten

Due to its increasing incidence, particularly in developed countries, GERD is leading to growing utilisation of health care resources (e.g., medical consultations, emergency room visits, hospitalisation, and medication) [14, 15]. Not only doctor visits and diagnosis carry high financial expenses, but also medication and operation costs need to be considered in the long run [17]. On a societal level, the disease burden can affect work productivity which in turn results in substantial societal burden and costs [11].[8]

1.2 Current clinical practice[1]

1.2.1 Diagnosis

ACG, AWMF, WGO & Lyon Consensus: Richtlinien zur Diagnose von GERD

According to the American College of Gastroenterology (ACG) evidence-based clinical guideline [3], the S2k consensus-based guideline of the Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF) [5], the World Gastroenterology Organisation (WGO) guideline [18] and results from the Lyon GERD consensus meeting (2017) [19], general recommendations for the diagnosis of GERD are the following[9]:

- **mutmaßliche Diagnose bei eindeutigen Symptomen**
  A presumptive diagnosis of GERD can be established in the setting of **typical symptoms of heartburn and regurgitation** (once or twice a week).
- **diagnostische Evaluation bei nicht kardialem Brustschmerz**
  Patients with **non-cardiac chest pain** suspected due to GERD should have a **diagnostic evaluation** before the beginning of therapy. A cardiac cause should be excluded in patients with chest pain before the commencement of a GI evaluation.
- **obere Endoskopie bei Hochrisikopat.**
  Upper endoscopy is not required in the presence of typical GERD symptoms, but it is recommended in the presence of alarm symptoms (e.g. anorexia, dysphagia, unexplained weight loss, and anaemia) and for the screening of patients at high risk for complications in patients who do not respond to empirical PPI therapy. However, normal endoscopy results do not exclude GERD, but in combination with a distal esophageal acid exposure time of <4% and <40 reflux episodes on pH-impedance monitoring off PPIs, it offers supportive evidence to refute GERD.
- **ambulante Messung des ösophagealen Refluxes vor chirurgischem Eingriff**
  Ambulatory **esophageal reflux monitoring (ph-metry and impedance) off PPI medication** may be helpful in patients with persistent reflux-like symptoms who have responded poorly to standard therapy. It can provide confirmatory evidence before the considerations of 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. Ambulatory reflux monitoring is

[7] **A0023** – How many people belong to the target population?

[8] **A0006** – What are the consequences of GERD for the society?

[9] **A0024** – How is GERD currently diagnosed according to published guidelines and in practice?

the only test that can assess reflux symptom association with GERD. However, reflux monitoring off therapy solely as a diagnostic for GERD in patients known to have endoscopic of LA grade C or D[10] reflux esophagitis or in patients with long-segment BE is not recommended.

Ösophagus Manometrie zur Abklärung von motorischen Funktionsstörungen

- Before anti-reflux surgery, **esophageal high-resolution manometry** should be used for preoperative evaluation in order to assess the motor function or to rule out achalasia in GERD patients. Hence, achalasia, peristalsis, and alternative major motility disorders can be detected in advance. Esophageal manometry is not recommended for the initial GERD diagnosis.

Schweregrade: mild, moderat, schwer

A generally accepted definition regarding 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.

1.2.2 Clinical management

Medical and lifestyle interventions[11]

Behandlung von GERD abhängig vom Schweregrad

Generally, a stepwise approach with respect to therapies in order to manage GERD is recommended [3, 5, 18]. The management of GERD is aligned with the frequency and severity of symptoms as well as the presence of erosive esophagitis or BE identified by upper endoscopy.

As a first step lifestyle modifications are suggested including [3, 5, 21]:

erster Schritt → Veränderung des Lebensstils

- **Weight loss** for GERD patients who are overweight or have recently gained weight (*conditional recommendation, moderate level of evidence*).
- **Head of bed elevation** and **avoidance of meals two to three hours before bedtime** for patients with nocturnal GERD (*conditional recommendation, low level of evidence*).

H2RA-Therapie bei milden & moderaten GERD-Symptomen

From mild to intermittent (less than two episodes per week) symptoms of GERD, first-line therapy with a low-dose histamine 2 receptor antagonist (H2RAs) is recommended [21].

PPI-Therapie bei bestehenden GERD-Symptomen

If GERD symptoms persist and H2RA therapy is not sufficient, a low-dose once-daily PPI therapy is suggested. Increases to standard doses for symptom control can be considered. If the symptoms are controlled, the therapy should be continued for at least eight weeks [3]. In patients with erosive esophagitis, BE or in cases of severe symptoms that impact the QoL, an initial therapy with standard PPI doses once daily is recommended. PPI therapy

[10] The Los Angeles (LA) classification is the most thoroughly evaluated classification for esophagitis and is the most widely used. It grades esophagitis severity by the extent of mucosal abnormality, with complications recorded separately. Grade A: One or more mucosal breaks each ≤5 mm in length, Grade B: At least one mucosal break >5 mm long, but not continuous between the tops of adjacent mucosal folds, Grade C: At least one mucosal break that is continuous between the tops of adjacent mucosal folds, but which is not circumferential, Grade D: Mucosal break that involves at least three-fourths of the luminal circumference [20].

[11] **A0025** – How is GERD currently managed according to published guidelines and in practice?

should be discontinued in GERD patients whose symptoms resolve, except for those with severe esophagitis, BE or patients with recurrent symptoms within three months of discontinuing PPI treatment. Non-responders to PPI therapy should be referred for evaluation [3, 5, 21].

~10 %-40 % der GERD-Pat. sprechen nicht auf die Standarddosis der PPI-Therapie an

Around 10%-40% of GERD patients fail to respond symptomatically, partially or completely to standard doses of PPIs. Insufficient acid suppression, reflux hypersensitivity, functional heartburn as well as an alternative aetiology can be reasons for continued symptoms. Patients who suffer from continued symptoms should be carefully reassessed especially considering the timing of and compliance to PPI treatment as well as the type of ongoing symptoms and the presentation of defined alarm symptoms (e.g. anorexia, dysphagia, unexplained weight loss) that could indicate a GI malignancy [4].

Behandlung von GERD nach PPI-Therapieversagen:

Further diagnostic evaluation and treatment of refractory GERD are based on the aforementioned alarm symptoms as well as the type of ongoing symptoms (see Figure 1-1). If alarm symptoms can not be identified via upper endoscopy the following management options are available for GERD patients [4]:

Anpassung der PPI-Therapie

- Initial management includes the reinforcement of lifestyle modifications as well as compliance with PPI treatment.
- If the symptoms persist despite a dose of once-daily PPI therapy a twice-daily administration can be suggested or patients can switch to a different PPI therapy.

Therapieentscheidung basierend auf ösophagealer Impedanz Analyse:

Subsequent management of GERD patients who have failed twice-daily PPI treatment includes esophageal pH testing (based on the pH of the refluxate). Dependent on the result of the pH testing the following treatment options are available [4]:

negativ: Schmerzmittel

- **Negative for acid reflux:** pain modulators can be administered such as tricyclics, selective serotonin reuptake inhibitors (SSRIs), trazodone or serotonin-norepinephrine reuptake inhibitors (SNRIs).

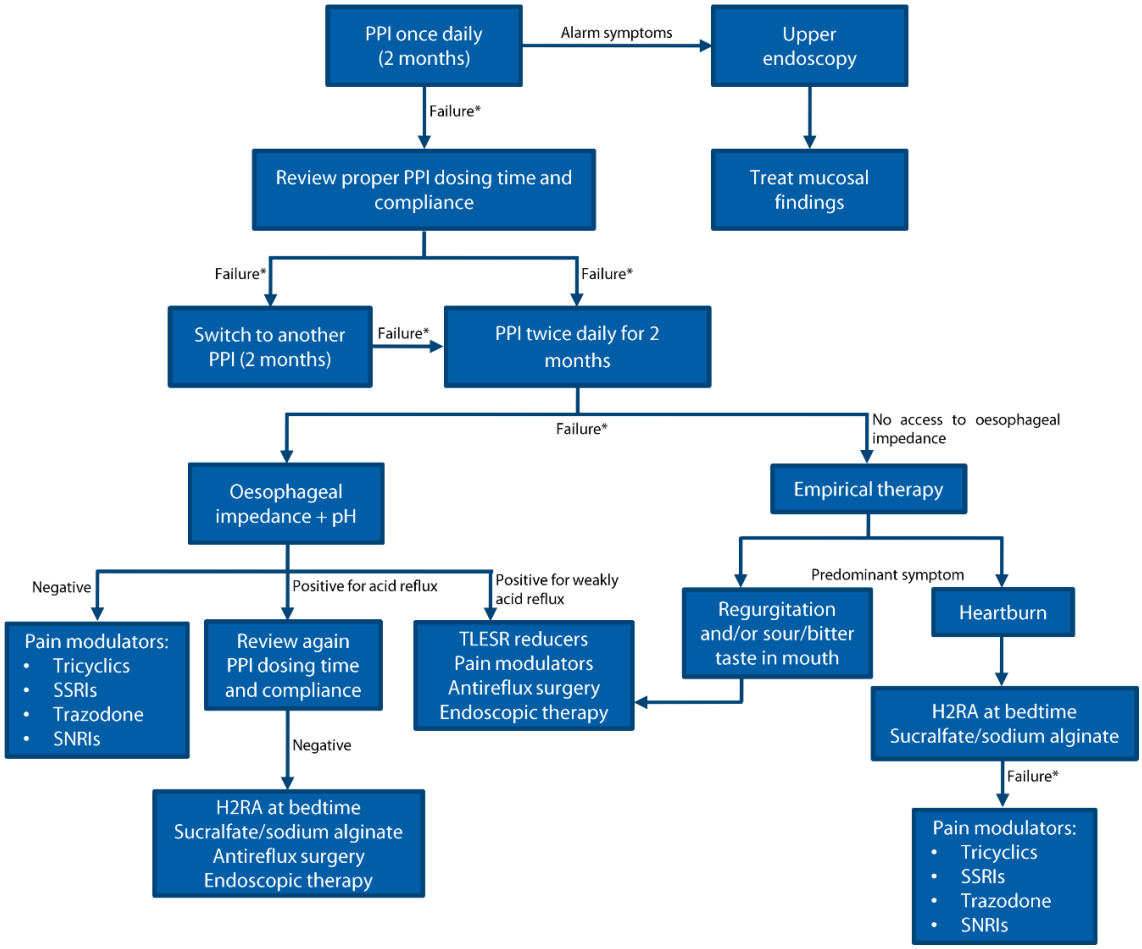
positiv: Anpassung der PPI-Therapie, H2RA abends, chirurgischer Eingriff

- **Positive for acid reflux:** another review of the actual dosing of PPIs as well as compliance with the treatment is suggested. Subsequently, H2RA at bedtime, sucralfate/sodium alginate, anti-reflux surgery, or endoscopic therapy is recommended.
- **Positive for weakly acid reflux**[12]**:** transient lower esophageal sphincter relaxation (TLESR) can be applied as well as pain modulators, anti-reflux surgery, or endoscopic therapy.

keine Verfügbarkeit einer Impedanzanalyse → Behandlung auf Basis vorherrschender Symptome wie z. B. Sodbrennen/Regurgitation

In those cases where there is no access to esophageal impedance analysis, empirical management depended on the type of ongoing symptoms should be in place. If the predominant symptom is heartburn, H2RA at bedtime or sucralfate/sodium alginate can be considered. Persistent symptoms can be treated via pain modulators including tricyclics, SSRIs, trazodone, or SNRIs. In the case of the symptom regurgitation (and/or sour/bitter taste in the mouth), patients should be treated similarly to those whose pH analysis result was positive for weakly acid reflux (see Figure 1-1) [4].

[12] Reflux episodes with a pH of 4.0 to 7.0 is also defined as weakly acidic reflux, and GERD with a pH above 7.0 weakly alkaline. However, weakly alkaline reflux episodes have a low prevalence. That is why reflux is generally divided into acidic and non-acidic [7, 22].



**Abbreviations: H2RA – Histamine 2 receptor antagonist, PPI – Proton pump inhibitor, SNRI – Serotonin-norepinephrine reuptake inhibitors, SSRI – Selective serotonin reuptake inhibitors, TLESR – Transient lower esophageal sphincter relaxation*

Figure 1-1: Algorithmic approach to medical treatment of refractory GERD (own depiction adapted from [4])

Surgical management[11]

schwacher UÖS → OP möglicherweise indiziert

präoperative Evaluation essentiell

Medication with PPI does not restore the function of a weak LES [23]. Therefore, surgical management is sometimes indicated in GERD patients. As mentioned above in section 1.2.1, preoperative evaluation including upper endoscopy, esophageal reflux monitoring, esophageal manometry is key for a surgery decision [3-5]. Radiological examinations should not be performed for the diagnosis of GERD [3, 5], but video-supported radiologic examinations in anti-reflux surgery may be useful for surgical preoperative and postoperative morphologic evaluation in order to assess structural disorders or motility disorders [5, 18]. Several factors have to be considered to choose the most appropriate treatment option, i.e. laparoscopic or endoscopic surgery. Besides the mentioned indications and factors for anti-reflux surgery as a treatment for confirmed chronic or chronic refractory GERD (see section 1.1), patients with documented pathologic acid reflux who respond completely or partially to PPI are good candidates for anti-reflux surgery [24].

The degree of esophageal shortening, local expertise with surgical techniques as well as prior operations have to be taken into account as well. Furthermore, esophageal motility disorders, and the size of the hiatal hernia can influence the choice of surgical therapy. Anti-reflux surgery should be performed by an experienced surgeon as an option for long-term treatment of patients with objective evidence of GERD, especially those who have severe reflux esophagitis (LA grade C or D), large hiatal hernias, and/or persistent, troublesome GERD symptoms [3].

verschiedene Einflussfaktoren auf die Wahl des chirurgischen Eingriffs

Laparoscopic fundoplication approaches (LF), especially Nissen or Toupet fundoplication, are regarded as gold standard among the surgical anti-reflux procedures in order to improve the function of the LES [3, 5, 6, 25]. The ACG recommends laparoscopic techniques with devices reinforcing the LES such as the laparoscopic magnetic sphincter augmentation (MSA) as an alternative to LF for patients with regurgitation who fail medical management [3]. The use of the RefluxStop™ (RS) device or electrical stimulation therapy (EST) has not yet found its way into current guidelines [3, 5, 6, 18, 26]. Patients undergoing surgery with one of these three devices should have no large (>3 cm) or paraesophageal hiatal hernias, or prior upper gastrointestinal tract surgery to comply with the indications for which the devices were approved [24, 27-30]. Furthermore, obesity (body mass index >35 kg/m^2) of patients is also a contraindication for using devices supporting the LES. Roux-en-Y gastric bypass is considered the surgical gold standard for attaining weight loss management and associated reflux in obese (BMI >35kg/m^2) patients with objective evidence of GERD subsequent to medical weight loss [31-33]. Details of the devices and current treatment standards are presented in the next section 1.3 in more detail.

laparoskopische Fundoplikatio (LF) ist chirurgischer Goldstandard

ACG: magnetische Sphinkter-Augmentation per Laparoskopie als Alternative zu LF

RefluxStop™ & Elektrostimulationstherapie noch kein Teil von Leitlinien

chirurgischer Goldstandard für übergewichtige Personen (BMI >35 kg/m²): Roux-en-Y-Magenbypass

1.3 Description and technical characteristics of lower esophageal sphincter devices for laparoscopic surgery[13]

Features of the technologies & marketed products[14,15]

Over the last 30 years, optional minimal-invasive laparoscopic and endoscopic approaches for the (surgical) treatment of GERD have been developed. The technologies under investigation in the present report are novel laparoscopic approaches for reinforcing the native LES, of which the following three implantable devices are currently available on the market:

laparoskopische Verfahren für den UÖS

- **Magnetic sphincter augmentation** (**MSA**) using a magnetic implant: **LINX® Reflux Management System** by Ethicon, Johnson & Johnson/ Torax Medical [34]
- **Non-active silicone implant** (**RS**): **RefluxStop™** by Implantica Trading AG [29]
- Surgically implanted LES pacemaker/**Electrical stimulation therapy** (**EST**): **EndoStim®** by EndoStim® Inc. [35]

magnetische Sphinkter-Augmentation (MSA): LINX®

nicht-aktives Silikonimplantat: RefluxStop™ (RS)

Elektrostimulationstherapie (EST): EndoStim®

[13] This section addresses the following assessment HTA CORE MODEL DOMAIN: TEC

[14] **B0001** – What are LES devices in laparoscopic surgery and the alternative standard treatment options?

[15] **B0003** – What is the phase of development and implementation of LES devices in laparoscopic surgery and the alternative standard treatment options?

alle 3 Verfahren gelten als "Lückentherapie"

All three approaches are seen as a gap therapy [23, 36-38] for GERD patients who …

bei Unwirksamkeit & Nebenwirkungen der PPI-Therapie, oder auf Wunsch des/der Pat.

- potentially fail medical management, since PPIs do not address he underlying incompetency of the LES
- are dissatisfied with PPI or experience substantial side effects
- choose to undergo a rather minimal-invasive procedure and want to avoid potential significant side effects of LF.

geeignete Pat: Ösophagitis LA Grad A&B, Hiatushernie ≤3 cm, BMI<35 kg/m²

As mentioned, patients eligible for laparoscopic surgery with devices reinforcing the LES should have low-grade erosive esophagitis (LA grade A and B), abnormal esophageal acid exposure, and a hiatal hernia ≤3 cm, a BMI<35 kg/m^2 as well as show partial (or higher) responses to PPI treatment [27, 28, 30].

potentielle Vorteile: weniger invasiv, sicherer als LF, weniger Krankenhaustage & Nebenwirkungen, steile Lernkurve

In general, the three approaches claim to be less invasive as well as safer compared to LF by achieving similar efficacy results [8, 11, 36, 37]. The operation technique is less difficult, hence its reproducibility is higher and the learning curve for the surgeon is also shorter [6, 24].

Furthermore, the approaches claim to be associated with fewer side-effects and a shorter hospital length of stay [29, 39, 40].[16]

Magnetic sphincter augmentation[17]

MSA: magnetischer Speiseröhren-Ring aus Titanperlen

The laparoscopic **MSA** device is a ring of magnetic beads made of titanium that is placed around the lower esophagus, just above the stomach, using laparoscopy under general anaesthesia (see Figure 1-2). The ring is available in different sizes with 13, 14, 15, 16, or 17 beads [34]. The goal of the intervention is to reinforce the weak LES. The magnetic attraction between the beads is intended to help the LES resist opening to gastric pressures, preventing reflux from the stomach into the esophagus. Swallowing forces temporarily break the magnetic bond, allowing food and liquid to pass normally into the stomach. The magnetic attraction of the device closes the LES immediately after swallowing, restoring the body's natural barrier to reflux [34].

Verstärkung des UÖS: Ösophagus-Magen

minimal invasiv/ laparoskopisch eingesetzt

The device does not require any anatomic alteration of the stomach. It is implanted under general anaesthesia, using a minimally invasive surgical technique (laparoscopy). In order to select the right size for the LINX® device, the esophagus is measured by placing a sizing tool around the esophageal tube at the LES and measuring the circumference to get the best fit. The measurement tool is then removed and the LINX® device is positioned around the LES using suture tails. The ends of the device are aligned and joined for secure closure [34].

1 Produkt auf dem Markt: LINX® Reflux-Management-System; 2 Medizinprodukt-Generationen

The LINX® device has two generations. The first-generation device used a Ti-Knot Replacement System (LSI Solutions) to secure the ends of the device around the esophagus. The second-generation device is the same as the first-generation device, except that the ends of the device are secured with a clasp instead of suture. Additionally, sizing of the esophagus with the first-gener-

[16] **B0002** – What is the claimed benefit LES devices in laparoscopic surgery in relation to the alternative standard treatment options?

[17] **B0008** – What kind of special premises are needed to use LES devices in laparoscopic surgery? &
B0009 – What supplies are needed to use LES devices in laparoscopic surgery? &
B0004 – Who administers LES devices in laparoscopic surgery and in what context and level of care are they provided?

ation device used a color-coded sizing device of connected beads. With the introduction of the second-generation device, a laparoscopic sizing tool was introduced. The principles of sizing the esophagus remained the same, with the only difference being the tool used [41].

The other difference between the two generations is the MRI compliance. The first-generation device is MRI conditional only up to 0.7 tesla. Patients implanted with this device (before May 22, 2015) cannot undergo MRI above 0.7 tesla. The second generation is compatible with MRI up to 1.5 tesla. The new system is compatible with MRI systems because it contains a different grade of magnets that have a higher resistance to being demagnetised when subjected to external magnetic fields.

MRI- Kompatibilität: 1. Generation: 0.7 tesla, 2. Generation: 1.5 tesla

The LINX® device received CE marking in 2008 for the minimally invasive treatment of chronic gastroesophageal reflux disease (GERD), as defined by abnormal pH testing, for patients who continue to have chronic GERD symptoms despite maximum medical therapy, patients who are >18 years, have a BMI ≤35kg/m^2, have not had an operation of the esophagus, or of the gastrointestinal tract, have a normal motility, have no strictures, varices, achalasia or eosinophile esophagitis, have had no significant psychological disorders, the maximum level of esophagitis is grade A or B, or have regurgitation. Patients with a hiatal hernia >3 cm are subject to evaluation based on the severity of their symptoms and the clinical picture [34][18].

CE-Kennzeichung seit 2008 für Pat. >18 Jahre, BMI ≤35kg/m^2, LA Grad A&B Ösophagitis

The LINX® device has FDA approval since 2012 for the same indications [27]. In 2015, former device manufacturer Torax Inc. announced the FDA approval for the second generation of LINX® with MRI compatibility in June 2015. Over 30,000 devices have been distributed and implanted worldwide until 2021 [42].

FDA-Zulassung seit 2012 bzw. 2015 für die 2. Generation

RefluxStop™[17]

The **RS** implant is a non-active, implantable, single use device made out of sterile medical silicon (size ~21.5x21.5x21.5 mm and weight 9 g). It is made out of 5 parts and does not contain any metal or electronic components. To make the implant visible on X-ray, it contains barium sulphate.

RS: nicht-aktives Implantat aus medizinischem Silikon

The RS procedure is performed using standard laparoscopic techniques. The aim of the procedure is to reconstruct the esophagogastric angle in order to strengthen the upper part of the stomach by intussusception of the device in the pocket created from the anterior wall of the fundus [29, 30]. The implant acts then like a mechanical stop against the diaphragm muscle parallel to the LES and the hiatus opening in the diaphragm, leaving the food passageway unaffected. The pressure in the abdomen assures that the LES can function normally and blocks movement of the LES up into the thorax through the opening in the diaphragm breathing muscle. When this movement happens, then the LES does not have enough power to close while breathing resulting in reflux.

Ziel: Rekonstruktion des ösophagogastrischen Winkels zur Stärkung des oberen Teils des Magens → UÖS kann in Folge normal funktionieren

In the course of the laparoscopic surgery, the implant is placed on the outside of the stomach top fundus wall and covered by stomach tissue to keep the device at its correct place (see Figure 1-2) [30]. The silicone implant needs to be placed high-up, clearly above the upper edge of the LES. When the implant is fully below the upper edge of the LES, the device cannot function properly.

Silikonimplantat muss mit Hilfe eines zusätzlichen Instruments deutlich über dem oberen Rand des UÖS platziert werden

[18] **A0020** – For which indications have LES devices in laparoscopic surgery received marketing authorisation or CE marking?

The placement of the device is done using a special instrument (RefluxStop™ deployment tool) that also compresses the device before insertion. Furthermore, the implant must be positioned close to the esophagus in order for the device to work correctly. The left lateral part of the esophagus should be attached to the stomach fundus wall by either three parallel continuous non-absorbable sutures ('larger' fundus) or by two continuous sutures in a Y-shape with short tail with one additional single suture in between the top of the Y ('smaller' fundus). Fat in the suture line attachments should be avoided as much as possible [30].

CE-Kennzeichnung seit 2018

RS and the deployment tool received CE mark approval on August 8, 2018 and is intended to reduce clinical acid reflux symptoms in patients with GERD [29][18].

Electrical stimulation therapy[17]

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

The EST comprises of three components: a bipolar stimulation lead with two stitch electrodes, an implantable pulse generator (IPG), and an external programmer [43]. 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 65x48x12mm and weight 49g), it is connected to the stimulation leads, and permanently implanted in a subcutaneous pocket in the left upper quadrant of the abdomen [43]. The IPG contains a medical grade lithium battery, microelectronics, communication coils, and an accelerometer for sensing patient posture [43]. The IPG is programmed by an external programmer via laptop PC software [43].

Implantation erfolgt mittels laparaskopischem Eingriff

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 (see Figure 1-2) [38]. Endoscopic visualisation of the gastroesophageal junction is used to ensure that the wires do not enter the lumen [38]. The wires are then connected to a stimulator placed in the subcutaneous pocket in left upper quadrant of the abdominal wall [38]. 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 [44].

durch die externe Programmierung kann der Stimulator ein- & ausgeschalten, sowie die Polarität & Stromstärke adaptiert werden

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 [38]. 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 personalised. Electrical stimulation is delivered using a 220 [39] or 215-ls pulse at 20 Hz and 3-8 mA in 30min sessions, 6-12 time per day with 90min breaks [44, 45].

derzeit ist EndoStim® das einzige zugelassene EST-Gerät

The EST technology is utilised by one product only, the EndoStim® LES stimulator, developed by EndoStim® Inc [38][19]. 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

[19] By the time the scoping phase was completed, the manufacturer EndoStim® Inc. was insolvent [46]. In the meantime, the website (www.endostim.com) is accessible again, but no comprehensive information is available and the contact form did not work in order to obtain new information. For these reasons, information from the original systematic review by the Ludwig Boltzmann Institute for HTA (LBI HTA) [47] and current information from the EndoStim® website are adopted for the description of the marketing authorisation.

25% thinner and has 40% less volume. EndoStim II® has a battery lasting approximately 7 years. Initial correspondence with EndoStim® Inc. indicated that the therapy delivered as well as the lead and electrodes used are identical in both devices [47].

Hauptunterschied zwischen EndoStim I® & 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 [47]. In the United States, EndoStim II® seeks approval by the FDA and is currently allowed for investigational use only [48][18].

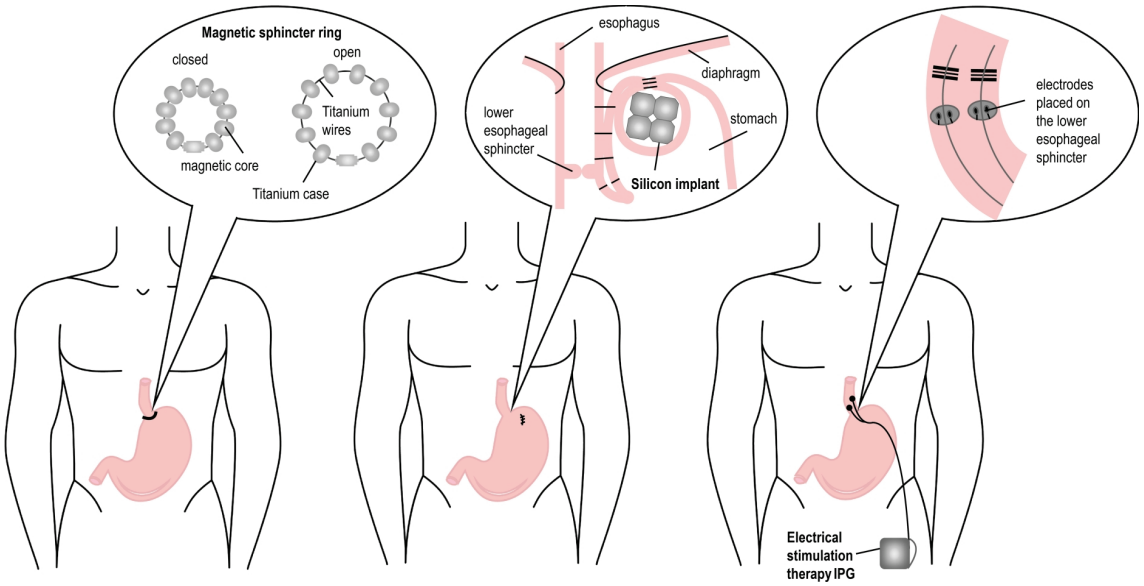


Figure 1-2: Devices/procedures for reinforcing the LES (from left to right): Magnetic sphincter-augmentation, Non-active silicone implant/RefluxStop™, Electrical stimulation therapy (© SBlagojevic_AIHTA/own depiction adapted from [30, 49, 50])

Current standard procedure[14,15,17]

chirurgischer Goldstandard: laparoskopische Fundoplikatio

The current standard surgical treatment of GERD is 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 already mentioned above in section 1.2.2 [3, 5, 6, 25]. It was first performed in 1955 and has become the standard surgical anti-reflux treatment[15]. Fundoplication has several modifications, which include Nissen fundoplication and partial 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 per annum in Austria. 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 (e.g., hospital stay, fewer complications) with no significant differences in late outcomes; although the reoperation rate is higher in short-term [6, 40]. It is a complete or total wrap that encompasses 360° of the esophagus posteriorly.

partielle Fundoplikatio: 270 Grad Manschette (Toupet-Fundoplikatio)

- 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 [40]. Partial fundoplication is associated with less postoperative 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 [6].

LF keine standardisierte Operationstechnik

Laparoscopic fundoplication 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 standardised to improve patient outcomes.

Necessary personnel, premises, and length of stay[17]

ähnliche Anforderungen für alle laparoskopischen Verfahren

Implantation of MSA, EST, and RS and laparoscopic fundoplication is performed under general anaesthesia by a foregut surgeon. The guidelines suggest that fundoplication is 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 minimise morbidity and improve patient outcomes [6]. The premises, the operation team, and the supplies are similar, the only difference being the device itself along with the sizing tool to determine the individual device size needed (MSA), or the deployment tool (RS).

Hospitalisierungsdauer: 2 Tage (MSA) bzw. 3 Tage (EST & RS)

Submitting hospitals estimate that the length of inpatient stay is typically 2 days (min. 1 day, max 5. days) for MSA and EST and 3 days (min. 3 days, max 7 days) for RS, respectively.

Service volume, reimbursement, and costs

geschätzte jährliche Nutzung: 100 (MSA, EST) Intervention in ganz Österreich bzw. 15 Intervention mit RS im einreichenden Krankenhaus (KH)

According to data from the Umbrella Association of Austrian Social Insurance Institutions (formerly known as the Main Association of Austrian Social Security Institutions), in 2014 in Austria, the Code LM030 (open fundoplication/hiatusplasty[20]) was reimbursed 98 times, the LM040 (laparoscopic fundoplication/hiatusplasty) was refunded 1,723 times. According to the submission materials, the expected annual utilisation of MSA or EST based on the previous years' experience is 100 interventions per year in Austria. The expected annual utilisation of RS at the submitting hospital is 15 interventions per year[21].

bislang nicht erstattet

Kosten: € 4.240 (MSA-Gerät), € 8.240 (EST-Gerät), keine öffentlich zugänglichen Kostendaten zu RS

MSA, EST, and implantation of the RS is currently not included in the Austrian catalogue of benefits according to the submission documents received. Since current costs for the MSA and EST equipment were not available, reference is made to the cost data from the original reports by the Ludwig Boltzmann Institute for Health Technology Assessment (LBI HTA) [47, 51]. The costs associated with the MSA operation include the price of the device, the sizing tool (€ 4,240 and € 100 respectively), and the operation procedure (facilities, staff, anaesthesia, hospital stay). To our knowledge, the EST was re-

[20] Whether these open fundoplications were primary open procedures or conversions is not clear from the data.

[21] **A0011** – How much are LES devices in laparoscopic surgery utilised?

imbursed in Germany until the insolvency of EndoStim® Inc. The current reimbursement status is unclear. The costs associated with the EST operation includ the price of the device (8.240 €), and the operation procedure (facilities, staff, anaesthesia, hospital stay). Price or cost data on the RS device are not publicly available. In comparison to LF, the material costs and the initial training of surgical staff to undertake the implantation procedures are additional to the costs of the operation procedure, although the procedures under investigation might cost slightly less due to the shorter operation time[22].

[22] **A0021** – What is the reimbursement status of LES devices in laparoscopic surgery?

2 Objectives and Scope

2.1 Scope

Two of the three devices under consideration (**MSA** and **EST**) were each already studied in a report by the LBI HTA in 2015/2016 [51] (**MSA**) and 2016/2017 [47] (**EST**), respectively. This report builds on the search strategy of the previous reports and additionally analyses another device for reinforcing the lower esophageal sphincter: **RefluxStop™**, a non-active silicone implant. In contrast to previous reports, we applied stricter selection criteria with regard to the study design and cut-off value in terms of number of patients. In addition, we used the indications for which the devices were originally approved as inclusion criteria.

2 der 3 Medizinprodukte bereits durch LBI HTA untersucht: MSA & EST

neu: RefluxStop™

2.2 PICO question

Is implantation of a device reinforcing the lower esophageal sphincter (LES) through laparoscopy in comparison to standard of care in patients with chronic GERD more effective and equally safe or equally effective and safer concerning improvements in health-related quality of life (HRQoL) as well as post-operative side effects and serious adverse events (SAEs)?

PIKO-Frage

2.3 Inclusion criteria

Inclusion criteria for relevant studies are summarised in Table 2-1.

Einschlusskriterien (krit.) für relevante Studien

Table 2-1: PICO scheme for LES devices in laparoscopic surgery

Population	Adult patients with objective evidence of chronic, chronic refractory or moderate chronic gastroesophageal reflux disease (GERD) (>6 months) with continued reflux symptoms (ICD-10 K21.0/K21.9 or ICD-11 D22) despite proton pump inhibitor (PPI) treatment. Patient should be diagnosed with esophageal 24h (transnasal cathether) or 48h (wireless) monitoring off from acid suppression medication, if a previous pH monitoring or an endoscopy showing long-segment Barrett's esophagus or severe reflux esophagitis (LA grade C or D) has not established the diagnosis of GERD. Furthermore, high-resolution manometry (HRM) should be applied before anti-reflux surgery to rule out motility disorders (achalasia and absent contractility). Other inclusion criteria: BMI ≤35kg/m2, hiatal hernia (≤3 cm) Exclusion criteria, precautions and specific contraindications for each device: ■ Magnetic sphincter augmentation (MSA): Large hiatal hernia (>3 cm) or paraesophageal hiatal hernias, severe (LA grade C or D) esophagitis, Barrett esophagus, obesity (body mass index >35 kg/m^2), esophageal dysmotility, or prior upper gastrointestinal tract surgery ■ Non-active silicone implant (RefluxStop™, RS): History of gastroesophageal surgery, anti-reflux or bariatric procedure, presence of a para-esophageal hernia or sliding hernia of >3 cm determined on endoscopy; presence of esophageal dysmotility disorder (not limited to scleroderma, achalasia, Nutcracker esophagus), severe (LA grade C or D) esophagitis, obesity (body mass index >35 kg/m^2) ■ Electrical stimulation therapy (EST): Significant cardiac arrhythmia, or ectopy, or significant cardiovascular disease, pregnant or nursing individuals, large (>3 cm) hiatal hernia, severe LA grade D esophagitis, long segment Barrett's esophagus or Barrett's esophagus with dysplasia

Population *(continuation)*	*MeSh terms: Gastroesophageal reflux disease (GERD)/Gastro-oesophageal reflux disease (GORD)/esophageal reflux/gastric acid reflux, (spontaneous) lower esophageal sphincter relaxation, incompetence of the lower esophageal sphincter*
Intervention	Implantation/insertion of a device reinforcing the lower esophagael sphincter (LES) through laparoscopic surgery[23]: ■ Magnetic sphincter augmentation (MSA) device (LINX® Reflux Management System), ■ Non-active silicone implant by the Forsell procedure (RefluxStop™, RS) ■ Electrical stimulation therapy (EST) device (EndoStim® LES stimulator), or *MeSH term: Laparoscopy/Laparoscopic assisted surgery/laparoscopic surgery, reinforcing/support of lower esophagael sphincter (LES)/gastroesophageal sphincter, magnetic titanium ring (MSA), electric stimulation therapy/therapeutic electric stimulation (EST), non-active implantable device (RefluxStop™)*
Control	■ PPI medication incl./excl. lifestyle modification ■ Standard surgical treatment of GERD: ■ If hiatal hernia >2 cm: Complete fundoplication (Nissen, Rosetti-Nissen) or partial fundoplication (Toupet) in combination with laparoscopic hiatusplasty ■ Sham treatment (placebo)
Outcomes	
Efficacy	Clinical endpoint: ■ GERD-Health-related quality of life (HRQoL) Intermediate outcomes: ■ Heartburn score ■ Regurgitation score ■ DeMeester score ■ Esophagitis ■ Discontinuation of anti-reflux medication (PPIs)
Safety	Adverse events (AEs) and adverse device effects (ADEs), serious adverse events (SAEs) and serious adverse device effects: ■ Any AEs and ADEs (device- and procedure related AEs including but not limited to dysphagia, excessive bloating, inability to belch or vomit, re-hospitalisation etc.) ■ SAEs and SADEs (device- and procedure related SAEs including but not limited to device explantation, re-surgery, device erosion etc.) ■ Death
Study design	
Efficacy	■ Randomised controlled trials ■ Prospective non-randomised controlled trials
Safety	■ Randomised controlled trials ■ Prospective non-randomised controlled trials ■ Prospective single-arm studies, prospective registry-based trials ■ Patient cut-off: min. 100 patients (MSA), min. 30 patients (EST, RS)

[23] If direct evidence is available, indirect comparisons – comparison of the different devices with each other – are excluded.

3 Methods

3.1 Research questions

EUnetHTA Core Model®

Assessment elements from the EUnetHTA Core Model® for the production of Rapid Relative Effectiveness Assessments (Version 4.2) were customised to the specific objectives of this assessment [52]. The assessment elements can be found in the Appendix and are referred to in footnotes in each chapter.

3.2 Clinical effectiveness and safety

3.2.1 Systematic literature search

systematische Literatursuche in 4 Datenbanken

The systematic literature search was conducted from 10th to 12th December 2021 in the following databases:

- Medline via Ovid
- Embase
- The Cochrane Library
- HTA-INAHTA

systematische Suche + Literatur Hersteller + Handsuche + bereits vorhandene Literatur: 460 Treffer (nach Deduplizierung)

The systematic literature search was conducted with no limitations to the study design. Since two of the three devices were already analysed in the course of an HTA report by the LBI HTA in the years 2015/2016 [51] and 2016/2017 [47], the literature search was limited to the year 2015 onwards. In the course of the two previous reports two relevant, additional publications were identified. By hand-search, no additional references were found. Moreover, two manufacturers (Implantica Trading AG, Ethicon) from the currently available LES devices (LINX®, RefluxStop™) were contacted. Only one manufacturer (Implantica Trading AG) responded and submitted one publication, which was already identified by the literature search. After deduplication, overall 460 citations were identified. The specific search strategy employed can be found in the Appendix.

Suche nach laufenden Studien: 100 potentielle Treffer

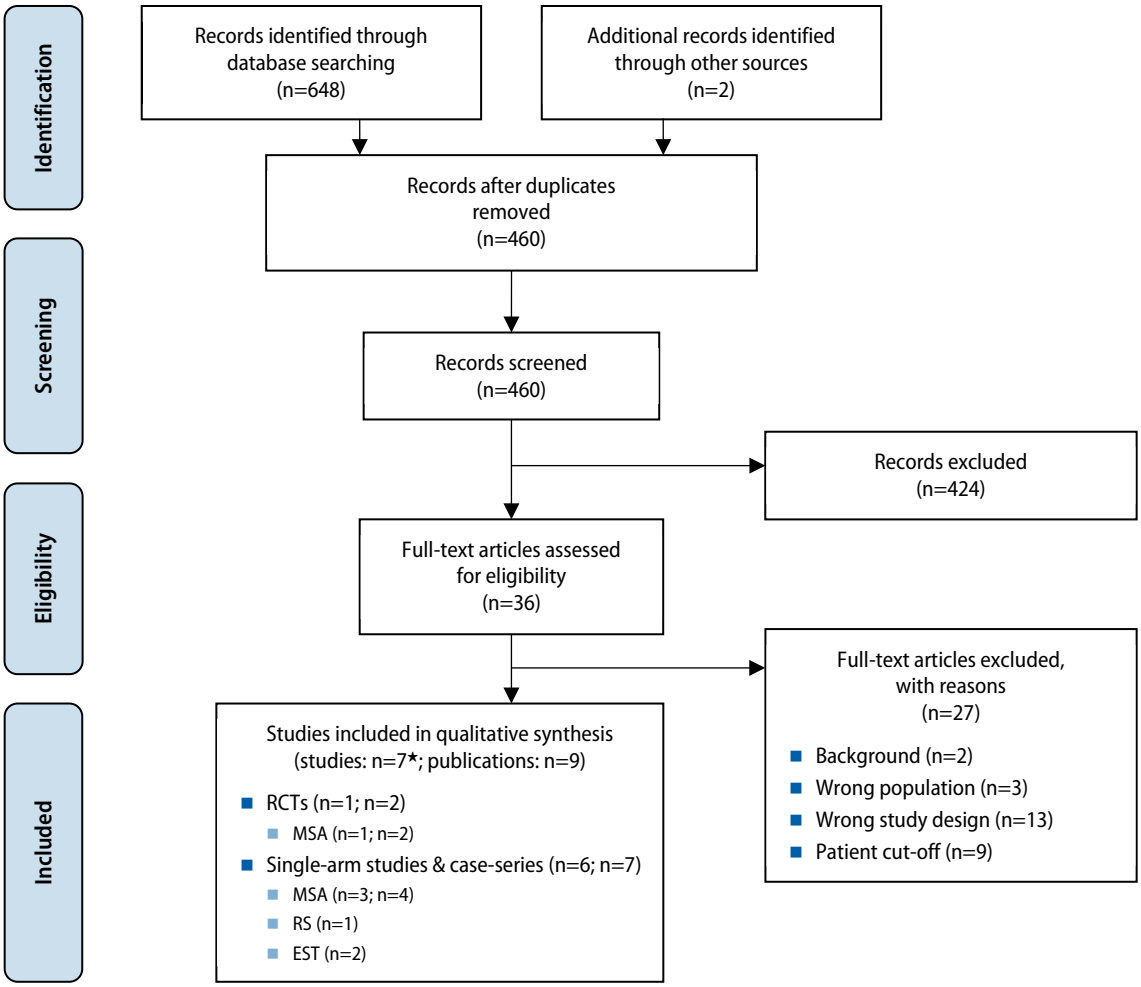
Furthermore, to identify ongoing and unpublished studies, a search in three clinical trials registries (ClinicalTrials.gov; WHO-ICTRP; EU Clinical Trials) was conducted on the 20th of January resulting in 100 potentially relevant hits (before deduplication). Ongoing prospective single-arm studies were only considered if they had enrolled at least 50 patients for each of the three devices.

3.2.2 Flow chart of study selection

Literaturauswahl: 7 Studien eingeschlossen (9 Publikationen)

MSA: 4 Studien
RS: 1 Studie
EST: 2 Studien

Overall 460 hits were identified after deduplication. The references were screened by two independent researchers (CS and JE) and in case of disagreement, a third researcher was involved to solve the differences. Generally, publications starting from 2015 onwards were included in the present report. Additionally, a threshold of at least 100 patients (MSA) and 30 patients (EST, RS) was applied in the case of prospective single-arm studies and prospective registry-based trials. Finally, seven studies (nine publications), four for MSA, two for EST, and one for RS were included for the qualitative analysis after applying predefined criteria (Table 2-1). The selection process is displayed in Figure 3-1.



** In the case of two studies additional publications (n=2) with different follow-up times were available.*
Abbreviations: EST – Electrical stimulation therapy, MSA – Magnetic sphincter augmentation, RS – RefluxStop™

Figure 3-1: Flow chart of study selection (PRISMA Flow Diagram).

3.2.3 Analysis

systematische Datenextraktion & Erhebung des Verzerrungspotentials

The data retrieved from the selected studies were systematically extracted into a data-extraction-table by one author (CS) and controlled by the respective co-author (JE) (see Table A-1, Table A-2, Table A-3, Table A-4). No further data processing (e.g., indirect comparison) was applied. Subsequently, two independent researchers (CS, JE) systematically assessed the risk of bias (RoB) of the included studies using the Cochrane RoB tool version 2.0 for randomised controlled studies (RCTs) [53] and the International Health Economics (IHE) [54, 55] checklist with 20 assessment elements for case series and single-arm studies (see Table A-5, Table A-6, Table A-7, Table A-8).

Overall RoB for single-arm studies was estimated using a predefined point score (range: 0-20; Table 3-1): a high score indicates a low RoB and a low score indicates a higher RoB. Detailed thresholds are presented in Table 3-2.

Table 3-1: Overall risk of bias (RoB) point scores for RoB assessment of case series and single-arm studies

Answers to specific questions of the IHE-20 checklist	Points
No	**0**
Partial	**0.5**
Unclear	**0.5**
Yes	**1**

Table 3-2: Cut-off criteria for the risk of bias (RoB) assessment of overall RoB of case series and single-arm studies

Criteria	Points
Low risk	**>18**
Moderate risk	**15.5 to 18**
High risk	**≤15**

3.2.4 Synthesis

Zusammenfassung der Ergebnisse mit GRADE

Based on the data-extraction-tables (see Table A-1, Table A-2, Table A-3, Table A-4), data on each selected outcome category were synthesised across studies according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE-)scheme [56]. The research questions were answered in plain text format with reference to GRADE evidence tables (see Table A-9).

4 Results: Clinical effectiveness and Safety

4.1 Outcomes

4.1.1 Clinical effectiveness outcomes

entscheidende Endpunkte für Wirksamkeit

The following clinical effectiveness outcomes were defined as *crucial* (*or critical*) to derive a recommendation:

- **Health-related quality of life (HRQoL)**
- **Heartburn score**
- **Regurgitation score**

HRQoL-, Regurgitation- & Sodbrennen-Score

Since, according to the traditional concept, GERD is a degenerative disease, the ultimate aim of the devices in question is to stop the process of degeneration by improving the function of the esophageal sphincter and thus improving patients' HRQoL. Besides, improvements in heartburn and regurgitation symptoms are considered as patient-relevant and therefore also included as *crucial* outcomes for a recommendation. Below the assessment of these crucial outcomes are presented in more detail.

HRQoL gemessen mit 2 Tools:

HRQoL can be measured by the following instruments:

- **GERD-Health Related Quality of Life Questionnaire (GERD-HRQL):**

  GERD-HRQL: 0-50; niedrigere Scores → bessere Lebensqualität

  The GERD-HRQL measures changes in typical GERD symptoms in response to surgical or medical treatment and includes questions about difficulties with swallowing, bloating, and medication intake. The best possible score is 0 (asymptomatic in each item) and the worst possible score is 50 (incapacitated in each item). It also reflects on the current patient satisfaction. This item is a numerical score and not reflected in the total GERD-HRQL score [10]. Currently, no value change indicating a minimal clinically important difference is available for the GERD-HRQL tool.

- **Foregut Symptom Questionnaire (FSQ):**

  FSQ-Score: 0-3; niedrigere Einstufung → mildere ösophageale Symptome

  The FSQ is a non-validated standardised survey that evaluates the severity of regurgitation, heartburn, and dysphagia symptoms. Regurgitation symptoms are classified in none, mild (after straining or large meals), moderate (predictable with position change, lying down, straining), and severe (constant). Scores for esophageal symptoms range from 0 (none) to 3 (severe) [57].

Regurgitation- & Sodbrennen-Score mittels GERD-HRQL & FSQ oder mit:

The heartburn score or the regurgitation score can be measured as part of the aforementioned GERD-HRQL and FSQ or with the following other quality-of-life survey:

- **Reflux Disease Questionnaire (RDQ):**

  RDQ-Tool: 1-5; niedrigere Scores → weniger & schwächere Symptome

  The RDQ is a self-administered questionnaire, which evaluates the frequency and severity of upper GI symptoms. The RDQ asks 12 questions addressing the symptom domains of heartburn, regurgitation, and dyspepsia by using a scale from 0 to 5 to rate the severity and frequency of 6 symptoms. Lower scores indicate lower frequencies as well as severities of symptoms [58, 59]. Currently, no value change indicating a minimal clinically important difference is available for the RDQ tool.

weitere relevante Endpunkte zur Beantwortung der Forschungsfragen: PPI-Medikation, Ösophagitis & ösophageale Säureexposition & DeMeester-Score

In addition to the *crucial* outcomes, the following outcomes were also considered relevant to answer the research questions:

- **PPI usage**: usage of PPI treatment at baseline and after the intervention has been performed.
- **Esophagitis and esophageal acid exposure**: Acid exposure in % of time with pH <4 and number of patients with esophagitis after last follow-up
- **DeMeester score**: Scoring system quantifying esophageal acid exposure time during long-term pH-metry.

4.1.2 Safety outcomes

entscheidende Sicherheitsendpunkte:

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

jegliche adverse & schwerwiegende adverse Ereignisse, Todesfälle

- **Any adverse events (AEs):** adverse device effects (ADEs) and procedure-related AEs including but not limited to dysphagia, excessive bloating, and inability to belch or vomit, re-hospitalisation etc.
- **Serious adverse events (SAEs):** serious adverse device effects (SADEs) and procedure-related SAEs comprising any adverse event with serious medical consequences, including post-operative mortality, complications that resulted in substantial morbidity or disability, an increase in the level of care (e.g., ICU), explantation/erosion of devices, endoscopic as well as laparoscopic re-surgery, admission to the hospital, or substantial prolongation of the hospital stay.
- **Death:** any reported death that could be intervention-related.

weitere sicherheitsrelevante Charakteristika

In addition to the *crucial* safety outcomes, further safety-related issues, such as susceptible patient groups or application relevant safety characteristics, were considered.

4.2 Included studies

4.2.1 Included studies clinical effectiveness

nur 1 kontrollierte Studie für Wirksamkeit von MSA

For evaluating clinical effectiveness outcomes, we exclusively considered RCTs and prospective NRCTs for all three devices (**MSA, EST, and RS**). In total, one RCT published in two publications [60, 61] investigating the clinical effectiveness of **MSA** device met the inclusion criteria[24] (Table 2-1). No

[24] In one prospective registry study published in two publications comparing MSA with laparoscopic fundoplication [62, 63], authors stated in the analysis protocol that the study was not a clinical study and not powered enough to test a hypothesis. Study authors report that there is an inherent bias built into the patient selection for the two treatments. A large proportion of the control group (LF) in the first publication and in the follow-up publication had a hiatal hernia >3cm (45.7% in [62] and 48.1% in [63]). In the MSA arm, only a very small proportion of patients (1.6%) had a hiatal hernia >3cm or exhibited LA esophagitis grade C or D (1%). Furthermore, patient populations in study arms significantly differed with respect to other characteristics such as age and presence of Barrett's esophagus. In addition, in both studies moderate GERD was prevalent in about 94%/90.8% of the population in the MSA arm compared to 38.3%/18.1% in the LP fundoplication arm. Hence, only the safety-relevant data of the MSA arm is considered for evaluation.

studies fulfilling the inclusion criteria were identified in the systematic literature search for assessing the clinical effectiveness of the **EST** and **RS** device.

Study characteristics

Magnetic sphincter augmentation

The identified RCT for the **MSA** device [60, 61] is a crossover RCT and initially included 152 patients (intervention group [IG]: 50 vs control group [CG]: 102) from 21 clinics in the USA. Two publications [60, 61] with different follow-ups (six and 12 months) were available. The comparator was medication therapy with PPI used twice a day (BID PPI) using omeprazole, 20mg. The study allowed eligible patients in the BID PPI arm to crossover in order to receive laparoscopic MSA after 6 months. Patients not qualified for crossover received a reduced 20mg daily dose of omeprazole (step-down PPI) over the subsequent 6-month follow-up.

MSA:
1 Cross-Over-RCT (n=152; Interventionsgruppe [IG]: 50 vs Kontrollgruppe [KG]: 102)

In this study [61], comparative data after the last follow-up of each cohort (either 6 or 12 months) based on the final treatment received are reported. The following reported comparisons are relevant for evaluation[25]:

- ***Comparison 1:*** Full MSA cohort (pooled) after six months[26] (n=75) vs BID PPI cohort at 6-month follow-up (n=87)
- ***Comparison 2:*** Primary MSA cohort (n=44) vs step-down PPI cohort (n=43) after 12 months[27]

2 Vergleichsszenarien: vollständige (vollst.) MSA-Kohorte (inkl. Cross-Over) vs PPI-Kohorte nach 6 Monaten & primäre MSA-Kohorte (ohne Cross-Over) vs PPI-Kohorte nach 12 Monaten

Over the 6-month follow-up [60], 13 patients (IG: 0 vs CG: 13) were lost-to-follow-up. Over the subsequent six months additional 9 patients (IG: 2 vs CG: 7) were lost-to-follow-up [61]. The study was sponsored by Ethicon/Torax Medical, Inc, the manufacturer of the LINX® Reflux Management System.

Studie finanziert durch Hersteller (Ethicon/Torax Medical)

Patient characteristics

Patients in the crossover RCT investigating the **MSA** device were eligible if they were 21 years or older, experienced moderate-to-severe regurgitation, had a hiatal hernia ≤3 cm, and had taken once-daily PPIs for more than eight weeks. Furthermore, patients were eligible if they had a BMI <35 kg/m^2, an abnormal pH test (DeMeester score with pH <4), and normal esophageal motility.

Einschlusskrit.:
≥21 Jahre, Hiatushernie ≤3 cm, PPI-Therapie ≥ 8 Wochen, BMI <35 kg/m^2

Exclusion criteria comprised among others Barretts' esophagus, LA grade C or D esophagitis, currently taking twice-daily PPIs or contraindication of twice-daily PPIs, history of gastric or gastroesophageal surgery or anti-reflux procedures, gastric cancer, or confirmed esophageal or gastric cancer, and titanium allergy (for the full list of exclusion criteria see Table A-1).

Ausschlusskrit.:
BE, Ösophagitis LA Grad C oder D, PPI 2x täglich, vergangene Anti-Reflux-OP etc.

[25] Within-group comparisons/prospective single-arm studies with n<100 were excluded in the PICO analysis. Only the effectiveness and safety data of the comparative analysis is used for evaluation.

[26] The full MSA cohort (n=75) includes the primary MSA cohort (n=44) and the crossover cohort (n=31) after 6 months.

[27] The primary MSA cohort (n=44) includes patients who initially received MSA and was followed over 12 months. The step-down cohort (n=43) consists of patients that received PPI over 12 months. Crossover patients are not considered in this comparison.

Alter: 21-76 Jahre (IG) bzw. 21-72 Jahre (KG), Median: 46 Jahre, durchschn. BMI: 28 kg/m², durchschn. Verwendung PPI: 8,4 Jahre

The baseline age of patients ranged from 21-76 years for the IG and from 21-72 years for the CG with both groups having a median of 46 years. The mean BMI was 28 kg/m^2 with standard deviations of 4.3 (IG) and 4.1 (CG), respectively. In the IG, 19 females (38%), and in the CG, 47 females (46%) were included. While 58% of patients in the IG had a hiatal hernia, this was the case in 49% of patients in the CG. At baseline, patients had an average PPI use of 8.4 years with a range of 0.3-35. The PPI use was not reported per intervention arm but over the whole patient population.

4.2.2 Additionally included safety studies

RCTs, NRCTs & prosp. einarmige Studien für Sicherheit

The study inclusion criteria for assessing safety differed from the ones for assessing clinical effectiveness. For evaluating safety-related outcomes of the three devices, we considered RCTs, prospective NRCTs and prospective studies (interventional single-arm studies, case series, prospective registry-based trials[28]) with at least 100 (**MSA**) or 30 (**EST** and **RS**) or more enrolled patients.

3 zusätzliche einarmige Beobachtungsstudien für Sicherheitsendpunkte von MSA

Additionally to the RCT already included for clinical effectiveness [60, 61] for **MSA**, three prospective studies (four publications) were included [41, 62-64]. The studies comprise of two prospective case series [41, 64] and one prospective registry-based trial with control group published in two publications [62, 63], with only the safety-relevant outcomes of the MSA group considered for evaluation because of the limitations mentioned above[24].

1 Studie für RS & 2 Studien für EST zu Sicherheitsendpunkten

For evaluating the safety domain for the **RS** device, one prospective single-arm study could be identified [30] and for evaluating safety-related outcomes for the **EST** device, two prospective case series [39, 65] were included.

Study as well as patient characteristics and trial results of all three devices are displayed in Table A-1 and Table A-2 (**MSA**), Table A-3 (**RS**), Table A-4 (**EST**) as well as in the evidence profiles in Table A-9.

Study characteristics

Magnetic sphincter augmentation

2 prosp. einarmige Studien & 1 registrierte registergestützte Studie (n=656) finanziert durch den Hersteller (Ethicon/Torax Medical), 240 Frauen & 416 Männer

Follow-Up: 3 bis 5 Jahre

Overall for **MSA**, 656 patients, of which 240 were women and 416 were men , were reported on in the prospective case series and registry-based trial [41, 62-64] that were all sponsored by the manufacturer Ethicon/Torax Medical Inc. In the prospective registry-based study, 456 underwent the MSA intervention where 166 were women and 290 men [62, 63]. Clinical follow-up time ranged from three [41, 63] to five years [64]. Loss to follow-up ranged from 0-15 patients. Mean operative time ranged from 36-47 minutes in the prospective case series [41, 64], and it was 43.2 minutes (median) in the prospective registry-based study [62, 63]. The latter study was carried out in the setting of real clinical practice in 22 medical centres in four countries (Austria, Germany, Italy, and the United Kingdom). The other two studies were conducted in Italy [41], the US (13 centres), and the Netherlands (one centre) [64].

[28] We excluded post-hoc studies or studies stating that the data was prospectively collected in databases and retrospectively reviewed/analysed.

RefluxStop™

The identified single-arm study [30] investigating the **RS** device reported clinical results of 50 patients and was sponsored by the manufacturer Implantica. In the study, 22 (44%) female and 28 (56%) male patients underwent the implantation of the device via laparoscopic surgery at four clinical sites. Clinical follow-up time was one year. During that period, three patients were lost-to-follow-up, with two patients discontinuing the study after only three and six months, respectively, because of successful treatment.

1 einarmige Studie (n=50) finanziert durch den Hersteller (Implantica), 22 Frauen & 28 Männer in 4 versch. Zentren, Follow-Up: 1 Jahr

Electrical stimulation therapy

Overall, out of the total of 81 patients included in the two studies investigating the **EST** device [39, 65], baseline characteristics data were reported on 79 patients, of which 35 were women and 44 were men. One study was sponsored by the manufacturer EndoStim® Inc. [39]. The Medical University of Vienna sponsored the second study [65]. Countries of recruitment were Colombia, India, Netherlands, Mexico, New Zealand, United Kingdom, Chile [39], and Austria [65].

2 einarmige Studien (n=81), 35 Frauen & 44 Männer, 1 Studie durch Hersteller (EndoStim®) & 1 Studie durch MedUni Wien finanziert

Clinical follow-up time ranged from six months [39] to two years [65]. Loss-to follow-up ranged from 0-6.8%. Operative time was 47 minutes (mean) in one study [39] and 55 minutes (median) in the second study [65]. Model versions of the technology (generations of EndoStim®) were not reported in any of the studies. The multi-centre case series study included 44 [39] and the single-centre case series included 37 patients [65].

2 Follow-Up-Zeiten: 6 Monate & 2 Jahre

Lost-to-Follow-Up: 0 %-6,8 % der Pat.

Patient characteristics

Magnetic sphincter augmentation

The studies' inclusion criteria for **MSA** showed some heterogeneity. Eligible patients needed to be 18 years or older in two studies [41, 64] and one study [62, 63] did not report the eligibility age. The median age of patients in years ranged from 44.5-53 years in two studies [41, 64]. Patients in the **MSA** arm of the third study [62, 63] had a mean age of 46.6 years.

Einschlusskrit. etwas heterogen

Furthermore, inclusion in the study required GERD symptoms to last for at least six months (two studies) [41, 64] and the presence of pathological/abnormal reflux (three studies) [41, 63, 64]. Data on median number of years with GERD were stated in the two prospective case series [41, 64] and ranged from 5.5-10 (median). The prospective registry-based study [62, 63] reported that the mean duration of GERD in years was 6.1 years. PPI resistant GERD was a criterion for inclusion in two studies (three publications) [41, 62, 63] and partial PPI responsive GERD was an inclusion criterion in one study [64]. Data on median number of years of PPI use were stated in all three studies (four publications) [41, 62-64] and ranged from 4-5 years (median) [41, 64] and 6.1 years (mean) [62, 63], respectively.

Symptome ≥6 Monate in 2 Studien, PPI-Resistenz in 2 Studien & partielles Ansprechen auf PPI in 1 Studie

Dauer PPI-Einnahme: 4 & 5 Jahre (Median) bzw. 6,1 Jahre (Mittel)

Exclusion criteria comprised of a hiatal hernia >3cm, severe esophagitis, BMI >35kg/m^2, allergy to the device's material in two studies [41, 64]. Confirmed allergy to metals as an exclusion criteria was reported in two studies (three publications) [41, 62, 64]. Regardless of the exclusion criteria, two patients in Bonavina 2013 had a hiatal hernia >3 cm and the same study included six esophagitis grade B patients [41]. The prospective registry-based trial [62, 63] was not explicit about exclusion criteria, but included patients with advanced GERD, hiatal hernias >3 cm and patients with a Barrett's esophagus.

Ausschlusskrit.: Hiatushernie >3 cm, schwere Ösophagitis, BMI>35 kg/m² in 2 Studien, Metall bzw. Materialallergie in 3 Studien; keine expliziten Ausschlusskrit. in 1 Studie

minimaler Anteil an Pat. mit Ösophagitis LA Grad C&D (1 %) & Hiatushernie >3 cm (1.6 %) in 1 Studie

Compared to the rest of the studies, only those patients who were diagnosed with esophagitis grade C and D were excluded, but the prospective registry-based trial [62, 63] included patients with esophagitis grade C or D. However, these patients were mainly from the LF arm that was not considered for evaluation of safety-related outcomes. In the MSA arm, only a very small proportion of patients (1.6%) had a hiatal hernia >3cm or exhibited LA esophagitis grade C or D (1%). The prospective registry-based trial [62, 63] reported that patients with known conditions that make it unlikely to complete a 3-year follow-up were excluded as well.

RefluxStop™

Einschlusskrit.: GERD-Symptome ≥6 Monate & nachgewiesen durch 24-h-pH-Überwachung, Ansprechen auf PPI

The identified study [30] included patients between 18 and 75 years. For inclusion, eligible patients had to have typical GERD symptoms longer than six months, respond to daily PPI medication, proven GERD with 24-h pH monitoring (off PPI medication) and a total distal esophageal pH-value ≤4 for more than 4.5% of the time during a 24-h monitoring.

Ausschlusskrit.: Hiatushernie >3 cm, Ösophagitis LA Grad C&D, BMI >35kg/m²

Patients with previous gastroesophageal surgery, anti-reflux or bariatric procedures, esophageal dysmotilities and presence of a para-esophageal hernia or sliding hernia of >3cm, LA grade C or D esophagitis were excluded. In addition, patients with a BMI >35kg/m² were excluded as well.

24 Pat. milde & 26 schwere GERD, durchschn. Alter: 51, 5 Jahre

At baseline, 24 patients had mild or moderate GERD and 26 patients experienced severe GERD. Mean age of study participants was 51.5 years. Of the 50 patients included, 13 patients (26%) had a grade A and 9 patients (18%) a grade B esophagitis. Previous PPI use in years or duration of GERD were not reported.

Electrical stimulationy therapy

mittleres Alter 49,6 & 54 in 2 Studien, Hiatushernien bei Pat. in 2 Studien

The mean age of patients varied between 49.6 [39] and 54 [65] years. In both studies the percentage share of patients with a BMI <30 was approximately 83%. Hiatal hernia in the multi-centre study [39] was present in 61% of patients (22% with hiatal hernia <2cm and 30% ≥2cm). In the single-centre study [65], numbers on the presence of hiatal hernia in patients were not explicitly reported, but 62.2% of patients underwent hiatal hernia repair.

~80-90 % der Pat. in 2 Studien nahmen PPI

The mean number of years that patients used PPIs was not reported, but PPI use in patients ranged from 83.8% [65] and 90% [39] of patients. The mean number of years that patients experienced GERD symptoms prior to the study was also not reported in either of the studies.

1 Studie berichtete explizit Einschlusskrit. (u. a. vorherige Reflux-Symptome & PPI-Medikation, GERD-HRQL-Score ≥20 etc.) & Ausschlusskrit. (u. a. Ösophagitis LA grade D, Hiatushernie ≥3 cm, BMI>35 kg/m²)

Patient inclusion and exclusion criteria were reported only for the multi-centre study [39]. The inclusion criteria were: Previous reflux symptoms, prior PPI use, GERD-HRQL score ≥20 off PPIs and an increase of ≥5 on PPIs, prior PPI use for 12 months, diagnosis based on 24-h pH monitoring result, LES end-expiratory pressure of 5–15mmHg, peristaltic contractions in ≥50% of swallows contraction amplitude of ≥30mmHg esophageal manometry, and excessive lower esophageal acid exposure as pH <4.0 for ≥5% of the total time. Exclusion criteria in the multi-centre study were: Multisystem disease, esophagitis LA grade D, Barrett's esophagus, any dysplasia, hiatal hernia ≥3cm, BMI >35kg/m², gastric malignancy, cardiac arrhythmia, cardiovascular disease, pregnancy, or implanted electro-medical devices.

Specific inclusion and exclusion criteria for the patients in the single-centre study [65] were not reported. Study authors only reported that all patients meeting the indication for anti-reflux surgery were eligible for the study and that the population was fairly inhomogeneous. While, the multi-centre study [39] excluded patients with a history of esophageal or gastric surgery, six patients had undergone previous foregut surgery in the single-centre study [65].

1 Studie schloss 6 Pat. mit vorangegangener OP am Vorderdarm ein

4.3 Results

4.3.1 Clinical effectiveness outcomes

In the following, the effectiveness-related outcomes are presented. Effectiveness outcomes were only available for the **MSA** device. For **EST** and the **RS** device no effectiveness outcomes were available.

Wirksamkeitsresultate nur für MSA verfügbar

Health-related quality of life

The included RCT [60, 61] (n=152, IG: 50 vs CG: 102) investigating the **MSA** device (LINX® management system) assessed disease-specific QoL via the GERD-HRQL questionnaire. Patients in the full MSA cohort (n=75) had a reduction in the mean GERD-HRQL score (improvement in QoL) from 30/24 (off PPI/on PPI at baseline) to 6 points compared to no improvement in the BID PPI cohort (n=84) at six months follow-up. After 12 months, the primary MSA cohort (n=44) experienced a reduction in the GERD-HRQL score from 30/24 (off PPI/on PPI at baseline) to 5 points compared to no improvement in the step-down PPI cohort (n=43). No p-values were reported for any of the group comparisons. Sixty-one patients (81%) in the full MSA cohort (n=75) had a GERD-HRQL score reduction of ≥50% from baseline after six months. In the CG (BID PPI, n=84) in turn, no patient had a ≥50% reduction in GERD-HRQL score. Whereas 41 patients (93%) in the primary MSA cohort (n=44) showed a GERD-HRQL score reduction of ≥50% from baseline, no patient in the step-down PPI cohort (n=43) exhibited a GERD-HRQL score reduction of ≥50% from baseline after 12 months (p-values= NR).[29]

HRQoL via GERD-HRQL

Verbesserung in beiden MSA-Kohorten vs keine Verbesserung in den PPI-Kohorten nach 6 bzw. 12 Monaten

Verringerung des GERD-HRQL-Scores von ≥50 % gegenüber dem Ausgangswert: 81 % (vollst. MSA-Kohorte) bzw. 93 % (primäre MSA-Kohorte) der Pat.

None of the studies investigated generic HRQoL measures such as EQ-5D in patients after application of LES devices in laparoscopic surgery.[30]

Morbidity

The *crucial* outcomes of *heartburn score* and *regurgitation score*, as well as the outcome *PPI usage*, *esophagitis and esophageal acid exposure*, and the *DeMeester score* were considered on how the devices affect GERD symptoms.

Endpunkte Morbidität: Sodbrennen, Regurgitation, PPI-Einnahme, Ösophagitis & DeMeester-Score

[29] **D0013** – What is the effect of LES devices in laparoscopic surgery on disease-specific quality of life?

[30] **D0012** – What is the effect of LES devices in laparoscopic surgery on generic health-related quality of life?

Heartburn score

Sodbrennen: vergleichbare Verbesserungen wie GERD-HRQL-Score für primäre MSA-Kohorte

With respect to heartburn, the RCT [60, 61] used the heartburn component of the GERD-HRQL score to assess heartburn symptoms. Authors reported that identical improvements after MSA were seen in the heartburn component of the GERD-HRQL for the primary MSA cohort (n=44) at 12 months and no improvement in related heartburn scores was seen in the step-down PPI cohort (n=43). The study only reported qualitative results on the heartburn score. No p-values were reported by the authors.[31]

Regurgitation

FSQ-Score: stat.sign. Reduktion mittelschwerer bis schwerer Regurgitation nach 6 Monaten (96 % der Pat.)

Regurgitation symptoms, resolution of moderate-to-severe regurgitation, and complete elimination of regurgitation was measured via the FSQ and RDQ score. The RCT [60, 61] showed that moderate-to-severe regurgitation (FSQ score) was eliminated in 72 patients (96%) of the full MSA cohort compared to 8 patients (11%) in the BID PPI cohort at 6-month follow-up ($p<0.001$), as reported on the FSQ.[32]

vollständige Beseitigung: stat.sign. Unterschied nach 6 Monaten (IG: 51 vs KG: 1 Pat.)

Complete elimination of regurgitation was only observed for the comparison between the full MSA cohort (n=75) and the step-down PPI cohort (n=43). Whereas, 51 patients in the full MSA cohort had a complete resolution of regurgitation symptoms according to the FSQ score, only one patient in the step-down PPI cohort was completely relieved from regurgitation ($p<0.001$).

RDQ-Score: Verbesserung beide MSA-Kohorten vs keine signifikante Verbesserung in den PPI-Kohorten nach 6 & 12 Monaten

The regurgitation score assessed via the RDQ showed a reduction (improvement) in the median score for the full MSA cohort after 6 months (off PPI at baseline: 4 [IQR: 3.25-4.75] and on PPI at baseline: 3.5 [IQR:2.5-4] to 0 [IQR: 0-1.125]). In comparison, the BID PPI cohort had no significant improvement at 6-month follow-up (p-value=NR). In the primary MSA cohort, the score decreased from 4 (off PPI with IQR: 3.25-4.75) and 3.5 (on PPI with IQR: 2.5-4) to 0 (IQR: 0-0.5), while the step-down PPI cohort experienced no significant improvement after 12 months (p-value=NR).

PPI usage

91 % der Pat. in der vollst. MSA-Kohorte beendeten PPI-Einnahme

Study authors of the included RCT [60, 61] reported that 68 of the 75 patients (91%) in the full MSA cohort discontinued PPIs.[33] It was not stated for the CGs.

Esophagitis and esophageal acid exposure

Ösophagitis: 7 % der vollst. MSA-Kohorte vs 17 % der PPI-Kohorte

At baseline, esophagitis confirmed by abnormal esophageal acid exposure was present in 42 of the 119 patients (35%) who completed 12-month evaluation. Esophagitis persisted in 7% of the full MSA cohort (5/72) compared to 17% (8/47) in patients of the step-down PPI cohort.

stat.sign. Verringerung der Säureexposition in beiden MSA-Kohorten

Median esophageal acid exposure time (% of time with pH<4) for the full MSA cohort decreased from 10.7% at baseline to 1.3% and for the primary MSA cohort the esophageal acid exposure time decreased from 11.5% to 1.3% at 12-month post-implantation (both $p<0.001$). No numbers were reported for the CGs.[34]

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[31] **D0005** – How do LES devices in laparoscopic surgery affect heartburn symptoms?

[32] **D0005** – How do LES devices in laparoscopic surgery affect regurgitation symptoms?

[33] **D0006** – How do LES devices in laparoscopic surgery affect the continuation of PPI therapy?

[34] **D0011** – What is the effect LES devices in laparoscopic surgery on patients' body functions?

DeMeester score

The study reported (mean) DeMeester scores only for the full MSA cohort (n=75). The score decreased from 40.5 (IQR: 25.7-49.5) at baseline to 5.3 (1.2-18.5). Authors stated that the DeMeester scores were similar for the crossover patients.[34]

Verringerung im mittleren DeMeester-Score von 40.5 auf 5.3 für vollst. MSA-Kohorte

4.3.2 Safety outcomes

Concerning safety of LES devices in GERD patients, any AEs, SAEs, and death were considered as *crucial* outcomes.

Endpunkte Sicherheit: AEs, schwerwiegende AEs (SAEs), Tod

Any adverse events[35]

A total of four studies (six publications), one RCT with the PPI comparison [60, 61], two prospective single-arm studies [41, 64], and one prospective registry-based trial (two publications) [62, 63], investigating the **MSA** device reported on AEs. For the **RS** device, AEs were reported on in the included single-arm study [30] and for the **EST** device, two prospective single-arm studies [39, 65] reported on AEs.

alle 7 Studien (9 Publikationen) berichteten über AEs

Since no RCT or NRCT was identified that compared surgical methods or LES devices with each other, no procedure- or device-related safety comparisons can be made for **MSA**. Only de novo excessive bloating or dysphagia can be compared between **MSA** and the PPI CG. In the absence of a CG for **RS** and **EST**, only safety-relevant outcomes directly attributable to the device- or procedure can be analysed.

keine sicherheitsrelevanten Vergleiche zwischen Verfahren/Produkten möglich

Magnetic sphincter augmentation

Considering the RCT investigating the **MSA** device and the three prospective studies without a CG, the follow-up time ranged from six [60, 61] to 60 months [63]. Of the 15 patients experiencing post-operative dysphagia in the RCT, two patients reported ongoing dysphagia (one severe and one moderate) and three patients at risk for developing dysphagia problems received oral corticosteroids. However, overall dysphagia decreased post-operatively compared to the PPI CG. The percentage of patients with bothersome swallowing everyday (dysphagia score ≥3) decreased in the full MSA cohort (off PPI: 27%/on PPI: 15% at baseline to 11% of patients) in comparison to the BID PPI cohort (no significant improvement) after six months. Whereas the percentage of patients with bothersome swallowing after surgery decreased further in the primary MSA cohort after 12 months (off PPI: 27%/on PPI: 15% at baseline to 7% of patients), the step-down PPI cohort experienced no significant improvement. No explicit device- or procedure related AEs were reported in the RCT [60, 61].

RCT: Dysphagie nahm postoperativ im Vergleich zur PPI-KG insgesamt ab

Anteil an Pat. mit Schluckbeschwerden im Alltag ging postoperativ zurück

In the two included prospective single-arm studies [41, 64] and the registry-based trial (two publications) [62, 63], the percentage of patients undergoing laparoscopic **MSA** with post-operative dysphagia was 7% after one year [62] and 2% after five years [64]. The 7% of patients with post-operative dysphagia after one year in the prospective single-arm study [62] corresponds to the percentage in the RCT after 12 months [60, 61]. Excessive bloating, which can also be a result of surgery, was present in 10% of patients after three years [62]

postoperative Dysphagie (Range): 7 % nach einem Jahr & 2 % nach fünf Jahren (3 Studien)

[35] **C0008** – How safe LES devices in laparoscopic surgery in comparison to laparoscopic fundoplication/PPI therapy/sham intervention?

exzessive Blähungen (Range): 10 % nach 3 Jahren & 2 % nach 5 Jahren (3 Studien); Unfähigkeit Aufstoßen & Erbrechen (Range): 1 %-2.4 % & 1 %-8.8 % (3 Studien)

and 2% of patients after five years [41]. Inability to belch and vomit was present in 1%-2.4% ([41]-[63]) and 1%-8.8% ([41]-[63]) of patients, respectively. Other reported non-serious AEs were mild odynophagia (4% of patients) and increased belching (3% of patients) reported in one study [41]. No further device- or procedure related AEs were reported.

RefluxStop™

8 verfahrensbezogene AEs über 12 Monate, Verringerung exzessiver Blähungen, keine neuen Dysphagie-Fälle & keine ADEs

The following eight procedure-related and other AEs occurred over a 12-month period in the single-arm study [30] assessing the **RS** device: abdominal pain and incisional hernia (n=1), accidental intraoperative instrumental hepatic lesion (small) (n=1), post-op delayed gastro-intestinal paralysis (one day) (n=1), procedural pneumothorax (n=1), gastritis (n=4). Excessive bloating in percentage of patients decreased from 84% at baseline to 19.1% at 12-months follow-up. No new cases of dysphagia occurred and no device-related AEs/ADEs were reported.

Electrical stimulation therapy

114 AEs in 2 zwei Studien nach 6 & 24 Monaten; 59 davon verfahrens- und gerätebezogen

In total, 114 AEs occurred in the two studies examining the **EST** device with a follow-up range of six [39] to 24 months [65]. Fifty-nine of these AEs were procedure-related and ADEs. In one study [39], the following device- or procedure-related AE occurred [39] (number of pts./%/events): constipation, epigastric pain, fever, mesh repair hernia cicatricialis in 1/2.4%/1, hiccups, inability to vomit in 2/4.8%/3, nausea/vomiting, post-operative bloating/belching in 3/7.1%/4, post-operative dysphagia in 4/9.5%/5, weight loss/anorexia in 5/11.9%/5, and pain/discomfort in 19/45.2%/24.

weitere AEs

The other study [65] reported on the following AEs: subcutaneous emphysema (1/2.7%/1) and mild thoracic sensations (2/5.4%/2). The following AEs occurred in both studies [39, 65] (n/%/events): impedance out of range (2/4.8%/2) and (4/10.1%/4).

Serious adverse events[35]

Magnetic sphincter augmentation

keine SADEs, keine Explantationen & 1 verfahrensbezogenes SAE im RCT: intraoperative Komplikationen: 8 von 465 Pat. in 1 register-basierten Studie

With respect to the **MSA** device in the RCT [60, 61], no SADEs were reported and no device was explanted, only one procedure-related SAE occurred in one patient (esophageal spasm shortly after surgery). Eight of 465 patients experienced intraoperative complications in the prospective registry-based trial [63].

4 Pat. Re-OP im RCT & Explantationsraten zwischen 2 %-7 % in 3 einarmigen Studien

Whereas four patients in the **MSA** RCT [60, 61] received re-surgery (endoscopic dilation, n=3; laparoscopic repair of hiatal hernia, n=1), device removal rates in the prospective single-arm studies examining the **MSA** device ranged from 2.4%[36]-7% ([63]-[64]).

RefluxStop™

7 verfahrensbezogene SAEs über 12 Monate & keine SADEs

In total, 7 procedure-related SAEs occurred in 5 of 47 patients over the 12-month follow-up in the study [30] examining the **RS** device: three events of mediastinal abscess, empyema and abdominal abscess (n=1), one intra-ab-

[36] The device was removed in 11 out of 459 patients. Seven removals after the first 12 months, 2 additional removals during the next 12 months, and 2 further removals during the last 12 months. Two patients underwent fundoplication at the time of the device removal.

dominal haemorrhage (n=1), one pleuritis (n=1), one removal of a foreign body (n=1), and one release of fundoplication sutures including renewal of the sutures (n=1). No SADEs occurred.

In the included **RS** single-arm study [30], no devices were explanted. The two reported SAEs, one removal of a foreign body (n=1), and one release of fundoplication sutures/renewal of sutures (n=1), made another surgical intervention necessary.

keine Geräteexplantationen

Electrical stimulation therapy

SADEs for the **EST** device were reported in both included studies with six [39] and 24 months [65] follow-up, respectively. In total, eight SADEs and procedure-related SAEs in eight of 79 patients were reported: one case of trocar perforation of the small bowel during laparoscopy and one case of device erosion in one single-arm study [39], two cases of device malfunctioning, and four cases of insufficient symptom control the other single-arm study [65].

8 SADEs und verfahrensbezogene SAE in 2 Studien in 8 von 79 Pat.

In all patients undergoing **EST** and experiencing SAEs, devices were explanted [39, 65]. In four of the six patients in one study [65], the device was removed due to technical issues. Another two patients had insufficient symptom control. These six patients underwent a conversion to Nissen fundoplication. The mentioned case of trocar perforation of the small bowel during laparoscopy and the case of device erosion made it necessary to explant the device in the other study [31]. 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, and correct IPG implantation are required.

Geräteexplantationen in allen 8 Pat. mit SAEs, 6 von 8 Pat. bekamen anschließend Nissen-Fundoplikation

Mortality

No deaths were reported in the included studies for any of the devices.[37]

kein Todesfall

Further safety-related issues[38,39]

Generally, patients eligible for laparoscopic surgery with respective devices reinforcing the LES should have low-grade erosive esophagitis (LA grade A and B), abnormal esophageal acid exposure, and a hiatal hernia ≤3cm, a BMI <35kg/m^2 as well as show partial (or higher) responses to PPI treatment. The application of the procedures in patients not satisfying the original approval indications is not recommended and precautions are necessary. [27-30, 34].

ursprüngliche Zulassungskriterien, Indikationen & weitere sicherheitsrelevante Aspekte

[37] **D0001** – What is the expected beneficial effect of LES devices in laparoscopic surgery on mortality? &
D0003 – What is the effect of LES devices in laparoscopic surgery on the mortality due to causes other than GERD?

[38] **C0005** – What are the susceptible patient groups that are more likely to be harmed through the use of LES devices in laparoscopic surgery? &
C0007 – Are LES devices in laparoscopic surgery associated with user-dependent harms?

[39] **C0002** – Are the harms related to dosage or frequency of applying LES devices in laparoscopic surgery? &
C0004 – How does the frequency or severity of harms change over time or in different settings?

Magnetic sphincter augmentation

Vorsicht geboten bei Pat. mit einem magnetischen Implantat oder bei MRI

uneingeschränkte Ernährung so früh wie möglich → Expansion des Rings/Metallkügelchen werden während der Heilung adäquat bewegt

Patients susceptible to be harmed through the use of **MSA** are those whose health condition already required a solution in the shape of a magnetic implant, such as implantable cardioverter-defibrillators. Also, patients who need to undergo MRI are at risk as, in the Bonavina 2013 study, two patients out of a total of eight patients undergoing MRI reported discomfort during the MRI and chest X-Ray for both of these patients showed the device in a more open geometry [41]. Malfunction of the device due to deficient user training is possible as it is crucial for patients to eat an unrestricted diet as soon as tolerated. The process of swallowing a solid bolus of food contributes to the expansion of the device or actuating the beads during healing [41]. The learning curve for placement of the **MSA** device is not steep. Risks related to administration of the device stem from the surgeon's ability to minimise the amount of dissection performed and to carefully locate and dissect the posterior vagus nerve [41]. The surgeon needs to avoid reverting back to the dissection technique, which is used to create a fundus wrap from the esophageal wall [41].

RefluxStop™

keine Evidenz zu suszeptiblen Pat.-Gruppen

einige (wenige) Aspekte zu berücksichtigen

No further evidence for the **RS** device was found concerning susceptible patient groups. With regard to user-depended harms, a few issues need to be emphasised [30]. Fat in the suture line attachments should be avoided as much as possible. Furthermore, the silicone implant needs to be placed high-up, clearly above the upper edge of the LES. When the implant is fully below the upper edge of the LES, the device cannot function properly. One patient had the device placed too low at surgery, refused re-surgery and discontinued the study at six-months with moderate dysphagia, minimal regurgitation and dissatisfaction [30].

Electrical stimulation therapy

Komorbiditäten erhöhen das Risiko für AEs, insb. bei kardialer Vorerkrankung

Patient groups that are most likely to be harmed through the use of **EST** 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 multi-centre study where a case of paroxysmal atrioventricular nodal re-entrant tachycardia (AVNRT) occurred several months after the start of the EST [39]. 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 [39].

flache Lernkurve, reversible Intervention Expertise nötig für korrektes Set-Up

The learning curve for the implantation procedure of the EST is claimed to be flat. EST is reversible, as the esophagogastric junction left is unaltered. When placing the electrodes, the surgeon needs to avoid perforation of the esophageal lumen [43]. Furthermore, correct set up of the electrical stimulation by the gastroenterologist is crucial to minimise the risk of device malfunctioning [66].

keine Evidenz zu zeitlichem Verlauf oder Abhängigkeit des Settings von AEs für alle 3 Medizinprodukte

Considering harms related to the frequency of applying all three devices, as well as the frequency or severity of harms that might change over time or in different settings, no evidence was available. Additionally, there is no evidence that harms increase or decrease in different organisational settings for all three devices.

5 Quality of evidence

The RoB for RCTs was analysed with the Cochrane Collaboration tool version 2.0 [53]; the RoB of prospective single-arm studies and case series was assessed with the IHE-20 checklist [54, 55]. The RoB assessments are presented in Table A-5 and Table A-6 (**MSA**), Table A-7 (**RS**), and Table A-8 (**EST**) in the Appendix.

RoB → Cochrane Collaboration Tool (RCTs) & IHE-Checkliste (prosp. einarmige Studien)

The RCT (two publications) [60, 61] for evaluating the effectiveness of the **MSA** device was graded with a *moderate* RoB (*some concerns*). One of the two prospective single-arm studies [64] and the prospective registry-based trial [62, 63] investigating the **MSA** device were rated with a *moderate* RoB, and one prospective study [41] had a *high* RoB. The single-arm study examining the **RS** device [30] had a *low* overall RoB. The two included prospective single-arm studies [39, 65] for evaluating the safety of the **EST** had both a *moderate* RoB.

low RoB: 1 RS-Studie
moderater RoB: 3 MSA-Studien & 2 EST-Studien

hoher RoB: 1 MSA-Studie

The main reasons for downgrading included studies examining the **MSA** device were the lack of maintaining the initial random allocation after crossover due to selective, single-arm crossover, initial unbalanced allocation [60, 61], lack of blinding of patients as well as outcome assessors, partial selective outcome reporting [41, 60-64], and unclear information whether patients were entering the study at a similar point in the disease [41, 62-64]. The reasons for downgrading the **RS** and **EST** studies were unclear information about whether patients were consecutively recruited [30, 39], and missing information about blinding of outcome assessors [30, 39, 65]. Other reasons were unclear information whether patients entering the study at a similar point in the disease [39, 65] or whether conclusions of the study were supported by the results [39].

Hauptgründe: selektives Cross-Over im RCT, fehlende Verblindung, selektive Berichterstattung unvollständige/unklare Informationen zur Rekrutierung etc.

The strength of evidence was rated for each endpoint individually according to the GRADE scheme [56]. Each critical outcome was rated by two researchers (CS, JE). In case of disagreement, a third researcher was involved to resolve the difference. A more detailed list of the criteria applied can be found in the recommendations of the GRADE Working Group [56].

Qualität der Evidenz nach GRADE

The GRADE scheme 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 grading of each *crucial* outcome according to the GRADE scheme can be found in the summary of findings table below (Table 5-1) and in the evidence profile in Table A-9 in the Appendix. To allow better comparability of the available evidence across study outcomes, the results of all study designs are combined in one summary of findings table (Table 5-1).

GRADE-Tabelle übernächste Seite & im Anhang

insgesamt niedrige (MSA) bzw. sehr niedrige (RS, EST) Evidenzstärke für Wirksamkeits- & Sicherheitsendpunkte

According to the GRADE scheme, only the outcomes defined as *crucial* to derive a recommendation were considered for the overall strength of evidence. In addition, the overall strength of evidence is generally based on the outcome with the lowest level of evidence. Therefore, the overall strength of evidence for the clinical effectiveness and safety of **MSA**, **RS**, and **EST** in comparison to laparoscopic surgery, PPI therapy and/or a sham intervention is *low* (**MSA**) and *very low* (**RS, EST**).

Table 5-1: Summary of findings table for LES devices in laparoscopic surgery [56]

Outcomes	Impact	№ of studies (Pts I vs C)	Certainty of the evidence (Importance)	Comments
Efficacy				
Magnetic sphincter augmentation (LINX® Reflux Management System)				
Elimination of moderate-to-severe regurgitation (number of patients (%)) assessed with: FSQ regurgitation score follow-up: 6 months	Full MSA cohort vs BID PPI cohort: 72 (96%) vs 8 (11%) study reported a stat. sign. difference in number of patients with elimination of moderate-to-severe regurgitation between full MSA cohort and BID PPI cohort after 6 months (p<0.001)	1 RCT [60, 61] (75 vs 87)	⊕⊕⊕◯ **Moderate**[a,b,c] **(Critical)**	-
Complete elimination of regurgitation (number of patients (%)) assessed with: FSQ regurgitation score follow-up: 6 months	Full MSA cohort vs BID PPI cohort: 51 (73%) vs 2* (2%) study reported a stat. sign. difference in number of patients with complete elimination of regurgitation between full MSA cohort and BID PPI cohort after 6 months (p<0.001)	1 RCT [60, 61] (75 vs 87)	⊕⊕⊕◯ **Moderate**[a,b,c] **(Critical)**	-
Elimination of moderate-to-severe regurgitation (number of patients (%)) assessed with: FSQ regurgitation score follow-up: 12 months	Primary MSA cohort vs step-down PPI cohort: 43 (98%) vs 8 (19%) study reported a stat. sign. difference in number of patients with elimination of moderate-to-severe regurgitation between primary MSA cohort vs step-down PPI after 12 months (p<0.001)	1 RCT [60, 61] (44 vs 43)	⊕⊕⊕◯ **Moderate**[a,b,c] **(Critical)**	-
Overall health-related quality of life (overall HRQoL), mean (SD) assessed with: GERD-HRQL follow-up: 6 months	Full MSA cohort vs BID PPI cohort: study reported a reduction in mean GERD-HRQL scores for full MSA cohort from baseline off PPI at baseline: 30 (10)/6 (NR) vs no improvement on PPI at baseline: 24 (10)/6 (NR) vs no improvement p=NR	1 RCT [60, 61] (75 vs 87)	⊕⊕⊕◯ **Moderate**[a,b,c] **(Critical)**	**GERD-HRQL:** lower scores indicate better HRQoL
Overall health-related quality of life (overall HRQoL), mean (SD) assessed with: GERD-HRQL follow-up: 12 months	Primary MSA cohort vs step-down PPI cohort: study reported a reduction in mean GERD-HRQL scores for primaryl MSA cohort from baseline off PPI at baseline: 30 (10)/5 (NR) vs no improvement on PPI at baseline: 24 (10)/5 (NR) vs no improvement p=NR	1 RCT [60, 61] (44 vs 43)	⊕⊕⊕◯ **Moderate**[a,b,c] **(Critical)**	GERD-HRQL: **lower scores indicate better HRQoL**
GERD-HRQL score reduction of ≥50% from baseline (number of patients (%)) assessed with: GERD-HRQL follow up: 6 months	Full MSA cohort vs BID PPI cohort: 61 (81%) vs no reduction number of patients with GERD-HRQL score reduction of ≥50% from baseline full MSA cohort and BID PPI cohort after 6 months (p=NR).	1 RCT [60, 61] (75 vs 87)	⊕⊕⊕◯ **Moderate**[a,b,c] **(Critical)**	-
GERD-HRQL score reduction of ≥50% from baseline (number of patients (%)) assessed with: GERD-HRQL follow-up: 12 months	Primary MSA cohort vs step-down PPI cohort: 41 (93%) vs no reduction number of patients with GERD-HRQL score reduction of ≥50% from baseline full MSA cohort and BID PPI cohort after 6 months (p=NR).	1 RCT [60, 61] (44 vs 43)	⊕⊕⊕◯ **Moderate**[a,b,c] **(Critical)**	-
Heartburn score (qualitative results) assessed with: GERD-HRQL follow-up: 6 months	Full MSA cohort vs BID PPI cohort: identical improvements as GERD-HRQL score vs no improvement	1 RCT [60, 61] (75 vs 87)	⊕⊕◯◯ **Low**[a,b,d] **(Critical)**	**GERD-HRQL heartburn score:** lower scores indicate better HRQoL

Outcomes	Impact	Nº of studies (Pts I vs C)	Certainty of the evidence (Importance)	Comments
Heartburn score (qualitative results) assessed with: GERD-HRQL follow-up: 12 months	Primary MSA cohort vs step-down PPI cohort: identical improvements as GERD-HRQL score vs no improvement	1 RCT [60, 61] (44 vs 43)	⊕⊕◯◯ **Low**[a,b,d] **(Critical)**	**GERD-HRQL** heartburn score: **lower scores indicate better HRQoL**
RDQ regurgitation score, mean (IQR) assessed with: RDQ follow-up: 6 months	Full MSA cohort vs BID PPI cohort: study reported a reduction in mean RDQ regurgitation scores for full MSA cohort from baseline off PPI at baseline: 4 (3.25-4.75)/0 (0-1.125) vs no improvement on PPI at baseline: 3.5 (2.5-4)/0 (0-1.125) vs no improvement p=NR	1 RCT [60, 61] (75 vs 87)	⊕⊕⊕◯ **Moderate**[a,b,c] **(Critical)**	**RDQ** regurgitation score**:** lower scores indicate lower frequency as well as severity of the symptom
RDQ regurgitation score, mean (IQR) assessed with: RDQ follow-up: 12 months	Primary MSA cohort vs step-down PPI cohort: study reported a reduction in mean RDQ regurgitation scores for primary MSA cohort from baseline off PPI at baseline: 4 (3.25-4.75)/0 (0-0.5) vs no improvement on PPI at baseline: 3.5 (2.5-4)/0 (0-0.5) vs no improvement p=NR	1 RCT [60, 61] (44 vs 43)	⊕⊕⊕◯ **Moderate**[a,b,c] **(Critical)**	**RDQ** regurgitation score: lower scores indicate lower frequency as well as severity of the symptom
RefluxStopTM				
Due to the lack of a controlled group, no data on effectiveness can be reported				
Electrical stimulation therapy (EndoStim®)				
Due to the lack of a controlled group, no data on effectiveness can be reported				
Safety				
Magnetic sphincter augmentation (LINX® Reflux Management System)				
Any adverse events (AEs) assessed with: number of patients, events follow-up range: 6 to 12 months	No device- or procedure related AEs were reported Of the 15 patients experiencing post-operative dysphagia, 2 patients reported ongoing dysphagia (one severe and one moderate). 3 patients at risk for developing dysphagia problems received oral corticosteroids. Overall, dysphagia decreased compared to baseline and PPI medication. Dysphagia score ≥3 (bothersome swallowing everyday): Full MSA cohort vs BID PPI cohort (after 6 months): off PPI at baseline: 27%/11% vs no significant improvement on PPI at baseline: 15%/11% vs no significant improvement Primary MSA cohort vs step-down PPI cohort (after 12 months): off PPI at baseline: 27%/7% vs no significant improvement on PPI at baseline: 15%/7% vs no significant improvement	1 RCT[e] [60, 61] (75 vs 87)	⊕⊕◯◯ **Low**[a,b] **(Critical)**	-
Serious adverse events (SAEs) assessed with: number of events and patients follow-up range: 6 to 12 months	No device-related SAEs were reported. 1 procedure-related SAE was reported: esophageal spasms shortly after surgery (n=1). 4 patients received re-surgery: endoscopic dilations (n=3), laparoscopic repair of a hiatal hernia (n=1) No device was explanted and no death was reported.	1 RCT[e] [60, 61] (75 vs 87)	⊕⊕◯◯ **Low**[a,b] **(Critical)**	-

Outcomes	Impact	№ of studies (Pts I vs C)	Certainty of the evidence (Importance)	Comments
Any adverse events (AEs) assessed with: % of patients follow-up range: 36 to 60 months	Excessive bloating: 2-10%, Inability to belch: 1-2.4%, Inability to vomit: 1-8.8%, Post-operative dysphagia: 2-7%, Other non-serious AE: mild odynophagia (4%), increased belching (3%) No other device- or procedure-related AEs were reported.	3 observational studies [41, 62-64] (636 vs-)	⨁◯◯◯ **Very low**[f,g] **(Critical)**	-
Serious adverse events (SAEs) assessed with: % and number of patients follow-up range: 36 to 60 months	Device removal: 2.4-7% Intraoperative complications: 1.8% (n=8) No deaths were reported.	3 observational studies [41, 62-64] (636 vs –)	⨁◯◯◯ **Very low**[f,g] **(Critical)**	-
RefluxStopTM				
Any adverse events (AEs) assessed with: events, number of patients follow-up: 12 months	Excessive bloating in percentage of patients decreased compared to baseline at 12-months follow-up: 84% to 19.1% of patients. No new dysphagia cases occurred. Over 12 months, 8 AEs (procedure-related and other AEs) occurred: abdominal pain and incisional hernia (n=1), accidental intraoperative instrumental hepatic lesion (small) (n=1), post-op delayed gastro-intestinal paralysis (one day) (n=1), procedural pneumothorax (n=1), gastritis (n=4). No device-related AEs were reported.	1 observational study [30] (47 vs –)	⨁◯◯◯ **Very low**[h] **(Critical)**	-
Serious adverse events (SAEs) assessed with: events, number of patients (%) follow-up: 12 months	In total, 7 procedure-related SAEs occurred in 5 patients over the 12-month follow-up: 3 events of mediastinal abscess, empyema and abdominal abscess (n=1), 1 intra-abdominal haemorrhage (n=1), 1 pleuritis (n=1), 1 removal of foreign body (n=1), and 1 release of fundoplication sutures/resuturation (n=1). No device-related SAEs occurred and no deaths were reported	1 observational study [30] (47 vs –)	⨁◯◯◯ **Very low**[h] **(Critical)**	-
Electrical stimulation therapy (EndoStim®)				
Any adverse events (AEs) assessed with: events, number of patients (%) follow-up range: 6 to 24 months	Overall, excessive bloating, esophagitis, and dysphagia decreased compared to baseline at 24-months follow-up. In, total 114 AE occured of which 59 events were device- or procedure related.	2 observational studies [39, 65] (79 vs –)	⨁◯◯◯ **Very low**[i,j,k,l] **(Critical)**	-
Serious adverse events (SAEs) assessed with: events, number of patients (%) follow-up range : 6 to 24 months	In total, 9 device-/procedure-related SAEs in 8 patients were reported: 1 trocar perforation of the small bowel during laparoscopy (1/47), 1 device erosion (1/47), 7 device removals (7/79). No deaths were reported.	2 observational studies [39, 65] (79 vs –)	⨁◯◯◯ **Very low**[i,k,l,m] **(Critical)**	-

Abbreviations: AEs – adverse events, BID PPI – proton pump inhibitor twice daily, C – control group, FSQ – foregut symptom questionnaire, GERD-HRQL – gastroesophageal reflux disease-health-related quality of life, I – intervention group, IQR – interquartile range, MSA – magnetic sphincter augmentation, NR – not reported, Pts – patients, RCT – randomised controlled trial, RDQ – reflux disease questionnaire, RoB – risk of bias, SAEs – serious adverse events, SD – standard deviation, stat. sign. – statistically significant.
** based on own calculation*

Explanations

[a] *Some concerns: Selective crossover/single-arm crossover (initial random allocation was not maintained after crossover), per-protocol analysis (potential for impact of the failure to analyse participants in the group to which they were randomised)*
[b] *Outcome comes from only one trial with 152 patients.*
[c] *Strong association/Large effect: When there is a (very) large magnitude of effect, we might be more certain that there is at least a small effect.*
[d] *No explicit numbers were reported*
[e] *Any grade AEs, SAEs, re-surgery data were considered from Bell 2019 [60] and 2020 [61].*
[f] *1/3 high RoB, 2/3 moderate RoB*
[g] *Heterogeneous results, homogeneous patient population partly unclear*
[h] *Outcome comes from only one relatively small (single-arm) study (n=50).*
[i] *Unclear risk of bias due to unclear allocation concealment; using the IHE-20 RoB checklist, both studies were evaluated to have a moderate risk of bias.*
[j] *One study reported that 76% of study participants experienced any grade AEs while the second study reported that 19% of study participants experienced any grade AEs.*
[k] *In one study, 6 patients had undergone previous foregut surgery while in the other study patients with history of esophageal or gastric surgery were included.*
[l] *Small sample size*
[m] *One study reported that 3 of 47 (6%) study participants experienced SAEs while the second study reported that 6 of 37 (16%) study participants experienced SAEs (e.g. device removal in one study was 6 times more likely with a smaller study population compared to the other study with 47 study participants).*

6 Discussion

Gastroesophageal reflux disease (GERD) is characterised as a condition that develops when the reflux of stomach contents causes troublesome symptoms and/or complications [3, 6]. GERD is considered troublesome if symptoms, such as heartburn, extra-oesophageal manifestations, or non-cardiac chest pain adversely affect an individual's quality of life (QoL) [3, 10].

GERD:
Reflux von Mageninhalt verursacht Symptome

GERD is the most common upper gastrointestinal disease in high-income countries with 10-20% of the population experiencing weekly symptoms [8, 9, 15]. Although most patients respond well to a daily PPI medication [4, 10, 16], approximately 42% of GERD patients are dissatisfied with their PPI treatment outcomes and are potential candidates for surgical therapy [10]. Furthermore, patients, who fail medical management since PPIs do not address the underlying incompetency of the LES, are also candidates for surgical therapy. Compared to the current surgical gold standard of laparoscopic fundoplication, magnetic sphincter augmentation (**MSA**), RefluxStop™ (**RS**), and electrical stimulation therapy (**EST**) are claimed to be lesser invasive, accompanied by fewer side effects and shorter hospitalisation periods [29, 39, 40], while achieving similar efficacy results [8, 11, 36, 37]. Furthermore, the operation technique is less difficult, hence its reproducibility is higher and the learning curve for the surgeon is also shorter [6, 24].

Prävalenz: 10 %-20 %

Unzufriedenheit mit PPI & Pat. mit inkompetenten UÖS → mögl. Kandidat*innen für OP

Ziel:
Bewertung der Wirksamkeit & Sicherheit von 3 laparoskopisch implantierbaren Medizinprodukten – magnetische Sphinkter-Augmentation (MSA), Silikonimplantat/ RefluxStop™ (RS) & Elektrostimulations-therapie (EST)

Against this background, the present systematic review aimed to investigate whether these three novel laparoscopic approaches for reinforcing the native lower esophegael sphincter (LES) in GERD patients are more effective and equally safe as, or equally effective but safer than standard therapies such as laparoscopic fundoplication or PPI therapy.

Summary and interpretation of the main results

Included studies

In total, seven studies (in nine publications) met the predefined inclusion criteria. Four studies, one RCT (published in two publications) [60, 61], two single-arm studies [41, 64], and one registry-based trial (in two publications) [62, 63], were investigating the **MSA** device (LINX® Reflux Management System). The RCT [60, 61] was used to evaluate the clinical effectiveness as well as safety of the MSA device, involving a total of 152 patients (intervention group [IG] treated with **MSA**: 50 vs control group [CG] treated with PPI: 102 over a follow-up period of 12 months. After six months, the study allowed eligible patients in the CG, who initially received twice-daily proton pump inhibitors (BID PPI), to cross over in order to receive laparoscopic MSA. After the crossover, medication therapy in the CG was reduced from BID PPI using 20mg of omeprazole to a daily dose of 20mg daily dose (step-down PPI) over the subsequent 6-month follow-up.

insgesamt 7 Studien für alle 3 Verfahren eingeschlossen

MSA: 1 Cross-Over-RCT mit PPI-Komparator & 3 einarmige Beobachtungsstudien;
RS: 1 prosp. einarmige Studie;
EST: 2 prosp. einarmige Studien

The other two prospective single-arm studies [41, 64] and the registry-based trial [62, 63], which included in total 656 patients over a follow-up range of three to five years, were used in addition to evaluate safety-related outcomes of the **MSA** device.

MSA – Cross-Over-RCT: n=152; IG: 50 vs KG: 102; 3 Beobachtungsstudien: n=656

RS – n=50
EST – n=81

keine Studie zur Bewertung der Wirksamkeit für RS & EST

For evaluating the safety domain of the **RS** device, one prospective single-arm study with 50 patients over a one-year follow up was included [30] and for evaluating safety-related outcomes for the **EST** device (EndoStim®), two prospective case series [39, 65] with a total of 81 patients were included. The identified studies on these two devices did not meet the inclusion criteria for clinical effectiveness evaluation.

Studien: Einschluss von Pat. mit BMI ≤35 kg/m²

Ausschluss von Pat. mit Hiatushernie >3 cm, Ösophagitis LA Grad C oder D (Ausnahme 1 Studie – Anzahl Pat. aber minimal: 1.6 % bzw. 1 %)

Studienpopulation recht homogen in den Studien (Ausnahme 1 Studie für EST)

All identified studies for each of the three devices included chronic and refractory GERD patients with a majority of studies reporting that large proportions of patients had a history of daily PPI use [30, 39, 41, 60-65]. All studies explicitly reported that they only included patients with a BMI ≤35kg/m^2. Furthermore, patients with a hiatal hernia of more than three centimetres and patients who exhibited Los Angeles grade C and D esophagitis were excluded from all trials except for two studies (three publications) [62, 63, 65]: One study investigating the **EST** device [65] did not report on inclusion or exclusion criteria in much detail and the prospective registry-based trial (**MSA**) [62, 63] included also patients with a hiatal hernia larger than three centimetres. However, the latter study [62, 63] included only a very small proportion of patients (1.6%) who had a hiatal hernia >3cm or exhibited LA esophagitis grade C or D (1%) [62, 63]. Overall, across and within studies that provided clear information on included patients, the study population seemed quite homogenous with exception of the single-centre study [65] investigating the **EST** device. Authors of the respective study [65] reported that the population was fairly inhomogeneous.

Effectiveness

nur 1 randomisierte kontrollierte Studie für Wirksamkeit von MSA vs PPI

The only study that was eligible to derive a recommendation concerning *crucial* effectiveness outcomes was the RCT investigating the **MSA** device, which compared the device to a PPI CG. The study used the disease-specific GERD-HRQL questionnaire for measuring health-related quality of life (HRQoL). For measuring (elimination of moderate-to-severe) regurgitation symptoms, the study utilised the foregut symptom questionnaire (FSQ), a non-validated questionnaire, and the reflux disease questionnaire (RDQ). For measuring heartburn symptoms, the study used the heartburn component of the GERD-HRQL questionnaire.

Verbesserungen in GERD-HRQL-Score ≥50 % von Baseline für MSA-Pat. vs keine Verbesserung für PPI-Pat. (beide Vergleichsszenarien)

Patients in the full **MSA** cohort (n=75) had a reduction in the mean GERD-HRQL score (improvement in QoL) from 30 off PPI/24 on PPI at baseline to 6 and also a large portion of patients (81%) had a GERD-HRQL score reduction of ≥50% from baseline compared to no improvement in the BID PPI cohort (n=84) at six months follow-up. The primary **MSA** cohort (n=44) experienced a similar reduction in the GERD-HRQL score compared to no improvement in the step-down PPI cohort (n=43) after 12 months. Whereas 41 patients (93%) in the primary **MSA** cohort (n=44) showed a GERD-HRQL score reduction of ≥50% from baseline, no patient in the step-down PPI cohort (n=43) exhibited a GERD-HRQL score reduction of ≥50% from baseline after 12 months. However, the study did not report on any p-values for any of the group comparisons for this outcome measure.

stat.sign. Reduktion mittelschwerer bis schwerer Regurgitation im Vergleich zu PPI

The study showed a statistically significant difference in elimination of moderate-to-severe regurgitation in the full **MSA** cohort compared to the BID PPI cohort at 6-month follow-up ($p<0.001$, IG: 72 patients [96%], CG: 8 patients [11%]). Whereas, 51 patients in the full **MSA** cohort (n=75) had a complete resolution of regurgitation, only one patient in the step-down PPI cohort (n=43) was completely relieved from regurgitation (difference statistically significant at $p<0.001$).

The regurgitation score assessed via the RDQ showed a reduction (improvement) in the median score for the full **MSA** cohort after six months in comparison to the BID PPI cohort that had no significant improvement at 6-month follow-up. In the primary **MSA** cohort, the score also decreased, while the step-down PPI cohort experienced no significant improvement after 12 months (p-values = not reported). Authors reported that identical improvements after **MSA** were seen in the heartburn component of the GERD-HRQL for the primary MSA cohort (n=44) at 12 months compared to no improvements in the step-down PPI cohort (n=43). The study only reported qualitative results on the heartburn score and no p-values were reported by the authors.

Verbesserung auch im RDQ-Score & Sodbrennen via GERD-HRQL

Safety

Concerning the safety profile, any AEs, SAEs, and death were regarded as *crucial* study outcomes to derive a recommendation.

Sicherheitsprofil

A total of four studies (six publications), one RCT in two publications with the PPI comparison [60, 61], two prospective single-arm studies [41, 64], and one prospective registry-based trial (two publications) [62, 63], investigating the **MSA** device reported on safety-related outcomes. For the **RS** and **EST** device, safety outcomes were reported on in one included single-arm study [30] and in two prospective single-arm studies [39, 65], respectively. Since no RCT was identified that compared surgical methods or LES devices with each other, no procedure- or device-related safety comparisons can be made.

MSA: 4 Studien
RS: 1 Studie
EST: 2 Studien

keine verfahrens-/ gerätebezogenen Sicherheitsvergleiche möglich

Overall, no significant de novo or excess dysphagia, which are common adverse events after surgery, were observed in the RCT for the large majority of **MSA** patients after 12 months [60, 61] (only two patients reported on ongoing dysphagia). Dysphagia even decreased post-operatively from baseline. A minor number of patients undergoing laparoscopic **MSA** in the two included prospective single-arm studies [41, 64] and the registry-based trial (two publications) [62, 63] experienced post-operative dysphagia, excessive bloating, and were not able to belch and vomit. Other reported non-serious AEs were mild odynophagia and increased belching reported in one study [41]. In the case of the **RS** device, also no new cases of dysphagia were reported and excessive bloating decreased over the follow-up period. Overall, excessive bloating, esophagitis, and dysphagia decreased compared to baseline at 24-months follow-up for patients receiving **EST**.

keine signifikante Zunahme an Dysphagie & exzessiven Blähungen bei allen 3 Verfahren

No explicit device-related AEs and SADEs were reported in the RCT for the **MSA** [60, 61], and no device was explanted. One procedure-related SAE (esophageal spasm shortly after surgery) occurred in one patient in the RCT and eight patients experienced intraoperative complications in the prospective registry-based trial [63] for the **MSA** device. In the case of the **RS** device, also no device-related AEs were reported on, but eight procedure-related and other non-device-related AEs in eight patients and seven procedure-related SAEs occurred in five of 47 patients over the 12-month follow-up [30]. The studies on the **EST** device reported on 59 procedure- and device-related AE, and eight device- and procedure-related SAEs in eight of 79 patients [39, 65].

MSA: 1 verfahrensbezogenes SAE & 8 intraoperative Komplikationen
RS: 8 nicht-gerätebezogene AEs & 7 verfahrensbezogene SAEs
EST: 59 AEs & 8 SAEs

Whereas four patients in the **MSA** RCT [60, 61] underwent re-surgery and device removal rates in the prospective single-arm studies examining the **MSA** device ranged from 2.4-7% ([63]-[64]), no **RS** device was explanted. In contrast, in all six patients undergoing **EST** and experiencing SAEs, devices were explanted [39, 65].

Geräteexplantation bei MSA & EST, keine Explanation bei RS

No deaths were reported in the included studies for any of the devices.

keine Todesfälle

Effectiveness and comparative safety data from observational studies

eingeschlossene Beobachtungsstudien liefern Evidenz zu entscheidenden Endpunkten & 1 prosp. registergestützte Studie liefert komparative Evidenz (MSA vs LF)

Although one RCT comparing **MSA** with PPI was available, no RCT or eligible NRCT was identified that compared **MSA** with other surgical approaches such as laparoscopic fundoplication (LF). The only identified study that compared **MSA** with LP was not eligible for evaluating effectiveness outcomes, since authors stated that the study was not a clinical study, not powered enough to test a hypothesis, and had an inherent bias built into the patient selection for the two treatments[24]. This prospective registry-based trial published in two publications [62, 63] was only included for evaluating safety-related outcomes for the **MSA** arm. Furthermore, the lack of RCTs and CTs for the **RS** and **EST** device restricted our analysis to single-arm prospective studies as the best available evidence. Consequently, no conclusions between surgical approaches or on effectiveness for **EST** and **RS** could be made. Nonetheless, the observational data from the prospective trials investigating the **MSA, RS**, and **EST** devices show a possible effect concerning *crucial* outcomes and the prospective registry-based trial gives some comparative evidence between **MSA** and LF.

Magnetic sphincter augmentation

Verbesserung in GERD-HRQL-Score für MSA größer als LF

Änderungen in Pat.-Zufriedenheit & PPI-Medikation post-OP ähnlich

intraoperative Komplikationen – MSA: 1.8 % vs LF: 1.2 %

verfahrensbezogene Komplikationen – MSA: 2 % vs 1.8 %

LF-Pat. haben tendenziell einen längeren KH-Aufenthalt

In the study (two publications) [62, 63] comparing **MSA** to LF not eligible for the evaluation of effectiveness outcomes, **MSA** patients had a mean reduction (improvement) in the GERD HRQL score of 16.6 compared to a mean reduction of 17.8 points in LF patients after three years. These changes indicate a higher improvement of GERD symptoms in LF patients compared to **MSA** patients [62, 63]. Satisfaction in patients after three years improved in both study arms to a comparable extent: 4.6% to 78.2% of patients in the **MSA** arm compared to a change from 3.7% to 76.5% of patients in the LF arm. A similar development was observed in patients reporting on their PPI usage. Whereas at baseline 97.8% of **MSA** patients used PPIs, 24.2% of patients still used PPIs at the 36-month follow-up compared to 95.8% of LF patients at baseline and 19.5% after 3 years. Dysphagia changed from 15.7% of patients in the **MSA** arm at baseline to 3.8% after 3 years versus 24.4% of LF patients at baseline and 4.8% at the 36-month follow-up. With regard to comparative evidence on safety between **MSA** and LF, 1.8% in MSA patients compared to 1.2% of LF patients experienced intra-operative complications and 2% of MSA patients experienced procedure-related complications compared to 1.8% of LF patients (p-values = NR). With regard to length of stay after surgery, 36.1% of **MSA** patients had a length of stay <24h versus 11.4% of patients with LF and 72.3% of patients with LF had a length of stay >48h versus 50.8% of patients with **MSA**. 2.4% of **MSA** patients experienced the inability to belch compared to 8.3% of LF patients, 8.8% of **MSA** patients experienced the inability to vomit compared to 32% of LF patients. 3.8% of MSA patients and 4.8% of LF patients experienced dysphagia at 3-year follow-up.

Wirksamkeitsresultate aus RCT & Beobachtungsstudien qualitativ relativ homogen

When additionally considering the two **MSA** case series [41, 64], which did not pass the inclusion criteria for clinical effectiveness, homogeneity in reported results between the RCT, case-series, and the registry-based trial can be observed with regard to GERD-HRQL, regurgitation, and discontinuation of PPI therapy. All of these outcomes showed a slight to significant improvement in the single-arm studies, registry-based trial, and the RCT. The heartburn results are only similar between the RCT and the two case series. When comparing heartburn results of the registry-based trial study to the case series, heterogeneity in results can be observed. The registry-based trial indicated a less significant decline of patients with heartburn in the **MSA** arm.

RefluxStop™

The single-arm study [30] investigating the **RS** device reported on improvements in the mean GERD-HRQL score from 28.8 to 3.2 ($p<0.001$) and 94% of patients had a score reduction >50% from baseline. Regurgitation in patients changed from 88% to 9% ($p<0.0001$) and only 2% of patients used PPI after one year (100% at baseline). Furthermore, excessive bloating in percent of patients changed from 84% to 19.1% at 1-year follow-up. Patient satisfaction increased as well (dissatisfied at baseline: n=45, dissatisfied at last follow-up: n=1).

stat.sign. Verbesserung GERD-HRQL-Score, Regurgitation

Reduktion von PPI-Medikation & übermäßigen Blähungen nach 1 Jahr

Electrical stimulation therapy

Both case series for the **EST** device report improvement in GERD HRQL (improvement of 16.5 [on PPI at baseline]/31 [off PPI at baseline] to 5 [39] and 41 to 8.5 [65]). Improvements were also reported in the percentage of days with heartburn and regurgitation. The results were heterogeneous with reference to patient satisfaction, which improved from 7-54% in the multicenter study [39] and from 5-92.8% in the single center study [65]. Dysphagia improved in the single-center study [65], it was not reported in the multi-centre study [39].

Verbesserung GERD-HRQL-Scores von Baseline

heterogene Ergebnisse bzgl. Pat.-Zufriedenheit

Quality of evidence

In summary, the overall quality of evidence was *low* for MSA considering both clinical effectiveness as well as safety outcomes. The overall quality of evidence considering safety-related outcomes for the **RS** device and **EST** was *very low*. In the case of clinical effectiveness outcomes for **MSA**, several factors contributed to the *low* to *moderate* level of evidence. On the one hand, the RoB assessment raised *some concerns* for the study and endpoints, and on the other hand, selective crossover, application of per-protocol analysis, only one study with a limited number of patients, and selective or missing reporting of numbers contributed to downgrading (Table A-9). Some effectiveness outcomes were graded up, because of the strong association for these endpoints. When large effect estimates are present, we might be more certain that there is at least a small effect despite other biases.

Evidenzqualität für Wirksamkeit & Sicherheit von MSA niedrig (selektives Cross-Over, Per-Protokoll-Analyse, selektive Berichterstattung)

Evidenzqualität für klinische Sicherheit von RS & EST sehr niedrig

Considering safety outcomes for **MSA,** prospective single-arm study design of the three additionally included trials and the partial heterogeneous results influenced the level of evidence in addition to the above mentioned factors. For the safety-related outcomes of **RS** and **EST**, the observational study design, heterogeneity of data and results (inconsistency), limited number of studies, and small sample size contributed to the decision to downgrade.

Herabstufungsgründe: Studiendesign, Inkonsistenz der Resultate/Daten (MSA, RS, EST) & kleine Stichprobe (RS & EST)

The overall RoB of the included **MSA** studies was considered *moderate* [60-64] (corresponds to *some concerns* for the RCT) to *high* [41], because blinding of patients and outcome assessors was not possible due to the nature of the intervention, partial selective outcome reporting was present, and unclear information whether patients were entering the study at a similar point in the disease [41, 62-64]. Especially, the lack of maintaining the initial random allocation after crossover due to selective, single-arm crossover, initial unbalanced allocation in the RCT led to downgrading due to a potential bias.

MSA: moderates bis hohes Verzerrungsrisiko

The reasons for the *moderate* RoB in the **RS** and **EST** studies were unclear information about whether patients were consecutively recruited [30, 39], missing information about blinding of outcome assessors [30, 39, 65]. Other reasons were unclear information whether patients entering the study at a simi-

RS & EST: moderates Verzerrungsrisiko

lar point in the disease [39, 65] or whether conclusions of the study were supported by the results [39]. In the case of one **EST** study [65], homogeneity of the included population was unclear.

u.a. kurzes Follow-Up im RCT (MSA), heterogene Ergebnisse/Daten (MSA, EST) & kleine einarmige Studien (RS, EST) beeinträchtigen Vertrauen in die Evidenz

The follow-up time in the **MSA** RCT [60, 61] providing comparative outcome results with one year was rather short. Although, long-term safety-related evidence was available for **MSA** (range three to five years), heterogeneous outcome reporting and heterogeneous results with regard to AEs across these single-arm studies affects the confidence in the results. Also for the **RS** device, only one single-arm study with an observation period of only one year and a relatively small sample (n=50) could be identified. Although a study with a two-year follow-up period could be identified in the case of **EST**, small sample size, heterogeneity of data and results across both included studies compromise the confidence in the evidence.

Limitations to the present report

keine Post-hoc- & retrospektiv analysierte Datenbankstudien

First of all, we excluded post-hoc studies or studies stating that the data were prospectively collected in databases but retrospectively reviewed and analysed. Particularly in the latter type of study, the selection of centres recruiting patients to the database and the enrolment and loss of patients to follow-up can strongly affect the validity of data obtained from the database.

Ausschluss retrospektiver Studien

prosp. Studien <100 (MSA) bzw <30 Pat. (RS & EST) ausgeschlossen

Einschlusskriterien gemäß Zulassungskriterien

Furthermore, we excluded retrospective studies since the sources of error due to confounding and bias are more common in retrospective studies than in prospective trials. Moreover, prospective case-series with a patient cut-off of at least 100 patients for **MSA** and 30 for **RS** and **EST** were considered. Presumably, some prospective studies with less than 100 patients for **MSA** and 30 patients for **RS** and **EST** were not included. With regard to patient inclusion criteria, we applied strict and stringent criteria to comply with the indications for which the devices were approved. We excluded studies with patients having a BMI>35kg/m^2 and studies, in which the proportion of patients with hiatal hernia >3cm or Los Angeles grade C and D esophagitis exceeded 2% of total patients. Roux-en-Y gastric bypass is considered the surgical gold standard in obese (BMI >35kg/m^2) patients with objective evidence of GERD following dietary and lifestyle modifications [3, 31-33].

nur narrative Analyse in GRADE

Lastly, due to the limitations in data reporting, only a narrative analysis within GRADE was possible.

Current evidence, clinical trials and upcoming evidence

bis dato keine RCTs mit direktem Vergleich MSA vs LF (Goldstandard)

für RS & EST auch keine RCTs veröffentlicht

Systematic reviews and meta-analyses of observational studies [67-69] have shown that **MSA** provides equivalent control to LF as measured by the need for postoperative PPI therapy and GERD-HRQL with an acceptable safety profile. However, no RCT directly comparing **MSA** with the gold standard LF has been published [3, 8]. Furthermore, there are limited long-term data regarding the safety and the incidence of ADEs and SADEs [3, 8]. To our knowledge, there are also no RCTs comparing the **RS** device (due to its novelty) and the **EST** with LP or PPI.

Empfehlung schwierig aufgrund fehlender robuster Evidenz aus RCTs (v. a. fehlender Vergleich mit LF)

While DeMeester argues that an RCT against PPIs is needed in the case of the **EST** device [70], Attwood suggests that a comparison between surgical options (e.g. EST vs LF) is required as only those patients who are dissatisfied with PPIs will be willing to undergo surgery [71]. Following the latter statement and the aforementioned aspects above, this train of thought also

applies for **MSA** and the **RS** device. With no randomised trials comparing these three procedures with the current gold standard or against each other, it is difficult to recommend one over the other currently [3, 67].

RCTs mit adäquaten Komparatoren, Pat.-relevanten Endpunkten & klarer Indikation nötig

The need for adequately controlled trials is especially important, because it is ambiguous what the appropriate comparator for the three devices is. On the one hand, LF is the only established surgical alternative, yet on the other hand, these three laparoscopic approaches claim to fill the therapeutic gap between patients who are dissatisfied with the PPI treatment, do not respond to medication therapy, and those who are reluctant to undergo LF [37]. According to the approved indication profile, the target population of the three devices seems to be less severe patients not indicated for fundoplication, which would change the cut-off point of a surgical intervention to the less diseased. Hence, there is an urgent need for quality RCTs with surgical comparators such as fundoplication to prove the comparative efficacy.

kein laufendes RCT mit LF-Vergleich für alle 3 Produkte

Through the clinical trial search, no ongoing registered or planned controlled trial comparing any of the three devices with LF could be identified (Table A-11). For **MSA**, four observational studies, one post-approval study (NCT01940185), one single-arm trial (ChiCTR-ONC-16009512), one single-arm database study (NCT04253392), and a further observational database study (NCT04695171) comparing **MSA** with LF including patients with hiatal hernia >3cm were identified. However, whether the trials add to the current evidence is questionable, since on the one hand, the validity of data obtained from databases is likely to be strongly influenced by selection bias, and on the other hand, MSA in patients with a hiatal hernia >3cm does not fulfil the indications for which the device was approved.

MSA: nur laufende Beobachtungsstudien → qualitativer Erkenntnisgewinn fraglich

RS: klinische Studien sind laut Hersteller geplant

According to the manufacturer of **RS**, Implantica Trading AG, results of a 5-year data collection process is expected to be ready by mid to late 2022. Furthermore, additional international clinical studies are being planned as well.

EST: 1 RCT wurde aufgrund der Insolvenz des Herstellers vorläufig beendet

One randomised controlled trial (NCT02749071) comparing the **EST** device with a sham treatment and an observational database study (NCT02441400) were terminated on October 18th, 2019, because the company was no longer operational at that time. After the scoping phase of the report, the company website (www.endostim.com) was accessible again, but no comprehensive information on business continuation or ongoing trials could be retrieved since the contact form was not operational.

Conclusion

keine vergleichende Evidenz für RS & EST; MSA zeigt größere Verbesserungen in relevanten Endpunkten im Vergleich zu PPI

Generally, for two of the three approaches, **RS and EST**, no comparative evidence could be identified. **MSA** seems to improve HRQoL and symptom scores over time, but only an improvement compared to PPI medication was identified. Large patient groups with non-acute diseases, such as the GERD patient group of this assessment, need the best evidence in form of randomised controlled trials to prove effectiveness.

keine klare Aussage zur Wirksamkeit und Sicherheit für alle 3 Produkte aufgrund fehlender robuster Evidenz

Overall, no clear conclusion can be made whether LES devices in laparoscopic surgery lead to substantially superior outcomes than the (investigated) comparators, since no robust clinical comparative data are available. LF, especially Nissen or Toupet fundoplication, is regarded as gold standard among the surgical anti-reflux procedures in order to improve the function of the LES. No randomised trial directly comparing **MSA, RS** or **EST** with the gold standard LF has been published to date. Furthermore, there are lim-

ited long-term data regarding the safety such as incidence of device-related erosions and no differences in the safety profile for any of the three devices to surgical comparators could be identified.

qualitativ hochwertige Studien mit längerer Nachbeobachtungszeit und mehr Pat. notwendig

In addition, the included studies showed a *very low* quality of evidence for **RS** and **EST**, and a *low* to *moderate* quality of evidence for outcomes of **MSA**. Thus, in combination with the aforementioned conflicting results, no reliable conclusions regarding the clinical effectiveness and safety for the three devices compared to laparoscopic fundoplication, PPI therapy and/or a sham intervention in chronic GERD patients can be drawn. The lack of RCTs and controlled trials with adequate comparators and longer follow-up (>2-3 years) involving larger number of patients (n>100) are urgently needed to clarify the currently uncertain available evidence and to add knowledge to the current evidence on the safety profile.

7 Recommendation

In Table 7-1, the scheme for recommendations is displayed and the according choice is highlighted.

Einschluss in Leistungskatalog aktuell nicht empfohlen

Table 7-1: Evidence-based recommendation

	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

Though low level evidence is suggesting that **magnetic sphincter augmentation (MSA)** is more effective and nearly safe as medical therapy with proton pump inhibitors (PPI), the current evidence is not sufficient to prove that the **MSA** approach for reinforcing the lower esophageal sphincter (LES) in laparoscopic surgery is more effective and equally safe or equally effective and safer than standard treatment such as laparoscopic fundoplication or PPI in chronic GERD patients. The current evidence for **RefluxStop™ (RS)** and **electrical stimulation therapy (EST)** is also not sufficient to prove that the devices is more effective and equally safe or equally effective and safer than standard treatment such as laparoscopic fundoplication or PPI in chronic GERD patients.

MSA > PPI aber keine robuste Evidenz

Evidenz zu RS & EST ist auch nicht ausreichend

Due to the methodological shortcomings of the available evidence and the lack of controlled evidence, especially between different surgical approaches, no solid conclusions can be drawn neither for clinical effectiveness nor for the safety of the devices at stake. Hence, there is a need for high-quality (comparative) studies showing consistent long-term effectiveness results as well as properly reported and detailed safety data.

hochwertige (vergleichende) Studien notwendig

New comparative effectiveness results based on identified ongoing trials (Table A-11) are not expected for any of the three devices, since the trials will not fill the current evidence gap on controlled trials with adequate comparators, large sample sizes, and long-term follow-up.

komparative, hochwertige Evidenz nicht in Aussicht

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Appendix

Evidence tables of individual studies included for clinical effectiveness and safety

Magnetic sphincter augmentation

Table A-1: MSA: Results from randomised controlled trials

Author, year	Bell 2019 [60]	Bell40 2020 [61]
Study design	Multicentre prospective, randomised controlled, double-arm crossover trial (NCT02505945)	
Country	USA (21 clinics)	USA (21 clinics)[41]
Sponsor	Ethicon/Torax Medical, Inc.	Ethicon/Torax Medical, Inc.
Intervention/Product	MSA (LINX® Reflux Management System)	MSA+MSA crossover[42] (LINX® Reflux Management System)
Comparator	BID PPI therapy (omeprazole, 20 mg)	BID PPI therapy (omeprazole, 20 mg)/Step-down PPI cohort[43]
Study duration	July 2015 – February 2017 (20 months)	July 2015 – February 2017 (20 months)
Number of pts, total, I vs C	n=152, 50[44] vs 102[45]	n=152[46], 50 vs 102

[40] This study is the second portion of the Bell 2019 study and allowed eligible patients in the BID PPI arm to cross over in order to receive laparoscopic MSA. In this study, individual results of the crossover MSA and the step-down cohorts are reported. Comparative data based on the final treatment received are reported at 6- and 12-month follow-up. Only comparative data based on the final treatment received is eligible to provide comparative evidence on effectiveness and safety. Furthermore, within-group comparisons or prospective single-arm studies with n<100 were excluded in the PICO analysis. Hence, only the effectiveness and safety data of the comparative analysis is presented in the table and used for the evaluation.

[41] In the abstract, the study lists only 20 clinic sites. However, authors report 21 clinics in the main text and the initial study with the 6 month post-treatment analysis (see Bell 2019) also lists 21 clinics.

[42] If both moderate-severe regurgitation persisted after the 6-month BID PPI therapy and impedance pH testing demonstrated persistent excess reflux burden (≥57 reflux episodes in a 24-hour period while on BID PPI), then patients were eligible to receive MSA.

[43] Patients not qualified for crossover received a reduced 20-mg daily dose of omeprazole.

[44] Three patients in the MSA arm did not receive allocated intervention (two patients voluntarily withdrew and in one patient the implant was aborted due to device sizing issues).

[45] One patient in the BDI PPI arm did not receive allocated intervention = lost to follow-up before starting the intervention.

[46] 152 patients were initially allocated in two treatment arms (MSA: 50 vs BID PPI: 102 patients). 79 patients initially randomised in the BID PPI treatment arm completed 6-month impedance/pH testing per protocol. 31 of these 79 (39%) patients in the BID PPI arm met all crossover requirements for MSA. They are included in the MSA arm of the final analysis after 12 months. 48 of the 79 patients did not qualify for crossover and received a reduced dose of 20-mg omeprazole daily (step-down arm). Results for the following comparison groups are considered: Full MSA cohort after 6 months (primary MSA cohort at 6-month follow-up + crossover cohort at 6-month follow-up: n=44+31=75) vs BID cohort (n=87) at 6-month follow-up; primary MSA cohort at 12-month follow-up (n=44) vs step-down PPI cohort (n=43) at 12-month follow-up; and full MSA cohort at 12-month follow-up (primary MSA cohort after 12 months follow-up + crossover cohort at 6-month follow-up: n=44+31=75) vs step-down PPI cohort at 12-month follow-up.

Author, year	Bell 2019 [60]	Bell40 2020 [61]
Inclusion criteria	■ Pts.≥21 years ■ Moderate-to-severe regurgitation ■ Hiatal hernia ≤3 cm ■ Once-daily PPIs for ≥8 weeks ■ BMI <34 kg/m^2 ■ Abnormal pH testing/DeMeester score with pH <4 ■ Normal esophageal motility	
Exclusion criteria	■ Presence of Barretts' esophagus ■ LA grade C or D esophagitis ■ Currently taking twice-daily PPIs/contraindicating of twice-daily PPIs ■ History of gastric or gastroesophageal surgery/anti-reflux procedures/gastroesophageal/gastric cancer ■ Prior endoscopic anti-reflux intervention for GERD and/or previous endoscopic intervention for treatment of Barrett's esophagus ■ Suspected or confirmed esophageal or gastric cancer ■ Distal esophageal motility (average of sensors 3 and 4) <35 mmHg peristaltic amplitude on wet swallows or <70% (propulsive) peristaltic sequences ■ Symptoms of dysphagia more than once per week within the previous 3 months ■ Scleroderma ■ Esophageal motility disorder ■ Esophageal stricture or gross esophageal anatomic abnormalities (Schatzki's ring, obstructive lesions, etc) ■ Esophageal or gastric varices ■ Any condition that may cause the patient to be non-compliant with or unable to meet the protocol requirements/limited life expectancy (i.e., <3 years) ■ Pregnancy/plans to become pregnant ■ Allergies (titanium, stainless steel, nickel, or ferrous materials)	
Primary outcome measure	■ Elimination of moderate-to-severe regurgitation (measured by FSQ regurgitation score)	
Secondary outcome measures	■ GERD-HRQL scores (change from baseline): GERD-HRQL questionnaire ■ Percentage of patients achieving ≥50% decrease in GERD-HRQL score (change from baseline) ■ RDQ score for regurgitation ■ GERD-HRQL heartburn score ■ Difference in esophageal reflux parameters (number of reflux episodes/percentage of time with pH <4) ■ PPI use at 6 months	
Baseline patient characteristics (I vs C)		
Age	Median (range): 46 (21-76) vs 46 (21-72)	Median (range): 46 (21-76) vs 46 (21-72) Mean (SD): 47.8 (13.1) vs 46.4 (13.7)
Sex, female:male, n (%)	19:31 (38:62%) vs 47:55 (46:54%)	
BMI, mean (SD), kg/m^2	28 (4.3) vs 28 (4.1)	27.7 (4.3) vs 28 (4.1)
Hiatal hernia, none:yes, n (%)	21:29 (42%:58%) vs 52:50 (51%:49%)	

Author, year	Bell 2019 [60]	Bell40 2020 [61]
Esophagitis, n (%)	None: 30[47] (61.2%) vs 66 (66%) LA grade A: 10 (20.4%) vs 24 (24%) LA grade B: 9 (18.4%) vs 10 (10%)	
PPI use (average in years)	8.4 years	8.4 years (0.3-35) 8.7 years (6.8) vs 8.2 years (6.5)
Duration of GERD	NR	NR
Follow-up	6 months	12 months
Lost to follow-up, n	0[48] vs 13[49]	6-month period: see Bell 2019 12-month period: 2 vs 7
Effectiveness results		
GERD symptoms		
FSQ regurgitation score		
Elimination of moderate-to-severe regurgitation, n (%)	Per-protocol: 42 (89%) vs 10 (10%) difference between I and C after 6 months: p<0.001 Intention-to-treat:[50] 42 (84%) vs 10 (10%) difference between I and C after 6 months: p<0.001	72 (96%) vs 8 (11%)[51,52] difference between I and C after 6 months: p<0.001 43 (98%) vs 8 (19%)[53] difference between I and C after 12 months: p<0.001
Complete elimination of regurgitation, n (%)	37/47 (89%) vs 3/101 (3%), p=NR	51 (73%) vs 1 (2%)[54] difference between I and C after 6 months: p<0.001
GERD-HRQL		
GERD-HRQL score, mean (SD) (baseline/follow-up)	Per-protocol: 24/6 vs 25/24[55] difference between I and C after 6 months: p<0.002	off PPI at baseline: 30 (10)/6 (NR) – on PPI at baseline: 24 (10)/6 (NR) vs no improvement[52,56] off PPI at baseline: 30 (10)/5 (NR) – on PPI at baseline: 24 (10)/5 (NR) vs no improvement[53,56]

[47] Three participants withdrew before undergoing the MSA procedure, and one participant failed to start PPI twice-daily therapy.

[48] In total, outcome data of 47 patients was analysed in the MSA arm.

[49] Four patients in the BID PPI arm did not return to clinical site after contact attempts. Eight patients voluntarily withdrew and one patient withdrew due to a PPI-related adverse event. In total, outcome data of 87 patients in the BID PPI arm was analysed.

[50] All analyses except the analysis of the elimination of moderate-to-severe regurgitation are per-protocol analyses.

[51] All analyses are per-protocol analyses.

[52] Full MSA cohort (n=75) vs BID cohort (n=87) after 6 months

[53] Primary MSA cohort (n=44) vs step-down PPI (n=43) after 12 months

[54] Full MSA cohort (n=75) vs step-down PPI (n=43) after 6 months

[55] Per protocol analysis

[56] No numbers for the comparator group and no p-values were reported

Author, year	Bell 2019 [60]	Bell40 2020 [61]
GERD-HRQL score reduction of ≥50% from baseline, n (%)	Per-protocol: 38 (81%) vs 7 (8%)[57] difference between I and C after 6 months: p< 0.001	61 (81%) vs no reduction[52,56] 41 (93%) vs no reduction[53,56]
Satisfaction, n (%)	Per-protocol: 38 (81%) vs 2 (2%) difference between I and C after 6 months: p=NR	NR
GERD-HRQL heartburn score (baseline/follow-up), median (IQR)	off PPI at baseline: 4.6 (3.3-5.5)/NR – on PPI at baseline: 3.4 (2.3-4.5)/NR vs off PPI at baseline: 4.5 (3.5-5.5)/NR – on PPI at baseline: 3.5 (2.5-5)[58]	identical improvements as in GERD-HRQL score vs no improvement[59]
RDQ regurgitation score (baseline/follow-up)	Per-protocol: Mean (SD): 4.2 to 1.6 vs 4.4 to 4.6 difference between I and C after 6 months: p=NR[60]	Median (IQR): off PPI at baseline: 4 (3.25-4.75)/0 (0-1.125) – on PPI at baseline: 3.5 (2.5-4)/0 (0-1.125) vs no significant improvement[52,56] off PPI at baseline: 4 (3.25-4.75)/0 (0-0.5) – on PPI at baseline: 3.5 (2.5-4)/0 (0-0.5) vs no significant improvement[53,56]
DeMeester score[61], mean (IQR) (baseline/follow-up)	8 (NR) vs 18 (NR), difference between I and C after 6 months: p=0.059	40.5 (25.7–49.5)/5.3 (1.2–18.5)[62] vs NR
PPI usage (discontinuation), n (%)	43 (91%) vs NR	68 (91%) vs NR
Reflux characteristics determined by impedance-pH testing	Number of reflux events per 24 hours, mean (IQR): 22.5 (13-40.5) vs 49 (31-76.78) difference between I and C after 6 months: p< 0.001 Number of patients with normal number of reflux episodes, n (%): 40 (91%) vs 46 (58%) Number of patients with normal esophageal acid exposure by percentage of time with ph<4, n (%): 39 (89%) vs 59 (75%) Number of patients with normal esophageal acid exposure by DeMeester score, n (%): 39 (89%) vs 56 (71%) Esophageal acid exposure (% of time with pH<4), mean: 2% vs 5% difference between I and C after 6 months: p=0.065	Esophageal acid exposure (% of time with pH<4), median (IQR)[52,63] 10.7% (IQR, 7.7%–13.9%)/1.3% (IQR, 0.4%–5.3%), p < .001 vs NR Esophageal acid exposure (% of time with pH<4), median (IRQ)[53,63] 11.5% (IQR, 7.9%–14.8%)/1.3% (IQR,0.2%–5.3%), p < .001 vs NR
Esophagitis (baseline/follow-up), %	NR	Patients completed 12-month evaluation: 35% (42/119)[64]/7% (5/72) vs 17% (8/47)[65]

[57] Per protocol analysis

[58] Only reported at baseline.

[59] Authors reported that identical improvements after MSA were seen in the heartburn component of the GERD-HRQL at 12 months and no improvement in GERD-HRQL or related heartburn scores was seen in the medically (step-down PPI) treated cohort. No numbers were reported.

[60] Per protocol analysis

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

[62] Authors reported DeMeester scores for the full MSA cohort (n=75) and stated only that the DeMeester scores were similar for the crossover patients.

[63] No numbers for the comparator group were reported

[64] Mixed group: cohort that received MSA and cohort that received PPI at baseline

[65] Here, the full MSA cohort (n=75) after 6 months was compared with patients maintained on single-dose PPI (n=47).

Author, year	Bell 2019 [60]	Bell40 2020 [61]
	Safety results	
Any AEs		
Device related AEs, n (%) events	0	0
Procedure-related AEs, n (%) events		
Dysphagia, n (%)	■ Total: 15 (32%) vs NR ■ Mild: 9 (19%) vs NR ■ Moderate: 4 (9%) vs NR ■ Severe: 2 (4%) vs NR ■ Medication (oral corticosteroids): 3 (20%)	Dysphagia score ≥3[66], n (%): off PPI at baseline: NR (27%)/8 (11%) – on PPI at baseline NR (15%)/8 (11%) vs no significant improvement[52,56], p=NR off PPI at baseline: NR (27%)/3 (7%) – on PPI at baseline NR (15%)/3 (7%) vs no significant improvement[53,56], p=0184
SAEs		
Device-related SAEs, n (%) events	0	0
Device erosion	0	0
Device migration	0	0
Other device-related SAEs	0	NR[67]/see Bell 2019
Device removal	0	0
Procedure-related SAEs (e.g. perioperative complications)		
Esophageal spasms shortly after surgery, n (%) events	1 (2%) 1	NR/see Bell 2019
Re-surgery, n (%) events:		
Endoscopic **Laparoscopic**	■ Endoscopic dilation: 3 ■ Laparoscopic repair of a hiatal hernia after an episode of severe vomiting months after surgery: 1[68]	NR/see Bell 2019
Death, n (%)	0	0

Abbreviations: AEs – Adverse events, BID PPI – Proton pump inhibitors twice daily, BMI – Body mass index, C – Control group, FSQ – Foregut symptom questionnaire, GERD-HRQL – Gastroesophageal reflux disease-health-related quality of life, I – Intervention group, IQR – Interquartile range, LES – Lower esophageal sphincter, LF – Laparoscopic fundoplication, MSA – Magnetic sphincter augmentation, NR – Not reported, PPI – Proton pump inhibitor, Pts. – Patients, RCT – Randomised controlled trial, RDQ – Reflux disease questionnaire, SAEs – Serious adverse events, SD – Standard deviation, stat. sign. – statistically significant.

[66] A dysphagia score ≥3 means that bothersome swallowing occurred every day or worse.

[67] Other adverse events in both groups were minor according to study authors and were not reported.

[68] No device was explanted.

Table A-2: MSA: Results from case series and single-arm studies

Author, year [Reference]	Bonavina 2013 [41]	Ganz 2015 [64]	Riegler 2015 [62]	Bonavina 2021 [63]
Study design	Single-centre, prospective case series	Multi-centre, prospective single-arm study (NCT00776997)	Multi-centre, prospective registry-based trial with control group[69,70] (NCT01624506)	Multi-centre, prospective registry-based trial with control group[69,70] (NCT01624506)
Country	Italy	USA (13 centres), Netherlands (1 centre)	Austria, Germany, Italy, United Kingdom (22 medical centres)	Austria, Germany, Italy, United Kingdom, (22 medical centres)
Sponsor	Ethicon/Torax Medical, Inc.	Ethicon/Torax Medical, Inc.	Ethicon/Torax Medical, Inc.	Ethicon/Torax Medical, Inc.
Intervention/Product	MSA (LINX® Reflux Management System)	MSA (LINX® Reflux Management System)	MSA (LINX® Reflux Management System)	MSA (LINX® Reflux Management System)
Comparator	NA	NA	Laparoscopic fundoplication	Laparoscopic fundoplication
Study duration	5 years	5 years	3 years and 7 months (January 2010-July 2013[71])	5 years (December2009-December 2014)
Number of pts, total, I vs C	n=100[72]	n=100	n=249, 202 vs 47	n=631, 465 vs 166
Inclusion criteria	■ Pts>18 years ■ GERD ≥6 months ■ PPI resistant reflux ■ pathologic reflux	■ Pts>18years and <75years ■ GERD ≥6mos ■ at least partial response to PPIs ■ pathologic reflux	■ Advanced GERD with hiatal hernia >3 cm[73] ■ Barrett's esophagus ■ Motility disorder, or esophagitis grade C or D ■ Moderate GERD with abnormal esophageal pH, reflux symptoms despite PPI use	
Exclusion criteria	■ Hiatal hernia >3 cm ■ Esophagitis grade B+ ■ BMI>35 ■ Barrett's esophagus, ■ Motility disorder ■ Gross esophageal anatomic abnormalities	■ Hiatal hernia ≥3 cm ■ LA grade C or D esophagitis, ■ BMI>35 ■ Barrett's esophagus ■ motility disorder	■ Known conditions that make it unlikely to complete a 3-year follow-up ■ Allergies to titanium, stainless steel, nickel or ferrous materials	

[69] In one prospective registry study published in 2 publications comparing MSA with LF [62, 63], authors stated in the analysis protocol that the study was not a clinical study and not powered enough to test a hypothesis. Study authors report that there is an inherent bias built into the patient selection for the two treatments. A large proportion of the control group (LF) in the first publication and in the follow-up publication had a hiatal hernia >3 cm (45.7% in [62] and 48.1% in [63]). In the MSA arm, only a very small proportion of patients (1.6%) had a hiatal hernia >3 cm or exhibited LA esophagitis grade C or D (1%). Furthermore, patient populations in study arms significantly differed with respect to other characteristics such as age and presence of Barrett's esophagus. In addition, in both studies moderate GERD was prevalent in about 94%/90.8% of the population in the MSA arm compared to 38.3%/18.1% in the LP fundoplication arm. Hence, only the safety-relevant data of the MSA arm is considered for evaluation.

[70] Riegler 2015 [62] reports 1-year results from 202 MSA patients. Bonavina 2021 [63] reports MSA data with a 3-year follow-up of 456 patients (including the original 202 MSA patients). Dependent on availability of outcome data, safety data from the last follow-up of Bonavina 2021 [63] is evaluated in GRADE. If no results are available for safety from Bonavina 2021 [63], data from Riegler 2015 [62] is used.

[71] Authors report the following: „As of July 2013, 249 patients had completed the one-year follow-up and were included in this report" and www.clinicaltrials.gov reports January 2010 as study start date of the study (NCT01624506).

[72] Patients 1 through 30 (30%) underwent the implantation procedure between March 2007 and May 2008 as part of a multi-centre (US, IT) pilot study of 41 patients (Bonavina 2008; treated with 1st generation LINX®). Patients 31 through 100 (70%) underwent the implantation procedure between December 2009 and February 2012 as part of a registry (treated with 2nd generation LINX®). Patients 1-30 from the multi-centre study were recorded under NCT01057992 in Italy.

[73] In the MSA arm, only a small proportion of patients (1.6%) had a hiatal hernia >3cm or exhibited LA esophagitis grade C or D (1%).

Author, year [Reference]	Bonavina 2013 [41]	Ganz 2015 [64]	Riegler 2015 [62]	Bonavina 2021 [63]
Exclusion criteria *(continuation)*	■ Allergy to the device's material (titanium, stainless steel, nickel, or ferrous materials)			
Baseline patient characteristics				
Age in years	Median (range): 44.5 (23-77)	Median (range): 53 (18-75)	Mean (SD): 46.6 (13.9) vs 52.8 (12.8), p=0.007	Mean (SD): 46.6 (13.6) vs 56.3 (12.6), p<0.0001
Sex, female:male, n (%)	26 vs 74	48:52	77:125 (38%:62%) vs 19:28 (40%:60%)	166:290 (36.3%:63.7%) vs 84:82 (50.6%:49.4%)
BMI, kg/m²	Median (range): 24 (17.3-33.0)	Median (range): 28 (20-35)	Mean (SD): 25.7 (3.8) vs 26.1 (5.3), p=0.611	Mean (SD): 25.7 (3.7) vs 27.81 (4), p<0.0001
Moderate GERD, %	NR	NR	94% vs 38.3%[74]	90.8% vs 18.1%[74]
Hiatal hernia, n (%)	Hiatal hernia ≤3 cm: 98[75] (98%)	NR	Hiatal hernia >3cm: 3[76] (1.6%) vs 21 (45.7%), p<0.001	Hiatal hernia >3cm: 7[76] (1.4%) vs 80 (48.1%), p<0.001
Esophagitis, %: LA grade A and B **LA grade C and D:**	16% 1%	NR	41.4% vs 44.7% 1% vs 8.5%	45.2% vs 46% 1.8% vs 13.2%
PPI use, in years	Median: 4	Median: 5	Mean (SD): 6.3 (5.4) vs 5.1 (4), p=0.098	Mean (SD): 6.1 (5.3) vs 5.7 (6), p=0.5184
Duration of GERD, in years	Median 5.5	Median: 10 (range 1-40)	Mean: 8.7 vs 7.3, p=0.086	Mean (SD): 9 (7.7) vs 9.2 (8.6), p=0.7950
Follow-up, years	3 (range 378 days-6 years)	5	1	3[77]
Lost to follow-up, n	5[78]	15	0	NR
Operative time, min	Mean: 47	Mean: 36[79]	NR	Median: 43.2 vs 79.7
Effectiveness results				
GERD symptoms				
Elimination of moderate-to-severe regurgitation according to FSQ score results (baseline/follow-up), n (%)	NR	NR	NR	NR
GERD-HRQL (baseline/follow-up)	Median: 24 (off PPIs)/2	Median: 27/4, p<0.001 Number of patients with reduction of ≥50% from baseline, n (%): 70[80], p=NR	Median: 20/3 vs 23/3.5, p=0.177	12mo mean change n =414 vs 152, (SD): -16.7 (10) vs -18.5 (11.5)[81] 24mo mean change, n =296 vs 103, (SD): -16.7 (10.6) vs -20 (10) 36mo mean change, n =278 vs 80, (SD): -16.6 (10.2) vs -17.8 (10.6)

[74] Moderate GERD is defined as hiatal hernia (≤3 cm), no Barrett's esophagus, no motility disorder, and esophagitis no greater than LA grade B

[75] Including the 21 patients that had no hiatal hernia. 77 patients had ≤3 cm hiatal hernia.

[76] Absolute numbers of patients (n) having a hiatal hernia >3cm are own calculations

[77] Outcomes were assessed after 12 months, 24 months and 36 months.

[78] Out of the 41 patients of the pilot study (Bonavina 2008) 11 patients were lost to follow-up. Out of the cohort of 100 patients (30 patients from the pilot study and 70 registry patients) 5 were lost to follow-up.

[79] This data comes from an earlier report of the same study of Ganz et al. 2013, Esophageal Sphincter Device for Gastroesophageal Reflux Disease.

[80] Seventy (83%) out of 84 patients available for the final analysis had an improvement.

[81] Statistical tests were only conducted for evaluating differences within-group changes over time. Mean changes from baseline for all follow-ups were significant at p-value <0.001.

Author, year [Reference]	Bonavina 2013 [41]	Ganz 2015 [64]	Riegler 2015 [62]	Bonavina 2021 [63]
Satisfaction, % (baseline/follow-up)	5%/87%	5%/92.8%[82]	NR/91.8% vs NR/86.7%	4.6%/78.2% vs 3.7%/76.5%[83]
Heartburn (baseline/follow-up)	Heartburn score, median: 15/2	Heartburn severity change, mean: 89%/11.9%, p<0.001	Heartburn waking from sleep, %: 30.8%/3.5% vs 40%/8.5%, p=0.229	NR
Regurgitation % (baseline/follow-up)	Daily regurgitation: 72%/2%	Daily regurgitation: 57%/1.2%, p<0.001	Moderate/severe regurgitation: 58.2%/3.1% vs 60%/13%, p=0.014	NR
Dysphagia, % (baseline/follow-up)	8%/0%[84]	5%/6%, (p=0.739)	NR/7% vs NR/10.6%[85], p=0.373	15.7%/3.8% vs 24.4%/4.8 %[86]
Extra-esophageal symptoms (asthma, chronic cough, laryngitis), % (baseline/ last follow-up)	52%/16%	NR	63.9%/22.3% vs 53.3%/17.4%, p=0.552	NR
DeMeester score87, median (baseline/follow-up)	30.1/11.2	36.6 (range 16.3-83.8)/NR	NR	NR
PPI usage (baseline/follow-up), %	Discontinuation: 85%	Discontinuation: 84.7%[88] (CI 95%, 81%-95%)	Discontinuation: 81.8% vs 63%, p=0.009	Use of PPIs: 97.8%/24.2% vs 95.8%/19.5%[89]
Barrett's esophagus (<2 cm), n (%)	NR	NR	NR[90]	NR[90]
Hospital discharge, %	96% (within 48 hours)	NR	NR	<33% vs 11.4% (within 24 hours) 49.2% vs ~75% (within 48 hours)
Esophagitis (baseline/follow-up), %	NR[91]	76.5%	NR[91]	NR[91]
Excessive bloating, % (baseline/follow-up)	48%/2%	52%/8.3%, p<0.001	NR/10% vs NR/31.9%, p<0.001	NR
Safety results				
Any AEs				
Device-/procedure-related AEs				
Inability to belch, %	1%	NR	1,6 % vs 10,1%, p=0.007	3.3%/2.4% vs 6.1%/8.3%[92]

[82] Authors reported on dissatisfaction: 95%/7.1%. Satisfaction numbers are own calculations.

[83] Baseline/12mo/24mo/36mo: 4.6%/75.4%/78.9%/78.2% vs 3.7%/77.2%/83.3%/76.5%

[84] Authors reported that at last follow-up 0% of patients experienced dysphagia. However, authors also report that one patient with dysphagia and odynophagia underwent esophageal dilation 5 days after implant with resolution of symptoms, and another other patient underwent esophageal dilation 335 days post implant for dysphagia that did not resolve and lead to an explantation of the device.

[85] Numbers at baseline were not reported. Authors stated that bothersome dysphagia was comparable between MSAD and LF.

[86] Baseline/12mo/24mo/36mo: 15.7%/8.8%/4.4%/3.8% vs 24.4%/7.6%/4.6%/4.8%

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

[88] At 5 years, 75.3% of patients reported complete cessation of PPIs, and 9.4% reported PPI use only as needed.

[89] Baseline/12mo/24mo/36mo: 97.8%/18.9%/21.4%/24.2% vs 95.8%/19.7%/18.1%/19.5%

[90] Only reported presence of Barrett's esophagus at baseline.

[91] Presence and type of esophagitis was only reported at baseline.

[92] Authors reported on ability to belch. Baseline/12mo/24mo/36mo: 96.7%/96.7%/97.2%/97.6% vs 93.9%/88.5%/92.5%/91.7%

Author, year [Reference]	Bonavina 2013 [41]	Ganz 2015 [64]	Riegler 2015 [62]	Bonavina 2021 [63]
Inability to vomit, %	1%	NR	8.7% vs 55.6%, p<0.001	3.4%/8.8% vs 8%/32%[93]
Other non-serious AE, %	4% mild odynophagia, 3% increased belching	NR	NR	NR
Post-operative dysphagia, % (baseline/follow-up)	8%/2%[84]	5%/6%, (p=0.739)	7% vs 10.6%[94]	15.7%/3.8%[86] vs 24.4%/4.8 %
(Post-operative) excessive bloating, % (baseline/follow-up)	48%/2%	52%/8.3%, p<0.001	NR/10% vs NR/31.9%[94], p<0.001	NR
SAEs				
Procedure related SAEs				
Intraoperative complications, n (%)	NR	NR	3 (1.49%) vs (2.13%) 1[95], (p=1.00)	8 (1.8%) vs 2 (1.2%)[96]
Procedure-related complications, n (%)	NR	NR	NR	9 (2%) vs 3 (1.8%)
Device-related SAEs				
Device erosion, n (%)	0	0	NR	NR
Device migration, n (%)	0	0	NR	NR
Device malfunction/unlocking, n (%)	0	0	NR	NR
Re-surgery (%)	NR	NR	4% vs 6.4%[97]	NR
Device removal, %	3%	7%	4%	2.4%[98]
Death	0	0	0	0

Abbreviations: AEs – Adverse events, BMI – Body mass index, C – Control group, EST – Electrical stimulation therapy, FSQ – Foregut symptom questionnaire, GERD-HRQL – Gastroesophageal reflux disease-health-related quality of life, I – Intervention group, IQR – Interquartile range, LES – Lower esophageal sphincter, LF – Laparoscopic fundoplication, MSA – Magnetic sphincter augmentation, NR – Not reported, PPI – Proton pump inhibitor, Pts. – Patients, RCT – Randomised controlled trial, RDQ – Reflux disease questionnaire, RoB – Risk of bias, RS – RefluxStop™, SAEs – Serious adverse events, SD – Standard deviation, stat. sign. – statistically significant.

[93] Authors reported on ability to vomit. Baseline/12mo/24mo/36mo: 96.6%/89.7%/85.8%/91.2% vs 92%/55.8%/52.6 %/68%

[94] Data are from the GERD-HRQL. It is % of patients reporting a response of ≥3 for the related question.

[95] An injury to the pleura in both groups, minor bleeding in two patients in the MSDA group.

[96] Absolute numbers of patients (n) having intraoperative or procedure-related complications are own calculations

[97] Reoperations in the MSAD group were performed for device removal due to dysphagia, pain or persistent GERD, while in the LF group were for persistent GERD and herniation of the fundic wrap.

[98] Authors reported that removal rates are cumulative across the 3 years: The device was removed in 11 out of 459 patients. Seven removals after the first 12 months, 2 additional removals during the next 12 months, and 2 further removals during the last 12 months. Two patients underwent fundoplication at the time of the device removal.

RefluxStop™

Table A-3: RefluxStop™: Results from case series and single-arm studies

Author, year [Reference]	Bjelovic 2020 [30]
Study design	Multi-centre, prospective single-arm study (NCT02759094)
Country	Hungary (4 clinical sites)
Sponsor	Implantica Trading AG
Intervention/Product	Non-active silicone implant (RefluxStop™)
Comparator	NA
Study duration	December 2016 – February 2018
Number of pts, total	50
Inclusion criteria	■ Pts ≥18 years and ≤75 years; ■ typical GERD symptoms >6 months ■ response to PPIs as anti-GERD medication ■ daily PPI anti GERD medication ■ subject has a 24-h pH monitoring proven GERD performed while off any anti-reflux medication or after discontinuation for at least 7 days prior to testing ■ Total distal esophageal pH must be ≤4 for ≥4.5% of the time during a 24-h monitoring
Exclusion criteria	■ History of gastroesophageal surgery, anti-reflux or bariatric procedure; ■ paraesophageal/sliding hernia >3 cm determined on endoscopy; ■ esophageal dysmotility (scleroderma, achalasia, Nutcracker esophagus) ■ LA grade C or D esophagitis ■ BMI > 35 kg/m^2
Primary outcome measure	■ Efficacy: GERD-HRQL total score (reduction) ■ Safety: Serious adverse device effects (SADEs), procedure-related serious adverse events (SAEs)
Secondary outcome measures	■ Safety: Adverse device effects (ADEs), procedure-related adverse events (AEs)
Baseline patient characteristics	
Age in years, mean (SD)	Mean (SD): 51.5 (11.8)
Sex, female:male, n (%)	22:28 (44%:56%)
BMI, kg/m^2	NR
Severity of regurgitation (at baseline), %: Mild and moderate Severe	34 (48%) 26 (52%)[99]
Hiatal hernia, n (%)	Hiatal hernia ≤3 cm: 50 (100%)
Esophagitis, n (%)	LA grade A: 13 (26%) LA grade B: 9 (18%)

[99] Own calculations: At baseline, 26 patients (52%) reported on severe regurgitation.

Author, year [Reference]	Bjelovic 2020 [30]
PPI use (in years)	NR[100]
Duration of GERD	NR
Follow-up	1 year
Lost to follow-up, n (%)	3[101] (6%)
Operative time, min	NR
Effectiveness results	
GERD symptoms	
GERD-HRQL (baseline/follow-up)	
baseline/6-month follow-up, mean (SD)	Score: 28.8 (7.3)/3.4 (6)[102], p<0.001 Score reduction >50% from baseline, n (%):45 (96%)
baseline/12-month follow-up, mean (SD)	Score: 28.8 (7.3)/3.2 (NR)[102], p<0.001 Score reduction >50% from baseline, n (%):44 (94%)
Satisfaction, n (%)	
baseline/6-month follow-up	Dissatisfied: 45 (90%)/2 (4%) neutral: 4/1 satisfied: 1/44
baseline/12-month follow-up	Dissatisfied: 45 (90%)/1 (2%) neutral: 4/1 satisfied: 1/43
Heartburn (baseline/12-month follow-up)	Heartburn score, median (range): 4 (0-5)/NR
Regurgitation, n (%) (baseline/follow-up)	
baseline/6-month follow-up	44 (88%)/NR
baseline/12-month follow-up	44 (88%)/4 (9%), p<0.0001
Dysphagia, n (%)	
baseline/6-month follow-up	15 (30%)/4 (9%)
baseline/12-month follow-up	15 (30%)/2 (4%)
DeMeester score[103] (baseline/follow-up)	NR
PPI usage (baseline/follow-up), n (%)	Use of PPIs: 50/1 (100%/2%)

[100] PPI use in years is not reported, but before surgery all 50 patients were taking PPIs until one week before baseline visit.

[101] Two patients with successful treatment results discontinued the study at 3 months and 6 months, and one patient had the device placed too low at surgery – refused re-surgery and discontinued at 6-months

[102] This corresponds to a reduction (improvement) of 88% after 6 months and 89% after 12 months.

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

Author, year [Reference]	Bjelovic 2020 [30]
Reflux characteristics determined by pH testing	Reduction overall time with pH <4 after 6 months, mean (SD): -16 (17.46), p<0.001 Overall time with pH <4 after 6 months, in percent: 16.35%/0.08%, p<0.001
Esophagitis (follow-up), %	NR[104]
Excessive bloating, % (baseline/follow-up)	84%/19.1%
Safety results	
Any AEs	8 (17%)[105] 9
Device-related AEs	0
Procedure-related AE, n (%) events (up to 12 months postoperative)	4 (8.5%) 5
Abdominal pain and incisional hernia, n (%) events	1 (2%) 2
Accidental intra-operative instrumental hepatic lesion (small), n (%) events	1 (2%) 1
Post-op delayed gastro-intestinal paralysis (one day), n (%) events	1 (2%) 1
Procedural pneumothorax, n (%) events	1 (2%) 1
Gastritis, n (%) events	4 (8.5%) 4[106]
Dysphagia, n (%) events	0[107]
Excessive bloating, % (baseline/follow-up)	84%/19.1%
SAEs	5 (10%) 7
Device-related SAEs	0
Procedure-related SAE up to 6 months postoperative, n (%) events (infection, bleeding etc.)	4 (8%) 6
Mediastinal abscess, empyema and abdominal abscess, n (%) events	1 (2%) 3
Intra-abdominal haemorrhage, n (%) events	1 (2%) 1
Pleuritis, n (%) events	1 (2%) 1
Removal of foreign body (part of a needle from the abdominal wall), n (%) events	1 (2%) 1
Procedure-related SAE between 6 months postoperative and 12 months, n (%) events (infection, bleeding etc.)	
Release of fundoplication sutures (re-sutured)	1 (2%) 1
Death, n (%)	0

Abbreviations: AEs – Adverse events, BMI – Body mass index, C – Control group, GERD-HRQL – Gastroesophageal reflux disease-health-related quality of life, I – Intervention group, IQR – Interquartile range, LES – Lower esophageal sphincter, LF – Laparoscopic fundoplication, NR – Not reported, PPI – Proton pump inhibitor, Pts. – Patients, RCT – Randomised controlled trial, RS – RefluxStop™, SAEs – Serious adverse events, SD – Standard deviation, stat. sign. – statistically significant.

104 Only reported at baseline.

105 At 12-month follow-up, data of 47 patients was available. Some patients could have experienced more than one event

106 Whether these events occurred in patients already experiencing an adverse event is not clear.

107 At the 1-year visit, 2 subjects reported minimal dysphagia. No new dysphagia cases were recorded.

Electrical stimulation therapy

Table A-4: EST: Results from case series and single-arm studies

Author, year [Reference]	Kapelle 2015 [39]	Paireder 2021 [65]
Study design	Multi-centre, prospective, international, open-label case series (NCT01574339)	Single-centre, prospective study (NCT02441400)
Country	Chile, Colombia, India, Netherlands, Mexico, New Zealand, United Kingdom[108]	Austria
Sponsor	EndoStim® Inc.	Medical University of Vienna
Intervention/Product	Electric stimulation therapy (EndoStim® LES Stimulator)	Electric stimulation therapy (EndoStim® LES Stimulator)
Study duration	5 years (August 2011-July 2016)[109]	4 years
Number of pts, total	n=44[110]	n=37[111],
Inclusion criteria	■ Pts>18years and <80years ■ Reflux symptoms ■ GERD-HRQL score ≥20 off PPIs and an increase of ≥5 on PPIs ■ Prior PPI use for 12 months ■ Diagnosis based on 24-h pH monitoring result ■ LES end-expiratory 5–15 mmHg ■ Peristaltic contractions in ≥50% of swallows with contraction amplitude of ≥30 mmHg esophageal manometry, ■ Excessive lower esophageal acid exposure as pH <4.0 for ≥5% of the total time.	NR[112]
Exclusion criteria	■ History of esophageal or gastric surgery ■ Gastroparesis, multisystem 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 kg/m^2 ■ T1DM or uncontrolled T2DM defined as HbA1c ≥9.5 in the previous 6ms, or T2DM for ≥10 years	

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

[109] Information according to www.clinicaltrials.gov

[110] Baseline characteristics on 42pts

[111] Six (15.8%) patients had had previous foregut surgery. One patient had four previous fundoplications, one patient three previous fundoplications, two patients had one previous fundoplication, one patient underwent a preceding POEM procedure, and one patient had a resection of the fundus due to perforation during redo fundoplication.

[112] All patients meeting the indication for anti-reflux surgery were eligible for the study. Six patients were included that had undergone previous foregut surgery.

Author, year [Reference]	Kapelle 2015 [39]	Paireder 2021 [65]
Exclusion criteria *(continuation)*	■ Suspected or confirmed esophageal or gastric cancer, any malignancy in last 2 years ■ Esophageal or gastric varices or dysphagia or esophageal peptic stricture ■ Significant cardiac arrhythmia or cardiovascular disease ■ Implanted electrical stimulator or chronic anticoagulant therapy ■ Pregnant pts.	NR
Baseline patient characteristics		
Age in years, mean (SD)	49.6 (12.3)	54 (15.8)
Sex, female:male, n (%)	18:24 (43%:57%)	17:20 (45.9%:54.1%)
BMI, kg/m^2, mean (SD) and distribution	27.2 (3.4) ≤25: 31%, >25 and ≤30: 52%, >30: 17%	NR <25: 56.8%, ≥25 and <30: 27%, ≥30: 16.2%
GERD symptoms, n (%): typical vs atypical **heartburn** **regurgitation** **dysphagia**	NR	29:16 (78.4%:43.2%) 32 (86.5%) 28 (75.7%) 7 (18.9%)
Hiatal hernia, none/<2 cm/>2 cm, %	39/22/39	NR[113]
Esophagitis, n (%): LA grade A and B **LA grade C and D**	16% 1%	NR
PPI use, n (%)	38 (90%)[114]	31 (83.8%)
Duration of GERD, in years	NR	NR
Follow-up, years	0.5	2
Lost to follow-up, % of patients	6.8%[115]	0
Operative time, min	Mean: 47	Median (IQR): 55 (41.4-70.3)
Effectiveness results		
GERD symptoms		
Improvement in median GERD HRQL score (pre-op./last follow-up) (IQR)	on-PPI: 16.5 (9.0–22.8)/5.0 (3.0–9.0) p<0.0001 off-PPI: 31.0 (26.2-36.8)/5.0 (3.0–9.0) p<0.0001	41 (21-49)/8.50 (4.25-20.5)
Satisfaction, % of patients (baseline/follow-up)	7%/54%[116]	5%/92.8%[117]

[113] 23 patients (62.2%) additionally underwent a hiatal hernia repair.

[114] In total, 90% of patients (38) used PPI at least once daily, 3 patients (7%) did not use any PPI and information of 1 (2%) patient was missing.

[115] 1 loss to follow-up, 1 Toupet fundoplication due to hiatal hernia >3 cm, 1 trocar perforation of the intestine during implant procedure

[116] 42 pts at baseline, 39 at last follow-up

[117] Authors reported on dissatisfaction: 95%/7.1%. Satisfaction numbers are own calculations and can only be interpreted as number of patients that are at least neutral and satisfied.

Author, year [Reference]	Kapelle 2015 [39]	Paireder 2021 [65]
Heartburn (baseline/follow-up)	Median heartburn % of days (IQR): Days: 16.5% (9.0–22.8)/5.0% (3.0–9.0) Nights: 31.0% (26.2-36.8)/5.0% (3.0–9.0)	Heartburn score, median (IQR): 21 (13-28)/5 (1.5-12.5), p<0.001
Regurgitation, % (baseline/follow-up)	Median regurgitation % of days (IQR): Days: 79% (54–100)/0% (0–21) Nights: 50% (15–79)/0% (0–7)	Regurgitation score, median (IQR): 18 (11-23.5)/3 (1.5-5.5), p<0.001
Dysphagia, n (%) (baseline/last follow-up)	NR	7 (18.9%)/0 (0%)
Extra-esophageal symptoms (asthma, chronic cough, laryngitis), n (%) (baseline/last follow-up)	NR	Regurgitation 28 (75.7%)/NR Chronic cough 11 (29.7%)/NR Stomach pain 6 (16.2%)/NR Retrosternal pain 6 (16.2%)/NR
DeMeester score[118], median (baseline/follow-up)	Median (IQR): 35.1 (27.1–51.9)/17.5 (10.9–23.4)[119]	NR
PPI usage (baseline/last follow-up), n (%)	NR	31 (83.8%)/9 (23.7%)[120]
Hospital stay, median (IRQ)	NR	2 (2–2.5)
Excessive bloating, % (baseline/follow-up)	48%/2%	NR/0%
Esophagitis (baseline/follow-up), %	None: 41%/51% LA grade A: 31%/31% LA grade B: 23%/18% LA grade C: 5%/0%	NR
Safety results		
Any AE, n (%) events	NR (NR) 107[121]	7[122] (19%) 7
Device/procedure related AEs, n (%) events	NR[123] (NR) 52	7 (19%) 7
Post-operative bloating/belching	3 (7.1%) 3	NR
Inability to bloat/belch	NR	0
Constipation	1 (2.4%) 1	NR
Post-operative dysphagia	4 (9.5%) 5	0

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

[119] 42 pts at baseline, 40 at last follow-up

[120] Data on PPI usage is only available for the 12-month follow-up.

[121] In total, 110 AEs (107) and SAEs (3) in 32 patients were reported, 56 AEs were classified as non-device- or procedure-related, 55 AEs were classified as device- or procedure-related.

[122] One patient experienced a subcutaneous emphysema, 2 patients mild thoracic sensations, and in 4 patients the impedance was out of range.

[123] Exact number of patients that had at most one event was not reported. Patients could experience more than one AE.

Author, year [Reference]	Kapelle 2015 [39]	Paireder 2021 [65]
Epigastric pain	1 (2.4%) 1	NR
Hiccups	2 (4.8%) 3	NR
Nausea/vomiting	3 (7.1%) 4	NR
Inability to vomit	2 (4.8%) 2	0
Weight loss/anorexia	5 (11.9%) 5	NR
Fever	1 (2.4%) 1	NR
Pain/discomfort	19 (45.2%) 24	NR
Impedance out of range	2 (4.8%) 2	4 (10.1%) 4
Mesh repair hernia cicatricialis	1 (2.4%) 1	NR
Subcutaneous emphysema	NR	1 (2.7%) 1
Mild thoracic sensations	NR	2 (5.4%) 2
Serious adverse events (device/procedure related SAEs), n (%) events	2 (NR) 2	6 (16%) 6
Trocar perforation of the small bowel during laparoscopy	1 (2.4%) 1	0
Device erosion	1 (2.4%) 1	NR
Insufficient symptom control	NR	2 (5.4%) 2
Device malfunction/unlocking	NR	4 (10.8%) 4
Device removal	2 (2.4%) 2[124]	6 (15.8%) 6[125]
Death	0	0

Abbreviations: AEs – Adverse events, BMI – Body mass index, C – Control group, EST – Electrical stimulation therapy, GERD-HRQL – Gastroesophageal reflux disease-health-related quality of life, Hb1c – Hemoglobin A1c ,I – Intervention group, IQR – Interquartile range, LES – Lower esophageal sphincter, NR – Not reported, PPI – Proton pump inhibitor, Pts. – Patients, RCT – Randomised controlled trial, SAEs – Serious adverse events, SD – Standard deviation, stat. sign. – statistically significant, T1DM/T2DM – Type 1/2 diabetes.

[124] The explantation was conducted due to the device erosion and because of the trocar perforation of the small bowel during laparoscopy and was considered procedure-related.

[125] In four of the six patients (10.8%), the device was removed due to technical issues/device malfunction. Another, two patients had insufficient symptom control. These six patients underwent a conversion to Nissen fundoplication.

Risk of bias tables

The 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 AIHTA [72]and in the Guidelines of EUnetHTA [52].

Magnetic sphincter augmentation

Table A-5: MSA: Risk of bias for randomised controlled trials, RoB 2.0 [53] – study level

Study: Author, year [Reference]	Bias arising from the randomization process	Bias arising from period or carry-over effects	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Overall risk of bias
Bell, 2019/2020 [60, 61]	Some concerns[126]	Some concerns[127,128,129]	Some concerns[130,131]	Some concerns[132]	Low	Low	Some concerns

[126] Within the first portion of the study (pre-crossover) the randomness of the allocation sequence was maintained (Bell 2019). The second portion of the study allowed only eligible patients in the BID PPI arm to crossover to MSA if both moderate-severe regurgitation persisted and impedance pH testing demonstrated persistent reflux burden. Initial random allocation was not maintained after crossover due to this selective, single-arm crossover. Hence, allocation of participants in the comparison of the data of the total MSA cohort (n=75) (i.e. primary MSA cohort after 6 months + crossover after 6 months) vs BID cohort after 6 months (n=87) is not completely random anymore. The same applies for the 12 months comparison between the primary MSA cohort (n=44) and the step-down PPI cohort (n=43).

[127] Initial allocation was 1:2 (MSA: 50, BID PPI: 102) meaning that PPI is over-represented, which can lead to a bias against it.

[128] Authors did not state in their analysis protocol that they account for period effects in their follow-up analysis after crossover happened.

[129] Authors reported that after 6 months, patients eligible for a MSA crossover receive treatment after a 7-day washout period.

[130] Nature of interventions makes (double-)blinding impossible

[131] Per-protocol analysis was conducted for the primary outcome measure FSQ regurgitation score (elimination of moderate-to-severe regurgitation) and for the secondary outcomes (GERD-HRQL, regurgitation, and heartburn). There was a potential for impact of the failure to analyse participants in the group to which they were randomised, as three of 78 patients in the MSA group (6-month FU analysis) and six of 49 patients in the step-down PPI group (12-month FU analysis) were excluded.

[132] Exact numbers of the GERD-HRQL and RDQ (secondary outcomes) are missing for the control group.

Table A-6: MSA: Risk of bias for single-arm studies and case series, IHE-20 checklist [54, 55] – study level

Study: Author, year [Reference]	Bonavina 2013 [41]	Ganz 2015 [64]	Riegler 2015 [62]	Bonavina 2021 [63]
	NA	NCT00776997	NCT01624506	
1. Is the hypothesis/aim/objective of the study stated clearly in the abstract, introduction, or methods section?	Yes	Yes	Yes	Yes
2. Was the study conducted prospectively	Yes	Yes	Yes	Yes
3. Were the cases collected in more than one centre?	No	Yes	Yes	Yes
4. Were participants recruited consecutively?	No[133]	Unclear[134]	Yes	Yes
5. Are the characteristics of the participants included in the study described?	Yes	Yes	Yes	Yes
6. Are the eligibility criteria (inclusion and exclusion criteria) for entry into the study explicit and appropriate?	Yes	Yes	Partially reported[135]	Partially reported[135]
7. Did participants enter the study at a similar point in the disease?	No	No	Unclear	Unclear
8. Was the intervention clearly described in the study?	Yes	Yes	Yes	Yes
9. Were additional interventions (co-interventions) clearly reported in the study?	Yes	No	Yes	Yes
10. Are the outcome measures clearly defined in the introduction or methods section (established a priori)?	Yes	Yes	Yes	Yes
11. Were outcome assessors blinded to the intervention that patients received?	No[136]	Unclear	Unclear	Unclear
12. Were relevant outcomes appropriately measured with objective and/or subjective methods?	Yes	Yes	Yes	Partial[137]
13. Were outcomes measured before and after intervention?	Yes	Yes	Yes	Yes
14. Were the statistical tests used to assess the relevant outcomes appropriate?	Yes	Yes	Yes	Yes
15. Was follow-up long enough for important events and outcomes to occur (follow-up reported)?	Yes	Yes	Yes	Yes
16. Was the loss to follow-up reported?	Yes	Yes	Yes	Unclear[138]
17. Does the study provide estimates of the random variability in the data analysis of relevant outcomes?	No	Yes	Yes	Yes
18. Are adverse events reported?	Yes	Yes	Yes	Yes
19. Are the conclusions of the study supported by results?	Yes	Yes	Partially[139]	Partially[139]
20. Are both competing interest and source of support for the study reported?	Yes	Yes	Yes	Yes
Overall Risk of bias	**High**	**Moderate**	**Moderate**	**Moderate**

[133] Patients 1 through 30 (30%) underwent the implantation procedure as part of a multi-centre pilot study of 41 patients (Magnetic Augmentation of the Lower Esophageal Sphincter: Results of a Feasibility Clinical Trial, Bonavina et al. 2008). Patients 31 through 100 (70%) underwent the implantation procedure as part of a registry.

[134] From the 257 patients that signed the consent 100 underwent device implant. The 157 who discontinued 96 eligibility criteria not met, 36 consent withdrawn, 24 discontinuation when implant limit met and 1 discontinuation by investigator (Ganz 2013).

[135] Exclusion criteria are unspecific (patients were excluded if they had known conditions that would make it unlikely for them to complete a 3-year follow-up).

[136] Study conception, design, acquisition of data, analysis, and interpretation of data was conducted by two of the study authors (Bonavino and Saino).

[137] Regurgitation- and heartburn-related outcome measures were not reported.

[138] Lost to follow-up was not clearly reported and number of patients were different in the analysis of different endpoints.

[139] Statements on the comparative effectiveness cannot be made.

RefluxStop™

Table A-7: RefluxStop™: Risk of bias for single-arm studies and case series, IHE-20 checklist [54, 55] – study level

Study: Author, year [Reference]	Bjelovic 2021 [30]
	NCT02759094
1. Is the hypothesis/aim/objective of the study stated clearly in the abstract, introduction, or methods section?	Yes
2. Was the study conducted prospectively	Yes
3. Were the cases collected in more than one centre?	Yes
4. Were participants recruited consecutively?	Unclear[140]
5. Are the characteristics of the participants included in the study described?	Yes
6. Are the eligibility criteria (inclusion and exclusion criteria) for entry into the study explicit and appropriate?	Yes
7. Did participants enter the study at a similar point in the disease?	Yes
8. Was the intervention clearly described in the study?	Yes
9. Were additional interventions (co-interventions) clearly reported in the study?	Yes
10. Are the outcome measures clearly defined in the introduction or methods section (established a priori)?	Yes
11. Were outcome assessors blinded to the intervention that patients received?	Unclear[141]
12. Were relevant outcomes appropriately measured with objective and/or subjective methods?	Yes
13. Were outcomes measured before and after intervention?	Yes
14. Were the statistical tests used to assess the relevant outcomes appropriate?	Yes
15. Was follow-up long enough for important events and outcomes to occur (follow-up reported)?	Yes
16. Was the loss to follow-up reported?	Yes
17. Does the study provide estimates of the random variability in the data analysis of relevant outcomes?	Yes
18. Are adverse events reported?	Yes
19. Are the conclusions of the study supported by results?	Yes
20. Are both competing interest and source of support for the study reported?	Yes
Overall Risk of bias	**Low**

[140] No clear information was provided about the method used to recruit patients in the study.

[141] PCG PharmaConsulting Group AB (name changed to Link Medical) handled the data collecting system Viedoc and collected and analyzed the data. It is unclear whether they were aware of the intervention.

Electrical stimulation therapy

Table A-8: EST: Risk of bias for single-arm studies and case series, IHE-20 checklist [54, 55] – study level

Study: Author, year [Reference]	Kappelle 2015 [39]	Paireder 2021 [65]
	NCT01574339	NCT02441400
1. Is the hypothesis/aim/objective of the study stated clearly in the abstract, introduction, or methods section?	Yes	Yes
2. Was the study conducted prospectively	Yes	Yes
3. Were the cases collected in more than one centre?	Yes	No
4. Were participants recruited consecutively?	Unclear[142]	Yes
5. Are the characteristics of the participants included in the study described?	Yes	Yes
6. Are the eligibility criteria (inclusion and exclusion criteria) for entry into the study explicit and appropriate?	Yes	No[143]
7. Did participants enter the study at a similar point in the disease?	Unclear	Unclear
8. Was the intervention clearly described in the study?	Yes	Yes
9. Were additional interventions (co-interventions) clearly reported in the study?	Yes	Yes
10. Are the outcome measures clearly defined in the introduction or methods section (established a priori)?	Yes	Yes
11. Were outcome assessors blinded to the intervention that patients received?	Unclear[141]	Unclear[144]
12. Were relevant outcomes appropriately measured with objective and/or subjective methods?	Yes	Yes
13. Were outcomes measured before and after intervention?	Yes	Yes
14. Were the statistical tests used to assess the relevant outcomes appropriate?	Yes	Yes
15. Was follow-up long enough for important events and outcomes to occur (follow-up reported)?	Yes	Yes
16. Was the loss to follow-up reported?	Yes	Yes
17. Does the study provide estimates of the random variability in the data analysis of relevant outcomes?	Yes	Yes
18. Are adverse events reported?	Yes	Yes
19. Are the conclusions of the study supported by results?	Partially reported[145]	Yes
20. Are both competing interest and source of support for the study reported?	Yes	Yes
Overall Risk of bias	**Moderate**	**Moderate**

142 Unclear: 110pts screened and 66 specified screen failures.

143 Explicit inclusion and exlcusion criteria were not reported.

144 The study did not report whether the outcome assessors were aware of the intervention.

145 Statements on the (comparative) effectiveness cannot be made.

GRADE evidence profiles

Table A-9: Evidence profile: efficacy and safety of LES devices in laparoscopic surgery

Certainty assessment							Impact	Certainty (Importance)
№ of studies (Pts I vs C)	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
Efficacy								
Magnetic sphincter augmentation (LINX® Reflux Management System)								
Elimination of moderate-to-severe regurgitation (number of patients (%)) assessed with: FSQ regurgitation score; follow up: 6 months								
1 [60, 61] (75 vs 87)	RCT	serious[a]	not serious	not serious	serious[b]	strong association[c]	Full MSA cohort vs BID PPI cohort: 72 (96%) vs 8 (11%) study reported a stat. sign. difference in number of patients with elimination of moderate-to-severe regurgitation between full MSA cohort and BID PPI cohort after 6 months (p<0.001)	⨁⨁⨁◯ **Moderate (Critical)**
Complete elimination of regurgitation (number of patients (%)) assessed with: FSQ regurgitation score; follow-up: 6 months								
1 [60, 61] (75 vs 87)	RCT	serious[a]	not serious	not serious	serious[b]	strong association[c]	Full MSA cohort vs BID PPI cohort: 51 (73%) vs 2* (2%) study reported a stat. sign. difference in number of patients with complete elimination of regurgitation between full MSA cohort and BID PPI cohort after 6 months (p<0.001)	⨁⨁⨁◯ **Moderate (Critical)**
Elimination of moderate-to-severe regurgitation (number of patients (%)) assessed with: FSQ regurgitation score; follow-up: 12 months								
1 [60, 61] (44 vs 43)	RCT	serious[a]	not serious	not serious	serious[b]	strong association[c]	Primary MSA cohort vs step-down PPI cohort: 43 (98%) vs 8 (19%) study reported a stat. sign. difference in number of patients with elimination of moderate-to-severe regurgitation between primary MSA cohort vs step-down PPI after 12 months (p<0.001)	⨁⨁⨁◯ **Moderate (Critical)**
Overall health-related quality of life (overall HRQoL), mean (SD) assessed with: GERD-HRQL; follow-up: 6 months								
1 [60, 61] (75 vs 87)	RCT	serious[a]	not serious	not serious	serious[b]	strong association[c]	Full MSA cohort vs BID PPI cohort: study reported a reduction in mean GERD-HRQL scores for full MSA cohort from baseline off PPI at baseline: 30 (10)/6 (NR) vs no improvement on PPI at baseline: 24 (10)/6 (NR) vs no improvement p=NR	⨁⨁⨁◯ **Moderate (Critical)**
Overall health-related quality of life (overall HRQoL), mean (SD) assessed with: GERD-HRQL; follow-up: 12 months								
1 [60, 61] (44 vs 43)	RCT	serious[a]	not serious	not serious	serious[b]	strong association[c]	Primary MSA cohort vs step-down PPI cohort: study reported a reduction in mean GERD-HRQL scores for primaryl MSA cohort from baseline off PPI at baseline: 30 (10)/5 (NR) vs no improvement on PPI at baseline: 24 (10)/5 (NR) vs no improvement p=NR	⨁⨁⨁◯ **Moderate (Critical)**
GERD-HRQL score reduction of ≥50% from baseline (number of patients (%)) assessed with: GERD-HRQL; follow-up: 6 months								
1 [60, 61] (75 vs 87)	RCT	serious[a]	not serious	not serious	serious[b]	strong association[c]	Full MSA cohort vs BID PPI cohort: 61 (81%) vs no reduction number of patients with GERD-HRQL score reduction of ≥50% from baseline full MSA cohort and BID PPI cohort after 6 months (p=NR).	⨁⨁⨁◯ **Moderate (Critical)**

Certainty assessment							Impact	Certainty (Importance)
Nº of studies (Pts I vs C)	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
GERD-HRQL score reduction of ≥50% from baseline (number of patients (%)) assessed with: GERD-HRQL; follow-up: 12 months								
1 [60, 61] (44 vs 43)	RCT	serious[a]	not serious	not serious	serious[b]	strong association[c]	Primary MSA cohort vs step-down PPI cohort: 41 (93%) vs no reduction number of patients with GERD-HRQL score reduction of ≥50% from baseline full MSA cohort and BID PPI cohort after 6 months (p=NR).	⨁⨁⨁◯ **Moderate (Critical)**
Heartburn score (qualitative results) assessed with: GERD-HRQL; follow-up: 6 months								
1 [60, 61] (75 vs 87)	RCT	serious[a]	not serious	not serious	very serious[b,d]	strong association[c]	Full MSA cohort vs BID PPI cohort: identical improvements as GERD-HRQL score vs no improvement	⨁⨁◯◯ **Low[a,b,d] (Critical)**
Heartburn score (qualitative results) assessed with: GERD-HRQL; follow-up: 12 months								
1 [60, 61] (44 vs 43)	RCT	serious[a]	not serious	not serious	very serious[b,d]	strong association[c]	Primary MSA cohort vs step-down PPI cohort: identical improvements as GERD-HRQL score vs no improvement	⨁⨁◯◯ **Low[a,b,d] (Critical)**
Regurgitation score, mean (IQR) assessed with: RDQ; follow-up: 6 months								
1 [60, 61] (75 vs 87)	RCT	serious[a]	not serious	not serious	serious[b]	strong association[c]	Full MSA cohort vs BID PPI cohort: study reported a reduction in mean RDQ regurgitation scores for full MSA cohort from baseline off PPI at baseline: 4 (3.25-4.75)/0 (0-1.125) vs no improvement on PPI at baseline: 3.5 (2.5-4)/0 (0-1.125) vs no improvement p=NR	⨁⨁⨁◯ **Moderate (Critical)**
Regurgitation score, mean (IQR) assessed with: RDQ; follow-up: 12 months								
1 [60, 61] (44 vs 43)	RCT	serious[a]	not serious	not serious	serious[b]	strong association[c]	Primary MSA cohort vs step-down PPI cohort: study reported a reduction in mean GERD-HRQL regurgitation scores for primary MSA cohort from baseline off PPI at baseline: 4 (3.25-4.75)/0 (0-0.5) vs no improvement on PPI at baseline: 3.5 (2.5-4)/0 (0-0.5) vs no improvement p=NR	⨁⨁⨁◯ **Moderate (Critical**
RefluxStopTM								
Due to the lack of a controlled group, no data on effectiveness can be reported								
Electrical stimulation therapy (EndoStim®)								
Due to the lack of a controlled group, no data on effectiveness can be reported								
Safety								
Magnetic sphincter augmentation (LINX® Reflux Management System)								
Any adverse events (AEs) assessed with: number of patients, events; follow-up range: 6 to 12 months								
1[e] [60, 61] (75 vs 87)	RCT	serious[a]	not serious	not serious	serious[b]	none	No device- or procedure related AEs were reported Of the 15 patients experiencing post-operative dysphagia, 2 patients reported ongoing dysphagia (one severe and one moderate). 3 patients at risk for developing dysphagia problems received oral corticosteroids.	⨁⨁◯◯ **Low (Critical)**

Certainty assessment							Impact	Certainty (Importance)
Nº of studies (Pts I vs C)	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
1[e] [60, 61] (75 vs 87) *(continuation)*							Overall, dysphagia decreased compared to baseline and PPI medication. Dysphagia score ≥3 (bothersome swallowing everyday): Full MSA cohort vs BID PPI cohort (after 6 months): off PPI at baseline: 27%/11% vs no significant improvement on PPI at baseline: 15%/11% vs no significant improvement Primary MSA cohort vs step-down PPI cohort (after 12 months): off PPI at baseline: 27%/7% vs no significant improvement on PPI at baseline: 15%/7% vs no significant improvement	
Serious adverse events (SAEs) assessed with: number of events and patients; follow-up range: 6 to 12 months								
1[e] [60, 61] (75 vs 87)	RCT	serious[a]	not serious	not serious	serious[b]	none	No device-related SAEs were reported. 1 procedure-related SAE was reported: esophageal spasms shortly after surgery (n=1). 4 patients received re-surgery: endoscopic dilations (n=3), laparoscopic repair of a hiatal hernia (n=1) No device was explanted and no death was reported.	⊕⊕◯◯ **Low (Critical)**
Any adverse events (AEs) assessed with: % of patients; follow-up range: 36 to 60 months								
3 [41, 62-64] (636 vs –)	observational studies	serious[f]	serious[g]	not serious	not serious	none	Excessive bloating: 2 – 10%, Inability to belch: 1-2.4%, Inability to vomit: 1-8.8%, Post-operative dysphagia: 2-7%, Other non-serious AE: mild odynophagia (4%), increased belching (3%) No other device- or procedure-related AEs were reported.	⊕◯◯◯ **Very low (Critical)**
Serious adverse events (SAEs) assessed with: % and number of patients; follow-up range: 36 to 60 months								
3 [41, 62-64] (636 vs –)	observational studies	serious[f]	serious[g]	not serious	not serious	none	Device removal: 2.4 – 7% Intraoperative complications: 1.8% (n=8) No deaths were reported.	⊕◯◯◯ **Very low (Critical)**
RefluxStopTM								
Any adverse events (AEs) assessed with: events, number of patients (%); follow-up: 12 months								
1 [30] (47 vs –)	observational studies	not serious	not serious	not serious	serious[h]	none	Excessive bloating in percentage of patients decreased compared to baseline at 12-months follow-up: 84% to 19.1% of patients. No new dysphagia cases occurred. Over 12 months, 8 AEs (procedure-related and other AEs) occurred: abdominal pain and incisional hernia (n=1), accidental intraoperative instrumental hepatic lesion (small) (n=1), post-op delayed gastro-intestinal paralysis (one day) (n=1), procedural pneumothorax (n=1), gastritis (n=4). No device-related AEs were reported.	⊕◯◯◯ **Very low (Critical)**

Certainty assessment							Impact	Certainty (Importance)
Nº of studies (Pts I vs C)	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
Serious adverse events (SAEs) assessed with: events, number of patients (%); follow-up: 12 months								
1 [30] (47 vs –)	observational studies	not serious	not serious	not serious	serious[h]	none	In total, 7 procedure-related SAEs occurred in 5 patients over the 12-month follow-up: 3 events of mediastinal abscess, empyema and abdominal abscess (n=1), 1 intra-abdominal haemorrhage (n=1), 1 pleuritis (n=1), 1 removal of foreign body (n=1), and 1 release of fundoplication sutures/resuturation (n=1). No device-related SAEs occurred and no deaths were reported	⨁◯◯◯ **Very low (Critical)**
Electrical stimulation therapy (EndoStim®)								
Any adverse events (AEs) assessed with: events, number of patients (%); follow-up range: 6 to 24 months								
2 [39, 65] (79 vs –)	observational studies	serious[i]	serious[j,k]	not serious	serious[l]	none	Overall, excessive bloating, esophagitis, and dysphagia decreased compared to baseline at 24-months follow-up. In total, 114 AE occured of which 59 events were device- or procedure related (2 studies).	⨁◯◯◯ **Very low[i,j,k,l] (Critical)**
Serious adverse events (SAEs) assessed with: events, number of patients (%); follow-up range: 6 to 24 months								
2 [39, 65] (79 vs –)	observational studies	serious[i]	serious[k,m]	not serious	serious[l]	none	In total, 8 device-/procedure-related SAEs in 8 patients were reported in 2 studies (all of the devices were explanted in these cases): 1 trocar perforation of the small bowel during laparoscopy (1/47), 1 device erosion (1/47), 2 cases of insufficient symptom control (2/37) 4 cases of device malfunction/unlocking (4/37) 8 device removals (8/79). No deaths were reported.	⨁◯◯◯ **Very low[i,k,l,m] (Critical)**

*Abbreviations: AEs – Adverse events, BID PPI – Proton pump inhibitor twice daily, C – Control group, FSQ – Foregut symptom questionnaire, GERD-HRQL – gastroesophageal reflux disease-health-related quality of life, I – Intervention group, IQR – Interquartile range, MSA – Magnetic sphincter augmentation, NR – Not reported, Pts – patients, RCT – Randomised controlled trial, RDQ – Reflux disease questionnaire, RoB – Risk of bias, SAEs – Serious adverse events, SD – Standard deviation, stat. sign. – statistically significant. * based on own calculation*

Explanations

[a] *Some concerns: Selective crossover/single-arm crossover (initial random allocation was not maintained after crossover), per-protocol analysis (potential for impact of the failure to analyse participants in the group to which they were randomised*

[b] *Outcome comes from only one trial with 152 patients.*

[c] *Strong association/Large effect: When there is a (very) large magnitude of effect, we might be more certain that there is at least a small effect if biases are present.*

[d] *No explicit numbers were reported*

[e] *Any grade AEs, SAEs, re-surgery data were considered from Bell 2019 [60] and 2020 [61].*

[f] *1/3 high RoB, 2/3 moderate RoB*

[g] *Heterogeneous results, partly heterogeneous patient population*

[h] *Outcome comes from only one relatively small (single-arm) study (n=50).*

[i] *Unclear risk of bias due to unclear allocation concealment; using the IHE-20 RoB checklist, both studies were evaluated to have a moderate risk of bias.*

[j] *One study reported that 76% of study participants experienced any grade AEs while the second study reported that 19% of study participants experienced any grade AEs.*

[k] *In one study, 6 patients had undergone previous foregut surgery while in the other study patients with history of esophageal or gastric surgery were included.*

[l] *Small sample size*

[m] *One study reported that 3 of 47 (6%) study participants experienced SAEs while the second study reported that 6 of 37 (16%) study participants experienced SAEs (e.g. device removal in one study was 6 times more likely with a smaller study population compared to the other study with 47 study participants).*

Applicability table

Table A-10: Summary table characterising the applicability of a body of studies

Domain	Description of applicability of evidence
Population	All studies included chronic patients with gastroesophageal reflux disease (GERD) who were refractory to proton pump inhibitor (PPI) therapy. The studies included a total of 152 patients for the analysis of effectiveness outcomes for magnetic sphincter augmentation (MSA) and an additional 831 patients for the safety profile. The study investigating the RefluxStop™ (RS) device included 50 patients and was only eligible for the analysis of effectiveness outcomes. The electrical stimulation therapy (EST) studies included in total 81 patients for the analysis of the safety profile only. The inclusion criteria of the studies are in accordance with the approved indications. Therefore, the body of evidence is directly applicable to the patient group for which the technologies are targeted: patients with a BMI <35 kg/m^2, without severe refractory GERD, without hiatal hernias >3 cm, Barrett's easophagus or grade C and D esophagitis, but only mild to moderate GERD with incomplete symptom control by PPIs. However, one study for the MSA device included a very small amount of patients with a hiatal hernia of more than three centimetres. Overall, there are no applicability concerns.
Intervention	Three different novel laparoscopic approaches for reinforcing the native lower esophegael sphincter (LES) in GERD patients from three manufacturers were used across the trials to treat GERD patients: ■ Magnetic sphincter augmentation (MSA): LINX® management system by Ethicon/Torax Medical Inc. ■ Non-active silicone implant (RS): RefluxStop™ by Implantica Trading AG ■ Electrical stimulation therapy (EST): EndoStim® by EndoStim® Inc.
Comparators	The following comparators were used in the included studies: ■ PPI therapy in the randomised controlled trial for the MSA device (n=1) The PPI comparison is adequate for patients who are dissatisfied with PPI therapy or for patients who want to avoid potential significant side effects of laparoscopic fundoplication (LF). Since, MSA and the other two approaches (EST, RS) should fill the therapeutic gap for patients who fail medical management, because of a potential underlying incompetency of the LES, the PPI therapy is not an adequate comparator. The same applies for patients, who experience substantial side effects of medical therapy. For these patients standard surgical therapy (laparoscopic fundoplication) would be an adequate comparator. Hence, the use of different comparators may affect the included comparative trial results.
Outcomes	Effectiveness outcomes reported in the RCT for the MSA device were health-related quality of life by GERD-HRQL, GERD symptoms such as heartburn, and elimination of moderate-to-severe regurgitation (via FSQ and RDQ). Device- and procedure related adverse events (AEs) and serious adverse events (SAEs) were reported in the studies for each device. The reported outcomes are clinically relevant for all three devices and outcomes on clinical effectiveness have shown benefits from the treatment with MSA. Nevertheless, the validity of the outcomes in the studies are limited, because of the lack of RCTs and controlled trials for two devices (RS, MSA), adequate comparators and RCTs with a longer follow-up (>2-3 years) involving larger number of patients (n>100) for all three devices.
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 and public hospitals, and academic and community medical centres. The studies were published between 2013 and 2021. It can be assumed that the settings of the studies reflect the clinical setting in which all three devices are intended to be used appropriately. No applicability issues are expected from the geographical setting. The surgeon's technical expertise likely determines the risk of local side effects. Hence, the treatment with any of the three devices will certainly be accompanied by a learning curve.

Abbreviations: AEs – Adverse events, CG – Control group, EST – Electrical stimulation therapy, FSQ – Foregut symptom questionnaire, GERD-HRQL – Gastroesophageal reflux disease-health-related quality of life, I – Intervention group, IQR – Interquartile range, LES – Lower esophageal sphincter, LF – Laparoscopic fundoplication, MSA – Magnetic sphincter augmentation, PPI – Proton pump inhibitor, RCT – Randomised controlled trial, RDQ – Reflux disease questionnaire, RoB – Risk of bias, RS – RefluxStop™, SAEs – Serious adverse events, SD – Standard deviation, stat. sign. – statistically significant.

List of ongoing trials

Table A-11: List of ongoing studies of LES devices in laparoscopic surgery in GERD patients

Identifier/Trial name	Patient population	Intervention	Comparison	Primary Outcome(s)	Estimated completion date	Sponsor
Magnetic sphincter augmentation						
Randomised controlled trials						
NA						
Observational controlled database trials						
NCT04695171	GERD with hiatal hernia >3 cm(450 patients)	MSA (LINX® Reflux Management System)	Laparoscopic fundoplication	Incidence of Hiatal Hernia Recurrence	January 2028	Foregut Research Foundation
Prospective single-arm studies with >50 patients						
NCT01940185	GERD (200 patients)	MSA (LINX® Reflux Management System)	-	Reduction of total GERD-HRQL score (Successful reduction of ≥ 50% in the total GERD-HRQL as compared to baseline) Serious, device-related adverse events	October 31, 2025	Torax Medical Incorporated
NCT04253392	GERD (500 patients)	MSA (LINX® Reflux Management System)	-	Safety – Adverse Events Safety – Explant/Removal Safety – Hiatal Hernia Reoccurrence	July 31, 2032	Ethicon
ChiCTR-ONC-1600951	GERD (80 patients)	MSA (NA)	-	Quality of life score	NA	NA
RefluxStopTM						
NA						
Electrical stimulation therapy						
Randomised controlled trials						
NCT02749071	GERD (161 patients)	EST (EndoStim®)	Sham	Rate of device and/or procedure-related serious adverse events 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)	Terminated October 2019	EndoStim® Inc.
Prospective single-arm studies with >50 patients						
NCT02441400	GERD (350 patients)	EST (EndoStim®)	-	Incidence and severity of adverse events	Terminated October 2019	EndoStim® Inc.

Abbreviations: EST – Electrical stimulation therapy, GERD – Gastroesophageal reflux disease, HRQL – Health-related quality of life questionnaire, MSA – magnetic sphincter augmentation, NA – Not available

Research questions

Table A-12: EUnetHTA Core Model® – Health problem and current use

Element ID	Research question
A0001	For which health conditions, and for what purposes are LES devices in laparoscopic surgery used?
A0002	What is the disease or health condition in the scope of this assessment?
A0003	What are the known risk factors for GERD?
A0004	What is the natural course of GERD?
A0005	What is the burden of disease for GERD patients?
A0006	What are the consequences of GERD for 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?

Table A-13: EUnetHTA Core Model® – Description of the technology

Element ID	Research question
B0001	What are LES devices in laparoscopic surgery and the alternative standard treatment options?
A0011	How much are LES devices in laparoscopic surgery utilised?
A0020	For which indications have LES devices in laparoscopic surgery received marketing authorisation or CE marking?
B0002	What is the claimed benefit LES devices in laparoscopic surgery in relation to the alter-native standard treatment options?
B0003	What is the phase of development and implementation of LES devices in laparoscopic surgery and the alternative standard treatment options?
B0004	Who administers LES devices in laparoscopic surgery and in what context and level of care are they provided?
B0008	What kind of special premises are needed to use LES devices in laparoscopic surgery?
B0009	What supplies are needed to use LES devices in laparoscopic surgery?
A0021	What is the reimbursement status of LES devices in laparoscopic surgery?

Table A-14: EUnetHTA Core Model® – Clinical effectiveness

Element ID	Research question
D0005	How do LES devices in laparoscopic surgery affect heartburn and regurgitation symptoms?
D0006	How do LES devices in laparoscopic surgery affect the continuation of PPI therapy?
D0011	What is the effect of LES devices in laparoscopic surgery on patients' body functions?
D0012	What is the effect of LES devices in laparoscopic surgery on generic health-related quality of life?
D0013	What is the effect of LES devices in laparoscopic surgery on disease-specific quality of life?

Table A-15: EUnetHTA Core Model® – Safety

Element ID	Research question
C0008	How safe are LES devices in laparoscopic surgery in comparison to fundoplicatio/standard laparoscopic surgery/ PPI therapy/sham intervention?
C0002	Are the harms related to dosage or frequency of applying LES devices in laparoscopic surgery?
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 LES devices in laparoscopic surgery?
C0007	Are LES devices in laparoscopic surgery associated with user-dependent harms?
D0001	What is the expected beneficial effect of LES devices in laparoscopic surgery on mortality?
D0003	What is the effect of LES devices in laparoscopic surgery on mortality due to causes other than GERD?

Literature search strategies

Search strategy for Cochrane

Search Name: Lower Esophageal Sphincter Devices for GERD	
Search date: 12.12.2021	
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	("esophageal reflux") (Word variations have been searched)
#5	("oesophageal reflux") (Word variations have been searched)
#6	gastric acid reflux (Word variations have been searched)
#7	("lower esophageal sphincter relaxation") (Word variations have been searched)
#8	("lower oesophageal sphincter relaxation") (Word variations have been searched)
#9	(incompeten* NEAR ("esophageal sphincter" OR "esophageal sphincter")) (Word variations have been searched)
#10	GER:ti,ab,kw
#11	GERD:ti,ab,kw
#12	GORD:ti,ab,kw
#13	MeSH descriptor: [Hernia, Hiatal] explode all trees
#14	hiatal NEXT hernia* (Word variations have been searched)
#15	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14
#16	("reflux management") (Word variations have been searched)
#17	("antireflux management") (Word variations have been searched)
#18	("anti-reflux management") (Word variations have been searched)
#19	("Magnetic Sphincter Augment*") (Word variations have been searched)
#20	MSA:ti,ab,kw
#21	MSAD:ti,ab,kw
#22	(magnetic NEAR (bead* OR band* OR ring* OR device*)) (Word variations have been searched)
#23	MeSH descriptor: [Magnets] explode all trees
#24	MeSH descriptor: [Esophageal Sphincter, Lower] explode all trees and with qualifier(s): [surgery - SU]
#25	("esophageal sphincter" NEAR (device* OR ring* OR band* OR bead*)) (Word variations have been searched)
#26	oesophageal sphincter NEAR (device* OR ring* OR band* OR bead*) (Word variations have been searched)
#27	((implant* OR insert*) NEXT (sphincter* OR ring* OR bead* OR band* OR device*)) (Word variations have been searched)
#28	MeSH descriptor: [Prostheses and Implants] explode all trees
#29	MeSH descriptor: [Esophageal Sphincter, Lower] explode all trees
#30	("esophageal sphincter*") (Word variations have been searched)
#31	oesophageal sphincter* (Word variations have been searched)
#32	MeSH descriptor: [Esophagogastric Junction] explode all trees
#33	("gastro*esophageal junction*") (Word variations have been searched)
#34	gastro*oesophageal junction* (Word variations have been searched)
#35	("esophagogastric junction*") (Word variations have been searched)
#36	oesophagogastric junction* (Word variations have been searched)
#37	("esophago*gastric junction*") (Word variations have been searched)
#38	("oesophago*gastric junction*") (Word variations have been searched)
#39	#29 OR #30 OR #32 OR #33 OR #35 OR #36 OR #37 OR #38 (Word variations have been searched)
#40	#28 AND #39 (Word variations have been searched)
#41	(LINX*)

#42	MeSH descriptor: [Electric Stimulation Therapy] explode all trees
#43	(Electric* NEAR Stimul*) (Word variations have been searched)
#44	MeSH descriptor: [Electric Stimulation] explode all trees
#45	therap* OR treatment* OR program* OR intervention* OR procedure* OR regimen* OR device* (Word variations have been searched)
#46	#44 AND #45 (Word variations have been searched)
#47	electro*stimul* (Word variations have been searched)
#48	(EST):ti,ab,kw
#49	EndoStim
#50	LES Stimul* (Word variations have been searched)
#51	(non-active NEAR implant*) (Word variations have been searched)
#52	(Forsell*) (Word variations have been searched)
#53	(Reflux*Stop*) (Word variations have been searched)
#54	#16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #27 OR #40 OR #41 OR #42 OR #43 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53
#55	#15 AND #54
#56	#15 AND #54 with Cochrane Library publication date Between Dec 2015 and Dec 2021
#57	#15 AND #54 with Publication Year from 2015 to 2021, in Trials
#58	#56 OR #57
#59	(conference abstract):pt
#60	(abstract):so
#61	(clinicaltrials OR trialsearch OR ANZCTR OR ensaiosclinicos OR Actrn OR chictr OR cris OR ctri OR registroclinico OR clinicaltrialsregister OR DRKS OR IRCT OR Isrctn OR rctportal OR JapicCTI OR JMACCT OR jRCT OR JPRN OR Nct OR UMIN OR trialregister OR PACTR OR R.B.R.OR REPEC OR SLCTR OR Tcr):so
#62	#59 OR #60 OR #61
#63	#58 NOT #62
Total hits: 62	

Search strategy for Embase

Search Name: Lower Esophageal Sphincter Devices for GERD		
Search date: 10.12.2021		
No.	Query Results	Results
#1.	'gastroesophageal reflux'/exp	70,419
#2.	'gastroesophageal reflux'	66,047
#3.	'gastrooesophageal reflux'	614
#4.	'gastro-esophageal reflux'	3,585
#5.	'gastro-oesophageal reflux'	5,87
#6.	'esophageal reflux'	4,737
#7.	'oesophageal reflux'	6,115
#8.	'gastric acid reflux'	87
#9.	'lower esophageal sphincter relaxation'	497
#10.	'lower oesophageal sphincter relaxation'	113
#11.	incompeten* NEAR/5 ('esophageal sphincter' OR 'oesophageal sphincter')	146
#12.	ger:ab,ti	4,38
#13.	gerd:ab,ti	19,288
#14.	gord:ab,ti	1,551
#15.	'hiatus hernia'/exp	13,684
#16.	hiatal NEAR/1 hernia*	8,465

#17.	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16	87,911
#18.	'reflux management'	156
#19.	'antireflux management'	8
#20.	'anti-reflux management'	6
#21.	'magnetic sphincter augmentation'/exp	75
#22.	'magnetic sphincter augmentation device'/exp	19
#23.	'magnetic sphincter augment*'	298
#24.	msa:ab,ti	9,909
#25.	msad:ab,ti	103
#26.	magnetic NEAR/4 (bead* OR band* OR ring OR device*)	14,083
#27.	'magnet'/exp AND 'therapy'/lnk	389
#28.	'anti reflux implant'/exp	194
#29.	'lower esophagus sphincter'/exp/dm_su	383
#30.	'esophageal sphincter' NEAR/7 (device* OR ring* OR band* OR bead*)	103
#31.	'oesophageal sphincter' NEAR/7 (device* OR ring* OR band* OR bead*)	18
#32.	(implant* OR insert*) NEAR/4 (sphincter* OR ring* OR bead* OR band* OR device*)	53,234
#33.	linx*	4,576
#34.	'electrotherapy'/mj	7,754
#35.	electric* NEAR/5 stimul*	103,091
#36.	'electrostimulation'/exp	88,169
#37.	electrostimul*	90,775
#38.	'electro-stimul*'	542
#39.	est:ti,ab	17,55
#40.	endostim	94
#41.	les:dn	15
#42.	les NEAR/1 stimul*	159
#43.	'non-active' NEAR/5 implant*	11
#44.	forsell*	518
#45.	refluxstop*	9
#46.	'reflux-stop*'	12
#47.	#18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46	251,492
#48.	#17 AND #47	1,2
#49.	#48 AND [14-12-2015]/sd NOT [11-12-2021]/sd	570
#50.	#49 AND ([english]/lim OR [german]/lim)	564
#51.	#50 AND 'Conference Abstract'/it	240
#52.	#50 NOT #51	324
Total hits: 324		

Search strategy for Medline

Search Name: Lower Esophageal Sphincter Devices for GERD	
Search date: 10.12.2021	
ID	Search
#1	exp Gastroesophageal Reflux/ (31633)
#2	gastro?esophageal reflux.mp. (40797)
#3	gastro-?esophageal reflux.mp. (2227)
#4	?esophageal reflux.mp. (3083)
#5	gastric acid reflux.mp. (70)
#6	lower ?esophageal sphincter relaxation.mp. (369)
#7	(incompeten* adj5 ?esophageal sphincter).mp. (100)
#8	GER.ti,ab. (3223)
#9	GERD.ti,ab. (12169)
#10	GORD.ti,ab. (1019)
#11	exp Hernia, Hiatal/ (7290)
#12	(hiatal adj hernia*).mp. (6094)
#13	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 (52056)
#14	reflux management.mp. (108)
#15	anti*reflux management.mp. (7)
#16	anti-reflux management.mp. (4)
#17	Magnetic Sphincter Augment*.mp. (289)
#18	MSA.ti,ab. (8602)
#19	MSAD.ti,ab. (86)
#20	(magnetic adj10 (bead* or band* or ring* or device*)).mp. (23519)
#21	exp Magnets/ (3757)
#22	"Therapeutic Use".fs. (2706695)
#23	21 and 22 (96)
#24	exp *Esophageal Sphincter, Lower/su (472)
#25	(esophageal sphincter adj10 (device* or ring* or band* or bead*)).mp. (111)
#26	(oesophageal sphincter adj10 (device* or ring* or band* or bead*)).mp. (16)
#27	((implant* or insert*) adj10 (sphincter* or ring* or bead* or band* or device*)).mp. (68479)
#28	exp "Prostheses and Implants"/ (657744)
#29	exp Esophageal Sphincter, Lower/ (2066)
#30	esophageal sphincter*.mp. (8197)
#31	oesophageal sphincter*.mp. (1380)
#32	exp Esophagogastric Junction/ (11248)
#33	gastro?esophageal junction*.mp. (4253)
#34	gastro-?esophageal junction*.mp. (446)
#35	esophagogastric junction*.mp. (11099)
#36	esophago-gastric junction*.mp. (331)
#37	oesophagogastric junction*.mp. (358)
#38	oesophago-gastric junction*.mp. (118)
#39	29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 (20843)
#40	28 and 39 (491)
#41	LINX*.mp. (568)
#42	exp Electric Stimulation Therapy/ (104710)
#43	(Electric* adj5 Stimul*).mp. (188424)
#44	exp Electric Stimulation/ (134075)

#45	(therap* or treatment* or program* or intervention* or procedure* or regimen* or device*).mp. (14726339)
#46	44 and 45 (28822)
#47	electrostimul*.mp. (4168)
#48	electro-stimul*.mp. (426)
#49	EST.ti,ab. (32324)
#50	EndoStim.mp. (32)
#51	LES Stimul*.mp. (90)
#52	(non-active adj5 implant*).mp. (10)
#53	Forsell*.mp. (9)
#54	Reflux?Stop*.mp. (2)
#55	Reflux-Stop*.mp. (8)
#56	14 or 15 or 16 or 17 or 18 or 19 or 20 or 23 or 24 or 25 or 26 or 27 or 40 or 41 or 42 or 43 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 (392258)
#57	13 and 56 (953)
#58	limit 57 to dt=20151211-20211210 (505)
#59	limit 58 to (english or german) (472)
#60	remove duplicates from 59 (254)
Total hits: 254	

Search strategy for HTA-INATHTA

Search Name: Lower Esophageal Sphincter Devices for GERD	
Search date: 12.12.2021	
ID	Search
#1	"Gastroesophageal Reflux"[mhe],"39","2021-12-12T03:21:26.000000Z"
#2	"gastroesophageal reflux","35","2021-12-12T03:22:22.000000Z"
#3	"gastrooesophageal reflux","1","2021-12-12T03:22:35.000000Z"
#4	"gastro-esophageal reflux","0","2021-12-12T03:22:42.000000Z"
#5	"gastro-oesophageal reflux","18","2021-12-12T03:22:47.000000Z"
#6	"esophageal reflux","0","2021-12-12T03:23:15.000000Z"
#7	"oesophageal reflux","18","2021-12-12T03:23:19.000000Z"
#8	"gastric acid reflux","0","2021-12-12T03:23:54.000000Z"
#9	"lower esophageal sphincter relaxation","0","2021-12-12T03:24:28.000000Z"
#10	"lower oesophageal sphincter relaxation","0","2021-12-12T03:24:35.000000Z"
#11	"incompetent esophageal sphincter","0","2021-12-12T03:25:12.000000Z"
#12	"incompetent oesophageal sphincter","0","2021-12-12T03:25:16.000000Z"
#13	"esophageal sphincter incompeten*","0","2021-12-12T03:26:25.000000Z"
#14	"oesophageal sphincter incompeten*","0","2021-12-12T03:26:31.000000Z"
#15	GER,"2","2021-12-12T03:26:49.000000Z"
#16	GERD,"24","2021-12-12T03:28:34.000000Z"
#17	GORD,"11","2021-12-12T03:29:12.000000Z"
#18	"Hernia Hiatal"[mhe],"0","2021-12-12T03:29:45.000000Z"
#19	Hiatal Hernia*,"3","2021-12-12T03:30:18.000000Z"
#20	(Hiatal Hernia*) OR ("Hernia Hiatal"[mhe]) OR (GORD) OR (GERD) OR (GER) OR ("oesophageal sphincter incompeten*") OR ("esophageal sphincter incompeten*") OR ("incompetent oesophageal sphincter") OR ("incompetent esophageal sphincter") OR ("lower oesophageal sphincter relaxation") OR ("lower esophageal sphincter relaxation") OR ("gastric acid reflux") OR ("oesophageal reflux") OR ("esophageal reflux") OR ("gastro-oesophageal reflux") OR ("gastro-esophageal reflux") OR ("gastrooesophageal reflux") OR ("gastroesophageal reflux") OR ("Gastroesophageal Reflux"[mhe]),"60","2021-12-12T03:30:53.000000Z"

#21	((Hiatal Hernia*) OR ("Hernia Hiatal"[mhe]) OR (GORD) OR (GERD) OR (GER) OR ("oesophageal sphincter incompeten*") OR ("esophageal sphincter incompeten*") OR ("incompetent oesophageal sphincter") OR ("incompetent esophageal sphincter") OR ("lower oesophageal sphincter relaxation") OR ("lower esophageal sphincter relaxation") OR ("gastric acid reflux") OR ("oesophageal reflux") OR ("esophageal reflux") OR ("gastro-oesophageal reflux") OR ("gastro-esophageal reflux") OR ("gastrooesophageal reflux") OR ("gastroesophageal reflux") OR ("Gastroesophageal Reflux"[mhe])) AND (English)[Language],"53","2021-12-12T03:31:37.000000Z"
#22	(((Hiatal Hernia*) OR ("Hernia Hiatal"[mhe]) OR (GORD) OR (GERD) OR (GER) OR ("oesophageal sphincter incompeten*") OR ("esophageal sphincter incompeten*") OR ("incompetent oesophageal sphincter") OR ("incompetent esophageal sphincter") OR ("lower oesophageal sphincter relaxation") OR ("lower esophageal sphincter relaxation") OR ("gastric acid reflux") OR ("oesophageal reflux") OR ("esophageal reflux") OR ("gastro-oesophageal reflux") OR ("gastro-esophageal reflux") OR ("gastrooesophageal reflux") OR ("gastroesophageal reflux") OR ("Gastroesophageal Reflux"[mhe])) AND (English)[Language]) AND (German)[Language],"0","2021-12-12T03:31:57.000000Z"
#23	((((Hiatal Hernia*) OR ("Hernia Hiatal"[mhe]) OR (GORD) OR (GERD) OR (GER) OR ("oesophageal sphincter incompeten*") OR ("esophageal sphincter incompeten*") OR ("incompetent oesophageal sphincter") OR ("incompetent esophageal sphincter") OR ("lower oesophageal sphincter relaxation") OR ("lower esophageal sphincter relaxation") OR ("gastric acid reflux") OR ("oesophageal reflux") OR ("esophageal reflux") OR ("gastro-oesophageal reflux") OR ("gastro-esophageal reflux") OR ("gastrooesophageal reflux") OR ("gastroesophageal reflux") OR ("Gastroesophageal Reflux"[mhe])) AND (English)[Language]) AND (German)[Language]) OR (((Hiatal Hernia*) OR ("Hernia Hiatal"[mhe]) OR (GORD) OR (GERD) OR (GER) OR ("oesophageal sphincter incompeten*") OR ("esophageal sphincter incompeten*") OR ("incompetent oesophageal sphincter") OR ("incompetent esophageal sphincter") OR ("lower oesophageal sphincter relaxation") OR ("lower esophageal sphincter relaxation") OR ("gastric acid reflux") OR ("oesophageal reflux") OR ("esophageal reflux") OR ("gastro-oesophageal reflux") OR ("gastro-esophageal reflux") OR ("gastrooesophageal reflux") OR ("gastroesophageal reflux") OR ("Gastroesophageal Reflux"[mhe])) AND (English)[Language]),"53","2021-12-12T03:32:28.000000Z"
#24	(((((Hiatal Hernia*) OR ("Hernia Hiatal"[mhe]) OR (GORD) OR (GERD) OR (GER) OR ("oesophageal sphincter incompeten*") OR ("esophageal sphincter incompeten*") OR ("incompetent oesophageal sphincter") OR ("incompetent esophageal sphincter") OR ("lower oesophageal sphincter relaxation") OR ("lower esophageal sphincter relaxation") OR ("gastric acid reflux") OR ("oesophageal reflux") OR ("esophageal reflux") OR ("gastro-oesophageal reflux") OR ("gastro-esophageal reflux") OR ("gastrooesophageal reflux") OR ("gastroesophageal reflux") OR ("Gastroesophageal Reflux"[mhe])) AND (English)[Language]) AND (German)[Language]) OR (((Hiatal Hernia*) OR ("Hernia Hiatal"[mhe]) OR (GORD) OR (GERD) OR (GER) OR ("oesophageal sphincter incompeten*") OR ("esophageal sphincter incompeten*") OR ("incompetent oesophageal sphincter") OR ("incompetent esophageal sphincter") OR ("lower oesophageal sphincter relaxation") OR ("lower esophageal sphincter relaxation") OR ("gastric acid reflux") OR ("oesophageal reflux") OR ("esophageal reflux") OR ("gastro-oesophageal reflux") OR ("gastro-esophageal reflux") OR ("gastrooesophageal reflux") OR ("gastroesophageal reflux") OR ("Gastroesophageal Reflux"[mhe])) AND (English)[Language])) FROM 2015 TO 2021,"8","2021-12-12T03:32:49.000000Z"
Total hits: 8	

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