Magnetic sphincter augmentation device (MSAD) in patients with gastroesophageal reflux disease (GERD)

Systematic Review

Ludwig Boltzmann Institut
Health Technology Assessment

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

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

CONTENT INFORMATION

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List of abbreviations

ACG ..... American College of Gastroenterology
ADE ..... Adverse device effect
AdHopHTA ..... Adopting Hospital Based Health Technology Assessment
AE ..... adverse event(s)
AWMF ..... Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften
BMI ..... Body Mass Index
C ..... comparator
CE mark ..... Conformité Européene mark
CRD database ..... Centre for Review and Dissemination database
DRG ..... Diagnosis-Related Group
FDA ..... Food and Drug Administration
FU ..... Follow-up
GERD ..... Gastroesophageal Reflux Disease
GRADE ..... Grading of Recommendations Assessment, Development and Evaluation
HRQL ..... Health-Related Quality of Life
HTA ..... Health Technology Assessment
H2RA ..... H2-receptor antagonist
I ..... intervention
LBI-HTA ..... Ludwig Boltzmann Institut für Health Technology Assessment
LES ..... Lower Esophageal Sphincter
LES-EST. ..... lower esophageal sphincter electrical stimulation therapy
LF ..... Laparoscopic Fundoplication
LP ..... Laparoscopic
LSG ..... Laparoscopic Sleeve Gastrectomy
min ..... minute(s)
mo ..... month(s)
MoH ..... Ministry of Health
MRI ..... Magnetic Resonance Imaging
MSA ..... Magnetic sphincter Augmentation
MSAD ..... Magnetic sphincter Augmentation Device
NA ..... data not available
NERD ..... Non-Erosive Reflux Disease
p-value ..... probability value
pH ..... potenz Hydrogen
POP database ..... Planned and Ongoing Projects database
PPI ..... Proton Pump Inhibitor
PRE-OP ..... pre-operative
pt ..... patient(s)
RCT ..... Randomized Controlled Trial
SADE ..... Serious adverse device effect
SAE ..... serious adverse event(s)
SAGES ..... Society of American Gastrointestinal and Endoscopic Surgeons
TIF ..... trans-oral incisionless fundoplication
vs ..... versus
yr ..... year(s)

Executive Summary

Introduction

Health Problem

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

gastroösophageale Refluxkrankheit

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

Funktionsstörung des unteren Schließmuskels der Speiseröhre

Description of Technology

Magnetic sphincter augmentation (MSA) represents a novel method for the surgical treatment of GERD. The magnetic sphincter augmentation 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. The goal of the intervention is to reinforce the weak lower esophageal sphincter (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.

Magnetische Speiseröhren Ring (MSAD) um den unteren Schließmuskel der Speiseröhre zu verstärken

Methods

The EUnetHTA Core Model for Rapid Relative Effectiveness was the main source for selecting relevant assessment elements. We conducted a systematic literature search (without restriction on publication date) in bibliographic databases, in the Cochrane Library and in the database of the Centre for Reviews and Dissemination, complemented by a SCOPUS hand search, to answer the research questions in the domains effectiveness and safety. Selection of relevant documents (in English and German) was done by two persons independently. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology was used for qualitatively summarising the results for the domains: "Safety" and "Clinical effectiveness".

basierend auf EUnetHTA Core Model; systematische Literatursuche in 5 Datenbanken; GRADE

Domain effectiveness

For analysing the clinical effectiveness, prospective controlled studies were included, provided that any of the defined outcomes were reported. The crucial outcome to derive a recommendation was the GERD HRQL score.

Einschlusskriterien für Wirksamkeit

Domain safety

For analysing the safety, prospective controlled and uncontrolled studies were included. The crucial outcomes to derive a recommendation were: overall complication rate, intraoperative complications, dysphagia, excessive bloating, device removal, migration, malfunction and erosion, re-operation rate, and re-hospitalization rate.

Einschlusskriterien für Sicherheit

Results

Available evidence

5 prospektive Fallserien, 1 prospektive Registerstudie mit Kontrollgruppe

A total of 5 single-arm prospective case series and one prospective registry with control group were eligible for inclusion in the current report, 3 of which provided short (1-5.8 months) and 3 long-term (1-5 years) follow-up data. Overall, the safety and efficacy was evaluated in 605 and 249 patients, respectively.

Clinical effectiveness

GERD HRQL: Verbesserung in beide Gruppen

One study with 249 participants fulfilled the inclusion criteria. GERD HRQL improved from 20 to 3 points in the MSAD, and from 23 to 3.5 in the laparoscopic fundoplication (LF) group. Due to the major differences in the two study groups, no direct conclusion on relative effectiveness of MSAD in comparison to the alternative treatment option LF can be drawn.

Safety

Dysphagia
Post-operative übermäßige Blähungen
intraoperative Komplikationen
Produktentfernung
Re-Operation
Re-Hospitalisierung

One prospective registry with control group with 249 patients fulfilled the inclusion criteria for comparing dysphagia, excessive bloating, re-operation, hospital re-admission, and intraoperative complications. For analysing device removal, migration, malfunction, and erosion, 5 prospective case series and one prospective registry with control group fulfilled the inclusion criteria. Dysphagia was 7% in the MSAD versus 10.6% in the LF group, excessive bloating occurred in 10% of MSAD and 31.9% of LF patients, re-operation rate and hospital readmission was 4% resp. 5.4% in the MSAD and 6.4% resp. 4.3% in the LF group. Intraoperative complications occurred in 3 patients (1.49%) in the MSAD and in 1 patient (2.13%) in the LF group. Device removal was reported in 4 of the case series, ranging from 0 to 7%, and in the registry study, with 4% of patients having the device removed.

Upcoming evidence

keine laufende RCTs

Currently, there are no registered ongoing or planned controlled trials comparing MSAD with LF for the treatment of GERD.

Reimbursement

nicht erstattet

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

Discussion

Bedarf an RCTs mit Langzeit-Outcomes

The available evidence for the technology is in its infancy and it is not sufficient to determine the safety and effectiveness of the LINX device. Future clinical trials should be comparative (favourably randomised), with a broader patient population. Crucial outcome measures should include the device's ability to reduce the likelihood of developing GERD complications, like esophageal cancer, and the long-term safety considerations, like the durability of the device and late device removals.

Conclusion

Evidenz für MSAD nicht ausreichend

nicht vergleichbare Population

The current evidence is not sufficient to prove that the assessed technology, MSAD, is at least equally effective and as safe as the comparator LF. Comparative data on the two procedures are available from a single registry study where the LF group was in a more severe stage of the disease and nevertheless achieved a similar improvement in GERD related quality of life as the MSAD group. Concerning safety, the re-operation and hospital re-admission rates were similar; the difference in other complications like dysphagia was statistically not significant. Significant difference is only shown in inability to belch or vomit and in excessive bloating.

Aufnahme derzeit nicht empfohlen

New study results will potentially influence the effect estimate considerably only if they are sham control studies or RCTs comparing MSAD and LF.

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

Zusammenfassung

Einleitung

Indikation und therapeutisches Ziel

gastroösophageale Refluxkrankheit (GERD): Prävalenz 15 %

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

Ernährung & Lebensstil

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

Typische Symptome von GERD sind: Sodbrennen, Aufstoßen, Magenschmerzen. Atypische Symptome sind: chronischer Husten, Heiserkeit, Dysphagie, Schmerzen in der Brust, chronische Aspiration, Bronchitis, Sinusitis. Auf Grundlage der Häufigkeit und Schwere der Reflux-Symptome, wird von milder, moderater und schwerer GERD gesprochen, jedoch ohne explizite Definition über die Dauer und die Messung.

progrediente Erkrankung

Der natürliche Verlauf der Erkrankung ist ungeklärt. Traditionell wird die Krankheit als Spektrum beginnend mit nicht-erosivem Reflux (NERD), der sich zu GERD (erosiver Ösophagitis, Stenose, Barrett-Ösophagus) entwickelt, beschrieben. Das Management von GERD wird durch die Schwere der Symptome bestimmt: Die Leitlinien der „American College of Gastroenterology“ (ACG) und der „Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften“ (AWMF) schlagen ein schrittweises Vorgehen vor: Als erste Interventionen werden Veränderungen in der Ernährung und im Lebensstil vorgeschlagen.

ACG & AWMF: schrittweises Vorgehen bei Interventionen

Gewichtsverlust,

- Gewichtsverlust für GERD-PatientInnen, die übergewichtig sind,

Vermeidung von Mahlzeiten vor Zubettgehen,

- Oberkörperhochlage und Vermeidung von Mahlzeiten 2-3 Stunden vor dem Zubettgehen für PatientInnen mit nächtlicher GERD,

H2RA Therapie,

- bei mild bis moderater Schwere der Symptome: ein H2-Rezeptor-Antagonist (H2RA) Therapie,

8 Wochen PPI, PPI Erhaltungstherapie,

- wenn H2RA Therapie nicht ausreichend ist, und der/die Patientin moderate bis schwere Symptome hat: Initiierung einer 8-wöchigen Therapie mit Protonenpumpeninhibitioren (PPI),
- bei anhaltenden GERD Symptomen ist eine PPI-Erhaltungstherapie (mit niedriger Dosierung) indiziert.

Operation: Therapie 2. Wahl

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

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

Minimal-invasive Verfahren wie der Magnetische Speiseröhren Ring (engl. Magnet sphincter augmentation device/MSAD) sind also Zweitlinien Behandlungen und erst nach Therapieversagen für chronische GERD-PatientInnen indiziert. Die Zielgruppe für MSAD sind erwachsenen PatientInnen mit moderater bis schwerer GERD, die für die chirurgische Behandlung wegen unvollständiger Kontrolle der Symptome trotz maximaler medikamentöser Behandlung oder schweren Komplikationen im Zusammenhang mit PPI-Therapie in Betracht gezogen werden.

Beschreibung der Technologie

Der Magnetische Speiseröhren Ring (MSAD) ist ein neues Verfahren für die chirurgische Behandlung von GERD. Eine aus magnetischen Titan-Perlen bestehende Kette wird als Ring oberhalb des Magens um den unteren Ösophagus platziert. Der Magnetismus verschließt damit den Ausgang der Speiseröhre zum Magen. Der Magnetische Speiseröhren Ring wird im Rahmen einer Bauchspiegelung laparoskopisch eingesetzt: Das Gerät benötigt keine anatomische Veränderung des Magens. Das Ziel der Intervention ist, den unteren Schließmuskels der Speiseröhre zu verstärken und so den Reflux aus dem Magen in die Speiseröhre zu verhindern. Bei Nahrungsaufnahme kann die Flüssigkeit oder feste Nahrung nach dem Schlucken den Schließmuskel passieren, nicht jedoch zur zurückfließen.

Magnetische Speiseröhren Ring (MSAD) aus Titan-Perlen

Verstärkung des Schließmuskels: Ösophagus-Magen

Nahrung kann passieren, Reflux nicht

Derzeit gibt es nur ein MSAD (Magnet sphincter augmentation device) auf dem Markt, das LINX® Reflux Management System. Es wurde von Torax Medical Inc. entwickelt. Das Medizinprodukt LINX® befindet sich derzeit in der 2. Generation am Markt. Die Produkte-Generationen unterscheiden sich durch den Verschluss des Speiseröhren Ring um den Ösophagus, aber auch durch ihre MRT-Compliance: Die 2. Generation ist MRT-kompatibel (bis 1,5 Tesla). Das LINX® Reflux Management System ist in Europa mit dem CE-mark (seit 2008) und in den USA durch die FDA (seit 2012) zugelassen. Weltweit wurden bislang ungefähr 4.000 LINX®-Systeme implantiert.

nur ein MSAD zugelassen: LINX® Reflux Management System

EU: 2008
USA: 2012

LINX® wurde für die minimal-invasive Behandlung der chronischen gastroösophagealen Refluxkrankheit, die durch abnorme pH-Werte, chronische GERD-Symptome trotz maximaler medikamentöser Therapie gekennzeichnet ist und für nicht operativ vorbehandelte PatientInnen > 18 Jahre, mit BMI ≤ 35 haben und mit einer Hiatushernie < 3 cm zugelassen. Bei Hiatushernie > 3cm bedarf es einer zusätzlichen klinischen Abklärung.

Zulassung für chronische GERD, abnorme pH-Werte, Symptome trotz max PPI Therapie

Die Standardmethode zur chirurgischen Behandlung von GERD ist die (offene oder laparoskopische) Fundoplikatio: zur Verhinderung eines Rückflusses von Mageninhalt in die Speiseröhre wird eine Fundusmanschette um den abdominalen Anteil der Speiseröhre gelegt. Der Speisebrei kann weiterhin von der Speiseröhre in den Magen befördert werden. Die dabei entstehende Füllung der Manschette komprimiert jedoch die abdominale Speiseröhre, so dass ein Reflux aus dem Magen in die Speiseröhre verhindert wird. Zwei Techniken sind zu unterscheiden: die Nissen Fundoplikatio (derzeit Gold-Standard) und die partielle oder Toupet Fundoplikatio. Die Rekonvaleszenzzeit nach laparoskopischer Fundoplikatio beträgt 4-6 Wochen und die PatientInnen dürfen für etwa eine Woche nach der Operation nur flüssige Nahrung zu sich nehmen, bevor sie nach und nach auf weiche, dann feste Nahrung übergehen können. In Guidelines wird empfohlen, dass die Fundoplikatio nur in GERD-Zentren mit hoher PatientInnen-Frequenz durchgeführt werden sollte.

chirurgische Standardmethode: Fundoplikatio

offen oder laparoskopisch

Fundusmanschette wird um Ösophagus gelegt

4-6 Wochen Rekonvaleszenz, zunächst nur flüssige Nahrung

Die von LINX® erwarteten Vorteile sind geringere Invasivität des chirurgischen Eingriffs und Reversibilität. Laut Hersteller ist die Operationszeit ebenso wie die Krankenhausaufenthaltsdauer kürzer, die Operationstechnik weniger schwierig und damit ihre Reproduzierbarkeit höher, die Lernkurve für ChirurgInnen kürzer, die Nebenwirkungen geringer. Zudem wird PatientInnen empfohlen, gleich nach dem Eingriff zur normalen Ernährung zurückkehren. Die Kosten für das LINX® Reflux Management System betragen zum einen die Kosten für das Medizinprodukt (4.340 €) sowie Kosten, die im Krankenhaus anfallen (Personal, Anästhesie, Krankenhausaufenthalt). Im Vergleich zur Fundoplikatio fallen Materialkosten (Medizinprodukt) und die Erstausbildung von ChirurgInnen an, hingegen kürzere OP-Zeiten.

vom Hersteller genannte Vorteile von LINX®: weniger invasiv, kürzere/r OP- und Krankenhausaufenthalt

Kosten: 4.340 €
Materialkosten

Methoden

Suche nach Publikationen in mehreren Datenbanken

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

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

Kontakt mit Hersteller

Zusätzlich wurde eine Handsuche durchgeführt und der Hersteller kontaktiert.

4-Augenprinzip bei Studienauswahl, Extraktion der Daten, Kontrolle

Die Studienauswahl erfolgte unabhängig durch beide AutorInnen (JE, MS). Die Erstautorin (JE) extrahierte die Studiendaten und der Zweitautor (MS) kontrollierte die Daten.

GRADE & Risk of Bias Beurteilung

Die Daten der für die Entscheidung herangezogenen Endpunkte wurden aus den einzelnen Studien zusammengefasst und nach GRADE (Grading of Recommendations Assessment, Development and Evaluation) bewertet.

Zusätzlich wurde das Bias-Risiko der Studien durch die Erstautorin (JE) bewertet und die Daten vom Zweitautor (MS) kontrolliert.

Klinische Wirksamkeit

entscheidender Endpunkt zur Beurteilung der Wirksamkeit: GERD HRQL

Zur Bewertung der Wirksamkeit des LINX® Reflux Management Systems wurden die folgenden *entscheidenden* Endpunkte für eine Empfehlung herangezogen:

- GERD HRQL score

Weitere *wichtige* Endpunkte wurden berücksichtigt: Sodbrennen, tägliches Aufstoßen, extra-ösophageale Symptome, Absetzen oder Reduktion von PPI-Medikamenten.

GERD HRQL score misst GERD-Symptome:

0-50 Punkte

GERD HRQL score: Da GERD eine degenerative Erkrankung ist, ist es das Ziel des Magnetische Speiseröhren Rings, den Prozess der Degeneration zu stoppen, die Funktion des Ösophagus-Schließmuskels zu übernehmen und damit die Lebensqualität zu verbessern. Der GERD HRQL score misst die Veränderungen in typischen GERD-Symptomen nach einer chirurgischen oder medizinischen Behandlung. Der GERD HRQL score enthält Fragen zu Sodbrennen, Schwierigkeiten beim Schlucken, Blähungen und zur Medikamenteneinnahme. Die bestmögliche Punktezahl ist 0 (asymptomatisch), die schlechteste Punktezahl ist 50.

Sicherheit

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

Zur Bewertung der Sicherheit des LINX® Reflux Management Systems wurden die folgenden *entscheidenden* Endpunkte für eine Empfehlung herangezogen:

- Dysphagie
- Post-operative übermäßige Blähungen
- Intraoperative Komplikationen
- Produktentfernung
- Produktmigration
- Produkterosion
- Produktdysfunktion
- Re-Hospitalisierung

Weitere *wichtige* Endpunkte wurden berücksichtigt: Unfähigkeit zu Rülpsen oder Erbrechen, andere AEs.

Ergebnisse

Wirksamkeit: Verfügbare Evidenz

Wirksamkeit: prospektive Registerstudie mit Kontrollgruppe (249 Pt)

Zur Beurteilung der Wirksamkeit von MSAD in der Behandlung von GERD erfüllte nur eine Studie die Einschlusskriterien: eine prospektive Registerstudie mit Kontrollgruppe, multizentrisch (n=22), in vier Ländern. Die Kontrollgruppe umfasst PatientInnen, die einer laparoskopischen Fundoplikatio (LF) unterzogen wurden. Die klinische Studie, vom Hersteller Torax Medical Inc. gesponsert, umfasst 249 PatientInnen (202 MSAD, 47 LF) mit 1 Jahr Follow-up, 77 Frauen und 125 Männer.

1 Jahr FU

Patientencharakteristika

Gruppenunterscheide bez. Schweregrade

LF-Gruppe schwerer krank

Die Patientencharakteristika waren in den beiden Gruppen unterschiedlich: LF-PatientInnen hatten schwerere GERD-Symptome in Bezug auf die Größe der Hiatushernien (45,7 % LF > 3 cm vs. 1,6 % MSAD). Zudem waren mehr PatientInnen mit Barrett-Ösophagus in der LF-Gruppe (19,1 % vs. 1,0 %) als in der MSAD-Gruppe und mit Ösophagitis Grad C und D (LF 8,5 % vs. 1 % MSAD). Der mittlere BMI-Score, die Anzahl der Jahre mit PPI-Therapie sowie die Anzahl der Jahre mit GERD waren dagegen ähnlich.

Diese genannten Unterschiede sind insofern bedeutsam, als sie Anzeichen von fortgeschrittener GERD sind, für die MSAD nicht indiziert ist.

Ergebnisse:

Verbesserungen in beiden Gruppen bei Sodbrennen, Aufstoßen, extra-ösophageale Symptome
Absetzen von PPI-Therapie zugunsten von MSAD

bei GERD HRQL kein Unterschied zwischen MSAD und LF

In der Registerstudie zeigten sich folgende Ergebnisse:

- Sodbrennen verbesserte sich vom Ausgangswert bei 30,8 % der MSAD PatientInnen auf 3,5 % vs. 40 % der LF-PatientInnen auf 8,5 % nach einem Follow-up von 1 Jahr.
- Aufstoßen verbesserte sich von 58,2 % der MSAD PatientInnen auf 3,1 % vs. 60 % der LF-PatientInnen auf 13 %.
- Extra-ösophageale Symptome wurden vor der Intervention bei 63,9 % der MSAD PatientInnen beobachtet, danach bei 22,3 % vs. 53,3 %/ 17,4 % in der LF-Gruppe.
- Absetzen der PPI-Medikamente: 81,8 % der PatientInnen mit MSAD setzten die PPI-Therapie ab vs. 63 % der PatientInnen in der LF-Gruppe.
- Im GERD HRQL score zeigten MSAD PatientInnen eine Verbesserung von 20 auf 3 Punkte vs. von 23 auf 3,5 bei LF-PatientInnen.
- Patientenzufriedenheit: 91,8 % der MSAD PatientInnen vs. 86,7 % der LF-PatientInnen zeigten sich beim Follow-up zufrieden.

Sicherheit

5 prospektive Fallserien (356 Pt),

1 Registerstudie mit Kontrollgruppe (249 Pt)

FU 1 Monat bis 5 Jahre

Zur Beurteilung der Sicherheit vom MSAD in der Behandlung von GERD erfüllten sechs Studien die Einschlusskriterien: fünf prospektive Fallserien und die schon zur Wirksamkeitsbeurteilung herangezogene prospektive Registerstudie mit Kontrollgruppe. Insgesamt wurden Ergebnisse von 356 PatientInnen in den fünf prospektiven Fallserien – alle vom Hersteller Torax Medical Inc. gesponsert – berichtet (144 Frauen und 212 Männer) sowie von 249 PatientInnen (davon 202 mit MSAD: 77 Frauen und 125 Männer) in der prospektiven Registerstudie. Wegen einer hohen Wahrscheinlichkeit von Doppelpublikation einzelner PatientInnen liegt die Gesamtzahl der PatientInnen, die (in den Studien) einer MSAD Operation unterzogen wurden, zwischen 558 und 435. Das Follow-up rangierte von einem Monat bis zu fünf Jahren.

heterogene Patientencharakteristika

Die Charakteristika der eingeschlossenen PatientInnen zeigten eine gewisse Heterogenität in Bezug auf Alter, Dauer der GERD-Symptome, PPI Therapieansprechen etc.. Das Alter rangierte zwischen 18 und 86, drei Studien schlossen nur PatientInnen mit GERD-Symptome ≥ mindestens 6 Monate ein; die durchschnittliche Anzahl der Jahre mit GERD wurde in vier Studien mit 4-10 Jahren angegeben; die durchschnittliche Anzahl der Jahre mit PPI-Medikamentierung wurde in vier Studien mit 1-6,3 Jahren berichtet.

Ø 4-10 Jahre GERD
Ø 1-6,3 Jahre PPI Therapie

Vergleich mit LF bei Sicherheit nur durch Registerstudie

Nur die Registerstudie ermöglicht einen Vergleich zur Fundoplikatio bei Dysphagie, übermäßigen Blähungen, Unfähigkeit zu Rülpsen oder Erbrechen, intraoperativen Komplikationen, Re-Operationen und Re-Hospitalisierungen.

Ergebnisse:

Die Ergebnisse der Registerstudie berichten:

Postoperative übermäßige Blähungen, Rülpen, Erbrechen zugunsten MSAD

- Postoperative übermäßige Blähungen kamen bei 10 % der MSAD PatientInnen vs. 31,9 % der LF-PatientInnen vor.

intraoperativen Komplikationsrate gleich

- Bei intraoperativen Komplikationsrate (1,49 % bei MSAD vs. 2,13 % in LF-PatientInnen) war kein signifikanter Unterschied zwischen den beiden Gruppen.
- 1,6 % der MSAD PatientInnen vs. 10,1 % der LF PatientInnen konnten nicht rülpsen.
- 8,7 % der MSAD PatientInnen vs. 56,6 % der LF PatientInnen konnten nicht erbrechen.
- 7 % der MSAD Patientinnen vs. 10,6 % der LF-PatientInnen hatten Dysphagie nach 1 Jahr Follow-up.

Re-Operationen, Re-Hospitalisierungen ähnlich häufig

- 4 % der MSAD PatientInnen vs. 6,4 % der LF-PatientInnen wurden re-operiert, um das Medizinprodukt wieder zu entfernen (MSAD) oder die Fundusmanschette zu adjustieren (LF).
- 5,4 % der MSAD PatientInnen vs. 4,3 % des LF-Innen wurden nochmals ins Krankenhaus aufgenommen (re-hospitaisiert).

Produkt-induzierte Komplikationen: alle Fallserien

Entfernen des Medizinprodukts, Erosion, Migration und Fehlfunktionen wurden in den Fallserien sowie der Registerstudie berücksichtigt:

Produktentfernung: 7 % nach 5 Jahren

- Produktentfernung wurde in fünf Studien berichtet: zwei Studien mit Follow-up bis zu 1 Jahr zeigten 0 % Explantationen; drei Langzeitstudien (Follow-up 1 bis 5 Jahre) zeigten eine Entfernungsrate von 4 % nach 1 Jahr Follow-up; 3 % nach drei Jahren Follow-up und 7 % nach fünf Jahren Follow-up.

kein Produktedefekt/ Entriegelung

- Erosion und Migration wurde in drei Studien berichtet: es trat in keiner ein Produktedefekt/Entriegelung auf.

Laufende Studien

keine laufende kontrollierte Studien MSAD vs. LF

Derzeit gibt es keine registrierten laufenden oder geplanten kontrollierten Studien die LINX® mit LF vergleichen. Eine laufende klinische Studie vergleicht LINX® mit Omeprazole (PPI); zwei weitere Studien haben keine Komparatoren: eine erprobt LINX® an einer neuen Patientengruppe (GERD-PatientInnen, die sich zuvor einer laparoskopischen „*Sleeve Gastrectomy*“ gegen Fettleibigkeit unterzogen haben) sowie die 5-Jahres-post-Zulassungsstudie von LINX®.

ABER: MSAD vs. PPI UND: neue Patientengruppe

Kostenerstattung

Im Jahr 2014 wurde in Österreich die Medizinische Einzelleistung LM030 (offene Fundoplikatio/Hiatusplastik) 98-mal, LM040 (laparoskopische Fundoplikatio/Hiatusplastik) 1723-mal abgerechnet. Das LINX® Reflux Management System wird bislang nicht erstattet, derzeit aber bereits in sechs Zentren – nach Angaben des Herstellers – implantiert.

2014:
LF 1723-mal abgerechnet

Diskussion

Der Magnetische Speiseröhren Ring ist ein relativ neuer Eingriff und es liegen nur wenige Daten über die klinische Wirksamkeit und Sicherheit des Verfahrens vor. Alle vorliegenden Studien wurden vom Produktehersteller gesponsert, Mehrfachpublikation von PatientInnen ist sehr wahrscheinlich. MSAD erhielt 2008 die Europäische Marktzulassung und 2012 die FDA-Zulassung basierend auf 2 Jahres-Follow-up-Daten. Die für die FDA-Zulassung post-marketing 5 Jahres Follow-up-Daten sind in der vorliegenden Bewertung einbezogen.

neues Verfahren
alle Studien Hersteller gesponsert

Zulassungen:
Europa 2008
USA 2012

Für die Beurteilung des LINX® wurde die best-verfügbare Evidenz herangezogen: eine prospektive Registerstudie mit Kontrollgruppe für die Beurteilung der Wirksamkeit, fünf (weitere) prospektive Fallserien für die Beurteilung der Sicherheit. Robuste klinische Daten aus (randomisierten) kontrollierten Studien zum Vergleich mit dem Gold-Standard Fundoplikatio liegen nicht vor und werden auch in naher Zukunft nicht vorliegen, da keine laufenden Studien registriert sind. Die Registerstudie zeigte bei einem Follow-up von 1 Jahr sehr ähnliche Ergebnisse zwischen den Gruppen. Wichtig ist, dass die Studie mit 5-jährigem Follow-up ein Wiederauftreten der Krankheit zeigte: Sodbrennen verbesserte sich bei 89 % der PatientInnen auf 3,2 % im ersten Jahr, nahm im zweiten Jahr auf 5,6 % zu, 8 % im dritten Jahr, 9,3 % im vierten Jahr und 11,9 % im fünften Jahr.

keine robuste Evidenz aus RCTs im Vergleich mit Gold-Standard (laparoskopische Fundoplikatio)

bei 5 J FU: langsames Wiederauftreten des Symptoms Sodbrennen auf 11,9 %

Die berichteten Ergebnisse zu den Wirksamkeits- und Sicherheitsendpunkten (Aufstoßen, extra-öophageale Symptome, Absetzen der PPI-Therapie, GERD HRQL und die allgemeine Zufriedenheit) zeigen Homogenität zwischen dem Register und den Fallserien. Wichtig ist aber, dass die Ergebnisse aus den Fallserien nicht nur den Ergebnissen aus der Registerstudie ähneln, sondern auch den Ergebnisse aus LF-Studien. Alle diese Ergebnisse haben leichte bis deutliche Verbesserung, sowohl in den einarmigen Studien wie in der Register-Studie gezeigt. Beide Gruppen in der Registerstudie hatten ähnliche Ergebnisse mit einer Ausnahme: 81,8 % der MSAD PatientInnen konnten die PPI-Therapie absetzen im Vergleich zu 63 % der LF-PatientInnen. Nur beim Endpunkt Dysphagia zeigten sich in den Fallserien keine einheitlichen Ergebnisse. Ergebnisse zur Sicherheit von MSAD basieren auf allen sechs prospektive Studien und zeigen die relative Sicherheit des Medizinprodukts; jedoch sind die postoperativen Nebenwirkungen im Vergleich zu LF aufgrund der unterschiedlichen Schwere der Erkrankung in den beiden Patientengruppen nicht direkt vergleichbar.

Ergebnisse in Registerstudie und Fallserien sehr ähnlich

leichte bis deutliche Verbesserungen durch MSAD und LF

Medizinprodukt gleich sicher

aber Patientencharakteristika nicht überall gleich

Nichtsdesto weniger sind die vom Hersteller genannten wichtigsten Vorteile des MSAD Verfahrens, dass es weniger invasiv und reversibel ist, dass es kürzere Krankenhausaufenthalte bedarf und eine schnellere Rückkehr zur normalen Ernährung ermöglicht. Offene Fragen bleiben bez. Langzeitsicherheit von MSAD aufgrund zunehmender Explantationen bei längerem Follow-up.

vom Hersteller genannte Vorteile: weniger invasiv, reversibel, kürzere Krankenhausaufenthalte

methodischen Einschränkungen der Studien

Die methodischen Einschränkungen der Studien sind der unklare Auswahlprozess der PatientInnen, nicht-konsekutive Rekrutierung der StudienteilnehmerInnen, Unklarheit, ob die Studienteilnahme zu einem ähnlichen Zeitpunkt in der Erkrankung stattfand etc.. Alle Wirksamkeits-ergebnisse waren „patient-reported-outcomes", und unterliegen daher (weil unverblindet) einem hohen Risiko für Bias.

Ambivalenz der Therapieoptionen:

nicht LF als Komparator

Indikationsstellung?

Indikationsausweitung wahrscheinlich

Unsicherheit kommt auch von der Ambivalenz der Therapieoptionen: Einerseits wird LF als Alternative vorgestellt, andererseits will MSAD die „therapeutische Lücke zwischen PatientInnen, die mit PPI Behandlung unzufrieden sind und diejenigen, die zögern, sich einer Fundoplikatio zu unterziehen" füllen. Die Zielpopulation von MSAD scheint jedenfalls die weniger schwer von GERD betroffenen PatientInnen zu sein. Eine laufende Studie vergleicht MSAD mit PPI, eine weitere untersucht voroperierte PatientInnen. Vor diesem Hintergrund wäre nicht ein RCT mit MSAD vs. LF, sondern ein RCT mit sham-Intervention notwendig, um die Wirksamkeit von MSAD zu bestätigen. In Ermangelung klarer Einstufungen von Schweregraden besteht die Gefahr der Indikationsausweitung.

weitere „emerging" Technologien

Es gibt einige andere „emerging" Technologien, die die oben genannte therapeutische Lücke zu füllen versuchen. Diese lassen sich in drei Gruppen einteilen:

1. Radiofrequenzablation des LES (Stretta System),
2. Transoral Incisionless Fundoplikatio (TIF),
3. Elektrische Stimulationstherapie des unteren Schließmuskels der Speiseröhre (LES-EST).

Verhinderung von Folgeerkrankungen & Verhinderung von langen, teuren PPI Therapien mit Nebenwirkungen bislang nicht untersucht

Unbehandelter chronischer Reflux kann zu Folgeerkrankungen wie Progression der GERD zu erosiver Ösophagitis, Ösophagusstriktur, Barrett-Ösophagus oder sogar Speiseröhrenkrebs führen, weshalb die Wirkung von MSAD auf die Verhinderung dieser Erkrankungen auch analysiert werden müssen. Auch müssen potentielle Einsparungen durch die Reduktion oder Verhinderung einer teuren PPI-Therapie den Kosten dieses minimal-invasiven Eingriffs gegenübergestellt werden. Darüber hinaus können langfristige PPI-Therapien schwere Nebenwirkungen wie Verringerung der Kalziumabsorption, Osteoporose, Clostridium difficile-Infektion, etc. und Wechselwirkungen mit anderen Medikamenten nach sich ziehen.

Empfehlung

ungenügende Evidenz

nur Beobachtungsstudie mit 249 Pt nicht vergleichbare Population

Die aktuelle Evidenz ist nicht ausreichend, um zu beweisen, dass die Technologie MSAD gleich wirksam und weniger sicher ist als der Komparator Fundoplikatio. Vergleichsdaten über die beiden Verfahren stehen aus einer einzigen Registerstudie mit Kontrollgruppe zur Verfügung: die LF-Gruppe befand sich allerdings in einem schwereren Stadium der Erkrankung und erzielte dennoch eine ähnliche Verbesserung in der GERD bezogenen Lebensqualität wie die MSAD PatientInnen. In Bezug auf die Sicherheitsendpunkte waren die Re-Operations- und Rehospitalisierungsraten ähnlich. Das Vertrauen in diese vergleichenden Ergebnisse ist allerdings aufgrund des Studiendesigns (Beobachtungsstudie), die begrenzte Anzahl von PatientInnen (249: 202 MSAD vs. 47 LF) sowie die Unterschiede in den Eigenschaften der PatientInnen in den beiden Studiengruppen eingeschränkt.

Aufnahme in den MEL-Leistungskatalog derzeit nicht empfohlen

Die Ergebnisse aus qualitativ hochwertigen kontrollierten Studien können die Effektschätzung erheblich beeinflussen. Die Aufnahme in den MEL-Leistungskatalog wird derzeit nicht empfohlen.

1 Scope

1.1 PICO question

PIKO-Frage

Is insertion of a magnetic sphincter augmentation device in comparison to the standard surgical treatments (Nissen fundoplication, partial or Toupet fundoplication) in patients with gastroesophageal reflux disease more effective or equally effective concerning improvement in GERD-Health-related quality of life, and discontinuation or reduction of anti-reflux medication (proton pump inhibitors), and safer regarding the post-operative side effects and serious adverse events?

1.2 Inclusion criteria

Einschlusskriterien für relevante Studien

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

Table 1-1: Inclusion criteria

Population	Second-line treatment for adult patients with chronic (>6 months) GERD diagnosed based on abnormal ambulatory pH study, endoscopic esophagitis, typical symptoms of GERD (heartburn or regurgitation), and at least partial response to a therapeutic trial of a proton pump inhibitor. Moderate to severe symptom chronic GERD and refractory GERD were considered in this assessment. International classification of diseases (ICD)-10-CM code: K21.9 Gastroesophageal reflux disease without esophagitis MeSH-term: C06.405.117.119.500.484 Gastroesophageal reflux
Intervention	Insertion of a magnetic sphincter augmentation device (MSAD) through laparoscopic surgery. Product name: LINX® Reflux Management System
Comparator[1]	Standard surgical treatment of GERD: Nissen fundoplication, partial or Toupet fundoplication MeSH-term: E04.210.390 Fundoplication
Outcomes	
Efficacy	*Clinical endpoint:* • GERD-Health-related quality of life (HRQoL) *Intermediate outcomes:* • Heartburn • Daily regurgitation • Dysphagia • Excessive bloating • Extra-esophageal symptoms • Discontinuation of antireflux medication (Proton Pump Inhibitors/PPIs)

[1] Comparator was selected based on recommended surgical treatment option in the Austrian/German guidelines for management of GERD. Fundoplication is currently the standard surgical treatment of GERD. There are other alternative treatments, but they are not standard treatments yet due to little evidence on their safety and effectiveness.

Safety	*Adverse device effects (ADE), serious adverse device effects (SADE):* • Dysphagia • Excessive bloating • Inability to belch or vomit • Device migration • Device erosion • Device malfunction • Device removal • Re-hospitalisation • Re-operation
Study design	
Efficacy	Randomised controlled trials Prospective non-randomised controlled trials
Safety	Randomised controlled trials Prospective non-randomised controlled trials Prospective single-arm studies (case-series, registries)

2 Methods

2.1 Research questions

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

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

Clinical Effectiveness	
Element ID	**Research question**
D0005	How does MSAD affect heartburn, regurgitation, and extraesophageal symptoms?
D0006	How does MSAD affect the continuation with PPI therapy?
D0011	What is the effect of MSAD on dysphagia and bloating?
D0016	How does MSAD affect activities of daily living?
D0013	What is the effect of MSAD on disease-specific quality of life?
D0017	Was the use of MSAD worthwhile?

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

2.2 Sources

Description of the technology

Quellen

- Handsearch in the POP, AdHopHTA and CRD databases for Health Technology Assessments
- Background publications identified in database search: see Section 2.3
- Documentation provided by the manufacturer
- Questionnaire completed by the submitting hospitals

Health problem and Current Use

- Handsearch in the POP, AdHopHTA and CRD databases for Health Technology Assessments
- Background publications identified in database search: see Section 2.3
- Documentation provided by the manufacturer
- Questionnaire completed by the submitting hospitals

2.3 Systematic literature search

The systematic literature search was conducted 11th-16th December 2015 in the following databases:

systematische Literatursuche in 5 Datenbanken

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

insgesamt 273 Publikationen identifiziert

The systematic search was (in Medline, Embase and PubMed) limited to Clinical Trials and Systematic Reviews/Meta Analyses. After deduplication, 214 citations remained for abstract screening. The systematic search was complemented by a Scopus search (citation tracking) conducted on 11.02.2016, which yielded a further 46 unique citations. Through hand searching another 12 references could be identified. One publication was supplied by Industry, bringing the total number of included citations to 273. The specific search strategies can be found in the Appendix.

2.4 Flow chart of study selection

Literaturauswahl

Overall 273 hits were identified. The references were screened by two independent researchers and in case of disagreement a third researcher was involved to solve the differences. The selection process is displayed in Figure 2-1.

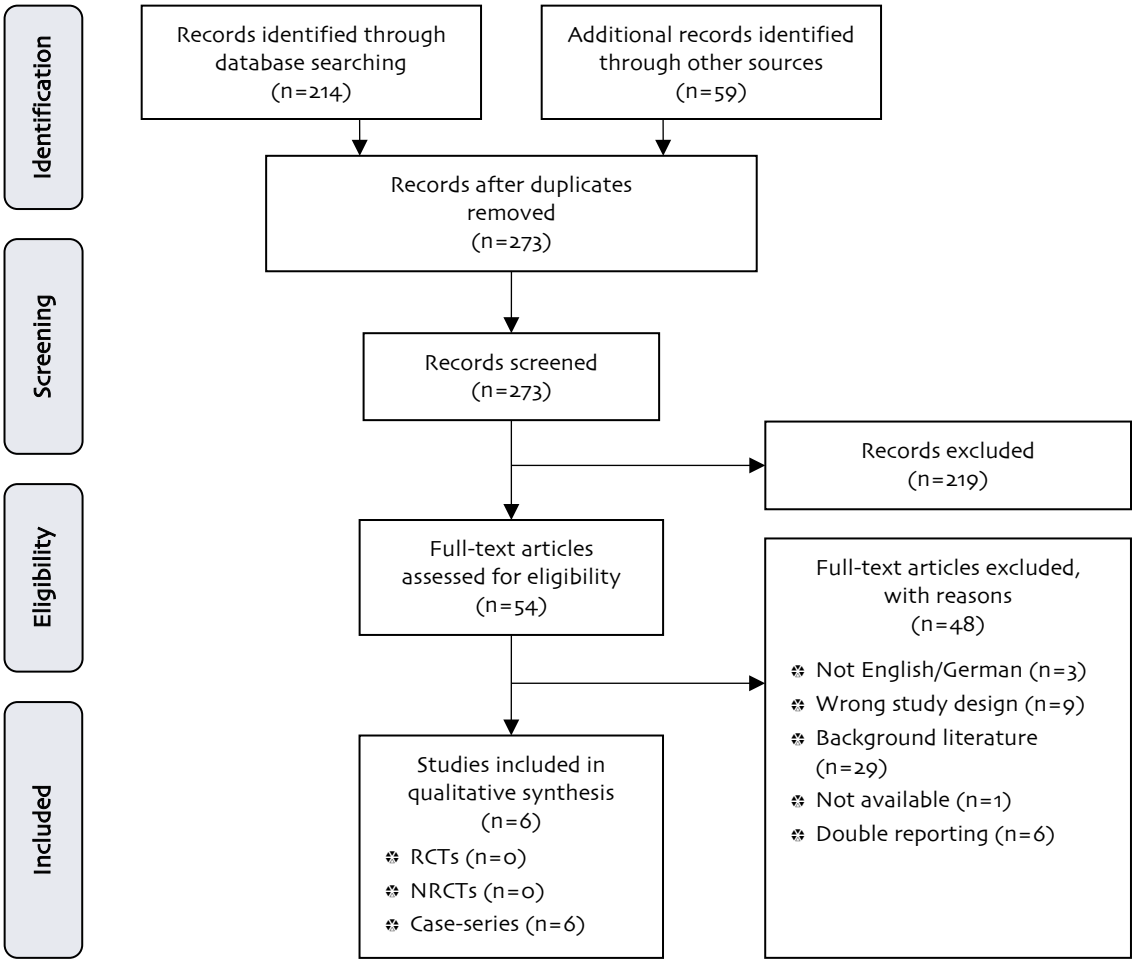


Figure 2-1: Flow chart of study selection (PRISMA Flow Diagram)

2.5 Analysis

The data retrieved from the selected studies (see Chapter 2.4) were systematically extracted into a data-extraction-table (see Appendix Table A-1 and Table A-2). No further data processing (e.g. indirect comparison) was applied. The studies were systematically assessed for quality and risk of bias using the checklists presented in the Appendix (Table A-3).

2.6 Synthesis

Based on the data-extraction-table (see Appendix), data on each selected outcome category were synthesised across studies according to GRADE (Grading of Recommendations Assessment, Development and Evaluation) [2]. The research questions were answered in plain text format with reference to GRADE evidence tables (see Table 7-1).

3 Description and technical characteristics of technology

Features of the technology and comparators

B0001 – What is magnetic sphincter augmentation (MSA) and the alternative standard surgical treatment(s)?

neue Verfahren in Antireflux Chirurgie: magnetische Speiseröhren Ring aus Titan-Perlen

Verstärkung des Schließmuskels: Ösophagus-Magen

Magnetic sphincter augmentation represents a novel method for the surgical treatment of GERD. The magnetic sphincter augmentation 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. The goal of the intervention is to reinforce the weak lower esophageal sphincter (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 [3].

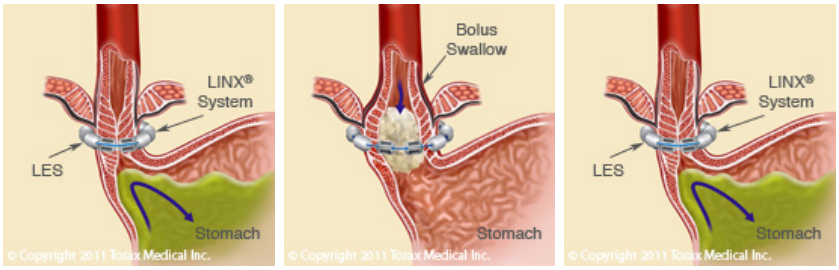


Figure 3-1: Operation principles of the MSAD

laparoskopisch eingesetzt, minimal invasiv

The device does not require any anatomic alteration of the stomach. It is implanted under general anaesthesia, using a minimally invasive surgical technique called 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 [3].

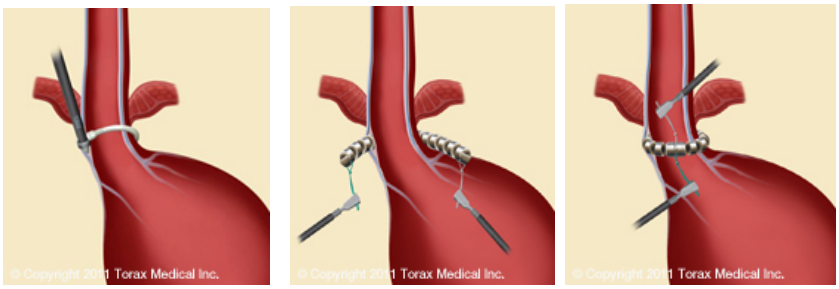


Figure 3-2: Operation procedure of MSAD

Marketed products

1 Produkt auf dem Markt: LINX® Reflux-Management-System

There is currently only one MSAD on the market, the LINX® Reflux Management System. It has been developed by Torax Medical Inc. [3]. 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-generation 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 [4].

2 Medizinprodukt-Generationen

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

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 demagnetized when subjected to external magnetic fields. Torax announced the FDA approval for the second generation of LINX with MRI compatibility in June 2015 [5, 6].

Unterschiede zwischen die 2 Generationen

Correspondence with Torax Medical Inc. indicated that approximately 4000 LINX systems have been implanted to date worldwide.

Table 3-1: Device generations of LINX®

Device generations	Device ends securing	Sizing tool	MRI compliance	Implanted until
1st generation	Ti-Knot Replacement System (suture)	Color-coded tool of connected beads	Up to 0.7 tesla	May 22, 2015
2nd generation	clasp	Laparoscopic sizing tool	Up to 1.5 tesla	To present

Current technology

chirurgiesche Standardmethode: Fundoplikatio

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

Nissen Fundoplikatio: vollständige Manschette wird um Ösophagus gelegt

- Nissen fundoplication is currently the gold-standard and most common surgical treatment with around an annual 2000 procedures carried out in Austria. It was first performed by Dr. Rudolph Nissen in 1955 by an open technique, but is now typically carried out laparoscopically, because high-quality evidence suggests its superiority to open surgery concerning early outcomes (hospital stay, fewer complications) with no significant differences in late outcomes, although the reoperation rate is higher in the short-term [1, 7]. It is a complete or total wrap that encompasses 360° of the esophagus in a posterior fashion.

partielle Fundoplikatio: 270 Grad Manschette

- Partial fundoplication has two versions, but only one is recommended for the treatment of GERD, i.e Toupet fundoplication (posterior wrap), which covers roughly 270° of the posterior esophagus [7]. Partial fundoplication is associated with less post-operative dysphagia, fewer re-operations, and its effectiveness is similar in controlling GERD symptoms compared to total fundoplication up to five years after surgery. However, there are concerns about the long-term effectiveness of partial fundoplication [1].

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

keine standardisierte Operationstechnik

The recovery time can be 4-6 weeks in fundoplication, and patients need to be on a pure liquid diet for one week after surgery before they can gradually start a soft food diet [8].

4-6 Wochen Rekonvaleszenz, zunächst nur flüssige Nahrung

Hiatal hernia and its repair

The esophagus passes through an opening in the diaphragm (the oesophageal hiatus) before it joins the stomach. If the stomach slips through the diaphragm into the chest, a condition called hiatus hernia develops. Hiatus hernia might be a cause of GERD [9], therefore, depending on its size, it is often repaired (posterior crural repair) at the time of anti-reflux surgery at the surgeons' discretion to ensure the success of the anti-reflux surgery. A sliding hernia of up to 3 cm can be effectively repaired by approximating the crura with interrupted stiches [10].

Hiatushernie Reparatur in Antireflux Chirurgie

Hiatal hernia repair can be done in both interventions. Fundoplication allows for a concurrent hiatal hernia repair. It is recommended for those who have a hiatal hernia >2 cm or if someone has a gastroesophageal junction in the chest [8].

A0020 – For which indications has the magnetic sphincter augmentation device (MSAD) received marketing authorisation or CE marking?

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≤35, 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 [3]. The LINX device has FDA approval since 2012 for the same indications [11].

CE Mark: 2008

FDA Zulassung: 2012

Zulassung für chronische GERD, abnorme pH-Werte, Symptome trotz max. PPI-Therapie

B0002 – What is the claimed benefit of MSAD in relation to the alternative standard surgical treatments?

The claimed major benefits of MSAD are its lesser invasiveness and reversibility [12]. Insertion of the device requires little dissection and few steps, therefore the operative time is shorter. The operation technique is less difficult, hence its reproducibility is higher and the learning curve for the surgeon is also shorter [1, 13].

Vom Hersteller genannte Vorteile von LINX®: weniger invasiv, kürzere/r OP- und Krankenhausaufenthalt

MSA procedure can be associated with fewer side-effects and a shorter hospital length of stay. Patients are advised to return to normal diet right after surgery [7].

B0003 – What is the phase of development and implementation of MSAD and the alternative standard surgical treatments?

neue Verfahren in Antireflux Chirurgie jetziges Medizinprodukt: 2.Generation

MSAD was first implanted in a clinical setting in 2007 in the clinical feasibility study of 44 patients (NCT01058070). It is a novel technology that is still in its emerging phase, hence it is not a standard clinical practice yet. The current device is the second generation, which is MRI compatible up to 1.5 tesla MRI compared to the first generation device, which can be used up to 0.7 tesla. Current clinical trials are investigating the use of the device in other subgroups of GERD patients (after laparoscopic sleeve gastrectomy) that had been so far excluded from the use of the device. New versions of the device with substantial improvements are not expected in the near future.

laufende Studie mit anderer PatientInnen-Population

chirurgische Standardmethode: Fundoplikatio

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

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

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

B0008 – What kind of special premises are needed to use MSAD and fundoplication?

B0009 – What supplies are needed to use MSAD and fundoplication?

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

Both MSA 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 minimize morbidity and improve patient outcomes [1].

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.

Regulatory & reimbursement status

A0021 – What is the reimbursement status of MSAD?

bislang nicht erstattet

Kosten: 4.340 € Materialkosten

According to the submission documents received from the Austrian Ministry of Health (MoH), MSAD is currently not included in the Austrian catalogue of benefits. 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). The information about the former two has been provided by the manufacturer.

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

In comparison to fundoplication, the material costs (device and sizing tool) and the initial training of surgical staff to undertake the implantation procedure are additional to the costs of the operation procedure, although the procedure itself might cost slightly less due to its shorter operation time. The LINX® device is in the German and Swiss DRG-Systems and is reimbursed up to the amount of € 8,100. In Austria, there are currently 6 centres where the LINX System is available, but according to the manufacturer, in 2016, this number is increasing to 10-15.

4 Health Problem and Current Use

Overview of the disease or health condition

A0001 – For which health conditions, and for what purposes is MSAD used?

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

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

GERD:
Reflux aus dem Magen in die Speiseröhre

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

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

Symptome:
Sodbrennen, Aufstoßen, Magenschmerzen

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

Symptom based approach differentiates between typical and atypical symptoms:

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

typische und atypische Symptome

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

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

acid oder non-acid Refluxkrankheit

Non-acid reflux is poorly understood yet [8].

A generally accepted definition on the severity of GERD is lacking. Based on the frequency and severity of the experienced reflux symptoms, the expressions used in the literature spread from mild, through moderate, to severe GERD, however, without any explicit definition about the duration and the measurement of them.

Schweregrade:
mild, moderat, schwer

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

There are anatomical and patient factors that can contribute to the development of reflux. The anatomical factors are related to the LES, the diaphragmatic crura, and the phrenoesophageal ligament. The patient factors include diet and lifestyle, as well as obesity. Eating refluxogenic foods, overeating, eating immediately before going to bed, increased fat consumption in the diet,

anatomische Faktoren, Ernährung & Lebensstil

and expanding proportion of obese individuals are significant risk factors for GERD. In obese patients, the intra-gastric pressure and the frequency of transient LES relaxations is chronically increased, which is thought to be the cause of GERD [8, 14].

A0004 What is the natural course of GERD?

ungeklärter natürliche Verlauf

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

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

GERD Komplikationen: erosiver Ösophagitis, Stenose, Barrett-Ösophagus

- The traditional concept sees the disease as a spectrum starting with non-erosive reflux disease (NERD) that might progress to complicated GERD (erosive esophagitis, stricture, Barrett's esophagus). 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 a BE. Patients with BE have an increased risk of esophageal adenocarcinoma with an incidence of 40 times greater than in the general population (14).

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

- The new concept considers GERD as a categorical disease with three distinct entities: NERD, erosive esophagitis, and Barrett's esophagus (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, but not progressive, however other studies confirm that progression of NERD to erosive esophagitis is possible in 10% of GERD patients [14].

These two concepts have in common that NERD might progress to GERD; it is debated though to what extent.

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

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

Lebensqualität

Quality of life is impacted through GERD symptoms such as heartburn, extra-esophageal (pulmonary or ear, nose, throat) manifestations, or non-cardiac chest pain [15].

Lebensstil, Ernährung

lebenslange Medikation

Patients often complain about sleep disturbance. Their diet is also affected as the foremost treatment suggested is life-style and diet modification. Presumably, they also need to take life-long medication, which might have serious side effects, be not well tolerated, or alter the absorption of minerals and vitamins, have metabolic effects on bone density, pharmacokinetics or pharmacodynamics and related drug interactions and effects, enhance infection risk and hypersensitivity response with consequent organ damage [12].

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

zunehmende Häufigkeit, wachsende Ressourcennutzung

Due to its increasing incidence (approximately 5 per 1000 person-years in the Western world [16]) GERD is leading to a growing utilisation of health resources (medical consultations, emergency room visits, hospitalization, and medication). Not only the doctor visits and diagnosis have high financial expenses, but also the medication in the long run and the operation [17].

The burden of disease on the individual affecting work productivity results in substantial societal burden and employer costs [12].

Current clinical management of the disease or health condition

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

ACG & AWMF: Richtlinien zur Diagnose der Refluxkrankheit

According to the American College of Gastroenterology (ACG) and the Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF) Guidelines [18, 19], the recommendations for the diagnosis of GERD (along with the level of evidence and the level of strength of the recommendation) are the following:

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

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

ACG & AWMF: schrittweises Vorgehen bei Interventionen

The management of GERD is aligned with the severity of symptoms. The ACG and AWMF Guidelines [18, 19] suggest a stepwise approach, which starts with lifestyle modifications, including:

Gewichtsverlust Vermeidung von Mahlzeiten vor Zubettgehen

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

From *mild to moderate* severity symptoms, first a

H2RA Therapie

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

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

8 Wochen PPI

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

PPI mit niedriger Dosierung indiziert

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

PPI-Erhaltungstherapie

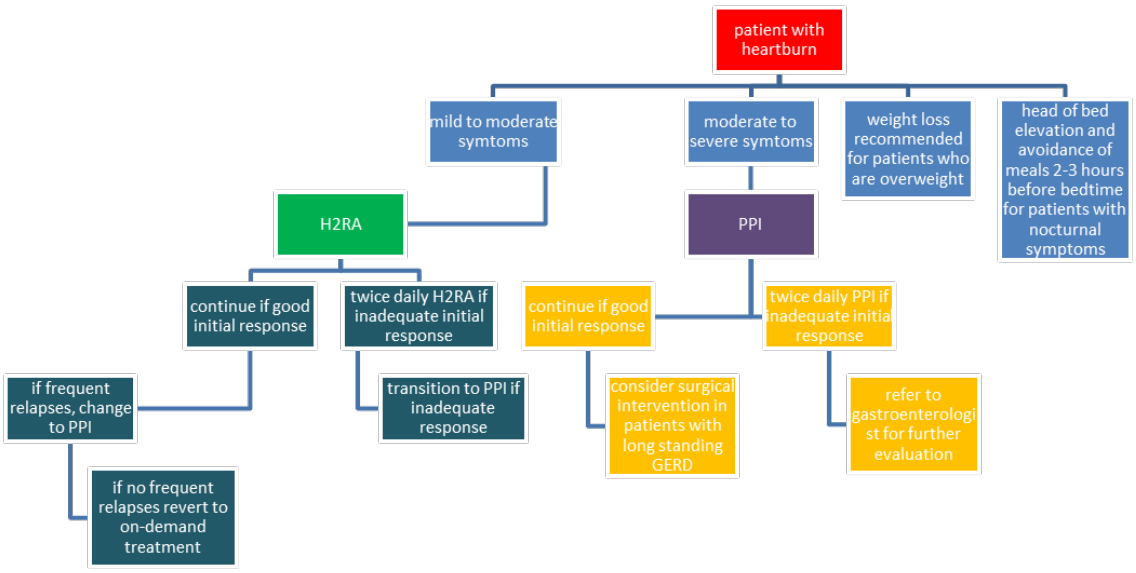
- **Maintenance of PPI therapy** should be administered for GERD patients who continue to have symptoms after PPI is discontinued and in patients with complications including erosive esophagitis and Barrett's esophagus (strong recommendation, moderate level of evidence). For patients who require long-term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

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

refraktär GERD: kein standardisierter Management-Algorithmus

For patients with refractory GERD, there is no standardized management algorithm. The primary goal of treatment is symptom reduction and eventual elimination [15].

The management of GERD is displayed in the following figure.



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

Figure 4-1: Algorithmic approach to medical treatment of GERD [12]

Operation: Therapie 2.Wahl

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

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

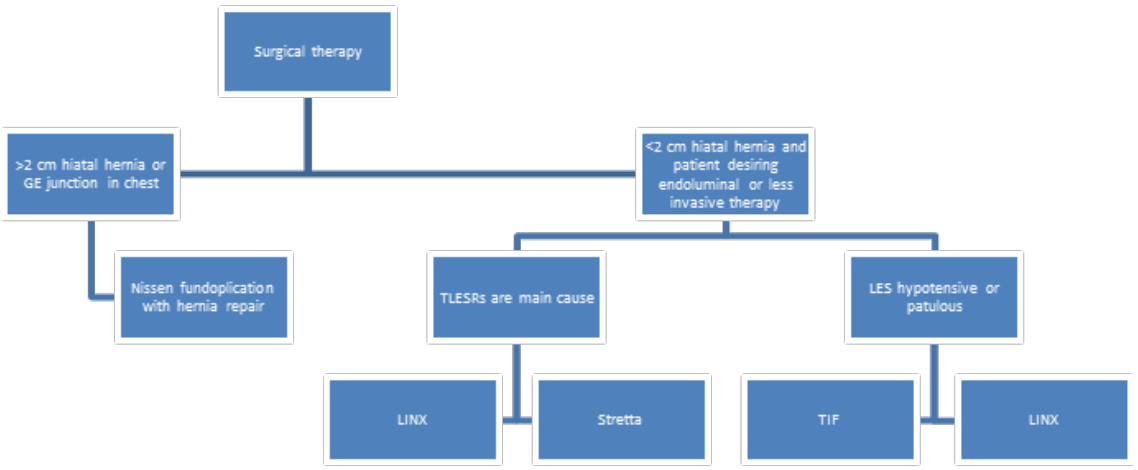
- have failed medical management (inadequate symptom control, severe regurgitation not controlled with acid suppression, or medication side effects);
- opt for surgery despite successful medical management (due to quality of life considerations, lifelong need for medication intake, expense of medications,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

The coexistence of Barrett's esophagus with gastroesophageal reflux symptoms is considered a clear indication for antireflux surgery. Surgical intervention for asymptomatic Barrett's esophagus is more controversial, however [1, 13].

It is important to note that there is no one best operation for all patients. Factors such as the degree of esophageal shortening, local expertise with laparoscopic techniques, prior operations and esophageal motility disorders, and the size of hiatal hernia can influence the choice of operation [13].

Entscheidungsbaum in Antireflux Chirurgie

Choice of surgical procedure is displayed in the following figure:



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

Figure 4-2: Decision tree in anti-reflux surgical therapy, adapted [8]

Target population

A0007 – What is the target population in this assessment?

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

A0023 – How many people belong to the target population?

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

The prevalence of GERD is around 15% [1, 18] and the incidence is increasing. It is the most common upper gastrointestinal disease in the Western countries, with 10-20% of the population experiencing weekly symptoms [14]. 25-42% of patients are refractory to a once-daily PPI, of which 25% would respond to an increase in PPI dosing to twice daily. However, 42% of GERD patients are dissatisfied with their PPI treatment outcomes [15].

In 2014, the Code LM030 (open fundoplication/hiatusplasty) was reimbursed 98 times, the LM040 (laparoscopic fundoplication/hiatusplasty) was refunded 1723 times.

A0011 – What is the expected utilisation of MSAD?

jährlich 100 Interventionen

The expected annual utilisation of MSAD, based on the previous years' experience, would be 100 interventions per year in Austria.

5 Clinical effectiveness

Research questions

Clinical Effectiveness	
Element ID	**Research question**
D0005	How does MSAD affect heartburn, regurgitation, and extraesophageal symptoms?
D0006	How does MSAD affect the continuation with PPI therapy?
D0011	What is the effect of MSAD on dysphagia and bloating?
D0016	How does MSAD affect activities of daily living?
D0013	What is the effect of MSAD on disease-specific quality of life?
D0017	Was the use of MSAD worthwhile?

5.1 Outcomes

The following outcomes were defined as *crucial* for patients:

- GERD HRQL score

Entscheidender Endpunkt zur Beurteilung der Wirksamkeit: GERD HRQL

Further outcomes considered were:

- Heartburn
- Daily regurgitation
- Dysphagia
- Excessive bloating
- Extra-esophageal symptoms
- Discontinuation with or reduction of PPIs

weitere wichtige Endpunkte: Sodbrennen, tägliches Aufstoßen, extra-ösophageale Symptome, Absetzen oder Reduktion von PPI-Medikamenten

GERD health-related quality of life score:

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

GERD HRQL score misst GERD-Symptome

5.2 Included studies

1 Studie wurde eingeschlossen

For assessing clinical effectiveness of MSAD on GERD, only one study fulfilled the inclusion criteria [22]. Study characteristics and results of included studies are displayed in Table A-1 and in the evidence profile in Table 7-1.

Study characteristics:

prospektive Registerstudie mit Kontrollgruppe (249 Pt) 1 Jahr FU

It was a prospective registry-based case control study done in the setting of real clinical practice in 22 medical centres in four countries. The control group included patients undergoing LF. The study was sponsored by the manufacturer Torax Medical Inc. Overall, 249 patients completed 1 year follow-up of which 202 underwent the MSAD intervention and 77 were women and 125 men [22]. Median operative time was not stated.

Patient characteristics:

Patientencharakteristika

Gruppenunterschiede bez. Schweregrade

LF-Gruppe schwerer krank

Important to note are the differences in inclusion criteria between MSAD and LF patients within the study. LF patients were in a more severe stage of GERD in terms of hiatal hernias sized >3 cm with 45.7% LF patients compared to only 1.6% MSAD patients. There were more patients with Barrett's esophagus in the LF group with 19.1% over 1.0% in MSAD and with esophagitis grade C and D, 8.5% in LF compared to 1% in MSAD. The mean BMI score, the number of years on PPIs as well as the number of years with GERD were similar. These above mentioned differences are significant because they are signs of more advanced GERD that MSAD is not indicated for.

5.3 Results

Mortality

No data on mortality were reported.

Ergebnisse:

D0005 – How does MSAD affect heartburn, regurgitation, extraesophageal symptoms, and frequency of esophageal symptoms?

Sodbrennen: 30.8 % auf 3.5 % bei MSAD vs. 40 % auf 8.5 % bei LF

In MSAD patients, the registry indicated an improvement in heartburn from baseline 30.8% to 3.5% at one year follow-up, whereas in the LF group, there was an improvement of 40% to 8.5% [22].

Aufstoßen: 58.2 % auf 3.1 % bei MSAD vs. 60 % auf 13 % bei LF

In the registry, regurgitation dropped from 60% to 13% in LF patients vs., 58.2% to 3.1% in the MSAD group [22].

Extra-ösophageale Symptome: 63.9 % auf 22.3 % bei MSAD vs. 53.3 % auf 17.4 % bei LF

In terms of frequency of extraesophageal symptoms, the registry study reported improvement of 63.9% to 22.3% in the MSAD group vs. 53.3% to 17.4% in the LF group [22].

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

PPI-Therapieabsetzen: 81.8 % MSAD vs. 63 % LF PatientInnen

In the registry study, 81.8% of patients with MSAD discontinued PPI therapy compared to 63% of patients undergoing LF [22].

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

The registry study only included data on post-operative excessive bloating with 10% in MSAD patients and 31.9% in LF patients, dysphagia was not reported on [22].

übermäßige Blähungen: 10 % MSAD vs. 31.9 % LF PatientInnen

D0013 – What is the effect of MSAD on disease-specific quality of life?

Comparing MSAD to LF, MSAD patients improved from 20 to 3 points in GERD HRQL and LF patients improved from 23 to 3.5 [22].

GERD HRQL: Verbesserung von 20 auf 3 Punkte bei MSAD vs. 23 auf 3,5 LF-PatientInnen

D0017 – Was the use of MSAD worthwhile?

Comparing MSAD to LF, 91.8% of MSAD patient were satisfied at follow-up compared to 86.7% of LF patients [22].

PatientInnen-zufriedenheit: 91.8 % MSAD vs. 86.7 % LF-PatientInnen

6 Safety

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

6.1 Outcomes

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

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

- Dysphagia
- Excessive bloating
- Device removal
- Device migration
- Device erosion
- Device malfunction
- Re-hospitalisation
- Re-operation
- Intraoperative complications

Further outcomes considered were:

weitere wichtige Endpunkte: Unfähigkeit zu Rülpsen oder Erbrechen, andere AEs

- Inability to belch or vomit
- Other AEs

In order to assess the relative effectiveness of an intervention, balancing harms against benefits is crucial. Procedure related AE and serious AEs are of special importance and were thus considered as crucial for assessing the safety profile of MSAD.

Due to the fact that MSAD is an implant foreign to the body, it carries with itself both safety benefits and concerns. On the one hand, the procedure is reversible, yet on the other, the way the body accepts the implant remains to be a safety concern. To monitor the process of acceptance of the implant, intraoperative complications (time period during operation), post-operative (any period after operation) dysphagia (difficulty with swallowing) and device removal, device migration, malfunction or erosion, re-hospitalisation and re-operation were chosen to be the crucial outcomes. Dysphagia was chosen to be the crucial outcome because it is the most common adverse event in fundoplication. Device removal is taken to be an indicator of both device failure as well as device non-tolerance.

6.2 Included Studies

6 Studien wurden eingeschlossen: 5 prospektive Fallserien, 1 prospektive Registerstudie mit Kontrollgruppe

For assessing safety of MSAD on GERD, six studies passed the inclusion criteria [4, 22-26]. The studies comprise five prospective case series [4, 23-26] and one prospective registry with control group [22]. Study characteristics and results of included studies are displayed in Table A-1, Table A-2 and in the evidence profile in Table 7-1.

Study characteristics:

356 PatientInnen in den Fallserien 249 PatientInnen in der Registerstudie, 202 implantiert mit MSAD

FU: 1 Monat – 5 Jahre

Overall, 356 patients were reported on in the prospective case series that were all sponsored by the manufacturer Torax Medical Inc., of which 144 were women and 212 were men. The prospective registry with control group included 249 patients, of which 202 underwent the MSAD intervention where 77 were women and 125 men [22]. However, because of a high probability of double reporting [4, 22], the total number of patients that have undergone the MSAD surgery ranges between 558 and 435. Clinical follow-up time ranged from one month to five years, with only two studies with longer mean follow-up of three and five years, respectively [4, 23]. Loss to follow-up ranged from 0-15 patients. Median operative time ranged from 23-60 minutes in the prospective case series, unreported in the registry.

Patient characteristics:

gewisse Heterogenität in der Charakteristika der eingeschlossenen PatientInnen: Alter, Dauer der GERD-Symptome, PPI-Therapieansprechen

Inclusion criteria showed some heterogeneity in terms of age, length of GERD symptoms, PPI resistance and responsiveness, and pathological reflux. The age of inclusion varied from 18-86 [26] to 20-68 [25] with one study [22] not reporting on the age range. Inclusion criteria in three studies required GERD symptoms to last for at least 6 months [4, 23, 24], while the remaining studies did not state the required length of confirmed GERD. Data on median number of years with GERD was stated in four studies [4, 22, 23, 25] and ranged from 4-10 years, but was left unreported in the remaining two studies. PPI resistant GERD was a criterion for inclusion in two studies [23, 24] and PPI responsive GERD was an inclusion criterion in three [4, 22, 24]. Data on median number of years of PPI use was again stated in four studies [4, 22, 23, 25] and ranged from 1-6.3 years, and was left unreported in the remaining two studies. Furthermore, confirmed pathological reflux was a requirement in two studies [4, 23].

Homogenität in den Ausschlusskriterien: Barrett Ösophagus, Hiatushernie > 3 cm, Motilitätsstörungen

Exclusion criteria were more homogenous with all studies restricting the study population to patients without Barrett's esophagus, even though two studies ended up operating on two and three patients with Barrett's esophagus respectively [4, 26]. All but one excluded patients with motility disorder [26] and hiatal hernias sized >3 cm [22]; it was the prospective registry study which included 1.6% of MSAD and 45.7% of LF patients with hiatal hernias >3 cm. Also, regardless of the exclusion criteria, two patients from Bonavina 2013 had a hiatal hernia >3 cm [4]. There was a set limit of 35 points in the BMI score in two studies [4, 23], while median BMI ranged from 24-28 with one study not reporting on this data [24]. Further heterogeneity in exclusion criteria was with reference to esophagitis, where two studies formally excluded patients with esophagitis grade B, C and D [4, 26], yet in practice, one of them included six esophagitis grade B patients [4]. Compared to the rest of the studies, only those patients who were diagnosed with esophagitis grade C and D were excluded, yet again, in practice, the prospective registry study included in both groups, 1% of MSAD and 8.5% of LF, the patients with esoph-

agitis grade C and D [22]. Confirmed allergy to metals was an exclusion criteria in three studies [4, 23] and further two studies had an extra exclusion criteria of esophageal anatomic abnormalities [4, 24].

6.3 Results

Patient safety

C0008 – How safe is MSAD in comparison to LF?

nur die Registerstudie ermöglicht einen Vergleich bei:

Dysphagie

Übermäßigen Blähungen

Unfähigkeit zu Rülpsen oder Erbrechen

intraoperative Komplikationen

Re-Operationen

Re-Hospitalisierung

Only the registry study allows for comparison of the dysphagia, excessive bloating, inability to belch or vomit, intraoperative complications, re-operation rate, and re-hospitalization rate between the MSAD and LF groups.

The registry study reported that post-operative excessive bloating was 10% in MSAD patients, compared to 31.9% in LF. No significant difference was observed between the two groups regarding the intraoperative complication rates (1.49% in MSAD vs. 2.13% in LF). 1.6% of MSAD patients experienced the inability to belch compared to 10.1% of LF patients, 8.7% of MSAD patients experienced the inability to vomit compared to 56.6% of LF patients. 7% of MSAD patients and 10.6% of LF patients experienced dysphagia at 1 year follow-up. 4% of MSAD patients were re-operated due to device removal, compared to 6.4% of patients in the LF group that were re-operated due to persistent GERD and herniation of the fundic wrap [22]. Hospital readmission rate was 5.4% for MSAD patients compared to 4.3% for LF patients [22].

Produktentfernung, Erosion, Migration und Fehlfunktionen wurden in den Fallserien sowie der Registerstudie berücksichtigt

Device removal, erosion, migration, and malfunctioning were considered in the case series and the registry study, because the effects directly attributable to the device can be analyzed without comparator group as well. Device removal was reported in five studies. Two studies with short-term (up to 1 year) follow-up indicated 0% of device removal rate [25, 26], compared to three long-term studies (1 to 5 year) that indicated the device removal rate of 4% at one year follow-up [22], 3% at three year follow-up[4], and 7% at five year follow-up [23]. Device erosion and migration was reported in three [4, 23, 26] resp. two studies [4, 23], but occurred in none. Device malfunctioning/unlocking was reported only in one study, but did not occur [23].

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

Sicherheit bei MRI Untersuchungen:
1.Generation:
bis zu 0.7 tesla
2.Generation:
bis zu 1.5 tesla

With the new generation of the device, the safety profile does not vary. The main difference between the device generations is in their MRI compliance. The first generation is up to 0.7 tesla, whereas the second is up to 1.5 tesla MRI compatible. Other minor differences include securing the ends of the device; in the first generation a Ti-Knot Replacement System (LSI Solutions) was used, whereas in the second generation a clasp was used instead of a suture [4]. Additionally, sizing of the esophagus in the first generation used a color-coded sizing device of connected beads, whereas in the second generation, a laparoscopic sizing tool was introduced [4].

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

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

vorhandene magnetische Implantate und MRI Untersuchungen sind Risikofaktoren

Patients susceptible to be harmed through the use of the technology 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, a total of 8 patients reported undergoing MRI out of which 2 patients reported discomfort during the MRI and chest X-Ray for both of these patients showed the device in a more open geometry [4].

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

Fehlfunktion des Medizinprodukts ist möglich bei verzögerter Rückkehr zur normalen Ernährung

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 of the beads during healing [4].

kürzere Lernkurve für ChirurgInnen, OP-Technik weniger schwierig

The learning curve for placement of the MSAD was not steep [27]. Risks related to administration of the device stem from the surgeon's ability to minimize the amount of dissection performed and to carefully locate and dissect the posterior vagus nerve [27]. The surgeon needs to avoid reverting back to the dissection technique used to create a fundus wrap from the esophageal wall [27].

7 Quality of evidence

Qualität der Evidenz nach GRADE

The strength of evidence was rated according to GRADE (Grading of Recommendations Assessment, Development and Evaluation) Schema [28] for each endpoint individually. Each study was rated by two independent researchers. In case of disagreement a third researcher was involved to solve the difference. A more detailed list of criteria applied can be found in the recommendations of the GRADE Working Group [28].

GRADE uses four categories to rank the strength of evidence:

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

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

Overall, the strength of evidence for the effectiveness and safety of MSAD in comparison to LF is very low to moderate.

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

No of studies/ patients	Study Design	Estimate of effect	Study limitations	Inconsistency	Indirectness	Other modifying factors	Strength of evidence
Efficacy							
Median GERD HRQL score (pre-op./last follow-up) I vs. C							
1/249	Prospective registry with control group	20/3 vs. 23/3.5 (p=0.177)	0	NA	0	0	Moderate
Safety							
Overall complication rate, % I vs. C							
1/249	Prospective registry with control group	NA	NA	NA	NA	NA	NA
Intraoperative complications, % I vs. C							
1/249	Prospective registry with control group	1.49 vs. 2.13 (p=1.00)	0	NA	0	0	Moderate
Dysphagia, % I vs. C							
1/249	Prospective registry with control group	7 vs. 10.6 (p=0.373)	0	NA	0	0	Moderate
Device removal, %							
5/336	Prospective case series + prospective registry with control group	0-7	-1	-1	0	-1[2]	Very low

Nomenclature for GRADE table:

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

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

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

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

Legend: I: intervention; C: control; GERD HRQL: gastroesophageal reflux disease health-related quality of life

[2] Out of the total of 5 prospective case series included in the analysis, only 4 are reporting on this outcome.

8 Discussion

Since MSAD is a new intervention, there is scarce data on the clinical effectiveness and safety of the device. MSAD received the FDA approval based on a 2 year follow-up data in 2012 with the required 5 year follow-up data available in 2015 included in this assessment [11]. For the purposes of the assessment, we have restricted our analysis to prospective studies as the best available evidence, of which we could identify six. Lacking randomized controlled trials, there is an absence of robust clinical data comparing MSAD with the best available alternative, LF.

neues Verfahren

keine robuste Evidenz aus RCTs im Vergleich mit Gold-Standard (laparoskopische Fundoplikatio)

In terms of clinical effectiveness, only one study fulfilled the inclusion criteria [22], which, with regards to patient characteristics as outlined in the clinical effectiveness section, included such different patient groups for each intervention that the comparative value of the study as such remains undermined.

1Studie eingeschlossen für Wirksamkeit, aber Patientencharakteristika nicht überall gleich

When comparing the registry study to the case series, which did not pass the inclusion criteria for clinical effectiveness, heterogeneity in results can be observed with regards to heartburn, where two studies reported a significant reduction in the percentage of patients experiencing heartburn within a short-term follow-up time of 1 month [25], and long-term follow-up time of 5 years [23]. The registry study indicated a less significant decline both in MSAD and LF groups with very similar results, within the follow-up of 1 year [22]. Important to note is that the five year study showed recurrence of the disease [23], where the baseline heartburn of 89% decreased to 3.2% at one year follow-up, but progressively grew to 5.6% at two year follow-up, 8% at three year follow-up, 9.3% at four year follow-up, and 11.9% at five year follow-up.

bei 5 J FU: langsames Wiederauftreten des Symptoms Sodbrennen auf 11,9 %

All the rest of the reported outcomes suggest homogeneity between the registry and the case series. Important to note is that the case series data not only match the clinical effectiveness data of MSAD, but, drawing upon the registry data, to a large extent, they match the clinical effectiveness data of LF as well. The homogenous outcomes include: regurgitation, extraesophageal symptoms, discontinuation of PPI therapy, GERD HRQL, and overall satisfaction. All of these outcomes have shown slight to significant improvement both in the single-arm studies and in the registry study. The two groups in the registry study had similar results in all but one outcome, 81.8% of MSAD patients discontinued PPI therapy compared to 63% of patients undergoing LF [22]. In the registry, dysphagia was not reported both pre- and post-operatively, but it remains important to highlight that the data in the case series varied greatly, whereby studies with short-term follow-up [24, 25] indicated a significant worsening in dysphagia and studies with long-term follow-up indicated improvement or slight worsening [4, 23].

Ergebnisse in der Registerstudie und Fallserien sehr ähnlich

leichte bis deutliche Verbesserungen durch MSAD und LF

Device-related safety data on MSAD based on all the six prospective studies included indicate relative safety of the device; however, based upon the registry study, the post-operative side-effects compared to LF cannot be directly assessed due to the different severity of the disease in the two patient groups. Nonetheless, the major advantages of the MSA procedure known to date are that it is less invasive and reversible, its implantation is associated with a shorter learning curve for the surgeon, it requires a shorter hospital stay, and allows a faster return to normal diet. One question mark remains with long-term safety of MSAD due to the device removal data, which seem to indicate a pattern of the longer the follow-up, the more device removals.

Medizinprodukt gleich sicher

aber Patientencharakteristika nicht überall gleich

methodischen Einschränkungen der Studien

Overall, the strength of evidence is moderate for efficacy and very low to moderate for safety outcomes. The case series were concluded to have a high risk of bias, the registry study being the only one with a low risk of bias. Three studies were conducted in multiple centres where multiple-reporting was probable. Bonavina 2013 [4] was reporting on the same cohort as studies that we excluded for that reason [27, 29-31]. The registry study [22] was with high probability including patients from Bonavina 2013 [4] and Schwameis 2014 [25]. The methodological limitations include: unclear selection process [23, 26], non-consecutive recruitment of study participants [4, 23], unclear if entering the study at a similar point in the disease [22, 24, 26] or clearly not fulfilling this criteria [4, 23, 25], non-reporting about competing interests or sources of support for the study [24-26], and a high loss to follow-up [23, 24]. All six studies were sponsored by the manufacturer Torax Medical Inc., and all of the effectiveness outcomes were patient reported, hence subject to high risk of bias.

Ambivalenz der Therapieoptionen: nicht LF als Komparator

Indikationsstellung?

Indikationsausweitung wahrscheinlich

Uncertainties about the applicability of evidence stem from the ambiguity of alternatives. On the one hand, LF is presented as an alternative, yet on the other hand, MSAD claims to fill the "therapeutic gap between patients who are dissatisfied with PPI treatment and those who are reluctant to undergo Nissen fundoplication" [31]. The target population of MSAD seems to be less severe patients not indicated for fundoplication, which changes the cut-off point of a surgical intervention to the less diseased. In the light of this ambiguity, ethicality of an RCT between MSAD and LF is put into question. Hence, under these circumstances, a sham RCT is needed to confirm the efficacy of MSAD.

andere „emerging" Technologien

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

1. radiofrequency ablation of the LES (Stretta System)
2. trans-oral incisionless fundoplication (TIF), i.e. suturing of the gastroesophageal junction
3. lower esophageal sphincter electrical stimulation therapy (LES-EST) [8, 15, 32].

The first two alternatives provide a non-surgical approach, while the LES-EST is a non-ablative and easily reversible minimally invasive surgical intervention, like MSA. The TIF seems to be safe and effective with 79-80% response rates, although with disappointing 2-year follow-up results, and it is recommended only for patients with hiatal hernia <2 cm. The Stretta System is recommended by SAGES for non-complicated GERD and it is the only one that has undergone rigorous evaluation with randomized trials with excellent results. The safety profile of LES-EST is also very good so far, effectiveness data are comparable to MSA and it is indicated for the same patient group [8, 15, 32].

Verhinderung von Folgeerkrankungen & Verhinderung von langen, teuren PPI Therapien mit Nebenwirkungen bislang nicht untersucht

Untreated chronic reflux might lead to secondary diseases, such as erosive esophagitis, oesophageal stricture, Barrett's esophagus, or even oesophageal cancer, therefore the effect of MSAD on these outcomes also needs to be analysed. In case MSAD fulfils the mentioned therapeutic gap, it can be considered as the first line surgical treatment for prevention of the oesophageal cancer and, on the long run, as an option bringing savings to the health care system when contrasted to the costly PPI therapy. Furthermore, long-term PPI therapy can have serious side-effects, such as decreased calcium absorption, osteoporosis, community acquired pneumonia, Clostridium difficile infection, small intestinal bacterial overgrowth, vitamin B12 deficiency, and drug interactions [32].

Further issues with MSAD are related to the change in the cut-off point of a surgical intervention in case MSAD fulfils the mentioned therapeutic gap. In the absence of clear severity scores supporting staging of well-defined indications, there is a potential risk of MSAD facilitating unhealthy behaviour instead of a change in the patient's dietary habits, particularly in the obese.

Bedarf an RCTs mit Langzeit-Outcomes und diversen Patientencharakteristika

Studies with longer follow-up, involving larger number of implanted patients with various patient characteristics (size of hiatal hernia and severity of esophagitis) should be conducted to help determine the exact patient group that would benefit most from the intervention.

9 Recommendation

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

Table 9-1: Evidence based recommendations

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

Reasoning:

The current evidence is not sufficient to prove that the assessed technology, MSAD, is at least equally effective and as safe as the comparator LF. Comparative data on the two procedures are available from a single registry study where the LF group was in a more severe stage of the disease and nevertheless achieved a similar improvement in GERD related quality of life as the MSAD group. Concerning safety, the re-operation and hospital re-admission rates were similar; the difference in other complications like dysphagia was statistically not significant. Significant difference is only shown in the inability to belch or vomit, and in excessive bloating. However the confidence in these comparative results is limited, due to the observational study design, the limited number of patients, and the differences in the patient characteristics in the two study groups. Results from high-quality sham control studies or RCTs comparing MSAD and LF will potentially influence the effect estimate considerably.

ungenügende Evidenz

nur Beobachtungsstudie
mit 249 Pt
nicht vergleichbare
Population

Currently, there are no registered ongoing or planned controlled trials comparing the LINX device with LF (Table A-5 in the Appendix). Additionally, one ongoing clinical trial is comparing the LINX device with Omeprazole (PPI); two trials do not have any comparators. One of them is assessing the LINX device in a new patient group (GERD patients who previously had laparoscopic sleeve gastrectomy for obesity) and the other one is a 5-year post-approval study of LINX.

keine laufende
kontrollierte Studien
MSAD vs. LF

ABER: MSAD vs. PPI
UND: neue
Patientengruppe

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Appendix

Evidence tables of individual studies included for clinical effectiveness and safety

Table A-1: MSAD: *Results from observational studies included for safety*

	Bonavina 2013 [4]	Schwameis 2014 [25]	Smith 2014 [26]	Reynolds 2014 [24]	Ganz 2015 [23]
Country	Italy	Austria	United States	United States	United States, Netherlands
Sponsor	Torax Medical Inc.	Torax Medical Inc.	Torax Medical Inc.	Torax Medical Inc.	Torax Medical Inc.
Study design	Single-centre prospective case series	Single-centre prospective case series	Single-centre prospective case series	Two-centre prospective case series	Multi-centre prospective case series
Intervention	LP MSAD	LP MSAD	LP MSAD	LP MSAD	LP MSAD
Number of pts	100[3]	23	66	67	100
Inclusion criteria	Pts>18yrs, GERD ≥6mos, PPI resistant reflux, pathologic reflux	At least partial response to PPIs, PPI resistant GERD	GERD, acceptable esophageal motility, clinical improvement on antisecretory medication with incomplete symptom control, medication intolerance, or side effects	Pts>18yrs, GERD> 6mos	Pts>18yrs <75yrs, GERD ≥6mos, at least partial response to PPIs, pathologic reflux
Exclusion criteria	Hiatal hernia >3 cm, esophagitis grade B+, BMI >35, Barrett's esophagus, motility disorder, gross esophageal anatomic abnormalities, allergy to the device's material (titanium, stainless steel, nickel, or ferrous materials)	Hiatal hernia >3 cm, Barrett's esophagus, motility disorder, dysphagia, esophagitis grade C or D, allergy to the device's material (titanium, stainless steel, nickel, ferrous materials)	Hiatal hernia>3 cm, advanced GERD, Barrett's esophagus, esophagitis grade B+	Hiatal hernia >3 cm, motility disorder, esophagitis grade C or D, Barrett's esophagus, gross esophageal anatomic abnormalities, allergy to the device's material (titanium, stainless steel, nickel, ferrous materials	Hiatal hernia ≥3 cm, esophagitis grade C or D, BMI>35, Barrett's esophagus, motility disorder
Baseline patient characteristics					
Median age, yrs	44.5 (range 23-77)	43 (range 20-68)	53.7 (range 18-86)	53 (range 19-81)	53 (range 18-75)
Sex, female vs. male	(26 vs. 74)	12 vs. 11	38 vs. 28	20 vs. 47	48 vs. 52

[3] 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.

	Bonavina 2013 [4]	Schwameis 2014 [25]	Smith 2014 [26]	Reynolds 2014 [24]	Ganz 2015 [23]
BMI	Median 24 (range 17.3-33.0)	Median 26 (range 20-32)	Mean 26 (range 17.6-34.1)	NA	Median 28 (range 20-35)
Hiatal hernia ≤=3 cm, %	98[4]	100[5]	67[6]	NA	NA
Median yrs of PPI use	4	1 (range 0-20)	NA	NA	5
Median yrs with GERD	5.5	4 (range 1-20)	NA	NA	10 (range 1-40)
Barrett's esophagus, n	2	NA	3	NA	NA
Esophagitis, % Grade A and B Grade C and D	 16 1	 21.7 NA	 NA NA	 NA NA	 NA NA
Follow-up time	3 yrs (range 378 days-6 yrs)	1 mo	5.8 mos (range 1-18.6 mos)	5 mos (range 3-14 mos)	5 yrs
Loss to follow-up, n	5[7]	0	1	15	15
Median operative time, min	47	23	NA	60	36[8]
Outcomes					
Efficacy					
Median GERD HRQL score (pre-op./last follow-up)	24 off PPIs/2	29/4 (p<0.001)	26/6	NA/4 (range 0-26)	27/4 (p<0.001)
Heartburn, % (pre-op./last follow-up)	NA	95.7/22 (p<0.001)	NA	NA	89/11.9 (p<0.001)
Daily regurgitation, % (pre-op./last follow-up)	72/2	65/57 (p>0.1)	NA	NA/44.2	57/1.2 (p<0.001)
Dysphagia, % (pre-op./last follow-up)	8/0	48/70 (p>0.1)	NA	0.02/82.7[9]	5/6 (p=0.739)
Excessive bloating, % (pre-op./last follow-up)	48/2	70/30 (p=0.006)	NA	NA	52/8.3 (p<0.001)

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

[5] Including the patients that had no hernia. The mean hiatal hernia size was 1.34 cm (range 0-2 cm).

[6] No information on the size of the hernia.

[7] 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.

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

[9] 55.8 described it as mild, characterized by a feeling of food sticking or occasional regurgitation. A total of 44.2 described their dysphagia as severe as characterized by daily regurgitation and the inability to eat

	Bonavina 2013 [4]	Schwameis 2014 [25]	Smith 2014 [26]	Reynolds 2014 [24]	Ganz 2015 [23]
Extra-esophageal symptoms (asthma, chronic cough, laryngitis), % (pre-op./last follow-up)	52/16	57/17 (p=0.039)	NA	NA	NA
Discontinuation of medication (PPIs), %	85	71.4[10]	83	76.9	84.7[11] (CI 95%, 81-95)
DeMeester pH score (pre-op./last follow-up)	Median 30.1/11.2	NA	Mean 32.3 (range 1.4-67)/NA	NA	Median 36.6 (range 16.3-83.8)[5]/NA
Hospital discharge, %	96 (within 48 hrs)	52 (within 24 hrs), 82.6 (within 48 hrs)	25 (within 24 hrs)	51 (within 12 hrs), 100 (within 36 hrs)	NA
Patient satisfaction, % (pre-op./last follow-up)	5/87	0/74	NA/92[12]	NA	5/92.9[13] (p<0.001)
Safety					
ADEs, SADEs %					
Inability to belch	1	0	NA	NA	NA
Inability to vomit	1	0	NA	NA	NA
Other non-serious ADEs	4 mild odynophagia, 3 increased belching	NA	NA[14]	0.67 dehydration, 2 urinary retentions	NA
Dysphagia	2	0.23	2.64	5.36	NA
Intraoperative complications	0	0	0	0	NA
Device erosion	0	NA	0	NA	0
Device migration	0	NA	NA	NA	0
Device malfunction/unlocking	NA	NA	NA	NA	0
Device removal	3	0	0	NA	7

[10] 2 patients (9.5%) were already off medication at baseline due to severe side-effects from PPIs. 2 further patients were able to halve their daily PPI dosage.

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

[12] Patients who were satisfied or neutral about the intervention.

[13] Defined through patient dissatisfaction where at baseline, 95% were dissatisfied and at 5 years, 7.1% were dissatisfied.

[14] A total of 8.58% of patients underwent 11.22% of contrast swallows, 4.62% of dilatations, 7.91% of EGDs (esophagogastroduodenoscopy), 3.3% of pH testing and 0.66% of motility test mainly for diagnosis. Dilatations were done in 2.64% of patients for dysphagia.

Table A-2: MSAD: *Results from prospective registry with control group included for effectiveness*

	Riegler 2015 [22]
Country	Austria, Germany, Italy, United Kingdom
Sponsor	Torax Medical Inc.
Study design	Multi-centre prospective registry with control group (NCT01624506)
Intervention (I)	LP MSAD
Comparator (C)	LF
Number of pts (I vs. C)	249 (202 vs. 47)
Inclusion criteria	Advanced GERD with hiatal hernia >3 cm, Barrett's esophagus, motility disorder, or esophagitis grade C or D Moderate GERD with abnormal esophageal pH, reflux symptoms despite PPI use
Exclusion criteria	Known conditions that make it unlikely to complete a 3-year follow-up
Baseline patient characteristics (I vs. C)	
Mean age, yrs	46.6 vs. 52.8 (p=0.007)
Sex, female vs. male	(77 vs. 125) vs. (19 vs. 28) (p=0.866)
Moderate GERD, %	94 vs. 38.3
Mean BMI	25.7 vs. 26.1 (p=0.611)
Hiatal hernia >3 cm, %	1.6 vs. 45.7 (p<0.001)
Mean yrs of PPI use	6.3 vs. 5.1 (p=0.098)
Mean yrs with GERD	8.7 vs. 7.3 (p=0.086)
Barrett's esophagus, %	1.0 vs. 19.1 (p<0.001)
Esophagitis, %	
Grade A and Grade B	41.4 vs. 44.7 (p=0.212)
Grade C and Grade D	1 vs. 8.5 (p=0.212)
Follow-up time, yrs	1
Loss to follow-up, n	0
Median operative time, min	NA
Outcomes	
Efficacy (I vs. C)	
Median GERD HRQL score (pre-op./last follow-up)[15]	20/3 vs. 23/3.5 (p=0.177)
Heartburn waking from sleep, % (pre-op./last follow-up)	30.8/3.5 vs. 40/8.5 (p=0.229)
Regurgitation, % (pre-op./last follow-up)	58.2/3.1 vs. 60/13 (p=0.014)
Extra-esophageal symptoms (asthma, chronic cough, laryngitis), % (pre-op./last follow-up)	63.9/22.3 vs. 53.3/17.4 (p=0.552)
Discontinuation with medication (PPIs), % at last follow-up	81.8 vs. 63 (p=0.009)
Median DeMeester pH score[16] (pre-op./last follow-up)	NA
Hospital discharge, %	NA
Patient satisfaction, % (last follow-up)	91.8 vs 86.7

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

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

	Riegler 2015 [22]
Safety	
ADEs, SADEs % at last follow-up (I vs. C)	
Inability to belch	1.6 vs. 10.1 (p=0.007)
Inability to vomit	8.7 vs. 56.6 (p<0.001)
Excessive bloating	10 vs 31.9 (p<0.001)
Dysphagia	7 vs. 10.6 (p=0.373)
Intraoperative complications	1.49 vs. 2.13[17] (p=1.00)
Reoperation rate	4 vs. 6.4[18]
Hospital readmission	5.4 vs. 4.3
Device erosion	NA
Device migration	NA
Device malfunction/unlocking	NA
Device removal	4

[17] An injury to the pleura in both groups, minor bleeding in 2 patients in the MSDA group.

[18] 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.

Risk of bias tables

Internal validity of the included studies was judged by two independent researchers. In case of disagreement a third researcher was involved to solve the differences. A more detailed description of the criteria used to assess the internal validity of the individual study designs can be found in the Internal Manual of the LBI-HTA [33] and in the Guidelines of EUnetHTA [34, 35].

Table A-3: Risk of bias – study level (case series), see [36].

Study reference/ID	Bonavina 2013 [4]	Schwameis 2014 [25]	Smith 2014 [26]	Reynolds 2014 [24]	Ganz 2015 [23]	Riegler 2015 [22]
1. Is the hypothesis/aim/objective of the study stated clearly in the abstract, introduction, or methods section?	Yes	Yes	Yes	Yes	Yes	Yes
2. Are the characteristics of the participants included in the study described?	Yes	Yes	Yes	Partially reported	Yes	Yes
3. Were the cases collected in more than one centre?	No	No	No	Yes	Yes	Yes
4. Are the eligibility criteria (inclusion and exclusion criteria) for entry into the study explicit and appropriate?	Yes	Yes	Yes	Yes	Yes	Partially reported[19]
5. Were participants recruited consecutively?	No[20]	Yes	Unclear[21]	Yes	Unclear[22]	Yes
6. Did participants enter the study at similar point in the disease?	No	No	Unclear	Unclear	No	Unclear
7. Was the intervention clearly described in the study?	Yes	Yes	Yes	Yes	Yes	Yes
8. Were additional interventions (co-interventions) clearly reported in the study?	Yes	Yes	Yes	Yes	No	Yes
9. Are the outcome measures clearly defined in the introduction or methods section?	Yes	Yes	Yes	Yes	Yes	Yes
10. Were relevant outcomes appropriately measured with objective and/or subjective methods?	Yes	Yes	Yes	Yes	Yes	Yes
11. Were outcomes measured before and after intervention?	Yes	Yes	Yes	No	Yes	Yes
12. Were the statistical tests used to assess the relevant outcomes appropriate?	Yes	Yes	No	Yes	Yes	Yes
13. Was the length of follow-up reported?	Yes	Yes	Yes	Yes	Yes	Yes
14. Was the loss to follow-up reported?	Yes	Yes	Yes	Yes	Yes	Yes

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

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

[21] 150 patients were evaluated for device implant, 68 were implanted. The selection process is not detailed.

[22] 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).

Study reference/ID	Bonavina 2013 [4]	Schwameis 2014 [25]	Smith 2014 [26]	Reynolds 2014 [24]	Ganz 2015 [23]	Riegler 2015 [22]
15. Does the study provide estimates of the random variability in the data analysis of relevant outcomes?	No	Yes	No	No	Yes	Yes
16. Are adverse events reported?	Yes	Yes	Yes	Yes	Yes	Yes
17. Are the conclusions of the study supported by results?	Yes	Yes	Yes	No	Yes	No
18. Are both competing interest and source of support for the study reported?	Yes	No	No	No	Yes	Yes
Overall Risk of bias	High	High	High	High	High	Low

Applicability table

Table A-4: Summary table characterizing the applicability of a body of studies

Domain	Description of applicability of evidence
Population	Study population represents a narrow spectrum of GERD patients as predifined by the manufacturer and hence for the most part, the target population does not differ from the enrolled population. The inclusion criteria predominantly do not reflect severe refractory GERD with hiatal hernias >3 cm, motility disorders, Barrett's easophagus or grade C and D esophagitis, but only mild to moderate GERD with incomplete symptom control by PPIs.
Intervention	Insertion of a magnetic sphincter augmentation device (MSAD) through laparoscopic surgery (LINX® Reflux Management System).
Comparators	Standard surgical treatment of GERD: Nissen fundoplication, partial or Toupet fundoplication. However, there is a slight ambiguity as MSAD attempts to place itself into the "treatment gap" for which there is no comparator. It aims at patients who have persistant GERD, incomplete symptom control by PPIs, but whose condition is not severe enough to undergo any type of invasive fundoplication.
Outcomes	Clinical effectiveness outcomes reported in the registry study are GERD HRQL, heartburn waking from sleep, regurgitation, discontinuation with PPI medication, and extra-esophageal symptoms. Follow-up time was 1 yr and hence long-term effectiveness on GERD may not be assessed.Regardless, the outcomes measured do present the most important benefits. Safety outcomes that are most frequently reported in the six studies considered are post-operative dysphagia, inability to belch or vomit, intraoperative complications, device removal, erosion, and migration. Follow-up time ranged from 1 mo to 5 yrs and hence safety profile of MSAD on GERD may be assessed even though its comparative safety to LF cannot. The outcomes measured do present the most important health threats associated with the MSAD.
Setting	All of the studies included were either single-centre or multi-centre studies, with clinical centres based in Europe and the United States. Clinical settings were not described in all of the studies, but it is likely that all patients received-standard care at university hospitals or transplant centres. Thus, it can be assumed that the results reflect a wide spectrum of clinical routines both with regard to patient selection and treatment modalities and, therefore, that results are transferable to the Austrian setting. The surgeon's technical expertise likely determines the risk of local side effects. If introduced as a new treatment method in European hospitals, the treatment with MSAD will certainly be accompanied by a learning curve.

List of ongoing trials

Table A-5: List of ongoing trials of LINX® Reflux Management System

Identifier/Trial name	Patient population	Intervention	Comparison	Primary Outcome	Primary completion date	Sponsor
NCT02505945/ The CALIBER Study Randomized Controlled Trial of LINX Versus Double-Dose Proton Pump Inhibitor Therapy for Reflux Disease	Patients with GERD	LINX device	Omeprazole	% of subjects with resolution of the GERD symptom of interest in each arm (time frame: 6 mos)	October 2016	Torax Medical Inc.
NCT01940185/ A Post-Approval Study of the LINX® Reflux Management System	Patients with GERD	LINX device	-	Reduction of total GERD-HRQL score (time frame: 6 mos, 12 mos, and annually to 60 mos] Serious, device-related adverse events (time frame: 60 mos)	September 2019	Torax Medical Inc.
NCT02429830/ A Study of Reflux Management With the LINX® System for Gastroesophageal Reflux Disease After Laparoscopic Sleeve Gastrectomy	Patients who have previously undergone laparoscopic sleeve gastrectomy (LSG) for obesity and have GERD	LINX device	-	Change in GERD-HRQL score (time frame: 6 mos) Number of participants with serious complications Change in total distal acid exposure % of subjects with esophagitis	August 2017	Torax Medical Inc.

Literature search strategies

Search strategy for Cochrane

Search Name: Magnetic Implants for GERD Last Saved: 16/12/2015 12:12:38.569	
ID	Search
#1	MeSH descriptor: [Gastroesophageal Reflux] explode all trees
#2	"gastro*esophageal reflux" (Word variations have been searched)
#3	"gastro-esophageal reflux" (Word variations have been searched)
#4	GER:ti,ab,kw (Word variations have been searched)
#5	GERD:ti,ab,kw (Word variations have been searched)
#6	GORD:ti,ab,kw (Word variations have been searched)
#7	"esophageal sphincter" or "oesophageal sphincter"
#8	#1 or #2 or #3 or #4 or #5 or #6 or #7
#9	Sphincter Augmentation* (Word variations have been searched)
#10	MSA:ti,ab,kw (Word variations have been searched)
#11	MSAD:ti,ab,kw (Word variations have been searched)
#12	magnetic near (bead* or band* or ring or device*) (Word variations have been searched)
#13	MeSH descriptor: [Magnets] explode all trees
#14	MeSH descriptor: [Esophageal Sphincter, Lower] explode all trees
#15	esophageal sphincter near (device* or ring* or band* or bead*) (Word variations have been searched)
#16	(implant* or insert*) next (sphincter* or ring* or bead* or band* or device*) (Word variations have been searched)
#17	MeSH descriptor: [Prostheses and Implants] explode all trees
#18	MeSH descriptor: [Esophageal Sphincter, Lower] explode all trees
#19	esophageal sphincter* (Word variations have been searched)
#20	MeSH descriptor: [Esophagogastric Junction] explode all trees
#21	gastro*esophageal junction* (Word variations have been searched)
#22	gastro-esophageal junction* (Word variations have been searched)
#23	esophagogastric junction* (Word variations have been searched)
#24	esophago-gastric junction* (Word variations have been searched)
#25	oesophago-gastric junction* (Word variations have been searched)
#26	oesophagogastric junction* (Word variations have been searched)
#27	#18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26
#28	#17 and #27
#29	"reflux management" (Word variations have been searched)
#30	"antireflux management" (Word variations have been searched)
#31	"anti-reflux management" (Word variations have been searched)
#32	LINX (Word variations have been searched)
#33	#9 or #10 or #11 or #12 or #13 or #14 or #15 #16 or #28 or #29 or #30 or #31 or #32
#34	#8 and #33
71 Hits	

CRD Search Strategy

1	MeSH DESCRIPTOR Gastroesophageal Reflux EXPLODE ALL TREES
2	(gastro*esophageal reflux)
3	(gastro-esophageal reflux)
4	(gastro-oesophageal reflux)
5	(GER)
6	(GERD)
7	(GORD)
8	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7
9	(Magnetic Sphincter Augmentation*)
10	(MSA)
11	(MSAD)
12	(magnetic NEAR (bead* OR band* OR ring OR device*))
13	MeSH DESCRIPTOR Magnets EXPLODE ALL TREES
14	MeSH DESCRIPTOR Esophageal Sphincter, Lower EXPLODE ALL TREES WITH QUALIFIER SU
15	(esophageal NEAR (device* OR ring* OR band* OR bead*))
16	(oesophageal NEAR (device* OR ring* OR band* OR bead*))
17	((implant* OR insert*) NEAR (sphincter* OR ring* OR bead* OR band* OR device*))
18	MeSH DESCRIPTOR Prostheses and Implants EXPLODE ALL TREES
19	MeSH DESCRIPTOR Esophageal Sphincter, Lower EXPLODE ALL TREES
20	(esophageal sphincter*)
21	(oesophageal sphincter*)
22	MeSH DESCRIPTOR Esophagogastric Junction EXPLODE ALL TREES
23	(gastro*esophageal junction*)
24	(gastro-esophageal junction*)
25	(gastro-oesophageal junction*)
26	(gastro-oesophageal junction*)
27	(esophagogastric junction*)
28	(oesophagogastric junction*)
29	(oesophago-gastric junction*)
30	(esophago-gastric junction*)
31	#19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28
32	#18 AND #31
33	(reflux management)
34	(antireflux management)
35	(anti-reflux management)
36	(LINX)
37	#10 OR #12 OR #13 OR #16 OR #17 OR #32 OR #33 OR #36
38	#8 AND #37
6 Hits	

14.12.2015

Search strategy for Embase

No.	Query Results	Results	Results Date
#27	'gastroesophageal reflux'/exp OR 'gastroesophageal reflux' OR 'gastrooesophageal reflux' OR 'gastro-esophageal reflux' OR 'gastro-oesophageal reflux' OR ger:ab,ti OR gerd:ab,ti OR gord:ab,ti AND ('magnetic sphincter augmentation' OR msa:ab,ti OR msad:ab,ti OR magnetic NEAR/4 (bead* OR band* OR ring OR device*) OR ('magnet'/exp AND 'therapy'/lnk) OR 'anti reflux implant'/exp OR 'lower esophagus sphincter'/exp/dm_su OR 'esophageal sphincter' NEAR/7 (device* OR ring* OR band* OR bead*) OR 'oesophageal sphincter' NEAR/7 (device* OR ring* OR band* OR bead*) OR (implant* OR insert*) NEAR/4 (sphincter* OR ring* OR bead* OR band* OR device*) OR 'reflux management' OR 'antireflux management' OR linx) AND ('clinical trial'/de OR 'clinical trial (topic)'/de OR 'comparative effectiveness'/de OR 'comparative study'/de OR 'controlled clinical trial'/de OR 'controlled study'/de OR 'major clinical study'/de OR 'multicenter study'/de OR 'prospective study'/de OR 'randomized controlled trial'/de OR 'randomized controlled trial (topic)'/de) OR ('gastroesophageal reflux'/exp OR 'gastroesophageal reflux' OR 'gastrooesophageal reflux' OR 'gastro-esophageal reflux' OR 'gastro-oesophageal reflux' OR ger:ab,ti OR gerd:ab,ti OR gord:ab,ti AND ('magnetic sphincter augmentation' OR msa:ab,ti OR msad:ab,ti OR magnetic NEAR/4 (bead* OR band* OR ring OR device*) OR ('magnet'/exp AND 'therapy'/lnk) OR 'anti reflux implant'/exp OR 'lower esophagus sphincter'/exp/dm_su OR 'esophageal sphincter' NEAR/7 (device* OR ring* OR band* OR bead*) OR 'oesophageal sphincter' NEAR/7 (device* OR ring* OR band* OR bead*) OR (implant* OR insert*) NEAR/4 (sphincter* OR ring* OR bead* OR band* OR device*) OR 'reflux management' OR 'antireflux management' OR linx) AND ([cochrane review]/lim OR [systematic review]/lim OR [controlled clinical trial]/lim OR [randomized controlled trial]/lim OR [meta analysis]/lim))	104	14 Dec 2015
#26	'gastroesophageal reflux'/exp OR 'gastroesophageal reflux' OR 'gastrooesophageal reflux' OR 'gastro-esophageal reflux' OR 'gastro-oesophageal reflux' OR ger:ab,ti OR gerd:ab,ti OR gord:ab,ti AND ('magnetic sphincter augmentation' OR msa:ab,ti OR msad:ab,ti OR magnetic NEAR/4 (bead* OR band* OR ring OR device*) OR ('magnet'/exp AND 'therapy'/lnk) OR 'anti reflux implant'/exp OR 'lower esophagus sphincter'/exp/dm_su OR 'esophageal sphincter' NEAR/7 (device* OR ring* OR band* OR bead*) OR 'oesophageal sphincter' NEAR/7 (device* OR ring* OR band* OR bead*) OR (implant* OR insert*) NEAR/4 (sphincter* OR ring* OR bead* OR band* OR device*) OR 'reflux management' OR 'antireflux management' OR linx) AND ([cochrane review]/lim OR [systematic review]/lim OR [controlled clinical trial]/lim OR [randomized controlled trial]/lim OR [meta analysis]/lim)	15	14 Dec 2015
#25	'gastroesophageal reflux'/exp OR 'gastroesophageal reflux' OR 'gastrooesophageal reflux' OR 'gastro-esophageal reflux' OR 'gastro-oesophageal reflux' OR ger:ab,ti OR gerd:ab,ti OR gord:ab,ti AND ('magnetic sphincter augmentation' OR msa:ab,ti OR msad:ab,ti OR magnetic NEAR/4 (bead* OR band* OR ring OR device*) OR ('magnet'/exp AND 'therapy'/lnk) OR 'anti reflux implant'/exp OR 'lower esophagus sphincter'/exp/dm_su OR 'esophageal sphincter' NEAR/7 (device* OR ring* OR band* OR bead*) OR 'oesophageal sphincter' NEAR/7 (device* OR ring* OR band* OR bead*) OR (implant* OR insert*) NEAR/4 (sphincter* OR ring* OR bead* OR band* OR device*) OR 'reflux management' OR 'antireflux management' OR linx) AND ('clinical trial'/de OR 'clinical trial (topic)'/de OR 'comparative effectiveness'/de OR 'comparative study'/de OR 'controlled clinical trial'/de OR 'controlled study'/de OR 'major clinical study'/de OR 'multicenter study'/de OR 'prospective study'/de OR 'randomized controlled trial'/de OR'randomized controlled trial (topic)'/de)	104	14 Dec 2015
#24	'gastroesophageal reflux'/exp OR 'gastroesophageal reflux' OR 'gastrooesophageal reflux' OR 'gastro-esophageal reflux' OR 'gastro-oesophageal reflux' OR ger:ab,ti OR gerd:ab,ti OR gord:ab,ti AND ('magnetic sphincter augmentation' OR msa:ab,ti OR msad:ab,ti OR magnetic NEAR/4 (bead* OR band* OR ring OR device*) OR ('magnet'/exp AND 'therapy'/lnk) OR 'anti reflux implant'/exp OR 'lower esophagus sphincter'/exp/dm_su OR 'esophageal sphincter' NEAR/7 (device* OR ring* OR band* OR bead*) OR 'oesophageal sphincter' NEAR/7 (device* OR ring* OR band* OR bead*) OR (implant* OR insert*) NEAR/4 (sphincter* OR ring* OR bead* OR band* OR device*) OR 'reflux management' OR 'antireflux management' OR linx)	392	14 Dec 2015
#23	'magnetic sphincter augmentation' OR msa:ab,ti OR msad:ab,ti OR magnetic NEAR/4 (bead* OR band* OR ring OR device*) OR ('magnet'/exp AND 'therapy'/lnk) OR 'anti reflux implant'/exp OR 'lower esophagus sphincter'/exp/dm_su OR 'esophageal sphincter' NEAR/7 (device* OR ring* OR band* OR bead*) OR 'oesophageal sphincter' NEAR/7 (device* OR ring* OR band* OR bead*) OR (implant* OR insert*) NEAR/4 (sphincter* OR ring* OR bead* OR band* OR device*) OR 'reflux management' OR 'antireflux management' OR linx	52,993	14 Dec 2015

#22	linx	99	14 Dec 2015
#21	'antireflux management'	7	14 Dec 2015
#20	'reflux management'	75	14 Dec 2015
#19	(implant* OR insert*) NEAR/4 (sphincter* OR ring* OR bead* OR band* OR device*)	35,158	14 Dec 2015
#18	'oesophageal sphincter' NEAR/7 (device* OR ring* OR band* OR bead*)	15	14 Dec 2015
#17	'esophageal sphincter' NEAR/7 (device* OR ring* OR band* OR bead*)	73	14 Dec 2015
#16	'lower esophagus sphincter'/exp/dm_su	385	14 Dec 2015
#15	'anti reflux implant'/exp	35	14 Dec 2015
#14	'magnet'/exp AND 'therapy'/lnk	276	14 Dec 2015
#13	magnetic NEAR/4 (bead* OR band* OR ring OR device*)	11,732	14 Dec 2015
#12	msad:ab,ti	66	14 Dec 2015
#11	msa:ab,ti	5,559	14 Dec 2015
#10	'magnetic sphincter augmentation'	45	14 Dec 2015
#9	'gastroesophageal reflux'/exp OR 'gastroesophageal reflux' OR 'gastrooesophageal reflux' OR 'gastro-esophageal reflux' OR'gastro-oesophageal reflux' OR ger:ab,ti OR gerd:ab,ti OR gord:ab,ti	54,873	14 Dec 2015
#8	gord:ab,ti	1,030	14 Dec 2015
#7	gerd:ab,ti	11,163	14 Dec 2015
#6	ger:ab,ti	3,902	14 Dec 2015
#5	'gastro-oesophageal reflux'	4,729	14 Dec 2015
#4	'gastro-esophageal reflux'	2,355	14 Dec 2015
#3	'gastrooesophageal reflux'	501	14 Dec 2015
#2	'gastroesophageal reflux'	44,392	14 Dec 2015
#1	'gastroesophageal reflux'/exp	48,258	14 Dec 2015

Search strategy for Medline

Database: Ovid MEDLINE(R) <1946 to November Week 3 2015>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <December 10, 2015>, Ovid MEDLINE(R) Daily Update <November 18, 2015>, Ovid OLDMEDLINE(R) <1946 to 1965>	
Search Strategy:	
1	exp Gastroesophageal Reflux/(23190)
2	gastro?esophageal reflux.mp. (27494)
3	gastro-?esophageal reflux.mp. (1293)
4	GER.mp. (3077)
5	GERD.mp. (6391)
6	GORD.mp. (719)
7	1 or 2 or 3 or 4 or 5 or 6 (30135)
8	Magnetic Sphincter Augmentation*.mp. (24)
9	MSA.mp. (4137)
10	MSAD.mp. (48)
11	(magnetic adj10 (bead* or band* or ring or device*)).mp. (8998)
12	exp Magnets/(5405)
13	"Therapeutic Use".fs. (1932854)
14	12 and 13 (258)
15	exp *Esophageal Sphincter, Lower/su (139)
16	(esophageal sphincter adj10 (device* or ring* or band* or bead*)).mp. (58)
17	(oesophageal sphincter adj10 (device* or ring* or band* or bead*)).mp. (14)

18	((implant* or insert*) adj10 (sphincter* or ring* or bead* or band* or device*)).mp. (30855)
19	exp "Prostheses and Implants"/(418917)
20	exp Esophageal Sphincter, Lower/(816)
21	esophageal sphincter*.mp. (5195)
22	oesophageal sphincter*.mp. (1215)
23	exp Esophagogastric Junction/(7352)
24	gastro?esophageal junction*.mp. (2029)
25	gastro-?esophageal junction*.mp. (194)
26	esophagogastric junction*.mp. (7238)
27	esophago-gastric junction*.mp. (171)
28	oesophagogastric junction*.mp. (223)
29	oesophago-gastric junction*.mp. (84)
30	20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 (12593)
31	19 and 30 (333)
32	reflux management.mp. (45)
33	antireflux management.mp. (5)
34	8 or 9 or 10 or 11 or 14 or 15 or 16 or 17 or 18 or 31 or 32 or 33 (44446)
35	7 and 34 (272)
36	((randomized controlled trial or controlled clinical trial).pt. or randomi#ed.ab. or placebo.ab. or drug therapy.fs. or randomly.ab. or trial.ab. or groups.ab.) not (exp animals/not humans.sh.) (3213876)
37	(((comprehensive* or integrative or systematic*) adj3 (bibliographic* or review* or literature)) or (meta-analy* or metaanaly* or "research synthesis" or ((information or data) adj3 synthesis) or (data adj2 extract*))).ti,ab. or (cinahl or (cochrane adj3 trial*) or embase or medline or psyclit or (psycinfo not "psycinfo database") or pubmed or scopus or "sociological abstracts" or "web of science").ab. or ("cochrane database of systematic reviews" or evidence report technology assessment or evidence report technology assessment summary).jn. or Evidence Report: Technology Assessment*.jn. or ((review adj5 (rationale or evidence)).ti,ab. and review.pt.) or meta-analysis as topic/or Meta-Analysis.pt. (259207)
38	36 or 37 (3371568)
39	35 and 38 (67)
40	remove duplicates from 39 (66)

11.12.2015