Appendix 3: Summary of the GRADE report of evidence for PICO questions on the management of patients with refractory reflux-like symptoms despite proton pump inhibitor therapy: evidence-based consensus statements

- If no comparator is mentioned, then the intervention is "continue usual care"
- **Proposed definition of rGERD**: Troublesome refractory reflux-like symptoms (mainly heartburn and regurgitation) in patients with or without an objective diagnosis of GERD, who continue to have reflux-like symptoms despite acid suppression therapy (PPI)
- Work up to exclude other reasons (ie, IHD, CD, etc.)
- Cover the LSMs in front of paper. Consider a separate systematic review on this
- Cover comparability of all PPIs at start of paper
- Addressing patient-relevant outcomes (ie, symptoms not diagnostic findings)

Diagnostic strategies

STATEMENT 1.

PICO question: Does a consultation supported by endoscopy provide greater reassurance than the consultation alone in a patient with refractory reflux-like symptoms?

Statement: In patients with refractory reflux-like symptoms, we suggest that upper gastrointestinal endoscopy should not be performed routinely in conjunction with a consultation solely for the purpose of providing patient reassurance.

GRADE: Conditional recommendation, very low quality of evidence (i.e., very low-quality evidence that consultation is reassuring [and improves health outcomes] but NO evidence that upper gastrointestinal endoscopy adds reassurance)
VOTE: strongly agree 16%; agree 74%; uncertain 0%; disagree 10%; strongly disagree 0%

Key evidence: The evidence was evaluated from two perspectives: the benefits of consultation alone to reassure patients, and the benefits of endoscopy alone.

In general, data suggest that patient satisfaction increases and health outcomes improve with a patient-centered consultation approach. A Cochrane systematic review identified 43 RCTs for a wide variety of diagnoses, that assessed interventions to promote "patient-centered" consultation approaches compared to usual care or placebo.[1] However, there were no studies specifically in patients with rGERD. These RCTs assessed a variety of outcomes from diverse specialties, although most trials were from primary care with general internal medicine, surgery, obstetrics and gynecology and oncology also represented. Seven RCTs (N=813) assessed patient

satisfaction and demonstrated an improvement in the patient-centered consultation group compared to the control group (standard mean difference [SMD], 0.35; 95% confidence interval [CI], 0.20-0.49) (Figure 1).[1] Similarly, the 7 RCTs (N=1373) that evaluated health outcomes demonstrated an improvement in the patient-centered consultation group (SMD, -0.25; 95% CI, -0.36, -0.15) (Figure 2).[1]

Figure 1. Meta-analysis of RCTs of endoscopy or control assessing patient satisfaction[1]

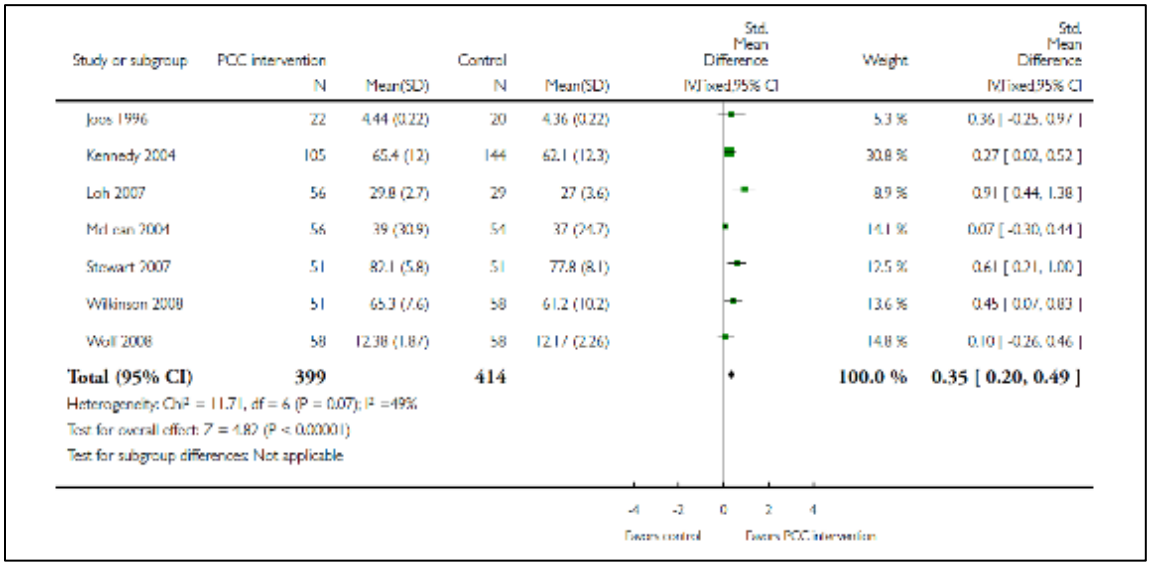
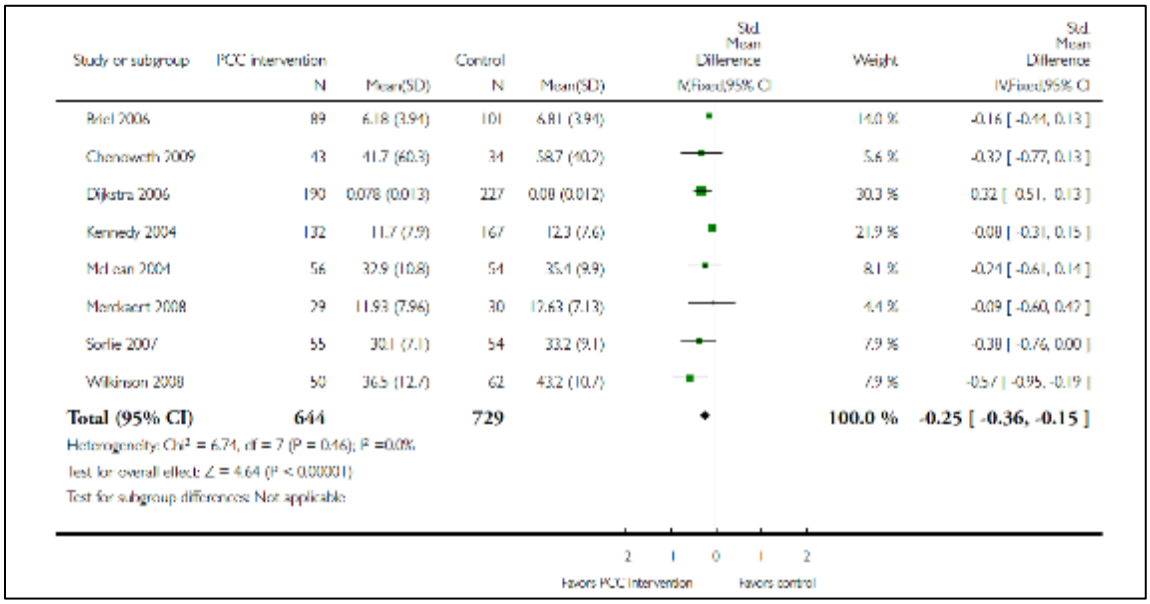


Figure 2. Meta-analysis of RCTs of endoscopy or control assessing health outcomes[1]



There was little RCT evidence on the value of endoscopy in patients with suspected GERD, and no trials in patients with rGERD. One RCT (N=612) in patients with reflux symptoms compared empiric high-dose PPI therapy or endoscopy with treatment according to endoscopic findings.[2] At the end of week 4 and week 24 week, the two management strategies were similar in terms of response to treatment and quality of life, but empiric PPI therapy was more cost-effective. Quality of life was also similar between the two groups.

Given the paucity of data the search was expanded to include patients presenting with dyspepsia. Five additional studies assessing symptomatic improvement included patients with dyspepsia. Meta-analysis of the 6 RCTs (N=2163) showed no statistically significant difference in improvement in upper gastrointestinal symptoms in the endoscopy group compared to control groups (risk ratio (RR), 0.97; 95% CI, 0.91, 1.03) (Figure 3).[2-7] In one RCT in patients with dyspepsia there was no improvement in patient satisfaction outcomes.[6] Analysis of 3 RCTs also showed no differences in general practitioner (GP) visits, although data were conflicting (Figure 4).[5, 8, 9] There was significant heterogeneity with two studies suggesting endoscopy reduced GP visits whilst one suggesting it increased GP visits. If the latter RCT was excluded there was a reduction in visits (0.8; 95% CI = 1.15 to 0.44) but conducting an endoscopy to reduce visits by <1 is not cost-effective.

Figure 3: Meta-analysis of RCTs of endoscopy or control in patients with dyspepsia or heartburn (proportion of patients without a symptomatic response)[2-7]

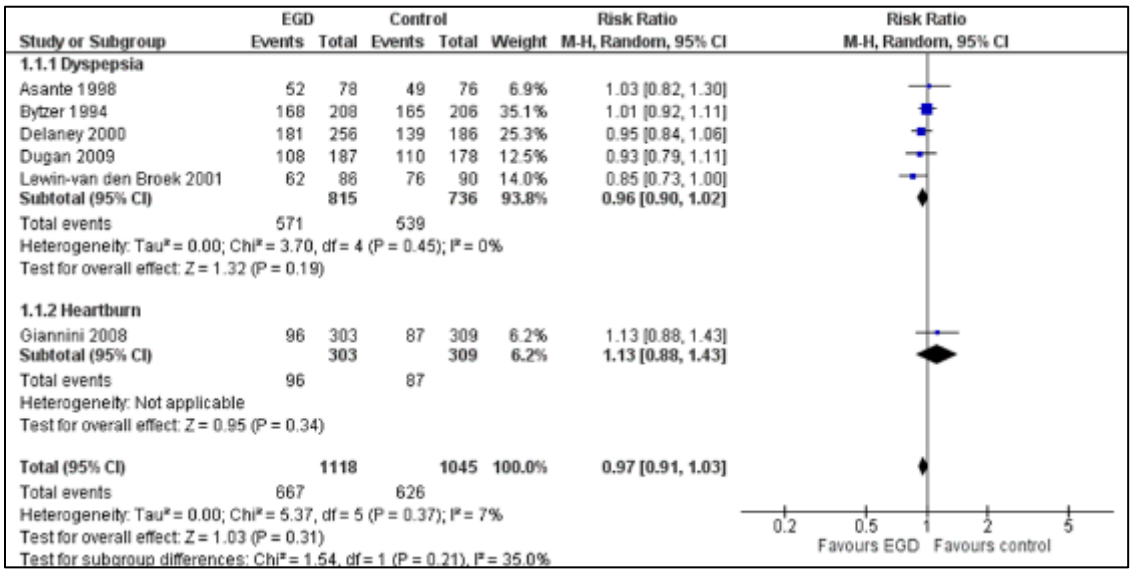
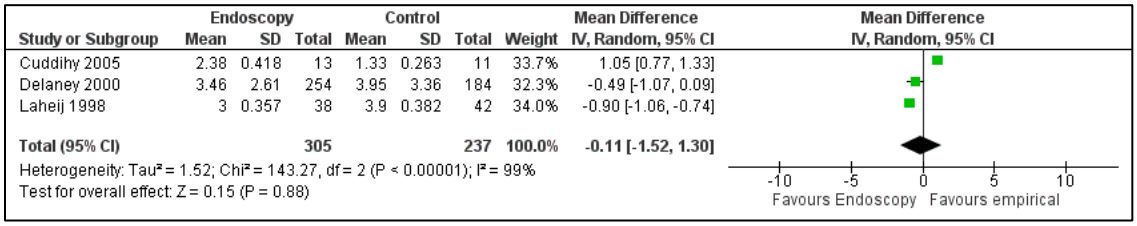


Figure 4. Meta-analysis of RCTs of endoscopy or control assessing number of GP visits[5, 8, 9]



Finally, a systematic review including data from other patient populations (non-gastrointestinal) as well as the aforementioned trials has suggested that, in general, diagnostic tests do not appear to provide reassurance to patients, and may increase anxiety (Figure 5).[10]

Figure 5. Systematic review assessing the general utility of diagnostic testing with a low pretest probability of serious disease[10]

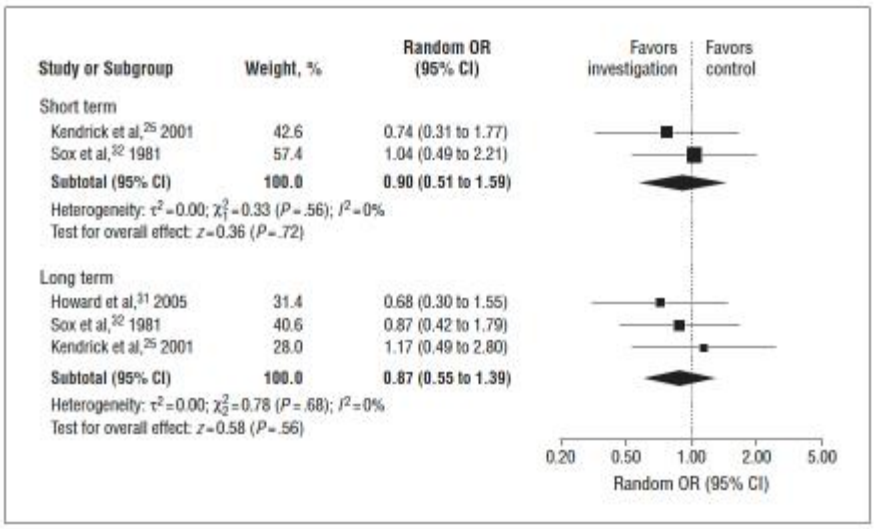


Figure 3. Effect of diagnostic testing on reduction of illness concern. The size of the data marker corresponds to the relative weight assigned in the pooled analysis using random-effects models. OR indicates odds ratio.

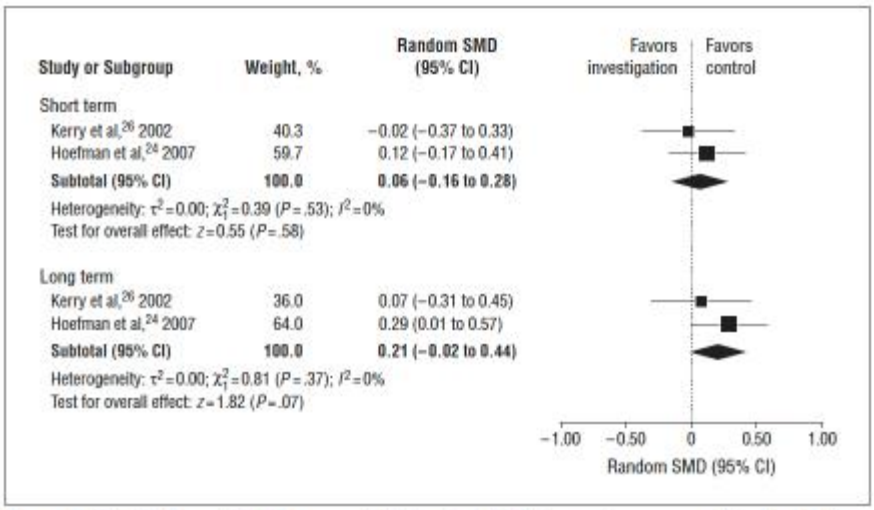


Figure 4. Effect of diagnostic testing on anxiety. The size of the data marker corresponds to the relative weight assigned in the pooled analysis using random-effects models. SMD indicates standardized mean difference.

STATEMENT 2.

PICO question: Does endoscopy in a patient with refractory reflux-like symptoms help guide therapy by identifying patients with erosive esophagitis?

Statement: In patients with refractory reflux-like symptoms, we suggest performing endoscopy to identify patients with erosive esophagitis, or other reflux-related injury.

GRADE: Conditional recommendation, low quality of evidence.
VOTE: strongly agree 21%; agree 68%; uncertain 10%; disagree 0%; strongly disagree 0%

Key evidence: A meta-analysis of data from 19 case series (N=3620) that provided endoscopy findings on all patients presenting with rGERD, demonstrated a 14% (95% CI, 10, 19%) prevalence of esophagitis at endoscopy (Figure 6).[11-29] There was a high degree of heterogeneity between studies (I^2 = 93%; 95% CI = 91 to 95%) with rates ranging from 0.6% to 47%. There was funnel plot asymmetry with smaller studies showing a greater proportion of esophagitis (Egger's bias test – $p<0.0001$) so the proportion with esophagitis is likely to be overestimated (Figure 7).

Figure 6. Meta-analysis of proportion of rGERD patients with esophagitis[11-29]

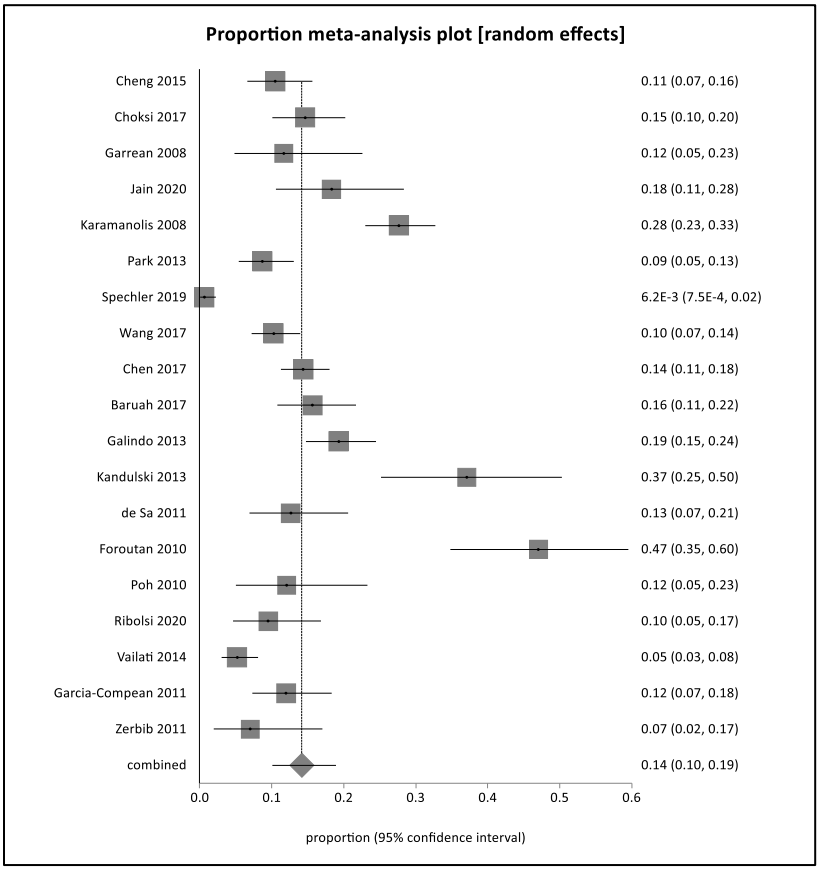


Figure 7. Funnel plot of studies reporting on esophagitis in rGERD[11-29]

Most studies did not record the Los Angeles (LA) classification of esophagitis, but in the 4 studies that did (N=842), 10% (95% CI, 4-18%) of cases were LA grade C or D (Figure 8).[12, 15, 20, 26] In the 5 studies that reported the prevalence of Barrett's esophagus, the overall rate in rGERD patients was 5% (95% CI, 4-7%) with no heterogeneity between studies (I^2 = 0%; 95% CI = 0 to 64%) (Figure 9).[13, 15, 21, 28, 29]

Figure 8. Meta-analysis of proportion of esophagitis cases that are LA grade C or D[12, 15, 20, 26]

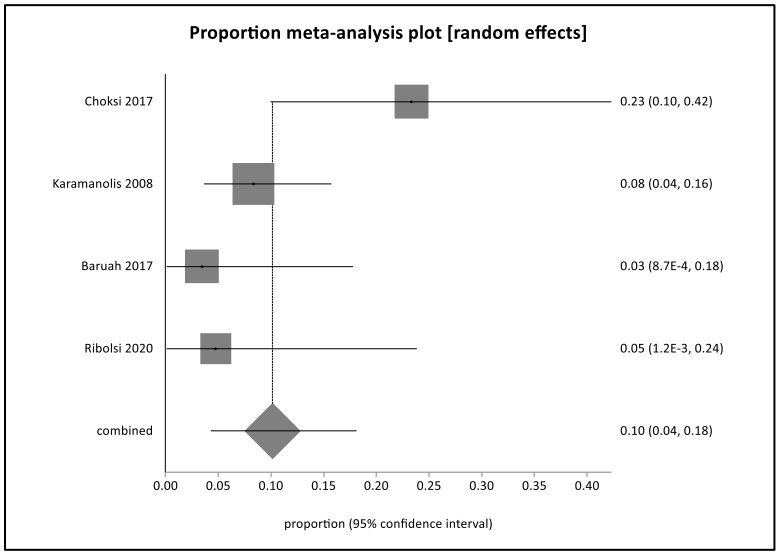
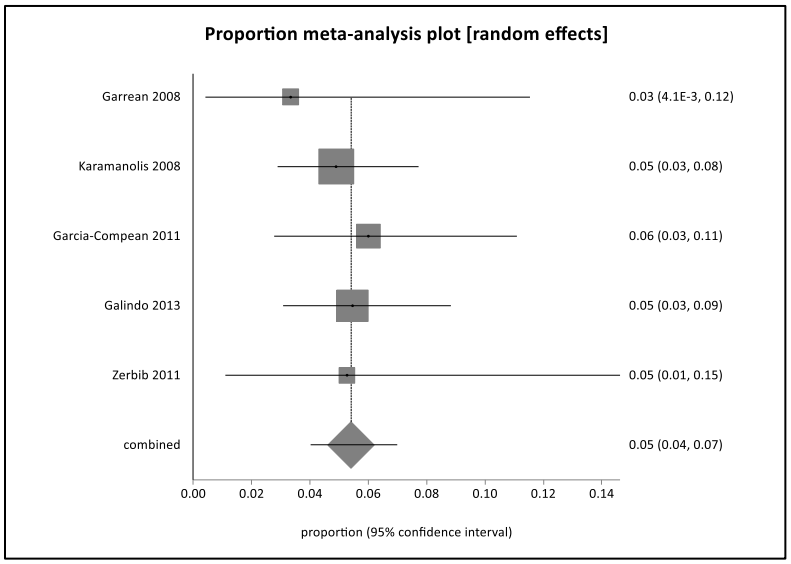


Figure 9. Meta-analysis of proportion of rGERD patients with Barrett's esophagus[13, 15, 21, 28, 29]



Only one study reported on the length of Barrett's esophagus detected and, in this study, all three cases were short segment Barrett's.[29]

NO CONSENSUS STATEMENT A.

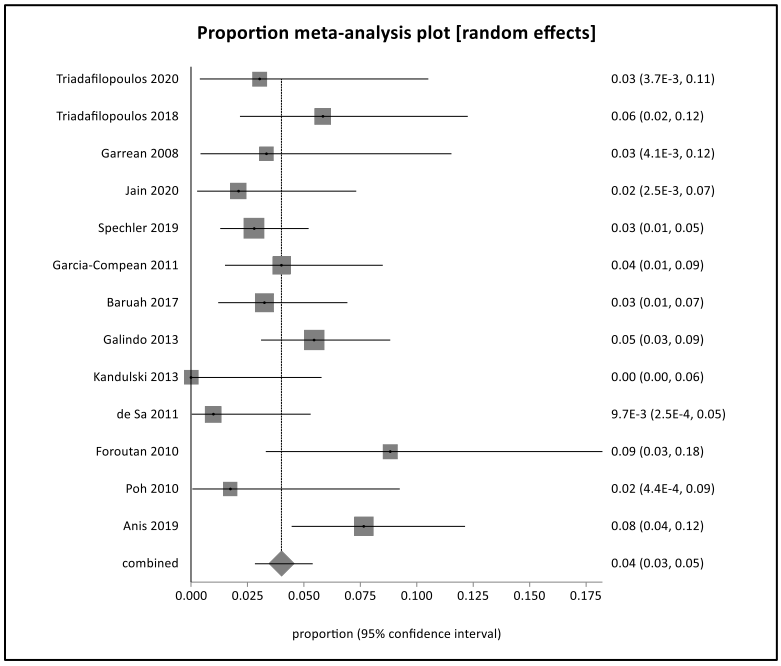
PICO question: Does endoscopy with esophageal biopsy in patients with refractory reflux-like symptoms help guide therapy by identifying patients with eosinophilic esophagitis?

No consensus A: In patients with refractory reflux-like symptoms undergoing endoscopy, the consensus group does not make a recommendation (for or against) addition of esophageal biopsy compared to endoscopy alone to identify patients with non-reflux-related pathology.

GRADE: NO recommendation, low quality of evidence.
VOTE (N=14): strongly agree 0%; agree 57%; uncertain 21%; disagree 21%; strongly disagree 0%

Key evidence: In a meta-analysis of 13 case series including 1759 patients with rGERD who underwent endoscopy and esophageal biopsy, EoE was identified in 4% (95% CI, 3 to 5%) of patients (range 0% to 9%) with moderate heterogeneity between studies (I^2 = 44%; 95% CI = 0 to 70%) and no evidence of funnel plot asymmetry (Egger's bias test p = 0.18) (Figure 10).[13, 14, 17, 20-25, 28, 30-32] Similarly, a more recent study (2021) found a prevalence of EoE of 4.7%.[33]

Figure 10. Meta-analysis of proportion of rGERD patients with EoE [13, 14, 17, 20-25, 28, 30-32]



STATEMENT 3.

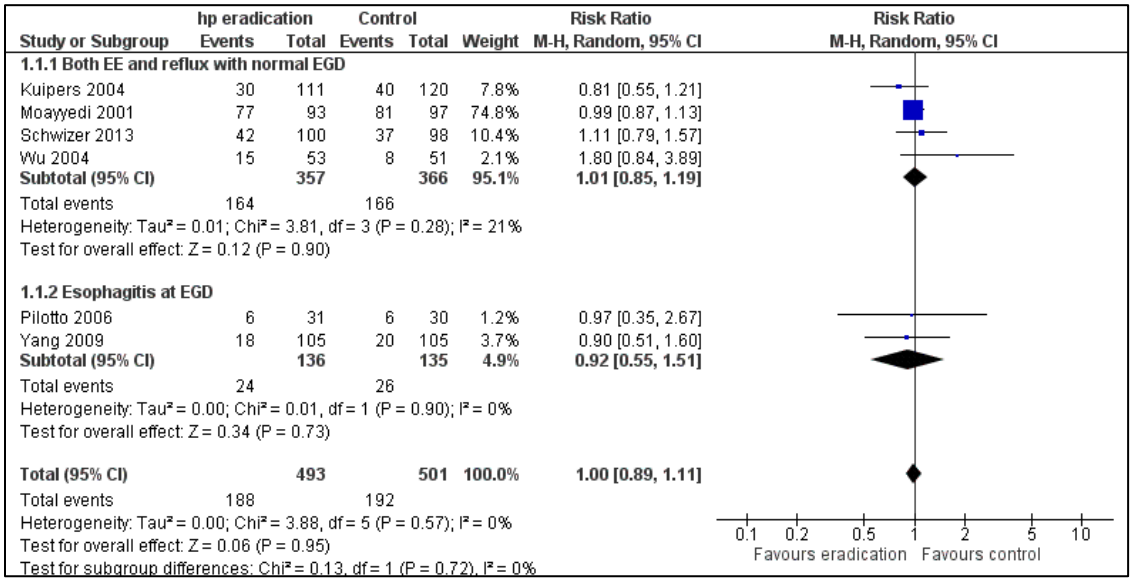
PICO question: Does treatment of confirmed H. pylori in a patient with refractory reflux-like symptoms lead to a greater proportion of patients reporting symptom relief than continued PPI (GERD) therapy?

Statement: In patients with refractory reflux-like symptoms, we recommend against treatment of confirmed H. pylori infection <u>solely</u> for the purpose of improving reflux symptoms.

GRADE: Strong recommendation, moderate quality of evidence
VOTE: strongly agree 37%; agree 57%; uncertain 0%; disagree 5%; strongly disagree 0%

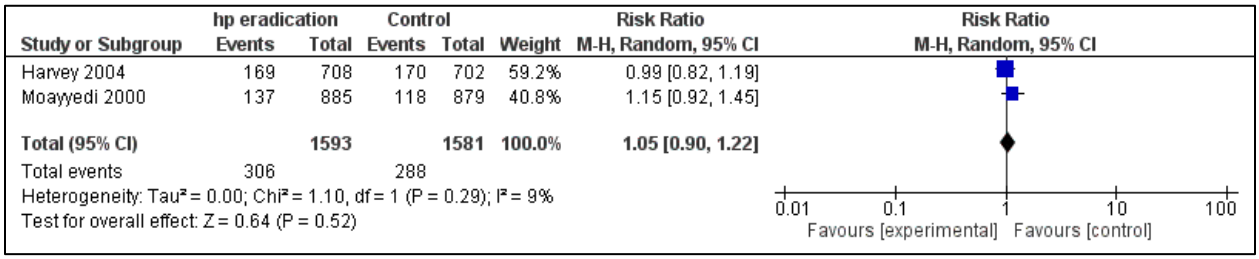
Key evidence: No RCTs evaluating *H. pylori* eradication in rGERD patients were found, however there were 6 RCTs (N=994) in GERD patients on PPI therapy, 4 of which evaluated either reflux symptoms or endoscopic esophagitis as an outcome and 2 that evaluated esophagitis as an outcome. Overall there was no impact on recurrence of GERD assessed as reflux symptoms or endoscopic esophagitis (RR, 1.00; 95% CI, 0.89, 1.11) with no heterogeneity between trials (I^2 = 0%) (Figure 11).[34-39] Two RCTs discontinued PPI therapy and followed patients for relapse,[35, 36] while the others continued PPI therapy.

Figure 11. RCTs of H. pylori eradication in patients with GERD[34-39]



To obtain more information on the impact of *H. pylori* eradication on GERD symptoms, we identified 2 population-based RCTs in adults with GERD (N=3174) not on PPI therapy, and found *H. pylori* eradication had no impact on reflux symptoms (RR, 1.05; 95% CI, 0.90, 1.22); there was no heterogeneity between trials (I^2 = 0%) (Figure 12).[40, 41]

Figure 12. RCTs of H. pylori eradication in general populations with GERD as an outcome[40, 41]



STATEMENT 4.

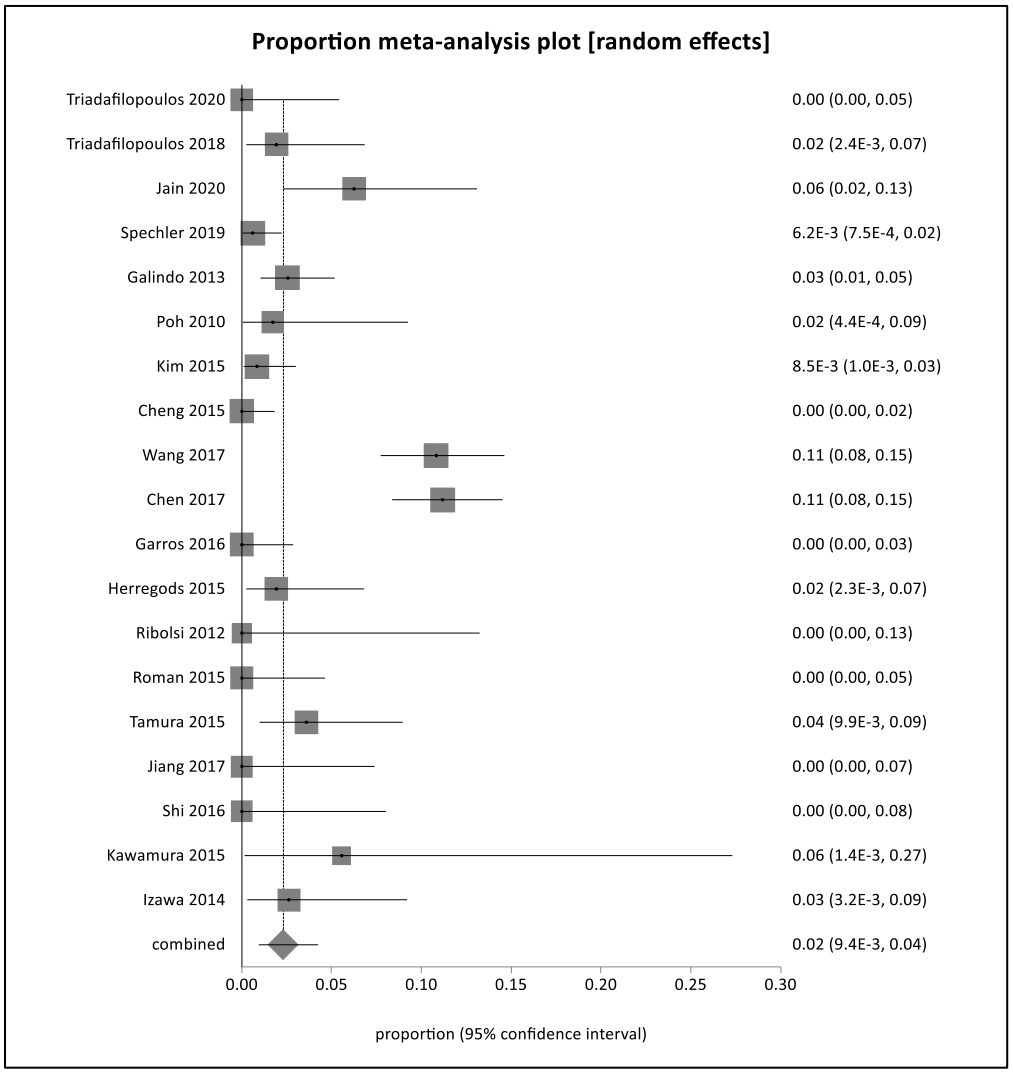
PICO question: Does esophageal manometry in a patient with refractory reflux-like symptoms identify diagnoses that guide future therapy?

Statement: In patients with refractory reflux-like symptoms, we suggest esophageal manometry to identify other causes for the symptoms.

GRADE: Conditional recommendation, very low quality of evidence
VOTE: strongly agree 32%; agree 63%; uncertain 0%; disagree 5%; strongly disagree 0%

Key evidence: Motility findings on manometry were reported in 19 case series (N=2769) in rGERD patients.[11, 14, 17-19, 21, 25, 30, 31, 42-51] The overall proportion of achalasia in patients with refractory GERD symptoms was 2% (95% CI, 0.9%, 4%) (Figure 13). There was a high degree of heterogeneity between studies (I^2 = 87%; 95% CI = 82 to 90.5%) with rates ranging from 0 to 11%. The test for funnel plot asymmetry was significant (Egger's bias test p=0.04) although this was not visually apparent on the funnel plot. The highest proportion was Chen and Wang (11%) and the lowest was Garros, Jiang, and Shi (no cases).[18, 19, 43, 48, 49]

Figure 13. Meta-analysis of proportion of rGERD patients with achalasia[11, 14, 17-19, 21, 25, 30, 31, 42-51]



STATEMENT 5.

PICO question: Does esophageal pH testing on PPI therapy in a patient with refractory reflux-like symptoms lead to more diagnoses that guide future therapy than esophageal pH testing off PPI therapy?

Statement: In patients with refractory reflux-like symptoms we suggest that esophageal pH testing should be performed off PPI therapy to determine whether the patient has excess acid gastroesophageal reflux as a cause for symptoms.

GRADE: Conditional recommendation, very low quality of evidence
VOTE: strongly agree 37%; agree 47%; uncertain 10%; disagree 0%; strongly disagree 5%

Key evidence: Nine studies (N=1155), published since 2000, reported esophageal pH findings in patients with refractory reflux-like symptoms; four (N=658) in patients on PPI therapy,[15, 52-54] and five (N=497) in patients off PPI therapy.[31, 55-58] The pooled proportion of patients that had abnormal acid reflux on PPI therapy was 28% (95% CI, 22%, 34%) with marked heterogeneity (I^2 = 60%; 95% CI = 0 to 84.5%) between studies (Figure 14).[15, 52-54] Whereas, the pooled proportion of patients who had abnormal acid reflux off PPI therapy was 43% (95% CI, 26%, 62%), also with marked heterogeneity (I^2 = 93%; 95% CI = 87 to 95.5%) between studies (Figure 15).[31, 55-58] Therefore, there was more acid related reflux diagnosed in patients off PPI therapy although it could be argued that some of these diagnoses were not relevant to the patient given that they continued to have symptoms on PPI therapy.

In contrast, functional heartburn was diagnosed in 63% (95% CI, 34%, 88%) of patients on PPI therapy although only two studies provided these data (Figure 16);[52, 53] and in 41% (95% CI, 29%, 53%) of those off PPI therapy with major heterogeneity (I^2 = 85%; 95% CI = 61 to 92%) between studies (Figure 17).[31, 55-58]

Figure 14. Meta-analysis of proportion of patients with acid related reflux symptoms ON PPI[15, 52-54]

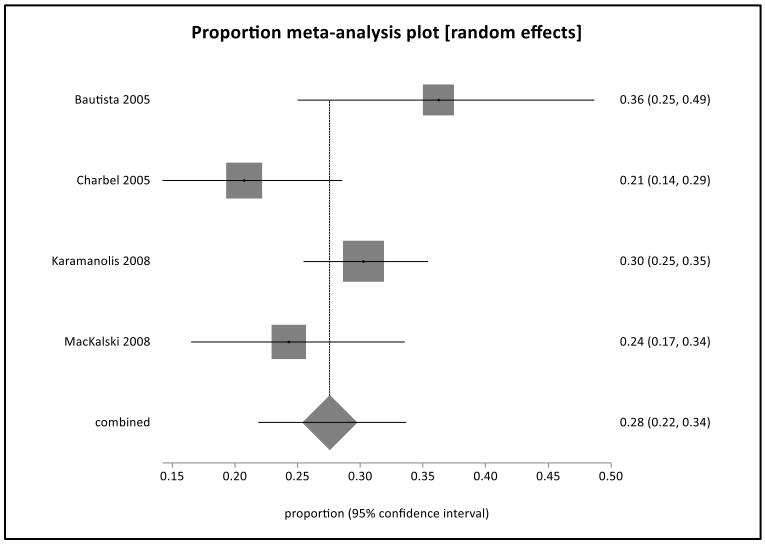


Figure 15. Meta-analysis of proportion of patients with acid related reflux symptoms OFF PPI [31, 55-58]

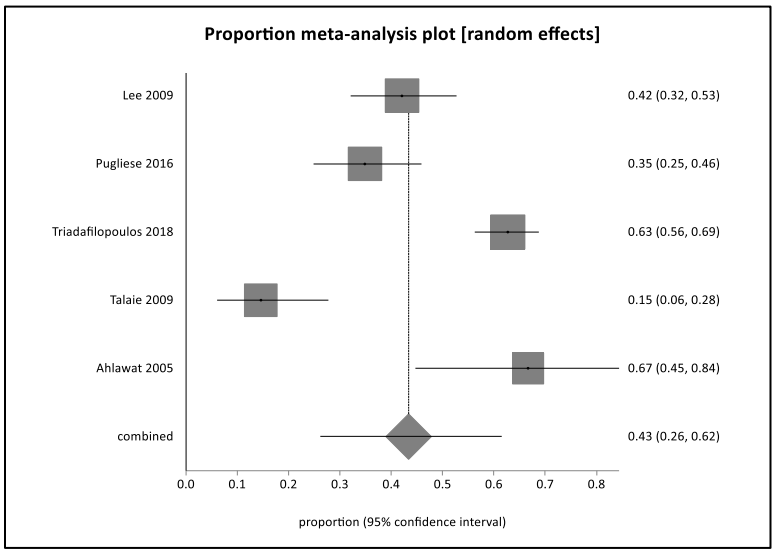


Figure 16. Meta-analysis of proportion of patients with functional heartburn ON PPI [52, 53]

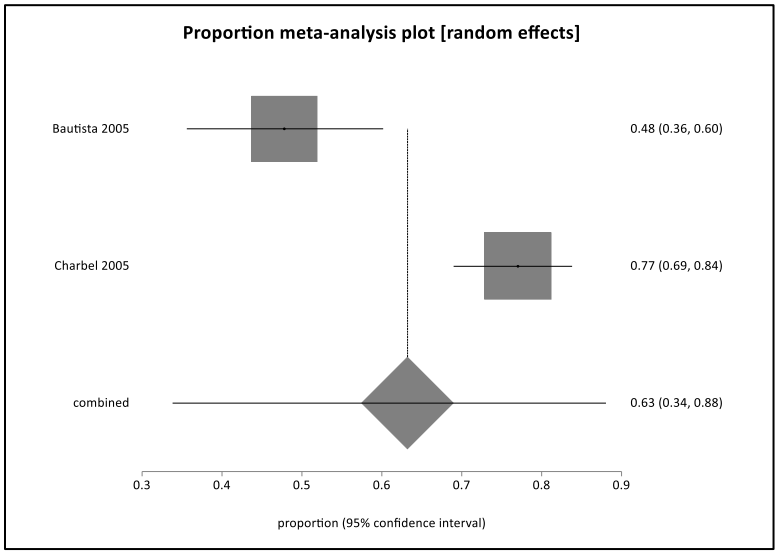
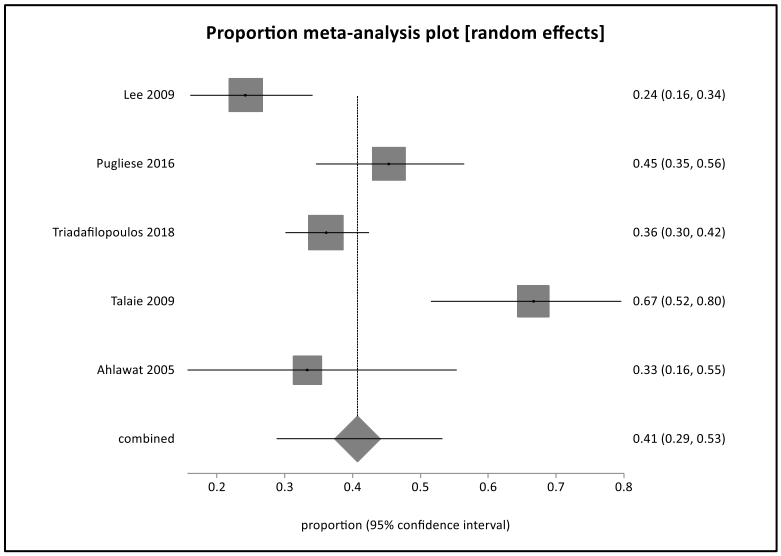


Figure 17. Meta-analysis of proportion of patients with functional heartburn OFF PPI[31, 55-58]



STATEMENT 6.

PICO question: Does esophageal pH-impedance testing on PPI therapy in a patient with refractory reflux-like symptoms lead to more diagnoses that guide future therapy than esophageal pH-impedance testing off PPI therapy?

Statement: In patients with refractory reflux-like symptoms we suggest esophageal pH-impedance testing off PPI therapy rather than esophageal pH-impedance testing on PPI therapy to determine whether the patient has excess acid gastroesophageal reflux as a cause for symptoms.

GRADE: Conditional recommendation, very low quality of evidence.
VOTE: strongly agree 32%; agree 53%; uncertain 10%; disagree 5%; strongly disagree 0%

Key evidence: There were 31 studies (N=3724) published since 2000 that reported esophageal pH-impedance findings in patients with refractory reflux-like symptoms; 16 (N=1209) in patients on PPI therapy,[43, 46, 47, 59-71] and 21 (N=2515) in patients off PPI therapy.[11, 14, 19, 21, 22, 26, 29, 43-45, 48, 49, 56, 60, 62, 63, 65, 67, 72-74] The pooled proportion of patients that had abnormal acid reflux on PPI therapy was 18% (95% CI, 13%, 24%) with marked heterogeneity (I^2 = 83%; 95% CI = 73 to 88%) between studies (Figure 18);[43, 46, 47, 59-71] The pooled proportion of patients that had abnormal acid reflux off PPI therapy was 32% (95% C, 24%, 41%) with marked heterogeneity (I^2 = 95%; 95% CI = 94 to 96%) between studies (Figure 19).[11, 14, 19, 21, 22, 26, 29, 43-45, 48, 49, 56, 60, 62, 63, 65, 67, 72-74] Therefore, there was more acid related reflux diagnosed with patients off PPI therapy although, as with pH studies, it could be argued that some of these diagnoses were not relevant to the patient given that they continued to have symptoms on PPI therapy.

In contrast, functional heartburn was diagnosed in 45% (95% CI, 39%, 52%) of patients on PPI therapy with major heterogeneity (I^2 = 80%; 95% CI = 67 to 86%) between studies (Figure 20);[43, 46, 47, 59-71] and 37% (95% CI, 29%, 46%) of patients off PPI therapy with major heterogeneity (I^2 = 94%; 95% CI = 93 to 95%) between studies (Figure 21).[11, 14, 19, 21, 22, 26, 29, 43-45, 48, 49, 56, 60, 62, 63, 65, 67, 72-74]

Figure 18. Meta-analysis of proportion of patients with acid related reflux symptoms ON PPI[43, 46, 47, 59-71]

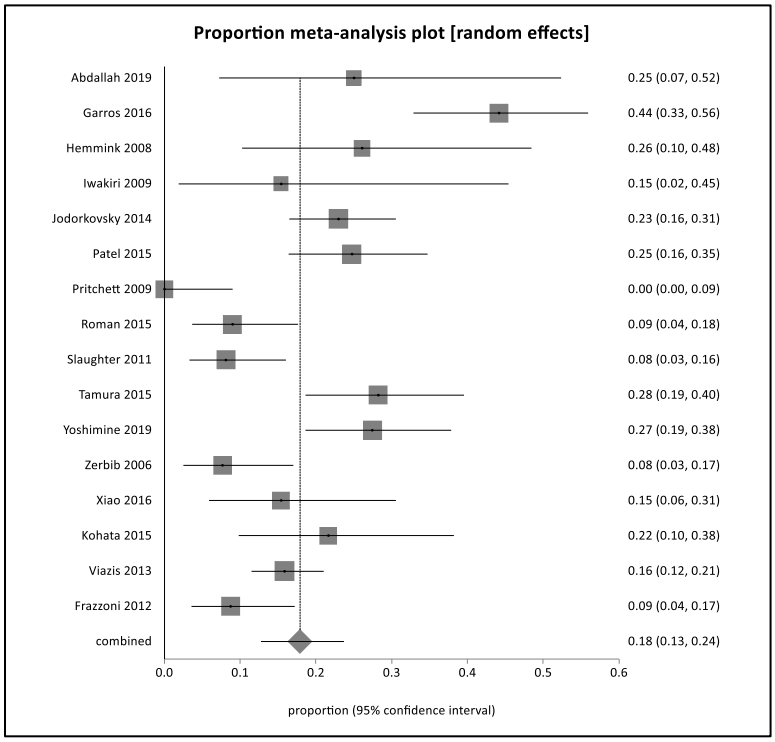


Figure 19. Meta-analysis of proportion of patients with acid related reflux symptoms OFF PPI[11, 14, 19, 21, 22, 26, 29, 43-45, 48, 49, 56, 60, 62, 63, 65, 67, 72-74]

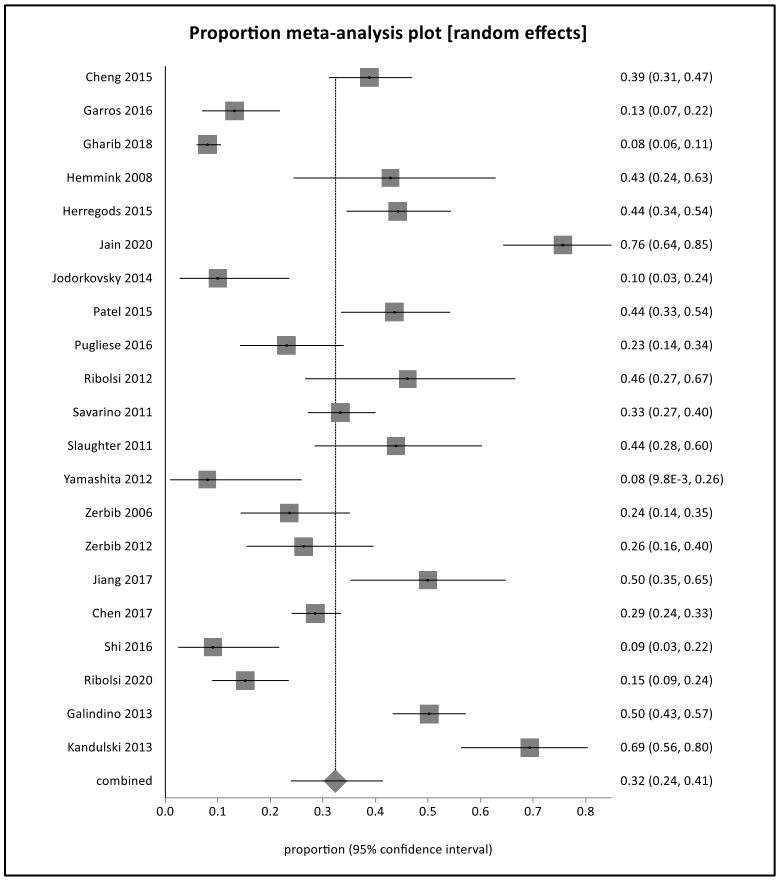


Figure 20. Meta-analysis of proportion of patients with functional heartburn ON PPI[43, 46, 47, 59-71]

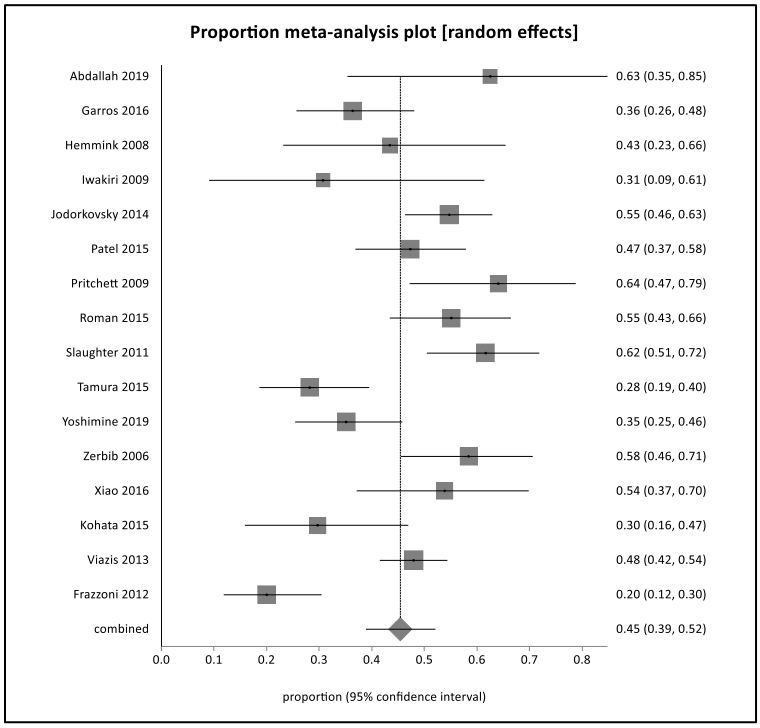
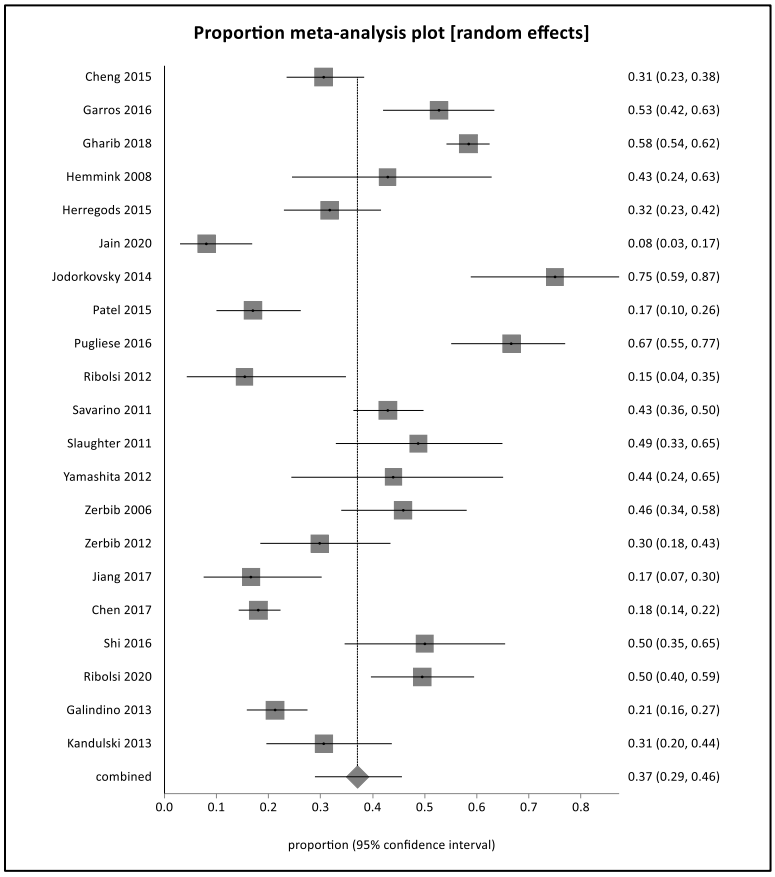


Figure 21. Meta-analysis of proportion of patients with functional heartburn OFF PPI[11, 14, 19, 21, 22, 26, 29, 43-45, 48, 49, 56, 60, 62, 63, 65, 67, 72-74]



STATEMENT 7.

PICO question: Does esophageal <u>pH-impedance</u> testing <u>on</u> PPI therapy in a patient with refractory reflux-like symptoms lead to more diagnoses that guide future therapy than esophageal <u>pH</u> testing <u>on</u> PPI therapy?

Statement: In patients with refractory reflux-like symptoms for whom testing is performed on PPI therapy, we suggest esophageal <u>pH-impedance</u> rather than esophageal <u>pH testing</u> to identify reflux as a cause for symptoms.

GRADE: Conditional recommendation, very low quality of evidence
VOTE: strongly agree 42%; agree 53%; uncertain 0%; disagree 5%; strongly disagree 0%

Key evidence: Since studies directly comparing diagnostic modalities in patients with refractory reflux-like symptoms were not found, data from the studies used in Statements 5 and 6 were used to make indirect comparisons. In the on-PPI studies, acid reflux-related symptoms were diagnosed in 28% (95% CI, 22%, 34%) of patients with pH-testing (4 studies; N=658),[15, 52-54] and in 18% (95% CI, 13%, 24%) of patients with pH-impedance studies (16 studies; N=1209).[43, 46, 47, 59-71] There was marked heterogeneity between studies for both pH-testing (I^2 = 60%; 95% CI = 0 to 84.5%) (Figure 22) and pH-impedance (I^2 = 83%; 95% CI = 73 to 88%) (Figure 23).

Figure 22. Meta-analysis of proportion of patients with acid related reflux symptoms ON PPI with pH testing[15, 52-54]

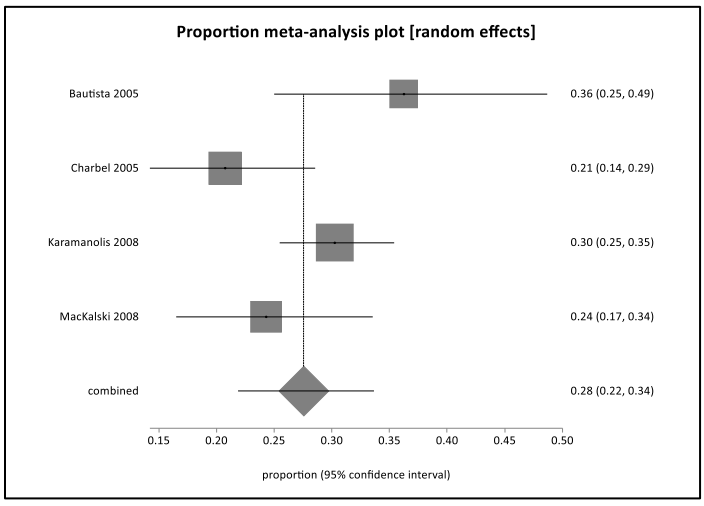
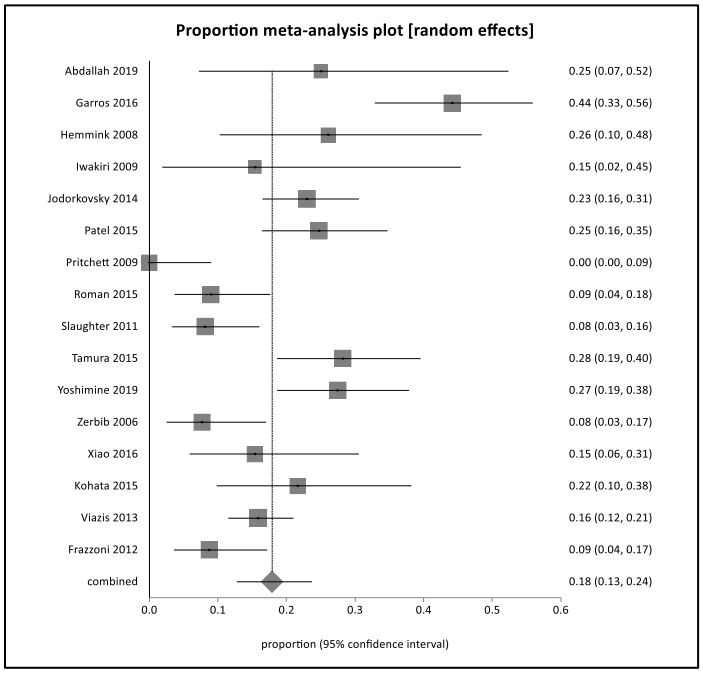


Figure 23. Meta-analysis of proportion of patients with acid related reflux symptoms ON PPI with pH impedance testing[43, 46, 47, 59-71]



There was a statistically significantly higher proportion of patients diagnosed with acid reflux using pH-testing versus pH-impedance (Cochrane Q, p = 0.016) although these studies are in different populations. Similarly, in the on-PPI studies, functional heartburn was diagnosed in 63% (95% CI, 34%, 88%) of patients with pH-testing (2 studies) (Figure 24);[52, 53] and in 45% (95% CI, 39%, 52%) of patients with pH-impedance (16 studies) with major heterogeneity (I^2 = 80%; 95% CI = 67 to 86%) between studies (Figure 25).[43, 46, 47, 59-71] The proportions of patients diagnosed with functional heartburn with the two modalities was not significantly different (Cochrane Q, p=0.21).

Figure 24. Meta-analysis of proportion of patients with functional heartburn ON PPI using pH studies[52, 53]

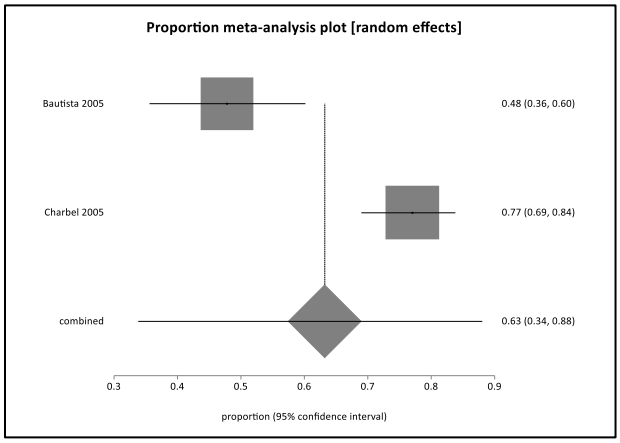
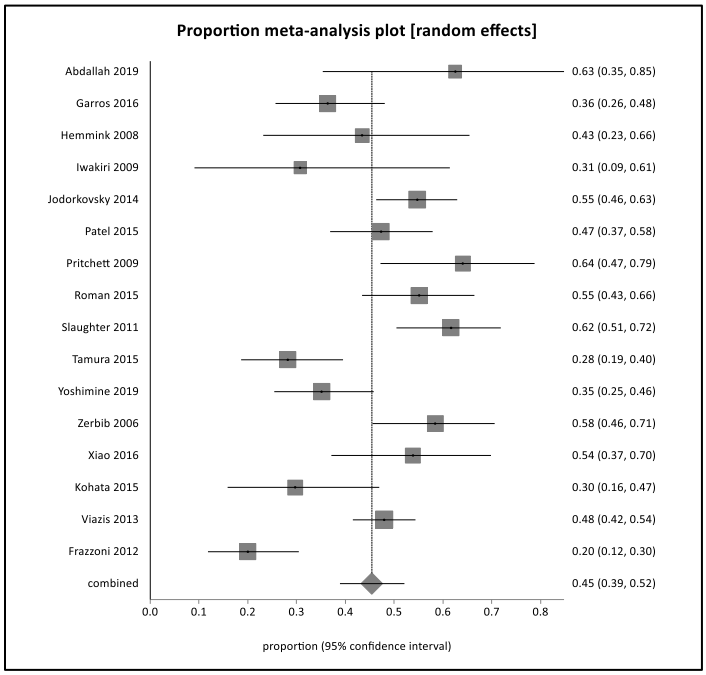


Figure 25. Meta-analysis of proportion of patients with functional heartburn ON PPI using impedance-pH studies[43, 46, 47, 59-71]



However, pH-impedance can also be used to diagnose non-acid reflux. In the 12 studies (N=765) performing pH-impedance that reported these data, 28% (95% CI, 21%, 35%) of patients had non-acid reflux as the likely cause of symptoms, with major heterogeneity between studies (I^2 = 76%; 95% CI = 53 to 85%) (Figure 26).[43, 47, 50, 61-65, 67-69, 71] There was also funnel

plot asymmetry (Eggers test p =0.02) with larger studies reporting a lower proportion of non-acid reflux so the 28% figure may be an overestimate (Figure 27).

Figure 26. Non-acid reflux on impedance studies in patients with resistant reflux like symptoms[43, 47, 50, 61-65, 67-69, 71]

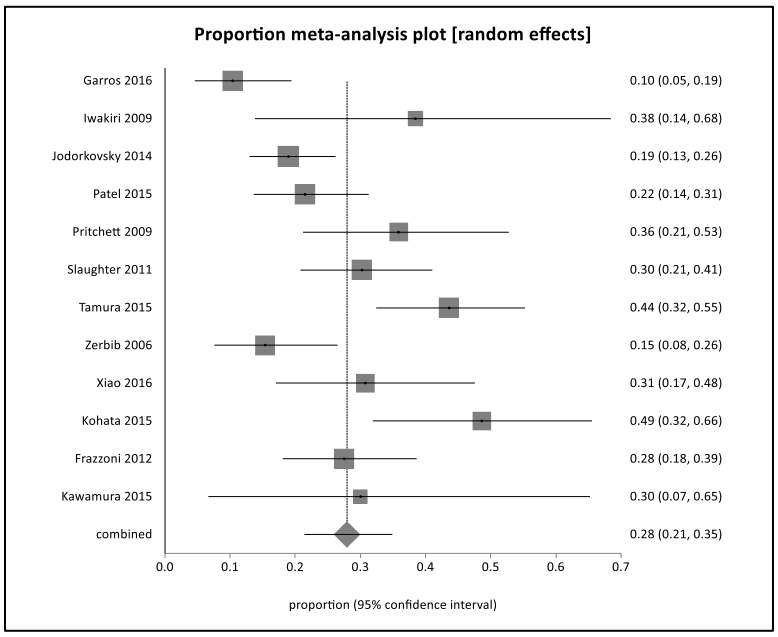
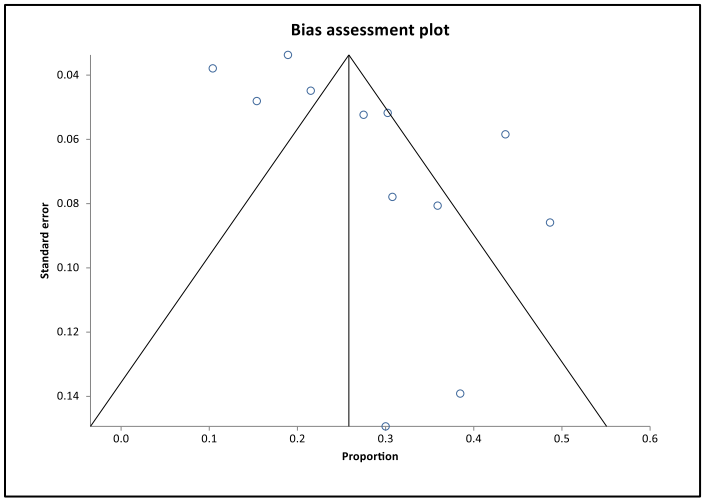


Figure 27. Funnel plot suggesting publication bias or other small study effects in non-acid reflux on impedance studies in patients with resistant reflux like symptoms[43, 47, 50, 61-65, 67-69, 71]



NO CONSENSUS STATEMENTS B AND C.

PICO question: Does esophageal <u>pH-impedance</u> testing <u>with symptom-reflux event correlation</u> evaluation <u>on</u> PPI therapy in a patient with refractory reflux-like symptoms lead more diagnoses that guide future therapy than esophageal pH-impedance testing <u>without</u> symptom-reflux event correlation evaluation on PPI therapy?

No consensus B: In patients with refractory reflux-like symptoms undergoing pH-impedance testing on PPI therapy, the consensus group does not make a recommendation (for or against) adding reflux-symptom association compared to pH-impedance testing alone to identify reflux-related symptoms.

PICO question: Does esophageal <u>pH</u> testing <u>with symptom-reflux event correlation</u> evaluation <u>on</u> PPI therapy in a patient with refractory reflux-like symptoms lead to more diagnoses that guide future therapy than esophageal pH testing <u>without</u> symptom-reflux event correlation evaluation on PPI therapy?

No consensus C: In patients with refractory reflux-like symptoms undergoing pH-testing on PPI therapy, the consensus group does not make a recommendation (for or against) adding reflux-symptom association compared to pH-testing alone to identify reflux-related symptoms.

GRADE for both statements: NO recommendation, NO evidence for or against.
VOTE for No consensus B (N=15): strongly agree 27%; agree 33%; uncertain 13%; disagree 13%; strongly disagree 13%
VOTE for No consensus C (N=15): strongly agree 0%; agree 7%; uncertain 7%; disagree 33%; strongly disagree 53%

Key evidence: Most studies in rGERD patients undergoing pH or pH-impedance testing have included symptom event correlation, therefore no comparator group is available to inform these statements. One study (Slaughter et al. 2011), a cross-sectional study of 254 patients with poor response to PPI, comparing pH-impedance on or off PPI therapy and wireless 48 hour pH studies off therapy. While they did evaluate symptom index and symptom associated probability, Monte Carlo simulations on the results found that symptom association was highly likely to have occurred by chance unless reflux rates were ≥10% (Figure 28).[65] Given that 70% of patients had reflux rates <10% suggests that the majority of the time symptom correlation may be prone to chance findings. Despite this paper being 10 years old no subsequent study quoted these findings or gave the proportion with frequent reflux in their results.

Figure 28. Monte Carlo simulation from Slaughter et al.[65]

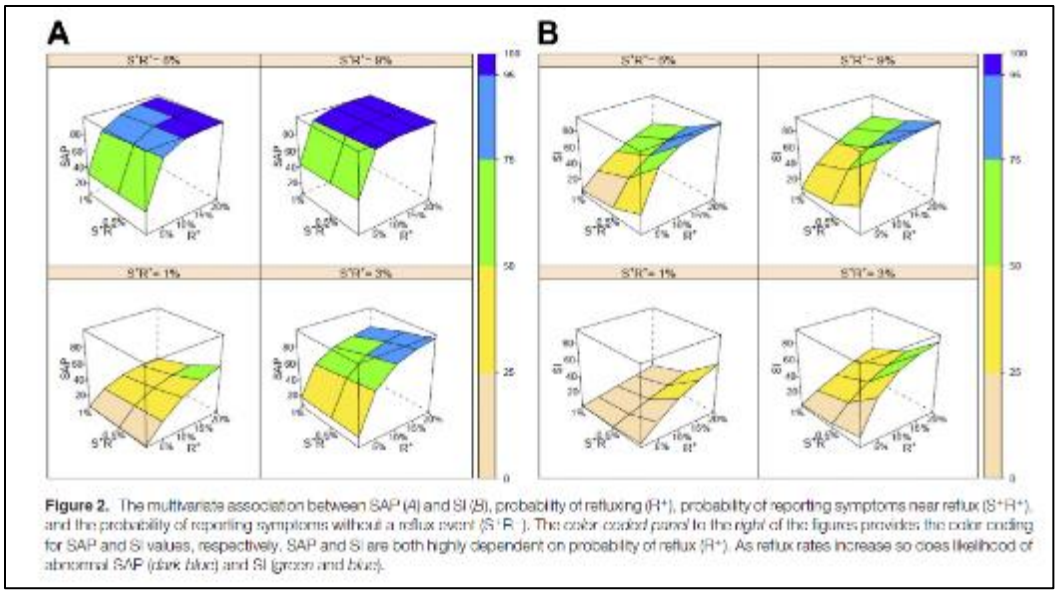


Figure 2. The multivariate association between SAP (*A*) and SI (*B*), probability of refluxing (R^+), probability of reporting symptoms near reflux (S^+R^+), and the probability of reporting symptoms without a reflux event (S^+R^-). The *color coded panel* to the *right* of the figures provides the color coding for SAP and SI values, respectively. SAP and SI are both highly dependent on probability of reflux (R^+). As reflux rates increase so does likelihood of abnormal SAP (*dark blue*) and SI (*green* and *blue*).

Pharmacological management strategies

STATEMENT 8.

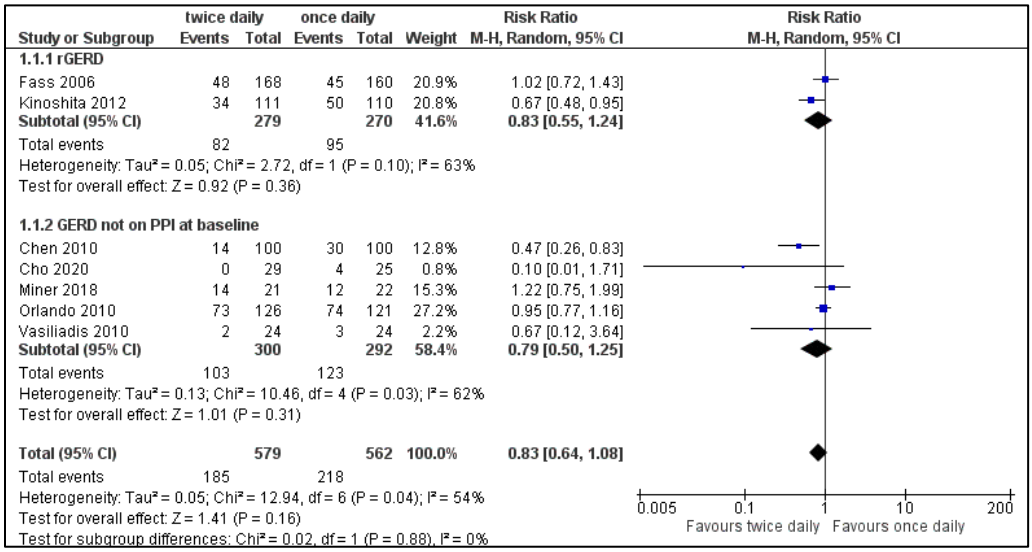
PICO question: Does <u>higher dose PPI therapy</u> in a patient with refractory reflux-like symptoms after 8 weeks of therapy with a BID PPI lead to a greater proportion of patients reporting symptom relief than continuing with BID PPI therapy?

Statement: In patients with refractory reflux-like symptoms after 8 weeks of twice-daily PPI therapy, we suggest <u>against using higher dose PPI therapy</u> compared to continuing twice-daily PPI therapy to improve symptoms.

GRADE: Conditional recommendation, very low quality of evidence.
VOTE: strongly agree 37%; agree 53%; uncertain 5%; disagree 0%; strongly disagree 5%

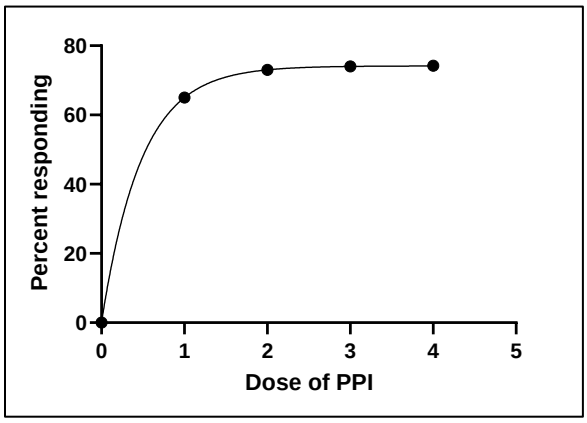
Key evidence: No studies were found that evaluated the impact on symptoms of dosing a PPI more frequently than twice-daily. To answer this PICO question, we therefore looked at the benefit of going from once-daily to twice-daily PPI and then extrapolated that if the same trajectory of therapeutic gain was applied in moving from once to twice daily was then achieved moving from twice to three times-daily, and so on. Seven RCTs (N=1141) assessed the benefit of twice-daily PPI dose compared to once-daily dosing and found no significant improvement in the risk of ongoing symptoms (RR, 0.83; 95% CI, 0.64, 1.08; p=0.16) (Figure 29).[75-81] Benefits were not significant in the rGERD studies (2 studies, N=549; RR, 0.83; 95% CI, 0.55, 1.24),[75, 76] or in patients with GERD who were not on PPI at baseline (5 studies, N=592; RR, 0.79; 95% CI, 0.5, 1.24).[77-81]

Figure 29: Meta-analysis of RCTs comparing PPI once-daily versus twice-daily in patients with rGERD or GERD (proportion of patients without a symptomatic response)[75-81]



Overall, there was an 8% (95% CI, 1%, 14%) improvement in the proportion of patients experiencing relief of symptoms. Extrapolating from a baseline response with once-daily PPI therapy of 65% in rGERD patients,[75, 76] an exponential curve that best fits the data predicts a 1% absolute benefit from moving from twice- to three-times daily and a negligible benefit of increasing to four-times daily (Figure 30). The graph was started at 0% with no treatment, however starting at 20% (to account for placebo response) did not alter the curve appreciably.

Figure 30: Exponential curve extrapolating the benefits of increasing the dosing schedule of PPI beyond twice-daily (proportion of patients <u>with</u> a symptomatic response)



NO CONSENSUS STATEMENT D.

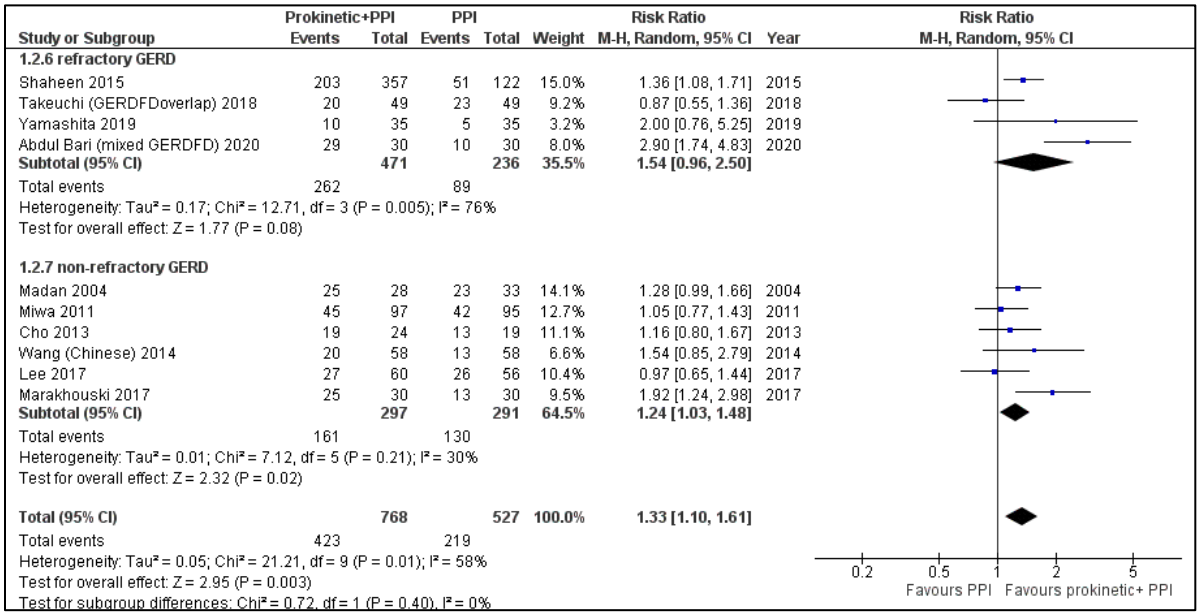
PICO question: Does the addition of a prokinetic in a patient with refractory reflux-like symptoms on BID PPI lead to a greater proportion of patients reporting symptom relief than continuing with BID PPI therapy alone?

No consensus D: In patients with refractory reflux-like symptoms after 8 weeks of twice-daily PPI therapy, the consensus group does not make a recommendation (for or against) adding a prokinetic to twice-daily PPI therapy to improve symptoms.

GRADE: NO recommendation, low quality of evidence.
VOTE (N=15): strongly agree 0%; agree 27%; uncertain 13%; disagree 47%; strongly disagree 13%

Key evidence: Meta-analysis of 4 RCTs (N=707) in patients with rGERD suggested an increases in the symptom response rate when a prokinetic was added to PPI therapy compared to PPI therapy alone, but this numerical increase was not statistically significant (RR, 1.54; 95% CI, 0.96-2.50, with major heterogeneity, I^2 = 76%) (Figure 31).[82-85] When the two trials that enrolled a mixture of patients with rGERD and resistant functional dyspepsia[83, 85] were removed the effect of combination therapy became significant (RR, 1.39; 95% CI, 1.11-1.73, with no heterogeneity, I^2 = 0%).[82, 84] However, these trials did not specify the PPI dose and it is very likely that some patients were taking once daily PPI. Another trial (which did not report dichotomous data, and was not included in the meta-analysis) compared prokinetic (domperidone 10 mg tid) plus high-dose PPI with PPI alone and found no differences between groups in overall symptom score and quality of life.[86]

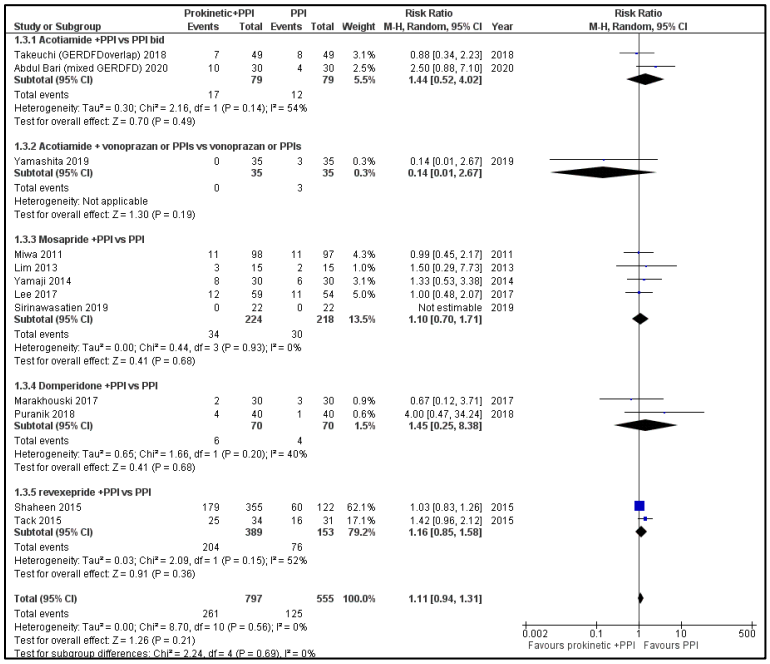
Figure 31: Meta-analysis of RCTs of prokinetic therapy added to PPI versus PPI alone in rGERD or GERD (proportion of patients without a symptomatic response)[82-85, 87-93]



Meta-analysis of 6 RCTs (N=558) in patients with GERD revealed superior results with prokinetic plus PPI compared to PPI alone (RR, 1.24; 95% CI, 1.03-1.48).[87, 88, 90-93] Finally, meta-analysis of all 10 RCTs (N=1295) demonstrated a significant effect of PPI plus prokinetic over PPI alone (RR, 1.33; 95% CI, 1.10-1.61) (Figure 31), with a number needed to treat (NNT) of 6 (95% CI, 3-20).[82-85, 87, 88, 90-93] Safety data from 12 trials demonstrated no significant increase in adverse events in the combination group compared to PPI alone.[82-85, 88, 92-97]

There was also no increase in adverse events in the prokinetic group (Figure 32).

Figure 32: Prokinetic added to a PPI adverse events[82-85, 88, 92-97]



STATEMENT 9.

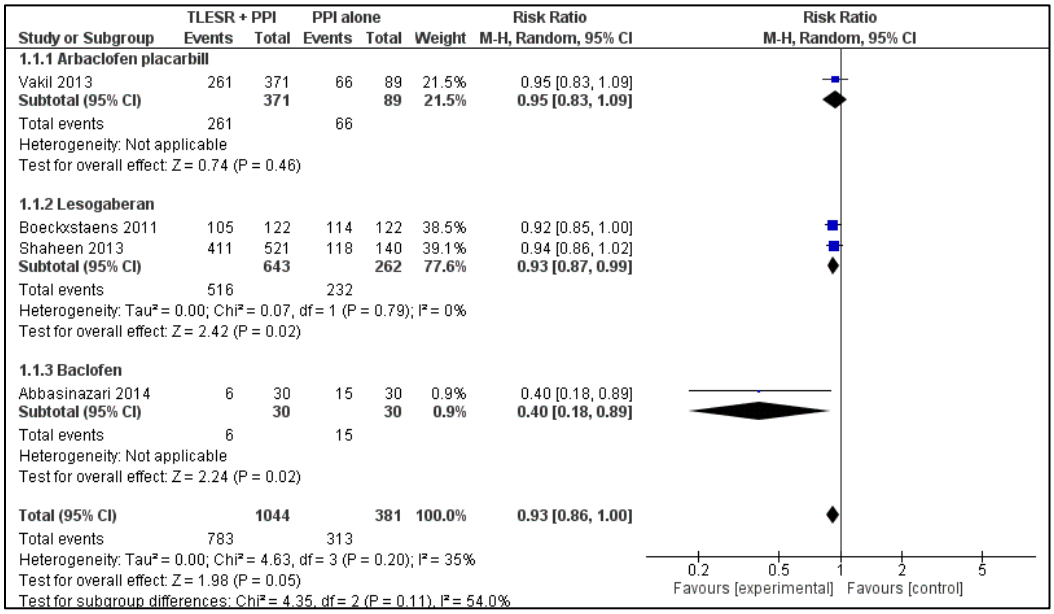
PICO question: Does the <u>addition of a TLESR inhibitor</u> in a patient with refractory reflux-like symptoms on BID PPI lead to a greater proportion of patients reporting symptom relief than continuing with BID PPI therapy alone?

Statement: In patients with refractory reflux-like symptoms after 8 weeks of twice-daily PPI therapy without objective evidence of GERD, we suggest <u>against</u> adding a TLESR inhibitor to twice-daily PPI therapy to improve symptoms.

GRADE: Conditional recommendation, low quality of evidence.
VOTE (N=13): strongly agree 31%; agree 69%; uncertain 0%; disagree 0%; strongly disagree 0%

Key evidence: Meta-analysis of 4 RCTs (N=1425) in patients with rGERD showed a marginally statistically significant (p=0.05) increase in the symptom response rate when a transient lower esophageal sphincter relaxation (TLESR) inhibitor was added to PPI therapy compared to PPI therapy alone (RR, 0.93; 95% CI, 0.86-1.00; with mild heterogeneity, I^2 = 35%) (Figure 33). Other trials that evaluated TLESR 24-hour pH or compared with placebo were excluded. The NNT was 14 (95% CI, 8 to 100).[98-101]

Figure 33: Meta-analysis of RCTs of TLESR inhibitor therapy added to PPI versus PPI alone in rGERD (proportion of patients without a symptomatic response)[98-101]



STATEMENT 10.

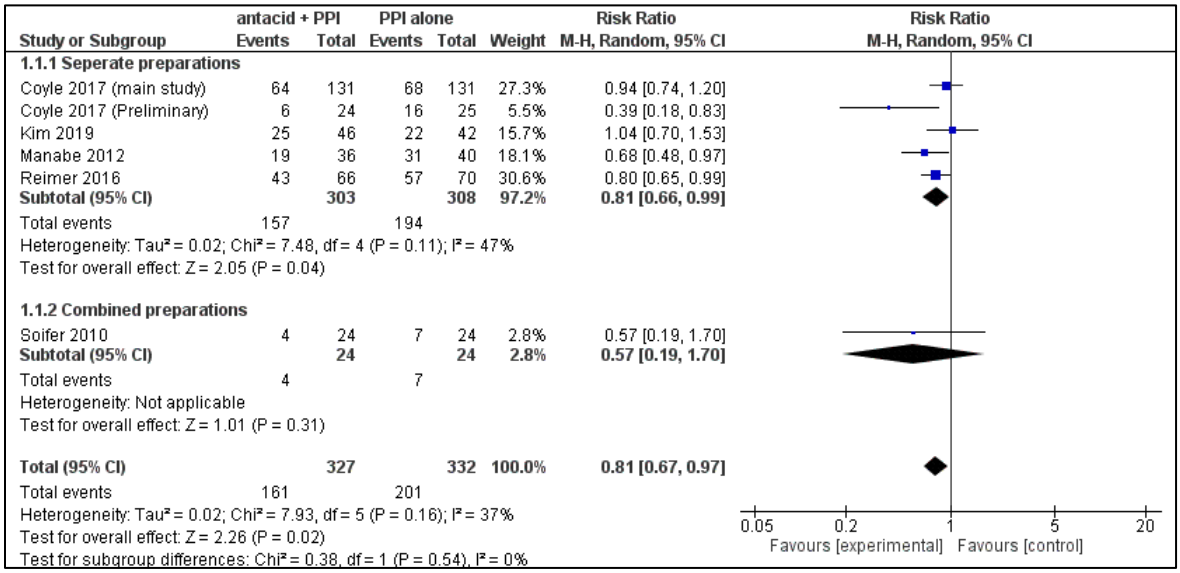
PICO question: Does the <u>addition of an alginate and/or antacid</u> in a patient with refractory reflux-like symptoms on BID PPI lead to a greater proportion of patients reporting symptom relief than continuing with BID PPI therapy alone?

Statement: In patients with refractory reflux-like symptoms after 8 weeks of twice-daily PPI therapy, we suggest adding an <u>alginate and/or antacid</u> to twice-daily PPI therapy to improve symptoms.

GRADE: Conditional recommendation, low quality of evidence.
VOTE: strongly agree 21%; agree 74%; uncertain 0%; disagree 5%; strongly disagree 0%

Key evidence: In a meta-analysis of 6 RCTs (N=659) in patients with GERD (5 studies[102-105]) or rGERD (1 study[106]) the addition of antacid/alginate to PPI therapy did improve reflux symptoms over PPI alone (RR, 0.81; 95% CI, 0.67, 0.97; p=0.02) with mild heterogeneity between studies (I^2 = 37%) (Figure 34).[103-106] The NNT was 7 (95% CI, 4, 33). Results of the one trial in patients with rGERD were similar to the results of the overall meta-analysis.[106]

Figure 34: Meta-analysis of RCTs of antacid/alginate plus PPI versus PPI alone in patients with GERD or rGERD (proportion of patients without a symptomatic response)[102-106]



STATEMENT 11.

PICO question: Does the <u>addition of a bile acid sequestrant</u> in a patient with refractory reflux-like on BID PPI lead to a greater proportion of patients reporting symptom relief than continuing with BID PPI therapy alone?

Statement: In patients with refractory reflux-like symptoms after 8 weeks of twice-daily PPI therapy, we suggest <u>against</u> adding a bile acid sequestrant to twice-daily PPI therapy to improve symptoms.

GRADE: Conditional recommendation, very low quality of evidence.
VOTE (N=15): strongly agree 20%; agree 73%; uncertain 7%; disagree 0%; strongly disagree 0%

Key evidence: One RCT (N=280) randomized patients with proven rGERD after once-daily PPI therapy to placebo or three different doses of a bile acid sequestrant (IW-3718).[107] Overall, 34% responded in the placebo group (n=70) and similar numbers responded in the 500 mg bid and 1000 mg bid groups. The 1500 mg bid group had a response rate of 46%, which the paper reported as statistically significantly but on direct comparison of the highest dose with placebo was not (p=0.15 according to our calculations). The study suggested there may be some benefit with higher doses, however, not all variables were adjusted for.

Endoscopic or surgical management strategies

STATEMENTS 12 AND 13.

PICO question: Does an endoscopic anti-reflux procedure in a patient with refractory reflux-like symptoms after 8 weeks of therapy with a BID PPI lead to a greater proportion of patients reporting symptom relief than continuing with BID PPI therapy alone?

Statement: In patients with refractory reflux-like symptoms after 8 weeks of twice-daily PPI therapy, without objective evidence of GERD, we suggest against performing an endoscopic anti-reflux procedure to improve symptoms.

PICO question: Does a surgical fundoplication procedure in a patient with refractory reflux-like symptoms after 8 weeks of therapy with a BID PPI lead to a greater proportion of patients reporting symptom relief than continuing with BID PPI therapy alone?

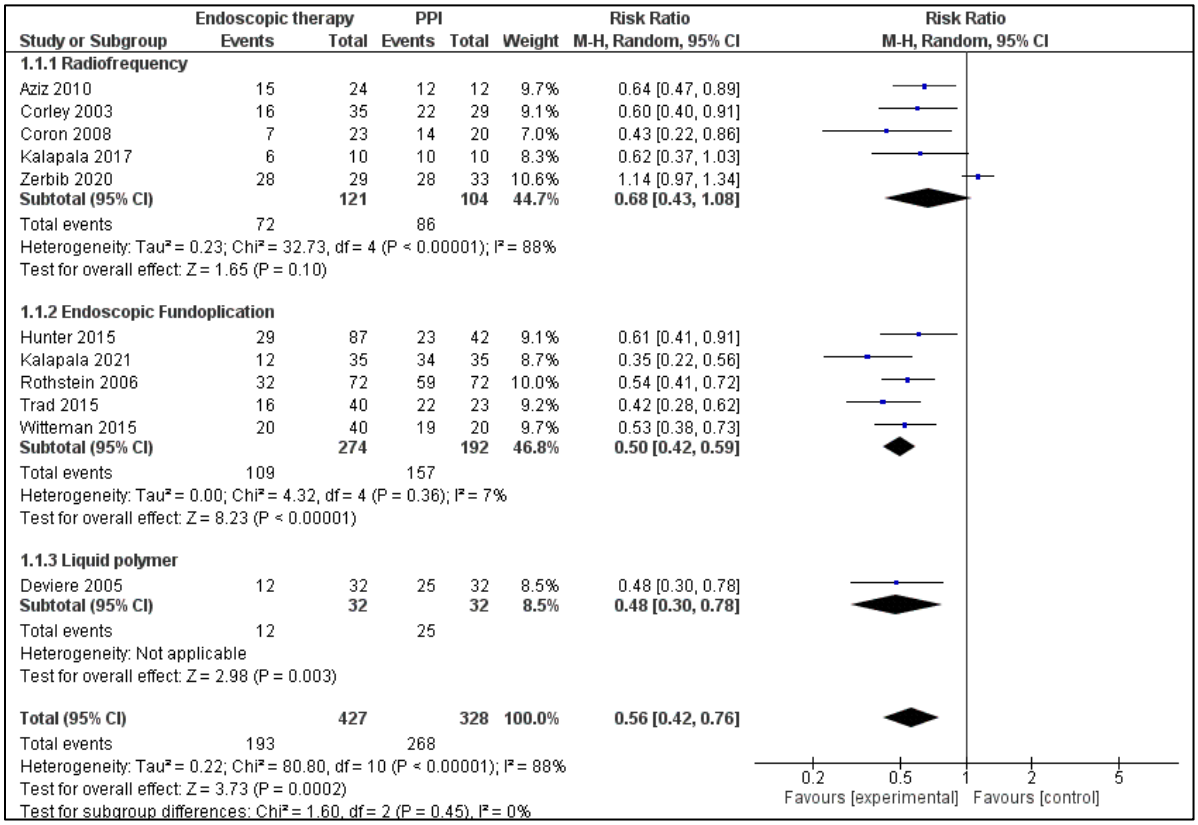
Statement: In patients with refractory reflux-like symptoms after 8 weeks of twice-daily PPI therapy without objective evidence of GERD, we recommend against performing surgical fundoplication to improve symptoms.

GRADE for statement 12: Conditional recommendation, low quality of evidence.
VOTE on statement 12 (N=15): strongly agree 60%; agree 40%; uncertain 0%; disagree 0%; strongly disagree 0%
GRADE for statement 13: Strong recommendation, very low quality of evidence.
VOTE on statement 13 (N=15): strongly agree 60%; agree 40%; uncertain 0%; disagree 0%; strongly disagree 0%

Key evidence:

Endoscopic anti-reflux therapy: Eleven RCTs (N=755) assessed any endoscopic device versus PPI therapy in patients with GERD (Figure 35).[108-118] Meta-analysis of the 5 RCTs (N=225) that assessed radiofrequency energy delivery showed no statistically significant improvement in reflux symptoms (RR, 0.68; 95% CI, 0.43-1.08).[108-112] Of these, the 2 trials (N=82) in rGERD patients also found no significant difference in reflux symptoms (RR, 0.87; 95% CI, 0.45-1.69).[111, 112]

Figure 35: Meta-analysis of RCTs of endoscopic therapy versus PPI therapy in GERD or rGERD (proportion of patients without a symptomatic response)[108-118]

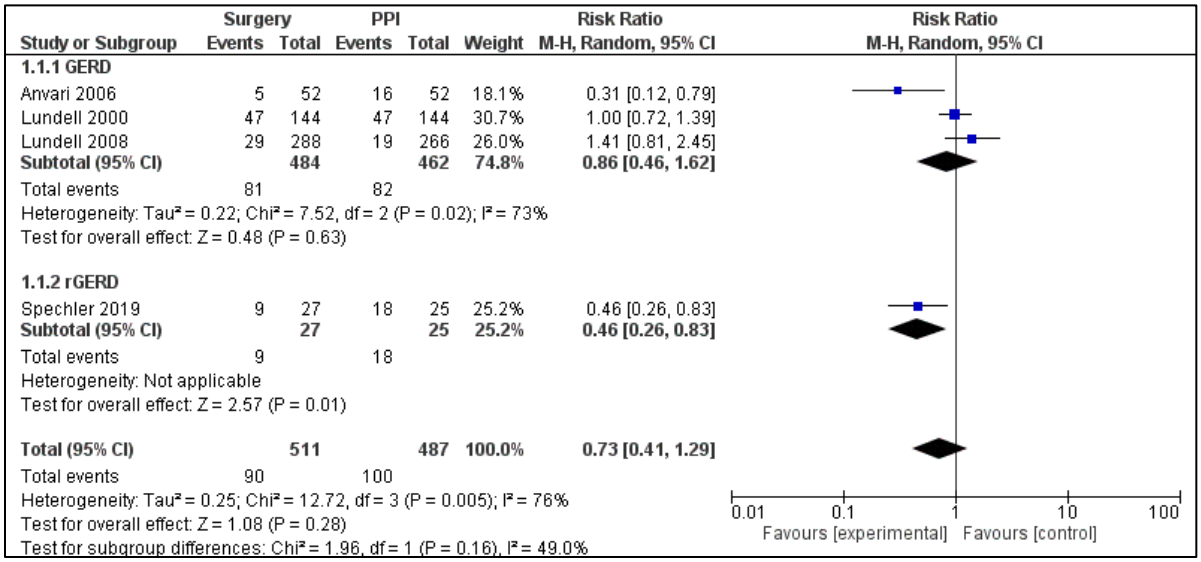


Meta-analysis of 5 RCTs (N=466) assessing endoscopic fundoplication, showed a significant reduction in reflux symptoms (RR, 0.50; 95% CI, 0.42-0.59).[113-117] In the 2 RCTs (N=192) in rGERD patients, there was also a significant reduction in reflux symptoms (RR, 0.5; 95% CI, 0.35-0.73) (Figure 35).[114, 116]

One additional trial assessing a non-resorbable copolymer implant in patients with GERD, found a significant improvement in symptoms (RR, 0.48; 95% CI, 0.30-0.78) (Figure 35).[118]

Surgical anti-reflux therapy: When surgical fundoplication therapy was compared to PPI therapy alone, meta-analysis of 4 RCTs (N=998) in patients with GERD or rGERD showed no statistically significant improvement in reflux symptoms (RR, 0.73; 95% CI, 0.41-1.29) (Figure 36).[17, 119-121] The single, small trial (N=52) in rGERD patients showed a significant reduction in reflux symptoms (RR, 0.46; 95% CI, 0.26-0.83).[17]

Figure 36: Meta-analysis of RCTs of surgical fundoplication therapy versus PPI therapy in GERD or rGERD (proportion of patients without a symptomatic response)[17, 119-121]



Magnetic sphincter augmentation (MSA) procedures have not been evaluated in a RCT for unselected patients with reflux symptoms encompassing heartburn or regurgitation; however, an uncontrolled, 5-year follow-up study did report improved quality of life scores, decreased PPI consumption, and a lower incidence of regurgitation compared to baseline in patients who had undergone MSA therapy.[122, 123] A subsequent RCT reported that MSA was superior to twice-daily PPI therapy for relief of moderate to severe regurgitation in GERD patients with persistent symptoms despite once-daily PPI therapy.[124, 125]

REFERENCES

1. Dwamena F, Holmes-Rovner M, Gaulden CM, et al. Interventions for providers to promote a patient-centred approach in clinical consultations. Cochrane Database Syst Rev 2012;12:CD003267.
2. Giannini EG, Zentilin P, Dulbecco P, et al. Management strategy for patients with gastroesophageal reflux disease: a comparison between empirical treatment with esomeprazole and endoscopy-oriented treatment. Am J Gastroenterol 2008;103:267-75.
3. Asante MA, Mendall M, Patel P, et al. A randomized trial of endoscopy vs no endoscopy in the management of seronegative Helicobacter pylori dyspepsia. Eur J Gastroenterol Hepatol 1998;10:983-9.
4. Bytzer P, Hansen JM, Schaffalitzky de Muckadell OB. Empirical H2-blocker therapy or prompt endoscopy in management of dyspepsia. Lancet 1994;343:811-6.
5. Delaney BC, Wilson S, Roalfe A, et al. Cost effectiveness of initial endoscopy for dyspepsia in patients over age 50 years: a randomised controlled trial in primary care. Lancet 2000;356:1965-9.
6. Duggan AE, Elliott CA, Miller P, et al. Clinical trial: a randomized trial of early endoscopy, Helicobacter pylori testing and empirical therapy for the management of dyspepsia in primary care. Aliment Pharmacol Ther 2009;29:55-68.
7. Lewin van den Broek NT, Numans ME, Buskens E, et al. A randomised controlled trial of four management strategies for dyspepsia: relationships between symptom subgroups and strategy outcome. Br J Gen Pract 2001;51:619-24.
8. Cuddihy MT, Locke GR, 3rd, Wahner-Roedler D, et al. Dyspepsia management in primary care: a management trial. Int J Clin Pract 2005;59:194-201.
9. Laheij RJ, Severens JL, Van de Lisdonk EH, et al. Randomized controlled trial of omeprazole or endoscopy in patients with persistent dyspepsia: a cost-effectiveness analysis. Aliment Pharmacol Ther 1998;12:1249-56.
10. Rolfe A, Burton C. Reassurance after diagnostic testing with a low pretest probability of serious disease: systematic review and meta-analysis. JAMA Intern Med 2013;173:407-16.
11. Cheng FK, Albert DM, Maydonovitch CL, et al. Categorization of patients with reflux symptoms referred for pH and impedance testing while off therapy. Clin Gastroenterol Hepatol 2015;13:867-73.
12. Choksi Y, Slaughter JC, Sharda R, et al. Symptom association probability does not reliably distinguish functional heartburn from reflux hypersensitivity. Aliment Pharmacol Ther 2018;47:958-965.
13. Garrean CP, Zhang Q, Gonsalves N, et al. Acid reflux detection and symptom-reflux association using 4-day wireless pH recording combining 48-hour periods off and on PPI therapy. Am J Gastroenterol 2008;103:1631-7.
14. Jain M, Agrawal V. Role of esophageal manometry and 24-h pH testing in patients with refractory reflux symptoms. Indian J Gastroenterol 2020;39:165-170.
15. Karamanolis G, Vanuytsel T, Sifrim D, et al. Yield of 24-hour esophageal pH and bilitec monitoring in patients with persisting symptoms on PPI therapy. Dig Dis Sci 2008;53:2387-93.
16. Park EY, Choi MG, Baeg M, et al. The value of early wireless esophageal pH monitoring in diagnosing functional heartburn in refractory gastroesophageal reflux disease. Dig Dis Sci 2013;58:2933-9.

17. Spechler SJ, Hunter JG, Jones KM, et al. Randomized trial of medical versus surgical treatment for refractory heartburn. N Engl J Med 2019;381:1513-1523.
18. Wang F, Li P, Ji GZ, et al. An analysis of 342 patients with refractory gastroesophageal reflux disease symptoms using questionnaires, high-resolution manometry, and impedance-pH monitoring. Medicine (Baltimore) 2017;96:e5906.
19. Chen X, Li P, Wang F, et al. Psychological results of 438 patients with persisting gastroesophageal reflux disease symptoms by symptom checklist 90-revised questionnaire. Euroasian J Hepatogastroenterol 2017;7:117-121.
20. Baruah B, Kumar T, Das P, et al. Prevalence of eosinophilic esophagitis in patients with gastroesophageal reflux symptoms: A cross-sectional study from a tertiary care hospital in North India. Indian J Gastroenterol 2017;36:353-360.
21. Galindo G, Vassalle J, Marcus SN, et al. Multimodality evaluation of patients with gastroesophageal reflux disease symptoms who have failed empiric proton pump inhibitor therapy. Dis Esophagus 2013;26:443-50.
22. Kandulski A, Jechorek D, Caro C, et al. Histomorphological differentiation of non-erosive reflux disease and functional heartburn in patients with PPI-refractory heartburn. Aliment Pharmacol Ther 2013;38:643-51.
23. de Sa CC, Kishi HS, Silva-Werneck AL, et al. Eosinophilic esophagitis in patients with typical gastroesophageal reflux disease symptoms refractory to proton pump inhibitor. Clinics (Sao Paulo) 2011;66:557-61.
24. Foroutan M, Norouzi A, Molaei M, et al. Eosinophilic esophagitis in patients with refractory gastroesophageal reflux disease. Dig Dis Sci 2010;55:28-31.
25. Poh CH, Gasiorowska A, Navarro-Rodriguez T, et al. Upper GI tract findings in patients with heartburn in whom proton pump inhibitor treatment failed versus those not receiving antireflux treatment. Gastrointest Endosc 2010;71:28-34.
26. Ribolsi M, Savarino E, Rogers B, et al. High-resolution manometry determinants of refractoriness of reflux symptoms to proton pump inhibitor therapy. J Neurogastroenterol Motil 2020;26:447-454.
27. Vailati C, Mazzoleni G, Testoni PA, et al. pH-Impedance findings and proton pump inhibitors-responsiveness in patients with typical gastroesophageal reflux disease symptoms in a large single-center Italian series. J Clin Gastroenterol 2014;48:613-9.
28. Garcia-Compean D, Gonzalez Gonzalez JA, Marrufo Garcia CA, et al. Prevalence of eosinophilic esophagitis in patients with refractory gastroesophageal reflux disease symptoms: A prospective study. Dig Liver Dis 2011;43:204-8.
29. Zerbib F, Belhocine K, Simon M, et al. Clinical, but not oesophageal pH-impedance, profiles predict response to proton pump inhibitors in gastro-oesophageal reflux disease. Gut 2012;61:501-6.
30. Triadafilopoulos G, Korzilius JW, Zikos T, et al. Ninety-six hour wireless esophageal pH study in patients with gerd shows that restrictive diet reduces esophageal acid exposure. Dig Dis Sci 2020;65:2331-2344.
31. Triadafilopoulos G, Zikos T, Regalia K, et al. Use of esophageal pH monitoring to minimize proton-pump inhibitor utilization in patients with gastroesophageal reflux symptoms. Dig Dis Sci 2018;63:2673-2680.
32. Anis K, Chandnani A, Ahmed MU, et al. Retrospective analysis of eosinophilic esophagitis in patients with refractory gastroesophageal reflux disease. Cureus 2019;11:e5252.

33. Oude Nijhuis RAB, Curvers WL, van der Ende M, et al. Utility of routine esophageal biopsies in patients with refractory reflux symptoms. Am J Gastroenterol 2021;116:816-820.
34. Kuipers EJ, Nelis GF, Klinkenberg-Knol EC, et al. Cure of Helicobacter pylori infection in patients with reflux oesophagitis treated with long term omeprazole reverses gastritis without exacerbation of reflux disease: results of a randomised controlled trial. Gut 2004;53:12-20.
35. Moayyedi P, Bardhan C, Young L, et al. Helicobacter pylori eradication does not exacerbate reflux symptoms in gastroesophageal reflux disease. Gastroenterology 2001;121:1120-6.
36. Schwizer W, Menne D, Schutze K, et al. The effect of Helicobacter pylori infection and eradication in patients with gastro-oesophageal reflux disease: A parallel-group, double-blind, placebo-controlled multicentre study. United European Gastroenterol J 2013;1:226-35.
37. Wu JC, Chan FK, Ching JY, et al. Effect of Helicobacter pylori eradication on treatment of gastro-oesophageal reflux disease: a double blind, placebo controlled, randomised trial. Gut 2004;53:174-9.
38. Pilotto A, Perri F, Leandro G, et al. Effect of Helicobacter pylori eradication on the outcome of reflux esophagitis and chronic gastritis in the elderly. A randomized, multicenter, eight-month study. Gerontology 2006;52:99-106.
39. Yang HB, Sheu BS, Wang ST, et al. H. pylori eradication prevents the progression of gastric intestinal metaplasia in reflux esophagitis patients using long-term esomeprazole. Am J Gastroenterol 2009;104:1642-9.
40. Harvey RF, Lane JA, Murray LJ, et al. Randomised controlled trial of effects of Helicobacter pylori infection and its eradication on heartburn and gastro-oesophageal reflux: Bristol helicobacter project. BMJ 2004;328:1417.
41. Moayyedi P, Feltbower R, Brown J, et al. Effect of population screening and treatment for Helicobacter pylori on dyspepsia and quality of life in the community: a randomised controlled trial. Leeds HELP Study Group. Lancet 2000;355:1665-9.
42. Kim SE, Kim N, Oh S, et al. Predictive factors of response to proton pump inhibitors in korean patients with gastroesophageal reflux disease. J Neurogastroenterol Motil 2015;21:69-77.
43. Garros A, Mion F, Marjoux S, et al. Factors associated with nonresponse to proton pump inhibitors therapy in patients referred for esophageal pH-impedance monitoring. Dis Esophagus 2016;29:787-793.
44. Herregods TV, Troelstra M, Weijenborg PW, et al. Patients with refractory reflux symptoms often do not have GERD. Neurogastroenterol Motil 2015;27:1267-73.
45. Ribolsi M, Emerenziani S, Borrelli O, et al. Impedance baseline and reflux perception in responder and non-responder non-erosive reflux disease patients. Scand J Gastroenterol 2012;47:1266-73.
46. Roman S, Keefer L, Imam H, et al. Majority of symptoms in esophageal reflux PPI non-responders are not related to reflux. Neurogastroenterol Motil 2015;27:1667-74.
47. Tamura Y, Funaki Y, Izawa S, et al. Pathophysiology of functional heartburn based on Rome III criteria in Japanese patients. World J Gastroenterol 2015;21:5009-16.

48. Jiang L, Ye B, Wang Y, et al. Esophageal body motility for clinical assessment in patients with refractory gastroesophageal reflux symptoms. J Neurogastroenterol Motil 2017;23:64-71.
49. Shi Y, Tan N, Zhang N, et al. Predictors of proton pump inhibitor failure in non-erosive reflux disease: A study with impedance-pH monitoring and high-resolution manometry. Neurogastroenterol Motil 2016;28:674-9.
50. Kawamura O, Hosaka H, Shimoyama Y, et al. Evaluation of proton pump inhibitor-resistant nonerosive reflux disease by esophageal manometry and 24-hour esophageal impedance and pH monitoring. Digestion 2015;91:19-25.
51. Izawa S, Funaki Y, Iida A, et al. The role of gastroesophageal reflux in relation to symptom onset in patients with proton pump inhibitor-refractory nonerosive reflux disease accompanied by an underlying esophageal motor disorder. Digestion 2014;89:61-7.
52. Bautista JM, Wong WM, Pulliam G, et al. The value of ambulatory 24 hr esophageal pH monitoring in clinical practice in patients who were referred with persistent gastroesophageal reflux disease (GERD)-related symptoms while on standard dose anti-reflux medications. Dig Dis Sci 2005;50:1909-15.
53. Charbel S, Khandwala F, Vaezi MF. The role of esophageal pH monitoring in symptomatic patients on PPI therapy. Am J Gastroenterol 2005;100:283-9.
54. Mackalski BA, Ilnyckyj A. Esophageal pH testing in patients refractory to proton pump inhibitor therapy. Can J Gastroenterol 2008;22:249-52.
55. Lee KJ, Kwon HC, Cheong JY, et al. Demographic, clinical, and psychological characteristics of the heartburn groups classified using the Rome III criteria and factors associated with the responsiveness to proton pump inhibitors in the gastroesophageal reflux disease group. Digestion 2009;79:131-6.
56. Pugliese D, Mauro A, Consonni D, et al. pH Impedance vs. traditional pH monitoring in clinical practice: an outcome study. J Gastroenterol 2016;51:130-7.
57. Talaie R, Forootan M, Donboli K, et al. 24-hour ambulatory pH-metry in patients with refractory heartburn: a prospective study. J Gastrointestin Liver Dis 2009;18:11-5.
58. Ahlawat SK, Mohi-Ud-Din R, Williams DC, et al. A prospective study of gastric acid analysis and esophageal acid exposure in patients with gastroesophageal reflux refractory to medical therapy. Dig Dis Sci 2005;50:2019-24.
59. Abdallah J, George N, Yamasaki T, et al. Most patients with gastroesophageal reflux disease who failed proton pump inhibitor therapy also have functional esophageal disorders. Clin Gastroenterol Hepatol 2019;17:1073-1080 e1.
60. Hemmink GJ, Bredenoord AJ, Weusten BL, et al. Esophageal pH-impedance monitoring in patients with therapy-resistant reflux symptoms: 'on' or 'off' proton pump inhibitor? Am J Gastroenterol 2008;103:2446-53.
61. Iwakiri K, Kawami N, Sano H, et al. Acid and non-acid reflux in Japanese patients with non-erosive reflux disease with persistent reflux symptoms, despite taking a double-dose of proton pump inhibitor: a study using combined pH-impedance monitoring. J Gastroenterol 2009;44:708-12.
62. Jodorkovsky D, Price JC, Kim B, et al. Multichannel intraluminal impedance-pH testing is clinically useful in the management of patients with gastroesophageal reflux symptoms. Dig Dis Sci 2014;59:1817-22.

63. Patel A, Sayuk GS, Gyawali CP. Parameters on esophageal pH-impedance monitoring that predict outcomes of patients with gastroesophageal reflux disease. Clin Gastroenterol Hepatol 2015;13:884-91.
64. Pritchett JM, Aslam M, Slaughter JC, et al. Efficacy of esophageal impedance/pH monitoring in patients with refractory gastroesophageal reflux disease, on and off therapy. Clin Gastroenterol Hepatol 2009;7:743-8.
65. Slaughter JC, Goutte M, Rymer JA, et al. Caution about overinterpretation of symptom indexes in reflux monitoring for refractory gastroesophageal reflux disease. Clin Gastroenterol Hepatol 2011;9:868-74.
66. Yoshimine T, Funaki Y, Kawamura Y, et al. Convenient method of measuring baseline impedance for distinguishing patients with functional heartburn from those with proton pump inhibitor-resistant endoscopic negative reflux disease. Digestion 2019;99:157-165.
67. Zerbib F, Roman S, Ropert A, et al. Esophageal pH-impedance monitoring and symptom analysis in GERD: a study in patients off and on therapy. Am J Gastroenterol 2006;101:1956-63.
68. Xiao Y, Liang M, Peng S, et al. Tailored therapy for the refractory GERD patients by combined multichannel intraluminal impedance-pH monitoring. J Gastroenterol Hepatol 2016;31:350-4.
69. Kohata Y, Fujiwara Y, Yamagami H, et al. Usefulness of baseline impedance in patients with proton pump inhibitor-refractory nonerosive reflux disease. J Gastroenterol Hepatol 2015;30 Suppl 1:36-40.
70. Viazis N, Karamanolis GP, Anastasiou J, et al. Refractory GERD: increased body mass index is associated with persisting acid exposure but not hypersensitive esophagus or functional heartburn. Eur J Gastroenterol Hepatol 2013;25:1450-5.
71. Frazzoni M, Conigliaro R, Mirante VG, et al. The added value of quantitative analysis of on-therapy impedance-pH parameters in distinguishing refractory non-erosive reflux disease from functional heartburn. Neurogastroenterol Motil 2012;24:141-6, e87.
72. Gharib A, Forootan M, Sharifzadeh M, et al. Diagnostic efficacy of 24-hr esophageal pH monitoring in patients with refractory gastroesophageal reflux disease. Open Access Maced J Med Sci 2018;6:1235-1238.
73. Savarino E, Marabotto E, Zentilin P, et al. The added value of impedance-pH monitoring to Rome III criteria in distinguishing functional heartburn from non-erosive reflux disease. Dig Liver Dis 2011;43:542-7.
74. Yamashita H, Ashida K, Fukuchi T, et al. Combined pH-impedance monitoring and high-resolution manometry of Japanese patients treated with proton-pump inhibitors for persistent symptoms of non-erosive reflux disease. J Smooth Muscle Res 2012;48:125-35.
75. Fass R, Sontag SJ, Traxler B, et al. Treatment of patients with persistent heartburn symptoms: a double-blind, randomized trial. Clin Gastroenterol Hepatol 2006;4:50-6.
76. Kinoshita Y, Hongo M, Japan TSG. Efficacy of twice-daily rabeprazole for reflux esophagitis patients refractory to standard once-daily administration of PPI: the Japan-based TWICE study. Am J Gastroenterol 2012;107:522-30.
77. Chen WY, Chang WL, Tsai YC, et al. Double-dosed pantoprazole accelerates the sustained symptomatic response in overweight and obese patients with reflux esophagitis in Los Angeles grades A and B. Am J Gastroenterol 2010;105:1046-52.

78. Cho JH, Shin CM, Yoon H, et al. Efficacy of a high-dose proton pump inhibitor in patients with gastroesophageal reflux disease: a single center, randomized, open-label trial. BMC Gastroenterol 2020;20:275.
79. Miner PB, Johnson DA, Katz PO, et al. Pilot, randomized, blinded, placebo-controlled trial investigating the correlation between acid control and heartburn relief with 14 days of esomeprazole treatment. Adv Ther 2018;35:2024-2040.
80. Orlando RC, Liu S, Illueca M. Relationship between esomeprazole dose and timing to heartburn resolution in selected patients with gastroesophageal reflux disease. Clin Exp Gastroenterol 2010;3:117-25.
81. Vasiliadis KV, Viazis N, Vlachogiannakos J, et al. Efficacy of three different dosages of esomeprazole in the long-term management of reflux disease: a prospective, randomized study, using the wireless Bravo pH system. Am J Gastroenterol 2010;105:308-13.
82. Shaheen NJ, Adler J, Dedrie S, et al. Randomised clinical trial: the 5-HT4 agonist revexepride in patients with gastro-oesophageal reflux disease who have persistent symptoms despite PPI therapy. Aliment Pharmacol Ther 2015;41:649-61.
83. Takeuchi T, Takahashi Y, Kawaguchi S, et al. Therapy of gastroesophageal reflux disease and functional dyspepsia overlaps with symptoms after usual-dose proton pump inhibitor: Acotiamide plus usual-dose proton pump inhibitor versus double-dose proton pump inhibitor. J Gastroenterol Hepatol 2018;33:623-630.
84. Yamashita H, Okada A, Naora K, et al. Adding acotiamide to gastric acid inhibitors is effective for treating refractory symptoms in patients with non-erosive reflux disease. Dig Dis Sci 2019;64:823-831.
85. Bari A, Hassan S, Sahar A, et al. A prospective study involving comparison of acotiamide with rabeprazole vs. double dose rabeprazole in patients having overlapping symptoms of proton pump inhibitor refractory gastroesophageal reflux disease and functional dyspepsia. Int J Res Granthaalayah 2020;8:1-11.
86. Taghvaei T, Kazemi A, Hosseini V, et al. Evaluation of the additive effect of domperidone on patients with refractory gastroesophageal reflux disease: A randomized double blind clinical trial. Middle East J Dig Dis 2019;11:24-31.
87. Madan K, Ahuja V, Kashyap PC, et al. Comparison of efficacy of pantoprazole alone versus pantoprazole plus mosapride in therapy of gastroesophageal reflux disease: a randomized trial. Dis Esophagus 2004;17:274-8.
88. Miwa H, Inoue K, Ashida K, et al. Randomised clinical trial: efficacy of the addition of a prokinetic, mosapride citrate, to omeprazole in the treatment of patients with non-erosive reflux disease - a double-blind, placebo-controlled study. Aliment Pharmacol Ther 2011;33:323-32.
89. Lim HC, Kim J-H, Youn YH, et al. Effects of the addition of mosapride to gastroesophageal reflux disease patients on proton pump inhibitor: a prospective randomized, double-blind study. J Neurogastroenterol Motil 2013;19:495.
90. Cho YK, Choi MG, Park EY, et al. Effect of mosapride combined with esomeprazole improves esophageal peristaltic function in patients with gastroesophageal reflux disease: a study using high resolution manometry. Dig Dis Sci 2013;58:1035-41.
91. Wang Y-P, Ji L-S, Ni M, et al. [Clinical effects of esomeprazole combined with mosapride for treatment of gastroesophageal reflux disease]. World Chinese J Digestol 2014;22.

92. Lee JY, Kim SK, Cho KB, et al. A double-blind, randomized, multicenter clinical trial investigating the efficacy and safety of esomeprazole single therapy versus mosapride and esomeprazole combined therapy in patients with esophageal reflux disease. J Neurogastroenterol Motil 2017;23:218-228.
93. Marakhouski KY, Karaseva GA, Ulasivich DN, et al. Omeprazole-domperidone fixed dose combination vs omeprazole monotherapy: A phase 4, open-label, comparative, parallel randomized controlled study in mild to moderate gastroesophageal reflux disease. Clin Med Insights Gastroenterol 2017;10:1179552217709456.
94. Yamaji Y, Isomura Y, Yoshida S, et al. Randomized controlled trial comparing the efficacy of mosapride plus omeprazole combination therapy to omeprazole monotherapy in gastroesophageal reflux disease. J Dig Dis 2014;15:469-76.
95. Sirinawasatien A, Kantathavorn N. Efficacy of the four weeks treatment of omeprazole plus mosapride combination therapy compared with that of omeprazole monotherapy in patients with proton pump inhibitor-refractory gastroesophageal reflux disease: a randomized controlled trial. Clin Exp Gastroenterol 2019;12:337-347.
96. Puranik R, Karandikar Y, Bhat S, et al. Pharmacoeconomic evaluation of pantoprazole and pantoprazole plus domperidone in treatment of patients with GERD. J Clin Diagnostic Res 2018;12:IC01-IC05.
97. Tack J, Zerbib F, Blondeau K, et al. Randomized clinical trial: effect of the 5-HT4 receptor agonist revexepride on reflux parameters in patients with persistent reflux symptoms despite PPI treatment. Neurogastroenterol Motil 2015;27:258-68.
98. Vakil NB, Huff FJ, Cundy KC. Randomised clinical trial: arbaclofen placarbil in gastro-oesophageal reflux disease--insights into study design for transient lower sphincter relaxation inhibitors. Aliment Pharmacol Ther 2013;38:107-17.
99. Boeckxstaens GE, Beaumont H, Hatlebakk JG, et al. A novel reflux inhibitor lesogaberan (AZD3355) as add-on treatment in patients with GORD with persistent reflux symptoms despite proton pump inhibitor therapy: a randomised placebo-controlled trial. Gut 2011;60:1182-8.
100. Shaheen NJ, Denison H, Bjorck K, et al. Efficacy and safety of lesogaberan in gastro-oesophageal reflux disease: a randomised controlled trial. Gut 2013;62:1248-55.
101. Abbasinazari M, Panahi Y, Mortazavi SA, et al. Effect of a combination of omeprazole plus sustained release baclofen versus omeprazole alone on symptoms of patients with gastroesophageal reflux disease (GERD). Iran J Pharm Res 2014;13:1221-6.
102. Coyle C, Crawford G, Wilkinson J, et al. Randomised clinical trial: addition of alginate-antacid (Gaviscon Double Action) to proton pump inhibitor therapy in patients with breakthrough symptoms. Aliment Pharmacol Ther 2017;45:1524-1533.
103. Kim JH, Lee YC, Kim EH, et al. The clinical efficacy of a pure alginate formulation (lamina G) for controlling symptoms in individuals with reflux symptoms: A randomized clinical study. Gut Liver 2019;13:642-648.
104. Manabe N, Haruma K, Ito M, et al. Efficacy of adding sodium alginate to omeprazole in patients with nonerosive reflux disease: a randomized clinical trial. Dis Esophagus 2012;25:373-80.
105. Soifer L, Pedrana R, Parrota M, et al. [On-demand treatment of nonerosive reflux disease: omeprazole plus bicarbonate powder versus omeprazole capsules]. Acta Gastroenterol Latinoam 2010;40:198-205.

106. Reimer C, Lodrup AB, Smith G, et al. Randomised clinical trial: alginate (Gaviscon Advance) vs. placebo as add-on therapy in reflux patients with inadequate response to a once daily proton pump inhibitor. Aliment Pharmacol Ther 2016;43:899-909.
107. Vaezi MF, Fass R, Vakil N, et al. IW-3718 reduces heartburn severity in patients with refractory gastroesophageal reflux disease in a randomized trial. Gastroenterology 2020;158:2093-2103.
108. Aziz AM, El-Khayat HR, Sadek A, et al. A prospective randomized trial of sham, single-dose Stretta, and double-dose Stretta for the treatment of gastroesophageal reflux disease. Surg Endosc 2010;24:818-25.
109. Corley DA, Katz P, Wo JM, et al. Improvement of gastroesophageal reflux symptoms after radiofrequency energy: a randomized, sham-controlled trial. Gastroenterology 2003;125:668-76.
110. Coron E, Sebille V, Cadiot G, et al. Clinical trial: Radiofrequency energy delivery in proton pump inhibitor-dependent gastro-oesophageal reflux disease patients. Aliment Pharmacol Ther 2008;28:1147-58.
111. Kalapala R, Shah H, Nabi Z, et al. Treatment of gastroesophageal reflux disease using radiofrequency ablation (Stretta procedure): An interim analysis of a randomized trial. Indian J Gastroenterol 2017;36:337-342.
112. Zerbib F, Sacher-Huvelin S, Coron E, et al. Randomised clinical trial: oesophageal radiofrequency energy delivery versus sham for PPI-refractory heartburn. Aliment Pharmacol Ther 2020;52:637-645.
113. Hunter JG, Kahrilas PJ, Bell RC, et al. Efficacy of transoral fundoplication vs omeprazole for treatment of regurgitation in a randomized controlled trial. Gastroenterology 2015;148:324-333 e5.
114. Kalapala R, Karyampudi A, Nabi Z, et al. Endoscopic full-thickness plication for the treatment of PPI-dependent GERD: results from a randomised, sham controlled trial. Gut 2022;71:686-694.
115. Rothstein R, Filipi C, Caca K, et al. Endoscopic full-thickness plication for the treatment of gastroesophageal reflux disease: A randomized, sham-controlled trial. Gastroenterology 2006;131:704-12.
116. Trad KS, Barnes WE, Simoni G, et al. Transoral incisionless fundoplication effective in eliminating GERD symptoms in partial responders to proton pump inhibitor therapy at 6 months: the TEMPO Randomized Clinical Trial. Surg Innov 2015;22:26-40.
117. Witteman BP, Conchillo JM, Rinsma NF, et al. Randomized controlled trial of transoral incisionless fundoplication vs. proton pump inhibitors for treatment of gastroesophageal reflux disease. Am J Gastroenterol 2015;110:531-42.
118. Deviere J, Costamagna G, Neuhaus H, et al. Nonresorbable copolymer implantation for gastroesophageal reflux disease: a randomized sham-controlled multicenter trial. Gastroenterology 2005;128:532-40.
119. Anvari M, Allen C, Marshall J, et al. A randomized controlled trial of laparoscopic nissen fundoplication versus proton pump inhibitors for treatment of patients with chronic gastroesophageal reflux disease: One-year follow-up. Surg Innov 2006;13:238-49.
120. Lundell L, Miettinen P, Myrvold HE, et al. Long-term management of gastro-oesophageal reflux disease with omeprazole or open antireflux surgery: results of a prospective, randomized clinical trial. The Nordic GORD Study Group. Eur J Gastroenterol Hepatol 2000;12:879-87.

121. Lundell L, Attwood S, Ell C, et al. Comparing laparoscopic antireflux surgery with esomeprazole in the management of patients with chronic gastro-oesophageal reflux disease: a 3-year interim analysis of the LOTUS trial. Gut 2008;57:1207-13.
122. Ganz RA, Peters JH, Horgan S, et al. Esophageal sphincter device for gastroesophageal reflux disease. N Engl J Med 2013;368:719-27.
123. Ganz RA, Edmundowicz SA, Taiganides PA, et al. Long-term outcomes of patients receiving a magnetic sphincter augmentation device for gastroesophageal reflux. Clin Gastroenterol Hepatol 2016;14:671-7.
124. Bell R, Lipham J, Louie B, et al. Laparoscopic magnetic sphincter augmentation versus double-dose proton pump inhibitors for management of moderate-to-severe regurgitation in GERD: a randomized controlled trial. Gastrointest Endosc 2019;89:14-22 e1.
125. Bell R, Lipham J, Louie BE, et al. Magnetic sphincter augmentation superior to proton pump inhibitors for regurgitation in a 1-year randomized trial. Clin Gastroenterol Hepatol 2020;18:1736-1743 e2.