Communication from the ASGE Standards of Practice Committee

GUIDELINE

ASGE American Society for Gastrointestinal Endoscopy

American Society for Gastrointestinal Endoscopy guideline on the diagnosis and management of GERD: methodology and review of evidence

Prepared by: ASGE STANDARDS OF PRACTICE COMMITTEE

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This document was reviewed and approved by the Governing Board of the American Society for Gastrointestinal Endoscopy.

This clinical practice guideline from the American Society for Gastrointestinal Endoscopy (ASGE) provides an evidence-based approach for strategies to diagnose and manage GERD. This document was developed using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) framework and serves as an update to the prior ASGE guideline on the role of endoscopy in the management of GERD (2014). The updated guideline addresses the indications for endoscopy in patients with GERD, including patients who have undergone sleeve gastrectomy (SG) and peroral endoscopic myotomy (POEM). It also discusses endoscopic evaluation of gastroesophageal junctional integrity comprehensively and uniformly. Important, this guideline discusses management strategies for GERD including lifestyle interventions, proton pump inhibitors (PPIs), and endoscopic antireflux therapy including transoral incisionless fundoplication (TIF), radiofrequency energy, and TIF combined with hiatal hernia repair (cTIF). The ASGE recommends upper endoscopy for the evaluation of GERD in patients with alarm symptoms. The ASGE suggests upper endoscopy for symptomatic patients with a history of SG and POEM. The ASGE recommends careful endoscopic evaluation, reporting, and photo-documentation of objective GERD findings and gastroesophageal junction landmarks and integrity to improve patient care and outcomes. In patients with GERD symptoms, the ASGE recommends lifestyle modifications. In patients with symptomatic and confirmed GERD with predominant heartburn symptoms, the ASGE recommends medical management including PPIs at the lowest dose for the shortest duration while initiating discussion about long-term management options. In patients with confirmed GERD with small hiatal hernia ($\leq$2 cm) and Hill grade I or II flap valve who meet specific criteria, the ASGE suggests evaluation for TIF as an alternative to long-term medical management. In patients with confirmed GERD with a large hiatal hernia (>2 cm) and Hill grade 3 or 4 flap valve, the ASGE suggests evaluation for combined endoscopic-surgical TIF (cTIF) in a multidisciplinary review. This document clearly outlines the methodology, analysis, and decision used to reach the final recommendations and represents the official ASGE recommendations on the above topics. (Gastrointest Endosc 2025;10:81-137.)

(footnotes appear on last page of article)

This guideline document was prepared by the Standards of Practice Committee of the American Society for Gastrointestinal Endoscopy (ASGE) using the best available scientific evidence and considering a multitude of variables including, but not limited to, adverse events, patients' values, and cost implications. The purpose of these guidelines is to provide the best practice recommendations that may help standardize patient care, improve patient outcomes, and reduce variability in practice.

We recognize that clinical decision making is complex. Guidelines, therefore, are not a substitute for a clinician's judgment. Such judgments may, at times,

seem contradictory to our guidance because of many factors that are impossible to fully consider by guideline developers. Any clinical decisions should be based on the clinician's experience, local expertise, resource availability, and patient values and preferences.

This document is not a rule and should not be construed as establishing a legal standard of care, or as encouraging, advocating for, mandating, or discouraging any particular treatment. Our guidelines should not be used in support of medical complaints, legal proceedings, and/or litigation because they were not designed for this purpose.

INTRODUCTION

GERD, defined as troublesome heartburn and/or regurgitation, is the most prevalent GI disorder affecting one-third of the adult U.S. population.[1-4] It can also be present in children but may be difficult to establish because of the inability to describe troublesome symptoms in the pediatric population.[5] Uncontrolled chronic GERD could lead to several adverse events including erosive esophagitis, peptic stricture, Barrett's esophagus (BE), and even esophageal adenocarcinoma. Moreover, the incidence of GERD and related consequences has been increasing in parallel with the rise in the global prevalence of obesity.[6] In addition, GERD can decrease quality of life and increase health care costs to both individuals and systems because of frequent physician visits and result in a higher number of endoscopies and treatment-related consequences.[7,8]

Since the last publication of the prior American Society for Gastrointestinal Endoscopy (ASGE) guidelines on GERD in 2015,[9] there have been several endoscopic advancements that can affect diagnosis and management of GERD. These include evolving indications for endoscopy among patients who have undergone sleeve gastrectomy (SG) and peroral endoscopic myotomy (POEM) and updated guidance regarding endoscopic antireflux therapies. Therefore, the ASGE aimed to develop an updated evidence-based guideline on the diagnosis and management of GERD.

AIMS AND SCOPE

The aim of this ASGE guideline is to provide evidence-based recommendations on the management of GERD. This document, subtitled "Methodology and Review of Evidence," provides a detailed account of the evidence synthesis process that ultimately led to our recommendations. A separate publication of "Summary and Recommendations" provides a summary of the main findings and final recommendations of the ASGE Standards of Practice (SOP) Committee for the diagnosis and management of GERD.

This guideline synthesizes the evidence and makes recommendations on the following clinical questions:

Question 1

1a: In patients with GERD symptoms, when should upper endoscopy be performed compared with no endoscopy?

1b: In patients who have undergone SG, should endoscopy be performed to screen for Barrett esophagus compared with no endoscopy?

1c: In patients having undergone POEM who have reflux symptoms, should endoscopy be performed compared with no endoscopy?

Question 2

In patients with GERD undergoing upper endoscopy, what are the criteria for high-quality endoscopy procedure and report?

Question 3

In patients with GERD, should lifestyle interventions be recommended to reduce GERD symptoms?

Question 4

In patients with GERD, does proton pump inhibitor compared with placebo reduce symptoms?

Question 5

5a: In patients with persistent GERD, how does transoral incisionless fundoplication (TIF) compare to standard medical therapy?

5b: In patients with confirmed GERD and a large hiatal hernia, how does hiatal hernia repair combined with TIF (cTIF) compare to standard medical therapy for GERD management?

Question 6

In patients with persistent GERD, how does radiofrequency energy to the lower esophageal sphincter (LES) compare to standard medical therapy for GERD management?

METHODOLOGY

Overview

This document was prepared by the SOP Committee of the ASGE and is a continuation of our society's effort to produce evidence-based clinical guidelines using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach as previously described.[10,11] In summary, GRADE is a standardized and transparent process for assessing and presenting summaries of evidence with the goal of informing evidence-based clinical practice recommendations.[12] The recommendations in this guideline document were based on up-to-date meta-analyses of the available literature for each clinical question. The quality or certainty of evidence and strength of recommendations

TABLE 1. Summary of recommendations

Recommendation	Best practice advice	Strength of recommendation	Quality of evidence
In patients with GERD symptoms, the ASGE recommends upper endoscopy in those with: - Alarm symptoms (dysphagia, odynophagia, weight loss, GI bleeding, persistent vomiting, or unexplained iron deficiency anemia).		Strong	Moderate
In patients with GERD symptoms, with no alarm symptoms, the ASGE suggests endoscopic evaluation in those with: - Barrett's esophagus (BE) risk factors (family history of BE or esophageal adenocarcinoma; GERD plus another risk factor [>50 y, male sex, white race, smoking and obesity]). - Infants and children with suggestive symptoms (poor weight gain, unexplained anemia, concern for GI bleeding, recurrent pneumonia, and regurgitation and/or vomiting).		Conditional	Low
- In patients having undergone sleeve gastrectomy with reflux symptoms, the ASGE suggests endoscopic evaluation. - In patients having undergone sleeve gastrectomy who are asymptomatic, the ASGE suggests endoscopic screening 3 y after sleeve gastrectomy and then every 5 y. - If BE is detected in this population, the ASGE recommends follow-up per existing BE surveillance guidelines.		Conditional	Very low
In patients having undergone POEM who have symptomatic GERD, the ASGE suggests endoscopic evaluation.	In patients having undergone POEM, endoscopists should be aware of the high rate of GERD post-POEM and should consider periodic endoscopic evaluation in asymptomatic patients.	Conditional	Very low

In patients undergoing endoscopic evaluation for GERD symptoms, the ASGE recommends careful endoscopic evaluation, reporting, and photodocumentation of the following to improve patient care and outcomes:
- Objective GERD findings, when present:
  - Erosive esophagitis (using LA grading system).
  - BE (using Prague classification).
  - Peptic stricture.
- Gastroesophageal junction (GEJ) landmarks and integrity.
  - Hiatal hernia dimensions using Hill grading or American Foregut Society (AFS) grading in forward view and retroflexion.
  - Location of top of gastric folds, Z line, diaphragmatic impression.
  - Existing fundoplication description (if present).
		Strong	Very low

In patients with GERD symptoms, the ASGE recommends the following lifestyle modifications: - Weight loss for patients who are overweight or obese. - Smoking cessation. - Elevation of head of bed. - Avoiding meals within 3 h of bedtime.		Strong	Low

(*continued on the next page*)

TABLE 1. Continued

Recommendation	Best practice advice	Strength of recommendation	Quality of evidence
In patients with symptomatic and confirmed GERD with predominant heartburn symptoms, the ASGE recommends medical management with proton pump inhibitors (PPIs) at the lowest possible dose for the shortest possible period of time while initiating discussion about long-term management options.	- Patients who have been on long-term PPI therapy (>6 mo) should be considered for optimization and de-escalation of medical management. - Providers should carefully consider the risks, benefits, and alternatives of PPI use with the patient with GERD. - Providers prescribing PPI therapy should be aware that adverse events from PPI in prospective data have been limited to increased risk of enteric infections; however, there is need for robust long-term data to prove or disprove any other putative adverse events.	Strong	Moderate
In patients with suboptimal clinical response to PPI therapy, the ASGE suggests testing CYP2C19 polymorphism and adjusting PPI dosage and selection accordingly.		Conditional	Very low
In patients with confirmed GERD with small hiatal hernia (≤2 cm) and Hill grade I or II who meet any of the following criteria, the ASGE suggests evaluation for TIF as an alternative to long-term medical management. Criteria: - Chronic GERD (at least 6 mo). - Long-term PPI use (at least 6 mo) for management of GERD symptoms. - Refractory GERD. - Regurgitation-predominant GERD. - Patient prefers to avoid long-term PPI use.		Conditional	Low
In patients with confirmed GERD with large hiatal hernia (>2 cm) and Hill grade III or IV, ASGE suggests evaluation for cTIF in a multidisciplinary review.	In patients with confirmed GERD and small hiatal hernia (<2 cm) and Hill grade I or II, Stretta can be considered when other alternatives (endoscopic or surgical fundoplication) are not available or feasible.	Conditional	Very low

ASGE, American Society for Gastrointestinal Endoscopy; *TIF*, transoral incisionless fundoplication; *cTIF*, combined TIF and hiatal hernia repair surgery; *POEM*, peroral endoscopic myotomy.

were based on the GRADE approach and followed the evidence-to-decision framework.

Evidence profiles were created with the help of GRADE methodologists (M.D., B.Q.), and a guideline development panel was held on March 10, 2023, in which the evidence was reviewed and recommendations were generated. In developing our recommendations, we took into consideration the certainty of the evidence, benefits and risk of harm of different management options, patient values and preferences, resource use including direct costs, cost-effectiveness, health equity, acceptability, and feasibility.

The final wording of the recommendations including direction and strength were approved by all members of the panel and the ASGE Governing Board. Strong recommendations are typically stated as "we recommend…" whereas conditional or more closely balanced recommendations are indicated by the phrase "we suggest…." The meanings and interpretations of various qualities of evidence and the implications of corresponding recommendations are summarized in Table 1.

Formulation of clinical questions

Six clinical questions were conceptualized by the authors of the documents and members of the ASGE SOP committee. These were then approved by the ASGE Governing Board. The questions followed the PICO format: P, population in question; I, intervention; C, comparator; and O, outcomes of interest. For all clinical questions, potentially relevant patient-important outcomes were identified a priori and rated from "critical" to "important" through a consensus process. A detailed list of the PICO questions and outcomes is provided in Table 2.

Literature search and study selection criteria

To inform the guideline panel, we performed systematic reviews and meta-analyses (SRMAs) to address each of the

TABLE 2. Summary of guideline questions according to population, intervention, comparator, and outcomes (PICO)

Population	Intervention	Comparator	Outcomes and importance
Patients with GERD symptoms	Timing of upper endoscopy	None	• Diagnosis of GERD: critical • Adverse events of GERD: critical • Diagnosis of Barrett's esophagus: critical
Patients who have undergone sleeve gastrectomy (SG)	Upper endoscopy	No endoscopy	• Diagnosis of GERD: critical • Adverse events of GERD: critical • Diagnosis of Barrett's esophagus: critical • Cost-effectiveness: important • Patient values and preferences: important
Patients with peroral endoscopic myotomy (POEM)	Upper endoscopy	No endoscopy	• Diagnosis of GERD: critical • Adverse events of GERD: critical • Diagnosis of Barrett's esophagus: critical • Cost-effectiveness: important • Patient values and preferences: important
Patients with GERD undergoing endoscopy	High-quality examination	None	• Documentation of objective GERD: critical • GEJ landmarks and integrity: critical
Patients with GERD	Lifestyle interventions	None	• GERD symptom remission: critical • Cost-effectiveness: important • Patient values and preferences: important
Patients with GERD	Proton pump inhibitors (PPIs)	Placebo	• GERD symptom remission: critical • Esophagitis healing: critical • Adverse events: critical • Cost-effectiveness: important • Patient values and preferences: important
Patients with persistent GERD	Transoral incisionless fundoplication (TIF)	Medical therapy (PPI) and/or sham	• PPI discontinuation: critical • Reduction in acid exposure time (% time pH <4): critical • Normalization of esophageal acid exposure time (per patient): critical • Symptom resolution (per patient): critical • Durable symptom resolution: critical • GERD score improvement: critical • Adverse events: critical • Cost-effectiveness: important • Patient values and preferences: important
Patients with confirmed GERD and a large hiatal hernia (>2 cm)	Combined TIF and hiatal hernia repair (cTIF)	Medical therapy (PPI) and/or sham	• PPI discontinuation: critical • Reduction in acid exposure time (% time pH <4): critical • Normalization of esophageal acid exposure time (per patient): critical • Symptom resolution (per patient): critical • Durable symptom resolution: critical • GERD score improvement: critical • Adverse events: critical • Cost-effectiveness: important • Patient values and preferences: important
Patients with persistent GERD	Stretta	Medical therapy (PPI) and/or sham	• PPI discontinuation: critical • Reduction in acid exposure time (% time pH <4): critical • Normalization of esophageal acid exposure time (per patient): critical • Symptom resolution (per patient): critical • Durable symptom resolution: critical • GERD score improvement: critical • Adverse events: critical • Cost-effectiveness: important • Patient values and preferences: important

PICO questions. We performed a literature search for individual questions 1 through 4 separately because the population and outcomes differed from each other. For questions 1 to 4, a systematic review of the literature was performed, and existing meta-analyses were used when available. A comprehensive literature search was performed by 2 of the authors (M.D. and W.R.) using Ovid MEDLINE, Embase, and Wiley Cochrane databases from the inception of the database to December 20, 2022. The searches were limited to randomized controlled trials (RCTs), prospective and retrospective observational studies, systematic reviews, and meta-analyses. The searches were limited to English-language articles. Animal studies and nonhuman studies, case reports, reviews, abstracts and conference proceedings, and editorials were excluded.

We performed a systematic literature search for questions examining endoscopic therapies (questions 5 and 6 and novel or emerging endoscopic therapies) for adults and pediatrics as a combined group. A comprehensive literature search was performed by a medical librarian using Ovid MEDLINE, Embase, and Wiley Cochrane databases from inception of the database through November 20, 2021, for endoscopic therapies. The full search strategy is provided in the Appendix 1 (available online at www.videogie.org). The searches were limited to RCTs, prospective and retrospective observational studies, and existing systematic review and meta-analysis published in the English language. An updated literature search was performed by the authors (M.D. and W.R.) on December 20, 2022. Case reports, case series with <10 patients, animal studies, reviews, editorials, conference posters, and abstracts were excluded. A separate search was performed for any ongoing or planned clinical trials relevant to the subject using the clinical trials search engine (clinicaltrials.gov). A secondary search of selected articles was performed via review of bibliography of eligible studies as well.

For PICO question 1, we used a systematic review to generate evidence profiles. We included systematic reviews that evaluated when upper endoscopy should be performed to diagnose GERD. Furthermore, we performed a systematic review on endoscopic screening for new-onset GERD among patients post-SG and post-POEM. We included studies that report the incidence of GERD symptoms, esophagitis from GERD, and BE in patients with normal anatomy (PICO 1a) and in those who have undergone SG (PICO 1b) or POEM (PICO 1c). We excluded patients with other altered anatomy, gastroparesis, or scleroderma or other special populations at risk for GERD. For PICO 2, we performed a systematic review to examine studies that evaluated the quality of reporting of objective findings regarding GERD (including adverse events) and components of antireflux barrier.

For PICO 3, we performed a systematic review to examine the role of lifestyle interventions for GERD symptom remission.

For PICO 4, we performed a systematic review to examine the role of PPI for GERD symptom remission, esophagitis healing, and adverse events. We excluded studies examining the role of non-PPI therapy for GERD management.

For PICO questions 5 and 6, we performed a systematic review with updated meta-analyses if there were no recent meta-analyses provided for the outcome of interest. We included existing or currently used antireflux endoscopic therapies as well as those under clinical evaluation. Endoscopic therapies that are outdated or are no longer existent for various reasons were not included in this review; this list includes and not limited to the following: TIF 1.0 (Endogastric Solutions, Redmond, Wash, USA), lower esophageal sphincter electrical stimulation therapy, injectable agents (Enteryx; Boston Sci Corp, Natick, Mass, USA), Gatekeeper reflux repair system (Medtronic, Minneapolis, Minn, USA), Durasphere (Carbon Medical Technologies, St Paul, Minn, USA), Plexiglas (Artes Medical, San Diego, Calif, USA), and a suturing device (EndoCinch; Bard Endoscopic Technologies, Billerica, Mass, USA). We also excluded interventions or technologies that have not been examined as part of a clinical trial. For novel or emerging antireflux endoscopic therapies among adults and pediatric populations, we performed a systematic literature review to examine the available evidence to determine whether there was sufficient evidence for GRADE review to derive a recommendation. If this was not possible, no GRADE review was performed for that question.

For each PICO question, a literature search for existing systematic reviews and meta-analyses was also performed. If none was identified, a full systematic review and meta-analysis (when possible) was conducted using the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-analyses criteria.[13] Citations were imported into EndNote (Thompson Reuters; Philadelphia, Pa, USA), and duplicates were removed. The EndNote library was then uploaded into Covidence (www.covidence.org). Studies were first screened by title and abstract and then by full text by 2 independent reviewers (M.D. and W.R.), and all conflicts were resolved by consensus. When applicable, available systematic reviews and meta-analyses were updated based on literature review as described above.

Data extraction and statistical analysis

Data were extracted by 2 independent reviewers (M.D. and W.R.) using Microsoft Excel (Microsoft Corporation, Redmond, Wash, USA). The primary estimate of effect was based on a priori–identified outcomes of interest.

We performed a meta-analysis to generate summary estimates of events, pooled relative risk (RR), odds ratio (OR), or proportions for questions in which an updated meta-analysis was required or there was no existing meta-analysis. We reported RRs or ORs for dichotomous outcomes and mean differences (MDs) for continuous

TABLE 3. Interpretation of the definitions of the strength of recommendation using Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework

Implications for	Strong recommendation	Conditional recommendation
Patients	Most individuals in this situation would want the recommended course of action, and only a small proportion would not.	Most individuals in this situation would want the suggested course of action, but many would not.
Clinicians	Most individuals should receive the test. Formal decision aids are not likely to be needed to help individual patients make decisions consistent with their values and preferences.	Recognize that different choices will be appropriate for individual patients and that you must help each patient arrive at a management decision consistent with his or her values and preferences. Decision aids may be useful in helping individuals to make decisions consistent with their values and preferences.
Policy makers	The recommendation can be adopted as policy in most situations. Compliance with this recommendation according to the guideline could be used as a quality criterion or performance indicator.	Policy making will require substantial debate and involvement of various stakeholders.

Adapted from Andrews et al.[133]

outcomes, with their respective 95% CIs. Meta-analysis was carried out with DerSimonian and Laird random effects models, given the anticipation of heterogeneity among abstracted studies. Heterogeneity was assessed using the I^2 and Q statistic. Significant heterogeneity was defined at I^2 >50% and significant P value (<.05) on the Q statistic. Random effects models were used for most analyses (if significant heterogeneity was detected); otherwise, fixed effects models were used. Studies were weighted based on size. Publication bias was assessed using funnel plots when there were at least 10 studies in the meta-analysis. Any concern for publication bias based on funnel plot asymmetry was further evaluated by the Egger regression test. Study quality and potential bias was evaluated among RCTs using the Risk of Bias (ROB) tool[14] and among cohort studies using the Qumseya scale.[15] When an existing systematic review and meta-analysis was used, quality of the study and potential bias was evaluated using the AMSTAR-2 scale.[16] Statistical analyses were performed using Cochrane Review Manager (RevMan), version 5.4 (Cochrane Collaboration, 2020).

Certainty of evidence. The certainty in the body of evidence (also known as quality of the evidence or confidence in the estimated effects) was assessed using the GRADE framework beginning with study design, and then assessing methodologic limitations, inconsistency, indirectness, imprecision, publication bias, potential large study effects, dose-response gradients, and plausible confounding. The final quality of evidence ranges from very low to high (Table 3).[12,17,18] The results of meta-analyses and the assessments above were used to prepare a GRADE evidence profile for each of the PICO questions by a GRADE methodologist using the GRADEpro GDT application (http://gdt.guidelinedevelopment.org/app). Evidence profiles were presented during the panel meeting and discussed in detail with all of the stakeholders before voting on the final recommendations. Approval of the final recommendations was based on a simple majority.

Notably, this guideline is restricted to GERD in the absence of any known GI motility disorders or congenital or anatomical gut abnormalities. Hence, the recommendations may not necessarily apply to patients with conditions affecting motility, including gastroparesis, scleroderma, and autonomic dysfunction, for which other published evidence can be considered. A summary of our final recommendations for management of patients with GERD is listed in Table 1.

Panel composition and conflict of interest management

We assembled a panel of stakeholders to review evidence and make recommendations. The panel consisted of lead authors (M.D. and W.R.); committee members with expertise in methodology, systematic reviews, and meta-analyses (N.F. and N.T.); content experts (M.C., M.A., A.S., J.S.S., B.A.); and committee chair (B.Q.). A patient representative from the International Foundation for Gastrointestinal Disorder was also included. Evidence was presented to a panel of experts representing various stakeholders in a meeting held in the IT&T center, Downers Grove, Illinois, on March 10, 2023. All panel members were required to disclose potential financial and intellectual conflicts of interest, which were addressed according to ASGE policies set forth in the ASGE & Journal Policy for Managing Declared Conflicts of Interest (COI) found at https://www.asge.org/docs/default-source/default-document-library/coi-full-policy-for-asge-and-publications_edd_2-10-20.pdf. Panel members who received funding for any technologies or companies associated with any of the PICOs or who had other relevant conflicts of interest were asked to declare this before the discussion and did not vote on the final recommendation addressing that specific PICO question. Lead authors and methodologists were also excluded from voting.

Outcomes and definitions

Relevant clinical outcomes included incidence of GERD symptoms, esophagitis, BE, objective endoscopic findings

of GERD including adverse events and morphology of the antireflux barrier, improvement in GERD symptoms or remission, change in GERD symptom-related scores (GERD health-related quality of life [HRQL] or similar scale), PPI discontinuation rates, acid exposure time, durable symptom remission, adverse events, cost-effectiveness, patient values, and preferences. PPI discontinuation was defined as cessation of ongoing PPI use after the intervention. Acid exposure time was the percentage of esophageal acid exposure time provided using 24-hour or 48-hour ambulatory acid reflux study from the study. Durable symptom remission was defined as remission of GERD symptoms at ≥5-year follow-up.

External review

The guideline was reviewed by the *GIE* Editorial Board, Governing Board, and made available for public comment for 30 days on the ASGE website.

RESULTS

For each clinical question, we have summarized the results for a priori–identified outcomes of interest. Other considerations including cost-effectiveness, patient preferences and acceptability, and equity that are common to more than 1 question have also been summarized.

Question 1a: In patients with GERD symptoms, when should upper endoscopy be performed compared with no endoscopy?

Recommendation 1a:

A) In patients with GERD symptoms, the ASGE recommends upper endoscopy in those with
   a. alarm symptoms (dysphagia, odynophagia, weight loss, GI bleeding, persistent vomiting, or unexplained iron deficiency anemia).

   (Strong recommendation, moderate quality evidence)

B) In patients with GERD symptoms, with no alarm symptoms, the ASGE suggests endoscopic evaluation in
   b. those with Barrett's esophagus (BE) risk factors (family history of BE or esophageal adenocarcinoma; GERD plus another risk factor [>50 years, male sex, white race, smoking, and obesity]).
   c. infants and children with suggestive symptoms (poor weight gain, unexplained anemia, concern for GI bleeding, recurrent pneumonia, and regurgitation and/or vomiting).

   (Conditional recommendation, low-quality evidence)

Evidence

We performed a systematic review of the published literature on this topic. Evidence for endoscopy for GERD evaluation was examined from existing ASGE guidelines.[9,17] This included endoscopy for alarm symptoms for further evaluation for GI neoplasia and/or other adverse events of GERD. Symptoms prompting evaluation include dysphagia, odynophagia, weight loss, GI bleeding, persistent vomiting, and/or unexplained iron deficiency anemia in the appropriate clinical setting. The ASGE guideline for screening and surveillance of BE examined the available current evidence. EGD is recommended for patients with risk factors for BE including family history of BE and/or esophageal adenocarcinoma, and those with GERD and another risk factor including age ≥50 years, male sex, white race, smoking, and/or obesity. Therefore, these symptoms were incorporated into the recommendation by the panel. Finally, GERD symptoms are observed differently in pediatric patients because children may not report typical GERD symptoms. Therefore, there should be increased vigilance to evaluate for atypical symptoms suggestive of GERD in pediatric patients, including poor weight gain, unexplained anemia, concern for GI bleeding, recurrent pneumonia, and regurgitation and/or vomiting.

Certainty of the evidence

Upper endoscopy leading to detection of cancer and other advanced pathologic conditions in the presence of alarm symptoms has been demonstrated by prior observational data[19] and was incorporated into prior ASGE guidelines.[9] Therefore, the certainty in the evidence was initially determined to be moderate. However, there is a lack of prospective data regarding the utility of upper endoscopy in the absence of alarm symptoms including change in survival by upper endoscopy for screening of BE as well as detection of GERD and adverse events among infants and children with symptoms that could be suggestive of GERD. Therefore, the overall certainty in the evidence was determined to be low.

Discussion

A diagnosis of GERD can be made based on symptoms and confirmed by a favorable response to antisecretory medical therapy. If a patient's symptoms are consistent with typical or uncomplicated GERD, an initial trial of empiric medical therapy is appropriate before consideration of endoscopy in most patients. However, the panel believed that endoscopy should be considered in patients with alarm symptoms including dysphagia, odynophagia, weight loss, GI bleeding, persistent vomiting, and/or unexplained iron deficiency anemia because these could be trigged by underlying advanced pathology including cancer or a adverse event related to GERD that would require earlier management to alter disease trajectory. The panel discussed that a high-quality EGD should be performed when alarm symptoms have occurred after a recent endoscopic evaluation in the absence of such symptoms. EGD would be necessary to detect erosive esophagitis, peptic stricture, esophageal

cancer, gastric outlet obstruction, and other potentially significant upper GI tract findings. Therefore, the panel made a strong recommendation in favor of upper endoscopy. EGD should also be considered in patients with risk factors as detailed in the previous guidelines on BE because early detection and surveillance is beneficial for cancer prevention.[17] Because the existing guidelines provided a conditional recommendation for endoscopy for this population, the panel supported a conditional recommendation as well. Additionally, EGD is often performed as part of the preoperative evaluation of patients being considered for antireflux surgery or for the placement of wireless esophageal pH-monitoring devices and is an inherent part of various endoscopic antireflux procedures. The panel supported these established recommendations, and these were incorporated into the existing indications for endoscopy for GERD. Because these indications are an established clinical practice and already part of prior ASGE guidelines,[9,17] the panel did not further review the quality of evidence or vote separately for the existing indications for endoscopy. Finally, the panel acknowledged the subtle nature of symptoms that could be suggestive of GERD or adverse events among infants and children. Therefore, the panel voted for a conditional recommendation in favor of endoscopy for this population.

Question 1b: In patients who have undergone sleeve gastrectomy (SG), should endoscopy be performed to screen for Barrett's esophagus compared with no endoscopy?

Recommendation 1b:

- In patients with reflux symptoms after SG, the ASGE suggests endoscopic evaluation.
- In patients who are asymptomatic after SG, the ASGE suggests endoscopic screening 3 years after sleeve gastrectomy and then every 5 years.
- If BE is detected in this population, the ASGE recommends follow-up per existing BE surveillance guidelines.

(Conditional recommendation, very low quality of evidence)

Question 1c: In patients having undergone peroral endoscopic myotomy (POEM) who have reflux symptoms, should endoscopy be performed compared with no endoscopy?

Recommendation 1c:

In patients who have symptomatic GERD after POEM, the ASGE suggests endoscopic evaluation.

(Conditional recommendation, very low quality of evidence)

Best practice advice:

In patients who have undergone POEM, endoscopists should be aware of the high rate of post-POEM GERD and should consider periodic endoscopic evaluation in asymptomatic patients.

Evidence

We performed a systematic review of the published literature on this topic. Emerging evidence indicates de novo GERD occurs among patients with history of SG and POEM. We used Ovid MEDLINE and Embase for all of the studies published through December 2022 to examine evidence for endoscopy among patients post-SG and post-POEM. We examined the rate of GERD symptoms, esophagitis, and BE in patients post-SG and post-POEM using major search terms "sleeve gastrectomy," "per oral endoscopic myotomy," "gastroesophageal reflux," "GERD," "acid reflux," "esophagitis," and "Barrett's esophagus." The systematic review was restricted to studies assessing outcomes comparing baseline incidence of GERD symptoms, erosive esophagitis, and BE and postintervention incidence of these events.

GERD post-SG. We identified 1 RCT and 1 meta-analysis examining incidence of GERD symptoms, erosive esophagitis, and BE post-SG.[20,21] There were no significant studies published after these that affected the results; therefore, a decision was made to use the existing published analysis from Qumseya et al.[20] There were 8 full-text manuscripts and 2 abstracts included in that study. Incidence of new-onset GERD, esophagitis related to GERD, and BE post-SG were compared to baseline rates (when reported) in this study. In aggregate, 680 patients from 10 observational studies who had undergone EGD 6 months to 10 years post-SG were analyzed. Additionally, Salminen et al[21] recently reported the long-term effects of laparoscopic sleeve gastrectomy compared with Roux-en-Y gastric bypass (RYGB) on weight loss, comorbidities, and reflux among 240 adults with obesity (the SLEEVEPASS Randomized Clinical Trial).[21] Considering all of the outcomes together, the overall quality of evidence was found to be "very low." According to the AMSTAR-2 scale,[16] the quality of the included existing systematic reviews was high. The evidence profile with summary of outcomes and their assessment can be seen in Table 4.

Incidence of do novo GERD. For incidence of de novo GERD post-SG, 4 observational studies were included. Among 210 patients undergoing SG, 45% (94/210, 95% CI, 35%-55%; $P = .11$) developed de novo GERD per pooled analysis at a follow-up ranging 6 months to 10 years. The heterogeneity (I^2) was moderate at 51%. Certainty in the evidence was rated down for imprecision (small sample size) and, therefore, was very low.

Incidence of esophagitis. For incidence of erosive esophagitis post-SG, there were 5 observational studies in which 39.1% (156/399) had erosive esophagitis noted on follow-up endoscopy post-SG compared with 21.9% (34/155) before the SG with a follow-up ranging 3 to 10 years. In 5 studies with long-term follow-up,[22-26] the relative increase in the rate of esophagitis was 86% (64%-109%, $P < .001$, $I^2 = 47\%$). Meta-regression showed that

TABLE 4. Evidence profiles for question 1(b): In patients who have undergone sleeve gastrectomy (SG), should screening endoscopy be performed to screen for Barrett's esophagus compared with no endoscopy?

Certainty assessment							No. of patients	
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Post- SG	Baseline
De novo GERD post sleeve gastrectomy (follow-up: range 6 mo-10 y; assessed with Qumseya et al[20] meta-analysis)								
4	Nonrandomized studies	Not serious	Not serious	Not serious	Serious*	None	94/210	
Esophagitis post sleeve gastrectomy (follow-up: range 3-10 y; assessed with Qumseya et al[20] meta-analysis)								
5	Nonrandomized studies	Not serious	Not serious	Not serious	Serious*	None	156/399 (39.1%)	34/155 (21.9%)
Barrett's esophagus post sleeve gastrectomy (follow-up: range 6 mo-10 y; assessed with Qumseya et al[20] meta-analysis)								
10	Nonrandomized studies	Not serious	Not serious	Not serious	Not serious	None	54/680	

*Small sample size, <400.

the risk of esophagitis increases 8% each year. In the existing RCT, investigators report a high rate of esophagitis among patients post-SG than post-RYGB (31% [n = 91] vs 7% [n = 85], $P < .001$). Evidence was rated down for imprecision (small sample size) and thus was very low.

Incidence of BE. Of 10 observational studies, 11.4% developed BE post-SG (54/680; 7.7%-16.6%, $P < .001$; $I^2 = 28.7\%$) at a follow-up ranging 6 months to 10 years. Authors also analyzed the studies with long-term follow-up, which showed a similar pooled prevalence of BE of 11.5% (7.8%-16.7%; $P < .001$, $I^2 = 46\%$). In the existing RCT, there was no significant difference in the rate of BE among patients who have undergone SG and RNYB (4% vs 4%, $P = .29$) at 10 years.[21]

Other considerations. There were no studies examining mortality or survival benefit from screening endoscopy among patients who have undergone SG with regard to BE or other GERD-related adverse events. There were no studies reporting patient values, cost-effectiveness, or equity.

Certainty of the evidence

Certainty in evidence was overall low owing to the majority of the studies being observational and to imprecision due to low sample size of the included studies for most outcomes.

Discussion

The panel noted that based on a 10% risk threshold previously set forth by the ASGE[17,27] for a screening program to have significant benefit, the pooled rate of BE post-SG crossed that threshold at 11.4%. Therefore, the panel suggests screening for BE in this patient population. The panel voted for a "conditional" recommendation for endoscopy among patients post-SG if they have reflux symptoms. For those without symptoms, the panel voted for conditional recommendation for endoscopy for BE screening after 3 years and then every 3 to 5 years because of high baseline risk. If BE is found, then recommendations should follow prior ASGE guidelines on this topic.[17]

GERD post-POEM. We identified 2 RCTs[28,29] and 3 existing meta-analyses[30-32] evaluating GERD after POEM. We noted that there have been changes in both POEM techniques (anterior vs posterior myotomy, shorter vs longer myotomy, and full-thickness vs selective myotomy), rates of GERD and related consequences, and treatment for GERD post-POEM with interventions (eg, PPI use, concurrent or post-POEM transoral incisionless fundoplication [TIF], and fundoplication), making it difficult to examine the true incidence of GERD post-POEM on the basis of the available data. The meta-analysis from Repici et al[30] first reported on the incidence of GERD, esophagitis, and BE post-POEM, which incorporated changes in technique and GERD management post-POEM. In aggregate, 1542 patients among 17 observational studies (enrollment 2008-2014) were included that reported post-POEM incidence of GERD, esophagitis, and abnormal acid exposure data.[30] Follow-up ranged from 2 to 30 months. Inclusion criteria among studies consisted of a mix of patients who were treatment-naïve and previously treated. Vespa et al[32] reported results of their meta-analysis of 11 studies (2017-2021) with a total of 2342 patients assessing outcomes after POEM for achalasia with a minimum median follow-up duration of 36 months. We found another systematic review and meta-analysis from Facciorusso et al[31] in which 6 RCTs of POEM, pneumatic dilation, and laparoscopic Heller myotomy were examined (indirect comparisons). Both latter meta-analyses had stringent inclusion criteria. According to the AMSTAR-2 scale, the quality of the included systematic reviews was high. A summary of the outcomes and their assessment are found in Table 5.

TABLE 4. Continued

Effect		Certainty	Importance
Relative (95% CI)	**Absolute (95% CI)**		
Rate ratio 45 (35-55)		⨁◯◯◯ Very low*	Critical
Not estimable		⨁◯◯◯ Very low*	Critical
Rate ratio 11.4 (7.7-16.6)		⨁⨁◯◯ Low	Critical

Incidence of de novo GERD symptoms. For the rate of de novo GERD, Repici et al[30] analyzed 17 observational studies, reporting a pooled rate of de novo GERD of 19% post-POEM (245 of 1275; 95% CI, 15.7%-22.8%; I^2 = 43.3%; P = .024) over a follow-up of 2 to 30 months. There was moderate heterogeneity (I^2 = 43.3%). Certainty of the evidence was rated down for imprecision (varying ranges of follow-up) and thus was very low. Vespa et al[32] reported a pooled rate of symptomatic reflux of 22.0% (95% CI, 14.4%-29.5%, I^2 = 73.1%; P < .001) at a median follow-up of 36 months, whereas Facciorusso et al[31] reported a pooled rate of daily reflux symptoms of 17.4% (2 RCTs, 168 patients, range 0%-39.9%, I^2 and P value not available).

Incidence of esophagitis. For esophagitis post-POEM, 12 studies were included. The pooled rate of esophagitis was 29.4% (449/1056, 18.5%-43.3%, I^2 = 93%, P < .01) over a follow-up of 2 to 30 months. Certainty of the evidence was rated down for imprecision and inconsistency (I^2 > 50%); thus, it was very low. Facciorusso et al[31] reported a pooled esophagitis rate of 45.4% (2 cohorts, 176 patients, range 38.1%-52.9%), whereas for severe esophagitis it was 5.3% (2 cohorts, 176 patients, range 2%-8.6%). In a meta-analysis by Vespa et al[32] with at least 36 months' follow-up, there were 5 studies (301 patients) reporting erosive esophagitis at long-term endoscopic follow-up, with rates ranging from 3.7% to 33.3%.

Incidence of BE. For incidence of BE, we only found 1 meta-analysis, with 11 studies.[32] At a median of 36-month follow-up, there was 1 case of BE among 2342 patients. We did not identify other studies reporting a high rate of BE post-POEM.

Other considerations. There were no studies reporting patient values, cost-effectiveness, mortality, or benefits from screening or equity.

Certainty of the evidence

Considering all of the outcomes together, the overall quality of evidence was "very low" owing to observational studies, inconsistency due to high heterogeneity, and imprecision due to wide follow-up intervals for the pooled estimates.

Discussion

The panel reviewed the available evidence on rates of post-POEM GERD, esophagitis, and BE. The panel acknowledged a high rate of GERD and esophagitis post-POEM, albeit precise rates may be available in the future, especially if GERD remains persistent or progresses and potentially warrants substantial future interventions. The panel acknowledged that there has been an evolution of POEM techniques over time, which may have contributed to the high rates of GERD reported initially. In addition, some studies did not examine rates of acid exposure before and after POEM. Data on high-grade esophagitis and low-grade esophagitis are also not consistent. The panel expressed concern regarding disruption of the antireflux barrier irrespective of POEM technique and acknowledged the risk of GERD post-POEM. The panel also discussed the varying sensitivity for symptoms related to reflux and a higher incidence of esophagitis compared with reported symptoms among this population. The panel expressed concern regarding the elevated risk of squamous cell cancer of the esophagus associated with long-term achalasia, and subsequent risk of adenocarcinoma from ongoing acid exposure. Therefore, the panel acknowledged the utility of endoscopy in patients with achalasia post-POEM; however, the evidence in favor of EGD is insufficient. Therefore, the panel voted for a "conditional" recommendation of endoscopic evaluation in patients with GERD symptoms post-POEM. The panel also discussed proton pump inhibitor (PPI) or similar therapy for erosive reflux disease when prior endoscopy showed evidence for it among these patients. Because robust

TABLE 5. Evidence profiles for question 1(c): In patients having undergone peroral endoscopic myotomy (POEM) who have reflux symptoms, should endoscopy be performed compared with no endoscopy?

Certainty assessment						
No. of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**
Incidence GERD symptoms (follow-up: range 2-30 mo; assessed with Repici et al[30] SRMA)						
17	Nonrandomized studies	Not serious	Not serious	Not serious	Serious*	None
Rate of abnormal acid exposure (follow-up: range 2-30 mo; assessed with Repici et al[30] SRMA)						
17	Nonrandomized studies	Not serious	Serious†	Not serious	Serious*	None
Rate of esophagitis (follow-up: range 2-30 mo; assessed with Repici et al[30] SRMA)						
17	Nonrandomized studies	Not serious	Serious†	Not serious	Serious*	None

SRMA, Systematic review with meta-analysis.
*Varying follow-up interval among studies.
†$I^2 > 50\%$.

data demonstrating a high post-POEM BE incidence are lacking, the panel did not strongly recommend screening endoscopy among these patients in the context of potential risk of adverse events related to upper GI endoscopy and cost. However, the panel also acknowledged that endoscopists should consider periodic endoscopic evaluation in asymptomatic patients because of a high rate of GERD post-POEM based on discussion with patients.

Question 2: In patients with GERD undergoing upper endoscopy, what are the criteria for high-quality endoscopy procedure and report?

Recommendation 2:

In patients undergoing endoscopic evaluation for GERD symptoms, the ASGE recommends careful endoscopic evaluation, reporting, and photo-documentation of the following to improve patient care and outcomes:

- Objective GERD findings, when present:
  - Erosive esophagitis (using the Los Angeles [LA] grading system)
  - Barrett's esophagus (using the Prague classification)
  - Peptic stricture
- Gastroesophageal junction landmarks and integrity
  - Hiatal hernia dimensions using Hill grading or American Foregut society (AFS) grading in forward view and retroflexion
  - Location of the top of gastric folds, Z line, diaphragmatic impression
  - Existing fundoplication description (if present)

(Strong recommendation, very low quality of evidence)

Evidence

This was an important question to address for our guideline panel, especially given recent advancements in the endoscopic management of GERD. This is not a comparative question and thus did not follow a GRADE format. We performed a systematic literature search for studies reporting use of endoscopic assessment for GERD. We used Ovid MEDLINE and Embase for all of the studies published through December 2022. We used major search terms and subheadings including "reporting," "evaluation," "assessment," "upper endoscopy," "esophagogastroduodenoscopy," "esophagitis," "hernia," and "Barrett's esophagus." The systematic review was restricted to studies assessing the standardized reporting of findings during upper endoscopy. Data that describe the standardization of reporting upper endoscopies, including documentation of gastroesophageal junction (GEJ) changes that are important in GERD, are scarce. Overall quality of evidence was "very low" because of the low number of studies.

We identified 1 observational study addressing this question. Boys et al[33] examined inconsistent reporting in their retrospective study of 100 EGD reports from different endoscopists in different patients, in which esophagitis was noted in 33 patients but graded in only 14 (42%). A hiatal hernia was noted in 61 patients (57%) but measured in only 31 (51%) and classified in just 26% of cases.

Certainty of the evidence

Certainty of the evidence was low because of a lack of substantial studies, and the available data were driven from a single observational study of low power.

Discussion

There is no prospectively validated standardized reporting for an upper endoscopy. However, it is essential to perform a high-quality upper endoscopy among patients with GERD for a variety of reasons. This includes diagnosis of GERD-related consequences including erosive esophagitis, BE, and peptic stricture. Another goal of endoscopy is also to evaluate for any disruption in the antireflux barrier. Among patients with GERD, disruption of the antireflux barrier is quite common in the form of hiatal hernia,

TABLE 5. Continued

No. of patients		Effect		Certainty	Importance
Post-POEM	Baseline	Relative (95% CI)	Absolute (95% CI)		
245/1275		Rate ratio 19 (16-23)		⨁◯◯◯ Very low*	Critical
112/289		Rate ratio 39 (25-56)		⨁◯◯◯ Very low*,†	Critical
449/1056		Rate ratio 29 (19-43)		⨁◯◯◯ Very low*,†	Critical

effacement of the flap valve, or both, which can be easily recognized at the time of upper endoscopy. Patients with GERD who do not improve with medical therapy for GERD are frequently referred to endoscopists or surgeons for consideration for procedural options. Proceduralists reviewing the endoscopy report would need to determine the type of appropriate treatment procedure on the basis of the integrity of the GEJ and the antireflux barrier, that is, the hiatal hernia length and Hill or AFS classification.

There could be subjective variations in each endoscopist's assessment of antireflux barrier and consequences of GERD (ie, grading of esophagitis, size of hiatal hernia, Hill or AFS grade, and BE). Lack of routine reporting of these anatomical characteristics in a standardized format could negatively impact endoscopic and surgical management of GERD. For example, endoscopy may need to be repeated before endoscopic or surgical therapy to examine the size of the hiatal hernia and assess for any adverse events from GERD before definitive therapy. GERD interventions have their associated adverse events, increases in total cost, and may also delay or change therapeutic management. Risk of upper endoscopy and sedation-related adverse events, albeit low, are not negligible as reviewed in the ASGE guideline on adverse events from EGDs and EGD-related techniques.[34] Also, lack of assessment of the antireflux barrier (hiatal hernia, flap valve morphology) represents the suboptimal quality of endoscopy reporting. Therefore, it is important to use a uniform grading scale given the novel interventions and need for uniform language across providers. The panel unanimously considered evaluation for and reporting of objective signs of GERD, which includes erosive esophagitis (Los Angeles [LA] grading),[35] BE (Prague Classification),[36] and/or peptic stricture, and GEJ landmarks and integrity highly important. Although there is a lack of prospective data, these are considered a quality benchmark. The panel agreed on reporting GEJ landmarks and integrity, including size of the hiatal hernia, presence or absence of the flap valve using a forward endoscopic view, and retroflexion in the fundus. The panel also agreed on using a standardized terminology in reporting and grading the severity of esophagitis using the established Los Angeles grading system[35] and hiatal hernia evaluation using Hill grading[37] of the flap valve or AFS classification for GEJ integrity and hiatus.[38] Thus, the panel agreed for a "strong" recommendation to establish a high-quality reporting benchmark. The panel also discussed the importance of adequate mucosal inspection and cleanliness (including use of existing scales, ie, Barcelona scale,[39] and Toronto Upper Gastrointestinal Cleaning Score[40]) to ensure detection of any precancerous lesions before making definitive management decisions and emphasized on achieving a high-quality inspection during the standard EGD.

Question 3: In patients with GERD, should lifestyle interventions be recommended to reduce GERD symptoms?

Recommendation 3:

In patients with GERD symptoms, the ASGE recommends lifestyle modifications. These include

- weight loss for patients who are overweight or obese,
- smoking cessation,
- elevation of head of bed, and
- avoiding meals within 3 hours of bedtime.

(Strong recommendation, low-quality evidence)

Evidence

We performed a systematic review of the published literature on this topic. We used Ovid MEDLINE, Embase, Scopus, and Cochrane for studies published through December 2022. We used major search terms and subheadings including "Gastroesophageal reflux disease," "lifestyle changes," "weight loss," "diet," "smoking," "alcohol," "head of bed elevation," "late evening meal," "diet," "coffee," "beverages," and "modification." We examined the literature to evaluate the role of different lifestyle modifications (eg, weight loss, smoking cessation, head of bed elevation, and late evening meals) on reduction of GERD

TABLE 6. Evidence profiles for question 3: In patients with GERD, should lifestyle interventions be recommended to reduce GERD symptoms?

Certainty assessment						
No. of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**
Weight loss and decreased AET (assessed with Ness-Jensen et al[41] CGH [2015] systematic review)						
3	Randomized trials	Serious*	Not serious	Not serious	Serious†,‡	None
Weight loss and decreased GERD scores (RDQ) (baseline and at 6-mo follow-up) (assessed with Singh et al,[45] prospective intervention study)						
1	Randomized trials	Serious*	Not serious	Not serious	Serious†	None
Weight loss and reduced reflux symptoms						
2	Nonrandomized studies	Not serious	Not serious	Not serious	Not serious	None
Smoking cessation and presence of GERD (assessed with Ness-Jensen et al[49] [no or less than weekly antireflux medications])						
1	Nonrandomized studies	Not serious	Not serious	Not serious	Not serious	None
Smoking cessation and presence of GERD (at least weekly antireflux medications, normal weight) (assessed with Ness-Jensen et al[49])						
1	Nonrandomized studies	Not serious	Not serious	Not serious	Serious#	None
Smoking cessation and improvement of RDQ (varenicline) (assessed with Kohata et al[48] [2016])						
1	Nonrandomized studies	Not serious	Not serious	Not serious	Serious†	None
Alcohol cessation and improvement of AET (assessed with Grande et al[134] [1996])						
1	Nonrandomized studies	Not serious	Not serious	Serious**	Serious†	None
Late evening meal (2 h before bedtime) or an early meal (6 h before bedtime) and supine pH reflux (bravo capsule) (assessed with Piesman et al[52] [2007])						
1	Nonrandomized studies	Not serious	Not serious	Not serious	Serious†	None
Head of bed elevation and reflux episodes (assessed with Stanciu and Bennett[51] observational study [1977] and Hamilton et al[50] RCT [1988])						
2	Nonrandomized studies	Not serious	Not serious	Not serious	Serious†,‡	None
Effect of beverages (replacement of 2 services with water) (follow-up: mean 262,641 patient-years; assessed with Mehta et al 2020[135])						
1	Nonrandomized studies	Not serious	Not serious	Not serious	Not serious	None
Citrus fruits and juices, decreased acid reflux (assessed by Kaltenbach et al[136] review, *JAMA*, 2006)						
Spicy foods (assessed by Kaltenbach et al[136] review, *JAMA* 2006)						

AET, Acid exposure time; *OR*, odds ratio; *RDQ*, reflux disease questionnaire.
*Interventional prospective trial (not true RCT: Singh et al[45]).
†Small sample size.
‡Inability to pool data.
#Wide CI.
**Study to assess a different outcome.

TABLE 6. Continued

No. of patients		Effect		Certainty	Importance
Lifestyle interventions	None	Relative (95% CI)	Absolute (95% CI)		
Unable to pool data, there were 3 RCTs showing decrease in AET after weight loss				⨁⨁◯◯ Low*,†,‡	Critical
RDQ; change in overall GERD score from 5.5 ± 4.3 to 1.8 ± 3.6. $P < .01$, n = 124				⨁⨁◯◯ Low*,†	Critical
Both studies showed dose-dependent improvement in symptoms with decrease in BMI. • Nurses' Health Study: 10,545 women, OR 0.64, 95% CI 0.42-0.97, BMI decreased >3.5 units, $P < .001$-13 fewer per 1,000). • Nord-Trondelag: 29,610 participants, OR 2.42, 95% CI 1.88-3.11, BMI decreased >3.5 units, $P < .001$)				⨁⨁◯◯ Low	Critical
		OR 0.95 (0.39-2.30)	1 fewer per 1,000 (from 2 fewer to 0 fewer)	⨁⨁◯◯ Low	Critical
		OR 5.67 (1.36-23.64)	6 fewer per 1,000 (from 24 fewer to 1 fewer)	⨁◯◯◯ Very low#	Critical
62/141 (44.0%)	9/50 (18.0%)	Not estimable		⨁◯◯◯ Very low†	Critical
• Does not have exact numbers in the article • No differences were seen in pHmetry variables at baseline and at late evaluation in both groups of alcoholic patients.				⨁◯◯◯ Very low†,**	Critical
• 2.3 ± 0.8 with a mean change of 5.2 ± 1.6, $P = .002$ • Late evening meal associated with significantly increased supine reflux. No significant increase in upright reflux after late evening meal.				⨁◯◯◯ Very low†	Important
• Unable to pool results because of slightly different interventions • Stanciu and Bennett et al.[51]: n = 63, difference in head of bed elevation and lying down; 102 reflux episodes vs 148, $P < .01$; % time pH <3, 4, and 5 is significant as well. Symptoms 2.0 ± 1.2 vs 3.0 ± 2.4, $P < .005$ • Hamilton et al[50]: does not have exact number. n = 15, sleeping on wedge: decreased AET but did not decrease the number of reflux episodes. Sleeping with head of bed elevation had decreased AET but was not statistically significant				⨁◯◯◯ Very low†,‡	Important
Coffee: HR, 0.96 (0.92-1.00) Tea: HR, 0.96 (0.92-1.00) Soda: HR, 0.92 (0.89-0.96)				⨁⨁◯◯ Low	Important
No studies exist to assess the effect of avoidance of citrus on GERD				-	
Lack of evidence examining effect of avoidance of spicy foods on GERD				-	

symptoms and decreasing GERD-related symptom scores or acid exposure time as an outcome. We also examined cost-effectiveness, equity, and patient values and preferences. A summary of outcomes and their assessment are found in Table 6.

Weight loss. For assessing the impact of weight loss on objective GERD improvement, our search identified an existing systematic review from Ness-Jensen et al[41] with data from the 15 studies it examined. According to the AMSTAR-2 scale, quality of the existing systematic review was moderate. There were 3 RCTs[42-44] in severely obese individuals (n = 57) that compared weight loss by gastric balloon distension with sham treatment combined with dietary guidance, physical exercise, and behavioral therapy. These showed reduced esophageal acid exposure with weight loss ranging between 11 and 44 kg over variable follow-up time from the intervention (13 weeks to 4 months).

For assessing the improvement in GERD symptoms and related symptom scores, 1 RCT of 332 obese patients randomized to a structured weight loss program (n = 167) or a telephone-based group conference on weight management (n = 165) demonstrated improvement of reflux disease questionnaire scores from a mean 5.5 to 1.8 ($P < .01$), with 81% of subjects showing reduction of GERD symptom scores after 6 months of weight loss (BMI decease from 34.7 to 30.2).[45] The prevalence of reflux symptoms also decreased (37% to 15%, $P < .01$). In a large observational cohort study of 10,545 women, it was noted that there was a dose-dependent decreased risk of reflux symptoms among women who had decrease in BMI by >3.5 units compared with women with no BMI change (OR 0.64, 95% CI, 0.42-0.97; P for trend < .001).[46] Another large prospective population-based cohort study of 29,610 patients also showed a dose-dependent relationship of weight loss and reduction of GERD. Patients with BMI decrease of >3.5 units had an adjusted OR of 1.98 (95% CI, 1.45-2.72) for loss of any reflux symptoms when on no or less than weekly antireflux medication and an OR of 3.95 (95% CI, 2.03-7.65) when on at least weekly antireflux medications.[47]

Smoking cessation

For assessing impact of smoking cessation on GERD symptoms, a literature search identified 2 cohort studies.[48,49] A prospective population-based cohort study of 29,610 participants demonstrated that smoking cessation was associated with decreased severe reflux symptoms in normal weight individuals on medical treatment. These individuals' reflux symptoms were compared to those of participants who continued smoking daily (OR 5.67, 95% CI, 1.36-23.64) but not in those using any or less than weekly antireflux medications or those who are overweight.[49] Those findings were further supported by the Kohata et al[48] study, which demonstrated improvement in health-related quality of life scores in the successful smoking cessation group aided with varenicline (n = 141) compared with those who did not succeed (n = 50) (43.9% vs 18.2%).

Head of bed elevation. For impact of head of bed elevation on GERD, 1 observational study and 1 RCT were identified.[50,51] One cohort study of 63 patients demonstrated that head of the bed elevation had fewer reflux episodes than in those without elevation (102 reflux episodes vs 148 reflux episodes, $P < .01$). The GERD symptom scores improved as well: 2 ± 1.2 versus 3 ± 2.4, $P < .005$. Acid exposure time improved with statistical significance as a less percentage of time in which the pH was <5.[51] In a crossover RCT of 15 patients, sleeping on a 10-inch wedge decreased acid exposure time (15% and 21%, respectively, $P < .05$) but did not decrease the number of reflux episodes compared with a flat position.[50]

Late evening meals. For impact of late evening meals on GERD, we identified 1 study of 32 patients in which late evening meal was associated with increased reflux while supine when compared with early meal (percentage supine pH <4: 2.3 ± 0.8 with a mean change of 5.2 ± 1.6, $P = .002$).[52]

Alcohol cessation, effect of beverages, citrus and spicy foods. For alcohol cessation, our literature search did not identify recent robust data to demonstrate that alcohol cessation improves GERD symptoms to make a recommendation. Other lifestyle interventions were assessed including decreased ingestion of various beverages and foods, but the data were inconclusive for improvement of GERD symptoms with these lifestyle modifications.

Other considerations. We did not identify data on cost-effectiveness, equity, or patient preferences for these interventions. We relied on our patient advocate who opted in for conservative measures over medications or surgery if they help with symptom reduction or remission.

Certainty of the evidence

Overall quality of evidence was very low when considering all of the outcomes together. This was due to either one or combinations of the following: risk of bias, imprecision (low sample size, varying CIs), indirectness, and inability to pool the data because of varying outcome definitions.

Discussion

Overall, the certainty in evidence was very low. The panel acknowledged that while there is lack of robust data, there is benefit of weight loss and smoking cessation from overall health improvement and cancer reduction. Data regarding other dietary interventions may be weak but these are low-risk interventions that can be incorporated as GERD-related lifestyle measures. Given the low cost to these interventions as well as the potential for other health benefits of these lifestyle interventions, the panel agreed that these lifestyle modifications should be recommended to decrease GERD symptoms based on the evidence available.

Question 4: In patients with GERD, does proton pump inhibitor compared with placebo reduce symptoms?

Recommendation 4:

- In patients with symptomatic and confirmed GERD with predominant heartburn symptoms, the ASGE recommends medical management with proton pump inhibitors (PPIs) at the lowest possible dose for the shortest possible period of time while initiating discussion about long-term management options.

  (Strong recommendation, moderate quality of evidence)

- In patients with suboptimal clinical response to PPI therapy, the ASGE suggests testing CYP2C19 polymorphism and adjusting PPI dosage and selection accordingly.

  (Conditional recommendation, very low quality of evidence)

Best practice advice:

- Patients who have been on long-term PPI therapy (>6 months) should be considered for optimization and de-escalation of medical management.
- Providers should carefully consider the risks, benefits, and alternatives of PPI use for patients with GERD.
- Providers prescribing PPI therapy should be aware that adverse events from PPI in prospective data have been limited to a modest increased risk of enteric infections; however, there is a need for robust long-term data to prove or disprove any other putative adverse events.

Evidence

We performed a systematic review of the published literature on this topic. We used Ovid MEDLINE, Embase, Scopus, and Cochrane for studies published through December 2022. We used major search terms and subheadings including "gastroesophageal reflux disease," "proton pump inhibitor," "antireflux therapy," "PPI," and "antisecretory therapy" to identify RCTs and existing systematic review and meta-analysis that examined the outcomes of PPI versus placebo (including non-PPI medical therapy) on GERD symptoms among RCTs. Outcomes examined were GERD symptom remission, healing of esophagitis, and adverse events from PPI. We also examined cost-effectiveness, equity, and patient values and preferences. Quality of the existing meta-analysis was determined by AMSTAR-2 tool and was high. A summary of the outcomes and their assessment can be seen in Table 7. In addition, we also examined the literature for clinical evidence regarding the assessment of CYP2C19 polymorphism and its impact on PPI metabolism.

Symptom remission. For assessing the outcome of symptom remission, our search identified an existing network meta-analysis by Zhang et al[53] that examined 98 RCTs of PPIs, H_2 blockers, and placebo comparisons, which included a total of 45,964 participants. There were 22 RCTs examining different PPIs in various dose-strengths (n = 41,373) compared with placebo (n = 5037) for symptom remission in this network meta-analysis. Patients with GERD taking PPIs were found to be 4 times more likely to have symptom relief compared with those taking a placebo with a pooled OR of 4.2 (95% CI, 3.25-5.48; $P < .01$). This network meta-analysis did not provide heterogeneity (I^2) for these outcomes. Evidence was rated down for indirectness due to network meta-analytic approach, and therefore the certainty of evidence was moderate.

Esophagitis healing

For assessing the outcome of esophagitis healing, we used the same existing network meta-analysis by Zhang et al.[53] There were 12 RCTs examining different PPIs in various dose-strengths (n = 22,669) compared with placebo (n = 5037) for esophagitis healing in this network meta-analysis. Patients with GERD taking PPIs were found to be 11 times more likely to have esophagitis resolution compared with those taking a placebo (OR 11.4, 95% CI, 8.17-16.3; $P < .01$). This network meta-analysis did not provide heterogeneity (I^2) for these outcomes. Evidence was rated down for indirectness due to network meta-analytic approach, and therefore the certainty of evidence was moderate.

Adverse events. For assessing the adverse events from PPI therapy, we identified 1 large RCT from Moayyedi et al[54] that examined 8791 patients receiving pantoprazole 40 mg once a day and 8807 patients receiving placebo for incidence of adverse events. The difference in adverse event rates at a mean follow-up of 3 years between PPI users compared with nonusers was nonsignificant: all-cause mortality (7.2% vs 7%; hazard ratio [HR], 1.03; 95% CI, 0.92-1.15; $P = .63$); cardiovascular events including myocardial infarction, stroke, and death (7.9% vs 7.6%, HR 1.04, 95% CI 0.93-1.15, $P = .50$); chronic kidney disease (2.1% vs 1.8%; OR 1.17, 95% CI, 0.94-1.45; $P = .51$); *Clostridium difficile* infection (0.1% vs 0%; OR 2.26, 95% CI, 0.7-7.34; $P = .18$); other enteric infections (1.4% vs 1.0%; OR 1.33; 95% CI, 1.01-1.75); pneumonia (3.6% vs 3.6%; OR 1.02, 95% CI, 0.87-1.19; $P = .82$); fractures (2.3% vs 2.4%; OR 0.96, 95% CI, 0.79-1.17; $P = .71$); and dementia (0.6% vs 0.5%; OR 1.2, 95% CI, 0.81-1.78; $P = .36$).[54] The certainty in evidence was high.

Cost-effectiveness. For assessing the cost-effectiveness of PPI therapy for GERD, our search identified a narrative review of 10 studies.[55] In this review, PPIs were found to be more effective in relieving heartburn in comparison with ranitidine but was not cost-effective compared with other medical therapies including H_2 blockers. On-demand PPI treatment strategy showed an incremental cost-effectiveness ratio of U.S.$2197 per quality-adjusted life year gained and was the most effective and cost saving

TABLE 7. Evidence profiles for question 4: In patients with GERD, does proton pump inhibitor compared with placebo reduce symptoms?

Certainty assessment						
No. of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**
Symptom relief (assessed with Zhang et al[53] [2017] meta-analysis)						
22	Randomized trials	Not serious	Not serious	Serious*	Not serious	None
Healing of esophagitis (assessed with Zhang et al[53] [2017] meta-analysis)						
12	Randomized trials	Not serious	Not serious	Serious*	Not serious	None
All-cause mortality (follow-up: mean 3 y; assessed with Moayyedi et al[54] [2019] RCT)						
1	Randomized trials	Not serious	Not serious	Not serious	Not serious	None
Cardiovascular events including myocardial infarction, stroke, death (follow-up: mean 3 y; assessed with Moayyedi et al[54] [2019] RCT)						
1	Randomized trials	Not serious	Not serious	Not serious	Not serious	None
Chronic kidney disease (follow-up: mean 3 y; assessed with Moayyedi et al[54] [2019] RCT)						
1	Randomized trials	Not serious	Not serious	Not serious	Not serious	None
Clostridium difficile infection (follow-up: mean 3 y; assessed with Moayyedi et al[54] [2019] RCT)						
1	Randomized trials	Not serious	Not serious	Not serious	Not serious	None
Pneumonia (assessed with Moayyedi et al[54] [2019] RCT)						
1	Randomized trials	Not serious	Not serious	Not serious	Not serious	None
Fractures (follow-up: mean 3 y; assessed with Moayyedi et al[54] [2019] RCT)						
1	Randomized trials	Not serious	Not serious	Not serious	Not serious	None
Dementia (follow-up: mean 3 y; assessed with Moayyedi et al[54] [2019] RCT)						
1	Randomized trials	Not serious	Not serious	Not serious	Not serious	None
Dementia (PPI use >5 y) (assessed with Desai et al[137] [2020] meta-analysis)						
4	Nonrandomized studies	Not serious	Not serious	Not serious	Not serious	None
Gastric cancer (assessed with Peng et al 2023[119] meta-analysis)						
16	Nonrandomized studies	Not serious	Serious†	Not serious	Not serious	None

HR, Hazard ratio; *OR*, odds ratio; *PPI*, proton pump inhibitor; *RCT*, randomized controlled trial.
*Zhang et al[53] (2017) network meta-analysis outcome; data on number of patients in each groups not available.
†High heterogeneity.

treatment compared with all of the other therapies. The average cost-effectiveness ratio was lower for rabeprazole therapy than for ranitidine therapy. Therefore, PPI was overall found to be more cost-effective than other medications.

Patient values and preferences. For assessing patient values and preferences of PPI therapy for GERD, our search identified a review of 12 eligible studies (7 surveys, 4 qualitative studies, 1 RCT) examining patient values and preferences.[56] Authors found that patients value symptom control highly and worry about symptoms returning if the PPI is reduced. Patients are encouraged to consider reducing their PPI if a clinician provides advice and education. Study results were limited by the small sizes of inclusion studies and the heterogeneous populations. This review concluded that weaning and/or cessation of PPI is a preference-sensitive decision; therefore, patient attitudes should be elicited and incorporated into the decision-making process.

CYP2C19 polymorphism. PPIs are mainly metabolized by cytochrome P450 2C19 (CYP2C19). PPI metabolism is affected by the genotypical variability of CYP2C19, which encodes the CYP450 isoenzyme. More than 40 polymorphic variants of CYP2C19 have been

TABLE 7. Continued

No. of patients		Effect		Certainty	Importance
PPI	Placebo	Relative (95% CI)	Absolute (95% CI)		
Network meta-analysis outcome Pooled OR 4.2 (3.25-5.48), raw numbers not available				⨁⨁⨁◯ Moderate*	Critical
Network meta-analysis outcome Pooled OR 11.4 (8.17-16.3), raw numbers not available				⨁⨁⨁◯ Moderate*	Critical
630/8791 (7.2%)	614/8807 (7.0%)	HR 1.03 (0.92-1.15)	2 more per 1000 (from 5 fewer to 10 more)	⨁⨁⨁⨁ High	Critical
691/8791 (7.9%)	668/8807 (7.6%)	HR 1.04 (0.93-1.15)	3 more per 1000 (from 5 fewer to 11 more)	⨁⨁⨁⨁ High	Critical
184/8791 (2.1%)	158/8807 (1.8%)	OR 1.17 (0.94-1.45)	3 more per 1000 (from 1 fewer to 8 more)	⨁⨁⨁⨁ High	Critical
9/8791 (0.1%)	4/8807 (0.0%)	OR 2.26 (0.70-7.34)	1 more per 1000 (from 0 fewer to 3 more)	⨁⨁⨁⨁ High	Critical
318/8791 (3.6%)	313/8807 (3.6%)	OR 1.02 (0.87-1.19)	1 more per 1000 (from 4 fewer to 6 more)	⨁⨁⨁⨁ High	Critical
203/8791 (2.3%)	211/8807 (2.4%)	OR 0.96 (0.79-1.17)	1 fewer per 1000 (from 5 fewer to 4 more)	⨁⨁⨁⨁ High	Critical
55/8791 (0.6%)	46/8807 (0.5%)	OR 1.20 (0.81-1.78)	1 more per 1000 (from 1 fewer to 4 more)	⨁⨁⨁⨁ High	Critical
		HR 1.10 (0.66-1.53)	1 fewer per 1000 (from 2 fewer to 1 fewer)	⨁⨁◯◯ Low	Critical
		OR 1.75 (1.28-2.40)	2 fewer per 1000 (from 2 fewer to 1 fewer)	⨁◯◯◯ Very low†	Critical

identified, and they are related to nearly 35 enzyme isoforms. Allelic variants are associated with defined metabolizer phenotype as follows: the poor metabolizer phenotype (presence of both alleles, either nonfunctional or null), intermediate metabolizer phenotype (1 null allele and 1 functional allele), normal metabolizer phenotype (wild-type phenotype, in which both alleles are functional), ultrarapid metabolizer (homozygous promoter region variants that potentiate gene expression, increasing the enzymatic activity of the protein), and rapid metabolizer phenotype (1 normal-function allele and 1 increased-function allele).

Although it has not largely been implemented in practice, there may be a role for assessment of CYP2C19 polymorphism and adjusting PPI therapy in patients who have GERD refractory to PPI therapy. We performed a literature search for existing evidence on assessing CYP2C19 polymorphism and impact on PPI metabolism for therapy of GERD.

For assessing CYP2C19 polymorphism and impact on GERD symptoms, we found an existing meta-analysis of 19 studies.[57] In this meta-analysis, analysis of 8 studies showed that rapid metabolizers with reflux esophagitis have an increased risk of being refractory to PPI therapy compared with poor metabolizers (OR, 1.6; 95% CI, 1.02-2.66; $P = .04$). Efficacy rates of PPIs for GERD resolution (including reflux esophagitis and nonerosive reflux

disease) varied significantly between CYP2C19 genotypes as well. In the intention-to-treat analysis, the efficacy of GERD resolution was 52.2% (315/604) among the rapid metabolizers, 56.7% (298/526) among the intermediate metabolizers, and 61.3% (138/225) among the poor metabolizers ($P = .047$).

Certainty of evidence

The overall quality of evidence was moderate for PPI efficacy and safety when considering all of the outcomes together. This was due to indirectness of the existing evidence synthesis from the network meta-analysis. Certainty of evidence was low for impact of the CYP2C19 polymorphism because of data from observational studies.

Discussion

Overall, the certainty of evidence was moderate. The panel acknowledged the high efficacy of PPIs for GERD symptom resolution and esophagitis healing compared with H_2 blockers and placebo. Although the efficacy of PPI therapy has been established from high-quality studies, several observational studies have also reported various adverse events associated with PPI use. These associations raise questions about long-term use, which causes anxiety among patients and providers despite short-term RCT data that do not demonstrate significant increased incidence of the studied adverse events, the exception being a slight increase in GI infections.[53,58-64] Furthermore, long-term PPI users may be partially responsive, intolerant, or searching for better options, so PPI de-escalation and stewardship should be discussed. The panel strongly recommended medical management including PPIs at the lowest dose for the shortest time while initiating discussion about long-term management options for patients with confirmed GERD. The panel also provided best practice advice for PPI advice on the use to guide clinical practice, including discussion of risks and benefits before starting therapy and consideration of de-escalation and dose optimization when symptoms are well controlled. Data regarding clinical utility of CYP2C19 phenotype assessment and changing the PPI therapy are not robust; however, the panel acknowledged the principle of assessing the phenotype to optimize the medication management when GERD symptoms are not responding in patients who are adherent to therapy. The panel acknowledged existing H_2 receptor blockers and their over-the-counter availability. Because the reviewed evidence demonstrated superiority of PPIs over H_2 receptor blockers for GERD therapy, PPIs are favored for patients with erosive esophagitis and uncontrolled GERD with confirmed objective acid reflux study. At the same time, the panel agreed on use of H_2 receptor blockers as an adjunct, as needed therapy, and when faster onset of action might be required on a case-by-case basis.

The panel also discussed the newer potassium channel competitive acid blockers (PCABs) and their positioning in the GERD management. These agents were not readily available in North America at the time of evidence review and panel meeting. A recent RCT demonstrated effectiveness of Vonoprazan over lansoprazole for healing and maintenance of healing of erosive esophagitis.[65] A recent systematic review and meta-analysis (19 studies, 7023 subjects) also showed that Vonoprazan is superior to PPI in first-line *Helicobacter pylori* eradication and erosive esophagitis but noninferior in other gastric acid–related diseases.[66] Panel agreed unanimously that existing data do not show superiority of PCABs for PPIs overall for GERD but likely that PCABs are more potent for erosive esophagitis and that their long-term adverse event data are not available. The panel, however, also agreed that with evolving data, PCABs likely will be used for confirmed patients with GERD after discussion of existing data and risks and benefits.

Question 5(a): In patients with persistent GERD, how does transoral incisionless fundoplication (TIF) compare to standard medical therapy?

Recommendation 5(a):

In patients with confirmed GERD with small hiatal hernia (≤2 cm) and Hill grade I or II who meet any of the following criteria, the ASGE suggests evaluation for TIF as an alternative to long-term medical management.

Criteria:

- Chronic GERD (at least 6 months)
- Long-term proton pump inhibitor (PPI) use (at least 6 months) for management of GERD symptoms
- Refractory GERD
- Regurgitation-predominant GERD
- Patient prefers to avoid long-term PPI use

(Conditional recommendation, low quality of evidence)

Evidence

We performed a systematic review of the published literature on this topic. We used Ovid MEDLINE, Embase, Scopus, and Cochrane for studies published through December 2022. We used major search terms and subheadings including "Gastroesophageal reflux disease," "endoscopic therapy," "transoral incisionless fundoplication," and "plication" (Appendix 1). The systematic review (Fig. 1) was restricted to studies assessing the efficacy and safety of TIF 2.0 for GERD compared with PPI and/or sham intervention. Our results were limited to available therapies (existing TIF 2.0 [Esophyx 2.0]) because prior versions are out of date. Our literature search identified 4 RCTs, 18 cohort studies, and 4 existing meta-analyses.[38,67-91] Risk of bias among these RCTs was assessed using the Cochrane Risk of Bias tool. From these 4 RCTs, details on outcomes of TIF 2.0 compared with PPI and/or sham intervention on GERD symptoms were collected. Outcomes examined

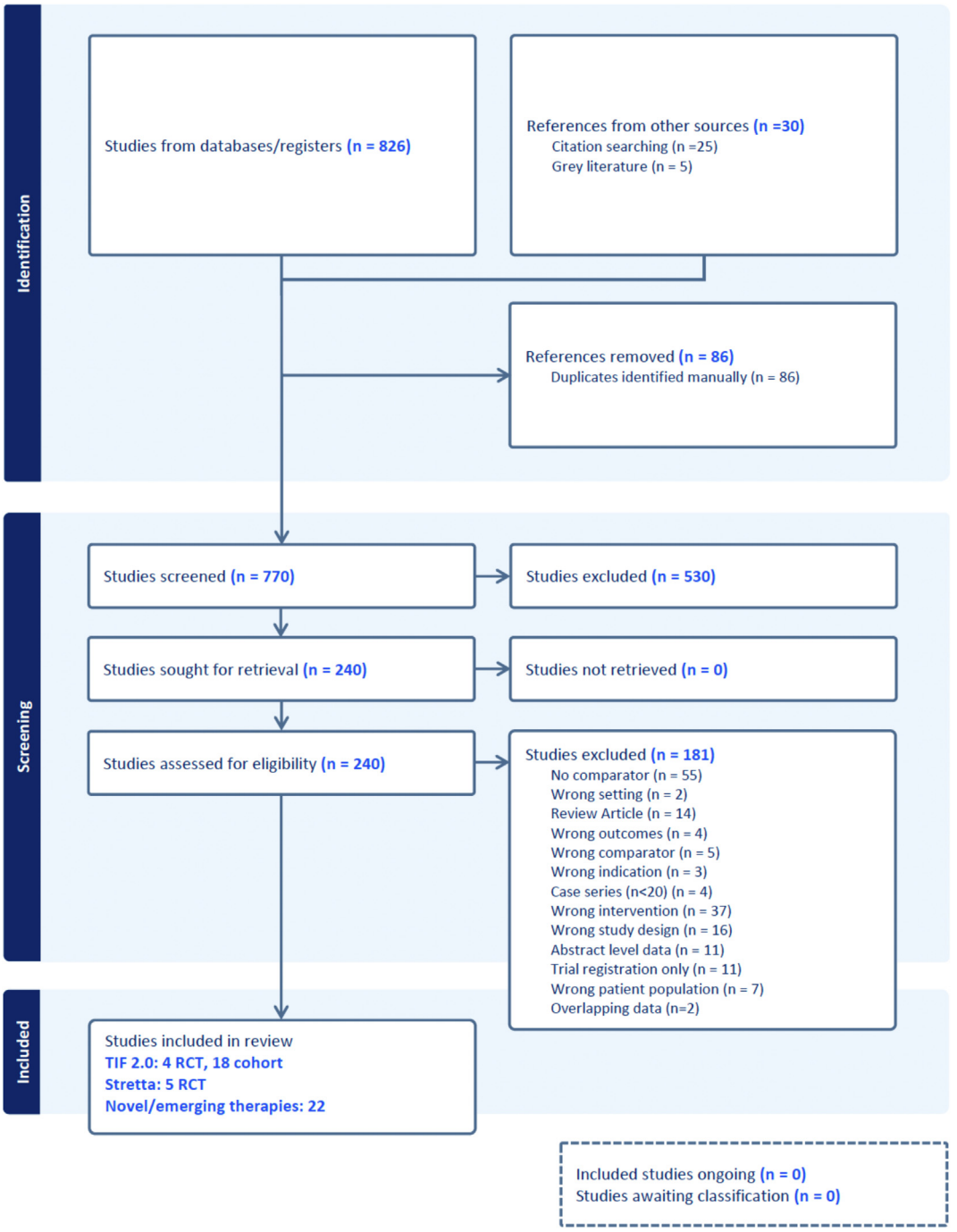

Figure 1. PRISMA diagram showing the studies included in the systematic review evaluating endoscopic therapies TIF 2.0, radiofrequency energy (Stretta), and novel and emerging endoscopic therapies in adult patients with GERD. *TIF 2.0*, Transoral incisionless fundoplication 2.0 (Esophyx 2.0); *RCT*, randomized controlled trial.

included PPI discontinuation, reduction in acid exposure time (percentage of time pH was <4), normalization of esophageal acid exposure time (per patient reporting), symptom resolution (per patient), durable symptom resolution, GERD score improvement (using GERD health-related quality of life [GERD-HRQL] or similar scales), and adverse events (including severe adverse events and post-TIF dysphagia). We also examined cost-effectiveness, equity, and patient values and preferences.

We performed an updated meta-analysis of eligible RCTs and cohort studies separately for outcomes in which no recent meta-analysis was found. Because there were overall low numbers of RCTs, a separate meta-analysis for outcomes of interest was performed for cohort studies to

TABLE 8. Evidence profiles for question 5(a): In patients with persistent GERD, how does transoral incisionless fundoplication (TIF) compare to standard medical therapy?

Certainty assessment						
No. of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**
Durable symptom resolution (RCT) (follow-up: mean 5 y; assessed with elimination of troublesome regurgitation [RDQ] by Trad et al[67])						
1	Randomized trials	Not serious	Not serious	Not serious	Serious*	None
Durable symptom resolution (RCT or cohort) (follow-up: mean 5 y; assessed with normalization of heartburn and regurgitation score by Testoni et al[72] meta-analysis)						
3	Nonrandomized studies	Not serious	Not serious	Not serious	Serious*	None
Score improvement (GERD-HRQL or similar) at 6 mo (RCT) (follow-up: mean 6 mo)						
4	Randomized trials	Not serious	Not serious	Not serious	Serious*†	None
Score improvement (GERD-HRQL) (Cohort only: pre-TIF and post-TIF data) (follow-up: mean 22.2 mo; assessed with updated meta-analysis)						
10	Nonrandomized studies	Not serious	Serious‡	Not serious	Not serious	None
AE (all types, RCT alone) (assessed with updated meta-analysis)						
4	Randomized trials	Not serious	Not serious	Not serious	Serious*	None
Severe Adverse events (RCT only) (assessed with: Updated meta analysis of significant/serious AE)						
4	Randomized trials	Not serious	Not serious	Not serious	Serious*	None
Severe AE (RCT + prospective observational) (assessed with Huang et al[74] [2017] meta-analysis)						
16	Nonrandomized studies	Not serious	Not serious	Not serious	Not serious	None
Post-TIF dysphagia (assessed with Chandan et al[73] [2021] meta-analysis)						
9	Nonrandomized studies	Not serious	Serious‡	Not serious	Not serious	None
PPI discontinuation (RCTs) (follow-up: mean 6 mo; assessed with updated meta-analysis)						
3	Randomized trials	Not serious	Serious‡	Not serious	Serious*	None
PPI discontinuation (Cohort only: Pre-TIF and post-TIF data) (follow-up: mean 19.1 mo; assessed with updated meta-analysis)						
14	Nonrandomized studies	Not serious	Serious‡	Not serious	Not serious	None
PPI discontinuation at 8-10 y (Cohort: Pre-TIF and post-TIF data) (assessed with Testoni et al[72] meta-analysis)						
2	Nonrandomized studies	Not serious	Not serious	Not serious	Serious*	None
Acid exposure time (% time pH <4) (RCT) TIF vs Sham (follow-up: mean 6 mo; assessed with Richter et al[71] [2018] meta-analysis)						
2	Randomized trials	Not serious	Not serious	Not serious	Serious*	None
Acid exposure time (% time pH <4) (RCTs) TIF vs PPI (follow-up: mean 6 mo; assessed with Richter et al[71] [2018] meta-analysis)						
2	Randomized trials	Not serious	Not serious	Not serious	Serious*	None
Acid exposure time (% time pH <4) (Cohort only: pretreatment and posttreatment data) (follow-up: mean 15.6 mo; assessed with updated meta-analysis)						
5	Nonrandomized studies	Not serious	Serious‡	Not serious	Serious*	None
Symptom resolution (per patient) (RCTs) (follow-up: mean 6 mo; assessed with updated meta-analysis [varying outcome assessment defined in each study])						
4	Randomized trials	Not serious	Not serious	Not serious	Very serious*,**	None
Normalization of esophageal acid exposure time (RCTs) (follow-up: mean 6 mo; assessed with updated meta-analysis: Hakensen[70] and Witteman[68])						
2	Randomized trials	Not serious	Not serious	Not serious	Serious*	None

AE, Adverse event; *AET*, acid exposure time; *GERD-HRQL*, GERD-health-related quality of life; *MD*, mean difference; *PPI*, proton pump inhibitor; *QOLRAD*, quality of life in reflux and dyspepsia; *RCT*, randomized controlled trial; *RR*, risk ratio; *TIF*, transoral incisionless fundoplication.

*Imprecision due to small sample size (n < 400).

†Inability to pool data.

‡High heterogeneity $I^2 > 50\%$.

#Witteman et al[68] (2015) not reporting all adverse event (AE) rates; Håkansson et al[70] (2015) rate for all AEs higher than the total population (so the model did not count the study).

**Different outcome definitions.

(*continued on the next page*)

TABLE 8. Continued

No. of patients		Effect		Certainty	Importance
Esophyx2.0 (TIF2)	Sham and/or PPI	Relative (95% CI)	Absolute (95% CI)		
38/44 (86.4%) with symptom resolution after TIF compared with 100% with symptoms at baseline				⨁⨁⨁◯ Moderate*	Critical
69/86 (86.3%) with symptom resolution after TIF				⨁◯◯◯ Very low*	Critical
4 RCTs for TIF: each used different population and different methods to measure outcomes (pooling of outcomes not possible). All showing significant improvement of each score used from before and after and between intervention and control. • Witteman et al[68]: TIF baseline, GERD-HRQL mean score 27.1, SD 8.4; 6-mo TIF, mean 11.1, SD 9.7; TIF2 (n = 45), mean 10.3, SD 7.8. vs PPI group: 28.2 ± 9.5 baseline to 25.1 ± 11.2 at 6 mo • Trad et al[67]: GERD-HRQL difference in mean score from baseline: −17.9 (−25.8 to −10.1) in the TIF group vs −3.6 (−9.6 to 2.4) in PPI group • Håkansson et al[70]: TIF group baseline QOLRAD score of 4.9 (1.96-6.44) improved to 6.4 (4.38-7) at 6 mo vs Sham and/or PPI baseline QOLRAD score of 4.8 (1.8-6.44) to no change at 6 mo, QOLRAD score 5.2 (4.28-6.88) • Hunter et al[69]: TIF baseline total composite heartburn and regurgitation score per RDQ, 3.1 (2.4-3.8) to 0.6 (0-1.3) at 6 mo vs sham and/or PPI baseline 3.3 (2.5-4) to 0.9 (0.1-2) at 6 mo				⨁⨁⨁◯ Moderate*,†	Critical
560	0	–	MD 19.91 lower(16.46 lower to 23.36 lower)	⨁◯◯◯ Very low‡	Critical
71/188 (37.8%)	15/105 (14.3%)	RR 2.56 (1.36-4.81)#	22 more per 100 (from 5 more to 54 more)	⨁⨁⨁◯ Moderate*	Critical
15/188 (8.0%)	2/105 (1.9%)	RR 2.94 (0.94-9.19)	4 more per 100 (from 0 fewer to 16 more)	⨁⨁⨁◯ Moderate*	Critical
16 studies (4 RCTs and 12 prospective observational trials) • AE incidence rate 2.4% (19/781) • Perforation 0.9% (7/781) • Post-TIF bleeding 0.6% (5/781) • Pneumothorax 0.5% (4/781) • Death 0.1% (1/781) (20 mo later)				⨁⨁◯◯ Low	Critical
3.6% (1.4%-8.8%), prediction interval 1-34				⨁◯◯◯ Very low‡	Critical
76/98 (77.6%)	4/63 (6.3%)	RR 12.70 (1.15-140.30)	74 more per 100 (from 1 more to 100 more)	⨁⨁◯◯ Low*,‡	Critical
Compared with 659/667 (98.8%) before TIF, only 179/625 (28.6%) subjects were PPI after TIF • Pooled RR 2.93 (2.06-4.15)				⨁◯◯◯ Very low‡	Critical
Of the total sample, 107 underwent TIF • Completely off PPI 34.4% (37/107) • Occasional users 91.7% (98/107)				⨁◯◯◯ Very low*	Critical
109	64	–	MD 2.38 lower (0.22 lower to 4.54 lower)	⨁⨁⨁◯ Moderate*	Critical
79	41	–	MD 2.61 higher (0.78 lower to 4.44 higher)	⨁⨁⨁◯ Moderate*	Critical
Compared with baseline (n = 176), • AET was 4.97 lower (MD, 95% CI 3.55-6.39) after TIF (n = 78)				⨁◯◯◯ Very low*,‡	Critical
120/176 (68.2%)	33/102 (32.4%)	RR 2.12 (1.27-3.54)	36 more per 100 (from 9 more to 82 more)	⨁⨁◯◯ Low*,**	Critical
35/62 (56.5%)	17/42 (40.5%)	RR 1.62 (0.30-8.62)	25 more per 100 (from 28 fewer to 100 more)	⨁⨁⨁◯ Moderate*	Critical

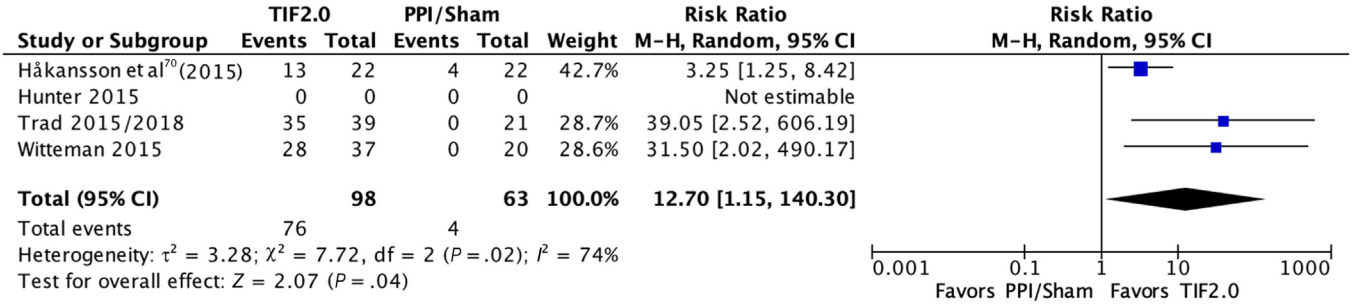

Figure 2. Forest plot of PPI discontinuation rates among TIF 2.0 versus PPI and/or sham RCTs. *M-H*, Mantel-Haenszel test; *PPI*, proton pump inhibitor; *RCTs*, randomized controlled trials; *TIF 2.0*, transoral incisionless fundoplication 2.0 (Esophyx 2.0).

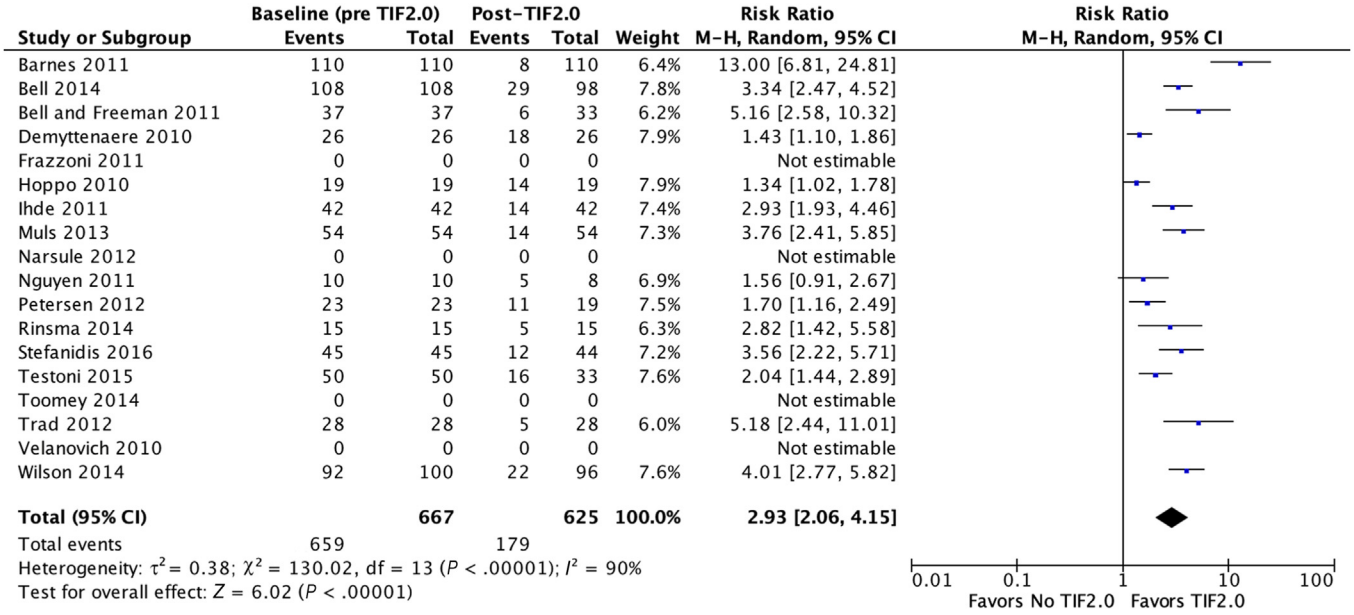

Figure 3. Forest plot of cohort studies showing PPI use at baseline and after TIF 2.0. *M-H*, Mantel-Haenszel test; *PPI*, proton pump inhibitor; *TIF 2.0*, transoral incisionless fundoplication 2.0 (Esophyx 2.0).

examine the evidence. There was no major risk of bias among inclusion RCTs (Appendix 2), and all of the included cohort studies scored ≥7 on the Qumseya scale. According to the AMSTAR-2 scale, the quality of the included existing systematic reviews was moderate to high. A summary of outcomes and their assessment can be seen in Table 8.

PPI discontinuation. For assessing PPI discontinuation rates, 3 RCTs were eligible for meta-analyses involving an aggregate of 98 patients in the TIF 2.0 group compared with 63 patients in the PPI and/or sham group. Patients undergoing TIF 2.0 were more likely to stop their PPI at a pooled RR of 12.7 at a mean follow-up of 6 months (77.6% vs 6.3%; 95% CI, 1.15-140.3; $P = .04$) (Fig. 2). There was considerable heterogeneity at an I^2 of 74%. Because of overall small sample size and high heterogeneity, the evidence was rated down, resulting in "low" for quality of evidence. There were 14 eligible cohort studies of TIF 2.0, including 667 patients who were eligible. Of 98.8% (659 of 667), only 28.6% (179 of 625) patients were taking PPI at a mean follow-up of 19.1 months after TIF 2.0 compared with baseline. Pooled RR was 2.93, suggesting that patients undergoing TIF 2.0 were 2.93 times (95% CI, 2.06-4.15) more likely to stop their PPI (Fig. 3). There was high heterogeneity with an I^2 of 90%. Additionally, a third of patients were completely off PPIs at a long-term follow-up of 8 to 10 years (2 observational studies, 34.4% [37/107]) after TIF. The quality of evidence was rated down for inconsistency and therefore was "very low."

Reduction in acid exposure time (percentage of time pH was <4). For assessing acid exposure time, there were 2 RCTs comparing 109 patients in the TIF 2.0 group to 64 patients in the sham intervention group. Acid exposure time was significantly lower among patients undergoing TIF 2.0 (pooled MD –2.38; 95% CI, –4.54 to −0.22; $P = .03$). There was low heterogeneity (I^2=37%). Moreover, there were 2 RCTs comparing 79 patients in the TIF 2.0 group to 41 patients in the PPI group. Acid exposure time was not lower among patients undergoing TIF 2.0 (pooled MD 2.61; 95% CI, 0.78-4.44;

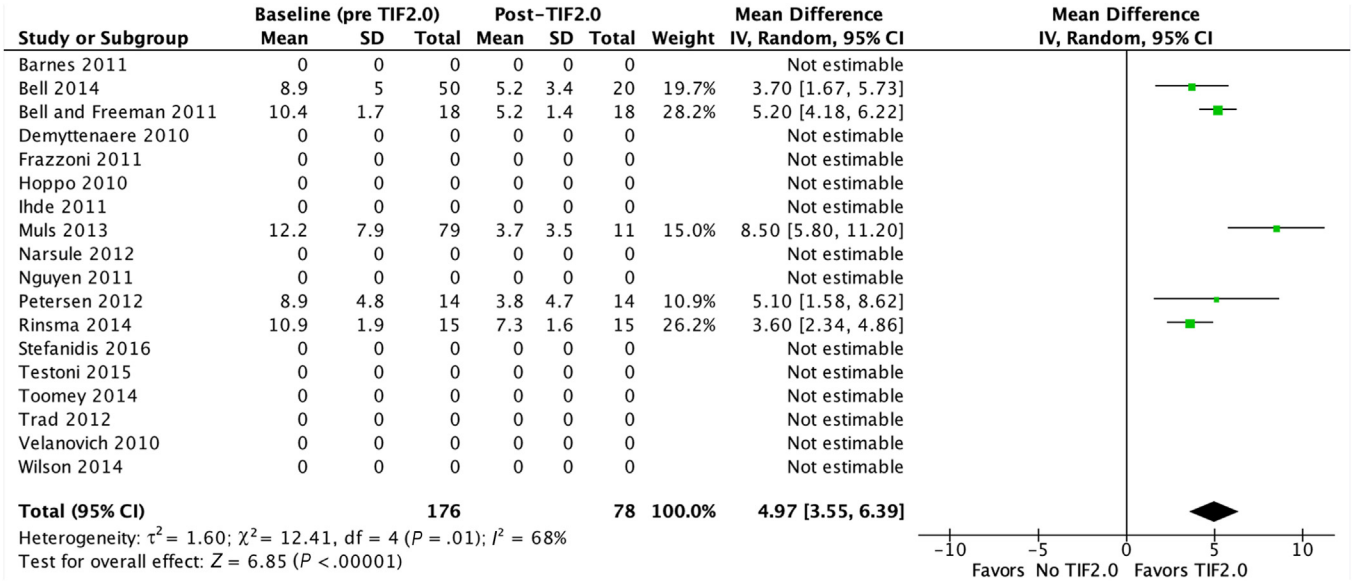

Figure 4. Forest plot of cohort studies showing acid exposure time at baseline and after TIF 2.0. *IV*, Independent variable; *TIF 2.0*, transoral incisionless fundoplication 2.0 (Esophyx 2.0).

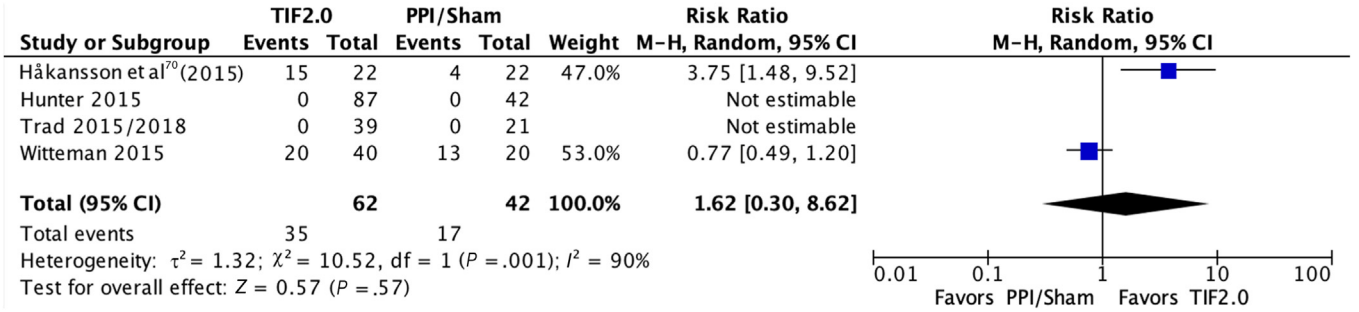

Figure 5. Forest plot of normalization of esophageal acid exposure among TIF versus PPI and/or sham RCTs. *M-H*, Mantel-Haenszel test; *PPI*, proton pump inhibitor; *RCTs*, randomized controlled trials; *TIF 2.0*, transoral incisionless fundoplication 2.0 (Esophyx 2.0).

P = .005). There was low heterogeneity (I^2 = 0%). Because of low sample size, the evidence was rated down for imprecision and therefore was "moderate." Among 5 cohort studies, patients undergoing TIF 2.0 were noted to have lower acid exposure time from baseline (n = 176) to postintervention (n = 78), with a pooled MD of 4.97 (95% CI, 3.55-6.39; P = .01) (Fig. 4). There was considerable heterogeneity, with an I^2 of 68%. The quality of evidence was rated down for imprecision due to low sample size (n < 400) and inconsistency (high heterogeneity) and therefore was overall "very low."

Normalization of esophageal acid exposure time (per patient). To assess normalization of esophageal exposure time, there were 2 RCTs in which 62 patients in the TIF 2.0 group were compared to 42 patients in the PPI and/or sham group. Normalization of acid exposure time was nonsignificantly higher among patients undergoing TIF 2.0 compared with medical therapy and/or sham intervention: 56.5% versus 40.5%; 2 RCTs; RR 1.62; 95% CI, 0.3-8.62 (Fig. 5). Heterogeneity was high at an I^2 of 90%. Evidence was rated down for small sample size and inconsistency (high heterogeneity). We did not find evidence for normalization of esophageal acid exposure time among cohort studies.

Symptom resolution (per patient). For assessing GERD symptom resolution, 4 RCTs with 176 patients in the TIF 2.0 group were compared to 102 patients in the PPI and/or sham group. Patients undergoing TIF 2.0 compared with medical therapy and/or sham intervention had higher a rate of GERD symptom resolution after TIF 2.0 compared with PPI and/or sham group at a mean 6-month follow-up: 68.2% versus 32.4%. The pooled RR was 2.12; 95% CI, 1.27 to 3.54; I^2 = 57%; P < .01 (Fig. 6). There was considerable heterogeneity, with an I^2 of 57%. The evidence was rated down for imprecision because of varying definitions of success and methods of success assessment among the studies, as well as a low sample size; therefore, the quality of evidence was "low." We did not find a homogenous definition of symptom resolution reporting among cohort studies.

Durable symptom resolution. For assessing durable symptom resolution, there was 1 RCT by Trad et al[67] that

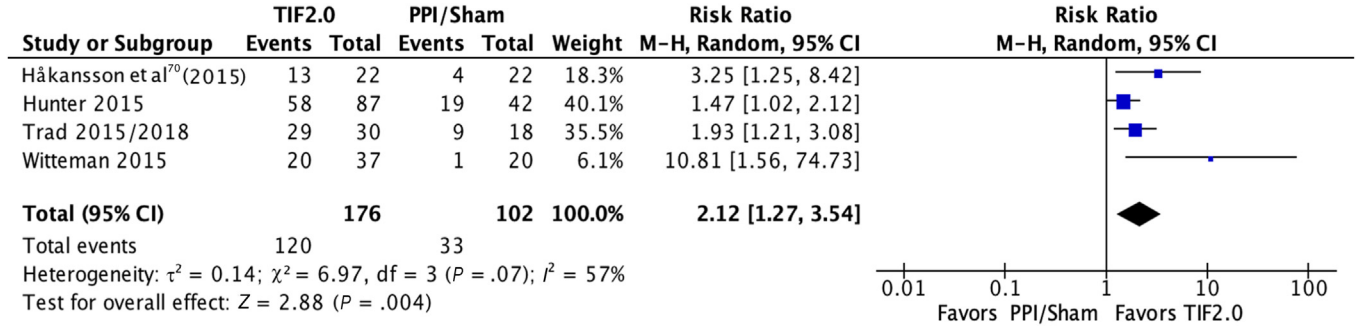

Figure 6. Forest plot of symptom resolution among RCTs of TIF versus medical therapy and/or sham intervention. *M-H*, Mantel-Haenszel test; *PPI*, proton pump inhibitor; *RCTs*, randomized controlled trials; *TIF 2.0*, transoral incisionless fundoplication 2.0 (Esophyx 2.0).

reported long-term symptom resolution at a mean of 5 years. Durable symptom relief was defined as elimination of troublesome regurgitation using reflux disease questionnaire score in this RCT. A total of 86.4% (38/44) patients had durable symptom resolution after TIF 2.0 at 5-year follow-up compared with 100% with symptoms at baseline.

GERD score improvement (using GERD-HRQL). For assessing GERD score improvement by GERD-HRQL, a meta-analysis was not possible among RCTs because of the use of different scales among the studies, and outcomes at follow-up were available for only 1 RCT. Overall, all 4 RCTs showed significant improvement in each of the scores used from before and after the intervention and between the intervention and control conditions. The mean GERD-HRQL score at baseline was 27.1 (SD 8.4) among the TIF 2.0 group in the Witteman et al study,[68] and this decreased at the 6-month follow-up to a mean GERD-HRQL score of 11.1 (SD 9.7). Compared with this, the PPI group had a mean score of 28.2 (SD 9.5) at baseline and a mean score of 25.1 (SD 11.2) at the 6-month follow-up. In the Trad et al[67] RCT, the MD in the GERD-HRQL scores from baseline was −17.9 (−25.8 to −10.1) in the TIF 2.0 group and −3.6 (−9.6 to 2.4) in the PPI group at 6 months. In the Håkansson et al study,[70] the TIF group baseline median quality of life in reflux and dyspepsia (QOLRAD) score was 4.9 (range 1.96-6.44); at 6 months, this improved to 6.4 (4.38-7) versus sham and/or PPI baseline median QOLRAD score of 4.8 (1.8-6.44) to no change at 6 months, for a median QOLRAD score of 5.2 (4.28-6.88). Finally, in the Hunter et al study,[69] the baseline total composite heartburn and regurgitation score per reflux disease questionnaire score was 3.1 (2.4-3.8) in the TIF 2.0 group, which decreased to 0.6 (0-1.3) at 6 months, versus the baseline score of 3.3 (2.5-4) and a 6-month score of 0.9 (0.1-2) in the sham and/or PPI group. In aggregate, the evidence was rated down for imprecision due to varying definitions and small sample size. Thus, quality of evidence was moderate.

For assessing improvement in GERD symptoms on the basis of GERD-HRQL scores, there were 560 patients among 10 cohort studies. Compared with baseline GERD-HRQL scores, there was significant improvement in the mean GERD-HRQL scores after TIF 2.0, with a pooled MD of 19.91, 95% CI, 16.46 to 23.36; $P < .01$ (Fig. 7). There was considerable heterogeneity, with $I^2 = 97\%$. The evidence was rated down for inconsistency and was very low.

Adverse events (including severe adverse events and post-TIF dysphagia). For adverse events analyses, there were 188 patients in TIF 2.0 group and 105 patients in PPI and/or sham group among the 4 RCTs. Adverse events included chest pain, nausea, vomiting, abdominal pain, bleeding, aspiration, perforation, fever, and dysphagia. The overall adverse event rate was higher after TIF 2.0 compared with the group undergoing medical therapy with PPI (and/or sham) (37.8% vs 14.3%) with a pooled RR of 2.56 with 95% CI, 1.36 to 4.81; $P < .01$ (Fig. 8). The rate of only significant and/or serious adverse events was not statistically higher after TIF 2.0 compared with the PPI and/or sham group per the meta-analysis of 4 RCTs: 8% versus 1.9%, pooled RR 2.94, 95% CI, 0.94 to 9.19; $P < .01$ (Fig. 9). There was overall low heterogeneity ($I^2 = 0\%$). The evidence was rated down for imprecision (low sample) and therefore was rated as moderate.

When rates of all adverse events and significant or serious adverse events were examined from RCTs and prospective observational studies, we found an existing meta-analysis with a total of 16 studies (4 RCT and 12 cohort studies), including a total of 781 patients who underwent TIF 2.0. The overall adverse event rate was 2.4% (19/781), the rate of perforation 0.9% (7/781), post-TIF bleeding 0.65 (5/781), and pneumothorax 0.5% (4/781). There was 1 death among the 781 patients who underwent TIF 2.0 procedures, and it was 20 months later from an unrelated cause. In aggregate, the quality of evidence was low.

When assessing the rate of dysphagia after TIF 2.0, we found an existing meta-analysis of 9 cohort studies. The pooled rate of dysphagia after TIF 2.0 was 3.6% with 95% CI, 1.4 to 8.8; $P = .05$. Heterogeneity was moderate, with an I^2 of 58%. Evidence was rated down for inconsistency and therefore was very low.

We also reviewed postmarketing surveillance data from the FDA Manufacturer and User Facility Device Experience (MAUDE) on TIF, which reporting 95 events and 131 patient adverse events, of which perforation (19.8%), pleural effusion

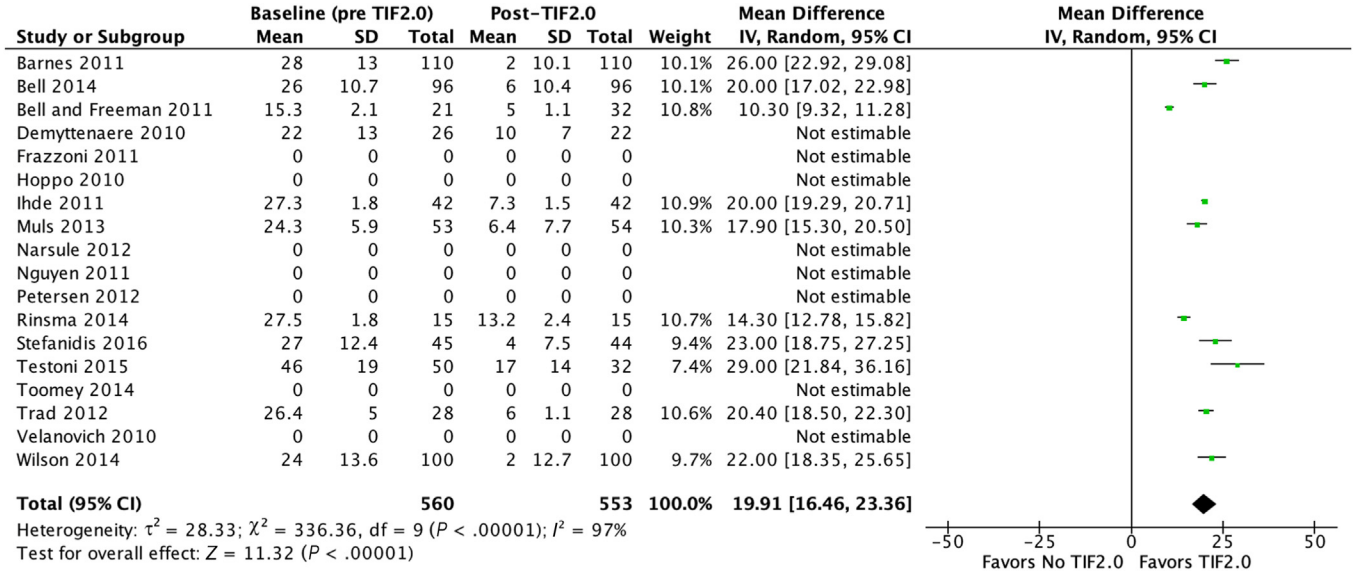

Figure 7. Forest plot of cohort studies showing improvement in GERD-HRQL scores between before and after TIF 2.0. *GERD-HRQL*, GERD-health-related quality of life; *IV*, independent variable; *TIF 2.0*, transoral incisionless fundoplication 2.0 (Esophyx 2.0).

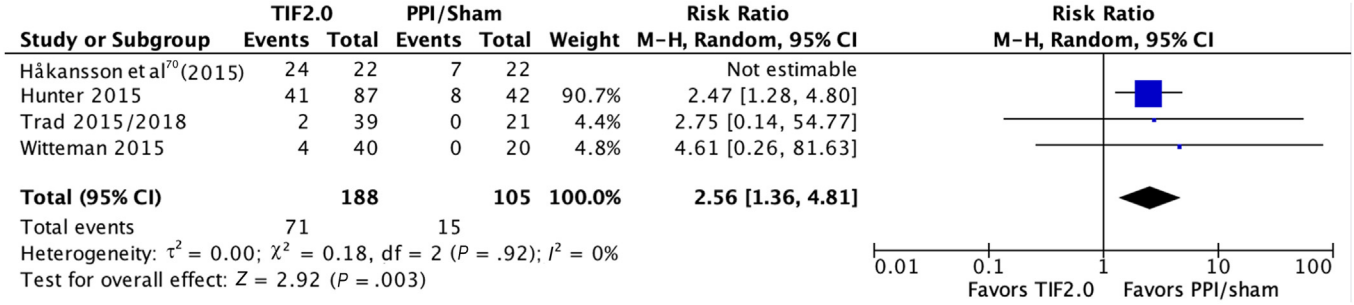

Figure 8. Forest plot of adverse events among RCTs of TIF versus medical therapy and/or sham intervention. *M-H*, Mantel-Haenszel test; *PPI*, proton pump inhibitor; *RCTs*, randomized controlled trials; *TIF 2.0*, transoral incisionless fundoplication 2.0 (Esophyx 2.0).

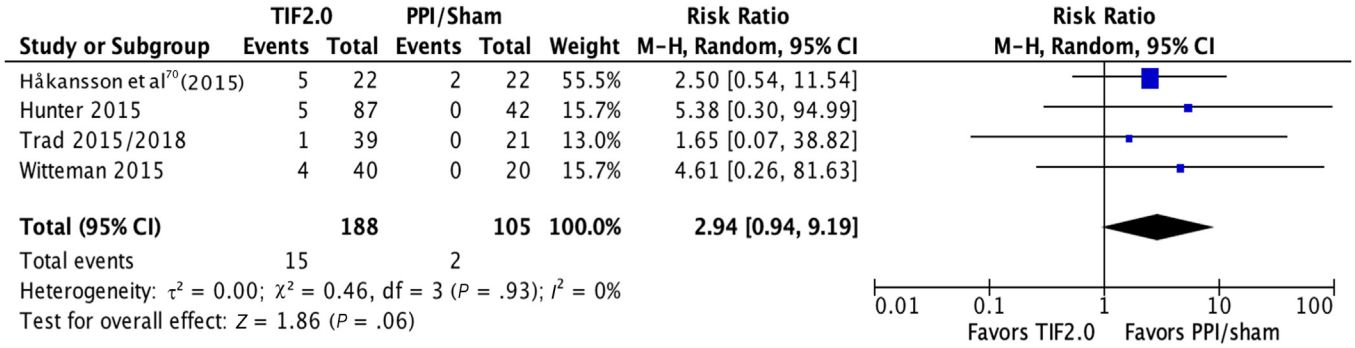

Figure 9. Forest plot of serious and significant adverse events among RCTs of TIF versus medical therapy and/or sham intervention. *M-H*, Mantel-Haenszel test; *PPI*, proton pump inhibitor; *RCTs*, randomized controlled trials; *TIF 2.0*, transoral incisionless fundoplication 2.0 (Esophyx 2.0).

(9.2%), and bleeding (9.2%) were the most common.[92] Most of these adverse events were managed endoscopically.

Cost-effectiveness. When comparing cost-analysis of TIF 2.0 and medical therapy, we found 2 studies.[67,93] TIF 2.0 had lower direct costs compared with laparoscopic Nissen fundoplication (LNF; $13,978.63 vs $17,658.47) although slightly higher than the cost of PPI (omeprazole 20 mg twice a day, $10,931.49).[93] However, compared with the PPI strategy, TIF 2.0 was cost-effective, with an incremental cost of $3047 and incremental effectiveness of 0.29 quality-adjusted life years.

In a retrospective study, the average total cost for intervention, hospitalization, and subsequent care over 2 years was found to be lower for TIF 2.0 ($71,691; n = 73) compared with LNF ($99,256; n = 2734).[67] In a subgroup of patients with resource use in the top quartile (ie, PPI-

TABLE 9. Evidence profiles for question 5(b): In patients with confirmed GERD and a large hiatal hernia, how does hiatal hernia repair combined with TIF (cTIF) compare to standard medical therapy for GERD management?

Certainty assessment						
No. of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**
PPI discontinuation (assessed with meta-analysis, PPI usage before and after)						
6	Nonrandomized studies	Not serious	Serious*	Not serious	Serious†	None
Symptom resolution (GERD-Health-Related Quality of Life score change) (assessed with meta-analysis)						
5	Nonrandomized studies	Not serious	Serious*	Not serious	Serious†	None
Serious adverse events (assessed with meta-analysis)						
6	Nonrandomized studies	Not serious	Not serious	Not serious	Serious†	None
Dysphagia (follow-up: median 12 mo; assessed with Jaruvongvanich et al [2022])[97]						
1	Nonrandomized studies	Not serious	Not serious	Not serious	Serious†	None

cTIF, Combined hiatal hernia repair and transoral incisionless fundoplication; *MD*, mean difference; *OR*, odds ratio; *PPI*, proton pump inhibitor; *TIF*, transoral incisionless fundoplication.
*High heterogeneity (I^2 > 50%).
†Small sample size.

(*continued on the next page*)

refractory GERD), the average cost of care over 2 years was much lower with TIF 2.0 compared with LNF ($66,000 vs $124,000).

Patient values and preferences. We did not find any studies assessing patient values and preferences of TIF 2.0 for GERD management compared with medical therapy as primary outcome; however, inclusion studies examined patient satisfaction rates that were overall high. When assessing patient values, we relied on our patient advocate to provide their opinion. Our patient advocate acknowledged that he is not clear regarding the procedure itself although he was aware of the intervention. Having a minimally invasive option allowing for cessation of medications was preferable compared with lifelong medications with inadequate symptom control and potential adverse effects. We did not find any studies examining equity.

Certainty of the evidence

Overall, certainty of the evidence was low when considering all of the outcomes. The decision to rate the evidence as low was due to the following: inconsistency due to high heterogeneity, imprecision (low sample size), varying outcome definitions, and inability to pool the data for certain critical outcomes.

Discussion

The panel acknowledged that available evidence consists of studies with varying patient populations and varying definitions of outcomes; however, overall, TIF 2.0 showed short-term improvement of GERD symptoms and durable symptom remission for up to 5 years with low serious adverse event rates. One possible explanation for the heterogeneity of outcomes could also be that the studies were performed over a decade with 3 to 4 different iterations of TIF devices and 3 TIF techniques used.[94] The panel discussed the role of TIF 2.0 for a subset of patients. This included patients with chronic GERD symptoms for at least 6 months, refractory GERD (defined as presence of persistent troublesome GERD symptoms despite double-dose PPI for at least 8 weeks in the setting of ongoing documented pathologic reflux),[95] regurgitation predominant symptoms,[67] those who have intolerance to PPI or wanting to be off of PPI, patients with Hill grade I or II, and hiatal hernia <2 cm. The panel evaluated established benefits and the lower noninvasive risk profile of existing medical therapy for the majority of the GERD population compared with invasive therapy, with the majority of the data on the short-term benefit for a subset of the population. The panel voiced concerns on appropriate selection of patients with GERD with persistent or refractory symptoms, need for objective confirmation study and other appropriate testing. Therefore, the panel made a "conditional" recommendation suggesting evaluation for TIF 2.0 among patients with chronic GERD with objectively confirmed disease, refractory GERD, patient preference to be off of PPI, small hiatal hernia (≤2 cm) or Hill grade I or II who are otherwise eligible as an alternative to long-term medical therapy.

Question 5(b): In patients with confirmed GERD and a large hiatal hernia, how does hiatal hernia repair combined with TIF (cTIF) compare to standard medical therapy for GERD management?

Recommendation 5(b):

In patients with confirmed GERD with large hiatal hernia (>2 cm) and Hill grade III or IV, ASGE suggests evaluation for cTIF in a multidisciplinary review. *(Conditional recommendation, very low quality of evidence)*

TABLE 9. Continued

No. of patients		Effect			
cTIF	Medical therapy alone (pre-cTIF or baseline)	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
95/253 (37.5%)	349/369 (94.6%)	OR 0.71 (0.48-0.93)	20 fewer per 1,000 (from 52 fewer to 4 fewer)	⨁◯◯◯ Very low*†	Critical
186	236	-	MD 21.87 lower (13.91 lower to 29.83 lower)	⨁◯◯◯ Very low*†	Critical
	2/358 (0.56%) cTIF			⨁◯◯◯ Very low†	Critical
7/125 (5.6%)	0/125 (0.0%)	Not estimable		⨁◯◯◯ Very low†	Critical

Evidence

We performed a systematic review of the published literature on this topic using Ovid MEDLINE, Embase, Scopus, and Cochrane for studies published through December 2022. We used major search terms and subheadings including "gastroesophageal reflux disease," "endoscopic therapy," "combined transoral incisionless fundoplication," "hiatal hernia repair," and "plication." The systematic review was restricted to studies assessing the efficacy and safety of combined TIF and hiatal hernia repair (cTIF) for GERD compared with PPI and/or sham intervention. Our literature search identified 7 cohort studies (3 prospective, 4 retrospective)[91,96-101] and an ongoing multicenter RCT (Clinical trials identifier: NCT04795934). Details on outcomes of cTIF compared with PPI and/or sham intervention on GERD symptoms were collected from existing cohort studies. Outcomes of interest included PPI discontinuation, reduction in acid exposure time (percentage of time pH was <4), normalization of esophageal acid exposure time (per patient), symptom resolution (per patient), durable symptom resolution, GERD score improvement (using GERD-HRQL or similar scales), and adverse events (including severe adverse events and post-TIF dysphagia). All of the included cohort studies scored ≥7 on the Qumseya scale.

A summary of outcomes and their assessment can be seen in Table 9.

PPI discontinuation. For assessment of PPI discontinuation rate, there were 6 cohort studies with 369 patients who underwent cTIF with baseline data of PPI use and 253 patients who had follow-up data available. Follow-up ranged from 6 to 12 months with a mean of 9.3 months. Compared with baseline (94.6%), only a third of patients (37.5%) were using PPI after undergoing cTIF at follow-up. Pooled OR was 0.71 with 95% CI, 0.48 to 0.93; $I^2 = 94\%$; $P < .01$ (Fig. 10). There was considerable heterogeneity, with an I^2 of 94%. Evidence was rated down for inconsistency and was very low.

Symptom resolution by improvement in GERD-HRQL scores. For GERD symptom resolution assessment, there were 6 cohort studies with 239 patients with baseline GERD-HRQL scores and 186 with GERD-HRQL scores at follow-up after cTIF at mean 9.3 months. Patients undergoing cTIF reported symptom resolution after the intervention with a pooled MD of 21.87 with 95% CI, 12.91 to 29.83; $P < .01$ (Fig. 11). There was considerable heterogeneity, with an I^2 of 100%. Evidence was rated down for inconsistency and considered "very low."

Serious adverse events (including dysphagia). For serious adverse events, there were 7 cohort studies with 358 patients undergoing cTIF. There were only 2 serious adverse events (0.56%). The rate of dysphagia was also low at 5.6% (7/125) after cTIF per 1 cohort study.

Other considerations. Objective outcomes for GERD assessment were inconsistently reported by available studies, and therefore a pooled analysis was not performed. There were no studies reporting long-term symptom resolution, patient values and preferences, or cost-effectiveness data.

Certainty of the evidence

Overall, the quality of evidence was very low primarily because of inconsistency (high heterogeneity) and imprecision (low sample size)

Discussion

The panel considered the evidence as important despite inadequacies due to small size studies. The panel also acknowledged the fact that the majority of patients with GERD contain a hiatal hernia >2 cm and that TIF 2.0 alone has shown evidence of efficacy in patients with small hiatal hernias (≤2 cm and Hill grade I or II). Therefore, the panel believed that if correction of a larger hiatal hernia (≥2 cm) is done surgically and subsequently if TIF 2.0 is performed,

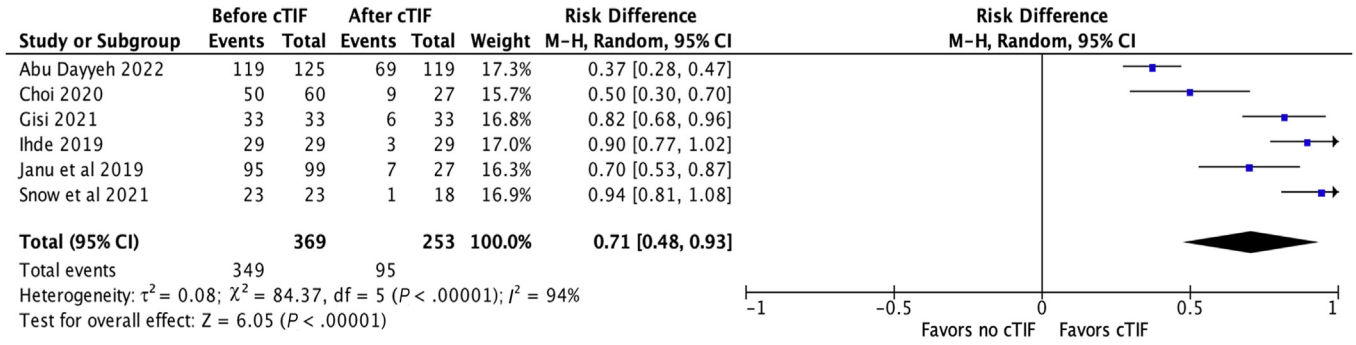

Figure 10. Forest plot of studies of PPI use at baseline (before cTIF) and after cTIF. *cTIF*, Combined hiatal hernia repair and transoral incisionless fundoplication; *M-H*, Mantel-Haenszel test; *PPI*, proton pump inhibitor.

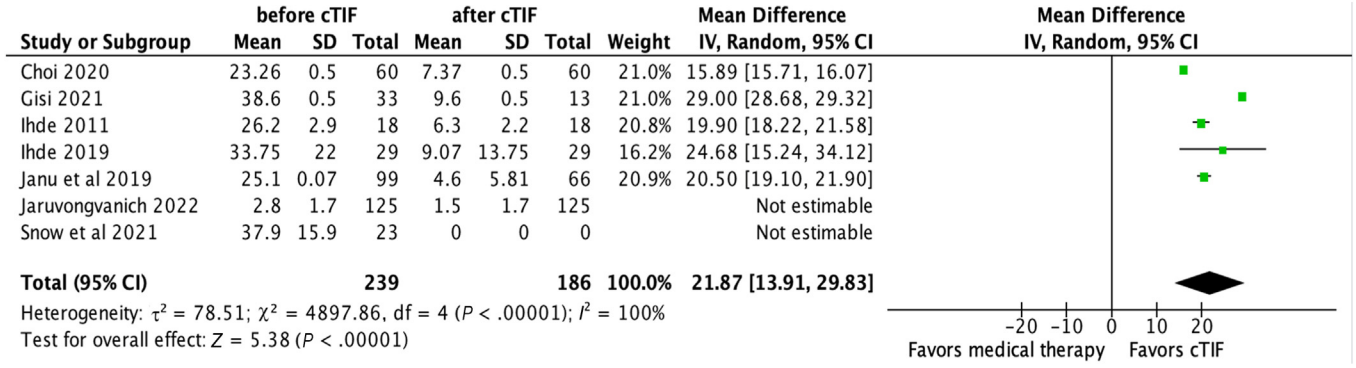

Figure 11. Forest plot of GERD-HRQL score at baseline and after cTIF. *cTIF*, Combined hiatal hernia repair and transoral incisionless fundoplication; *GERD-HRQL*, GERD health-related quality of life; *IV*, independent variable.

outcomes may be similar to those achieved in patients undergoing TIF 2.0 with a small hiatal hernia. In addition, the panel also discussed that combined endoscopic-surgical intervention cTIF could serve as an alternative to existing surgical therapies or serve as an additional option in the armamentarium. Evidence for surgical therapies have been established, and whether combined endoscopic-surgical therapy with cTIF is comparable has not yet been demonstrated. The panel made a "conditional" recommendation suggesting either cTIF or surgical therapies based on multidisciplinary review for patients with confirmed GERD and large hiatal hernia (>2 cm) and Hill grade III or IV.

Question 6: In patients with persistent GERD, how does radiofrequency energy to the lower esophageal sphincter (LES) compare to standard medical therapy for GERD management?

Best practice advice:

In patients with confirmed GERD, small hiatal hernia (<2 cm), and Hill grade I or II, radiofrequency energy to the LES can be considered when other alternatives (endoscopic or surgical fundoplication) are not available or feasible.

Summary of evidence

We performed a systematic review of the published literature on this topic. We used Ovid MEDLINE, Embase, Scopus, and Cochrane for studies published through December 2022. We used major search terms and subheadings including "gastroesophageal reflux disease," "endoscopic therapy," "radiofrequency energy," "ablation," "radiofrequency therapy," and "stretta" (Appendix 1). Our literature search identified 5 eligible RCTs and 1 existing meta-analyses.[102-107] From these 5 RCTs, details on outcomes of radiofrequency energy (Stretta) compared with PPI and/or sham intervention on GERD symptoms were collected. The outcomes examined included PPI discontinuation, reduction in acid exposure time (percentage of time pH was <4), normalization of esophageal acid exposure time (per patient), symptom resolution (per patient), durable symptom resolution, GERD score improvement (using GERD-HRQL or similar scales), and adverse events (including severe or serious adverse events). We also examined cost-effectiveness, equity, and patient values and preferences.

We performed an updated meta-analysis of eligible RCTs and cohort studies separately for outcomes in which no recent meta-analysis was found. Because there was overall a low number of RCTs, a separate meta-analysis for outcomes of interest was performed for cohort studies

to examine the evidence. A priori random effects meta-analysis (assuming common effect of the intervention across all studies) was performed using Review Manager version 5.4 (Cochrane Collaboration, 2020) statistical software. The studies were weighted based on effect size and sample size. We assessed heterogeneity using the I^2 statistic and publication bias by funnel plot. If total studies were <10, funnel plot analysis was not performed. Any concern for publication bias based on funnel plot asymmetry was further evaluated by the Egger regression test. According to the Risk of Bias tool, the included RCTs had overall low quality and risk of bias becaue of small sample size, inadequate follow-up, unclear design, and power calculation for different outcomes (Appendix 2). According to the AMSTAR-2 scale, the quality of the included existing systematic reviews were high. A summary of outcomes and their assessment can be seen in Table 10.

PPI discontinuation. For assessing PPI discontinuation rates, we performed a meta-analysis. Four RCTs were eligible for meta-analysis involving an aggregate of 80 patients in the Stretta group compared with 71 patients in the PPI and/or sham group. Patients undergoing Stretta were numerically more likely to stop their PPI at a pooled RR of 2.98 at a mean follow-up of 6 months; however, there was no significant statistical difference between the 2 groups: 28.7% versus 12.7%, 95% CI, 0.71 to 12.56; P = .14 (Fig. 12). There was moderate heterogeneity at an I^2 of 45%. Because of the overall small sample size (n < 400) and high risk of bias in included studies, the evidence was rated down, resulting in low certainty of evidence. There were 23 prospective studies reporting baseline and post Stretta findings. An existing meta-analysis from Fass et al[107] examined this outcome. Almost half of the patients were able to stop the PPI after Stretta (47.4%) compared with baseline (97.1%) at follow-up of 25.4 months. Pooled RR was 0.49 with 95% CI, of 0.4 to 0.6; P < .01. There was considerable heterogeneity at an I^2 of 95%. Evidence was rated down for inconsistency and imprecision (varying follow-up periods among inclusion studies) and therefore the certainty of evidence was very low.

Reduction in acid exposure time (percentage of time pH was <4). For assessing the acid exposure time, there were 3 RCTs comparing 70 patients in the Stretta group to 61 patients in the PPI and/or sham intervention group at 6 to 12 months' follow-up. Updated meta-analysis showed nonsignificant pooled MD of −0.22 with 95% CI, of −2.52 to 2.07; P = .85 (Fig. 13). There was moderate heterogeneity, I^2 = 41%. Evidence was rated down for risk of bias and imprecision (low sample size n < 400) and therefore was low. Existing meta-analysis by Fass et al[107] examined 11 cohorts (including observational studies and RCTs) in which 364 patients underwent Stretta with follow-up available of 25.4 months. Compared to baseline acid exposure time, after Stretta there was a statistically significant pooled MD: −3.01, 95% CI, –3.72 to −2.3; P < .01. There was moderate heterogeneity, with an I^2 of 35%. Evidence was rated down for imprecision (low sample size n < 400), and therefore the certainty of evidence was very low.

Normalization of esophageal acid exposure time (per patient). For assessing normalization of esophageal acid exposure time, there were 2 RCTs available with 35 patients in the Stretta group and 28 patients in the PPI and/or sham group. Updated meta-analysis showed that normalization of esophageal acid exposure was not significantly different among patients undergoing Stretta compared with PPI and/or sham group at 6 to 12 months' follow-up with a pooled RR of 1.55, 95% CI, 0.04 to 65.35; P = .82 (Fig. 14). There was considerable heterogeneity, with an I^2 of 78%. Evidence was rated down for risk of bias, inconsistency, and imprecision (low sample size n < 400), and therefore the certainty of evidence was very low.

Among 8 cohort studies (including RCTs), 30% of patients (43/144) had normalization of acid exposure time after Stretta compared with baseline at 25.4 months per existing meta-analysis by Fass et al.[107] Evidence was rated down because of imprecision (low sample size n < 400), and therefore the certainty of evidence was very low.

Symptom resolution (per patient) and durable symptom resolution. For assessing symptom resolution, there were 2 RCTs with 32 patients in the Stretta arm and 26 in the PPI and/or sham arm. Again, an updated meta-analysis was performed. There was no significant difference in symptom resolution at 12 months among both groups in meta-analysis with pooled RR of 1.24, 95% CI, 0.35 to 4.36; P = .73 (Fig. 15). There was low heterogeneity in this outcome, I^2 = 25%. Evidence was rated down for risk of bias and imprecision (low sample size n < 400), and therefore the certainty of evidence was low. This outcome was not reported among cohort studies in the existing meta-analysis.

All RCTs examined outcomes for less than 24 months. There was 1 cohort study examining durable symptom resolution at 10 years.[108] Symptom resolution was defined as normalization of GERD-HRQL in ≥70% patients in this study. Compared with all patients with symptoms at baseline (n = 99), 71.7% had durable resolution at follow-up. Evidence was rated down for imprecision (low sample size n < 400), and therefore the certainty of evidence was very low.

GERD score improvement (GERD-HRQL). For assessing symptom improvement by GERD-HRQL scale, there were 2 RCTs with 47 patients in the Stretta group and 41 patients in the PPI and/or sham group. Updated meta-analysis showed that there was no significant improvement in mean GERD-HRQL scores after Stretta compared with PPI and/or sham intervention at 6 to 12 months' follow-up with a pooled MD of −3.99, 95% CI, 17.11-9.13; P = .55 (Fig. 16). There was considerable heterogeneity in this outcome with I^2 = 91%. Evidence was rated down for risk of bias and imprecision (low sample size n < 400), and therefore the certainty of evidence was low. There were 11 cohort studies (including RCTs) examined in an existing meta-analysis by Fass et al,[107] with 507 patients undergoing Stretta

TABLE 10. Evidence profiles for question 6: In patients with persistent GERD, how does radiofrequency energy to the lower esophageal sphincter (LES) compare to standard medical therapy for GERD management?

Certainty assessment						
No. of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**
PPI discontinuation (RCTs; follow-up: range 3-12 mo; assessed with updated meta-analysis)						
4	Randomized trials	Serious*	Not serious	Not serious	Serious†	None
PPI discontinuation (cohort and RCT; follow-up: mean 25.4 mo; assessed with PPI usage baseline vs follow-up; Fass et al[107] [2017] meta-analysis)						
23	Nonrandomized studies	Not serious	Serious‡	Not serious	Serious#	None
Acid exposure time (% time pH <4) (RCTs; follow-up: range 6-12 mo; assessed with updated meta-analysis)						
3	Randomized trials	Serious*	Not serious	Not serious	Serious†	None**
Acid exposure time (% time pH <4) (cohort and RCT; follow-up: mean 25.4 mo; assessed with Fass et al[107] [2017] meta-analysis)						
11	Nonrandomized studies	Not serious	Not serious	Not serious	Serious#	None
Symptom resolution at 12 mo (per patient, RCTs; assessed with updated meta-analysis [GERD symptoms <3 per wk and GERD-HRQL≤11])						
2	Randomized trials	Serious*	Not serious	Not serious	Serious†	None**
Score improvement (GERD-HRQL score) (RCTs; follow-up: range 6-12 mo; assessed with updated meta-analysis)						
2	Randomized trials	Serious*	Not serious	Not serious	Serious†	None**
Score improvement (GERD-HRQL) (cohort and RCT; follow-up: mean 25.4 mo; assessed with Fass et al[107] [2017] meta-analysis)						
11	Nonrandomized studies	Not serious	Serious‡	Not serious	Serious#	None
Durable symptom resolution (follow-up: mean 10 y; assessed with normalization of GERD-HRQL in ≥70% patients)						
1	Nonrandomized studies	Not serious	Not serious	Not serious	Serious†	None
Overall adverse events (RCT only; assessed with updated meta-analysis)						
4	Randomized trials	Serious*	Not serious	Not serious	Serious†	None**
Overall adverse events (RCT and cohort; assessed with Fass et al[107] [2017] meta-analysis)						
26	Nonrandomized studies	Not serious	Not serious	Not serious	Not serious	None
Severe and serious adverse events (RCT only; assessed with updated meta-analysis)						
4	Randomized trials	Serious*	Not serious	Not serious	Serious†,‡‡	None
Severe and serious adverse events (RCT and cohort; assessed with Fass et al[107] [2017] meta-analysis)						
26	Nonrandomized studies	Not serious	Not serious	Not serious	Not serious	None
Normalization of esophageal acid exposure (RCTs; follow-up: range 6-12 mo; assessed with updated meta-analysis)						
2	Randomized trials	Serious*	Serious‡	Not serious	Serious†	None**
Normalization of esophageal acid exposure (cohort and RCT; follow-up: mean 25.4 mo; assessed with Fass et al[107] [2017] meta-analysis)						
8	Nonrandomized studies	Not serious	Not serious	Not serious	Serious#	None

GERD-HRQL, GERD-health-related quality of life; *MD*, mean difference; *PPI*, proton pump inhibitor; *RCT*, randomized controlled trial; *RFA*, radiofrequency ablation; *RR*, risk ratio.
–, not available
*Xie et al[67] network meta-analysis: low overall quality of Stretta (RFA) studies.
†Imprecision due to small sample size (n < 400).
‡High I^2, >50%.
#Varying follow-up times.
**Kalapala et al[106]; the authors only report interim 3-month reports, but the study was not completed. Long-term data are not available.
††For Stretta, small erosions and mucosal lacerations were the most frequent adverse event (AE) (<1%), whereas for laparoscopic fundoplication, subcutaneous emphysema was the most frequent AE at 3%. Sixteen of the total 23 AEs in the Stretta were erosions; mucosal lacerations that did not require further follow-up.
‡‡Wide CI.

(*continued on the next page*)

TABLE 10. Continued

No. of patients		Effect			
Stretta (radiofrequency energy)	Sham and/or PPI	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
23/80 (28.7%)	9/71 (12.7%)	RR 2.98 (0.71-12.56)	251 more per 1,000 (from 37 fewer to 1,000 more)	⨁⨁◯◯ Low*,†	Critical
Pre-Stretta 1,743/1,795 (97.1%) using PPI and after intervention 850/1,795 (47.4%); RR 0.49 (0.4-0.6)				⨁◯◯◯ Very low‡,#	Critical
70	61	–	MD 0.22 lower (2.52 lower to 2.07 higher)	⨁⨁◯◯ Low*,†,**	Critical
364	–	–	MD 3.01 lower (3.72 lower to 2.3 lower)	⨁◯◯◯ Very low#	Critical
13/32 (40.6%)	8/26 (30.8%)	RR 1.24 (0.35-4.36)	74 more per 1,000 (from 200 fewer to 1,000 more)	⨁⨁◯◯ Low*,†,**	Critical
47	41	–	MD 3.99 lower (17.11 lower to 9.13 higher)	⨁⨁◯◯ Low*,†,**	Critical
507	–	–	MD 14.6 lower (16.48 lower to 12.73 lower)	⨁◯◯◯ Very low‡,#	Critical
71/99 (71.7%)	0/0	Not pooled	See comment	⨁◯◯◯ Very low†	Critical
34/81 (42.0%)	8/72 (11.1%)	RR 3.06 (1.09-8.60)	229 more per 1,000 (from 10 more to 844 more)	⨁⨁◯◯ Low*,†,**	Critical
23/2468 (0.9%)††	1/52 (1.9%)	Not estimable		⨁⨁◯◯ Low	Critical
3/81 (3.7%)	1/72 (1.4%)	RR 1.90 (0.26-14.06)	12 more per 1,000 (from 10 fewer to 181 more)	⨁⨁◯◯ Low*,†‡‡	Critical
7/2468 (0.3%)	1/52 (1.9%)	Not pooled	See comment	⨁⨁◯◯ Low	Critical
6/35 (17.1%)	3/28 (10.7%)	RR 1.55 (0.04-65.35)	59 more per 1,000 (from 103 fewer to 1,000 more)	⨁◯◯◯ Very low*,†,‡,**	Critical
43 of 144 subjects (30%) had normalization of 24-h pH testing after Stretta therapy				⨁◯◯◯ Very low#	Critical

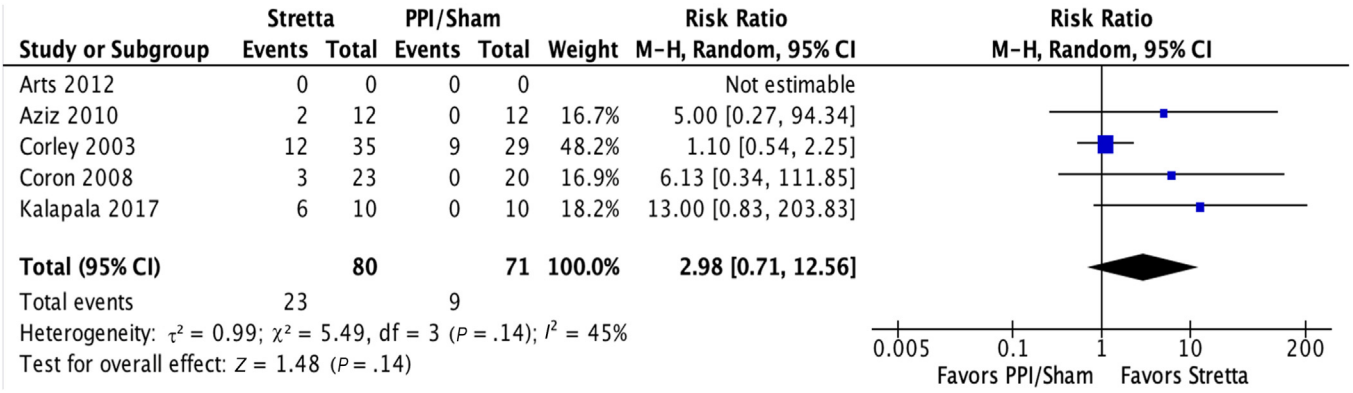

Figure 12. Forest plot of PPI discontinuation rate among RCTs examining Stretta and PPI and/or sham therapy. *M-H*, Mantel-Haenszel test; *PPI*, proton pump inhibitor; *RCTs*, randomized controlled trials.

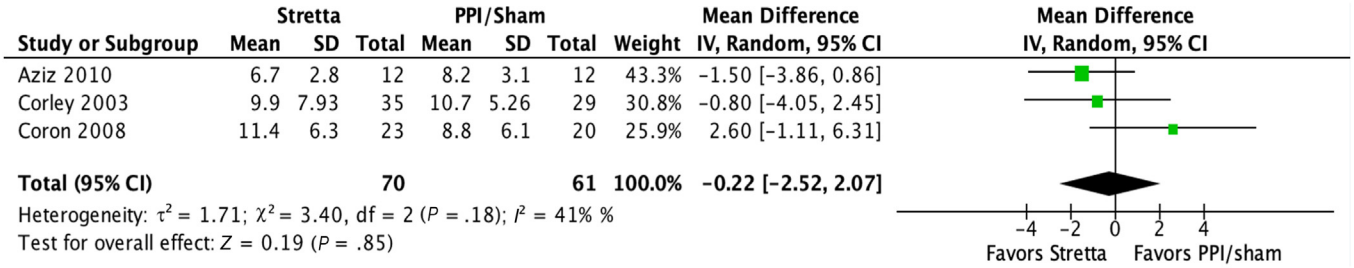

Figure 13. Forest plot of acid exposure time among RCTs examining Stretta and PPI and/or sham therapy. *IV*, Independent variable; *PPI*, proton pump inhibitor; *RCTs*, randomized controlled trials.

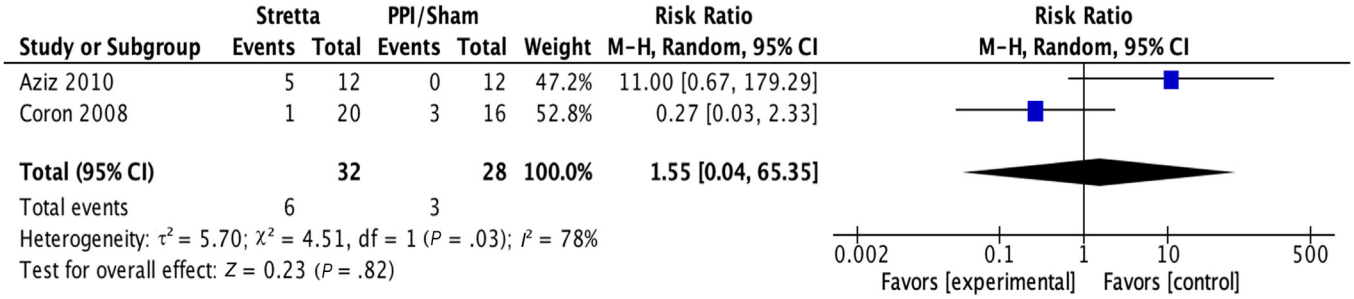

Figure 14. Forest plot of normalization of esophageal acid exposure rate among RCTs examining Stretta and PPI and/or sham therapy. *M-H*, Mantel-Haenszel test; *PPI*, proton pump inhibitor; *RCTs*, randomized controlled trials.

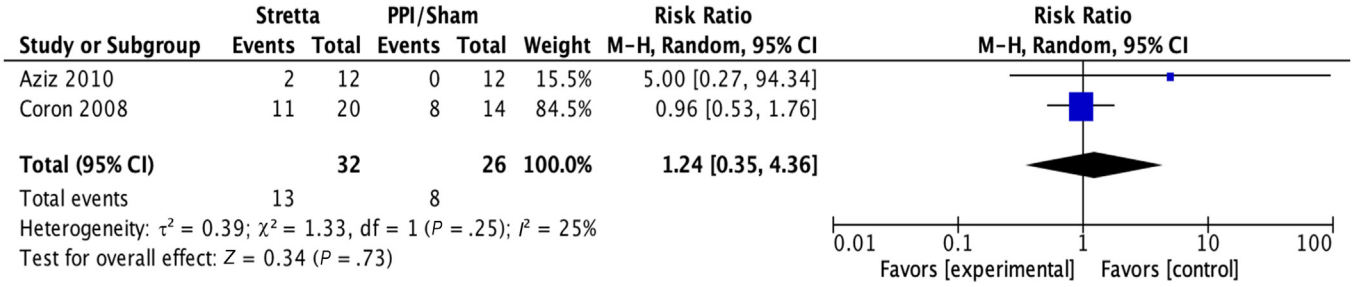

Figure 15. Forest plot of symptom resolution rate among RCTs examining Stretta and PPI and/or sham therapy. *M-H*, Mantel-Haenszel test; *PPI*, proton pump inhibitor; *RCTs*, randomized controlled trials.

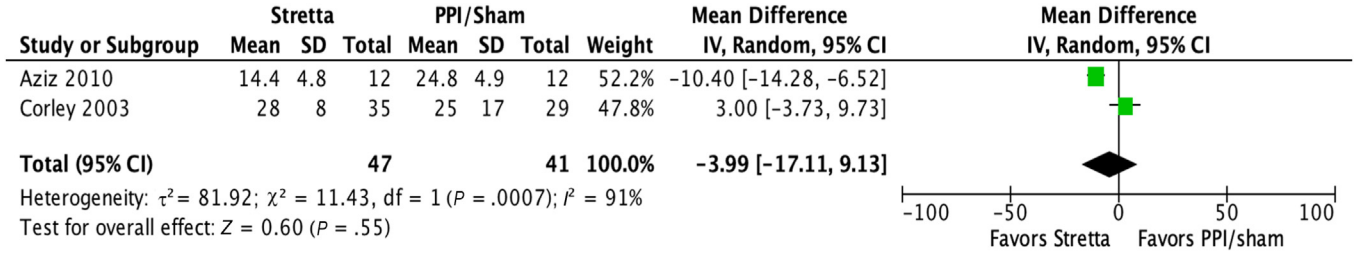

Figure 16. Forest plot of difference in GERD-HRQL scores among RCTs examining Stretta and PPI and/or sham therapy. *GERD-HRQL*, GERD-health-related quality of life; *IV*, independent variable; PPI, proton pump inhibitor; RCTs, randomized controlled trials.

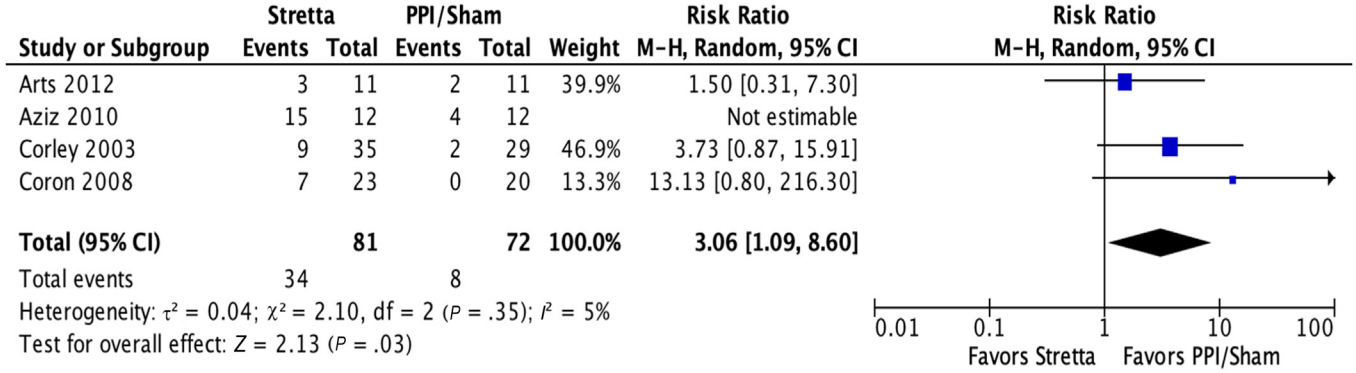

Figure 17. Forest plot of adverse events among RCTs of Stretta versus medical therapy and/or sham intervention. *M-H*, Mantel-Haenszel test; *PPI*, proton pump inhibitor; *RCTs*, randomized controlled trials.

intervention. Compared with baseline GERD-HRQL scores, after Stretta, there was a significant improvement in GERD-HRQL scores at 25.4 months' follow-up with a pooled MD of −14.6, 95% CI, −16.48 to −12.73; $P < .01$. There was considerable heterogeneity in this outcome with $I^2 = 82\%$. Evidence was rated down for inconsistency and imprecision (low sample size n < 400), and therefore the certainty of evidence was very low.

Adverse events. For assessing overall adverse events, there were 4 RCTs with 81 patients in the Stretta group and 72 in the PPI and/or sham group. In the updated meta-analysis, the pooled adverse event rate overall was higher among Stretta compared with PPI and/or sham, with a pooled RR of 3.06, 95% CI, 1.09-8.6, 42% versus 11.1%; $P < .01$ (Fig. 17). There was low heterogeneity in this outcome with $I^2 = 5\%$. Evidence was rated down for risk of bias and imprecision (low sample size n < 400), and therefore the certainty of evidence was low. However, when data on overall adverse events were examined from 26 cohort studies (including RCTs) from the existing meta-analysis from Fass et al,[107] the rate was only 0.9% (23/2468) after Stretta compared with 1.4% after PPI and/or sham group (1/72). Certainty of evidence was low.

When data on severe or serious adverse events were examined from the available 4 RCTs with 81 patients in the Stretta group and 72 in the PPI and/or sham group, there was a nonsignificant difference between Stretta and PPI and/or sham group with a pooled RR of 1.9; 3.7% versus 1.4%, 95% CI, 0.26 to 14.06; $P = .53$ (Fig. 18). There was low heterogeneity with $I^2 = 0\%$. Evidence was rated down for risk of bias and imprecision (low sample size n < 400), and therefore the certainty of evidence was low. When severe or serious adverse events were examined from 26 cohort studies (including RCTs) in the existing meta-analysis from Fass et al,[107] the rate was 0.3% (7/2468) after Stretta compared with 1.9% after PPI and/or sham (1/52) intervention. The certainty of evidence was low.

Cost-effectiveness. For assessing cost-effectiveness, no direct cost-effectiveness study done recently in the United States was found. In a study based in Canada (2008), compared with LNF and Stretta, PPIs exhibited the lowest cost and greatest number of symptom-free months (ie, $40 per symptom-free month); however, both LNF and Stretta were associated with high incremental costs ($353,000 and $393,000, respectively) compared with PPI.[109]

Other considerations. When examining patient values, we relied on our patient advocate who preferred having a minimally invasive option for durable symptom relief compared with lifelong medical therapy with potential side effects. The patient advocate did not distinguish between existing endoscopic therapies but emphasized a preference for evidence-based therapy that could provide durable benefit.

Certainty of the evidence

Overall, certainty of the evidence was very low. This was due to risk of bias, imprecision (low sample size, varying follow-up durations, wide CIs) and inconsistency (high heterogeneity), and differing results from RCTs and observational data.

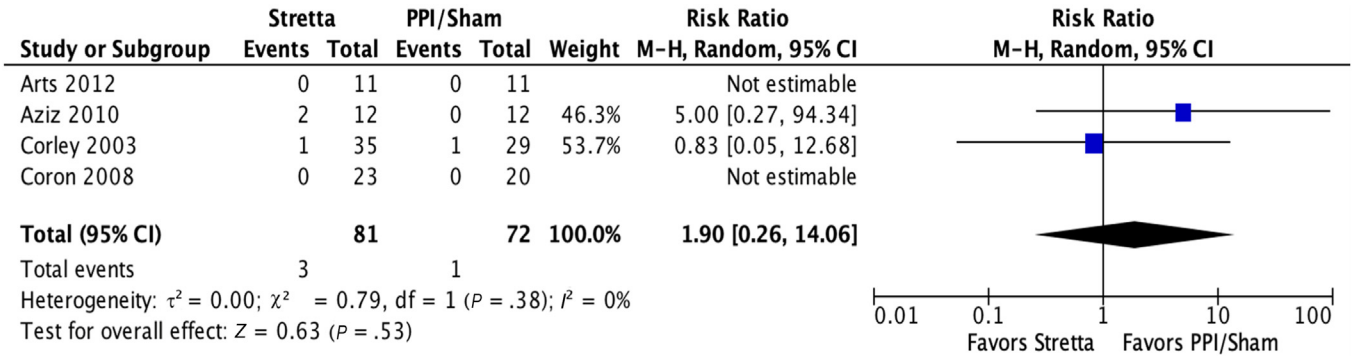

Figure 18. Forest plot of serious adverse events among RCTs of Stretta versus medical therapy and/or sham intervention. *M-H*, Mantel-Haenszel test; *PPI*, proton pump inhibitor; *RCTs*, randomized controlled trials.

Discussion

Overall, the certainty in the evidence was low to very low. The majority of RCTs done using Stretta were published several years ago with an increased risk of bias and provide nonsignificant results with a low study power. On the other hand, cohort studies report improvement in outcomes after Stretta compared with baseline. The panel acknowledged that evidence on Stretta includes differing results from RCTs and cohort studies; however, there are several other challenges including lack of durable benefit, availability of better treatments, and reimbursement concerns. Stretta is only applicable to patients with GERD with small hiatal hernias (≤2 cm) Hill grade I or II. In addition there is no significant evidence in favor of or against Stretta from recent years. Another issue is the reimbursement-related challenges and lack of wide-scale adoption of this technology after reports of lack of benefit from prior evidence and better available therapies. Therefore, the panel did not make any recommendations in favor of or against Stretta. Because Stretta has been available before TIF, and the latter requires expertise and additional resources, the panel believed that Stretta could be considered as an alternative when TIF is not feasible or available for a subset of patients.

OTHER CONSIDERATIONS

Endoscopic therapies in pediatric patients

We performed a systematic review of the published literature on this topic. We used Ovid MEDLINE, Embase, Scopus, and Cochrane for studies published through December 2022. We used major search terms and subheadings including "gastroesophageal reflux disease," "endoscopic therapy," "pediatric," and "age less than 18 years" (Appendix 1). A systematic review was performed examining the role of endoscopic therapies compared with medical therapy with PPI (and/or sham intervention) among pediatric patients with chronic GERD. Outcomes examined were PPI discontinuation, reduction in acid exposure time (percentage of time pH was <4), normalization of esophageal acid exposure time (per patient), symptom resolution (per patient), durable symptom resolution, GERD score improvement (using GERD-HRQL or similar scales), and adverse events. Because of the relative scarcity of literature, certainty of evidence and quality of studies were not evaluated.

Our systematic review found a total of 3 case series with a small number of patients and a case report.[110-113] Two[110,111] reported the use of TIF, one[104] on the use of Stretta, and one case report of the use of Stretta after TIF.[105] These small studies demonstrate that both techniques, Stretta and TIF, may be feasible in pediatric patients. TIF seemed to demonstrate improved results in children with 91% (10/11) patients in one study having resolution of GERD and 80% (8/10) patients in another study having discontinuation of PPIs.

Discussion

The panel recognized this as an important area of future research because refractory GERD is increasingly prevalent among the pediatric population, and many of these patients may have anatomical or neurological diseases in which medical therapy may not provide optimal symptom relief and surgery may not be feasible or could lead to high morbidity. Furthermore, given the early presentation of GERD, these pediatric patients may be at risk for developing earlier adverse events related to GERD. Larger studies need to be performed to better assess which patients in the pediatric population may be considered for endoscopic antireflux therapies. Due to lack of data on this subject, the panel could not provide any recommendation in favor of or against the endoscopic therapy and considered it as an investigational use only in the setting of a research study.

Novel endoscopic GERD therapies

We performed a systematic review of the published literature on this topic. We used Ovid MEDLINE, Embase, Scopus, and Cochrane for studies published through December 2022. We used major search terms and subheadings including "gastroesophageal reflux disease," "Endoscopic therapy," "endoscopic antireflux therapy," "transoral incisionless fundoplication," "TIF," "plication," "GERDx," "Esophyx," "Radiofrequency ablation," "RFA," "Stretta," "ReStech," "ablation," "GERDx," "Esophyx," "MUSE," "APC," "hybrid APC," "H-APC," "argon plasma coagulation," "hybrid argon plasma coagulation," "suturing," "resection," "banding" (Appendix 1). We restricted the search to emerging and novel antireflux

endoscopic interventions in this field that included EMR (using band ligation or other forms of resection with or without plication), endoscopic mucosal ablation (using hybrid argon plasma coagulation or other forms of ablation), Ultrasonic Surgical Endostapler device (MUSE, Medigus, Omer, Israel) and plication-based therapies including GERDxTM (G-SURG GmbH, Seeon-Seebruck, Germany). We also excluded interventions or technology that are out of date or unavailable, or have not been examined as a part of a clinical trial. A systematic review of RCTs and existing meta-analyses was performed examining role of novel endoscopic therapies compared with medical therapy with PPI (and/or sham intervention) among adult patients with chronic GERD. Outcomes examined were PPI discontinuation, reduction in acid exposure time (percentage of time pH was <4), normalization of esophageal acid exposure time (per patient), symptom resolution (per patient), durable symptom resolution, GERD score improvement (using GERD-HRQL or similar scales), and adverse events. Because of the scarcity of literature, certainty of evidence and quality of studies were not evaluated.

Our literature search identified 1 RCT[114] and 1 prospective trial[115] examining endoscopic full-thickness fundoplication (EFTP) using a novel GERDxTM, 7 single-arm interventional cohort studies of MUSETM,[116-122] 1 existing meta-analysis examining 10 noncontrolled trials of antireflux mucosectomy,[123] 2 clinical trials (1 for clip-band ligation antireflux therapy [C-BLART],[124] and 1 endoscopic band ligation alone[125]) of endoscopic band ligation, 3 studies of resection and plication (RAP),[126-128] and 1 existing meta-analysis examining 3 nonrandomized trials of antireflux mucosal ablation[129-131] as endoscopic antireflux interventions among patients with chronic GERD. We also found that there is an RCT examining antireflux mucosectomy (Clinical trials identifier: NCT04194723) and 2 RCTs examining antireflux mucosal ablation (Clinical trials identifier: NCT04711655; NCT05570448) underway. Because there is lack of robust data on single therapy, evidence was not reviewed to generate a recommendation. We have summarized the key findings of our review below:

EFTP using device GERDxTM. Our literature search identified 1 RCT[114] and 1 prospective trial[115] examining EFTP using a novel GERDxTM. Kalapala et al[114] reported on the efficacy and safety of this device among 70 patients with PPI-dependent GERD in an RCT in which eligible patients were randomized to either EFTP or a sham procedure in 1:1 ratio. The primary outcome, ≥50% improvement in the health-related quality of life (ie, GERD-HRQL) score at 3 months, was more frequently achieved in the EFTP group (65.7% vs 2.9%; $P < .001$). Median (IQR) percentage improvement in GERD-HRQL was significantly higher in the EFTP group at 6 (81.4 [60.9-100.0] vs 8.0 [2.2-21.6]; $P < .001$) and 12 (92.3 [84.4-100.0] vs 9.1 [4.8-36.0]; $P < .001$) months. Significantly higher numbers of patients were off of PPI at 23 months in the EFTP group compared with 11.4% in the sham group (62.8% vs 11.4%, $P < .001$). The 24-hour pH impedance study done at 3 (n = 70; EFTP = 35 and sham = 35) and 12 (n = 27; EFTP = 27 and sham = 9) months after the intervention showed a reduction in the esophageal acid exposure from baseline in the EFTP group; however, the difference did not reach statistical significance. No major procedure-related adverse events were encountered in either group. Weitzendorfer et al[115] reported clinical feasibility results from a prospective clinical trial of 40 chronic PPI-dependent patients with GERD reporting improvement in questionnaires for quality of life (GIQLI) score among 30 patients at 3 months after intervention from a mean of 92.45 ± 18.47 to 112.03 ± 13.11 ($P < .001$). The general reflux-specific score increased from a mean of 49.84 ± 24.83 to 23.93 ± 15.63 ($P < .001$), and the DeMeester score from a mean of 46.48 ± 30.83 to 20.03 ± 23.62 ($P < .001$). Although there were no intraoperative adverse events, 4 of 40 patients had postoperative adverse events and 7 of 40 patients underwent laparoscopic fundoplication 3 months after the intervention because of persistent symptoms. Authors of this trial reported a long-term follow-up separately as well.[132] At a median follow-up time of 57 months (36-74 months), there were significant improvements in the DeMeester score, GIQLI, and reflux symptoms between preoperative and postoperative values in short- and long-term follow-up. However, authors identified at least 55% of patients as failures of the plication device because of repeated operations with laparoscopic fundoplication in 25% and/or continued PPI use for symptoms in 40%. We did not identify any ongoing clinical trials of GERDx in our search.

MUSE. Our literature search identified 6 observational studies and 1 existing meta-analysis examining long-term outcomes with MUSE and TIF.[72,116-122] Overall, the clinical success rates ranged from 69% to 92% with follow-up durations from 6 months to 4 to 5 years. The risk of serious adverse events (ie, empyema, hemorrhage, and esophageal perforation) was 3.5% to 13.9%. We did not identify any RCTs of this device, and because of high serious adverse event rates, ongoing use of this over other relatively safer existing modalities, including TIF 2.0, is not recommended.

Antireflux mucosectomy. Our literature search identified 1 existing systematic review and meta-analysis examining safety and efficacy of antireflux mucosectomy in refractory GERD with 10 studies (8 prospective, 2 retrospective) included.[123] Clinical response was defined as discontinuation (complete) or reduction (partial) of PPIs post-antireflux mucosectomy (ARMS) at follow-up. In aggregate, there were 307 patients included. In meta-analysis, the technical success was 97.7% (95% CI, 94.6-99.0) and the clinical response rate was 80.1% (95% CI, 61.6-91.0). The pooled rate of complete and partial clinical response was 65.3% (95% CI, 51.4-77.0) and 21.5% (95% CI 14.2-31.2), respectively. The rate of adverse events was 17.2% (95% CI, 13.1-22.2), with the most common adverse event being dysphagia and/or esophageal stricture followed by bleeding with rates of 11.4% and 5.0%, respectively. GERD-HRQL scores (MD = 14.9, $P < .001$), GERD Questionnaire (GERD-Q) scores (MD = 4.85, $P < .001$), and mean acid exposure time (MD = 2.39, $P = 0.01$) decreased significantly post-

ARMS as compared with preprocedure. There was no difference in terms of clinical response and AEs between ARMS and ARMS with banding on subgroup analysis.

Antireflux mucosal ablation (ARMA). Our literature search found 1 existing systematic review and meta-analysis of 3 prospective studies examining safety and efficacy of ARMA for GERD.[131] In aggregate, 130 patients underwent 150 ARMA procedures. Clinical success was defined as complete postprocedural cessation of PPIs. The pooled rate of short-term clinical success was 81% (3 studies, 95% CI, 56-97, $I^2 = 0\%$). One study reported 1-year and 3-year clinical success at 89% (81%-94%) and 72.2%, respectively, among 100 patients. Two studies reported a PPI discontinuation rate at short-term follow-up of 70% (61-78%, $I^2 = 0\%$), whereas 1 study reported a PPI discontinuation rate at 1 year of 68% among 100 patients. The overall adverse event rate was 13% (7%-20%; $I^2 = 0\%$), and dysphagia requiring intervention was 10% (4%-16%; $I^2 = 0\%$) among 126 patients from 3 studies.

Discussion

Because of primarily uncontrolled data of different modalities and short-term data, the evidence could not be evaluated further using GRADE methodology. Although there is a potential for efficacy, there was no robust evidence for any of these examined modalities in the United States. The panel acknowledged that there is lack of evidence of benefit of one form of novel endoscopic antireflux therapy, and the data on several of these are still emerging. Short-term follow-up among these studies demonstrated improvement in GERD symptoms or related scores with minimal to moderate adverse event profile. However, to establish their positioning in the GERD armamentarium, there needs to be comparative trials against medical therapy and TIF 2.0 and/or surgical fundoplication. Like TIF 2.0, these strategies are primarily used for patients with chronic, objectively confirmed GERD with small hiatal hernia defined as $\leq$2 cm. The panel recognized the promise of these emerging technologies that may become more prevalent as more data become available. Therefore, the panel believed that more data, especially prospective controlled data compared with medical therapy or other existing GERD therapies, are needed to demonstrate any substantial benefit and for grading the evidence. The panel could not derive any recommendation because of lack of controlled long-term data of benefit. Nevertheless, there are clinical trials in process examining a few of these modalities, so in the future there will be more information to determine the role and positioning of these modalities. Therefore, the panel did not provide any recommendation in favor of or against the novel endoscopic antireflux therapies at the current time.

GUIDELINE UPDATE

ASGE guidelines are reviewed for updates approximately every 5 years, or in the event that new data may influence a recommendation. Updates follow the same ASGE guideline development process.

DISCLOSURES

N. C. Thosani is a consultant for and has received travel compensation and food and beverage from PENTAX of America, Inc, and Boston Scientific Corporation; is a speaker for and has received travel compensation and food and beverage from AbbVie Inc, and is a consultant for Ambu Inc. A. Saeed is a consultant for Endogastric Solutions, Medtronic, Boston Scientific Corporation, and Olympus. B. Abu Dayyeh is a consultant for Endogenex, Endo-TAGSS, Metamodix, and BFKW; is a consultant for and receives grant or research support from USGI, Apollo Endosurgery, Spatz Medical, Aspire Bariatrics, and Boston Scientific; has speaker roles with Olympus, Johnson and Johnson; is a speaker for and receives grant or research support from Medtronic and Endogastric Solutions; and receives grant support from ERBE Medical. M.I. Canto is a principal investigator on a research grant study with The Johns Hopkins University sponsored by Endogastric Solutions; is a consultant and on the scientific advisory board for Cernostics; has a research grant and clinical trial through Pentax Medical Corporation; was a consultant for ClearNote Health and Cernostics; and receives royalties from UpToDate. W. Abidi is a consultant for and has received food and beverage from Ambu Inc, Apollo Endosurgery US Inc, CONMED Corporation; has received research support from GI Dynamics; and has received food and beverage from Olympus America Inc, AbbVie Inc, Boston Scientific Corporation, RedHill Biopharma Inc, and Salix Pharmaceuticals. S.K. Amateau is a consultant for and has received travel compensation and food and beverage from Boston Scientific Corporation; is a consultant and on the advisory board for Merit Medical; is a consultant and has received food and beverage from Olympus Corporation of the Americas; is a consultant for MTEndoscopy, US Endoscopy, and Heraeus Medical Components, LLC; and is a consultant and has received food and beverage from Cook Medical LLC. N. Cosgrove is a consultant for Olympus Corporation of the Americas; is a consultant and has received food and beverage from Boston Scientific Corporation; and has received food and beverage from Ambu Inc S.E. Elhanafi has received food and beverage from Medtronic, Inc, Nestle HealthCare Nutrition Inc, Ambu Inc, Salix Pharmaceuticals, Takeda Pharmaceuticals U.S.A., Inc, and Merit Medical Systems Inc. N. Forbes has been a consultant for Boston Scientific Corporation and PENTAX of America, Inc; has been on the speaker bureau for PENTAX of America, Inc, and Boston Scientific Corporation; and has received research support from PENTAX of America, Inc D.R. Kohli has been a consultant for and has received a research grant from Olympus Corporation of the Americas. L.L. Fujii-Lau is a consultant for Boston Scientific Corporation and has received food and beverage from Pfizer Inc and AbbVie Inc. J.D. Machicado is a consultant for and has received food and beverage from Mauna Kea

Technologies, Inc; and has received food and beverage from Boston Scientific Corporation. N.B. Marya is a consultant for and has received food and beverage from Boston Scientific Corporation; and has received food and beverage from Apollo Endosurgery US Inc S. Ngamruengphong is a consultant for Boston Scientific Corporation, Olympus, and Neptune Medical; and has received food and beverage from Medtronic, Inc, Boston Scientific Corporation, PENTAX of America, Inc, and Ambu Inc S. Pawa is a consultant for Boston Scientific Corporation. N.R. Thiruvengadam has received a grant from Boston Scientific Corporation. B.J. Qumseya is a consultant for and has received food and beverage from Medtronic, Inc; is a consultant for Assertio Management, LLC; is a speaker for Castle Biosciences; and has received food and beverage from FUJIFILM Healthcare Americas Corporation and Boston Scientific Corporation. The other authors disclosed no financial relationships.

ACKNOWLEDGMENTS

The authors are grateful to Philip Daiza, a patient representative from the International Foundation for Gastrointestinal Disorders (I.F.G.D.) for participating in our panel, as well as Robyn Rosasco (librarian) for assistance with searching for articles. The authors also thank Drs Luis Lara, Dennis Jensen, and Nalini Guda on behalf of the *GIE* Editorial Board and ASGE Governing Board for their review of the guidelines. This guideline was funded exclusively by the ASGE; no outside funding was received during the development of this guideline.

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Abbreviations: AE, adverse event; ARMA, antireflux mucosal ablation; ARMS, antireflux mucosectomy (mucosal resection); ASGE, American Society for Gastrointestinal Endoscopy; BE, Barrett esophagus; COI, conflict of interest; cTIF, combined hiatal hernia repair and transoral incisionless fundoplication; GEJ, gastroesophageal junction; GERD-HRQL, GERD health-related quality of life; GIE, GI endoscopy; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; IQR, interquartile range; LNF, laparoscopic Nissen fundoplication; MUSETM, Medigus Ultrasonic Surgical Endostapler; OR, odds ratio; PICO, population, intervention, comparator, outcome; POEM, peroral endoscopic myotomy; PPI, proton pump inhibitor; QOLRAD, quality of life in reflux and dyspepsia; RCT, randomized controlled trial; RDQ, reflux disease questionnaire; RFA, radiofrequency ablation; SG, sleeve gastrectomy; SOP, Standards of Practice; TIF, transoral incisionless fundoplication.

2468-4481
https://doi.org/10.1016/j.vgie.2024.10.001

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APPENDIX 1

Search Strategies: Adults

Database: Ovid MEDLINE ALL
Number of Results: 733
Search Date: 20 November 2021
Limits: English-language only; human studies only (clinical trials, RCTs, prospective and retrospective studies, systematic reviews, meta-analyses); publication date after January 1, 2001
Excluded: Case reports, case series, editorials, letters, comments, conference abstracts

1 exp Gastroesophageal Reflux/
2 (gastro-oesophageal$ or gastro-esophageal$ or gastrooesophageal$ or gastroesophageal$).tw,kf.
3 acid reflux$.tw,kf.
4 (GERD or GORD).tw,kf.
5 GER.tw,kf.
6 ((oesophag$ or esophag$ or gastr$) adj3 (reflux or acid)).tw,kf.
7 (heartburn or "heart burn" or heart-burn).tw,kf. or exp heartburn/
8 (gastr* and regurgitat*).tw,kf.
9 or/1-8
10 exp adolescent/ or exp child/ or exp infant/ or (infant disease* or childhood disease*).ti,ab,kf. or (adolescen* or babies or baby or boy? or boyfriend or boyhood or girlfriend or girlhood or child* or girl? or infan* or juvenil* or kid? or minors or minors* or neonat* or neo-nat* or newborn* or new-born* or paediatric* or peadiatric* or pediatric* or perinat* or preschool* or puber* or pubescen* or school* or teen* or toddler? or underage? or under-age? or youth*).ti,ab,kf. or (pediatric* or paediatric* or infan* or child* or adolescen* or "young adult*").jn,jw. or (pediatric* or paediatric* or infan* or child* or adolescen* or "young adult*").in.
11 9 not 10
12 endoscopy, digestive system/ or endoscopy, gastrointestinal/ or duodenoscopy/ or esophagoscopy/ or gastroscopy/ or ((gastr* adj2 endoscop*) or (esophagi* adj2 endoscop*) or (oesophagi* adj2 endoscop*) or duodenoscop* or eosophagoduodenoscop* or eosophagogastroduodenoscop* or esophago?gastro?duodenoscop* or oesophago?gastro?duodenoscop* or esophagogastro?duodenoscop* or oesophago?gastro?duodenoscop* or eosphagoscop* or esophagoduodenoscop* or esophagogastroduodenoscop* or esophagoscop* or gastroscop* or oesophagoduodenoscop* or oesophagogastroduodenoscop* or oesophagoscop* or (upper adj2 endoscop*)).ti,ab. or endoscop*.jw. or (((radiofrequency or radio frequency) and (endoscop* or ablation or catheter*)) or Stretta or ReStech).ti. or (fundoplication or plication or TIF or GERDx or "GERD x" or GERD?x or EsophyX or "Esophy X" or "Esophy?X").ti.
13 11 and 12
14 exp Fundoplication/
15 Natural Orifice Endoscopic Surgery/
16 (transoral incisionless fundoplication or trans?oral incisionless fundo?plication or TIF or fundoplication or plication or fundo?plication or (endoscop* adj3 anti?reflux) or GERDx or "GERD x" or GERD?x or EsophyX or "Esophy X" or "Esophy?X").tw,kf.
17 or/14-16
18 ((radiofrequency or radio frequency) and (endoscop* or ablation or catheter*)).tw,kf.
19 exp Radiofrequency Ablation/

20 (gastr* and ablation).tw,kf.
21 (RTAF or RFA).tw,kf.
22 (Stretta or ReStech).tw,kf.
23 or/18-22
24 ((exp Surgical Staplers/ or Stapl*.tw,kf.) and (endoscop*.tw,kf. or exp endoscopy/)) or (Medigus adj2 Ultrasonic adj2 Surgical adj2 Endostapl*).tw,kf. or (MUSE? adj3 (endoscop* or stapl* or Medigus)).tw,kf.
25 exp Argon Plasma Coagulation/ or ((argon adj5 plasma adj5 coagulat$) or (argon adj5 beam adj5 coagulat$) or APC or HAPC or H-APC or "H APC" or (hybrid and coagulat$)).tw,kf. or (thermoablati* or thermo ablation or thermo destruc* or thermal destruc* or thermo coag* or thermal coag* or electrocoagulation or transvenous ablati* or laser coag*).tw,kf.
26 (exp sutures/ or exp suture techniques/ or (suture or sutures or suturing or sutured).tw,kf.) and (endoscop*.tw,kf. or exp endoscopy/)
27 exp Endoscopic Mucosal Resection/ or mucosectom$.tw,kf. or ((resect$ or dissect$ or "strip biops$").tw,kf. and (endoscop*.tw,kf. or exp endoscopy/))
28 exp ligation/ or (((band* and (gastr* or esophag* or oesophag*)) or (endoscop* or band* or rubber)) and ligat*).tw,kf.
29 exp proton pump/ai or exp proton pump inhibitors/ or exp omeprazole/ or ((proton adj3 pump adj3 inhibitor$) or ppi or ppis or omeprazole or lansoprazole or pantoprazole or rabeprazole or esomeprazole).tw,kf.
30 exp histamine h2 antagonists/ or exp cimetidine/ or exp famotidine/ or exp nizatidine/ or exp ranitidine/ or ((histamine or H2) adj3 (recept* or block* or antagon*)).tw,kf. or (cimetidine or famotidine or nizatidine or ranitidine or esomeprazole).tw,kf.
31 ((anti-reflux or antireflux or "anti reflux").tw,kf. and (exp Surgical Procedures, Operative/ or (surgery or surgical or surgeries or laparoscop*).ti,ab. or "surgery".fs. or (Nissen$ or Toupet$).tw,kf.)) or ((anti-reflux or antireflux or "anti reflux") adj3 therap*).tw,kf.
32 exp Placebos/ or (placebo* or (sham and (treatment* or procedure*)) or (dummy and (treatment* or procedure*)) or "no intervention*" or "non intervention*" or nonintervention*).tw,kf.
33 ((randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or dt.fs. or randomly.ab. or trial.ab. or groups.ab.) not (exp animals/ not humans.sh.)
34 ("clinical trial" or "clinical trial, phase i" or "clinical trial, phase ii" or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or "multicenter study" or "randomized controlled trial").pt. or double-blind method/ or clinical trials as topic/ or clinical trials, phase i as topic/ or clinical trials, phase ii as topic/ or clinical trials, phase iii as topic/ or clinical trials, phase iv as topic/ or controlled clinical trials as topic/ or randomized controlled trials as topic/ or early termination of clinical trials as topic/ or multicenter studies as topic/ or ((randomi?ed adj7 trial*) or (controlled adj3 trial*) or (clinical adj2 trial*) or ((single or doubl* or tripl* or treb*) and (blind* or mask*))).ti,ab,kw. or ("4 arm" or "four arm").ti,ab,kw. or clinicaltrials*.si.
35 Epidemiologic studies/ or exp case control studies/ or exp cohort studies/ or Case control.tw. or (cohort adj (study or studies)).tw. or Cohort analy$.tw. or (Follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or Longitudinal.tw. or Retrospective.tw. or Cross sectional.tw. or Cross-sectional studies/ or cohort.ti,ab. or prospective.ti,ab.
36 (((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. or Systematic-Review.pt.
37 or/33-36
38 (addresses or biography or case reports or comment or directory or editorial or festschrift or interview or lectures or legal cases or legislation or letter or news or newspaper article or patient education handout or popular works or congresses or consensus development conference or consensus development conference, nih or practice guideline).pt. or (exp animals/ not humans.sh.)
39 37 not 38
40 17 or 23 or 24 or 25 or 26 or 27 or 28
41 29 or 30 or 31 or 32
42 13 and 39 and 40 and 41
43 limit 42 to english language
44 limit 43 to dt=20010101-20211231

Database: Embase.com (Elsevier)
Number of Results: 469
Search Date: 20 november 2021
Limits: English-language only; human studies only (clinical trials, RCTs, prospective and retrospective studies, systematic reviews, meta-analyses); publication date after January 1, 2001
Excluded: Case reports, case series, editorials, letters, comments, conference abstracts

1 'gastroesophageal reflux'/exp
2 (gastro-oesophageal* OR gastro-esophageal* OR gastrooesophageal* OR gastroesophageal*):ti,ab,kw
3 (acid NEAR/3 reflux*):ti,ab,kw
4 (GERD OR GORD):ti,ab,kw
5 GER:ti,ab,kw
6 ((oesophag* OR esophagi* OR gastr*) NEAR/3 (reflux OR acid)):ti,ab,kw
7 (heartburn OR "heart burn" OR heart-burn):ti,ab OR 'heartburn'/exp
8 (gastr* AND regurgitat*):ti,ab,kw
9 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
10 adolescence/exp OR adolescent/exp OR child/exp OR childhood disease/exp OR infant disease/exp OR (infant disease* OR childhood disease*):ti,ab,kw OR (adolescen* OR babies OR baby OR boy? OR boyfriend OR boyhood OR girlfriend OR girlhood OR child* OR girl? OR infan* OR juvenil* OR kid? OR minors OR minors* OR neonat* OR neo-nat* OR newborn* OR new-born* OR paediatric* OR peadiatric* OR pediatric* OR perinat* OR preschool* OR puber* OR pubescen* OR school* OR teen* OR toddler? OR underage? OR under-age? OR youth*):ti,ab,kw OR (pediatric* OR paediatric* OR infan* OR child* OR adolescen* OR "young adult*"):ta,jt OR (pediatric* OR paediatric* OR infan* OR child* OR adolescen* OR "young adult*"):jt
11 #9 NOT #10
12 'endoscopy'/de OR 'digestive tract endoscopy'/de OR 'gastrointestinal endoscopy'/de OR 'duodenoscopy'/de OR 'esophagoscopy'/de OR 'gastroscopy'/de OR

'esophagogastroduodenoscopy'/de OR ((gastr* NEAR/2 endoscop*) OR (esophagi* NEAR/2 endoscop*) OR (oesophagi* NEAR/2 endoscop*) OR duodenoscop* OR eosophagoduodenoscop* OR eosophagogastroduodenoscop* OR esophago?gastro?duodenoscop* OR oesophago?gastro?duodenoscop* OR esophagogastro?duodenoscop* OR oesophago?gastro?duodenoscop* OR eosphagoscop* OR esophagoduodenoscop* OR esophagogastroduodenoscop* OR esophagoscop* OR gastroscop* OR oesophagoduodenoscop* OR oesophagogastroduodenoscop* OR oesophagoscop* OR (upper adj2 endoscop*)):ti,ab OR endoscop*:jt OR (((radiofrequency OR radio frequency) AND (endoscop* OR ablation OR catheter*)) OR Stretta OR ReStech):ti OR (fundoplication OR plication OR TIF OR GERDx OR "GERD x" OR GERD?x OR EsophyX OR "Esophy X" OR "Esophy?X"):ti

13 #11 AND #12

14 'stomach fundoplication'/exp

15 'natural orifice transluminal endoscopic surgery'/de

16 ("transoral incisionless fundoplication" OR "trans?oral incisionless fundo?plication" OR "TIF" OR fundoplication OR plication OR fundo?plication OR (endoscop* NEAR/3 "anti?reflux") OR GERDx OR "GERD x" OR GERD?x OR EsophyX OR "Esophy X" OR "Esophy?X"):ti,ab,kw

17 #14 OR #15 OR #16

18 ((radiofrequency OR "radio frequency") AND (endoscop* OR ablation OR catheter*)):ti,ab,kw

19 'radiofrequency ablation'/exp

20 (gastr* AND ablation):ti,ab,kw

21 (RTAF OR RFA):ti,ab,kw

22 (Stretta OR ReStech):ti,ab,kw

23 #18 OR #19 OR #20 OR #21 OR #22

24 (('stapler'/exp OR 'surgical staple'/exp OR Stapl*:ti,ab,kw) AND (endoscop*:ti,ab,kw OR 'endoscopy'/exp)) OR (Medigus NEAR/2 Ultrasonic NEAR/2 Surgical NEAR/2 Endostapl*):ti,ab,kw OR (MUSE? NEAR/3 (endoscop* OR stapl* OR Medigus)):ti,ab,kw

25 'argon plasma coagulation'/exp OR ((argon NEAR/5 plasma NEAR/5 coagulat*) OR (argon NEAR/5 beam NEAR/5 coagulat*) OR "APC" OR "HAPC" OR "H-APC" OR "H APC" OR (hybrid AND coagulat*)):ti,ab,kw OR (thermoablati* OR "thermo ablation" OR "thermo destruc*" OR "thermal destruc*" OR "thermo coag*" OR "thermal coag*" OR electrocoagulation OR "transvenous ablati*" OR "laser coag*"):ti,ab,kw

26 ('suture'/exp OR 'suture technique'/exp OR (suture OR sutures OR suturing OR sutured):ti,ab,kw) AND (endoscop*:ti,ab,kw OR 'endoscopy'/exp)

27 'endoscopic mucosal resection'/exp OR mucosectom*:ti,ab,kw OR ((resect* OR dissect* OR "strip biops*"):ti,ab,kw AND (endoscop*:ti,ab,kw OR 'endoscopy'/exp))

28 'ligation'/exp OR (((band* AND (gastr* OR esophag* OR oesophag*)) OR (endoscop* OR band* OR rubber)) AND ligat*):ti,ab,kw

29 'proton pump inhibitor'/exp OR 'omeprazole'/exp OR ((proton NEAR/3 pump NEAR/3 inhibitor*) OR PPI OR PPIs OR omeprazole OR lansoprazole OR pantoprazole OR rabeprazole OR esomeprazole):ti,ab,kw

30 'histamine H2 receptor antagonist'/exp OR 'cimetidine'/exp OR 'famotidine'/exp OR 'nizatidine'/exp OR 'ranitidine'/exp OR ((histamine OR H2) NEAR/3 (recept* OR block* OR antagon*)):ti,ab,kw OR (cimetidine OR famotidine OR nizatidine OR ranitidine OR esomeprazole):ti,ab,kw

31 'antireflux operation'/de OR ((anti-reflux OR antireflux OR "anti reflux"):ti,ab,kw AND ('surgery'/exp OR (surgery OR surgical OR surgeries OR laparoscop*):ti,ab,kw OR surgery:lnk OR (Nissen* OR Toupet*):ti,ab,kw)) OR ((anti-reflux OR antireflux OR "anti reflux") NEAR/3 therap*):ti,ab,kw
32 'placebo'/exp OR (placebo* OR (sham AND (treatment* OR procedure*)) OR (dummy AND (treatment* OR procedure*)) OR "no intervention*" OR "non intervention*" OR nonintervention*):ti,ab,kw
33 (Clinical trial/de OR Randomized controlled trial/de OR Randomization/de OR Single blind procedure/de OR Double blind procedure/de OR Crossover procedure/de OR Placebo/de OR ("randomi?ed controlled trial*" OR "random allocation" OR "randomly allocated" OR "allocated randomly" OR (allocated NEAR/2 random) OR "single blind*" OR "double blind*" OR ((treble or triple) NEAR (blind*)) OR Placebo*):ti,ab,kw OR Prospective study/exp OR ((randomi?ed NEAR/7 trial*) OR (controlled NEAR/3 trial*) OR (clinical NEAR/2 trial*) OR ((single OR doubl* OR tripl* OR treb*) AND (blind* OR mask*))):ti,ab,kw OR ("4 arm" OR "four arm"):ti,ab,kw) NOT (Case study/de OR Case report:ti,ab,kw OR abstract report/de OR letter/de)
34 Clinical study/de OR Case control study/de OR Family study/de OR Longitudinal study/de OR Retrospective study/de OR (Prospective study/de NOT Randomized controlled trials/de) OR Cohort analysis/de OR (Cohort NEAR (study OR studies)):ti,ab,kw OR ("Case control" NEAR (study OR studies)):ti,ab,kw OR ("follow up" NEAR (study OR studies)):ti,ab,kw OR (observational NEAR (study or studies)):ti,ab,kw OR (epidemiologic* NEAR (study OR studies)):ti,ab,kw OR ("cross sectional" NEAR (study OR studies)):ti,ab,kw
35 ('Meta Analysis'/exp OR 'systematic review'/exp OR ((meta NEAR analy*) or metaanalys*):ti,ab,kw OR (systematic NEAR (review* OR overview*)):ti,ab,kw OR cancerlit:ab OR Cochrane:ab OR Embase:ab OR (psychlit OR psyclit):ab OR (psychinfo OR psycinfo):ab OR (cinahl OR cinhal):ab OR science citation index:ab OR bids:ab OR reference lists:ab OR bibliography*:ab OR hand-search*:ab OR manual search*:ab OR relevant journals:ab OR ((data extraction:ab OR selection criteria:ab) AND Review:it)) NOT (Letter:it OR Editorial:it OR (animal/de NOT (animal/de AND human/de)))
36 #33 OR #34 OR #35
37 ([conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim OR [data papers]/lim OR [editorial]/lim OR [erratum]/lim OR [letter]/lim OR [note]/lim OR [review]/lim OR [short survey]/lim OR ‘case report'/de OR 'review'/de) OR ((rat:ti,tt OR rats:ti,tt OR mouse:ti,tt OR mice:ti,tt OR swine:ti,tt OR porcine:ti,tt OR murine:ti,tt OR sheep:ti,tt OR lambs:ti,tt OR pigs:ti,tt OR piglets:ti,tt OR rabbit:ti,tt OR rabbits:ti,tt OR cat:ti,tt OR cats:ti,tt OR dog:ti,tt OR dogs:ti,tt OR cattle:ti,tt OR bovine:ti,tt OR monkey:ti,tt OR monkeys:ti,tt OR trout:ti,tt OR marmoset*:ti,tt) AND ‘animal experiment’/de) OR (‘animal experiment’/de NOT (‘human experiment'/de OR ‘human’/de))
38 #36 NOT #37
39 #17 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32
40 #13 AND #38 AND #39
41 #40 AND English:la
42 #41 AND [01/01/2001]/sd

Database: Cochrane Library (Wiley)
Number of Results: 213

Search Date: 20 November 2021
Limits: Publication date after January 1, 2001
Excluded: N/A

1 [mh "Gastroesophageal Reflux"]
2 (gastro-oesophageal* OR gastro-esophageal* OR gastrooesophageal$ OR gastroesophageal*):ti,ab,kw
3 (acid reflux*):ti,ab,kw
4 (GERD OR GORD):ti,ab,kw
5 GER:ti,ab,kw
6 ((oesophag* OR esophagi* OR gastr*) NEAR/3 (reflux OR acid)):ti,ab,kw
7 (heartburn OR "heart burn" OR heart-burn):ti,ab,kw OR [mh heartburn]
8 (gastr* AND regurgitat*):ti,ab,kw
9 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
10 [mh adolescent] OR [mh child] OR [mh infant] OR (infant disease* OR childhood disease*):ti,ab,kw OR (adolescen* OR babies OR baby OR boy? OR boyfriend OR boyhood OR girlfriend OR girlhood OR child* OR girl? OR infan* OR juvenil* OR kid? OR minors OR minors* OR neonat* OR neo-nat* OR newborn* OR new-born* OR paediatric* OR peadiatric* OR pediatric* OR perinat* OR preschool* OR puber* OR pubescen* OR school* OR teen* OR toddler? OR underage? OR under-age? OR youth*):ti,ab,kw
11 #9 NOT #10
12 [mh "endoscopy, digestive system"] OR [mh "endoscopy, gastrointestinal"] OR [mh duodenoscopy] OR [mh esophagoscopy] OR [mh gastroscopy] OR ((gastr* NEAR/2 endoscop*) OR (esophagi* NEAR/2 endoscop*) OR (oesophagi* NEAR/2 endoscop*) OR duodenoscop* OR eosophagoduodenoscop* OR eosophagogastroduodenoscop* OR esophago?gastro?duodenoscop* OR oesophago?gastro?duodenoscop* OR esophagogastro?duodenoscop* OR oesophago?gastro?duodenoscop* OR eosphagoscop* OR esophagoduodenoscop* OR esophagogastroduodenoscop* OR esophagoscop* OR gastroscop* OR oesophagoduodenoscop* OR oesophagogastroduodenoscop* OR oesophagoscop* OR (upper NEAR/2 endoscop*)):ti,ab,kw OR (((radiofrequency OR radio frequency) AND (endoscop* OR ablation OR catheter*)) OR Stretta OR ReStech):ti OR (fundoplication OR plication OR TIF OR GERDx OR "GERD x" OR GERD?x OR EsophyX OR "Esophy X" OR "Esophy?X"):ti
13 #11 AND #12
14 [mh Fundoplication]
15 [mh ^"Natural Orifice Endoscopic Surgery"]
16 (transoral incisionless fundoplication OR trans?oral incisionless fundo?plication OR TIF OR fundoplication OR plication OR fundo?plication OR (endoscop* NEAR/3 anti?reflux) OR GERDx OR "GERD x" OR GERD?x OR EsophyX OR "Esophy X" OR "Esophy?X"):ti,ab,kw
17 #14 OR #15 OR #16
18 ((radiofrequency OR radio frequency) AND (endoscop* OR ablation OR catheter*)):ti,ab,kw
19 [mh "Radiofrequency Ablation"]
20 (gastr* AND ablation):ti,ab,kw
21 (RTAF OR RFA):ti,ab,kw
22 (Stretta OR ReStech):ti,ab,kw
23 #18 OR #19 OR #20 OR #21 OR #22

24 (([mh "Surgical Staplers"] OR Stapl*:ti,ab,kw) AND (endoscop*:ti,ab,kw OR [mh endoscopy])) OR (Medigus NEAR/2 Ultrasonic NEAR/2 Surgical NEAR/2 Endostapl*):ti,ab,kw OR (MUSE? NEAR/3 (endoscop* OR stapl* OR Medigus)):ti,ab,kw
25 [mh "Argon Plasma Coagulation"] OR ((argon NEAR/5 plasma NEAR/5 coagulat*) OR (argon NEAR/5 beam NEAR/5 coagulat*) OR APC OR HAPC OR H-APC OR "H APC" OR (hybrid AND coagulat*)):ti,ab,kw OR (thermoablati* OR "thermo ablation" OR "thermo destruc*" OR "thermal destruc*" OR "thermo coag*" OR "thermal coag*" OR electrocoagulation OR "transvenous ablati*" OR "laser coag*"):ti,ab,kw
26 ([mh sutures] OR [mh "suture techniques"] OR (suture OR sutures OR suturing OR sutured):ti,ab,kw) AND (endoscop*:ti,ab,kw OR [mh endoscopy])
27 [mh "Endoscopic Mucosal Resection"] OR mucosectom*:ti,ab,kw OR ((resect* OR dissect* OR "strip biops*"):ti,ab,kw AND (endoscop*:ti,ab,kw OR [mh endoscopy]))
28 [mh ligation] OR (((band* AND (gastr* OR esophag* OR oesophag*)) OR (endoscop* OR band* OR rubber)) AND ligat*):ti,ab,kw
29 [mh "proton pump inhibitors"] OR [mh omeprazole] OR ((proton NEAR/3 pump NEAR/3 inhibitor*) OR PPI OR PPIs OR omeprazole OR lansoprazole OR pantoprazole OR rabeprazole OR esomeprazole):ti,ab,kw
30 [mh "histamine h2 antagonists"] OR [mh cimetidine] OR [mh famotidine] OR [mh nizatidine] OR [mh ranitidine] OR ((histamine OR H2) NEAR/3 (recept* OR block* OR antagon*)):ti,ab,kw OR (cimetidine OR famotidine OR nizatidine OR ranitidine OR esomeprazole):ti,ab,kw
31 (anti-reflux OR antireflux OR "anti reflux"):ti,ab,kw
32 [mh Placebos] OR (placebo* OR (sham AND (treatment* OR procedure*)) OR (dummy AND (treatment* OR procedure*)) OR "no intervention*" OR "non intervention*" OR nonintervention*):ti,ab,kw
33 #17 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28
34 #29 OR #30 OR #31 OR #32
35 #13 AND #33 AND #34

Search Strategies: Pediatrics

Database: Ovid MEDLINE ALL
Number of Results: 197
Search Date: 20 november 2021
Limits: English-language only; human studies only (clinical trials, RCTs, prospective and retrospective studies, systematic reviews, meta-analyses, case reports, case series); publication date after January 1, 2001
Excluded: editorials, letters, comments, conference abstracts

1 exp Gastroesophageal Reflux/
2 (gastro-oesophageal$ or gastro-esophageal$ or gastrooesophageal$ or gastroesophageal$).tw,kf.
3 acid reflux$.tw,kf.
4 (GERD or GORD).tw,kf.
5 GER.tw,kf.
6 ((oesophag$ or esophag$ or gastr$) adj3 (reflux or acid)).tw,kf.
7 (heartburn or "heart burn" or heart-burn).tw,kf. or exp heartburn/

8 (gastr* and regurgitat*).tw,kf.
9 or/1-8
10 exp adolescent/ or exp child/ or exp infant/ or (infant disease* or childhood disease*).ti,ab,kf. or (adolescen* or babies or baby or boy? or boyfriend or boyhood or girlfriend or girlhood or child* or girl? or infan* or juvenil* or kid? or minors or minors* or neonat* or neonat* or newborn* or new-born* or paediatric* or peadiatric* or pediatric* or perinat* or preschool* or puber* or pubescen* or school* or teen* or toddler? or underage? or under-age? or youth*).ti,ab,kf. or (pediatric* or paediatric* or infan* or child* or adolescen* or "young adult*").jn,jw. or (pediatric* or paediatric* or infan* or child* or adolescen* or "young adult*").in.
11 9 and 10
12 endoscopy, digestive system/ or endoscopy, gastrointestinal/ or duodenoscopy/ or esophagoscopy/ or gastroscopy/ or ((gastr* adj2 endoscop*) or (esophagi* adj2 endoscop*) or (oesophagi* adj2 endoscop*) or duodenoscop* or eosophagoduodenoscop* or eosophagogastroduodenoscop* or esophago?gastro?duodenoscop* or oesophago?gastro?duodenoscop* or esophagogastro?duodenoscop* or oesophago?gastro?duodenoscop* or eosphagoscop* or esophagoduodenoscop* or esophagogastroduodenoscop* or esophagoscop* or gastroscop* or oesophagoduodenoscop* or oesophagogastroduodenoscop* or oesophagoscop* or (upper adj2 endoscop*)).ti,ab. or endoscop*.jw. or (((radiofrequency or radio frequency) and (endoscop* or ablation or catheter*)) or Stretta or ReStech).ti. or (fundoplication or plication or TIF or GERDx or "GERD x" or GERD?x or EsophyX or "Esophy X" or "Esophy?X").ti.
13 11 and 12
14 exp Fundoplication/
15 Natural Orifice Endoscopic Surgery/
16 (transoral incisionless fundoplication or trans?oral incisionless fundo?plication or TIF or fundoplication or plication or fundo?plication or (endoscop* adj3 anti?reflux) or GERDx or "GERD x" or GERD?x or EsophyX or "Esophy X" or "Esophy?X").tw,kf.
17 or/14-16
18 ((radiofrequency or radio frequency) and (endoscop* or ablation or catheter*)).tw,kf.
19 exp Radiofrequency Ablation/
20 (gastr* and ablation).tw,kf.
21 (RTAF or RFA).tw,kf.
22 (Stretta or ReStech).tw,kf.
23 or/18-22
24 ((exp Surgical Staplers/ or Stapl*.tw,kf.) and (endoscop*.tw,kf. or exp endoscopy/)) or (Medigus adj2 Ultrasonic adj2 Surgical adj2 Endostapl*).tw,kf. or (MUSE? adj3 (endoscop* or stapl* or Medigus)).tw,kf.
25 exp Argon Plasma Coagulation/ or ((argon adj5 plasma adj5 coagulat$) or (argon adj5 beam adj5 coagulat$) or APC or HAPC or H-APC or "H APC" or (hybrid and coagulat$)).tw,kf. or (thermoablati* or thermo ablation or thermo destruc* or thermal destruc* or thermo coag* or thermal coag* or electrocoagulation or transvenous ablati* or laser coag*).tw,kf.
26 (exp sutures/ or exp suture techniques/ or (suture or sutures or suturing or sutured).tw,kf.) and (endoscop*.tw,kf. or exp endoscopy/)
27 exp Endoscopic Mucosal Resection/ or mucosectom$.tw,kf. or ((resect$ or dissect$ or "strip biops$").tw,kf. and (endoscop*.tw,kf. or exp endoscopy/))
28 exp ligation/ or (((band* and (gastr* or esophag* or oesophag*)) or (endoscop* or band* or rubber)) and ligat*).tw,kf.

29 exp proton pump/ai or exp proton pump inhibitors/ or exp omeprazole/ or ((proton adj3 pump adj3 inhibitor$) or ppi or ppis or omeprazole or lansoprazole or pantoprazole or rabeprazole or esomeprazole).tw,kf.
30 exp histamine h2 antagonists/ or exp cimetidine/ or exp famotidine/ or exp nizatidine/ or exp ranitidine/ or ((histamine or H2) adj3 (recept* or block* or antagon*)).tw,kf. or (cimetidine or famotidine or nizatidine or ranitidine or esomeprazole).tw,kf.
31 ((anti-reflux or antireflux or "anti reflux").tw,kf. and (exp Surgical Procedures, Operative/ or (surgery or surgical or surgeries or laparoscop*).ti,ab. or "surgery".fs. or (Nissen$ or Toupet$).tw,kf.)) or ((anti-reflux or antireflux or "anti reflux") adj3 therap*).tw,kf.
32 exp Placebos/ or (placebo* or (sham and (treatment* or procedure*)) or (dummy and (treatment* or procedure*)) or "no intervention*" or "non intervention*" or nonintervention*).tw,kf.
33 ((randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or dt.fs. or randomly.ab. or trial.ab. or groups.ab.) not (exp animals/ not humans.sh.)
34 ("clinical trial" or "clinical trial, phase i" or "clinical trial, phase ii" or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or "multicenter study" or "randomized controlled trial").pt. or double-blind method/ or clinical trials as topic/ or clinical trials, phase i as topic/ or clinical trials, phase ii as topic/ or clinical trials, phase iii as topic/ or clinical trials, phase iv as topic/ or controlled clinical trials as topic/ or randomized controlled trials as topic/ or early termination of clinical trials as topic/ or multicenter studies as topic/ or ((randomi?ed adj7 trial*) or (controlled adj3 trial*) or (clinical adj2 trial*) or ((single or doubl* or tripl* or treb*) and (blind* or mask*))).ti,ab,kw. or ("4 arm" or "four arm").ti,ab,kw. or clinicaltrials*.si.
35 Epidemiologic studies/ or exp case control studies/ or exp cohort studies/ or Case control.tw. or (cohort adj (study or studies)).tw. or Cohort analy$.tw. or (Follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or Longitudinal.tw. or Retrospective.tw. or Cross sectional.tw. or Cross-sectional studies/ or cohort.ti,ab. or prospective.ti,ab.
36 (((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. or Systematic-Review.pt.
37 case report.pt. or case series.tw. or (case adj3 report$).tw,kf.
38 or/33-37
39 (addresses or biography or comment or directory or editorial or festschrift or interview or lectures or legal cases or legislation or letter or news or newspaper article or patient education handout or popular works or congresses or consensus development conference or consensus development conference, nih or practice guideline).pt. or (exp animals/ not humans.sh.)
40 38 not 39
41 17 or 23 or 24 or 25 or 26 or 27 or 28
42 29 or 30 or 31 or 32
43 13 and 40 and 41 and 42
44 limit 43 to english language
45 limit 44 to dt=20010101-20211231

Database: Embase.com (Elsevier)
Number of Results: 313
Search Date: 27 October 2021
Limits: English-language only; human studies only (clinical trials, RCTs, prospective and retrospective studies, systematic reviews, meta-analyses, case reports, case series); publication date after January 1, 2001
Excluded: editorials, letters, comments, conference abstracts

1 'gastroesophageal reflux'/exp
2 (gastro-oesophageal* OR gastro-esophageal* OR gastrooesophageal* OR gastroesophageal*):ti,ab,kw
3 (acid NEAR/3 reflux*):ti,ab,kw
4 (GERD OR GORD):ti,ab,kw
5 GER:ti,ab,kw
6 ((oesophag* OR esophagi* OR gastr*) NEAR/3 (reflux OR acid)):ti,ab,kw
7 (heartburn OR "heart burn" OR heart-burn):ti,ab OR 'heartburn'/exp
8 (gastr* AND regurgitat*):ti,ab,kw
9 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
10 adolescence/exp OR adolescent/exp OR child/exp OR childhood disease/exp OR infant disease/exp OR (infant disease* OR childhood disease*):ti,ab,kw OR (adolescen* OR babies OR baby OR boy? OR boyfriend OR boyhood OR girlfriend OR girlhood OR child* OR girl? OR infan* OR juvenil* OR kid? OR minors OR minors* OR neonat* OR neo-nat* OR newborn* OR new-born* OR paediatric* OR peadiatric* OR pediatric* OR perinat* OR preschool* OR puber* OR pubescen* OR school* OR teen* OR toddler? OR underage? OR under-age? OR youth*):ti,ab,kw OR (pediatric* OR paediatric* OR infan* OR child* OR adolescen* OR "young adult*"):ta,jt OR (pediatric* OR paediatric* OR infan* OR child* OR adolescen* OR "young adult*"):jt
11 #9 AND #10
12 'endoscopy'/de OR 'digestive tract endoscopy'/de OR 'gastrointestinal endoscopy'/de OR 'duodenoscopy'/de OR 'esophagoscopy'/de OR 'gastroscopy'/de OR 'esophagogastroduodenoscopy'/de OR ((gastr* NEAR/2 endoscop*) OR (esophagi* NEAR/2 endoscop*) OR (oesophagi* NEAR/2 endoscop*) OR duodenoscop* OR eosophagoduodenoscop* OR eosophagogastroduodenoscop* OR esophago?gastro?duodenoscop* OR oesophago?gastro?duodenoscop* OR esophagogastro?duodenoscop* OR oesophago?gastro?duodenoscop* OR eosphagoscop* OR esophagoduodenoscop* OR esophagogastroduodenoscop* OR esophagoscop* OR gastroscop* OR oesophagoduodenoscop* OR oesophagogastroduodenoscop* OR oesophagoscop* OR (upper adj2 endoscop*)):ti,ab OR endoscop*:jt OR (((radiofrequency OR radio frequency) AND (endoscop* OR ablation OR catheter*)) OR Stretta OR ReStech):ti OR (fundoplication OR plication OR TIF OR GERDx OR "GERD x" OR GERD?x OR EsophyX OR "Esophy X" OR "Esophy?X"):ti
13 #11 AND #12
14 'stomach fundoplication'/exp
15 'natural orifice transluminal endoscopic surgery'/de

16 ("transoral incisionless fundoplication" OR "trans?oral incisionless fundo?plication" OR "TIF" OR fundoplication OR plication OR fundo?plication OR (endoscop* NEAR/3 "anti?reflux") OR GERDx OR "GERD x" OR GERD?x OR EsophyX OR "Esophy X" OR "Esophy?X"):ti,ab,kw
17 #14 OR #15 OR #16
18 ((radiofrequency OR "radio frequency") AND (endoscop* OR ablation OR catheter*)):ti,ab,kw
19 'radiofrequency ablation'/exp
20 (gastr* AND ablation):ti,ab,kw
21 (RTAF OR RFA):ti,ab,kw
22 (Stretta OR ReStech):ti,ab,kw
23 #18 OR #19 OR #20 OR #21 OR #22
24 (('stapler'/exp OR 'surgical staple'/exp OR Stapl*:ti,ab,kw) AND (endoscop*:ti,ab,kw OR 'endoscopy'/exp)) OR (Medigus NEAR/2 Ultrasonic NEAR/2 Surgical NEAR/2 Endostapl*):ti,ab,kw OR (MUSE? NEAR/3 (endoscop* OR stapl* OR Medigus)):ti,ab,kw
25 'argon plasma coagulation'/exp OR ((argon NEAR/5 plasma NEAR/5 coagulat*) OR (argon NEAR/5 beam NEAR/5 coagulat*) OR "APC" OR "HAPC" OR "H-APC" OR "H APC" OR (hybrid AND coagulat*)):ti,ab,kw OR (thermoablati* OR "thermo ablation" OR "thermo destruc*" OR "thermal destruc*" OR "thermo coag*" OR "thermal coag*" OR electrocoagulation OR "transvenous ablati*" OR "laser coag*"):ti,ab,kw
26 ('suture'/exp OR 'suture technique'/exp OR (suture OR sutures OR suturing OR sutured):ti,ab,kw) AND (endoscop*:ti,ab,kw OR 'endoscopy'/exp)
27 'endoscopic mucosal resection'/exp OR mucosectom*:ti,ab,kw OR ((resect* OR dissect* OR "strip biops*"):ti,ab,kw AND (endoscop*:ti,ab,kw OR 'endoscopy'/exp))
28 'ligation'/exp OR (((band* AND (gastr* OR esophag* OR oesophag*)) OR (endoscop* OR band* OR rubber)) AND ligat*):ti,ab,kw
29 'proton pump inhibitor'/exp OR 'omeprazole'/exp OR ((proton NEAR/3 pump NEAR/3 inhibitor*) OR PPI OR PPIs OR omeprazole OR lansoprazole OR pantoprazole OR rabeprazole OR esomeprazole):ti,ab,kw
30 'histamine H2 receptor antagonist'/exp OR 'cimetidine'/exp OR 'famotidine'/exp OR 'nizatidine'/exp OR 'ranitidine'/exp OR ((histamine OR H2) NEAR/3 (recept* OR block* OR antagon*)):ti,ab,kw OR (cimetidine OR famotidine OR nizatidine OR ranitidine OR esomeprazole):ti,ab,kw
31 'antireflux operation'/de OR ((anti-reflux OR antireflux OR "anti reflux"):ti,ab,kw AND ('surgery'/exp OR (surgery OR surgical OR surgeries OR laparoscop*):ti,ab,kw OR surgery:lnk OR (Nissen* OR Toupet*):ti,ab,kw)) OR ((anti-reflux OR antireflux OR "anti reflux") NEAR/3 therap*):ti,ab,kw
32 'placebo'/exp OR (placebo* OR (sham AND (treatment* OR procedure*)) OR (dummy AND (treatment* OR procedure*)) OR "no intervention*" OR "non intervention*" OR nonintervention*):ti,ab,kw
33 (Clinical trial/de OR Randomized controlled trial/de OR Randomization/de OR Single blind procedure/de OR Double blind procedure/de OR Crossover procedure/de OR Placebo/de OR ("randomi?ed controlled trial*" OR "random allocation" OR "randomly allocated" OR "allocated randomly" OR (allocated NEAR/2 random) OR "single blind*" OR "double blind*" OR ((treble or triple) NEAR (blind*)) OR Placebo*):ti,ab,kw OR Prospective study/exp OR ((randomi?ed NEAR/7 trial*) OR (controlled NEAR/3 trial*) OR (clinical NEAR/2 trial*) OR ((single OR doubl* OR tripl* OR treb*) AND (blind* OR mask*))):ti,ab,kw OR ("4 arm" OR "four

arm"):ti,ab,kw) NOT (Case study/de OR Case report:ti,ab,kw OR abstract report/de OR letter/de)
34 Clinical study/de OR Case control study/de OR Family study/de OR Longitudinal study/de OR Retrospective study/de OR (Prospective study/de NOT Randomized controlled trials/de) OR Cohort analysis/de OR (Cohort NEAR (study OR studies)):ti,ab,kw OR ("Case control" NEAR (study OR studies)):ti,ab,kw OR ("follow up" NEAR (study OR studies)):ti,ab,kw OR (observational NEAR (study or studies)):ti,ab,kw OR (epidemiologic* NEAR (study OR studies)):ti,ab,kw OR ("cross sectional" NEAR (study OR studies)):ti,ab,kw
35 ('Meta Analysis'/exp OR 'systematic review'/exp OR ((meta NEAR analy*) or metaanalys*):ti,ab,kw OR (systematic NEAR (review* OR overview*)):ti,ab,kw OR cancerlit:ab OR Cochrane:ab OR Embase:ab OR (psychlit OR psyclit):ab OR (psychinfo OR psycinfo):ab OR (cinahl OR cinhal):ab OR science citation index:ab OR bids:ab OR reference lists:ab OR bibliography*:ab OR hand-search*:ab OR manual search*:ab OR relevant journals:ab OR ((data extraction:ab OR selection criteria:ab) AND Review:it)) NOT (Letter:it OR Editorial:it OR (animal/de NOT (animal/de AND human/de)))
36 'case report'/exp OR 'case study'/exp OR (case NEAR/3 (report OR study OR studies)):ti,ab,kw
37 #33 OR #34 OR #35 OR #36
38 ([conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim OR [data papers]/lim OR [editorial]/lim OR [erratum]/lim OR [letter]/lim OR [note]/lim OR [review]/lim OR [short survey]/lim OR 'review'/de) OR ((rat:ti,tt OR rats:ti,tt OR mouse:ti,tt OR mice:ti,tt OR swine:ti,tt OR porcine:ti,tt OR murine:ti,tt OR sheep:ti,tt OR lambs:ti,tt OR pigs:ti,tt OR piglets:ti,tt OR rabbit:ti,tt OR rabbits:ti,tt OR cat:ti,tt OR cats:ti,tt OR dog:ti,tt OR dogs:ti,tt OR cattle:ti,tt OR bovine:ti,tt OR monkey:ti,tt OR monkeys:ti,tt OR trout:
ti,tt OR marmoset*:ti,tt) AND 'animal experiment'/de) OR ('animal experiment'/de NOT ('human experiment'/de OR 'human'/de))
39 #37 NOT #38
40 #17 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32
41 #13 AND #39 AND #40
42 #41 AND English:la
43 #42 AND [01/01/2001]/sd

Database: Cochrane Library (Wiley)
Number of Results: 30
Search Date: 27 October 2021
Limits: Publication date after January 1, 2001
Excluded: N/A

1 [mh "Gastroesophageal Reflux"]
2 (gastro-oesophageal* OR gastro-esophageal* OR gastrooesophageal$ OR gastroesophageal*):ti,ab,kw
3 (acid reflux*):ti,ab,kw
4 (GERD OR GORD):ti,ab,kw
5 GER:ti,ab,kw
6 ((oesophag* OR esophagi* OR gastr*) NEAR/3 (reflux OR acid)):ti,ab,kw
7 (heartburn OR "heart burn" OR heart-burn):ti,ab,kw OR [mh heartburn]

8 (gastr* AND regurgitat*):ti,ab,kw
9 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
10 [mh adolescent] OR [mh child] OR [mh infant] OR (infant disease* OR childhood disease*):ti,ab,kw OR (adolescen* OR babies OR baby OR boy? OR boyfriend OR boyhood OR girlfriend OR girlhood OR child* OR girl? OR infan* OR juvenil* OR kid? OR minors OR minors* OR neonat* OR neo-nat* OR newborn* OR new-born* OR paediatric* OR peadiatric* OR pediatric* OR perinat* OR preschool* OR puber* OR pubescen* OR school* OR teen* OR toddler? OR underage? OR under-age? OR youth*):ti,ab,kw
11 #9 AND #10
12 [mh "endoscopy, digestive system"] OR [mh "endoscopy, gastrointestinal"] OR [mh duodenoscopy] OR [mh esophagoscopy] OR [mh gastroscopy] OR ((gastr* NEAR/2 endoscop*) OR (esophagi* NEAR/2 endoscop*) OR (oesophagi* NEAR/2 endoscop*) OR duodenoscop* OR eosophagoduodenoscop* OR eosophagogastroduodenoscop* OR esophago?gastro?duodenoscop* OR oesophago?gastro?duodenoscop* OR esophagogastro?duodenoscop* OR oesophago?gastro?duodenoscop* OR eosphagoscop* OR esophagoduodenoscop* OR esophagogastroduodenoscop* OR esophagoscop* OR gastroscop* OR oesophagoduodenoscop* OR oesophagogastroduodenoscop* OR oesophagoscop* OR (upper NEAR/2 endoscop*)):ti,ab,kw OR (((radiofrequency OR radio frequency) AND (endoscop* OR ablation OR catheter*)) OR Stretta OR ReStech):ti OR (fundoplication OR plication OR TIF OR GERDx OR "GERD x" OR GERD?x OR EsophyX OR "Esophy X" OR "Esophy?X"):ti
13 #11 AND #12
14 [mh Fundoplication]
15 [mh ^"Natural Orifice Endoscopic Surgery"]
16 (transoral incisionless fundoplication OR trans?oral incisionless fundo?plication OR TIF OR fundoplication OR plication OR fundo?plication OR (endoscop* NEAR/3 anti?reflux) OR GERDx OR "GERD x" OR GERD?x OR EsophyX OR "Esophy X" OR "Esophy?X"):ti,ab,kw
17 #14 OR #15 OR #16
18 ((radiofrequency OR radio frequency) AND (endoscop* OR ablation OR catheter*)):ti,ab,kw
19 [mh "Radiofrequency Ablation"]
20 (gastr* AND ablation):ti,ab,kw
21 (RTAF OR RFA):ti,ab,kw
22 (Stretta OR ReStech):ti,ab,kw
23 #18 OR #19 OR #20 OR #21 OR #22
24 (([mh "Surgical Staplers"] OR Stapl*:ti,ab,kw) AND (endoscop*:ti,ab,kw OR [mh endoscopy])) OR (Medigus NEAR/2 Ultrasonic NEAR/2 Surgical NEAR/2 Endostapl*):ti,ab,kw OR (MUSE? NEAR/3 (endoscop* OR stapl* OR Medigus)):ti,ab,kw
25 [mh "Argon Plasma Coagulation"] OR ((argon NEAR/5 plasma NEAR/5 coagulat*) OR (argon NEAR/5 beam NEAR/5 coagulat*) OR APC OR HAPC OR H-APC OR "H APC" OR (hybrid AND coagulat*)):ti,ab,kw OR (thermoablati* OR "thermo ablation" OR "thermo destruc*" OR "thermal destruc*" OR "thermo coag*" OR "thermal coag*" OR electrocoagulation OR "transvenous ablati*" OR "laser coag*"):ti,ab,kw
26 ([mh sutures] OR [mh "suture techniques"] OR (suture OR sutures OR suturing OR sutured):ti,ab,kw) AND (endoscop*:ti,ab,kw OR [mh endoscopy])
27 [mh "Endoscopic Mucosal Resection"] OR mucosectom*:ti,ab,kw OR ((resect* OR dissect* OR "strip biops*"):ti,ab,kw AND (endoscop*:ti,ab,kw OR [mh endoscopy]))

28 [mh ligation] OR (((band* AND (gastr* OR esophag* OR oesophag*)) OR (endoscop* OR band* OR rubber)) AND ligat*):ti,ab,kw
29 [mh "proton pump inhibitors"] OR [mh omeprazole] OR ((proton NEAR/3 pump NEAR/3 inhibitor*) OR PPI OR PPIs OR omeprazole OR lansoprazole OR pantoprazole OR rabeprazole OR esomeprazole):ti,ab,kw
30 [mh "histamine h2 antagonists"] OR [mh cimetidine] OR [mh famotidine] OR [mh nizatidine] OR [mh ranitidine] OR ((histamine OR H2) NEAR/3 (recept* OR block* OR antagon*)):ti,ab,kw OR (cimetidine OR famotidine OR nizatidine OR ranitidine OR esomeprazole):ti,ab,kw
31 (anti-reflux OR antireflux OR "anti reflux"):ti,ab,kw
32 [mh Placebos] OR (placebo* OR (sham AND (treatment* OR procedure*)) OR (dummy AND (treatment* OR procedure*)) OR "no intervention*" OR "non intervention*" OR nonintervention*):ti,ab,kw
33 #17 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28
34 #29 OR #30 OR #31 OR #32
35 #13 AND #33 AND #34

APPENDIX 2

Quality of included randomized controlled trials for transoral incisionless fundoplication 2.0 and Stretta using Cochrane Risk of Bias tool