UEG and EAES Rapid Guideline: Update systematic review, network meta-analysis, CINeMA and GRADE assessment, and evidence-informed European recommendations on surgical management of GERD

PROTOCOL

Introduction

Background

Gastroesophageal reflux is a common condition affecting up to 26% of the European population with substantial impact on the quality of life. A proportion of these patients do not respond to lifestyle modifications and antireflux medication. Antireflux surgery is highly effective in improving typical reflux and reflux-associated symptoms.

Previous clinical practice guidelines are either not pertinent, or they have been based upon pairwise comparisons of complete and partial antireflux operations. Advanced evidence synthesis methods allow comparison of multiple interventions in the same model, allowing more precise effect estimates and facilitating the ranking of probabilities of an intervention being the most effective or least harmful. A survey of members of the European Association for Endoscopic Surgery prioritized the surgical management of gastroesophageal reflux disease (GERD) to be addressed by a practice guideline.

Objective

The objective of this rapid guideline is to provide transparently developed, reliable recommendations on the best treatment of GERD, informed by evidence from a network meta-analysis of benefits and harms.

Methods

The present protocol adheres to AGREE-S and PRISMA-P reporting standards. It will be available on the EAES website for access by healthcare professionals, and EAES members will be asked to comment on the content. Relevant comments will be considered by the steering group.

Funding

The project is funded by the European Association for Endoscopic Surgery. The funding body will not have any influence on the guideline development process.

Steering group

The steering group consists of general surgeons, members of the EAES Research Committee/Guideline Subcommittee, and experts in guideline development and evidence synthesis.

Guideline methodologist

The first author is a certified guideline methodologist, has participated in the development of more than 15 clinical practice guidelines, has experience in evidence synthesis, and will serve as a guideline methodologist in this guideline. A lead member of the AGREE Collaboration will act as external auditor and will supervise the methodology of the guideline development process.

Guideline panel and external advisors

The guideline panel will consist of three general surgeons, two gastroenterologists, an anesthetist, and a patient representative. The guideline panel's contribution will be acknowledged by authorship in the resulting journal publication of this guideline.

Guideline question

The clinical question was formulated by the steering group and thresholds for clinical importance of outcomes will be set under consideration of panel members' voting. One clinical question framework will address the use of 360°, 270°, 300°, anterior 180°, posterior 180°, anterior 120°, anterior 90° fundoplications, Hill and LINX® for the management of GERD.

Guideline development methodology

The guideline development process will adhere to GRADE, G-I-N and AGREE-S guideline development standards, and methodology parameters of rapid recommendations. The guideline panel will comment on the clinical question, will vote to set minimal important differences, and will rate the importance of outcomes on a 9-point scale as proposed by GRADE. Any additional outcomes proposed by the panel will be considered for inclusion.

An ad hoc evidence outreach team will update an EAES-sponsored recent systematic review and network meta-analysis addressing the guideline question. We will adopt the search strategy of this systematic review, supplemented by a search on LINX®, which was not addressed in the previous systematic review. Randomized controlled trials comparing any of the competing interventions or proton pump inhibitors (PPI) will be considered for inclusion. PPI treatment will serve as common comparator to enhance the indirect information in the network. Risk of bias of eligible studies will be performed de novo using RoB 2. Study selection, risk of bias assessment and data extraction will be performed independently by two reviewers and the senior author will act as an arbitrator. Statistical analyses will be performed by biostatisticians using the methodology reported below.

Assessment of the certainty of evidence will be performed using the CINeMA software and relevant methodology, however judgements on precision of effect estimates will be informed by minimal important differences set a priori by the guideline panel in line with relevant GRADE methodological considerations within a fully contectualized approach. GRADE summary of findings tables will be constructed and presented to the guideline panel in a consensus meeting. In addition, for each outcome, we will stratify interventions by certainty (moderate-to-high or low-to-very low). We will group interventions within each stratum into 3 groups according to their statistical ranking: among the best, inferior to the best/better than the worst, and among the worst. The classified rankings will be considered by panel members as complementary to the GRADE evidence tables. This process facilitates assessment of both the certainty of the evidence on each intervention along with their ranking. Draft recommendation(s) within a GRADE evidence-to-decision framework to choose from multiple interventions will be formulated, and direction/strength of recommendation(s) will be defined and refined/validated through an online anonymous Delphi process. Comments by the Delphi panel must be in accordance with the GRADE methodology to be considered. Formulation of recommendations will be informed by GRADE and AGREE-REX.

Evidence synthesis methodology

A random effects meta-analysis model will be applied as we expect some variation in the patients/ intervention/ comparator criteria among trials. Mantel-Haenszel pooled odds ratios will be calculated for binary variables and the standardized mean difference for continuous variables, with corresponding 95% confidence intervals. Relative treatment effects will be estimated using odds ratios (OR) and 95% confidence intervals (CI). The

restricted maximum likelihood method will be used to estimate heterogeneity. The restricted maximum likelihood method will be used to estimate heterogeneity assuming a common estimate for heterogeneity across the different comparisons. Differences between direct and indirect evidence for the same comparisons will be explored by comparing direct and indirect estimates and computing the inconsistency factor within each closed loop of evidence. The node-splitting approach, which compares the direct estimate for each comparison to the respective indirect one once this comparison had been removed from the network, will also be employed.

Small-study effects within each treatment comparison when compared in at least 10 studies were explored using funnel plot. Contour-enhanced funnel plots will be used in an attempt to disentangle publication bias from small-study effects. The ranking probabilities for all treatments of being at each possible rank for each intervention will be estimated using the netrank command in Stata.

In sensitivity analyses we will group 270° with Lind fundoplication and anterior 120° with anterior 90° fundoplication.

Target users

This guideline is intended to be used by general surgeons, gastroenterologists, primary care physicians, hospital administrators, policy makers, and patients. The guideline publication will contain a short abstract in plain language to be used by patients.

Publication and dissemination strategy

As a EAES Research Committee/Guideline Subcommittee project, this guideline will be submitted for publication in Surgical Endoscopy, official journal of the Association.

Feedback

The steering group will consider constructive feedback received during the conduct of the project via various routes and sources such as letters to the editor and the social media. Such feedback will be taken into account in the guideline development process or a future update of the guideline.

Monitoring, update and future steps

Use of the guideline by EAES members will be monitored through an online survey 2 years after publication. The timing of the update of the guideline will be decided by the steering group on the basis of new research data on this topic.

Discussion

Implications for practice and research

Stringent criteria defined by G-I-N, GRADE and AGREE-S will be applied to collate, appraise and analyze the available evidence. The guideline is expected to inform decision making, and guide clinical practice and health policy. Guidance will be provided on direction and implications for future research in light of identified evidence gaps.

Strengths and limitations

The strengths and limitations of rapid guidelines have been previously reported. The merits of rapid guidelines, including trustworthiness, credibility, and time efficiency have to outweigh the shortcomings, such as the narrow scope and possible missing of resources due to the rapid review process.

Research ethics

Conflicts of interest statements will be collected by all participants before and upon completion of the project. Participants with substantial conflicts will be either re-assigned functions or replaced as per G-I-N recommendations.

Conclusion

This rapid guideline will provide recommendations on the best treatment of GERD through an evidence-informed approach and an evidence-to-decision framework.