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Endoscopic plication therapy in patients with gastroesophageal reflux disease (GERD)

Systematic Review

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Content

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List of abbreviations

ACG ..... American College of Gastroenterology
AEs ..... Adverse events
AWMF ..... Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften
BE..... Barrett's oesophagus
BMI ..... Body mass index
C ..... Control group
CRD ..... Centre for Review and Dissemination
DARE..... The Database of Abstracts of Reviews of Effects
GEJ ..... gastro-oesophageal junction
GERD ..... gastroesophageal reflux disease
GERD-HRQL..... GERD-Health Related Quality of Life Questionnaire
GI..... Gastrointestinal
GIQLI ..... Gastrointestinal Quality of Life Index
GRADE..... Grading of Recommendations Assessment, Development and Evaluation
H2RAs..... histamine 2 receptor antagonist
HRQoL ..... Health-related quality of life
HTA ..... Health Technology Assessment
IG..... Intervention group/Interventionsgruppe
IHE..... International Health Economics
INAHTA ..... International Network of Agencies for Health Technology Assessment
KG ..... Kontrollgruppe
LES..... Lower oesophageal sphincter
LQ ..... Lebensqualität
NERD ..... Non-erosive reflux disease
NRCTs ..... Non-randomised controlled studies
Pat. ..... Patient*innen
PPI..... Proton pump inhibitor
QoL ..... Quality of life
QoLRAD..... Quality of Life in Reflux and Dyspepsia
RCTs ..... Randomised controlled studies
RDQ ..... Reflux Disease Questionnaire
RoB..... Risk of bias
ROBINS-I ..... Risk Of Bias In Non-randomized Studies of Interventions assessment tool
SAEs ..... Serious adverse events
SNRIs..... Serotonin-norepinephrine reuptake inhibitors
SoF ..... Summary of findings
ss..... Statistical significant/statistisch signifikant
SSRIs..... Selective serotonin reuptake inhibitors
TIF ..... Transoral Incisionless Fundoplication
TLESR ..... Transient lower oesophageal sphincter relaxation
US..... United States

Executive Summary

Introduction

Health problem

Gastroesophageal reflux disease (GERD) is defined as a condition in which stomach contents rise up into the oesophagus resulting in troublesome symptoms and/or complications. It is a common health problem in the Western World and affects around 10-20% of the population. Although a lot of patients respond well to proton pump inhibitors (PPIs), about 42% of GERD patients are dissatisfied with their treatment and are thereby potential candidates for surgical therapy.

GERD: stomach contents from the stomach into the oesophagus

prevalence 10-20%

Description of technology

Alternative endoscopic approaches for the treatment of GERD have evolved over the last two decades. Nowadays, they are a second-line treatment option for chronic GERD patients with the main aim to reduce the lifelong use of PPI medication or to avoid laparoscopic surgery (e.g. fundoplication). Endoscopic therapy claims to be less invasive as well as safer compared to surgical fundoplication and should result in shorter periods of hospitalisation.

endoscopic plication: 2nd line treatment option for chronic GERD patients

In general, endoscopic therapies can be divided into radiofrequency heat treatment, antireflux resection of the gastroesophageal junction (GEJ) mucosa by electrocoagulation and endoscopic plication therapies. The technologies of interest in the present report are endoscopic plication systems, of which the following three devices are currently available on the market: ultrasound endoscopic endostapler (MUSE™), transoral incisionless fundoplication (EsophyXZ®) and endoscopic full-thickness plication (GERDx™).

3 devices under review: MUSE™, EsophyXZ®, GERDx™

Research question

Is endoscopic plication in comparison to standard care (e.g., PPIs or laparoscopic surgical treatments) in patients with chronic GERD more effective and equally safe or equally effective and safer concerning improvements in health-related quality of life (HRQoL) as well as post-operative side effects and serious adverse events (SAEs)?

research question

Methods

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

systematic literature search in 5 databases

Domain effectiveness

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

***crucial* outcomes for effectiveness ...**

Domain safety

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

... and safety

Results

Available evidence

6 RCTs, 1 NRCT, 1 prospective single-arm study included

A total of six randomised controlled studies (RCTs), one non-randomised controlled study (NRCT) as well as one prospective single-arm trial were eligible for inclusion in the present report. A cut-off of 100 or more patients was defined as an inclusion criterion for prospective single-arm studies. Overall, data on clinical effectiveness and safety was evaluated in 423 and 580 patients, respectively.

Clinical effectiveness

HRQoL:

statistically significant (ss) HRQoL improvement in the intervention group (IG) (1 RCT)

heartburn & regurgitation:

ss improvement in the IG (1 RCT)

To assess the clinical effectiveness of endoscopic plication therapy, the six RCTs and the NRCT were considered. Concerning the a priori defined *crucial* clinical effectiveness outcomes, a statistically significant improvement in HRQoL scores ($p<0.001$) in the intervention group (EsophyX$_2^{®}$) compared to the control group (PPI therapy) could only be shown in one RCT. Two other RCTs reported no statistically significant differences between study groups. In contrast, the NRCT showed a statistically significant difference ($p=0.016$) between treatment groups but favouring the control arm (laparoscopic surgery). Considering the crucial outcomes of heartburn and regurgitation symptoms, one RCT reported statistically significant improvements in the intervention group compared to the control group (laparoscopic surgery) after three (heartburn: $p<0.0001$, regurgitation: $p=0.005$) and twelve (heartburn: $p=0.01$, regurgitation: $p<0.05$) months follow-up.

Safety

safety profile:

ss improvement in bloating in the IG over time (1 RCT)

more pts. with SAEs in the CG? (1 RCT)

1 death (unclear cause of death) & 22 re-surgeries after endoscopic plication therapy

Concerning the safety profile, seven studies investigating all three devices of interest reported any AEs. No statistically significant differences could be observed between study groups. One RCT showed a statistically significant improvement in bloating symptoms in the intervention group over time. However, the NRCT noted a shorter hospitalisation period in the control group (laparoscopic surgery) compared to the intervention group. Considering SAEs in comparative trials, no differences between study groups could be observed, except for one RCT that showed higher percentages of patients in the control group suffering from moderate to SAEs. In the case of the prospective single-arm study, 18 patients had to stay longer in the hospital or were re-admitted due to SAEs. Death was reported in one RCT, where one patient died in the intervention group eleven months after endoscopic surgery. Across all studies, re-surgeries were required in 26 patients, of which 22 were necessary after endoscopic plication therapy.

Upcoming evidence

1 ongoing RCT & 2 ongoing prospective single-arm trials

Currently, there are one ongoing RCT (NCT03322553) and two ongoing prospective single-arm studies (NCT01118585 & ChiCTR2000036041). However, these studies will not provide evidence for more than twelve months of follow-up, and thus, will not fill the current gap of long-term evidence. Nevertheless, the ongoing studies will supplement the currently available evidence with information on the latest available device generations (e.g., GERDx^{TM}).

Reimbursement

endoscopic plication therapy not reimbursed in Austria

At this point, endoscopic plication therapy is not refunded by the Austrian health care system. However, endoscopic plication therapy via GERDx™ is currently reimbursed in Germany, where the costs associated with an endoscopic surgery are around € 5,360 including the price of the device and the operation procedure (e.g., facilities, staff, anaesthesia, hospital stay).

Discussion & conclusion

no solid conclusions possible considering the clinical effectiveness & safety of endoscopic plication therapy

high-quality evidence including large sample sizes and long-term follow-up needed in the future

Overall, no conclusion can be made whether endoscopic plication leads to better outcomes than the investigated comparators (laparoscopic surgery, PPI therapy and/or a sham intervention) in chronic GERD patients, since HRQoL results were contradicting. Also, no robust conclusions can be made regarding the safety of endoscopic plication as no differences in the safety profile of endoscopic plication therapy and respective comparators could be identified. Indeed, the current safety data is lacking quality as well as degree of detail. Altogether, the included studies showed an overall very low quality of evidence. Therefore, higher quality of evidence including larger RCTs and/or NRCTs with longer follow-up periods are needed. In particular, currently available generations of devices (e.g., GERDx™) should be investigated in the near future.

Zusammenfassung

Einleitung

Indikation und therapeutisches Ziel

GERD: Reflux aus dem Magen in die Speiseröhre

Prävalenz 10-20 %

42 % unzufrieden mit medikamentöser Therapie

Gastroösophagealer Reflux (GERD) ist gekennzeichnet durch den Rückfluss von Mageninhalt in die Speiseröhre. Dies führt zu unangenehmen Symptomen bzw. Komplikationen bei den Patient*innen. In der westlichen Welt zählt GERD zu einem der häufigsten Gesundheitsprobleme und betrifft in etwa 10-20 % der Bevölkerung. Obwohl die Mehrheit der Patient*innen auf eine Protonenpumpeninhibitoren (PPI-)Therapie ansprechen, sind ungefähr 42 % aller GERD Patient*innen mit der Behandlung unzufrieden und somit potenzielle Kandidat*innen für eine chirurgische Behandlung. Aufgrund der steigenden Inzidenzzahlen führt GERD unter anderem zu einer zunehmenden Inanspruchnahme von Ressourcen im Gesundheitswesen (z. B. Arztbesuche, Krankenhausaufenthalte, Medikamente etc.). Als größte Belastung für die GERD-Patient*innen wird die Beeinträchtigung der Lebensqualität (QoL) durch Symptome wie Sodbrennen, extraösophageale Manifestationen oder nicht-kardiale Brustschmerzen wahrgenommen.

Beschreibung der Technologie

endoskopische Eingriffe: Zweitlinientherapie-option für chronische GERD-Patient*innen

Ziel: Reduktion der Einnahme von PPI-Medikamenten & Fundoplikatio-Eingriffen

In den letzten zwei Jahrzenten kam es zunehmend zu Entwicklungen von alternativen endoskopischen Ansätzen zur Behandlung von GERD. Heutzutage wird der endoskopische Eingriff häufig als Zweitlinientherapie eingesetzt. Dazu zählen vor allem Patient*innen, bei denen eine medikamentöse Behandlung mit PPI keine vollständige Symptomlinderung erzielt oder Symptome trotz anfänglich erfolgreicher PPI-Behandlung Wiederauftreten. Ebenso wird ein endoskopischer Eingriff auch für all jene Patient*innen empfohlen, die eine lebenslange medikamentöse Behandlung ablehnen oder unter den Nebenwirkungen der PPI-Therapie leiden. Das Hauptziel von endoskopischen GERD-Therapien ist daher, sowohl die lebenslange Einnahme von PPI-Medikamenten zu reduzieren, als auch einen laparoskopischen Eingriff (z. B.: Fundoplikatio) zu vermeiden. Im Allgemeinen gilt der endoskopische Eingriff im Vergleich zur Fundoplikatio als weniger invasiv und sicherer und sollte die Krankenhausaufenthalte verkürzen.

3 Devices für die endoskopische Plikatobehandlung am Mark:

MUSE™, EsophyXZ®, GERDx™

Generell werden endoskopische GERD-Eingriffe in die Radiofrequenz-Wärmebehandlung, die Antireflux-Resektion des gastroösophagealen Übergangs (GEJ) mittels Elektrokoagulation, sowie die endoskopischen Plikatiotherapien unterteilt. Der Fokus des vorliegenden Berichts liegt auf den endoskopischen Plikationssysteme, wovon derzeit folgende drei Devices auf dem Markt erhältlich sind: ultraschallfähiger endoskopischer Endostapler (MUSE™), transorale inzisionslose Fundoplikatio (EsophyXZ®) und endoskopische „full-thickness“ Plikatio (GERDx™).

Fragestellung

Fragestellung

Ist die endoskopische Plikatio im Vergleich zur Standardbehandlung (z. B. PPI-Medikation oder laparoskopische chirurgische Behandlung) bei Patient*innen mit chronischem GERD effektiver und gleich sicher oder gleich effektiv und sicherer in Bezug auf die Verbesserung der gesundheitsbezogenen Lebensqualität (HRQoL), postoperativer Nebenwirkungen und schwerwiegender unerwünschter Ereignisse (SAEs)?

Methode

systematische Literaturrusche in 5 Datenbanken

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

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

Bewertung der Evidenzqualität nach dem GRADE-Schema

Zusätzlich wurde eine Handsuche durchgeführt und der Hersteller kontaktiert. Die Studienauswahl erfolgte unabhängig durch zwei Autorinnen (SW, NG). Studiendaten wurden von drei Autorinnen extrahiert und von den jeweils anderen kontrolliert. Die Bewertung der Qualität der Evidenz nach GRADE (Grading of Recommendations Assessment, Development and Evaluation) wurde von zwei Autor*innen vorgenommen. Zusätzlich wurde das Verzerrungsrisiko der Studien bewertet.

Klinische Effektivität

***entscheidende* Endpunkte für die Wirksamkeit ...**

Zur Bewertung der klinischen Effektivität von endoskopischen Eingriffen mittels Picatorsystemen wurden die folgenden Endpunkte als *entscheidend* für eine Empfehlung eingestuft: HRQoL, Sodbrennen and Regurgitation Score.

Sicherheit

... und Sicherheit

Zur Bewertung der Sicherheit von endoskopischen Eingriffen mittels Plicatorsystemen wurden die folgenden *entscheidenden* Endpunkte für eine Empfehlung herangezogen: alle unerwünschten Nebenwirkungen (AEs), SAEs, Tod, und Re-Operationsrate.

Ergebnisse

Verfügbare Evidenz

8 eingeschlossene Studien: 6 RCTs, 1 NRCT, 1 prospektive (prosp.) einarmige Studie

Wirksamkeit: n=423; Interventionsgruppe (IG): 267 vs Kontrollgruppe (KG): 186

Sicherheit: n=580

Insgesamt erfüllten acht Studien die vorab definierten Einschlusskriterien. Zu zwei von den acht Studien konnten weitere fünf Publikationen mit unterschiedlichen Nachbeobachtungszeiträumen identifiziert werden. Sechs der acht Studien waren randomisierte kontrollierte Studien (RCTs). Zusätzlich wurde eine nicht-randomisierte kontrollierte Studie (NRCT) und eine prospektive einarmige Studie identifiziert. Für den Einschluss von prospektiven einarmigen Studien wurde ein Cut-off von mindestens 100 Patient*innen definiert. Für die Analyse der Wirksamkeit wurden lediglich die komparativen Studien herangezogen, wodurch die Daten von insgesamt 423 Patient*innen (Interventionsgruppe [IG]: 267 versus Kontrollgruppe [KG]: 186) ausgewertet werden konnten. Für die Sicherheitsanalyse wurde zusätzlich eine prospektive einarmige Studie mit insgesamt 580 Patient* innen miteinbezogen.

Klinische Wirksamkeit

7 komparative Studien (6 RCTs & 1 NRCT): → 2 Crossoverstudien

3 verschiedene Komparatoren

unterschiedliche Messinstrumente für die Erhebung von QoL & Symptomen

Sieben vergleichende Studien wurden für die Bewertung der Wirksamkeit herangezogen. In zwei der sieben Studien war ein Crossover nach sechs Monaten Follow-up von der Kontrollgruppe in die Interventionsgruppe erlaubt. Aufgrund des daraus resultierenden einarmigen Studiendesign-Charakters wurden alle nach dem Crossover berichteten Ergebnisse ausschließlich für die Sicherheitsanalyse herangezogen. Die Komparatoren in den kontrollierten Studien waren die laparoskopische Operation, PPI-Therapie und/oder eine Scheinintervention. Insgesamt wurden alle drei verfügbaren endoskopischen Plicatordevices in den eingeschlossenen Studien untersucht, wobei unterschiedliche Devicegenerationen angewendet wurden. Sowohl für die Evaluierung des Outcomes HRQoL (Fragebögen: GERD-HRQL, GIQLI, QoLRAD) als auch für die Bewertung von Sodbrennen- und Regurgitationsymptomen (Fragebögen: GERD-HRQL, RDQ, nicht-validierter Score) wurden verschiedene Tools angewendet.

HRQoL: 6 Studien

ss Verbesserungen in der IG: Baseline vs Follow-up (4 RCTs)

ss Verbesserungen in der IG vs KG (1 RCT)

Der für die Empfehlung *entscheidende* Endpunkt HRQoL wurde in sechs vergleichenden Studien untersucht. Diese sechs Studien umfassten alle drei am Markt erhältlichen endoskopischen Devices, jedoch unterschiedliche Devicegenerationen. In vier RCTs kam es in der Interventionsgruppe zu statistisch signifikanten HRQoL-Verbesserungen zum Ende des Follow-ups. Jedoch lediglich ein RCT zeigte eine statistisch signifikante Verbesserung der HRQoL-Scores ($p<0{,}001$) in der Interventionsgruppe (EsophyX2®) im Vergleich zur Kontrollgruppe (PPI-Therapie), während zwei weitere RCTs keine statistisch signifikanten Unterschiede zwischen den Studiengruppen berichteten (The Plicator™/NDO Plicator vs. laparoskopische Operation). Im Gegensatz dazu zeigte das NRCT einen statistisch signifikanten Unterschied ($p=0{,}016$) zwischen den Behandlungsgruppen (laparoskopische Chirurgie vs. SRS™) zugunsten des Kontrollarms.

Sodbrennen & Regurgitation: 3 RCTs

ss Verbesserungen in IG: Baseline vs. Follow-up (2 RCTs)

ss Verbesserung in IG vs KG (1 RCT)

Sodbrennen- und Regurgitationsymptome wurden in drei RCTs untersucht. Diese RCTs verwendeten welche die folgenden Devices für die endoskopische Behandlung: EsophyX®, EsophyX2®, NDO Plicator. Sie zeigten eine Verbesserung der Symptome im Verlauf der Studie sowohl für Sodbrennen als auch Regurgitation in der Interventionsgruppe. In zwei der drei RCTs waren die Verbesserungen in der Interventionsgruppe statistisch signifikant ($p<0{,}001$). Im Gegensatz dazu, berichtete das dritte RCT eine statistisch signifikante Symptomverbesserung bezüglich Regurgitation und Sodbrennen zu Follow-up-Ende in der Kontrollgruppe (Scheinintervention + PPI-Medikation). Darüber hinaus wurde eine statistisch signifikante Verbesserung in der Interventionsgruppe (NDO Plicator) im Vergleich zur Kontrollgruppe (laparoskopische Operation) nach drei (Sodbrennen: $p<0{,}0001$, Regurgitation: $p=0{,}005$) und zwölf (Sodbrennen: $p=0{,}01$, Regurgitation: $p<0{,}05$) Monaten in einem der drei RCTs festgestellt.

Sicherheit

Sicherheitsprofil

Insgesamt berichteten sieben Studien (fünf RCTs, ein NRCT und eine prospektive einarmige Studie) über AEs. Die sieben Studien umfassten alle drei am Markt erhältlichen endoskopischen Devices. Generell konnten keine statistisch signifikanten Unterschiede zwischen den Studiengruppen bezüglich den AEs festgestellt werden, mit Ausnahme von einem RCT, dass eine statistisch signifikante Verbesserung der Blähungssymptome in der Interventionsgruppe über den Studienverlauf aufzeigte. Im NRCT wurde hingegen eine kürzere Hospitalisierungsdauer in der Kontrollgruppe (laparoskopische Operation) im Vergleich zur Interventionsgruppe (SRS™) festgestellt. Darüber hinaus berichteten fünf Studien über SAEs. Die Vergleichsstudien zeigten keine Unterschiede zwischen den Studiengruppen bezüglich den SAEs, mit Ausnahme von einer Studie, die einen höheren Prozentsatz an Patient*innen mit moderaten bis SAEs in der Interventionsgruppe aufwies. In der prospektiven einarmigen Studie mussten 18 Patient*innen aufgrund von SAEs länger im Krankenhaus bleiben oder erneut aufgenommen werden. Hinsichtlich der berichteten Todesfälle verstarb in einem RCT elf Monate nach dem endoskopischen Eingriff ein/e Patient*in. Die Todesursache konnte jedoch nicht geklärt werden. Außerdem waren bei insgesamt 26 Patient*innen Re-Operationen notwendig, wovon 22 Re-operationen nach einem endoskopischen Plikatioeingriff erfolgten.

Nebenwirkungen: 7 Studien →

Verbesserung von Blähsymptomen jedoch längere Hospitalisierung nach endoskopischer Plikatio in IG

1 Todesfall in IG, aber Todesursache unklar

22 Re-Operationen nach endoskopischer Plikatio

Laufende Studien

1 laufendes RCT zu GERDx™ (Beobachtungszeitraum <12 Monaten & n<100)

Derzeit gibt es ein laufendes RCT (NCT03322553), das weitere Evidenz hinsichtlich der Wirksamkeit und Sicherheit von endoskopischer Plikatio mittels GERDx™ im Vergleich zu einer Scheinintervention liefern wird. Die untersuchte Studienkohorte umfasst weniger als 100 Patient*innen und eine Nachbeobachtungszeit von unter zwölf Monaten. Somit kann durch diese Studie die aktuelle Evidenzlücke von großen (n>100) und längerfristigen komparativen Studien nicht gefüllt werden. Nichtsdestotrotz untersucht das laufende RCT das neueste verfügbare Devise des ehemaligen Plicator™ Devices, wodurch neue Informationen zu der aktuellsten Technik GERDx™ verfügbar werden.

2 pros. einarmige Studien zu MUSE™ & EsophyX®

Des Weiteren konnten zwei laufende prospektive einarmige Studien zu EsophyX® (NCT01118585) und MUSE™ (ChiCTR2000036041) identifiziert werden. In der EsophyX®-Studie werden in etwa 270 Patient*innen eingeschlossen, wodurch die endoskopische Plikatio in einer größeren nicht-komparativen Studie analysiert wird als in der derzeit vorliegenden Evidenz. Darüber hinaus werden möglicherweise weitere Erkenntnisse über die neuesten Generationen des MUSE™ Devices zugänglich.

Kostenerstattung

endoskopische Plikatio derzeit in Österreich nicht erstattet

Zum jetzigen Zeitpunkt wird das endoskopische Plikatioverfahren in Österreich nicht erstattet. Allerdings wird die endoskopische Plikatio mittels GERDx™ derzeit in Deutschland refundiert. Dort belaufen sich die mit einem Eingriff verbundenen Kosten auf zirka. 5.360 € einschließlich des Preises für das Device und das Operationsverfahre (z. B. Ausstattung, Personal, Anästhesie, Krankenhausaufenthalt).

Diskussion und Fazit

aktuell keine klare Aussage zur Wirksamkeit und Sicherheit von endoskopischer Plikatio möglich

Aufgrund der widersprüchlichen HRQoL-Ergebnisse kann keine Aussage darüber getroffen werden, ob die endoskopische Plikatio bei chronischen GERD-Patient*innen zu besseren Ergebnissen führt als die untersuchten Komparatoren (laparoskopische Operation, PPI-Therapie und/oder einer Scheinintervention). Darüber hinaus kann auch keine klare Aussage hinsichtlich der Sicherheit berichtet werden, da keine Unterschiede im Sicherheitsprofil der endoskopischen Plikatiotherapie im Vergleich zu den jeweiligen Komparatoren identifiziert wurden. Zudem ist die Qualität und der Detailgrad der vorliegenden Sicherheitsdaten unzureichend. Insgesamt wiesen die eingeschlossenen Studien eine sehr niedrige Qualität der Evidenz auf. Aus diesem Grund wird in Zukunft höherwertige Evidenz, z. B. RCTs und/oder NRCTs mit einer größeren Stichprobe und längeren Nachbeobachtungszeiten erforderlich sein. Im Speziellen sollten die derzeit neuesten verfügbaren Devicegenerationen (z. B. GERDx^{TM}) untersucht werden.

qualitative hochwertige Studien mit längerer Nachbeobachtungszeit und mehr Patient*innen notwendig

Empfehlung

Aufnahme in Leistungskatalog vorerst nicht empfohlen

Aufgrund von methodischen Defiziten lässt die vorhandene Evidenz keine Rückschlüsse zu, ob die endoskopische Plikatio bei chronischen GERD-Patient*innen mindestens gleich wirksam und genauso sicher ist wie die Komparatoren laparoskopische Operation, PPI-Medikation und/oder eine Scheinintervention. Aus diesem Grund wird das endoskopische Verfahren mittels Plikatorsystemen vorerst nicht für die Aufnahme in den österreichischen Krankenhausleistungskatalog empfohlen.

Re-Evaluierung frühestens nach 2023 empfohlen

Eine Re-Evaluierung wird frühestens 2023 empfohlen, nachdem die Ergebnisse des laufenden RCTs zur neuesten verfügbaren Devicegeneration (GERDx^{TM}) veröffentlicht und eventuell adäquate zusätzliche Studien zugänglich sind.

1 Background

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

Endoscopic therapy is used in patients with gastroesophageal reflux disease (GERD), which is defined according to the Montreal consensus as a condition that develops when the reflux of stomach contents causes troublesome symptoms and/or complications. Symptoms are considered troublesome if they adversely affect an individual's well-being [1]. Endoscopic antireflux therapy is a second-line treatment for GERD patients in whom proton pump inhibitor (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 [2]. The main aim of endoscopic plication therapy is to reduce the use of long-term PPI and fundoplication, by endoluminal plication or suture of the gastro-oesophageal junction (GEJ) [2, 3].[2, 3]

GERD: Reflux aus dem Magen in die Speiseröhre

endoskopische Plikatio: 2. Linien Behandlung für chronische GERD-Pat nach Protonenpumpen-inhibitoren (PPI) Therapie

From a surgical perspective, GERD is the failure of the antireflux barrier, which, when functioning improperly, allows abnormal reflux of gastric contents into the oesophagus. It is a mechanical disorder caused by a defective lower oesophageal sphincter (LES), a gastric emptying disorder, or failed oesophageal peristalsis. The abnormalities result in a spectrum of disease ranging from symptoms only, such as heartburn, to oesophageal tissue damage with or without subsequent complications, including malignancy or airway disease [1].[3]

Symptome: Sodbrennen, Aufstoßen, Magenschmerzen

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, and expanding proportion of obese individuals are significant risk factors for GERD [1, 4]. Factors that may contribute to the association of obesity and GERD include, increased intra-abdominal pressure, a higher prevalence of hiatal hernia, a higher gradient of abdominal to thoracic pressure, increased levels of oestrogen, and increased production of bile and pancreatic enzymes [3].[4]

Risikofaktoren: anatomische Faktoren, Ernährung & Lebensstil

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

ungeklärter natürliche Verlauf

- The traditional concept considers the disease as a spectrum that starts with non-erosive reflux disease (NERD) and might progress to complicated GERD (erosive esophagitis, stricture, Barrett's oesophagus [BE]). This concept focuses on oesophageal mucosal injury as the most signif-

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

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

[2] A0001 – For which health conditions and for what purposes is endoscopic plication therapy used? &
A0007 – What is the target population in this assessment?

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

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

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

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

icant clinical outcome in GERD. Patients with severe esophagitis are at high risk of developing a stricture and long-standing reflux symptoms are a major risk for developing BE. Patients with BE have an increased risk of oesophageal adenocarcinoma with 40 times greater incidence than in the general population [4].

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

- The new concept considers GERD as a categorical disease with three distinct entities: NERD, erosive esophagitis, and BE. According to this concept, these are different disorders and the movement among them is limited. This concept focuses on mechanisms leading to symptom generation rather than mucosal injury. Some studies suggest that GERD is a chronic disease that is not progressive. However, other studies confirm that the progression of NERD to erosive esophagitis is possible in ten per cent of GERD patients [4].

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

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

The major burden for GERD patients is the impact on quality of life (QoL) through the experience of GERD symptoms such as heartburn, extra-oesophageal manifestations (pulmonary or ear, nose, throat), or non-cardiac chest pain [5]. Moreover, patients often complain about sleep disturbance. Presumably, they also need to take life-long medication that may have serious side effects, be badly tolerated, alter the absorption of minerals and vitamins, have metabolic effects on bone density, pharmacokinetics or pharmacodynamics [6].[6]

Prävalenz ~15 %

10-40 % PPI-refraktär

42 % potentielle Kandidat*innen für OP

The global prevalence of GERD is around 15% [1, 7] and the incidence is increasing. It is the most common upper gastrointestinal (GI) disease in the Western countries with 10-20% of the population experiencing weekly symptoms [8]. 10-40% of these patients are refractory to a once-daily PPI, of which 25% would respond to an increase in PPI dosing to twice daily [5, 9]. However, 42% of GERD patients are dissatisfied with their PPI treatment outcomes and are potential candidates for surgical therapy [5].[7]

zunehmende Häufigkeit, steigende Ressourcennutzung & gesellschaftliche Kosten

Due to its increasing incidence (approximately four per 1,000 person-years in developed countries [10]), GERD is leading to growing utilisation of health care resources (e.g., medical consultations, emergency room visits, hospitalisation, and medication). Not only doctor visits and diagnosis carry high financial expenses, but also medication and operation costs need to be considered in the long run [11]. On a societal level, the disease burden can affect work productivity which in turn results in substantial societal burden and employer costs [6].[8]

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

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

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

1.2 Current clinical practice[1]

ACG & AWMF: Richtlinien zur Diagnose der Refluxkrankheit:

According to the American College of Gastroenterology (ACG) an evidence-based clinical guideline [12], the S2k consensus-based guideline of the Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF) [7], and results from the Lyon GERD consensus meeting (2017) [13], recommendations for the diagnosis of GERD are the following:

- A presumptive diagnosis of GERD can be established in the setting of **typical symptoms of heartburn and regurgitation**.

  mutmaßliche Diagnose bei eindeutigen Symptomen

- Patients with **non-cardiac chest pain** suspected due to GERD should have a **diagnostic evaluation** before the institution of therapy. A cardiac cause should be excluded in patients with chest pain before the commencement of a GI evaluation.

  diagnostische Evaluation bei nicht kardialem Brustschmerz

- **Upper endoscopy** is recommended in the presence of alarm symptoms and for the screening of patients at high risk for complications. However, normal endoscopy results do not exclude GERD, but in combination with a distal oesophageal acid exposure time of <4% and <40 reflux episodes on pH-impedance monitoring off PPIs, it offers supportive evidence to refute GERD.

  obere Endoskopie bei Hochrisikopat.

- Ambulatory **oesophageal reflux monitoring** is indicated in the case of all potential reflux diseases. Nevertheless, it can provide confirmatory evidence before the considerations of endoscopic or surgical therapy in patients with NERD, as part of the evaluation of those patients who are refractory to PPI therapy and in situations when the diagnosis of GERD is in question. Ambulatory reflux monitoring is the only test that can assess reflux symptom association.

  ambulante Messung des ösophagealen Refluxes vor chirurgischem Eingriff

- Before any antireflux surgery, **oesophageal high-resolution manometry** should be used to assess the motor function in GERD patients. Hence, peristalsis and alternative major motor disorders can be detected in advance.

  Ösophagus Manometrie zur Abklärung von motorischen Funktionsstörungen

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

However, non-acid reflux is poorly understood yet [14].

Schweregrade: mild, moderat, schwer

A generally accepted definition regarding the severity of GERD is lacking. Based on the frequency and severity of the experienced reflux symptoms, expressions used in the literature range from mild, through moderate, to severe GERD. However, there is no explicit definition clarifying the duration and measurement of the symptoms.[9]

Kategorisierung nach Symptomen oder Art: Behandlung von GERD abhängig vom Schweregrad

The management of GERD is aligned with the frequency and severity of symptoms as well as the presence of erosive esophagitis or BE identified by upper endoscopy. As a first step lifestyle modifications are suggested including [7, 12, 15]:[10]

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

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

erster Schritt → Veränderung des Lebensstils

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

H2RA Therapie bei milden und moderaten GERD-Symptomen

From mild to intermittent (less than two episodes per week) symptoms of GERD, first-line therapy with a low-dose histamine 2 receptor antagonist (H2RAs) is recommended [15].

PPI Therapie bei bestehenden GERD Symptomen

If GERD symptoms persist and H2RA therapy is not sufficient a low-dose once-daily PPI therapy is suggested. Increases to standard doses for symptom control can be considered. The therapy should be continued, if the symptoms are controlled, for at least eight weeks. In patients with erosive esophagitis, BE or in cases of severe symptoms that impact the QoL an initial therapy with standard PPI doses once daily is recommended. PPI therapy should be discontinued in GERD patients whose symptoms resolve, except for those with severe esophagitis, BE or patients with recurrent symptoms within three months of discontinuing PPI treatment. Non-responders to PPI therapy should be referred for evaluation [7, 12, 15].

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

Around 10-40% of GERD patients fail to respond symptomatically, partially or completely to standard doses of PPIs. Insufficient acid suppression, reflux hypersensitivity, functional heartburn as well as an alternative aetiology can be reasons for continued symptoms. Patients who suffer from continued symptoms should be carefully reassessed especially considering the timing and compliance of PPI treatment as well as the type of ongoing symptoms and the presentation of defined alarm symptoms (e.g., anorexia, dysphagia, unexplained weight loss) that could indicate a GI malignancy [9].[10]

Behandlung von GERD nach PPI Therapieversagen:

Further diagnostic evaluation and treatment of refractory GERD are based on the aforementioned alarm symptoms as well as the type of ongoing symptoms (Figure 1-1). If alarm symptoms can not be identified via upper endoscopy the following management options are available for GERD patients [9]: [10]

Anpassung der PPI Therapie

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

Therapieentscheidung basierend auf ösophagealer Impedanz Analyse:

Subsequent management of GERD patients who have failed twice-daily PPI treatment includes oesophageal pH testing (based on the pH of the refluxate). Dependent on the result of the pH testing the following treatment options are available [9]:[10]

negativ: Schmerzmittel

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

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

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

In those cases where there is no access to oesophageal impedance analysis, empiric management depended on the type of ongoing symptoms should be in place. If the predominant symptom is heartburn, H2RA at bedtime or sucralfate/sodium alginate can be considered. Persistent symptoms can be treated via pain modulators including tricyclics, SSRIs, trazodone, or SNRIS. In the case of the symptom regurgitation (and/or sour/bitter taste in the mouth), patients should be treated similarly to those whose pH analysis result was positive for weakly acidic reflux (see Figure 1-1) [9].[10]

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

Considering surgical therapy, e.g., laparoscopic or endoscopic surgery, several factors have to be considered to choose the most appropriate treatment option. On the one hand, the degree of oesophageal shortening, local expertise with laparoscopic techniques as well as prior operations have to be taken into account. On the other hand, oesophageal motility disorders, and the size of the hiatal hernia can influence the choice of surgical therapy. Thus, patients eligible for endoscopic therapy should have low-grade erosive esophagitis (Los Angeles A and B), abnormal oesophageal acid exposure, and a hiatal hernia smaller than 2 cm as well as show partial (or higher) responses to PPI treatment.[10]

Entscheidungs-faktoren für antireflux Chirurgie: z. B. vorherige OPs, Größe der Hiatushernie

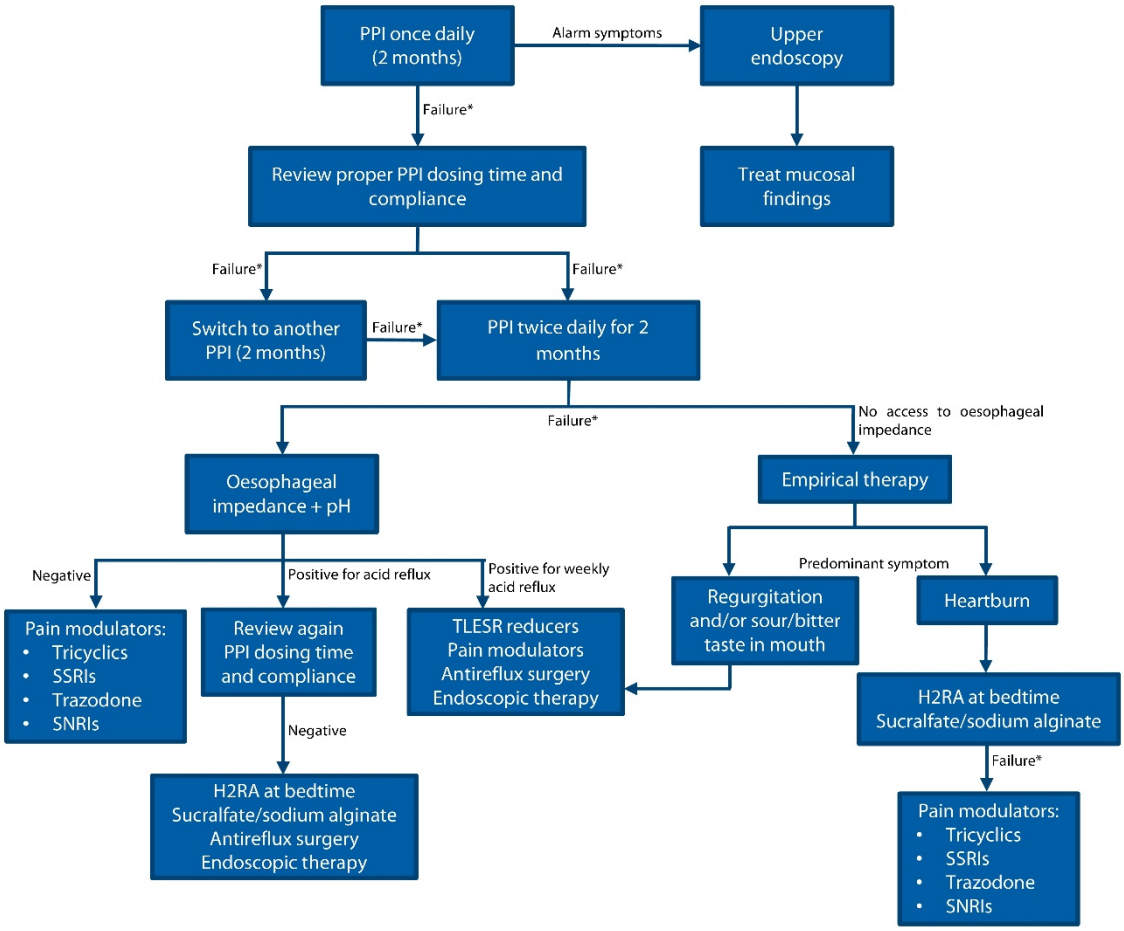

Figure 1-1: Algorithmic approach to medical treatment of refractory GERD. Adapted from [9].
Abbreviations: H2RA – Histamine 2 receptor antagonist, PPI – Proton pump inhibitor, SNRI – Serotonin-norepinephrine reuptake inhibitors, SSRI – Selective serotonin reuptake inhibitors, TLESR – Transient lower oesophageal sphincter relaxation

1.3 Description and technical characteristics of endoscopic plication therapy[11]

Features of the technologies & marketed products[12]

endoskopische Plikatio

Over the last 20 years, endoscopic alternative approaches for the (surgical) treatment of GERD have been developed [16].[13] Endoscopic therapies can be generally divided into radiofrequency heat treatment, antireflux resection of the GEJ mucosa by electrocoagulation as well as endoscopic plication therapies [17]. The technologies of interest in the present report are endoscopic plication systems, of which the following three devices are currently available on the market (see Table 1-1):

3 Devices: MUSE™, EsophyXZ®, GERDx™

- Ultrasound endoscopic endostapler: MUSE™
- Transoral Incisionless Fundoplication (TIF): EsophyXZ®
- Endoscopic full-thickness plication: GERDx™

potentielle Vorteile: weniger invasiv, Krankenhaustage & Nebenwirkungen

In general, endoscopic plication therapy claims to be lesser invasive as well as safer compared to surgical fundoplication by achieving similar efficacy results. Moreover, patients should be less dependent on PPIs or other oral GERD medications and hospital stays are shorter compared to laparoscopic surgery [16].[14]

geschätzte jährliche Nutzung von endoskopischer Plikatio n~50

According to data from the Umbrella Association of Austrian Social Insurance Institutions (formerly known as the Main Association of Austrian Social Security Institutions), in 2014 in Austria, the Code LM030 (open fundoplication/hiatusplasty) was reimbursed 98 times, the LM040 (laparoscopic fundoplication/hiatusplasty) was refunded 1,723 times. In contrast, the expected annual utilisation of endoscopic plication therapy, according to the submitting hospital, based on the previous years' experience, are 50 interventions per year in Austria.[15]

Ultrasound endoscopic endostapler: MUSE™[16]

MUSE™ endoskopisches Klammersystem inklusive eines Ultraschallgerätes

The MUSE™ device (formerly SRS™ Endoscopic Stapling System) consists of a light source, a control unit as well as a flexible surgical endostapler equipped with a miniature camera with an ultrasonic sight and range finder [18, 19]. The miniature camera in combination with the light source enables the direct visualisation of the staple site selection. In addition, the ultrasonic range finder facilitates the assessment of the tissue thickness before the application of staples [20].

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

[12] B0001 – What is endoscopic plication therapy and the alternative standard treatment options?

[13] B0003 – What is the phase of development and implementation of endoscopic plication therapy and the alternative standard treatment options?

[14] B0002 – What is the claimed benefit of endoscopic plication therapy in relation to the alternative standard treatment options?

[15] A0011 – How much is endoscopic plicaton therapy utilised?

[16] B0008 – What kind of special premises are needed to use the endoscopic plicationtherapy? &
B0009 – What supplies are needed to use the the endoscopic plication therapy? &
B0004 – Who administers endoscopic plication therapy and in what context and level of care are they provided?

Ablauf des endoskopischen Eingriffes mittels MUSE™

Procedures by using the MUSE™ device are performed under general anaesthesia with endotracheal intubation. The transoral stapler is advanced into the stomach through a previously placed overtube. After the identification of the stapling location, the stapler is pulled back to place the staple cartridge in the oesophagus about three cm proximal to the GEJ. Subsequently, the device is bent to press the fundus against the oesophagus and to deploy the screws. Next, the operator fires the stapler and thereby delivers a quintuplet pattern of five standard 4.8 mm surgical staples simultaneously. The procedure can be repeated to add additional staples [19].

keine Kosten verfügbar; CE zertifiziert

The MUSE™ device has received a CE mark for the treatment of chronic GERD (year of granting is not available) (Table 3-2).[17] In addition, no price or reimbursement information on the MUSE™ device was accessible or provided by the manufacturer.[18]

Transoral Incisionless Fundoplication (TIF): EsophyXZ®[16]

EsophyXZ® Vorgängermodelle: EsophyX2®, EsophyX®

seit 2009 neues modifiziertes Verfahren TIF 2.0 mittels EsophyXZ® & EsophyX2®

The TIF procedure via the EsophyXZ® device (formerly EsophyX2®, EsophyX®) is performed under general anaesthesia by two endoscopists (gastroenterologists or surgical endoscopists): one to manipulate the device and the second one to operate the gastroscope [18, 21]. In 2007 the TIF 1.0 procedure was introduced (performed by the EsophyX®), which created an esophagogastric plication by using twelve fasteners that were placed approximately one centimetre above the z-line. Since 2009 a modified procedure was established called the TIF 2.0 that can be performed by the second generation of the device EsophyX2® as well as the latest introduced device generation EsophyXZ®. Modifications included: an increase in fasteners up to 23, fasteners are placed more proximally (1–3 cm above the z-line) and the length was enhanced along the greater curve of the stomach [18].

CE zertifiziert seit 2006

FDA Zulassung seit 2007

In 2006, EsophyX® has received a CE mark for the treatment of chronic GERD patients (Table 3-2). Moreover, approval by the Food and Drug Administration (FDA) was initially granted in 2007 for the EsophyX® device, and later on in 2009 as well as 2016 also for the next generation of devices (EsophyX2® and EsophyXZ®).[17] Currently, no price or reimbursement information was accessible or provided by the manufacturer.[18]

Endoscopic full-thickness plication: GERDx™[16]

GERDx™ Vorgängermodelle: NDO Plicator, PLICATOR™

The GERDx™ system is the latest generation of the formerly introduced NDO Plicator and The PLICATOR™ devices that are no longer available on the market (Figure 1-2). Compared to the former generations of the devices, GERDx™ is a single-use device that utilises hydraulic elements for controlling [22, 23].

Ablauf des endoskopischen Eingriffes mittels GERDx™

The whole procedure is performed under general anaesthesia. The GERDx™ device is then introduced to the stomach via a guidewire and an endoscope is passed through the device. About one centimetre below the GEJ the distal end of the GERDx™ is retroflexed to the anterior gastric cardia. The device arms are opened and an endoscopic tissue retractor is penetrated to the gastric cardia (see Figure 1-3). The tissue is gathered between the open arms which are then closed and a pre-tied transmural pledged suture is deployed [23].

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17 A0020 – For which indications have the endoscopic plication devices received marketing authorisation or CE marking?

18 A0021 – What is the reimbursement status of endoscopic plication therapy?

Figure 1-2: GERDx™ device.
The image was provided by the manufacturer G-SURG GmbH [24].

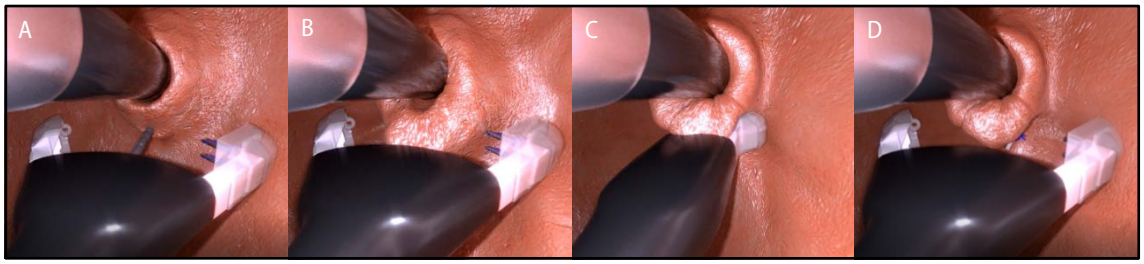

Figure 1-3: GERDx™ procedure: (A) helix is pulled inside, (B) tissue is pulled between arms, (C) arms of the device gets closed, (D) tissue gets fixed. The images were provided by the manufacturer G-SURG GmbH.

GERDx™ Kosten in Deutschland: ~5.360 €

im Vergleich zur Fundoplikatio: ↑ Materialkosten, Erstausbildung von Chirurg*innen vs. ↓ kürzere OP-Zeit

To our knowledge, endoscopic plication therapy via GERDx™ is currently only reimbursed in Germany. There, the costs associated with endoscopic surgery are around € 5,360 including the price of the device and the operation procedure (e.g., facilities, staff, anaesthesia, hospital stay). The aforementioned information was provided by the manufacturer [24]. In comparison to fundoplication, the material costs (device) and the initial training of surgical staff to undertake the implantation procedure are additional to the costs of the LF operation procedure; although the endoscopic plication procedure might cost slightly less due to its shorter operation time.[18]

CE zertifiziert

GERDx™ has received a CE mark in 2014 for the treatment of chronic GERD patients (Table 3-2).[18]

Current standard procedure[12]

chirurgische Standardmethode: Fundoplikatio

The current standard surgical treatment of GERD means wrapping the fundus of the stomach around the oesophagus to create a new valve at the level of the esophagogastric junction, a technique called fundoplication. It was first performed in 1955 and has become the standard surgical antireflux treatment.[13] Fundoplication has several modifications, which include Nissen fundoplication and partial fundoplication:

Nissen Fundoplikatio: vollständige Manschette wird um Ösophagus gelegt

- Nissen fundoplication is currently the gold-standard and the most common surgical treatment with around 2000 procedures carried out in Austria per annum. It was first performed in 1955 by an open technique, but it is now typically carried out laparoscopically. High-quality evidence suggests the superiority of laparoscopy to open surgery concerning early outcomes (e.g., hospital stay, fewer complications) with no significant differences in late outcomes; although the reoperation rate is higher in short-term [1, 25]. It is a complete or total wrap that encompasses 360° of the oesophagus posteriorly.

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 oesophagus [25]. Partial fundoplication is associated with less postoperative dysphagia, fewer reoperations, and its effectiveness is similar to total fundoplication in terms of controlling GERD symptoms up to five years after surgery. However, there are concerns about the long-term effectiveness of partial fundoplication [1].

laparoskopische Fundoplikatio keine standardisierte Operationstechnik

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

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

Laparoscopic fundoplication should be performed under general anaesthesia by a foregut surgeon. The guidelines suggest that laparoscopic fundoplication has to be performed in high-volume centres by experienced foregut surgeons. Surgeons with little experience should have expert supervision during their early experience with the procedure to minimise morbidity and improve patient outcomes [1]. The premises, the operation team, and the supplies are comparable; with differing devices.[19]

Übersichtstabelle im Folgenden

An overview of the assessed interventions and comparator interventions is given in Table 1-1.

[19] B0004 – Who administers endoscopic plication therapy and fundoplication and in what context and level of care are they provided? &
B0008 – What kind of special premises are needed to use endoscopic plication therapy and the alternative standard treatment options? &
B0009 – What supplies are needed to use endoscopic plication therapy and the alternative standard treatment options?

Table 1-1: Endoscopic plication devices for the therapy of chronic GERD patients [1, 17, 21, 23, 26]

	Interventions/Technologies			Comparator interventions
Name	Endoscopic full-thickness plication	Ultrasound endoscopic endostapler	Transoral incisionless fundoplication	Nissen fundoplication and partial or Toupet fundoplication
Proprietary name	GERDx™	MUSE™ (Medigus Ultrasonic Surgical Endostapler)	EsophyXZ®	-
Manufacturer	G-SURG GmbH, Seeon-Seebruck, Germany	Medigus Ltd, Omer, Israel	EndoGastric Solutions, Redmond, Wash, USA	-
Former proprietary names (manufacturers)	■ PLICATOR™ (Ethicon Endosurgery) ■ NDO Plicator (NDO Surgical INC.)	SRS™ Endoscopic Stapling System (Medigus Ltd)	■ EsophyX$_2$® (EndoGastric Solutions) ■ EsophyX® (EndoGastric Solutions)	-
Names in other countries	NA	NA	NA	-
CE mark, year of granting	CE-marked in 2014.	CE-marked; year unknown	CE-marked in 2006	-
FDA approval	Not approved by the FDA	Initially FDA approved in 2014	EsophyX® FDA approved in 2007, EsophyX2® in 2009, EsophyXZ® in 2016	-
Characteristics	■ Microhydraulic technology ■ Video endoscope passes through the GERDx™ device ■ Deployment of a pre-tied transmural pledged suture	■ Equipped with an endostapler and an ultrasound transducer ■ Endostaples deployed 3 cm above the GEJ	■ Endoscopically reconstruction of the LES and restoration of the Hiss angle ■ Full-thickness plications and fixation with polypropylene fasteners	Nissen fundoplication: ■ Gold-standard & most common surgical treatment ■ First performed in 1955 ■ Complete/total wrap that encompasses 360° of the oesophagus Partial fundoplication (e.g., Toupet): ■ Posterior wrap covers roughly 270° of the posterior oesophagus ■ Effectiveness is similar to total fundoplication

Abbreviations: FDA – Food and Drug Administration, GEJ – gastroesophageal junction, NA – not available, LES – lower oesophageal sphincter.

2 Objectives and Scope

2.1 PICO question

PIKO-Frage

Is endoscopic plication in comparison to standard care (e.g., proton pump inhibitors or laparoscopic surgical treatments) in patients with chronic GERD more effective and equally safe or equally effective and safer concerning improvement in health-related QoL (HRQoL) and post-operative side effects and serious adverse events (SAEs)?

2.2 Inclusion criteria

Einschlusskriterien für relevante Studien

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

Table 2-1: Inclusion criteria

Population	Adult patients with chronic GERD (>6 months) with at least one typical reflux symptom despite PPI treatment. Patients should be diagnosed with oesophagal 24 h monitoring. The pathologic oesophagal acid exposure documented by a reflux-related DeMeester should be <30, hiatal hernia <2 cm, BMI <35 kg/m^2, and an endoscopic Hill grade of I-III.
Intervention	Endoscopic plication therapy (GERDx™, EsophyX®, MUSE™)
Control	■ Sham treatment (placebo) ■ Standard surgical treatment of GERD: Nissen/Toupet fundoplication ■ proton pump inhibitor therapy
Outcomes	
Efficacy	Clinical endpoint: ■ Health-related quality of life (HRQoL) Intermediate outcomes: ■ Heartburn score ■ Regurgitation score ■ DeMeester score ■ Discontinuation of anti-reflux medication (PPIs) ■ Esophagitis
Safety	Adverse events (AEs), serious adverse events (SAEs): ■ Any AEs (including re-hospitalisation) ■ Severe AEs ■ Perioperative complications ■ Death ■ Re-surgery: endoscopic/laparoscopic
Study design	
Efficacy	Randomised controlled trials Prospective non-randomised controlled trials
Safety	Randomised controlled trials Prospective non-randomised controlled trials Prospective single-arm studies & registries with n≥100
Time period	Publications from the last ten years

Abbreviations: GERD – Gastroesophageal reflux disease, PPI – Proton pump inhibitor.

3 Methods

3.1 Research questions

EUnetHTA Core Model®

Assessment elements from the EUnetHTA Core Model® for the production of Rapid Relative Effectiveness Assessments (Version 4.2) were customised to the specific objectives of this assessment [27].

Table 3-1: Health problem and current use

Element ID	Research question
A0001	For which health conditions, and for what purposes is endoscopic plication therapy used?
A0002	What is the disease or health condition in the scope of this assessment?
A0003	What are the known risk factors for GERD?
A0004	What is the natural course of GERD?
A0005	What is the burden of disease for GERD patients?
A0006	What are the consequences of GERD for society?
A0024	How is GERD currently diagnosed according to published guidelines and in practice?
A0025	How is GERD currently managed according to published guidelines and in practice?
A0007	What is the target population in this assessment?
A0023	How many people belong to the target population?

Table 3-2: Description of the technology

Description of the technology	
Element ID	**Research question**
B0001	What is endoscopic plication therapy and the alternative standard treatment options?
A0011	How much is endoscopic plication therapy utilised?
A0020	For which indications have the endoscopic plication devices received marketing authorisation or CE marking?
B0002	What is the reimbursement status of endoscopic plication therapy?
B0003	What is the phase of development and implementation of endoscopic plication therapy and the alternative standard treatment options?
B0004	Who administers the endoscopic plication therapy and in what context and level of care are they provided?
B0008	What kind of special premises are needed to use endoscopic plication therapy?
B0009	What supplies are needed to use endoscopic plication therapy?
A0021	What is the reimbursement status of endoscopic plication therapy?

Table 3-3: Clinical effectiveness

Element ID	Research question
D0005	How does endoscopic plication therapy affect heartburn and regurgitation symptoms?
D0006	How does endoscopic plication therapy affect the continuation of PPI therapy?
D0011	What is the effect of endoscopic plication on patients' body functions?
D0016	How does the use of endoscopic plication therapy affect activities of daily living?
D0012	What is the effect of endoscopic plication therapy on generic health-related quality of life?
D0013	What is the effect of endoscopic plication therapy on disease-specific quality of life?

Table 3-4: Safety

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

3.2 Clinical effectiveness and safety

3.2.1 Systematic literature search

systematische Literatursuche in 5 Datenbanken

The systematic literature search was conducted from December 15th to 16th in the following databases:

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

systematische Suche + Literatur von Hersteller + Handsuche: 569 Treffer (nach Deduplizierung)

The systematic literature search was conducted with no limitations to the study design. After deduplication, overall 565 citations were included. The specific search strategy employed can be found in the Appendix. Moreover, all three manufacturers (G-SURG GmbH, Medigus Ltd, EndoGastric Solutions) from the currently available endoscopic products (MUSE™, Esophy-XZ®, GERDx™) were contacted. Only one manufacturer (G-SURG GmbH) responded and submitted eight publications of which three new citations were identified. By hand-search, 30 references were found, resulting in overall 569 hits without duplicates.

Suche nach laufenden Studien ergab 51 Teffer

Furthermore, to identify ongoing and unpublished studies, a search in three clinical trials registries (ClinicalTrials.gov; WHO-ICTRP; EU Clinical Trials) was conducted on the 14th of January resulting in 51 potential relevant hits. Ongoing prospective single-arm studies were only considered if they had enrolled at least 100 patients.

3.2.2 Flow chart of study selection

Literaturauswahl: 8 Studien eingeschlossen (13 Publikationen)

Overall 569 hits were identified after deduplication. The references were screened by two independent researchers (NG and SW) and in case of disagreement, a third researcher was involved to solve the differences. Generally, publications of the last ten years were included in the present report. Additionally, a threshold of at least 100 patients was applied in the case of prospective single-arm studies. Finally, eight studies (in 13 publications) were included for the qualitative analysis after applying predefined criteria Table 2-1. The selection process is displayed in Figure 3-1.

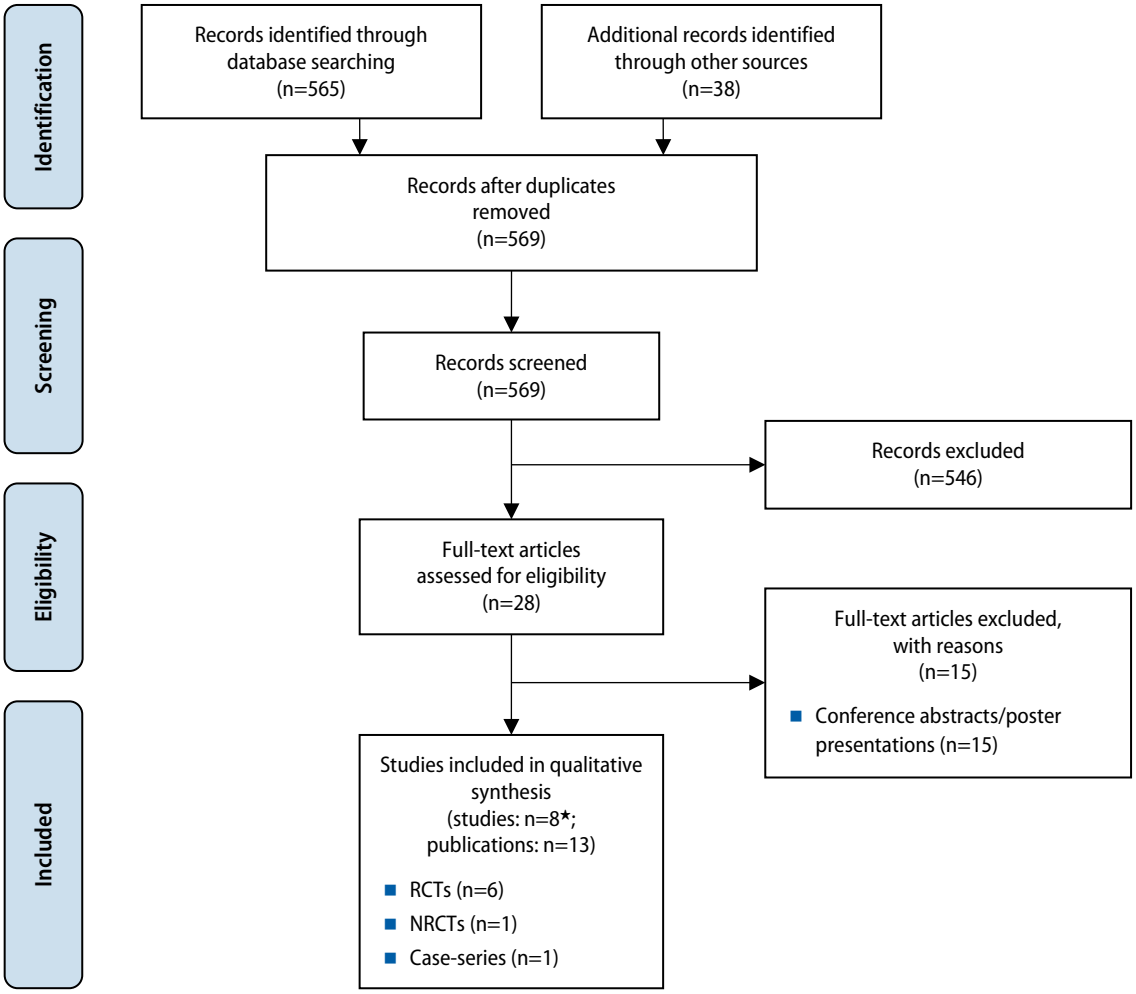

Figure 3-1: Flow chart of study selection (PRISMA Flow Diagram).
** In the case of two studies additional publications (n=5) with different follow-up times were available.*

3.2.3 Analysis

systematische Datenextraktion und Erhebung des Verzerrungspotentials

The data retrieved from the selected studies were systematically extracted into a data-extraction-table by three authors (NG, SW, CW) and controlled by the respective other authors (see Appendix Tables A-1, A-2, A-3). No further data processing (e.g., indirect comparison) was applied. Subsequently, two independent researchers (NG, SW) systematically assessed the risk of bias (RoB) of the included studies using the Cochrane RoB tool version 1.0 for randomised controlled studies (RCTs) [28], the Risk Of Bias In Non-randomized Studies of Interventions assessment tool (ROBINS-I) [29] for non-randomised controlled studies (NRCTs) and the International Health Economics (IHE) [30] checklist for single-arm studies (see Table A-2).

Overall RoB for single-arm studies was estimated using a predefined point score (range: 0 – 20; Table 3-5): a high score indicates a low RoB and a low score indicates a higher RoB. Detailed thresholds are presented in Table 3-6.

Table 3-5: Overall risk of bias (RoB) point scores for RoB assessment of case series

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

Table 3-6: Cut-off criteria for the risk of bias (RoB) assessment of overall RoB of case series

Criteria	Points
Low risk	**>18**
Moderate risk	**14.5 to 18**
High risk	**≤14**

3.2.4 Synthesis

Zusammenfassung der Ergebnisse mit GRADE

Based on the data-extraction-tables (see Appendix Tables A-1, A-2, A-3), data on each selected outcome category were synthesised across studies according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE-)scheme [31]. The research questions were answered in plain text format with reference to GRADE evidence tables (see Table 4-1).

4 Results: Clinical effectiveness and Safety

4.1 Outcomes

4.1.1 Clinical effectiveness outcomes

entscheidende Endpunkte für Wirksamkeit

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

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

HRQoL, Regurgitation & Sodbrennen Score

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

HRQoL gemessen mit 3 Tools:

HRQoL can be measured by different validated tools:

- **GERD-Health Related Quality of Life Questionnaire (GERD-HRQL):**
  The GERD-HRQL measures changes in typical GERD symptoms in response to surgical or medical treatment and includes questions about difficulties with swallowing, bloating, and medication intake. The best possible score is 0 (asymptomatic in each item) and the worst possible score is 50 (incapacitated in each item). It also reflects on the current patient satisfaction. This item is a numerical score and not reflected in the total GERD-HRQL score [5]. Currently, no value change indicating a minimal clinically important difference is available for the GERD-HRQL tool.

GERD-HRQL: 0-50; niedrigere Scores – bessere Lebensqualität (LQ)

- **Gastrointestinal Quality of Life Index (GIQLI):**
  The GIQLI is a GI-specific questionnaire, which includes 36 questions and five subscales (GI symptoms, emotion, physical function, social function, and medical treatment) as well as a total score. The total score ranges from 0-144 and subscale scores from 0-4, whereby better HRQoL scores are represented by higher scores [32, 33]. The minimal clinically important difference for the GIQLI tool is currently unknown [34].

GIQLI: 0-144; höhere Scores – bessere LQ

- **Quality of Life in Reflux and Dyspepsia (QoLRAD):**
  The QoLRAD questionnaire comprises 25 questions and the following five subdomains: emotional distress, sleeping disorders, eating/drinking disorders, physical/social function and vitality. The questionnaire is answered by patients via a 7-point Likert scale, whereby low scores indicate a low HRQoL and high scores a high HRQoL [35]. A change of 0.5 is proposed to be an approximate value for a minimally relevant change [36].

QoLRAD: 1-7; höhere Scores – bessere LQ

Regurgitation & Sodbrennen Score mittels GERD-HRQL oder mit:

The heartburn score as well as the regurgitation score can be measured as part of the aforementioned GERD-HRQL or with one of the following scores:

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

- **Reflux Disease Questionnaire (RDQ):**
  The RDQ is a self-administered questionnaire, which evaluates the frequency and severity of upper GI symptoms. It includes three subscales that assess regurgitation, heartburn, and dyspepsia. Responses can be given via a 5-point Likert scale, whereby lower scores indicate lower frequencies as well as severities of symptoms [37]. Currently, no value change indicating a minimal clinically important difference is available for the RDQ tool.

einem nicht validierten Score: 0-4; niedrigere Einstufung – mildere Symptome

- **Non-validated score:**
  The applied non-validated score assesses the severity of ten reflux-associated symptoms on a 5-point scale. Particularly symptoms like heartburn, regurgitation, bloating, diarrhoea, gas, epigastric pain, dysphagia, asthma, hoarseness and cough are included. Scores range from mild (0) to severe (4) [38].

weitere relevante Endpunkte zur Beantwortung der Forschungsfragen: Medikation, Barrett-Ösophagus & Refluxepisoden

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

- **PPI usage**: usage of PPI treatment at baseline and after the intervention has been performed.
- **Presence of BE:** the presence of damaged oesophagus cells due to acid reflux at baseline and after the intervention has been performed
- **Total number of reflux episodes:** the number of reflux episodes at baseline and after the intervention has been performed.

4.1.2 Safety outcomes

entscheidende Endpunkte für Sicherheit:

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

jegliche & schwerwiegende Komplikationen, Todesfälle, Re-Operationsrate

- **Any adverse events (AEs)**: any reported post-operative adverse events of any grade.
- **SAEs**: comprise any adverse event with serious medical consequences, including post-operative mortality, complications that resulted in substantial morbidity or disability, an increase in the level of care (e.g., ICU), admission to the hospital, or substantial prolongation of the hospital stay.
- **Death:** any reported death that could be intervention-related.
- **Re-surgery**, including endoscopic as well as laparoscopic re-surgery.

4.2 Included studies

4.2.1 Included studies clinical effectiveness

For evaluating clinical effectiveness outcomes, we exclusively considered RCTs and prospective NRCTs (see Chapter 2.2). In total, six RCTs [38-46] and one NRCT [47] met our inclusion criteria (see Table 2-1).

kontrollierte Studien für Wirksamkeits-endpunkte

Study characteristics

Overall, the six RCTs and the NRCT included 453 patients (intervention group [IG]: 267 vs control group [CG]: 186), assessing the clinical effectiveness of endoscopic plication in GERD patients. In the case of one RCT, four publications [40-43] with different follow-up periods (6- and 12-months, 2-, 3-, and 5-years) were available. Comparators of the included studies were either laparoscopic surgery, PPI therapy and/or a sham intervention.

6 RCTs & 1 NRCT (n=453; Interventionsgruppe [IG]: 267 vs Kontrollgruppe [KG]: 186)

Currently, three manufacturers (G-SURG GmbH, Medigus Ltd., EndoGastric Solutions) are providing endoscopic plication devices: GERDx™, MUSE™, EsophyXZ®. For all three devices, older generations were formerly accessible on the market (Table 1-1).

3 Hersteller vertreten endoskopische Plikatio Devices

In four RCTs (n=296; IG: 189 vs CG: 107) [39-45] endoscopic plication therapy was performed using the **EsophyX$_2$®** or **EsophyX®** device, of which two compared the intervention to PPI therapy, one to sham intervention and one to combined PPI and sham treatment. Two RCTs [39-43] allowed crossover to the intervention group after six months of follow-up. Therefore, data from further follow-up analyses were only considered for the safety profile given the single-arm character. Across the four RCTs, the follow-up times ranged from six months to five years and a total of 60 (20.3%) patients were lost to follow-up. The studies were conducted in the United States (US), the Netherlands, Belgium, France, and Sweden.

EsophyX (international): 4 RCTs (IG: 189 vs KG: 107), Kontrolle → PPI Therapie und/oder Scheinintervention 2/4 RCTs Crossoverstudien

The other two identified RCTs (n=130; IG: 67 vs CG: 63) [38, 46] applied two former generations of the nowadays available **GERDx™** device (**The Plicator™** and the **NDO Plicator**). Both studies were conducted in Austria and performed laparoscopic surgery in patients of the comparison group. Follow-up times ranged from three to twelve months and in total eleven (8.5%) patients were lost to follow-up.

Plicator (Österreich): 2 RCTs (IG: 67 vs KG: 63), Kontrolle → laparoskopische Operation

The only eligible NRCT (n=27; IG: 11 vs CG: 16) [47] compared the **SRS™ Endoscopic Stapling System**, an older generation of the **MUSE™** device, to laparoscopic surgery. It was conducted in Turkey and had a follow-up time of about six months. The number of patients lost to follow-up was not reported.

SRS (Türkei): 1 NRCT (IG: 11 vs KG: 16), Kontrolle → laparoskopische Operation

Patient characteristics

Patients in the four RCTs [39-45] investigating the **EsophyX2®/EsophyX®** device were eligible if they were 18 years or older, had chronic GERD disease and were dependent upon daily PPIs for at least six months. In two RCTs [44, 45], patients also had to have normal or near-normal oesophageal motility. Exclusion criteria of the four RCTs included a body mass index (BMI) of ≥35 kg/m^2, pregnancy, esophagitis grade D in two studies [39, 44] and grade C or D in the respective other two RCTs [40-43]. Besides, a hiatal hernia of >2 cm was an exclusion reason in the case of three studies compared to one RCT [44] that enrolled patients with a hiatal hernia of 0-3 cm.

EsophyX Einschlusskriterien: ≥18 Jahre, ≥6 Monate PPI Therapie, etc. Ausschlusskriterien: BMI ≥35 kg/m^2, Ösophagitis Grad C/D, Hiatushernie >2 cm

EsophyX Pat. (IG: 189 vs KG:107):

Alter IG: 51-55 vs KG: 48-62

median BMI IG: 26.6-28.9 vs KG: 27.5-28.5 kg/m²

The median age of patients in three RCTs [40-45] ranged from 51-55 years in the intervention groups and from 48-62 years in the comparison groups, while the other RCT [39] only reported mean values: 42.4 versus 49.3 years. In total, 296 patients (IG: 189 vs CG: 107) were included in the four RCTs out of those 141 were female (IG: 90 vs CG: 51). The median BMI values of three RCTs [40-45] ranged from 26.6-28.9 kg/m² in the intervention groups and 27.5-28.5 kg/m² in the comparison groups, while the other RCT [39] only reported mean values: mean BMI of 26 kg/m² in both study groups. Across all four RCTs, the absence of a hiatal hernia at baseline was reported in 42 patients of the intervention arms and 27 patients of the control arms.

Plicator Einschlusskriterien: DeMeester Score ≥14.7, Hiatushernie <2 cm, etc.

Considering the two RCTs [38, 46] that have used **The Plicator™** and the **NDO Plicator** device, several inclusion criteria were applied: a DeMeester Score of ≥14.7, a positive symptom index of ≥50% of troublesome symptoms for patients as well as at least one typical reflux symptom (e.g., heartburn, regurgitation, or epigastric pain). Patients were ineligible if they had a hiatal hernia larger than two centimetres, oesophageal strictures, BE, or a poor physical status. In addition, pregnant patients were excluded.

Plicator Pat. (IG: 67 vs KG: 63):

Alter IG: 45-47 vs KG: 46-48

median BMI IG: 26.8-27.1 vs KG: 28.2-28.5 kg/m²

The mean age of patients ranged from 45.3-46.5 years in the intervention groups and from 46.3-48.1 years in the comparator groups. A total of 130 patients were included in the two RCTs (IG: 67 vs CG: 63); however, the distribution of sex was only reported in one study [46], which included eleven and 16 females in the intervention and the comparison group, respectively. The mean BMI values ranged from 26.8-27.1 kg/m² in the intervention arms and from 28.2-28.5 kg/m² in the comparison arms. The absence of a hiatal hernia was not reported in one study; however, for the other RCT, only percentages were available (intervention: 40.0% versus comparison: 42.1%).

SRS Einschlusskriterien: DeMeester score >14.7, Hiatushernie <3 cm etc.

The single NRCT [47] investigated the **SRS™ Endoscopic Stapling System** in patients with GERD typical symptoms responding to PPIs of more than one-year duration with a DeMeester score of >14.7. Exclusion criteria included a BMI of >35 kg/m², severe esophagitis or other complications such as BE, strictures or a hiatal hernia longer than three centimetres.

SRS Pat. (IG: 11 vs KG: 16):

Alter IG: 41 vs KG: 38

BMI IG: 26.6 vs KG: 25.8 kg/m²

The median age of the included patients was 41 years in the intervention group and 38 years in the comparison group. Overall, 27 patients (IG: 11 vs CG: 16) were enrolled in the NRCT, of whom about one-half (~48%) were females in both study groups. The mean BMI was 26.6 in the intervention group and 25.8 in the comparison group. The presence of hiatal hernia was solely reported for hernias larger than three centimetres, which was only present in four patients of the control group.

4.2.2 Additionally included safety studies

RCTs, NRCTs und pros. einarmige Studien für Sicherheit

For evaluating safety-related outcomes, we considered RCTs, prospective NRCTs and prospective single-arm studies with 100 or more enrolled patients (Table 2-1).

selben 6 RCTs & 1 NRCT wie für Wirksamkeit, + 1 pros. einarmige Studie

Additionally to the studies already included [38-47] for clinical effectiveness, one prospective single-arm, open-label study was included [48-50].

Study characteristics

3 Publikationen → 3 Follow-up Zeiten

For the selected single-arm study, which was conducted in multiple centres in the US, three publications [48-50] with different follow-up times (6-, 12- and 24-months) were available.

The included prospective single-arm study [48-50] assessed the clinical effectiveness and safety of endoscopic plication therapy with the **EsophyX$_2$®** device in a total of 100 patients during six and twelve months follow-up and in 127 patients at 24-months follow-up. A total of 23 patients were lost to follow-up after 24-months.

EsophyX2®
6 & 12 Monate Follow-up: n=100
24 Monate Follow-up: n=127

Patient characteristics

In the prospective single-arm study [48-50], chronic GERD patients older than 18 years were included. In addition, patients had to have a history of PPI usage of more than six months and a Hill grade of II or III. Other inclusion criteria involved moderate to severe typical or atypical GERD symptoms off PPIs as well as proven GERD by either endoscopy, ambulatory pH, or barium swallow testing.

Einschlusskriterien: erwachsene chronische GERD Pat. Hill Grade II/III, etc.

On the contrary, exclusion criteria of the study included a BMI of >35 kg/m^2, esophagitis grade D, BE >2 cm, oesophageal ulcer as well as fixed oesophageal stricture or narrowing. Furthermore, incompletely reducible hiatal hernia with residual of >5 mm, coagulation disorder, pregnancy, as well as portal hypertension and/or varices were additional reasons for exclusion.

Ausschlusskriterien: BMI >35 kg/m^2, Ösophagitis Grad D, BE >2 cm, etc.

The baseline age of the patients ranged from 18 to 75 years with a median age of 53. In the study cohort, 65 patients (65.0%) were females at baseline and had a median BMI of 26.4 kg/m^2. Besides, BE of <2 cm was present in five patients (5.0%) and 21 patients (21.0%) had no signs of a hiatal hernia at baseline.

Pat.: 18-75 Jahre, 65% weiblich, medianer BMI 26.4 kg/m^2, 21% wiesen keine Hernie auf, etc.

Study as well as patient characteristics and trial results are displayed in Table A-1, Table A-2 as well as Table A-3 and in the evidence profile in Table A-7.

Extraktionstabellen im Anhang

4.3 Results

To allow better readability as well as study comparisons a summary of the applied endoscopic plication devices, utilised comparators and assessed outcomes that are used in the included studies are presented in Table 4-1.

Studiencharakteristika & Endpunkte aufgeschlüsselt

Table 4-1: Summary of study characteristics considering devices, comparators, effectiveness as well as safety outcomes.

Study design	Studies	Devices			Comparators				Effectiveness Outcomes					Safety Outcomes			
		EsophyX	Plicator	SRS	Laparoscopic surgery	Sham treatment	PPI	PPI + Sham	Reg.	HB	HRQoL	PPI	Reflux episodes	Any AEs	SAEs	Resurgeries	Death
RCT	[39]	x					x				x	x			x	x	x
	[40-43]	x					x		x	x	x	x		x		x	
	[44]	x				x					x	x		x	x		
	[45]	x						x	x	x			x	x	x		
	[51]		x		x						x	x	x	x	x	x	
	[38]		x		x				x	x	x	x		x			
NRCT	[47]			x	x						x	x		x	x		
Pros. single-arm	[48-50]	x			Not applicable.				Not applicable, since prospective single-arm studies were only considered for the safety profile of endoscopic plication therapy.					x	x	x	

Abbreviations: AEs – adverse events, HB – heartburn, HRQoL – health-related quality of life, Pros. – prospective, PPI – proton pump inhibitor medication, Reg. – regurgitation, SAEs – severe adverse events.

Morbidity

Endpunkte Morbidität: Sodbrennen, Regurgitation, PPI Einnahme

The *crucial* outcomes of *heartburn score* and *regurgitation score*, as well as the outcome *PPI usage*, were considered on how endoscopic plication therapy affects GERD symptoms.

Heartburn score

Sodbrennen: 3 RCTs (IG: 157 vs KG: 95): 2 EsophyX & 1 NDO Plicator

Three RCTs (n=252; IG: 157 vs CG: 95) [38, 40-43, 45] measured heartburn symptoms with three different tools (GERD-HRQL, RDQ, and a non-validated score). Out of the three RCTs, two performed endoscopic plication via the **EsophyX$_2$®** device [40-43, 45] and one used the **NDO Plicator** [38].[20]

Sodbrennen-EsophyX: 2 RCTs (IG: 127 vs KG: 65) → GERD-HRQL & RDQ score

Baseline versus 6 Monate Follow-up statistisch signifikante (ss) Verbesserung

The two RCTs (n=192; IG: 127 vs CG: 65) [40-43, 45] investigating the **EsophyX$_2$®** device**,** measured heartburn symptoms via the GERD-HRQL and the RDQ during a follow-up period of six months. Both studies reported a statistically significant before vs after improvement in each group ($p<0.001$ and $p<0.001$) in heartburn symptoms comparing baseline values and six months follow-up results (RDQ score). One of the two RCTs [40-43] reported score reductions of 2.54 (2.99 vs 0.63) in the intervention group. The other RCT [45] showed a reduction of 2.1 (2.6 vs 0.5) comparing baseline and follow-up values in the intervention group and a 2.2 (3.0 versus 0.8) reduction in the control group (sham intervention + PPI therapy).[20]

keine ss Unterschiede zwischen den Studiengruppen

In the same RCT [45] also study group comparisons were performed; however, those showed no statistically significant differences in heartburn scores between the intervention and control group ($p=0.936$). The other RCT [40-43] additionally assessed heartburn symptoms via the GERD-HRQL and again reported a statistically significant improvement in heartburn symptoms over time (17.69 versus 3.74; $p<0.001$), but no between-group differences were accessible.[20]

Sodbrennen-Plicator: 1 RCT (IG: 30 vs KG: 30)

ss Unterschied zwischen den Studiengruppen

One RCT (n=60; IG: 30 vs CG: 30) [38] investigating the **NDO Plicator** (follow-up time: 12 months) used a non-validated scale to assess regurgitation symptoms. Comparing mean scores of the intervention and the control group (laparoscopic surgery) after twelve months follow-up, a reduction of 0.90 could be noted considering heartburn symptoms. A statistically significant difference between the two study groups could be noted ($p=0.01$).[20]

Regurgitation score

Regurgitation: 3 RCTs (IG: 157 vs KG: 95): 2 EsophyX & 1 NDO Plicator

Three RCTs (n=252; IG: 157 vs CG: 95) [38, 40-43, 45] measured regurgitation symptoms with three different tools (GERD-HRQL, RDQ, and a non-validated score). Out of the three RCTs, two performed endoscopic plication via the **EsophyX$_2$®** device [40-43, 45] and one used the **NDO Plicator** [38].[21]

Regurgitation-EsophyX: 2 RCTs (IG: 127 vs KG: 65) → RDQ score keine ss Unterschied zw. Studiengruppen (1 RCT)

Two RCTs (n=192; IG: 127 vs CG: 65) [40-43, 45] investigating the **EsophyX$_2$®** device evaluated regurgitation symptoms via the RDQ score. Both studies showed statistically significant regurgitation score improvements of 2.75 (2.94 vs 0.19; $p<0.001$) and 3.0 (3.5 vs 0.5; $p<0.001$) comparing baseline and six months follow-up measurements in the intervention group. The latter one [45] also reported statistically significant improvements in the control group (sham intervention + PPI therapy) over time (3.8 vs 0.8; $p<0.001$) as well as a comparison of the two study groups which was not statistically significant ($p=0.072$). No information on the control group and group comparisons were available in the other RCT [40-43].[21]

[20] D0005 – How does endoscopic plication therapy affect heartburn symptoms?

[21] D0005 – How does endoscopic plication therapy affect regurgitation symptoms?

Regurgitation-Plicator: 1 RCT (IG: 30 vs KG: 30) → nicht validierte Skala

ss Unterschied zw. den Studiengruppen

One RCT (n=60; IG: 30 vs CG: 30) [38] investigating the **NDO Plicator** used a non-validated scale to assess regurgitation symptoms. Comparing mean scores of the intervention and the control group (laparoscopic surgery) after twelve months follow-up, a reduction of 0.46 could be noted considering regurgitation symptoms. The symptom improvement was statistically significant comparing the two study groups ($p<0.05$).[21]

PPI usage

PPI Einnahme: 5 RCTs (IG: 169 vs KG: 128) & 1 NRCT (IG: 11 vs KG: 16):

PPI usage was reported in five RCTs (n=297; IG: 169 vs CG: 128) [38-44, 46] and one NRCT (n=27; IG: 11 v CG: 16) [47] investigating all three devices of interest.[22]

EsophyX: 3 RCTs (IG: 102 vs KG: 65)

PPI Einnahme nach 6 Monaten in 10-41 % der Pat. (3 RCTs)

ss weniger Einnahmen von PPI in der IG (1 RCT)

Considering the **EsophyX2®/EsophyX®** device, three RCTs (n=167; IG: 102 vs CG: 65) [39-44] reported on the PPI usage at baseline and after six months follow-up. All studies stated a 100% daily PPI usage at baseline. After six months of follow-up, the daily, as well as the occasional use of PPIs, was reduced in all three RCTs. Thus, PPI usage was still present in 10% to 41% of patients after follow-up. Two of the three RCTs [39-43] compared the intervention to PPI therapy; thus, PPI usage in the control groups of those studies did not drop and no group comparisons were presented. On the contrary, one RCT (n=44; IG: 22 vs CG: 22) [44] used a sham intervention in the comparison group and could show that statistically significantly fewer patients in the intervention group used PPI therapy compared to the sham group after six months follow-up (41% versus 82%, $p=0.01$).[22]

Plicator: 2 RCTs (IG: 67 vs KG: 63)

reduzierte PPI Einnahmen → stärkere Verbersserung in der KG (1 RCT)

ss weniger PPI Einahmen in der IG (1 RCT)

The two RCTs (n=130; IG: 67 vs CG: 63) [38, 46] investigating **The Plicator™** and the **NDO Plicator** device both compared the intervention to laparoscopic surgery but had different follow-up times (six versus twelve months). In the six months follow-up RCT (n=70; IG: 37 vs CG: 33) [46], the PPI usage decreased by 56% in the intervention group compared to 73% in the control group. Hence, fewer patients in the comparison group needed PPI treatment after six months of follow-up (36% versus 16%). However, no statistical analysis considering group differences was performed. In the twelve months follow-up RCT (n=60; IG: 30 vs CG: 30) [38], 11% of patients in the intervention group compared to 52% of patients in the control group were still on PPI medication after treatment. The group difference was statistically significant ($p<0.02$).[22]

SRS: 1 NRCT (IG: 11 vs KG: 16) weniger PPI Einnahmen in der KG (Unterschied ss)

In the single NRCT (n=27; IG: 11 vs CG: 16) [47] the device **SRS™ Endoscopic Stapling System** was evaluated compared to laparoscopic surgery with a follow-up time of about six months. Baseline PPI usage after six months showed a higher usage of PPI medication in the intervention group compared to the control group (27% versus 6%, $p>0.05$).[22]

Function

Endpunkte Körperfunktionen: Auftreten von BE & Refluxepisoden

The outcomes *presence of BE* and the *total number of reflux episodes* were considered concerning the evaluation of endoscopic plication on GERD patients' body functions.

Presence of BE

keine Studie berichtete über Auftreten von BE

None of the seven included controlled studies reported any cases of BE after follow-up neither in the intervention nor the control group.

[22] D0006 – How does endoscopic plication therapy affect the continuation of PPI therapy?

Total number of reflux episodes

The total number of reflux episodes was reported in two RCTs (n=199; IG: 124 vs CG: 75), one investigating the **EsophyX$_2$®** [45] and the other one **The Plicator™** device [46].

Refluxepisoden: ↓
2 RCTs (IG: 124 vs KG: 75)
→ EsophyX & Plicator
ss Unterschied in Refluxspisoden IG vs KG (EsophyX)

In the case of the **EsophyX$_2$®** RCT (n=129; IG: 87 vs CG: 42)[45], a sham intervention in combination with PPI therapy was used in the comparison group. Generally, a reduction in both treatment groups considering the total number of reflux episodes could be achieved after six months of follow-up (IG: 135 vs 94; CG: 125 vs 122). The difference between treatment groups was statistically significant (p=0.003).

In **The Plicator™** RCT [46] (n=70; IG: 37 vs CG: 33) again both groups showed a reduction in total reflux episodes after three months of follow-up (IG: 78.65 vs 50.33; CG: 80.70 vs 13.83). The difference between the control group (laparoscopic surgery) and the intervention group was statistically significant (p=0.000).[23]

ss Reduktion von Refluxspisoden in KG (Plicator)

Additionally, information on the impact of the intervention on the patient's body function can be found in one of the subsequent sections on patient's safety.

Health-related quality of life

A total of five RCTs (n=297; IG: 169 vs CG: 128) [38-44, 46] and the NRCT (n=27; IG: 11 vs CG: 16) [47] assessed disease-specific QoL via the following three tools: GERD-HRQL, GIQLI, and QoLRAD. Endoscopic plication therapy was performed by the **EsophyX$_2$®/EsophyX®** device in three RCTs [39-44], via former versions of the **GERDx™** device (**The Plicator™**, **NDO Plicator**) in two RCTs [38, 46], and by the **SRS™ Endoscopic Stapling System** (nowadays **MUSE™**) in the NRCT [47].[24]

HRQoL: 5 RCTs & 1 NRCT (IG: 180 vs KG: 144)

3 HRQoL Tools: GERD-HRQL, GIQLI, QoLRAD

The three RCTs (n=167; IG: 102 vs CG: 65) [39-44] investigating the **EsophyX$_2$®/EsophyX®** device had a follow-up time of six months and used two different HRQoL tools (GERD-HRQL and QoLRAD). Two of the three RCTs applied the GERD-HRQL, of which one RCT [39] demonstrated a statistically significant difference (p<0.001) of >50% improvement in GERD-HRQL scores between study groups (EsophyX$_2$® versus PPI therapy) at six months follow-up. On the contrary, the second RCT [40-43] only reported statistically significantly improved GERD-HRQL scores from baseline to six months follow-up (IG: 26.25 vs 5.23; p<0.001); however, group differences were not tested and control group results were not reported. The third RCT [44] used the QoLRAD score to evaluate the HRQoL of study participants. Again only differences in baseline values and six months follow-up results (4.9 vs 6.4) of the intervention group showed statistically significant improvements (p= 0.0005); between-group differences were not analysed.[24]

EsophyX: 3 RCTs (IG: 102 vs KG: 65) GERD-HRQL & QoLRAD

ss Unterschied zw. den Studiengruppen (1 RCT)

ss LQ-Verbesserungen Baseline versus Follow-up in IG (2 RCTs)

[23] D0011 – What is the effect of endoscopic plication on patients' body functions? & D0016 – How does the use of endoscopic plication affect activities of daily living?

[24] D0013 – What is the effect of endoscopic plication therapy on disease-specific quality of life?

Plicator: 2 RCTs (IG: 67 vs KG: 63) GIQLI

keine ss LQ-Verbesserung IG vs KG (2 RCTs)

ss LQ-Verbesserung Baseline vs Follow-up in beiden Gruppen (2 RCTs)

Two versions of the **Plicator** device (**The Plicator™** and **NDO Plicator**) were under evaluation in two RCTs (n=130; IG: 67 vs CG: 63) [38, 46] with two different follow-up times (six and twelve months). In both RCTs, the GIQLI score was used to assess the HRQoL of GERD patients and laparoscopic surgery was performed in the control group. Considering the six months follow-up RCT [46], a statistically significant improvement (p=not reported) before vs after the surgery could be noted in both groups, but no statically significant difference between groups either at baseline or on follow-up was observable (p=not reported). Comparing the follow-up GIQLI values of the intervention and the control group in the twelve months follow-up trial [38], no statistically significant difference between groups could be identified neither after three months follow-up (IG: 114.2 vs CG: 114.7; p=0.99) nor after twelve months (IG: 119.2 vs CG: 123.7; p=0.66).[24]

SRS: 1 NRCT (IG: 11 vs KG: 16)

GERD-HRQL

ss Unterschied zwischen den Studiengruppen (IG: 8.9 vs KG: 4.1)

The included NRCT [47] (n=27; IG: 11 vs CG: 16), which performed endoscopic plication via the **SRS™ Endoscopic Stapling System**, had a follow-up time of about six months and applied the GERD-HRQL tool. Mean GERD-HRQL score improvements dropped in 64% versus 87% (p>0.05) of patients of the intervention and the control group (laparoscopic surgery), respectively. Comparing the follow-up GERD-HRQL values of the intervention and the control group (IG: 8.9 vs CG: 4.1) at six months follow-up, a statistically significant difference between study groups could be observed (p=0.016).[24]

None of the studies investigated the generic HRQoL of GERD patients after endoscopic plication therapy.[25]

Patient safety

Endpunkte Sicherheit: AEs, schwerwiegende AEs (SAEs), Re-Operationen, Todesrate

Concerning safety of endoscopic plication for GERD patients the *crucial* outcomes *any AEs*, *SAEs* and *re-surgeries* and *death* were considered.

Any adverse events

AEs: 5 RCTs, 1 NRCT, 1 prospektive (pros.) einarmige Studie

A total of seven studies (five RCTs [38, 40-46], one NRCT [47], and one prospective single-arm study [48-50]) investigating all three devices of interest reported any AEs.[26]

EsophyX: 3 RCTs (IG: 149 vs KG: 87) & 1 pros. einarmige Studie (n=127)

RCTs: Interventionsgruppe → höherer Anteil an Pat. mit Nebenwirkungen (1 RCT), ss Verbesserung von Blähungen & Flatulenzen (1 RCT),

generell kein Unterschied in AEs (1 RCT)

Any AEs in the case of the application of **EsophyX$_2$®/EsophyX®** device were investigated in three RCTs (n=236; IG: 149 vs CG: 87) [40-45] and one prospective single-arm study (6-months follow-up: n=100 & 12-months follow-up: n=127) [48-50]. Considering the three RCTs, the follow-up time ranged from three to twelve months. Moreover, the comparator was either solely PPI therapy [40-43], a sham intervention [44], or a sham intervention in combination with PPI medication [45]. In one of the three RCTs (n=44; IG: 22 vs CG: 22) [44], moderate and SAEs were reported jointly. This study showed that more moderate and SAEs occurred in patients of the intervention group compared to the comparison group (109% versus 35%), except for diarrhoea which occurred more commonly in the control group (0% versus 5%). Another RCT (n=63; IG: 40 vs CG: 23) [40-43] reported a statistically significant improvement in bloating (p=0.009) and flatulence (p=0.016) in the intervention group compared to the control group, but no statistically significant difference considering dysphagia (p=0.366) after six months follow-up. In addi-

[25] D0012 – What is the effect of endoscopic plication therapy on generic health-related quality of life?

[26] C0008 – How safe is endoscopic plication therapy in comparison to laparoscopic surgery/PPI therapy/sham intervention?

tion, the RCT reported de novo excess flatulence in one patient. In the third RCT (n=129; IG: 87 vs CG: 42) [45], no differences in postoperative epigastric pain, complications, and adverse effects were observable between treatment groups at the follow-up. However, one patient in the intervention group and two patients in the control group developed de novo dysphagia.[26]

The prospective single-arm study (n=127), which investigated the **EsophyX$_2$®** device, noted postoperative pain in 39% of patients (n=50/127) ranging from mild (n=43/50, 86%) to moderate (n=6/50, 12%) and severe (n=1/50, 2%) at which twelve months follow-up. Considering dysphagia, bloating and flatulence an overall improvement comparing baseline and six months follow-up could be observed. After twelve months of follow-up, de novo dysphagia (n=2), bloating (n=1), as well as flatulence (n=2) occurred and after 24 months follow-up de novo flatulence occurred in further two patients.[26]

pros. einarmige Studie (n=127) EsophyX:

postoperativer Schmerz bei 39%

Considering **The Plicator** and the **NDO Plicator** device, one RCT (n=70; IG: 37 vs CG: 33) [46] reported results on any AEs, whereby the second RCT (n=60; IG: 30 vs CG: 30) [38] solely mentioned changes in Gastroesophageal Reflux Symptom Scores. Overall, changes in symptom scores improved in both treatment groups after three and twelve months of follow-up. Over time the only detriment could be observed in the control group (laparoscopic surgery) regarding the symptom gas after twelve months follow-up. Concerning any AEs in the other RCT [46], post-procedural gastric bleeding occurred in one patient (2.7%) in the intervention group. The other observed AEs, peritonitis and pneumoperitoneum, occurred in the control group (laparoscopic surgery) also in one patient each (3.0%).[26]

Plicator: 2 RCTs (IG: 37 vs KG: 33)

Verbesserungen von Symptomen (1 RCT)

kein Unterschied von AEs zw. den Studiengruppen (1 RCT)

Any AEs concerning the **SRS™ Endoscopic Stapling System** were investigated in the NRCT (n=27; IG: 11 vs CG: 16) [47] with a follow-up period of about six months. No information on AEs was reported, but mean hospital discharge times were available, namely on average 1.2 in the control group and three days in the intervention group, except for one complicated patient in the intervention group who stayed 21 days.[26]

SRS: 1 NRCT (IG: 11 vs KG: 16)

kürzere durchschnittliche Spitalsaufenthalt in I

Serious adverse events

SAEs were reported in four RCTs [39, 44-46], one NRCT [47] and in the prospective single-arm study [48-50] investigating all three devices of interest.[26]

SAEs: 4 RCTs, 1 NRCT, 1 pros. einarmige Studie

SAEs after the application of the **EsophyX$_2$®/EsophyX®** device were reported in three RCTs (n=233; IG: 149 vs CG: 84) [39, 44, 45] and one prospective single-arm study (n=127) [48-50] with follow-up times ranging from six to 24 months. In the case of one RCT (n=60; IG: 40 vs CG: 20) [39], SAEs were only reported in the intervention group, namely pneumonia in 7.5% (n=3/40) and severe gastric pain in 2.5% (n=1/40) of the patients. As already mentioned before, one RCT [44] did not differentiate between moderate and SAEs. Hence, information on the safety data of this trial was already mentioned in the upper section on any AEs. In the third RCT (n=129; IG: 87 vs CG: 42) [45], SAEs were only narratively listed; however, information on the frequency of these events is lacking. Considering the prospective single-arm study (n=127) [48-50], 13.4% (n=17/127) of patients had to stay for an extra day in the hospital due to pain, anxiety, nausea or postoperative urinary retention. Another patient had to stay for additional four days due to pulmonary issues, and re-admission after two days was necessary for one patient because of immediate postoperative pain.[26]

EsophyX: 3 RCTs (IG:149 vs KG: 84) & 1 pros. einarmige Studie (n=127)

SAEs in 10% der IG (1 RCT)

13.4% hatten einen längeren Spitalsaufenthalt (1 pros. einarmige Studie)

Plicator: 1 RCT (IG: 37 vs KG: 33) → 1 SAE in KG

Considering **The Plicator** device one RCT (n=70; IG: 37 vs CG: 33) [46] reported pneumatic dilatation due to severe dysphagia in one patient of the control group (laparoscopic surgery). No SAEs were reported in the intervention group.[26]

SRS: 1 NRCT (IG: 11 vs KG: 16) → 1 SAE in IG

SAEs after the application of the **SRS™ Endoscopic Stapling System** were investigated in the NRCT (n=27; IG: 11 vs CG: 16) [47], where only one major complication (chest pain and odynophagia after the procedure) was observed in the intervention group. No SAEs were reported in the control group.[26]

Re-surgeries

Re-Operationsrate: 3 RCTs & 1 pros. einarmige Studie

Performed re-surgeries were reported in three RCTs (n=193; IG: 117 vs CG: 76) [39-43, 46] with a follow-up time of three months to five years and in one prospective single-arm study (n=127) [48-50] with two-year follow-up results. Devices under investigation were the **$EsophyX_2^{®}$** and **The Plicator**.[26]

EsophyX: 2 RCTs (IG: 80 vs KG: 43) + 1 pros. einarmige Studie (n=127) → 14 Re-Operationen

The re-surgery rate concerning the **$EsophyX_2^{®}$** device was reported in two RCTs (n=123; IG: 80 vs CG: 43) [39-43] and one prospective single-arm study (n=127) [48-50]. The two RCTs reported data on crossed-over patients, who in total had undergone six laparoscopic re-surgeries. Furthermore, the single-arm study noted eight re-surgeries, of which one was performed endoscopically and seven laparoscopically.[26]

Plicator: 1 RCT (IG: 37 vs KG: 33) 15 Re-Operationen: 11 endoskopische & 4 laparoskopische (13 in der IG)

Moreover, one RCT (n=70; IG: 37 vs CG: 33) [46] reported information on re-surgeries after endoscopic plication therapy with **The Plicator** device at three months follow-up. Regarding the intervention group, a total of 13 re-surgeries were performed, of which eleven were endoscopically and two laparoscopically. In contrast, two laparoscopic and no endoscopic re-surgeries were reported in the control group of the trial.[26]

keine Evidenz zu zeitl. Verlauf von AEs, anfällige Pat. Gruppen, anwenderabhängige Schäden

Considering harms related to the frequency of applying endoscopic plication, as well as the frequency or severity of harms that might change over time or in different settings, no evidence was available.[27]

Moreover, no evidence was found concerning susceptible patient groups, as well as user-dependent harms of the technologies.[28]

Mortality

1 Todesfall in einem RCT (IG: 40 vs KG: 20)

genaue Ursache unbekannt

Solely one death was reported in one RCT (n=60; IG: 40 vs 20) [39] investigating the **EsophyX2®** device. The patient was initially randomised to the control group (PPI therapy) but crossed over after six months of follow-up to the intervention group. The death occurred eleven months after the procedure. The exact cause of death is unknown but assumed to be due to cardiac or neurological issues.[29]

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[27] C0002 – Are the harms related to dosage or frequency of applying endoscopic plication therapy? &
C0004 – How does the frequency or severity of harms change over time or in different settings?

[28] C0005 – What are the susceptible patient groups that are more likely to be harmed through the use of endoscopic plication therapy? &
C0007 – Are endoscopic plication procedures associated with user-dependent harms?

[29] D0001 – What is the expected beneficial effect of endoscopic plication therapy on mortality? &
D0003 – What is the effect of endoscopic plication therapy on the mortality due to causes other than GERD?

5 Quality of evidence

The RoB for RCTs was analysed with the Cochrane Collaboration tool version 1.0 for assessing the RoB of RCTs [52]; the RoB of NRCTs was evaluated with the ROBINS-I [29]; the RoB of prospective single-arm studies was assessed with the IHE-checklist [30]. The RoB assessments are presented in Tables A-4, A-5, and A-6 in the Appendix.

RoB → Cochrane Collaboration Tool (RCTs), ROBINS-I (NRCT), IHE-Checkliste (pros. einarmige Studie)

Four of the six RCTs were graded with a *high* and two with a *moderate* RoB. The included NRCT was graded with a *serious* RoB and the prospective single-arm study was rated with a *moderate* RoB.

hoher RoB in 5 Studien, 2 Studien moderater RoB

The main reasons for downgrading included the lack of blinding of patients as well as outcome assessors, selective outcome reporting especially regarding AEs, but also several effectiveness results were not reported in full detail. Other reasons involved the sponsoring of the studies by the manufacturers as well as unclear reporting of confounding variables.

Hauptgründe: fehlende Verblindung, unvollständige Daten, Interessenskonflikte, etc.

The strength of evidence was rated for each endpoint individually according to the GRADE scheme [31]. Each critical outcome was rated by two researchers. In case of disagreement, a third researcher was involved to resolve the difference. A more detailed list of the criteria applied can be found in the recommendations of the GRADE Working Group [31].

Qualität der Evidenz nach GRADE

The GRADE scheme uses four categories to rank the strength of evidence:

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

The ranking of each *crucial* outcome according to the GRADE scheme can be found in the summary of findings table below (Table 5-1) and in the evidence profile in Appendix Table A-7.

GRADE Tabelle nächste Seite & Anhang

Separate GRADE assessments were performed in all instances where different follow-up times were applied in the studies, while different scoring tools were graded jointly, but transparently highlighted in the impact column. To allow better comparability of the available evidence across study outcomes, the results of all study designs are combined in one summary of findings table.

separate Bewertung bei unterschiedlichen Follow-up Perioden

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

insgesamt sehr niedrige Evidenzstärke für Wirksamkeits- & Sicherheitsendpunkte

Table 5-1: Summary of findings table of endoscopic plication therapy [31]

Outcomes	Impact	Nº of studies (Pts I vs. C)	Certainty of the evidence (Importance)	Comments
Efficacy				
Overall health-related quality of life (overall HRQoL) assessed with: GERD-HRQL, QOLRAD, GIQLI follow up: mean 6 months	1 study (**GERD-HRQL**) reported a ss improvement between the study groups (p<0.001), 2 other studies reported ss improvements from baseline to 6-months post operating (**GERD-HRQL:** p<0.001 and **QOLRAD:** p=0.0005), 1 study (**GIQLI**) reported no ss differences between study groups at baseline and after follow-up **Ranges of GERD-HRQL scores, I vs. C, baseline/6-months, mean (n=2):** 26.25-26.5/5.23-12.4 vs. NR **GIQLI (n=1):** no exact values available **QOLRAD score, I vs. C, baseline/6-months, median (n=1):** 4.9/6.4 vs. 4.8/5.2	4 RCTs [39-44, 46] (139 vs. 98)	⨁◯◯◯ **VERY LOW** [a,b,c] **(Crucial)**	**GERD-HRQL:** lower scores indicate better HRQoL **QOLRAD:** higher scores indicate better HRQoL **GIQLI:** higher scores indicate better HRQoL
Overall health-related quality of life (overall HRQoL) assessed with: GIQLI follow up: mean 12 months	no ss. improvement between study groups: **GIQLI:** p=0.66 **GIQLI score, I vs. C, baseline/12-months, mean (n=1):** 96.3/119.2 vs. 88.4/123.7	1 RCT [38] (30 vs. 30)	⨁⨁◯◯ **LOW** [d,e] **(Crucial)**	**GIQLI:** higher scores indicate better HRQoL
Overall health-related quality of life (overall HRQoL) assessed with: GERD-HRQL follow up: mean 6 months	ss improvements in the control group at 6-months follow-up: **GERD-HRQL:** p=0.016 **GERD-HRQL score, I vs. C, baseline/6-months, mean (n=1):** 24.8/8.9 vs. 29.3/4.1	1 NRCT [47] (11 vs. 16)	⨁⨁◯◯ **LOW** [d,e] **(Crucial)**	**GERD-HRQL:** lower scores indicate better HRQoL
Heartburn score (Heartburn score) assessed with: GERD-HRQL, RDQ follow up: mean 6 months	1 study reported a ss improvement (**RDQ:** p<0.001; **GERD-HRQL:** p<0.001) from baseline to 6-months post operating, 1 study reported a ss improvement (**RDQ:** p<0.001) from baseline to follow-up, but no ss improvement between study groups (p=0.936) **RDQ score, I vs. C, baseline/6-months, mean (n=1):** 2.99/0.45 vs. NR **RDQ score, I vs. C, baseline/6-months, median (n=1):** 2.6/0.5 vs. 3.0/0.8 **GERD-HRQL, I vs. C, baseline/6-months, mean (n=1):** 17.69/3.74 vs. NR	2 RCTs [40-43, 45] (127 vs. 65)	⨁⨁◯◯ **LOW** [b,f] **(Crucial)**	**GERD-HRQL:** lower scores indicate better HRQoL **RDQ:** lower scores indicate lower frequency as well as severity of the symptom
Heartburn score assessed with: non validated score follow up: mean 12 months	ss improvement between treatment groups: **non validated score:** p=0.01 **Non validated score, I vs. C, baseline/12-months, mean (n=1):** 2.50/1.07 vs. 2.96/0.17	1 RCT [38] (30 vs. 30)	⨁⨁◯◯ **LOW** [d,e] **(Crucial)**	**Non validated score:** lower scores indicate milder symptoms
Regurgitation score assessed with: RDQ follow up: mean 6 months	1 study reported a ss improvement (**RDQ:** p<0.001) from baseline to 6-months post operating, 1 study reported a ss improvement (**RDQ:** p<0.001) from baseline to follow-up, but no ss improvement between study groups (**RDQ:** p=0.072) **RDQ score, I vs. C, baseline/6-months, mean (n=1):** 2.94/0.19 vs. NR **RDQ score, I vs. C, baseline/6-months, median (n=1):** 3.5/0.5 vs. 3.8/0.8	2 RCTs [40-43, 45] (127 vs. 65)	⨁⨁◯◯ **LOW** [b,f] **(Crucial)**	**RDQ:** lower scores indicate lower frequency as well as severity of the symptom
Regurgitation score assessed with: non validated regurgitation score follow up: mean 12 months	ss improvement between treatment groups: **non validated score:** p<0.05 **Non validated score, I vs. C, baseline/12-months, mean (n=1):** 1.52/0.57 vs. 1.96/0.11	1 RCT [38] (30 vs. 30)	⨁⨁◯◯ **LOW** [d,e] **(Crucial)**	**Non validated score:** lower scores indicate milder symptoms
Safety				
Any adverse event (Any AEs) assessed with: number of patients follow up: range 3 to 12 months	1 study reported a ss improvement in bloating between study groups (p=0.009), but no ss difference between groups considering dysphagia (p=0.366), 1 study reported more percentages of patients suffering from moderate to severe AEs in the intervention group compared to the control group, 2 studies reported no ss differences between study groups	4 RCTs [40-46] (186 vs. 120)	⨁◯◯◯ **VERY LOW** [b,c,g] **(Crucial)**	-

Outcomes	Impact	№ of studies (Pts I vs. C)	Certainty of the evidence (Importance)	Comments
Any AEs assessed with: discharge time follow up: mean 6 months	The mean discharge times for the control and the intervention groups were 1.2 and 3 days, respectively (p<0.05) → except for one complicated patient in the intervention group who stayed 21 days.	1 NRCT [47] (11 vs. 16)	⨁⨁◯◯ **LOW** [d,e] **(Crucial)**	-
Any AEs assessed with: number of patients follow up: range 6 to 24 months	Overall dysphagia, bloating and flatulence improved comparing baseline and 6-months follow-up. After 12-month follow-up de novo dysphagia (n=2), bloating (n=1), and flatulence (n=2) occurred. After 24-month follow-up, de novo flatulence occurred in 2 patients.	1 observational study [48-50] (100 vs. -) [h]	⨁⨁◯◯ **LOW** [h] **(Crucial)**	-
Severe adverse events (SAEs) assessed with: number of patients follow up: range 3 to 12 months	all 3 studies reported no ss differences between study groups	3 RCTs [39, 44, 46] (99 vs. 75)	⨁⨁⨁◯ **Moderate** [c,i] **(Crucial)**	-
	no ss difference between treatment groups (p=0.219)	1 NRCT [47] (11 vs. 16)	⨁⨁◯◯ **LOW** [d,e] **(Crucial)**	-
SAEs assessed with: number of patients follow up: mean 6 months	Extra hospital day due to pain, anxiety, nausea or postoperative urinary retention: 17 (13.4%) Additional 4 hospital days due to pulmonary issues: 1 (0.8%*) Re-admission 2 days after the procedure due to immediate postoperative pain: 1 (0.8%*)	1 observational study [48-50] (100 vs. -) [h]	⨁⨁◯◯ **LOW** [h] **(Crucial)**	-
Death assessed with: number of patients follow up: range 3 to 12 months	1 patient who had undergone interventional procedure after crossover died, death occurred 11 months after the procedure	1 RCT [39] (40 vs. 20)	⨁⨁◯◯ **LOW** [d,e] **(Crucial)**	-
	No death was reported	1 observational study [48-50] (100 vs. -) [h]	⨁⨁◯◯ **LOW** [h] **(Crucial)**	-
Re-surgery assessed with: number of patients/re-surgeries follow up: range 3 to 12 months	2 studies reported 18 re-surgeries 14 in the intervention group (11 endoscopic, 3 laparoscopic) and 4 in the control group (all laparoscopic)	2 RCTs [39, 46] (77 vs. 53)	⨁⨁◯◯ **LOW** [c,e] **(Crucial)**	-
	8 re-surgeries (1 endoscopic, 7 laparoscopic)	1 observational study [48-50] (100 vs. -) [h]	⨁⨁◯◯ **LOW** [h] **(Critical)**	-

*Abbreviations: AEs – adverse events, I – intervention group; C: control group, NRCT – non-randomised controlled trial, Pts – patients, RCT – randomised controlled trial, ss – statistically significant. * based on own calculation*

Explanations

[a] *3/4 high RoB, 1/4 moderate RoB*
[b] *different trends of improvements comparing treatment groups*
[c] *different generation of devices*
[d] *power calculations are lacking*
[e] *high RoB*
[f] *1/2 high RoB, 1/2 moderate RoB*
[g] *2/4 high RoB, 2/4 moderate RoB*
[h] *Initially 100 patients were included in the study, however, in the 24-months follow-up cohort 127 patients were analysed.*
[i] *power calculations available in 2/3 RCTs*

6 Discussion

Gastroesophageal reflux disease (GERD) is defined as a condition that develops when the reflux of stomach contents causes troublesome symptoms and/or complications [1]. The major burden for GERD patients is the impact on quality of life (QoL) through the experience of GERD symptoms, such as heartburn, extra-oesophageal manifestations, or non-cardiac chest pain [5]. GERD is a common problem affecting 10-20% of the adult population in the Western World [8]. Most patients respond well to daily pharmaceutical therapy, namely proton pump inhibitors (PPIs), still, 42% of them are dissatisfied with their PPI treatment and are potential candidates for surgical therapy [5]. Compared to the current standard surgical treatment like laparoscopic fundoplication, endoscopic plication therapy claims to be lesser invasive accompanied by fewer side effects and shorter hospitalisation periods [16].

GERD:
Reflux aus dem Magen in die Speiseröhre

Prävalenz 10-20%

42% unzufrieden mit Protoneninhibitor Therapie → potentielle Kandidat*innen für Operation

Against this background, the present systematic review aimed to investigate whether endoscopic plication therapy in chronic GERD patients is more effective and equally safe or equally effective but safer in comparison to standard therapies namely laparoscopic surgery, PPI therapy and/or sham intervention.

Ziel: Bewertung der Wirksamkeit & Sicherheit von endoskopischer Plikatio

Summary and interpretation of the main results

A total of eight studies, including five additional publications of two of the studies with different follow-up times, met the predefined inclusion criteria. Out of the eight eligible studies, six randomised controlled trials (RCTs) [38-46] and one non-randomised controlled trial (NRCT) [47] were used to evaluate the clinical effectiveness as well as safety of endoscopic plication therapy, involving a total of 453 (intervention group [IG]: 267 vs control group [CG]: 186) chronic GERD patients. Comparators included laparoscopic surgery, PPI therapy and/or a sham intervention. Considering the two RCTs that allowed a crossover of patients to the intervention group after six months follow-up [40-43], results after crossover were only used for the safety profile of endoscopic plication therapy, due to the single-arm character. In addition, one prospective single-arm study [48-50], including 127 patients at 24-month follow-up, was also solely considered for the safety profile of endoscopic plication therapy.

8 Studien (n=453; IG: 267 vs KG: 186): 6 RCTs, 1 NRCT, & 1 pros. einarmige Studie

→ davon 2 Crossoverstudien

3 unterschiedliche Komparatoren

All identified studies included chronic GERD patients with a history of daily PPI use over the last six months. Patients with a hiatal hernia of more than two centimetres were excluded from all trials except for two studies that also enrolled patients with hiatal hernias up to three centimetres [44, 47]. Follow-up times of the studies ranged from three months to five years.

Ausschluss von Pat. mit einer Hiatushernie >2 cm (außer in 2 Studien)

All three endoscopic plication devices of interest were applied in the included studies, whereby different versions of the EsophyX® device were the most commonly analysed (five studies, [39-45, 48-50]), followed by predecessor models of the GERDx™ device (two studies, [38, 46]) and predecessor models of the MUSE™ device (one study, [47]). Overall, the studies used different tools to measure health-related quality of life (HRQoL) outcomes (GERD-HRQL, GIQLI, QoLRAD), heartburn and regurgitation symptoms (GERD-HRQL, RDQ, non validated score).

3 Devises: EsophyX®, GERDx™, MUSE™ unterschiedliche QoL & Symptom Messinstrumente

HRQoL: 6 Studien ss LQ-Verbesserungen: Baseline vs Follow-up (4 RCTs)

ss LQ-Verbesserungen: IG vs KG (1 RCT, 1 NRCT)

Concerning the clinical effectiveness outcomes *crucial* to derive a recommendation, HRQoL scores were measured in six studies [38-44, 46, 47] investigating all three devices of interest. Statistically significant improvements in the intervention group comparing baseline and follow-up values were present in four RCTs [39-44, 46]. Only one RCT [39] showed a statistically significant improvement in HRQoL scores ($p<0.001$) in the intervention group (Esophy$X_2^{®}$) compared to the control group (PPI therapy); while two other RCTs [38, 46] reported no statistically significant differences between study groups (The Plicator^{TM}/NDO Plicator vs laparoscopic surgery). Contrary, the NRCT [47] showed a statistically significant difference ($p=0.016$) between treatment groups (laparoscopic surgery vs SRS^{TM}) favouring the control arm.

Sodbrennen & Regurgiation: 3 RCTs

ss Verbesserungen: Baseline vs. Follow-up (2 RCTs) & ss Verbesserung:

IG vs KG (1 RCT)

Heartburn and regurgitation symptoms were measured in three RCTs investigating the Esophy$X^{®}$/Esophy$X_2^{®}$ [40-43, 45] and the NDO Plicator device [38]. The three RCTs showed improved heartburn and regurgitation scores comparing baseline and follow-up values, of which two improvements were statistically significant ($p<0.001$) in the intervention group. One RCT [45] also reported statistically improved scores considering regurgitation as well as heartburn symptoms in the control group (sham intervention + PPI medication). In addition, one RCT [38] reported statistically significant improvements in the intervention group (NDO Plicator) compared to the control group (laparoscopic surgery) after three (heartburn: $p<0.0001$, regurgitation: $p=0.005$) and twelve (heartburn: $p=0.01$, regurgitation: $p<0.05$) months follow-up.

Sicherheitsprofil

Nebenwirkungen: 7 Studien → Verbesserung von Blähsymptomen, jedoch längere Hospitalisierung nach endoskopischer Plikatio

1 Todesfall (Todesursache unklar)

22 Re-Operationen nach endoskopischer Plikatio

Concerning the safety profile, any AEs, SAEs, death and re-surgeries were regarded as *crucial* study outcomes to derive a recommendation. Overall, seven studies (five RCTs [38, 40-46], one NRCT [47], and one prospective single-arm study [48-50]) reported any AEs investigating all three devices of interest. No statistically significant differences could be observed between study groups, except for one RCT [40-43] that showed a statistically significant improvement in bloating symptoms over time. However, the NRCT [47] noted a shorter hospitalisation period in the control group (laparoscopic surgery) compared to the intervention group (SRS^{TM}). Moreover, five studies [39, 44, 46-50] reported on SAEs applying all three devices of interest. The comparative trials showed no differences between study groups, except for one study [44] that showed higher percentages of patients suffering from moderate to SAEs. In the prospective single-arm study [48-50], 18 patients had to stay longer in the hospital or were re-admitted due to SAEs. Overall, in one RCT [39] one patient died in the intervention group eleven months after endoscopic surgery. Furthermore, re-surgeries were necessary in 26 patients, of which 22 were needed after endoscopic plication therapy [39-43, 46, 48-50].

Quality of evidence

Evidenzstärke für klinische Wirksamkeit und Sicherheit sehr schwach: hohes Biasrisiko, unterschiedliche Devicegenerationen etc.

Overall, the quality of evidence was *very low* considering both clinical effectiveness as well as safety outcomes. In the case of clinical effectiveness outcomes, several factors attributed to the rather low level of evidence. On the one hand, a high RoB was observed across all endpoints, different trends of symptom improvements could be recognised resulting in inconsistency, several studies included a low number of participants (27 to 129 patients), as well as different generations of devices, were used in the RCTs and the NRCT (Table A-7). Considering safety outcomes, additively to the abovementioned factors, the prospective single-arm study design of one included trial influenced the level of evidence.

The overall RoB of the included studies was considered moderate to high because in many instances no blinding was performed and selective outcome reporting was present especially regarding AEs. Other reasons for downgrading involved the sponsoring of the studies by the manufacturers as well as unclear reporting of confounding variables (see Tables A-4, A-5, A-6).

moderates bis hohes Verzerrungsrisiko

Furthermore, in two RCTs [39-43] all patients from the control group crossed over to the intervention group after six months follow-up. After crossover subsequent results were solely considered for the safety profile since no control group was in place. This also affects the included study with the longest follow-up of five years. Hence, follow-up times of comparative outcome results were rather short, ranging from three to twelve months. Besides, the inclusion criteria across trials varied, which lead to the enrolment of patients with severe disease (e.g., hiatal hernia >2cm). In addition, also the sex distribution was unbalanced in some instances.

2 RCTs mit Crossover → kurze follow-up Zeiten für komparative Ergebnisse

variierende Einschlusskriterien

The comparison of results across the included studies is difficult due to the use of different QoL as well as symptom questionnaires, but also because of varying statistical measures (mean versus median). Moreover, some studies lacked information on the number of patients of subgroup analysis as well as of lost to follow-up.

Vergleichbarkeit der Studienergebnisse schwierig, z. B. unterschiedliche Messinstrumente

Limitations to the present report

First of all, included studies were restricted to the last ten years of publication. However, the latest available evidence was sought to be more conclusive, since the devices, as well as procedures, have improved over the last years. Moreover, the number of studies was not balanced regarding the different devices of interest (EsophyX$_2$®/EsophyX®: n=5; The Plicator™/NDO Plicator: n=2; SRS™: n=1). Nevertheless, studies of the newest device generations were either not available or did not fulfil the predefined inclusion criteria and thus were not considered for the analyses. This can affect the applicability of the presented results to the nowadays available devices. Besides, different comparators have been used in the included studies that may affect RCT as well as NRCT results.

Publikationen der letzten 10 Jahre

kaum verfügbare Evidenz zu neuesten Device Generationen

unterschiedliche Komparatoren

In contrast, we excluded retrospective studies since the sources of error due to confounding and bias are more common in retrospective studies than in prospective trials. Moreover, prospective case-series with a patient cut-off of at least 100 patients were considered. Presumably, some prospective studies with less than 100 patients were not included. Lastly, due to the aforementioned variances in data reporting and the use of different patient-reported outcome tools, only a narrative analysis within GRADE was possible.

Ausschluss retrospektiver Studien

pros. einarmige Studie mit <100 Pat. ausgeschlossen

Upcoming evidence

Through the clinical trial search, three relevant ongoing studies could be identified involving one ongoing RCT and two ongoing uncontrolled studies. The ongoing RCT (NCT03322553, study completion date: December 30, 2019) may provide further data on the clinical effectiveness and safety of endoscopic plication therapy with GERDx™ controlled by a sham intervention in chronic GERD patients (Table A-9). However, the trial has a follow-up period below twelve months as well as a study cohort of fewer than 100 patients and will thereby not fill the gap of long-term comparative evidence exceeding twelve months. Nevertheless, it investigates the latest available device of the former available Plicator™ device and will thereby update the available evidence with the most recently utilised technique (GERDx™).

1 laufende RCT zu GERDx™ (Beobachtungszeitraum <12 Monaten)

2 pros. einarmige Studien zu MUSE™ & EsophyX®

Two additional prospective single-arm studies are ongoing investigating EsophyX® (NCT01118585) and MUSE™ (ChiCTR2000036041) in chronic GERD patients. Considering the EsophyX® trial around 270 patients are included, hence endoscopic plication will be analysed in a larger sample size than currently available, still in an uncontrolled design. Moreover, additional evidence on the latest generation of the MUSE™ device may get accessible.

Conclusion

keine klare Aussage zur Wirksamkeit und Sicherheit von endoskopischer Plikatio

Overall, no conclusion can be made whether endoscopic plication leads to better outcomes than the investigated comparators since HRQoL results were contradicting. Generally, endoscopic plication therapy seems to improve HRQoL and symptom scores over time. However, considering the four available study group differences only an improvement compared to PPI medication could be identified, but comparisons to laparoscopic surgery showed either no difference or were favouring the control arm. Altogether, no differences in the safety profile of endoscopic plication therapy and respective comparators could be identified. Moreover, current safety data is lacking quality as well as degree of detail.

qualitative hochwertige Studien mit längerer Nachbeobachtungszeit und mehr Pat. notwendig

In addition, the included studies showed an overall very low quality of evidence. Thus, in combination with the aforementioned contradicting results and poor data quality, no reliable conclusions regarding the clinical effectiveness and safety for endoscopic plication compared to laparoscopic surgery, or PPI therapy and/or a sham intervention in chronic GERD patients can be drawn. Further RCTs and/or NRCTs with a higher quality of evidence are needed, investigating currently available generations of devices. Thus, comparative studies with larger sample sizes (n>100) and longer follow-up times of at least three years are crucial to clarify the currently uncertain available evidence on endoscopic plication and to add knowledge to the current scarce evidence on the safety profile.

7 Recommendation

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

Einschluss in Leistungskatalog aktuell nicht empfohlen

Table 7-1: Evidence-based 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:

Evidenz unzureichend: Bedarf an qualitativ hochwertiger Langzeitdevidenz

The current evidence is not sufficient to prove that endoscopic plication is more effective and equally safe or equally effective and safer than laparoscopic surgery, PPI therapy and/or sham treatment in chronic GERD patients. Due to the methodological shortcomings of the available evidence no solid conclusions can be drawn neither for clinical effectiveness nor for the safety of endoscopic plication therapy. Hence, there is a need for high-quality studies showing consistent long-term effectiveness results as well as properly reported and detailed safety data.

Re-Evaluierung frühestens nach 2023 empfohlen

New results based on a relevant ongoing RCT (NCT03322553), may potentially influence the effect estimates, since the newest available device generation (GERDx™) is applied. However, it will not fill the current evidence gap on controlled trials with large sample sizes and long-term follow-up. Therefore, a re-evaluation is recommended in 2023 at the earliest after the results of the ongoing RCT are published and adequate additional trials have potentially become accessible.

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Appendix

Evidence tables of individual studies included for clinical effectiveness and safety

Table A-1: Endoscopic plication therapy: Results from randomised controlled trials

Author, year	Witteman 2015 [39]	Trad 2014 [40], 2015 [41], 2017 [42], 2018 [43]	Håkansson, 2015 [44]	Hunter, 2015 [45]	Kaindlstorfer, 2013 [46]	Antoniou, 2011 [38]
Study design	Prospective multicentre, randomised controlled trial (interim analysis)	Prospective, multicentre, open-label, randomised comparative trial	Prospective, multicentre, randomised controlled trial	Prospective, multicentre, randomised, placebo-controlled trial	Prospective, single-centre parallel randomised controlled open trial	Prospective, single-centre randomised controlled trial
Country	US, Netherlands	US	Belgium, France, Sweden	US	Austria	Austria
Sponsor	Maastricht University funding	EndoGastric Solutions, Inc.	EndoGastric Solutions, Inc.	EndoGastric Solutions, Inc.	NR	NR
Intervention/ Product	EsophyX2	EsophyX2	EsophyX	EsophyX2 + 2 weeks after the intervention PPI therapy (omeprazole) + subsequently placebo	The Plicator	NDO Plicator
Comparator	PPI therapy (at 6 months cross over to the intervention group was allowed)[30]	PPI therapy (at 6 months: PPI+TF crossover)[31]	Sham intervention	Sham intervention + PPI therapy (omeprazole)	Laparoscopic antireflux surgery	Laparoscopic antireflux surgery
Study duration	2008 – 2011	June 2012 – August 2012	January 2011 – January 2013	June 2011 – September 2013	April 2007 – July 2010	October 2006 – April 2010
Number of pts, total, I vs. C	Baseline: n=60, 40 vs. 20 6-month follow-up: n=57, 37 vs. 20 12-month follow-up: n=45 (all patients have crossed over)	n=63, 40 vs. 23	n=44, 22 vs. 22	Baseline: n=129, 87 vs. 42 6-month follow-up: n=104, 76 vs. 28	n=70, 37 vs. 33	n=60, 30 vs. 30
Inclusion criteria	■ GERD patients, controlled with PPI therapy, but who opted for an intervention over lifelong drug dependence ■ 18-75 years	■ Gastroesophageal reflux disease duration: >1year ■ daily troublesome regurgitation and/or ■ atypical GERD symptoms (Montreal criteria) on PPIs ■ 18-80 years	■ chronic GERD symptoms and without severe anatomic deterioration of the gastro-oesophageal junction ■ 18-80 years	■ more than 6 months of GERD symptoms and troublesome regurgitation, despite a minimum PPI dose of 40 mg daily ■ 18-80 years	GERD documented by 24-hour ambulatory multi-channel impedance-pH monitoring of antisecretory therapy and/or gastroscopy by one or more of the following criteria:	■ at least one typical reflux symptom (heartburn, regurgitation, or epigastric pain)

[30] Results from 12 months follow-up should be considered as prospective observational study results since all patients have crossed over an no comparator is available.

[31] At 6 months comparative data available for TIF (EsophyX) vs PPI was extracted (2014, 2015), thereafter – due to crossover – all patients in the follow-up publications (2017, 2018) had undergone TIF (EsophyX) and therefore no comparative data was available. The follow-up publications (2017, 2018) without comparator should be considered as prospective observational studies.

Author, year	Witteman 2015 [39]	Trad 2014 [40], 2015 [41], 2017 [42], 2018 [43]	Håkansson, 2015 [44]	Hunter, 2015 [45]	Kaindlstorfer, 2013 [46]	Antoniou, 2011 [38]
Inclusion criteria *(continuation)*	■ hiatal hernia ≤2 cm ■ proven reflux while off PPIs ■ daily PPIs for ≥1 year ■ normal or reduced LES resting pressure (5-40 mm Hg)	■ abnormal 48-hour ambulatory pH test defined as % time pH <4 greater than 5.3% of the total recording period ■ history of daily PPI use for >6 months ■ Hill grade I or II ■ Willingness to undergo pH testing ■ Willingness to adhere to a postoperative diet for 6 weeks ■ Availability for follow-up visits ■ Willingly and cognitively signed informed consent	■ daily PPIs for >6 months ■ persistent GERD symptoms without PPI therapy ■ evidence of two or more of the following while off PPI therapy (>10 days): erosive oesophagitis grade A, B or C, abnormal ambulatory pH study, moderate to severe GERD symptoms, normal or near-normal oesophageal motility	■ troublesome symptoms, specifically heartburn or regurgitation, while on PPI ■ hernia ≤2 cm ■ dependent upon daily PPIs for >6 months ■ abnormal ambulatory pH study off PPI therapy for 7 days ■ normal or near-normal oesophageal motility	■ Total number of reflux events ≥73/24 h ■ A DeMeester Score (reflux-related) ≥14.7 ■ Positive symptom index (SI) ≥50% for symptoms troublesome for the patient, with a frequency of at least 3/24 hours; and ■ Macroendoscopically distinct mucosal breaks	■ pathologic oesophagal acid exposure as documented by a reflux-related DeMeester score ≥14.7 ■ symptom correlation ≥50% or reflux episodes
Exclusion criteria	■ BMI ≥35 kg/m^2 ■ hiatal hernia >2 cm ■ esophagitis grade D ■ Barrett's oesophagus ■ oesophageal stricture or ulcer ■ motility disorders ■ previously splenectomy ■ gastroparesis ■ pregnancy ■ immunosuppression ■ ASA >2 ■ portal hypertension ■ previous antireflux procedure	■ BMI ≥35 kg/m^2 ■ hiatal hernia >2 cm ■ esophagitis grade C or D ■ oesophageal stricture or ulcer ■ Hill grade valve III or IV ■ Barrett's oesophagus >2 cm ■ portal hypertension and/or varices ■ pregnancy ■ active gastroduodenal ulcer disease ■ gastroparesis, gastric outlet obstruction, or stenosis ■ coagulation disorder ■ history of any of the following: resective gastric or oesophageal surgery, antireflux surgery with anatomy unsuitable for transoral incisionless fundoplication (TIF) procedure per physician judgment, cervical spine fusion, Zenker's diverticulum, oesophageal epiphrenic diverticulum, achalasia,scleroderma ordermatomyositis, eosinophilic esophagitis, or cirrhosis	■ BMI ≥35 kg/m^2 ■ hiatal hernia >3 cm ■ Hill grade IV ■ esophagitis grade D ■ oesophageal ulcer ■ oesophageal stricture ■ Barrett's oesophagus (Prague: C > 1, M ≥ 2) ■ oesophageal motility disorder ■ severe gastric paralysis ■ pregnancy ■ immunosuppressive therapy ■ ASA >2 ■ portal hypertension ■ a history of: respective gastric/oesophageal surgery, cervical spine fusion, Zenker's diverticulum, oesophageal epiphrenic diverticulum, achalasia, scleroderma/ dermatomyositis, eosinophilic oesophagitis, cirrhosis/coagulation disorders	■ BMI >35 kg/m^2 ■ Hiatal hernia >2 cm ■ Esophagitis grade C or D ■ Oesophageal ulcer ■ Oesophageal stricture ■ Oesophageal motility disorder ■ Pregnancy ■ Immunosuppression ■ ASA >2 ■ Portal hypertension/varices ■ History of previous resective gastric/oesophageal surgery, cervical spine fusion, Zenker's diverticulum, oesophageal epiphrenic diverticulum, achalasia, scleroderma or dermatomyositis, eosinophilic esophagitis/cirrhosis ■ Active gastro-duodenal ulcer disease ■ Gastric outlet obstruction/ stenosis ■ Severe gastroparesis/delayed gastric emptying confirmed by solid-phase gastric emptying study if patient complains of postprandial satiety during assessment ■ Coagulation disorders	■ hiatal hernia detectable by gastroscopy or barium (≥2 cm) ■ Radiography ■ Oesophageal strictures ■ Barrett oesophagus with dysplasia; ■ Poor physical status (ASA III/IV); and ■ Pregnancy	■ hiatal hernia >2 cm ■ paraesophageal hernia ■ previous oesophageal or gastric surgery

Author, year	Witteman 2015 [39]	Trad 2014 [40], 2015 [41], 2017 [42], 2018 [43]	Håkansson, 2015 [44]	Hunter, 2015 [45]	Kaindlstorfer, 2013 [46]	Antoniou, 2011 [38]
Exclusion criteria *(continuation)*				■ Interprocedural determination of anatomical presentation which in the opinion of the surgeon does not allow safe device introduction		
Primary outcome measure	GERD symptoms → GERD-HRQL score	Elimination of daily troublesome GERD symptoms other than heartburn as evaluated by GERD-HRQL, RSI, and RDQ instruments.	Time to 'treatment failure' during the first 6 months after the intervention	Elimination of troublesome regurgitation assessed with the RDQ	Improvement of symptom scores, quality of life (GIQLI), and characteristics of oesophagal exposure to gastric contents	Improvement of quality-of-life and symptom scores (GIQLI)
Secondary outcome measures	■ Adverse events ■ Esophagel acid exposure ■ Number of reflux episodes ■ PPI usage ■ Appearance of the gastroesophageal valve ■ Healing of reflux esophagitis	■ normalization of esophageal acid exposure (EAE) ■ PPI usage ■ improvement in symptom scores ■ patient health satisfaction ■ healing of esophagitis	■ Gerd symptoms (QOLRAD questionnaire, GSRS) ■ PPI usage ■ Oesophageal acid exposure ■ Healing of reflux oesophagitis ■ Geometry of GOJ (Hill grading) ■ Adverse events (side-effects	■ Early failure: defined as moderate to severe regurgitation at any time >12 weeks after surgery and after a doubling of medication, PPI, or placebo ■ Control of intraesophageal acid exposure ■ Improvement in various symptom scores (particularly heartburn) ■ Healing of esophagitis ■ Common side effects associated with treatment (bloating and dysphagia) ■ Significant adverse events	NR	NR
Baseline patient characteristics (I vs. C)						
Age	Mean (SD): 42.4 (13.3) vs. 49.3 (11.3)	Median (range): *(2015)* 54.8 (35.7-73.3) vs. 50.1 (32.5-63.3)	Median (range): 41 (21-67) vs. 62 (31-76)	Median (range): 52 (22-74) vs. 55 (22-73)	Mean (SD): 45.3 (12.7) vs. 48.1 (13.7)	Mean (SD): 46.5 (NR) vs. 46.3 (NR)
Sex, female:male, n (%)	16 (40):24 (60) vs. 6 (30):14 (70)	*(2015)* 20 (51):19 (49) vs. 13 (62): 8 (38)	14 (63.3):8 (36.7) vs. 6 (30.0):16 (70.0)	40 (45.9):47 (54.1) vs. 26 (61.9):16 (38.1)	11 (29.7):26 (70.3) vs. 16 (48.5):17 (51.5)	NR
BMI	Mean (SD): 26 (3.7) vs. 26 (3.4)	*2015:* median (range): 28.9 (20.5-34.9) vs. 28.3 (24.5-34.9)	Median (range): 26.6 (18.6-33.9) vs. 27.5 (22.5-33.1)	Median (range): 27.1 (20.3-35.5) vs. 27.8 (20.4-38.9)	Mean (SD): 26.8 (3.5) vs. 28.5 (5.0)	Mean (SD): 27.12 (NR) vs. 28.20 (NR)
Hiatal hernia: none, n (%)	9 (23) vs. 9 (45)	*2015:* 3 (8) vs. 5 (24)	3 (13.6*) vs. 0 (0.0*)	27 (30.2) vs. 13 (31.0)	exact numbers are NR, but all patients had hiatal hernias ≤2 cm	Mean (SD): 27.12 (NR) vs. 28.20 (NR)
PPI therapy duration, median years (range)	NR	*2015:* 7 (1-25) vs. 8 (1-22)	6 (2-20) vs. 6 (2-18)	9 (1-30) vs. 8 (1-23)	NR	NR
Duration of GERD, median years (range)	4.5 (0.05-18.95) vs. 5.4 (0.33-20.30)	*2015:* 10 (2-50) vs. 10 (1-20)	10 (2-25) vs. 8 (2-30)	10 (0.6-37) vs. 10 (0.9-38)	NR	NR

Author, year	Witteman 2015 [39]	Trad 2014 [40], 2015 [41], 2017 [42], 2018 [43]	Håkansson, 2015 [44]	Hunter, 2015 [45]	Kaindlstorfer, 2013 [46]	Antoniou, 2011 [38]
Follow-up	6- & 12-months	6 months, 12 months *(2014)* [40] 6 months *(2015)* [41] 3 years *(2017)* [42] 5 years *(2018)* [43]	6 months	6 months	3 months	3 & 12 months
Lost to follow-up, n (%)	15 (25)	*(2014, 2015) at 6- & 12-months follow-up:* 3: 1 vs 2 *(2017) at 2-years follow-up:* 8 *(2017) at 3-years follow-up:* 11 *(2018) at 5-years follow-up:* 19	1 (4.6*) vs. 1 (4.6*)[32]	1 (1.2) vs. 1 (2.4)[33]	3 (8.1) vs. 4 (12.1)	1 (3.5*) vs. 3 (11.1*)
Effectiveness results						
GERD symptoms						
Overall HRQoL	**GERD-HRQL:** *Baseline/6-months follow-up, mean (SD):* 26.5 (8.0)/12.4 (10.0) p<0.001 vs. 28.2 (9.5)/ 25.1 (11.2) p=NR GERD-HRQL >50% impr. at 6 months follow-up, n (%): 20 (55) vs. 1 (5) p<0.001 *Baseline/6-months/ 12-months, mean (SD):* 27.1 (8.4)/ 11.1 (9.7) p<0.05/ 10.3 (7.8) p<0.05	**GERD-HRQL:** *Baseline/6-months off PPIs/12-months off PPIs, mean (SD), (2014):* 26.25 (10.51)/5.23 (7.14)/5.41 (6.80) 6-months vs. baseline: p<0.001 12-months vs. baseline: p<0.001 6-months vs. 12-months: p=0.995 *Baseline/6-months on PPIs/6-months after crossover, mean (SD), (2014):* 26.43 (7.22)/18.86 (9.12)/10.05 (13.54) 6-months PPI vs. baseline: p=0.053 6-months after crossover vs. baseline: p<0.001 6-months PPI vs. 6.months after crossover: p=0.020 *Baseline/3-year follow-up, mean (SD), (2017):* 26.4 (9.4)/5.0 (9.2), p<0.0001 *Baseline/5-year follow-up, mean (SD), (2018):* 26.4 (9.4)/6.8 (NR), p<0.001	**QOLRAD:** *Baseline (off PPIs)/6-months, median (range):* 4.9 (1.96-6.44)/6.4 (4.38-7) p=0.0005 vs. 4.8 (1.80-6.44)/5.2 (4.28-6.88) p=0.34	**GERD-HRQL:** Baseline, median (range): On PPIs: 25 (0-41) vs. 27 (7-45) p=0.108 Off PPIs: 29 (3-47) vs. 31 (9-50) p=0.450 Follow-up: NR	**GIQLI:** GIQLI scores were statistically significantly higher on follow-up in both groups with no statistical differences between the groups either at baseline or on follow-up. No exact values are vailable.	**GIQLI:** *Baseline/3-months/ 12-months, mean (SD):* 96.3 (NR)/114.2 (NR)/ 119.2 (NR) vs. 88.4 (NR)/114.7 (NR)/ 123.7 (NR) I vs. C: 3 months: p=0.99 12 monhs: p=0.66
Heartburn score	NR	**Heartburn (GERD-HRQL):** *Baseline/6-months off PPIs/12-months off PPIs, mean (SD), (2014):* 17.69 (7.51)/3.74 (5.51)/3.76 (4.50) 6-months vs. baseline: p<0.001 12-months vs. baseline: p<0.001 6-months vs. 12-months: p>0.999	NR	**Heartburn (RDQ):** *Baseline/6-months, median (25%, 75% quartiles):* 2.6 (1.5, 3.8)/0.5 (0, 1.6) p<0.001 vs 3.0 (2.0, 4.1)/ 0.8 (0, 2) p<0.001 I vs. C: p=0.936	NR	**Non-validated score:** *Baseline/3-months/ 12-months, mean (SD):* 2.50 (NR)/1.04 (NR)/ 1.07 (NR) vs. 2.96 (NR)/ 0.04 (NR)/0.17 (NR)

[32] An additional amount of 3 patients showed early failures in the control group.

[33] Additionally, 8 patients were excluded due to no troublesome regurgitation, 2 because of a normal pH at screening and 13 due to early failures.

Author, year	Witteman 2015 [39]	Trad 2014 [40], 2015 [41], 2017 [42], 2018 [43]	Håkansson, 2015 [44]	Hunter, 2015 [45]	Kaindlstorfer, 2013 [46]	Antoniou, 2011 [38]
Heartburn score *(continuation)*		*Baseline/6-months on PPIs/6-months after crossover, mean (SD), (2014):* 16.90 (5.75)/11.67 (6.94)/7.48 (9.81) 6-months PPI vs. baseline: p=0.078 6-months after crossover vs. baseline: p<0.001 6-months PPI vs. 6.months after crossover: p=0.189 **Heartburn (RDQ):** *Baseline/6-months off PPIs/12-months off PPIs, mean (SD), (2014):* 2.99 (2.55)/0.45 (0.86)/0.63 (1.01) 6-months vs. baseline: p<0.001 12-months vs. baseline: p<0.001 6-months vs. 12-months: p=0.776 For 2/3-years follow-up *(2017)* only a merged score including: heartburn, chest pain, indigestion or stomach acid coming up is available. 5-years follow-up *(2018)*: NR				I vs. C: 3 months: p<0.0001 12 monhs: p=0.01
GERSS	NR	NR	NR	*Baseline, median (range):* On PPIs: 22 (3-54) vs. 27 (8-56) p=0.052 Off PPIs: 30 (5-60) vs. 34 (9-60) p=0.185	NR	
Regurgitation score	NR	**Regurgitation (RDQ):** *Baseline/6-months off PPIs/12-months off PPIs, mean (SD) (2014):* 2.94 (1.45)/0.19 (0.40)/0.33 (0.69) 6-months vs. baseline: p<0.001 12-months vs. baseline: p<0.001 6-months vs. 12-months: p=0.995 *Elimination of troublesome regurgitation 1- vs. 2- vs. 3-years follow-up, n (%) (2017):* 42/48 (88) vs. 41/44 (90) vs. 37/41 (90) *Total regurgitation scores – baseline on PPIs/ 3-years follow-up off PPIs, mean (SD), (2017):* 3.0 (NR)/0.5 (NR), p<0.0001 *Elimination of troublesome regurgitation 5-years follow up, n (%):* 37/43 (86) *Total regurgitation scores – baseline on PPIs/ 3-years follow-up off PPIs, mean (SD), (2018):* 3.0 (NR)/0.7 (NR), p<0.001	NR	**Regurgitation (RDQ):** *Baseline/6-months, median (25%, 75% quartiles):* 3.5 (3, 4.3)/0.5 (0, 1.5) p<0.001 vs 3.8 (2.9, 4.5)/0.8 (0, 2) p<0.001 I vs. C: p=0.072 Eliminiation of troublesome regurgitation after 6 months follow-up, n (%): 58 (67) vs. 19 (45) I vs. C: p=0.023	NR	**Non-validated score:** *Baseline/3-months/12-months, mean (SD):* 1.52 (NR)/0.56 (NR)/0.57 (NR) vs. 1.96 (NR)/0.08 (NR)/0.11 (NR) I vs. C: 3 months: p=0.005 12 monhs: p<0.05

Author, year	Witteman 2015 [39]	Trad 2014 [40], 2015 [41], 2017 [42], 2018 [43]	Håkansson, 2015 [44]	Hunter, 2015 [45]	Kaindlstorfer, 2013 [46]	Antoniou, 2011 [38]
DeMeester score (baseline/ follow-up), mean (SD)	NR	*Baseline/6-months follow-up, mean (95% CI), (2015):* -11.6 (-17.4 to -5.9) p<0.001/-16.5 (-23.0 to -10.0) p<0.001 *Baseline/1-/2-/3-years follow-up, mean (SD) (2017):* 36.0 (12.2)/26.5 (15.2)/26.3 (16.3)/26.9 (18.2), all intervals vs. baseline p≤0.0173, between 1-, 2-, and 3-yeard´s follow-ups p≥0.9981 *2018:* NR	NR	33.6/23.9 p<0.001 vs 30.9/32.7 p=NS I vs. C: p=0.005	20.08 (14.00)/14.49 (14.13) p=0.078 vs. 25.85 (26.88)/1.08 (0.86) p=0.000 I vs. C: Baseline: p=0.262 Follow-up: p=0.000	NR
PPI usage (baseline/ follow-up), n (%)	*Baseline/6-months:* 40 (100)/9 (26) vs. 20 (100)/20 (100) Baseline/12 months: 60 (100)/20 (44)	*Baseline/6-months/12-months (excluding cross over) intervention group:* 39 (100)/NR (10)/NR (18) *1-year/2-years/3-years/5-years (after cross over, esxcluding lost to follow-up):* *13 (22*)/13 (24*)/ 15 (29*)/24 (54)*	22 (100)/9 (40.9) vs. 22 (100)/18 (81.8) I vs. C: p=0.01	NR	NR (91.43)/NR (35.48) vs. NR (89.29)/NR (16.00)	(96.2)/(11) vs. (93.8)/(52) I vs. C: 12 months: p<0.02
Barrett's oesophagus (<2 cm), n (%)	NR	NR	NR	NR	NR	NR
Reflux characteristics determined by pH testing	NR	*2015:* only Changes in Mean 48-Hour pH Parameters From Before Treatments to 6-Month Follow-Up in Both Treatment Groups are available. *Baseline/1-/2-/3-years follow-up, mean (SD) (2017):* Number of refluxes: 169.8 (80.0)/ 117.1 (61.8)/106.6 (50.8)/105.1 (72.8) Number of long refluxes (>5 min): 12.5 (6.2)/10.2 (7.2)/10.3 (8.1)/8.9 (7.4) Duration of longest reflux (min): 29.4 (15.0)/ 24.2 (14.8)/20.2 (23.4)/18.6 (19.1) Fraction time pH <4 (%): 10.5 (3.5)/ 7.6 (4.6)/7.7 (5.1)/7.8 (5.7)	NR	■ Total number of reflux episodes, baseline/ 6 months, mean: 135/94 p<0.001 vs. 125/122 p=NS I vs. C: p=0.003 ■ Fraction time pH < 4, baseline/6 months, %: 9.3/6.4 p<0.001 vs. 8.6/8.9 p=NS I vs. C: p=0.003	■ Total number of reflux episodes, baseline/ 3 months, mean (SD): 78.65 (42.62)/ 50.33 (31.98) p=0.000 vs. 80.70 (34.29)/13.83 (12.73) p=0.000 I vs. C: p=0.827/p=0.000	NR
Gastroesophageal junction anatomy assessed using endoscopy	*Baseline/6-months/ 12-months, n (%):* ■ Hiatal hernia: 42 (70)/ 20 (37)/25 (55) ■ Hill grade I: 4 (6)/ 21 (39)/16 (35) ■ Hill grade II: 34 (58)/ 22 (42)/16 (35) ■ Hill grade III: 18 (30)/ 20 (19)/11 (25) ■ Hill grade IV: 4 (6)/ 0 (0)/2 (5)	NR	*Baseline/6-months, n (%):* ■ Hiatal hernia: NR ■ Hill grade I: 0 (0.0*)/4 (26.7*) vs. 1 (7.1*)/1 (10.0*) ■ Hill grade II: 4 (26.7*)/ 8 (53.3*) vs. 2 (14.3*)/ 2 (20.0*) ■ Hill grade III: 11 (73.3*)/ 3 (20.0*) vs. 11 (78.6*)/ 5 (50.0*) ■ Hill grade IV: 0 (0.0*) 0 (0.0*) vs. 0 (0.0*)/2 (20.0*)	Baseline, n (%): ■ Hill grade I: 4 (4.6) vs. 5 (12.2) ■ Hill grade II: 57 (66.3) vs. 26 (63.4) ■ Hill grade III: 25 (29.1) vs. 10 (24.4)	NR	NR

Author, year	Witteman 2015 [39]	Trad 2014 [40], 2015 [41], 2017 [42], 2018 [43]	Håkansson, 2015 [44]	Hunter, 2015 [45]	Kaindlstorfer, 2013 [46]	Antoniou, 2011 [38]
Esophagitis	*Baseline/6-months, n (%):* 13 (33)/ 5 (14) p>0.05 vs. 6 (30)/2 (10) p=NR	*Complete healing/reduction in reflux esophagitis at 6-months (2015):* I (off PPIs): 90% (n=18/20) vs. C (on PPI): 38% (n=5/13); RR = 2.3, 95% CI = 1.2-4.7, p=0.018; *Baseline vs. 1- vs. 2- vs. 3-years follow-up, n (%), (2017)* 33/60 (55) vs. 3/59 (5) vs. 5/50 (10) vs. 5/51 (12) *2018:* NR	NR	*Baseline/6-months, n (%):* 17 (19.5)/7 (8.1*) vs. 6 (14.3)/5 (11.9*) De novo esophagitis eas present in 4 intervention patients and 5 control group patients after 6 months follow-up.	NR	NR
Safety results						
Any grade AEs, n (%)	Exact numbers of AEs are NR	*2014*: There were no reports of de novo dysphagia or bloating at 12-month follow-up; one patient reported de novo excess flatulence (from score 0 at screening on PPIs to score 3 off PPIs at 12-month follow-up). *6-months follow-up, I vs. C, n (%) (2015):* Elimination of daily troublesome **dysphagia:** 11/12 (92) vs. 6/8 (75), RR=1.2 (95% CI 0.8-1.9), p=0.366 **Dysphagia scores:** 1 patient in the I group reported worsening dysphagia (score from 1 to 4); in the C group, 2 patients reported worsening (score from 1 to 3 and score from 2 to 3). Improvement in **bloating**: 19/24 (79) vs. 4/16 (25), RR=3.2 (95% CI 1.3-7.6), p=0.009 **Bloating score:** of 5 patients in the I group who reported daily troublesome bloating at 6-month follow-up, 3 improved slightly (scores from 4 to 3) and 2 patients reported unchanged severity of bloating (scores 3 to 3 and scores 5 to 5); in the C group, of 12 patients who reported daily troublesome bloating at 6-month follow-up, 3 patients reported unchanged symptoms and 9 patients reported worsening of bloating. Elimination of daily troublesome **flatulence** at 6-month: 17/21 (81) vs. 2/12 (17), RR=4.9 (95% CI 1.3-17.5), p=0.016 *2018:* NR	Moderate to severe adverse events: ■ Dysphagia: 4 (18) vs. 2 (10) ■ Bloating: 4 (18) vs. 2 (10) ■ Flatulence: 2 (9) vs. 1 (5) ■ Post-operative epigastric and abdominal pain: 10 (45) vs. 1 (5) ■ Musculoskeletal pain (left shoulder): 3 (14) vs. 0 (0) ■ Vomiting: 1 (5) vs. 0 (0) ■ Diarrhoea: 0 (0) vs. 1 (5) → none of differences are statistically significant	With the exception of postoperative epigastric pain, complications, and adverse effects were not different between the treatment groups. One patient in the intervention group and 2 patients in the control group developed de novo dysphagia. The Gastroesophageal Reflux Symptom Scores for bloating and dysphagia were assessed but exact meassures are not reported.	Postprocedural gastric bleeding: 1 (2.7) vs. peritonitis and pneumoperitoneum: 1 (3.0)	No exact numbers are available, solely differences between baseline and follow-up of assessed Gastroesophageal Reflux Symptom Scores are available *Baseline/3 months/ 12 months, mean (SD values are NR):* Bloating: 1.88/1.32/1.50 vs.1.96/1.92/1.33 Diarrhea: 0.92/0.28/0.36 vs. 0.88/0.83/0.50 Gas: 1.80/1.52/1.43 vs. 2.08/2.50/2.22 Epigastric pain: 1.36/0.68/0.57 vs. 1.64/0.64/0.39 Dysphagia: 0.50/0.08/0.14 vs. 0.92/0.60/0.22 Asthma: 0.76/0.28/0.14 vs. 0.52/0.12/0.11 Hoarseness: 1.04/0.80/0.64 vs. 0.84/0.60/0.00 Cough: 1.52/0.72/0.71 vs. 1.08/0.52/0.29

Author, year	Witteman 2015 [39]	Trad 2014 [40], 2015 [41], 2017 [42], 2018 [43]	Håkansson, 2015 [44]	Hunter, 2015 [45]	Kaindlstorfer, 2013 [46]	Antoniou, 2011 [38]
SAEs, n (%)	Interventional group: ■ Pneumonia 3 (7.5*) ■ Severe epigastric pain: 1 (2.5*)	NR	See any grade AEs, since no difference was made between moderate and severe AEs.	SAEs are listed, without exact information on patient numbers.	NR vs. pneumatic dilatation due to severe dysphagia: 1 (3.0)	NR
Perioperative complications, n (%)	Interventional group: Pneumoperitoneum 1 (2.5*)	NR	NR	NR	NR	NR
Death, n (%)	1 patient who had undergone TIF procedure after crossover died, death occurred 11 months after the procedure.	NR	NR	NR	NR	NR
Re-surgery: ■ **Endoscopic, n** ■ **Laparoscopic, n**	■ None ■ 3 (1 from the TIF group and 2 patients who had crossed over to the TIF group)	■ No endoscopic re-operation was reported. **Laparoscopic surgery:** ■ NR (2014, 2015) ■ 2 re-operation between 1 and 2 years follow-up (DOR fundoplication & LNF) *(2017)* ■ 1 re-operation until 5-years follow-up (LNF) *(2017)* ■ *(2018):* NR	NR	NR	■ n=11 vs. n=0 ■ n=2 vs. n=2	NR

*Abbreviations: AEs – adverse events, ASA – American Society of Anaesthesiologists, BMI – body mass index, C – control group, GERD – gastroesophageal reflux disease, GIQLI – Gastrointestinal Quality of Life index, I – intervention group, LNF – Laparoscopic Nissen fundoplication, NR – not reported, NS – not significant, PPI – proton-pump inhibitors, SAEs – severe adverse events, TIF – transoral incisionless fundoplication, QOLRAD – Quality Of Life in Reflux and Dyspepsia, vs. – versus. * own calculation*

Table A-2: Endoscopic plication therapy: Results from non-randomised controlled trials

Author, year	Danalioglu, 2014 [47]
Study design	Prospective, non-randomised controlled trial
Country	Turkey
Sponsor	NR
Intervention/Product	SRS™ Endoscopic Stapling System (later on MUSE)
Comparator	Laparoscopic anti-reflux surgery: ■ Nissen fundoplication: n=9 ■ Toupet fundoplication: n=7
Study duration	September 2011 to December 2011
Number of pts, I vs. C	n=27, 11 vs. 16
Inclusion criteria	GERD with symptoms of more than 1-year duration: ■ typical symptoms responding to proton pump inhibitors [PPI] ■ presence of esophagitis at gastroscopy ■ Biopsy-proven Barrett's disease or a DeMeester score of >14.7 in pH-meter analysis were also considered evidence for GERD in symptomatic patients without esophagitis
Exclusion criteria	In the I group[34]: ■ BMI >35 ■ severe esophagitis ■ complications such as Barrett's, strictures or a hernia longer than 3 cm
Primary outcome measure	NR
Secondary outcome measure	NR
Baseline patient characteristics (I vs. C)	
Median age, years (range)	41 (26-60) vs. 38 (24-58)
Sex, female:male, n (%)	6 (54.5):5 (45.5) vs. 7 (43.8):9 (56.2)
■ **Mean BMI, (SD)** ■ **Hiatal hernia:none, n (%)** ■ **PPI therapy duration, median (range)** ■ **Duration of GERD, median (range)**	■ 26.6 (3.4) vs. 25.8 (3.9) ■ NR; hiatal hernia >3 cm, n: 0 vs. 4 ■ NR ■ NR
Follow-up (months)	Mean (SD): 5.9 (1.4)
Lost to follow-up, n (%)	NR
Effectiveness results	
GERD symptoms	
Overall HRQoL	GERD-HRQL: Mean GERD HRQL score improvement dropped in: 64% vs. 87%, p>0.05 from: 24.8 (5.9)/8.9 (9.2) vs. 29.3 (3.0)/4.1 (2.2) I vs. C: Baseline: p=0.192 Follow-up: p=0.016
Heartburn score	NR
Regurgitation score	NR
DeMeester score	NR
PPI usage (baseline/follow-up), n (%)	Baseline values are NR only after 6 months follow-up: 3 (27.3) vs. 1 (6.3) I vs. C: p>0.05
Barrett´s oesophagus (<2 cm), n (%)	NR
Reflux characteristics determined by pH testing	NR

[34] This exclusion criteria have not been applied to the control group, hence different baseline patient characteristics were present between groups.

Author, year	Danalioglu, 2014 [47]
Gastroesophageal junction anatomy assessed using endoscopy	NR
Esophagitis (baseline/follow-up), n (%)	Follow-up values are NR only baseline values: 5 (45.5) vs. 14 (87.5) p=NR
Safety results	
Any grade AEs, n (%)	The mean discharge times for the control and the intervention groups were 1.2 and 3 days, respectively (p<0.05). Excluding the complicated patient in the intervention group who stayed 21 days, the length of hospital stay was nearly identical in both groups: 1.2 for the intervention group and 1.1 days for the control group (p<0.05).
SAEs, n (%)	1 (9.1) vs. 0 (0.0) p=0.219 During the study period, only one major complication was observed in the intervention group (i.e. a patient who experienced chest pain and odynophagia soon after the procedure)
Perioperative complications, n (%)	NR
Death, n (%)	NR
Re-surgery: ■ **Endoscopic** ■ **Laparoscopic**	NR

*Abbreviations: AEs – adverse events, BMI – body mass index, C – control group, GERD – gastroesophageal reflux disease, I – intervention group, NR – not reported, NS – not significant, PPI – proton-pump inhibitors, SAEs – severe adverse events, vs. – versus. * own calculation*

Table A-3: Endoscopic plication therapy: Results from observational studies

Author, year	Bell 2012 [48] & 2014 [49], Wilson 2014 [50]
Study design	Prospective, open-label, multicenter, single-arm study
Country	US
Sponsor	EndoGastric Solutions
Intervention/Product	EsophyX2 device
Comparator	None
Study duration	1 year (January 2010 – February 2011)
Number of pts.	*Total cohort 6-/12-month follow-up*: n=100[35] Typical subgroup: n=38 LPR subgroup[36]: n=51 *Total cohort 24-month follow-up*: n=127
Inclusion criteria	■ Chronic GERD ■ 18-75 years ■ GERD duration >1 year ■ History of daily PPIs use >6 months ■ Moderate to severe typical or atypical GERD symptoms off PPIs ■ Complete (responders) or partial (non-responders) symptom control on PPIs ■ Deteriorated gastroesophageal junction (Hill grade II or III) ■ Proven gastroesophageal reflux by either endoscopy, ambulatory pH, or barium swallow testing ■ Willingness to undergo pH/impedance testing, if required ■ Willingness to adhere to a postoperative diet for 6 weeks ■ Availability for follow-up visits at 6 months and 12 months ■ Willingly and cognitively signed informed consent

[35] Of the 100 pts. enrolled, 4 lacked complete quality of life questionnaires and 7 did not meet stratification criteria because their preoperative GERD-HRQL, GERSS and RSI were within normal. Of the remaining 89 pts., 38 had dominant typical GERD symptoms and comprised the typical symptom group. The remaining 51 pts. had dominant laryngopharyngeal reflux (LPR) symptoms (88.0% of these had bothersome typical symptoms as well), and comprised the LPR group.

[36] Pts. with total RSI score >19 are considered to have LPR.

Author, year	Bell 2012 [48] & 2014 [49], Wilson 2014 [50]
Exclusion criteria	■ BMI >35 kg/m^2 ■ Incompletely reducible hiatal hernia with residual of >5 mm ■ Esophagitis grade D; Barrett's oesophagus >2 cm; oesophageal ulcer; fixed oesophageal stricture or narrowing ■ Portal hypertension and/or varices ■ Active gastroduodenal ulcer disease ■ Gastric outlet obstruction or stenosis ■ Gastroparesis or delayed gastric emptying confirmed by solid-phase gastric emptying study, if patient complains of postprandial satiety during assessment ■ Coagulation disorder ■ History of any of the following: resective gastric or oesophageal surgery, antireflux surgery with anatomy unsuitable for TIF procedure per physician judgment, cervical spine fusion, Zenker's diverticulum, oesophageal epiphrenic diverticulum, achalasia, scleroderma or dermatomyositis, eosinophilic esophagitis, or cirrhosis ■ Pregnancy or plans of pregnancy in the next 12 months ■ Enrolment in another device or drug study that may confound the results
Primary outcome measure	Typical and atypical GERD symptoms: ■ 3 standardised and validated questionnaires: GERD-HRQL (including the separate total heartburn score), GERSS, RSI ■ 1 non-validated regurgitation score
Secondary outcome measures	■ PPI usage ■ Satisfaction with the current health condition (GERD-HRQL, RIS, GERSS) ■ Reflux characteristics determined by pH testing ■ Gastroesophageal junction anatomy assessed using EGD (i.e., reflux esophagitis, size of hiatal hernia, GEJ [hill grade]) ■ AEs: serious (intraoperative and postoperative, e.g. mediastinitis, oesophagal perforation, blood transfusion), device- or procedure-related, post fundoplication side effects, re-surgery
Baseline patient characteristics	
Median age, years (range) **Mean age, years (SD)**	*Total cohort 6-/12-month follow-up*: 53 (18-75) Typical subgroup: 55 (23-74) LPR subgroup: 53 (19-75) *Total cohort 24-month follow-up*: 53.1 (13.4)
Sex, female: n (%)	*Total cohort 6-/12-month follow-up*: 65 (65.0) Typical subgroup: 20 (53.0) LPR subgroup: 39 (76.0) *Total cohort 24-month follow-up*: 86 (67.7)
Median BMI, (range) **Mean BMI, (SD)**	*Total cohort 6-/12-month follow-up*: 26.4 (18.0-35.1) Typical subgroup: 26.7 (18.2–34.9) LPR subgroup: 25.1 (18.0–35.1) *Total cohort 24-month follow-up*: 26.8 (4.3)
Duration of GERD, median years (range) **Duration of GERD, mean years (SD)**	*Total cohort 6-/12-month follow-up:* 9 (1–35) Typical subgroup: 7 (1–35) LPR subgroup: 10 (1–24) *Total cohort 24-month follow-up:* 10 (6.9)
PPI therapy duration, median years (range) **PPI therapy duration, mean years (SD)**	*Total cohort 6-/12-month follow-up:* 7 (1–20) Typical subgroup: 8 (1–20) LPR subgroup: 6 (1–20) *Total cohort 24-month follow-up:* 8.3 (5.9)
Barrett's esophagus (<2 cm), n (%)	*Total cohort 6-/12-month follow-up*: 5 (5.0) Typical subgroup: 4 (11.0) LPR subgroup: 0 (0.0) *Total cohort 24-month follow-up*: 6 (4.7)

Author, year	Bell 2012 [48] & 2014 [49], Wilson 2014 [50]
Hiatal hernia: none, n (%)	*Total cohort 6- & 12-month follow-up*: 21* (21*) Typical subgroup: 11* (29*) LPR subgroup: 8* (16*) *Total cohort 24-month follow-up*: 44* (34.6*)
Follow-up (months)	6 months [48] 12 months [50] 24 months [49]
Lost to follow-up, n (%)	At 6-month follow-up: NR At 12-month follow-up: 4 (4.0*) At 24-month follow-up: 19 (15.0)
Effectiveness results	
GERD symptoms	
Overall HRQoL	**GERD-HRQL:** *At 6-month follow-up:* **n (%):** Total score ≤12: 63 (76) Total score ≤6: 49 (59) **Median reduction from baseline to follow-up (range):** Total cohort (n=85): 26 (4-47) vs. 4 (0-44), p<0.001 Typical subgroup: 22 (5-38) vs. 5 (0-35), p<0.001 *At 12-month follow-up:* **n (%):** Total score reduction by ≥50%: 62 (73) Total score normalization: 55 (65) **Median reduction from baseline to follow-up (range):** Total cohort: 26 (4-47) vs. 4 (0-44), p<0.001 *At 24-month follow-up (n=96)*: **n (%):** Total score reduction by ≥50%: 63 (66.0) **Median reduction from baseline to follow-up (range):** Total cohort: 26 (10-47) vs. 6 (0-36), p<0.001
Heartburn score	*At 6-month follow-up:* **Elimination of daily bothersome heartburn symptoms, n (%):** Total cohort: 61/85 (72) Typical subgroup: 25 (66) **Median reduction from baseline to follow-up (range):** Total cohort: 19 (0-30) vs. 3 (0-25), p<0.001 Typical subgroup: 16 (2-30) vs. 4 (0-24), p<0.001 *At 12-month follow-up:* Total score reduction by ≥50%: 62 (73) Total score normalization: 66 (78) **Median reduction from basline to follow-up (range):** Total cohort: 19 (0-30) vs. 1 (0-27), p<0.001 *At 24-month follow-up*: Total score reduction by ≥50% in 53 of 78 (68) patients
RIS (LPR symptoms)	*At 6-month follow-up:* **n (%):** Total score ≤13: 47/67 (70) LPR subgroup score ≤13: 35 (69) **Median reduction from baseline to follow-up (range):** Total cohort: NR LPR subgroup: 28 (20-41) vs. 7 (0-44), p<0.001

Author, year	Bell 2012 [48] & 2014 [49], Wilson 2014 [50]
RIS (LPR symptoms) *(continuation)*	*At 12-month follow-*up (n=72): **n (%):** Total score reduction by ≥50%: 53 (74) Total score ≤13: 46 (64) **Median reduction from baseline to follow-up (range):** Total cohort: 24 (14-41) vs. 6 (0-44), p<0.001 *At 24-month follow-up (n=82)*: **n (%):** Total score reduction by ≥50%: 53 (65) Total score ≤13: 53 (65) **Median reduction from baseline to follow-up (range):** Total cohort: 24 (14-41) vs. 6 (0-3), p<0.001
GERSS	*At 6-month follow-up (n=59):* **n (%):** Total score ≤18: 51 (86) **Median reduction from baseline to follow-up (range):** Total cohort: 35 (19-60) vs. 4 (0-54), p<0.0001 *At 12-month follow-up:* **n (%):** Total score reduction by ≥50%: 51 (86) Total score ≤18: 52 (88) **Median reduction from baseline to follow-up (range):** Total cohort: 35 (19-60) vs. 4 (0-54), p<0.001 *At 24-month follow-up (n=68)*: **n (%):** Total score reduction by ≥50%: 49 (72) Total score ≤18: 50 (74) **Median reduction from baseline to follow-up (range):** Total cohort: 35 (19-60) vs. 5 (0-48), p<0.001
Reguration score	*At 6-month follow-up:* **Elimination of daily bothersome regurgitation symptoms, n (%):** Total cohort: 76 (89.0) Typical subgroup: 33 (87.0) **Median reduction from baseline to follow-up (range):** Total cohort: 16 (0-30) vs. 0 (0-25), p<0.001 Typical subgroup: 10 (0-30) vs. 1 (0-16), p<0.001 *At 12-month follow-up:* **n (%):** Total score reduction by ≥50%: 46 (79) Total score normalization: 48 (83) **Median reduction from baseline to follow-up (range):** Total cohort: 20 (6-30) vs. 0 (0-25), p<0.001 *At 24-month follow-up*: **n (%):** Total score reduction by ≥50%: 62 (70) **Median reduction from baseline to follow-up (range):** Total cohort: 19 (6-30) vs. 1 (0-30), p<0.001
DeMeester score	NR
PPI usage, n (%)	*Basline vs. 6-months (n=96) vs. 12-months follow-up,* %: **Off/Occasional/Daily PPI:** 8 vs. 80 vs. 74/0 vs. 9 vs. 3/92 vs. 11 vs. 22 *At 24-month follow-up:* Daily PPI use was eliminated in 69 of 98 pts. (70%) and 29 of 98 pts. (30%) continued daily use of PPI.

Author, year	Bell 2012 [48] & 2014 [49], Wilson 2014 [50]
Reflux characteristics determined by pH testing[37]	*Baseline/6 months/12 months/24 months:* ■ Number of refluxes: 119.7 (68.9)/84.6 (54.1)/84.6 (55.6)/71.4 (50.6) ■ Number of long refluxes (>5 min): 9.7 (5.8)/6.2 (5.1)/6.7 (4.1)/5.8 (6.0) ■ Duration of longest reflux, min: 40.6 (59.4)/21.3 (24.02)/21.5 (12.6)/22.5 (19.7) ■ Fraction time pH <4, %: 8.9 (5.0)/5.6 (4.6)/6.1 (4.7)/5.2 (3.4)
Gastroesophageal junction anatomy assessed using EGD	*At 6-month follow-up (n=41),* n (%): ■ Hill grade improvement: 33 (80) ■ Hill grade stagnation: 6 (15) ■ Hill grade deterioation: 2 (5) *At 6-month follow-up (n=43),* n (%): ■ Complete reduction of hiatal hernia: 29 (67) ■ Reduction of hiatal hernia to some extent: 7 (16) ■ Existing hiatal hernia (based on screening): 36 (84) *At 12-month follow-up (n=36),* n (%) ■ Complete reduction of hiatal hernia: 25 (69) ■ Reduction of hiatal hernia to some extent: 29 (81) ■ Existing hiatal hernia (based on screening): 5 (14*) *At 24-month follow-up (n=31),* n (%) ■ Hill Grade I valve: 23 (74) ■ Eliminated or reduced hiatal hernia (n=27), 17 (63) ■ De novo hiatal hernia: 2 (6.5*)
Esophagitis (assessed with EGD)	*At 6-month follow-up (n=20)*, n (%): ■ Healed: 15 (75) ■ Improved: 2 (10) ■ Unchanged: 3 (15) *At 12-month follow-up (n=17)*, n (%) ■ Healed: 13 (76) ■ Improved: 2 (12) ■ Unchanged: 1 (6*) ■ Worsening: 1 (6*) *At 24-month follow-up,* n (%) With esophagitis: 16 (52) ■ Healing: 12 (75) ■ De novo Grade A or B: 2 (13)
Safety results	
Any grade AEs, n (%)	Postoperative pain (n=127): 50 (39) ■ Mild: 43 (86) ■ Moderate: 6 (12) ■ Severe: 1 (2) ***Symptom score improvements:*** *At 6-month follow-up* (baseline vs. follow-up), n (%): ■ Dysphagia improvement: 27 vs. 3 ■ Bloating improvement: 47 vs. 5 ■ Flatulence improvement: 43 vs. 5 *At 12-month follow-up* (baseline vs. follow-up): **Median (range):** ■ Dysphagia score improvement: 1 (0-5) vs. 0 (0-5), p<0.001 ■ Bloating score improvement: 2 (0-5) vs. 0 (0-5), p<0.001 ■ Flatulence score improvement: 2 (0-5) vs. 0 (0-5), p<0.001

[37] Information is based on the publication by Bell et al. 2014.

Author, year	Bell 2012 [48] & 2014 [49], Wilson 2014 [50]
Any grade AEs, n (%) *(continuation)*	**n (%):** ■ De novo dysphagia: 2 ■ De novo bloating: 1 ■ Worsening flatulence: 2 *At 24-month follow-up* (baseline vs. follow-up): **Median (range):** ■ Dysphagia GERD-HRQL improvement: 2 (0-5) vs. 0 (0-5), p<0.001 ■ Dysphagia GERSS improvement: 6 (0-12) vs. 0 (0-6), p<0.001 ■ Bloating GERD-HRQL improvement: 2 (0-5) vs. 0 (0-5), p<0.001 ■ Flatulence score improvement: 3 (0-5) vs. 0 (0-5), p<0.001 **n (%):** ■ De novo dysphagia: 0 ■ De novo bloating: 0 ■ Worsening flatulence: 2
SAEs, n (%)	■ Extra hospital day due to pain, anxiety, nausea or postoperative urinary retention (n=127): 17 (13.4) ■ Additional 4 hospital days due to pulmonary issues: 1 (0.8*)[38] ■ Re-admittion 2 days after the procedure due to immediate postoperative pain: 1 (0.8*)
Perioperative complications, n (%)	NR
Death, n (%)	0 (0)
Re-surgery, n (%) ■ **Endoscopic** ■ **Laparoscopic** ■ **Endoscopic** ■ **Laparoscopic**	*At 6-month follow-up*: NR *Between 6- and 12-month follow-up*: 6 (6.3)[39] ■ 1 (17) ■ 5 (83) *Between 12- and 24-month follow-up:* 2 (NR) ■ 0 (NR) ■ 2 (NR)

Abbreviations: AEs – Adverse events, BMI – Body mass index, EDG – Esophagogastroduodenoscopy, GEJ – Gastroesophageal junction, GERD – Gastroesophageal reflux disease, GERD-HRQL – Gastroesophageal reflux disease health-related quality of life, GERSS – Gastroesophageal reflux symptom score, GTD – Greatest transverse dimension, LPR – Laryngopharyngeal reflux, NR – Not reported, PPI – Proton pump inhibitor, Pts. – Patients, QoL – Quality of life, RSI – Reflux symptom index, SD – Standard deviation, TIF – Transoral incisionless fundoplication, US – United States

* *Own calculation*

[38] This patient had a history of chronic lung disease.

[39] Revisional procedure due to recurrence of severe GERD symptoms that could not be controlled with PPIs between 8 and 11 months after TIF. The worst clinical outcomes observed during the study were assigned to these 6 pts. who were considered as failures. All 6 pts. were on daily PPIs before TIF. 1/6 pts. had a 3 cm hiatal hernia at screening. 1/6 pts. had severe vomiting after the procedure and 2/6 pts. did not follow the recommended postoperative diet.

Risk of bias tables and GRADE evidence profile

The internal validity of the included studies was judged by two independent researchers. In case of disagreement, a third researcher was involved to solve the differences. A more detailed description of the criteria used to assess the internal validity of the individual study designs can be found in the Internal Manual of the AIHTA [53] and in the Guidelines of EUnetHTA [54].

Table A-4: The Cochrane Collaboration's tool version 1.0 for assessing the risk of bias of randomized-controlled studies [28]

Trial: Author, year [Reference]	Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding		Incomplete outcome data	Selective outcome reporting unlikely	No other aspects which increase the risk of bias	Risk of bias – study level
			Patient	Treating Physician				
Wittemann, 2015 [39]	Yes	Yes	No	No	Yes	No[40]	Unclear[41]	**High**
Trad, 2014, 2015, 2017 & 2018 [43]	Yes	Yes	No	No	Yes	No[42]	No[43]	**High**
Håkansson, 2015 [44]	Yes	Yes	Yes	Yes	Yes	Unclear[44]	No[45]	**Moderate**
Hunter, 2015 [45]	Yes	Yes	Yes	No	Yes	No[40]	No[44]	**Moderate**
Kaindlstorfer, 2013 [46]	Yes	Unclear	No	No	Yes	No[46]	Unclear[47]	**High**
Antoniou, 2011 [38]	No	No	No	No	Yes	No[48]	Unclear[47]	**High**

[40] Detailed information on adverse events is missing.

[41] Due to crossover of patients after just 6 months of follow-up.

[42] Detailed information on adverse events is missing especially for longer follow-up analyses after 6 months.

[43] The study was sponsored by the manufacturer of the intervention and after 6-months patients were able to crossover to the intervention group.

[44] Several outcomes such as perioperative complications, re-surgery etc. as well as follow-up results e.g. for HRQoL are not reported.

[45] The study was sponsored by the manufacturer of the intervention.

[46] Several exact results are lacking which are solely presented in figures such as the GIQLI score or the total number of PPI usage.

[47] No funding information available.

[48] Several values are missing such as exact numbers of adverse events and standard deviations of GIQLI scores.

Table A-5: Outcome – specific risk of bias of non-randomised studies comparing, see [3]

	Author, year [reference]		
	Signalling questions	**Description**	**Response options**
Bias due to confounding			
	1.1 Is there potential for confounding of the effect of intervention in this study? If N/PN to 1.1: the study can be considered to be at low risk of bias due to confounding and no further signalling questions need be considered		PY
	If Y/PY to 1.1: determine whether there is a need to assess time-varying confounding:	Exclusion criteria were only valid for the intervention group. Therefore, different baseline characteristics were present between groups.	
	1.2 Was the analysis based on splitting participants' follow up time according to intervention received? If N/PN, answer questions relating to baseline confounding (1.4 to 1.6) If Y/PY, go to question 1.3.		N
	1.3 Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome? If N/PN, answer questions relating to baseline confounding (1.4 to 1.6) If Y/PY, answer questions relating to both baseline and time-varying confounding (1.7 and 1.8)		
	Questions relating to baseline confounding only		
	1.4 Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	No analysis method that controls for confounding was mentioned.	PN
	1.5 If Y/PY to 1.4: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?		
	1.6 Did the authors control for any post-intervention variables that could have been affected by the intervention?		
	Questions relating to baseline and time-varying confounding		
	1.7 Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	See the previous comment	PN
	1.8 If Y/PY to 1.7: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?		
	Risk of bias judgement	**Critical**	
	Optional: What is the predicted direction of bias due to confounding?	Favours experimental	
Bias in selection of participants into the study			
	2.1 Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? If N/PN to 2.1: go to 2.4		N

	Author, year [reference]		
	Signalling questions	**Description**	**Response options**
	2.2 If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention? 2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?		
	2.4 Do start of follow-up and start of intervention coincide for most participants?		Y
	2.5 If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?		
	Risk of bias judgement	**Low**	
	Optional: What is the predicted direction of bias due to selection of participants into the study?	Towards null	
Bias in classification of interventions			
	3.1 Were intervention groups clearly defined?		Y
	3.2 Was the information used to define intervention groups recorded at the start of the intervention?		Y
	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?		PN
	Risk of bias judgement	**Low**	
	Optional: What is the predicted direction of bias due to classification of interventions?	Towards null	
Bias due to deviations from intended interventions			
	If your aim for this study is to assess the effect of assignment to intervention, answer questions 4.1 and 4.2		
	4.1 Were there deviations from the intended intervention beyond what would be expected in usual practice?	Different baseline characteristics of groups due to different exclusion criteria.	PY
	4.2 If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups *and* likely to have affected the outcome?		PY
	If your aim for this study is to assess the effect of starting and adhering to intervention, answer questions 4.3 to 4.6		
	4.3 Were important co-interventions balanced across intervention groups?		NI
	4.4 Was the intervention implemented successfully for most participants?		PY
	4.5 Did study participants adhere to the assigned intervention regimen?		PY
	4.6 If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?		
	Risk of bias judgement	**Serious**	
	Optional: What is the predicted direction of bias due to deviations from the intended interventions?	In favour of the intervention arm.	

	Author, year [reference]		
	Signalling questions	**Description**	**Response options**
Bias due to missing data			
	5.1 Were outcome data available for all, or nearly all, participants?		PN
	5.2 Were participants excluded due to missing data on intervention status?		NI
	5.3 Were participants excluded due to missing data on other variables needed for the analysis?		NI
	5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?		NI
	5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?		NI
	Risk of bias judgement	**Moderate**	
	Optional: What is the predicted direction of bias due to missing data?	Unpredictable	
Bias in measurement of outcomes			
	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?		PY
	6.2 Were outcome assessors aware of the intervention received by study participants?		Y
	6.3 Were the methods of outcome assessment comparable across intervention groups?		Y
	6.4. Were any systematic errors in measurement of the outcome related to intervention received?		NI
	Risk of bias judgement	**Serious**	
	Optional: What is the predicted direction of bias due to measurement of outcomes?	Unpredictable	
Bias in selection of the reported result			
	Is the reported effect estimate likely to be selected, on the basis of the results, from ...		
	7.1 ... multiple outcome *measurements* within the outcome domain?		PN
	7.2 ... multiple *analyses* of the intervention-outcome relationship?		PN
	7.3 ... different *subgroups*?		PN
	Risk of bias judgement	**Low**	
	Optional: What is the predicted direction of bias due to selection of the reported result?	Towards null	
Overall bias			
	Risk of bias judgement	**Serious**	
	Optional: What is the overall predicted direction of bias for this outcome?	Unpredictable	

Table A-6: Risk of bias – study level (case series), IHE checklist [30]

Study reference/ID	Bell 2012 [48] Wilson 2014 [50] Bell 2014 [49][49]
Study objective	
1. Was the hypothesis/aim/objective of the study clearly stated?	Yes
Study design	
2. Was the study conducted prospectively?	Yes
3. Were the cases collected in more than one centre?	Yes
4. Were patients recruited consecutively?	Yes
Study population	
5. Were the characteristics of the patients included in the study described?	Yes
6. Were the eligibility criteria (i.e. inclusion and exclusion criteria) for entry into the study clearly stated?	Yes
7. Did patients enter the study at a similar point in the disease?	Yes
Intervention and co-intervention	
8. Was the intervention of interest clearly described?	Yes
9. Were additional interventions (co-interventions) clearly described?	Yes[50]
Outcome measures	
10. Were relevant outcome measures established a priori?	Yes
11. Were outcome assessors blinded to the intervention that patients received?	Unclear
12. Were the relevant outcomes measured using appropriate objective/subjective methods?	Yes
13. Were the relevant outcome measures made before and after the intervention?	Yes
Statistical Analysis	
14. Were the statistical tests used to assess the relevant outcomes appropriate?	Yes
Results and Conclusions	
15. Was follow-up long enough for important events and outcomes to occur?	Yes
16. Were losses to follow-up reported?	Partial[51]
17. Did the study provided estimates of random variability in the data analysis of relevant outcomes?	Partial
18. Were the adverse events reported?	Partial[52]
19. Were the conclusions of the study supported by results?	Yes
Competing interests and sources of support	
20. Were both competing interests and sources of support for the study reported?	Yes
Overall Risk of bias	**Moderate**

[49] The three publications report on different follow-up period (6, 12, 24 months) of the same clinical trial (NCT01118585). Therefore, a joint risk of bias assessment was performed.

[50] PPI usage.

[51] The lost-to follow-up numbers were reported in the publication of the 24-month follow-up in more detail (Figure 1); however, the first two publications reported on a total number of 100 patients, while the 24-month publication report on 127 patients. Furthermore, most of the scores are reported for different patient subgroups, therefore, it is not always clear for how many patients one score was assessed.

[52] Adverse events (including severe and procedure-/device-related adverse events) were only reported selectively in a narrative form.

Table A-7: Evidence profile: efficacy and safety of endoscopic plication therapy

Certainty assessment							Impact	Certainty (Importance)
№ of studies (Pts I vs. C)	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**		
Efficacy								
Overall health-related quality of life (follow up: mean 6 months; assessed with: GERD-HRQL [n=2], QOLRAD [n=1], GIQLI [n=1])								
4 [39-44, 46] (139 vs. 98)	RCT	serious [a]	serious [b]	serious [c]	not serious	none	1 study (**GERD-HRQL**) reported a ss improvement between the study groups (p<0.001), 2 other studies reported ss improvements from baseline to 6-months post operating (**GERD-HRQL:** p<0.001 and **QOLRAD:** p=0.0005), 1 study (**GIQLI**) reported no ss differences between study groups at baseline and after follow-up **Ranges of GERD-HRQL scores, I vs. C, baseline/6-months, mean (n=2):** 26.25-26.5/5.23-12.4 vs. NR **GIQLI (n=1):** no exact values available **QOLRAD score, I vs. C, baseline/6-months, median (n=1):** 4.9/6.4 vs. 4.8/5.2	⊕◯◯◯ **VERY LOW (Critical)**
Overall health-related quality of life (follow up: mean 12 months; assessed with: GIQLI [n=1])								
1 [38] (30 vs. 30)	RCT	serious [e]	not serious	not serious	serious [d]	none	no ss. improvement between study groups: **GIQLI:** p=0.66 **GIQLI score, I vs. C, baseline/12-months, mean (n=1):** 96.3/119.2 vs. 88.4/123.7	⊕⊕◯◯ **LOW (Critical)**
Overall health-related quality of life (follow up: mean 6 months; assessed with: GERD-HRQL [n=1])								
1 [47] (11 vs. 16)	NRCT	serious [e]	not serious	not serious	serious [d]	none	ss improvements in the control group at 6-months follow-up: **GERD-HRQL:** p=0.016 **GERD-HRQL score, I vs. C, baseline/6-months, mean (n=1):**24.8/8.9 vs. 29.3/4.1	⊕⊕◯◯ **LOW (Critical)**
Heartburn score (follow up: mean 6 months; assessed with: GERD-HRQL [n=1], RDQ [n=2][53])								
2 [40-43, 45] (127 vs. 65)	RCT	serious [f]	not serious	serious [b]	not serious	none	1 study reported a ss improvement (**RDQ:** p<0.001; **GERD-HRQL:** p<0.001) from baseline to 6-months post operating, 1 study reported a ss improvement (**RDQ:** p<0.001) from baseline to follow-up, but no ss improvement between study groups (p=0.936) **RDQ score, I vs. C, baseline/6-months, mean (n=1):** 2.99/0.45 vs. NR **RDQ score, I vs. C, baseline/6-months, median (n=1):** 2.6/0.5 vs. 3.0/0.8 **GERD-HRQL, I vs. C, baseline/6-months, mean (n=1):** 17.69/3.74 vs. NR	⊕⊕◯◯ **LOW (Critical)**
Heartburn score (follow up: mean 12 months; assessed with: non validated heartburn score [n=1])								
1 [38] (30 vs. 30)	RCT	serious [e]	not serious	not serious	serious [d]	none	ss improvement between treatment groups: **non-validated score:** p=0.01 **Non-validated score, I vs. C, baseline/12-months, mean (n=1):** 2.50/1.07 vs. 2.96/0.17	⊕⊕◯◯ **LOW (Critical)**

[53] In one study GERD-HRQL as well as RDQ was used to assess heartburn symptoms.

Certainty assessment							Impact	Certainty (Importance)
Nº of studies (Pts I vs. C)	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
Regurgitation score (follow up: mean 6 months; assessed with: RDQ [n=2])								
2 [40-43, 44] (127 vs. 65)	RCT	serious [f]	not serious	serious [b]	not serious	none	1 study reported a ss improvement (**RDQ:** p<0.001) from baseline to 6-months postoperating, 1 study reported a ss improvment (**RDQ:** p<0.001) from baseline to follow-up, but no ss improvment between study groups (**RDQ:** p=0.072) **RDQ score, I vs. C, baseline/6-months, mean (n=1):** 2.94/0.19 vs. NR **RDQ score, I vs. C, baseline/6-months, median (n=1):** 3.5/0.5 vs. 3.8/0.8	⨁⨁◯◯ **LOW (Critical)**
Regurgitation score (follow up: mean 12 months; assessed with: non validated regurgitation score [n=1])								
1 [38] (30 vs. 30)	RCT	serious [e]	not serious	not serious	serious [d]	none	ss improvement between treatment groups: **non-validated score:** p<0.05 **Non-validated score, I vs. C, baseline/12-months, mean (n=1):** 1.52/0.57 vs. 1.96/0.11	⨁⨁◯◯ **LOW (Critical)**
Safety								
Any adverse event (follow up: range 3 months to 12 months; assessed with: number of patients)								
4 [40-46] (186 vs. 120)	RCT	serious [g]	serious [c]	serious [b]	not serious	none	1 study reported a ss improvement in bloating between study groups (p=0.009), but no ss difference between groups considering dysphagia (p=0.366), 1 study reported more percentages of patients suffering from moderate to severe AEs in the intervention group compared to the control group 2 studies reported no ss differences between study groups	⨁◯◯◯ **VERY LOW (Critical)**
Any adverse event (follow up: mean 6 months; assessed with: discharge time)								
1 [47] (11 vs. 16)	NRCT	serious [e]	not serious	not serious	serious [d]	none	The mean discharge times for the control and the intervention groups were 1.2 and 3 days, respectively (p<0.05) → except for one complicated patient in the intervention group who stayed 21 days.	⨁⨁◯◯ **LOW (Critical)**
Any adverse event (follow up: range 6 to 24 months; assessed with: number of patients)								
1 [48-50] (100 vs. -) [h]	observational study	not serious	not serious	not serious	not serious	none	Overall dysphagia, bloating and flatulence improved comparing baseline with 6-months follow-up. After 12-month follow-up de novo dysphagia (n=2), bloating (n=1), and flatuence (n=2) occured. After 24-month follow-up de novo flatulence occured in 2 patients.	⨁⨁◯◯ **LOW (Critical)**
Severe adverse events (follow up: range 3 to 12 months; assessed with: number of patients)								
3 [39, 44, 46] (99 vs. 75)	RCT	not serious	serious [c]	not serious	not serious [i]	none	All 3 studies reported no ss differences between study groups.	⨁⨁⨁◯ **Moderate (Critical)**
Severe adverse events (follow up: range 3 to 12 months; assessed with: number of patients)								
1 [47] (11 vs. 16)	NRCT	serious [e]	not serious	not serious	serious [d]	none	No ss difference between treatment groups (p=0.219).	⨁⨁◯◯ **LOW (Critical)**

Certainty assessment							Impact	Certainty (Importance)
№ of studies (Pts I vs. C)	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
Severe adverse events (follow up: mean 6 months; assessed with: number of patients)								
1 [48-50] (100 vs. -) [h]	observational study	not serious	not serious	not serious	not serious	none	Extra hospital day due to pain, anxiety, nausea or postoperative urinary retention: 17 (13.4%) Additional 4 hospital days due to pulmonary issues: 1 (0.8%*) Re-admission 2 days after the procedure due to immediate postoperative pain: 1 (0.8%*)	⊕⊕◯◯ **LOW (Critical)**
Death (follow up: range 3 to 12 months; assessed with: number of patients)								
1 [39] (40 vs. 20)	RCT	serious [e]	not serious	not serious	serious [d]	none	1 patient who had undergone interventional procedure after crossover died, death occurred 11 months after the procedure.	⊕⊕◯◯ **LOW (Critical)**
Death (follow up: range 3 to 12 months; assessed with: number of patients)								
1 [48-50] (100 vs. -) [h]	observational study	not serious	not serious	not serious	not serious	none	No death was reported.	⊕⊕◯◯ **LOW (Critical)**
Re-surgery (follow up: range 3 to 12 months; assessed with: number of patients/re-surgeries)								
2 [39, 46] (77 vs. 53)	RCT	serious [e]	serious [c]	not serious	not serious	none	2 studies reported 18 re-surgeries 14 in the intervention group (11 endoscopic, 3 laparoscopic) and 4 in the control group (all laparoscopic).	⊕⊕◯◯ **LOW (Critical)**
Re-surgery (follow up: range 3 to 12 months; assessed with: number of patients/re-surgeries)								
1 [48-50] (100 vs. -) [h]	observational study	not serious	not serious	not serious	not serious	none	8 re-surgeries (1 endoscopic, 7 laparoscopic)	⊕⊕◯◯ **LOW (Critical)**

*Abbreviations: I – Intervention group, C – control group, № – number, NR – not reported, NRCT – non-randomised controlled trial, Pts – patients, RCT – randomised controlled trial, ss – statistically significant. * based on own calculation.*

Explanations

[a] *3/4 high RoB, 1/4 moderate RoB*

[b] *different trends of improvements comparing treatment groups*

[c] *different generation of devices*

[d] *power calculations are lacking*

[e] *high RoB*

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

[g] *2/4 high RoB, 2/4 moderate RoB*

[h] *Initially 100 patients were included in the study, however, in the 24-months follow-up cohort 127 patients were analysed.*

[i] *power calculations available in 2/3 RCTs*

Applicability table

Table A-8: Summary table characterising the applicability of a body of studies

Domain	Description of applicability of evidence
Population	All studies included chronic GERD patients. The studies included a total of 453 patients for the analyses of effectiveness outcomes and an additional 127 patients for the safety profile. The median age of included patients ranged 51-55 years in the intervention groups and from 48-62 years in the comparison groups, while one RCT only reported mean values: 42.4 versus 49.3 years. All identified studies included chronic GERD patients with a history of daily PPI use over the last six months. The inclusion criteria and the population in the studies seem to be in accordance with the intended patient population for the technology. However, patients with a hiatal hernia of more than two centimetres were excluded from all trials except for two studies that also enrolled patients with hiatal hernias up to three centimetres.
Intervention	Different devices (EsophyX2®/EsophyX®, The Plicator™/NDO Plicator, SRS™ Endoscopic Stapling System) were used across the trials to treat GERD patients of the included studies. The included devices were not the newest available ones and some of them are not on the market anymore. In addition, non of the studies applied the newest available device generation, which can impact the applicability of the presented results.
Comparators	The following comparators were used in the included studies: laparoscopic surgery (n=3), PPI therapy (n=2), sham treatment (n=1), PPI medication plus a sham intervention (n=1). The use of different comparators may affect the included comparative trial results.
Outcomes	The most frequently reported crucial outcomes were health-related quality of life measures as well as GERD symptoms and any adverse events. The outcomes on clinical effectiveness have shown benefits from the treatment with endoscopic plication over time. However, considering study group comparisons contradicting findings could be identified. For the safety assessment, no major complications were reported across studies. Nevertheless, the presented data in the studies are limited, especially due to small sample sizes in prospective studies and short follow-up times, but also the data quality and reporting is poor.
Setting	Overall, all studies were carried out across six European countries and four were conducted in the US. No applicability issues are expected from the geographical setting. The studies were published between 2011 and 2018. On a European level, the intervention was performed in University or public hospitals. Studies conducted in the US also performed the intervention in academic and community medical centres. The settings of the studies reflect the clinical setting in which the technology is intended to be used appropriately. No applicability issues are expected from the geographical setting.

Abbreviations: GERD – gastroesophageal reflux disease, US – United States.

List of ongoing randomised controlled trials

Table A-9: List of ongoing studies of endoscopic plication in GERD patients

Identifier/ Trial name	Patient population	Intervention	Comparison	Primary Outcome	Estimated completion date	Sponsor
Randomised controlled trials						
NCT03322553 (GERDX01)	GERD (around 70 pts)	Endoscopic full-thickness plication: GERD-X	Sham comparator	Improvement in GERD-HRQL by more than 50% from baseline at 3 months	December 2019 (no results published)	Asian Institute of Gastroenterology, India
Prospective single-arm studies with >100 patients						
NCT01118585 (D00960)	GERD (around 278 pts)	TIF	-	GERD symptom elimination evaluated with GERD-HRQL, GSRS, RSI [time frame: 6-month follow-up]	December 2018 (no results published)	EndoGastric Solutions, US
ChiCTR2000036041	GERD (around 106 pts)	TIF by the Muse endoscope	-	Improvement rate of reflux symptoms	September 2022	Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine, China

Abbreviations: GERD – Gastro Oesophageal Reflux Disease, GSRS – GERD Symptom Rating Score, HRQL – Health-Related Quality of Life Questionnaire, pts – patients, RSI – Reflux Symptom Index, TIF – Transoral Incisionless Fundoplication, US – United States.

Literature search strategies

Search strategy for Cochrane

Search Name: Endoscopic plication for GERD	
Search date: 15.12.2020	
ID	Search
#1	MeSH descriptor: [Gastroesophageal Reflux] explode all trees
#2	"gastro*esophageal reflux" (Word variations have been searched)
#3	"gastro-esophageal reflux" (Word variations have been searched)
#4	GER:ti,ab,kw (Word variations have been searched)
#5	GERD:ti,ab,kw (Word variations have been searched)
#6	GORD:ti,ab,kw (Word variations have been searched)
#7	#1 or #2 or #3 or #4 or #5 or #6
#8	(plication*) (Word variations have been searched)
#9	(gastroplication*) (Word variations have been searched)
#10	(sutur*) (Word variations have been searched)
#11	MeSH descriptor: [Suture Techniques] explode all trees
#12	MeSH descriptor: [Sutures] explode all trees
#13	MeSH descriptor: [Natural Orifice Endoscopic Surgery] explode all trees
#14	MeSH descriptor: [Endoscopy, Digestive System] explode all trees
#15	(endoscop*) (Word variations have been searched)
#16	#14 OR #15 (Word variations have been searched)
#17	(transoral* OR trans-oral* OR endoluminal* OR endo-luminal* OR full-thickness*) (Word variations have been searched)
#18	#16 AND #17 (Word variations have been searched)
#19	((endoscop* OR endo-scop* OR transoral* OR endolum*) NEAR (plication* OR gastroplication* OR sutur* OR incision* OR (full NEXT thickness*))) (Word variations have been searched)
#20	(MUSE):ti,ab,kw (Word variations have been searched)
#21	(EsophyX*) (Word variations have been searched)
#22	#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #18 OR #19 OR #20 OR #21
#23	#7 AND #22
#24	(GERDx*) (Word variations have been searched)
#25	(GERD-X*) (Word variations have been searched)
#26	#23 OR #24 OR #25 (Word variations have been searched)
Total hits:107	

Search strategy for CRD

Search Name: Endoscopic plication for GERD (MEL2021) NG/SW	
Search date: 16.12.2020	
ID	Search
#1	MeSH DESCRIPTOR Gastroesophageal Reflux EXPLODE ALL TREES
#2	(gastro*esophageal reflux)
#3	(gastro-esophageal reflux)
#4	(gastro-oesophageal reflux)
#5	(GER)
#6	(GERD)

#7	(GORD)
#8	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7
#9	(plication*)
#10	(gastroplication*)
#11	(sutur*)
#12	MeSH DESCRIPTOR Suture Techniques EXPLODE ALL TREES
#13	MeSH DESCRIPTOR Sutures EXPLODE ALL TREES
#14	MeSH DESCRIPTOR Natural Orifice Endoscopic Surgery EXPLODE ALL TREES
#15	MeSH DESCRIPTOR Endoscopy, Digestive System EXPLODE ALL TREES
#16	(endoscop*)
#17	#15 OR #16
#18	(transoral* OR trans-oral* OR endoluminal* OR endo-luminal* OR full-thickness*)
#19	#17 AND #18
#20	((endoscop* OR endo-scop* OR transoral* OR trans-oral* OR endolum* OR endo-lum*) NEAR (plication* OR gastroplication* OR sutur* OR incision* OR full-thickness*))
#21	(MUSE)
#22	(EsophyX*)
#23	#9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #19 OR #20 OR #21 OR #22
#24	#8 AND #23
#25	(GERDx*)
#26	(GERD-X*)
#27	#24 OR #25 OR #26
Total hits: 18	

Search strategy for Embase

Search Name: Endoscopic plication for GERD	
Search date: 16.12.2020	
ID	Search
#1	'gastroesophageal reflux'/exp
#2	'gastroesophageal reflux':ti,ab,lnk,de,kw
#3	'gastrooesophageal reflux':ti,ab,lnk,de,kw
#4	'gastro-esophageal reflux':ti,ab,lnk,de,kw
#5	'gastro-oesophageal reflux':ti,ab,lnk,de,kw
#6	ger:ti,ab
#7	gerd:ti,ab
#8	gord:ti,ab
#9	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
#10	'plication'/exp
#11	plication*:ti,ab,lnk,de,kw
#12	gastroplication*:ti,ab,lnk,de,kw
#13	'suture technique'/exp/mj
#14	'suture material'/exp/mj
#15	'suture'/exp/mj
#16	sutur*:ti,ab,lnk,de,kw
#17	'transoral endoscopy'/exp
#18	'natural orifice transluminal endoscopic surgery'/exp
#19	'digestive tract endoscopy'/exp

#20	endoscop*:ti,ab,lnk,de,kw
#21	#19 OR #20
#22	transoral*:ti,ab,lnk,de,kw OR 'trans oral*':ti,ab,lnk,de,kw OR endoluminal*:ti,ab,lnk,de,kw OR 'endo luminal*':ti,ab,lnk,de,kw OR 'full thickness*':ti,ab,lnk,de,kw
#23	#21 AND #22
#24	((endoscop* OR 'endo scop*' OR transoral* OR 'trans oral*' OR endolum* OR 'endo lum*') NEAR/5 (plication* OR gastroplication* OR sutur* OR incision* OR 'full thickness*')):ti,ab,lnk,de,kw
#25	muse:ti,ab,dn
#26	'esophyx'/exp
#27	esophyx*:ti,ab,lnk,de,kw,dn
#28	#10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #23 OR #24 OR #25 OR #26 OR #27
#29	#9 AND #28
#30	#29 AND ([cochrane review]/lim OR [systematic review]/lim OR [meta analysis]/lim OR [controlled clinical trial]/lim OR [randomized controlled trial]/lim)
#31	'crossover procedure':de OR 'double-blind
#32	#29 AND #31
#33	#29 AND ('meta analysis'/de OR 'meta analysis topic'/de OR 'systematic review'/de OR 'systematic review topic'/de)
#34	'biomedical technology assessment'/exp
#35	'technolog* assessment*':ti,ab,lnk,de,kw
#36	hta*:ti,ab,lnk,de,kw
#37	#34 OR #35 OR #36
#38	#29 AND #37
#39	gerdx*:ti,ab,lnk,de,kw,dn
#40	'gerd-x*':ti,ab,lnk,de,kw,dn
#41	#30 OR #32 OR #33 OR #38 OR #39 OR #40
#42	#41 AND ([english]/lim OR [german]/lim)
Total hits: 213	

Search strategy for HTA-INATHTA

Search Name: Endoscopic plication for GERD	
Search date: 16.12.2020	
ID	Search
#1	"Gastroesophageal Reflux"[mhe],"22","2020-12-16T12:13:31.000000Z"
#2	"gastroesophageal reflux*","34","2020-12-16T12:17:42.000000Z"
#3	"gastro-esophageal reflux*","0","2020-12-16T12:18:05.000000Z"
#4	"gastrooesophageal reflux*","1","2020-12-16T12:18:15.000000Z"
#5	"gastro-oesophageal reflux*","17","2020-12-16T12:18:25.000000Z"
#6	(GER)[Title] OR (GER)[abs],"2","2020-12-16T12:19:10.000000Z"
#7	(GERD)[Title] OR (GERD)[abs],"23","2020-12-16T12:19:47.000000Z"
#8	(GORD)[Title] OR (GORD)[abs],"11","2020-12-16T12:20:16.000000Z"
#9	((GORD)[Title] OR (GORD)[abs]) OR ((GERD)[Title] OR (GERD)[abs]) OR ((GER)[Title] OR (GER)[abs]) OR ("gastro-oesophageal reflux*") OR ("gastrooesophageal reflux*") OR ("gastro-esophageal reflux*") OR ("gastroesophageal reflux*") OR ("Gastroesophageal Reflux"[mhe]),"56","2020-12-16T12:20:43.000000Z"
#10	plication*,"0","2020-12-16T12:21:05.000000Z"
#11	gastroplication*,"4","2020-12-16T12:21:20.000000Z"
#12	"gastro-plication*","0","2020-12-16T12:21:51.000000Z"
#13	"gastro-plication","0","2020-12-16T12:21:56.000000Z"
#14	sutur*,"55","2020-12-16T12:22:14.000000Z"

#15	"Suture Techniques"[mhe],"19","2020-12-16T12:22:56.000000Z"
#16	"Sutures"[mhe],"15","2020-12-16T12:23:17.000000Z"
#17	"Natural Orifice Endoscopic Surgery"[mhe],"3","2020-12-16T12:23:43.000000Z"
#18	"Endoscopy Digestive System"[mhe],"103","2020-12-16T12:24:19.000000Z"
#19	endoscop*,"261","2020-12-16T12:24:36.000000Z"
#20	(endoscop*) OR ("Endoscopy Digestive System"[mhe]),"301","2020-12-16T12:24:45.000000Z"
#21	transoral* OR "trans-oral*" OR endoluminal* OR "endo-luminal*" OR "full-thickness*","28","2020-12-16T12:25:25.000000Z"
#22	(transoral* OR "trans-oral*" OR endoluminal* OR "endo-luminal*" OR "full-thickness*") AND ((endoscop*) OR ("Endoscopy Digestive System"[mhe])),"7","2020-12-16T12:25:36.000000Z"
#23	(endoscop* OR "endo-scop*" OR transoral* OR "trans-oral*" OR endolum* OR "endo-lum*") AND (plication* OR gastroplication* OR sutur* OR incision* OR full-thickness*),"25","2020-12-16T12:27:57.000000Z"
#24	MUSE,"2","2020-12-16T12:28:21.000000Z"
#25	EsophyX*,"3","2020-12-16T12:28:39.000000Z"
#26	(EsophyX*) OR (MUSE) OR ((endoscop* OR "endo-scop*" OR transoral* OR "trans-oral*" OR endolum* OR "endo-lum*") AND (plication* OR gastroplication* OR sutur* OR incision* OR full-thickness*)) OR ((transoral* OR "trans-oral*" OR endoluminal* OR "endo-luminal*" OR "full-thickness*") AND ((endoscop*) OR ("Endoscopy Digestive System"[mhe]))) OR ("Natural Orifice Endoscopic Surgery"[mhe]) OR ("Sutures"[mhe]) OR ("Suture Techniques"[mhe]) OR (sutur*) OR ("gastro-plication") OR ("gastro-plication*") OR (gastroplication*) OR (plication*),"91","2020-12-16T12:30:22.000000Z"
#27	((EsophyX*) OR (MUSE) OR ((endoscop* OR "endo-scop*" OR transoral* OR "trans-oral*" OR endolum* OR "endo-lum*") AND (plication* OR gastroplication* OR sutur* OR incision* OR full-thickness*)) OR ((transoral* OR "trans-oral*" OR endoluminal* OR "endo-luminal*" OR "full-thickness*") AND ((endoscop*) OR ("Endoscopy Digestive System"[mhe]))) OR ("Natural Orifice Endoscopic Surgery"[mhe]) OR ("Sutures"[mhe]) OR ("Suture Techniques"[mhe]) OR (sutur*) OR ("gastro-plication") OR ("gastro-plication*") OR (gastroplication*) OR (plication*)) AND (((GORD)[Title] OR (GORD)[abs]) OR ((GERD)[Title] OR (GERD)[abs]) OR ((GER)[Title] OR (GER)[abs]) OR ("gastro-oesophageal reflux*") OR ("gastrooesophageal reflux*") OR ("gastro-esophageal reflux*") OR ("gastroesophageal reflux*") OR ("Gastroesophageal Reflux"[mhe])),"12","2020-12-16T12:30:48.000000Z"
#28	GERDx*,"0","2020-12-16T12:31:23.000000Z"
#29	"GERD-X*","0","2020-12-16T12:31:55.000000Z"
#30	("GERD-X*") OR (GERDx*) OR (((EsophyX*) OR (MUSE) OR ((endoscop* OR "endo-scop*" OR transoral* OR "trans-oral*" OR endolum* OR "endo-lum*") AND (plication* OR gastroplication* OR sutur* OR incision* OR full-thickness*)) OR ((transoral* OR "trans-oral*" OR endoluminal* OR "endo-luminal*" OR "full-thickness*") AND ((endoscop*) OR ("Endoscopy Digestive System"[mhe]))) OR ("Natural Orifice Endoscopic Surgery"[mhe]) OR ("Sutures"[mhe]) OR ("Suture Techniques"[mhe]) OR (sutur*) OR ("gastro-plication") OR ("gastro-plication*") OR (gastroplication*) OR (plication*)) AND (((GORD)[Title] OR (GORD)[abs]) OR ((GERD)[Title] OR (GERD)[abs]) OR ((GER)[Title] OR (GER)[abs]) OR ("gastro-oesophageal reflux*") OR ("gastrooesophageal reflux*") OR ("gastro-esophageal reflux*") OR ("gastroesophageal reflux*") OR ("Gastroesophageal Reflux"[mhe]))),"12","2020-12-16T12:32:10.000000Z"
#31	("GERD-X*") OR (GERDx*) OR (((EsophyX*) OR (MUSE) OR ((endoscop* OR "endo-scop*" OR transoral* OR "trans-oral*" OR endolum* OR "endo-lum*") AND (plication* OR gastroplication* OR sutur* OR incision* OR full-thickness*)) OR ((transoral* OR "trans-oral*" OR endoluminal* OR "endo-luminal*" OR "full-thickness*") AND ((endoscop*) OR ("Endoscopy Digestive System"[mhe]))) OR ("Natural Orifice Endoscopic Surgery"[mhe]) OR ("Sutures"[mhe]) OR ("Suture Techniques"[mhe]) OR (sutur*) OR ("gastro-plication") OR ("gastro-plication*") OR (gastroplication*) OR (plication*)) AND (((GORD)[Title] OR (GORD)[abs]) OR ((GERD)[Title] OR (GERD)[abs]) OR ((GER)[Title] OR (GER)[abs]) OR ("gastro-oesophageal reflux*") OR ("gastrooesophageal reflux*") OR ("gastro-esophageal reflux*") OR ("gastroesophageal reflux*") OR ("Gastroesophageal Reflux"[mhe]))),"12","2020-12-16T12:32:55.000000Z"
Total hits: 12	

Search strategy for Medline

Search Name: Endoscopic plication for GERD	
Search date: 15.12.2020	
ID	Search
#1	exp Gastroesophageal Reflux/ (30544)
#2	gastro?esophageal reflux*.mp. (39520)
#3	gastro-?esophageal reflux*.mp. (2141)
#4	GER.ti,ab. (3133)
#5	GERD.ti,ab. (11450)
#6	GORD.ti,ab. (1018)

#7	1 or 2 or 3 or 4 or 5 or 6 (43366)
#8	plication*.mp. (4887)
#9	gastroplication*.mp. (78)
#10	sutur*.mp. (129715)
#11	exp *Suture Techniques/ (23117)
#12	exp *Sutures/ (11200)
#13	exp Natural Orifice Endoscopic Surgery/ (5496)
#14	exp *Endoscopy, Digestive System/ (66204)
#15	endoscop*.mp. (323382)
#16	14 or 15 (338278)
#17	(transoral* or trans-oral* or endoluminal* or endo-luminal* or full-thickness*).mp. (41371)
#18	16 and 17 (5949)
#19	((endoscop* or endo-scop* or transoral* or trans-oral* or endolum* or endo-lum*) adj5 (plication* or gastroplication* or sutur* or incision* or full-thickness*)).mp. (4024)
#20	MUSE.ti,ab. (717)
#21	EsophyX*.mp. (80)
#22	8 or 9 or 10 or 11 or 12 or 13 or 18 or 19 or 20 or 21 (147675)
#23	7 and 22 (1243)
#24	limit 23 to clinical trial, all (91)
#25	((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.) (5467286)
#26	23 and 25 (287)
#27	limit 23 to multicenter study (55)
#28	24 or 26 or 27 (333)
#29	limit 23 to (meta analysis or "systematic review") (28)
#30	(((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. (755884)
#31	23 and 30 (61)
#32	29 or 31 (61)
#33	exp Technology Assessment, Biomedical/ (12855)
#34	Technolog* Assessment*.mp. (18771)
#35	HTA*.mp. (6908)
#36	33 or 34 or 35 (23783)
#37	23 and 36 (3)
#38	28 or 32 or 37 (367)
#39	GERDX*.mp. (8)
#40	GERD-X*.mp. (2)
#41	38 or 39 or 40 (371)
#42	limit 41 to (english or german) (355)
#43	remove duplicates from 42 (277)
Total hits: 277	

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