

SUPPLEMENTARY APPENDIX 2: SUMMARY OF THE GRADE REPORT OF EVIDENCE FOR PICO QUESTIONS DEEMED TO BE REDUNDANT OR NOT NECESSARY IN THIS GUIDELINE

Diagnostic strategies
Withdrawn PICO 1. Does high dose PPI therapy result in a higher proportion of patients with symptom resolution in those with histological evidence of reflux compared with those without histological features in patients with refractory reflux-like symptoms on BID PPI therapy? GRADE: No evidence
Withdrawn PICO 2. Does <u>wireless</u> esophageal pH testing <u>on</u> PPI therapy in a patient with refractory reflux-like symptoms lead to more diagnoses that guide future therapy than <u>catheter-based</u> esophageal pH testing <u>on</u> PPI therapy? GRADE evidence: Very low quality of evidence supporting the statement
Pharmacological management strategies
Withdrawn PICO 3. Does PCAB therapy 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? GRADE evidence: Low quality of evidence AGAINST this statement
Withdrawn PICO 4. Does higher dose PPI therapy result in a higher proportion of patients with symptom resolution in those with erosive esophagitis compared with those without erosive esophagitis in patients with refractory reflux-like symptoms on BID PPI therapy? GRADE evidence: Low quality of evidence supporting this statement
Withdrawn PICO 5. Does PCAB therapy result in a higher proportion of patients with symptom resolution in those with erosive esophagitis compared with those without erosive esophagitis in patients with refractory reflux-like symptoms on BID PPI therapy? GRADE: Addressed in PICO 14
Withdrawn PICO 6. Does the addition of an H2RA 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? GRADE evidence: Neither for or against
Withdrawn PICO 7. Does the addition of a (tricyclic) antidepressant 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? GRADE evidence: Very low quality of evidence supporting the statement
Withdrawn PICO 8. Is an abnormal pH or pH-impedance study result in patients with refractory reflux-like symptoms associated with a greater proportion of patients achieving symptom relief after an anti-reflux procedure than a normal pH or pH-impedance study result? GRADE evidence: Not collected: surgery not done on patients with normal pH impedance studies
Endoscopic or surgical management strategies
Withdrawn PICO 9. Does a <u>surgical anti-reflux procedure (e.g. Linx)</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 alone? GRADE: Evidence difficult to interpret. 1 cross-over RCT

Diagnostic strategies

WITHDRAWN PICO 1.

Does high dose PPI therapy result in a higher proportion of patients with symptom resolution in those with histological evidence of reflux compared with those without histological features in patients with refractory reflux-like symptoms on BID PPI therapy?

GRADE: No evidence

Key evidence: There were no RCTs that evaluated esophageal histology as a predictor of PPI response in refractory reflux-like symptoms (rRLS) or rGERD and there was, therefore, no evidence to answer this question. Histological features of reflux disease vary according to study, but the main literature related to this compares histological features in those with non-erosive reflux disease versus those with reflux esophagitis, healthy controls with no symptoms, or those with functional heartburn.^{1,2} Routine esophageal biopsy in patients with rRLS has a low diagnostic yield in the absence of typical symptoms or endoscopic features of eosinophilic esophagitis.³

WITHDRAWN PICO 2.

Does wireless esophageal pH testing on PPI therapy in a patient with refractory reflux-like symptoms lead to more diagnoses that guide future therapy than catheter-based esophageal pH testing on PPI therapy?

GRADE: Very low quality of evidence supporting the statement

Key evidence: The Lyon 2.0 consensus states that prolonged wireless pH monitoring off antisecretory therapy is the preferred diagnostic tool in unproven GERD when available and may provide highest diagnostic yield with study duration of 96 hours.⁴ However, there is no recommendation regarding wireless pH testing in patients with rRLS on PPI therapy and there were no studies that compared these two diagnostic modalities in rRLS patients on therapy with refractory reflux-like symptoms. We therefore must rely on indirect comparisons from the data presented for the PICO question underlying **Statement 7**. Sixteen studies (N=1209) performed pH-impedance studies on PPI therapy with a pooled proportion who had acid reflux related

symptoms of 18% (95% CI, 13 to 24%) with marked heterogeneity ($I^2 = 83\%$; 95% CI, 73 to 88%) between studies (Figure 1).⁵⁻²⁰ There were three studies evaluating 248 patients with resistant reflux symptoms with wireless esophageal pH testing on PPI therapy that had a pooled acid reflux proportion of 23% (95% CI, 12 to 35%) with marked heterogeneity ($I^2 = 71\%$; 95% CI, 0 to 89%) between studies (Figure 2).²¹⁻²³ There was no statistical difference between the two proportions (Cochrane Q, $p=0.44$). Most studies of wireless pH monitoring include patients not on PPI therapy. One study evaluating patients with NERD who were on or off PPIs reported that acid reflux was a cause of the symptoms in 36% of patients with a catheter-based system ($n=55$) and 39% with a wireless system ($n=66$).²⁴ They concluded that any gain with wireless 48-hour pH assessment was not clinically relevant and any deficiency was compensated by the ability to measure non-acid reflux. However, only 13 patients had PPI resistant symptoms, and this group was not reported separately so this study could not be included.²⁴

Figure 1: Proportion of patients with acid related reflux symptoms ON PPI with pH impedance testing⁵⁻²⁰

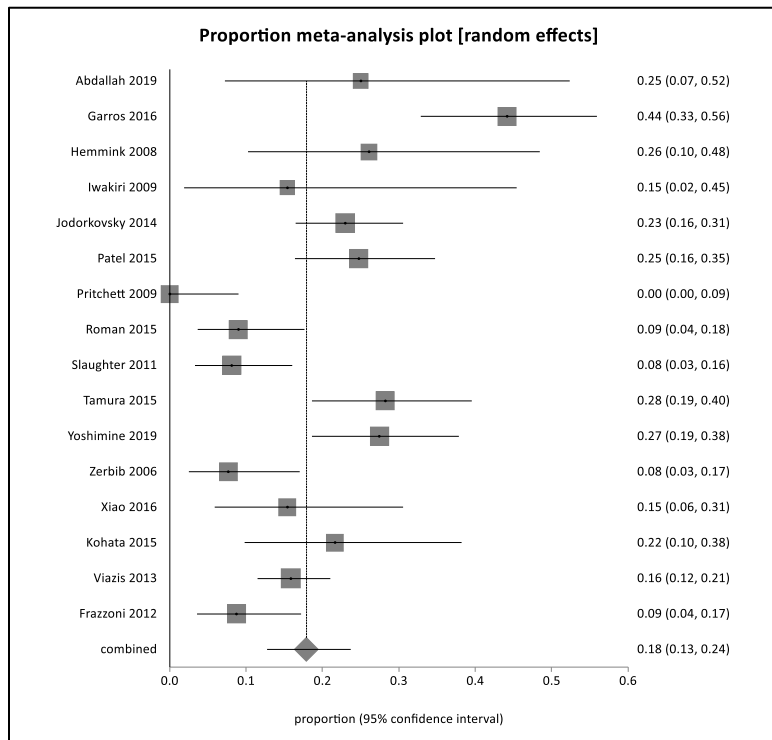
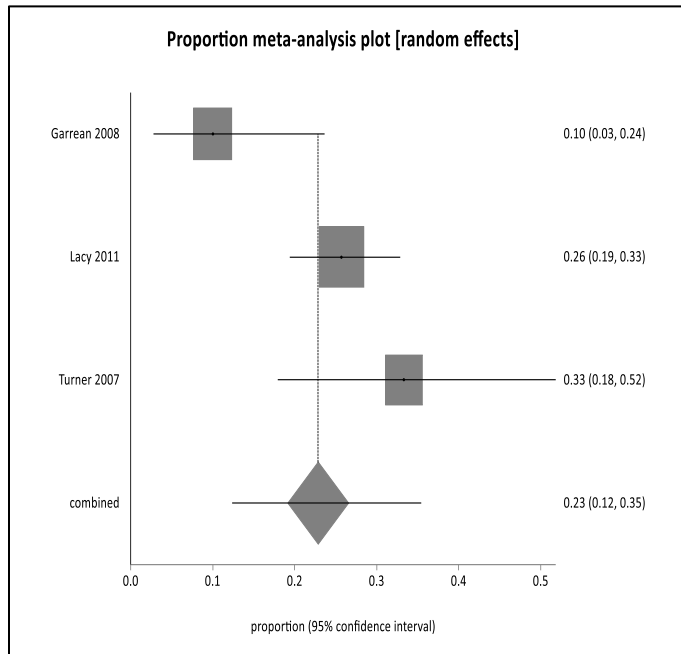


Figure 2: Proportion of patients with acid related reflux symptoms ON PPI with wireless pH testing²¹⁻²³



Pharmacological management strategies

WITHDRAWN PICO 3.

Does PCAB therapy 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?

GRADE: Low quality of evidence AGAINST this statement

Key evidence: RCTs have not focused on refractory reflux symptoms but there are trials of PPIs versus PCABs in GERD patients. There were 4 trials in patients with esophagitis (N=2119) that found similar healing rates with PPIs and PCABs (RR = 1.02; 95% CI, 0.98 to 1.05) with no heterogeneity (Figure 3).²⁵⁻²⁸ More recent meta-analyses have reported that P-CABs are associated with a higher 8-week healing than PPIs in 9 RCTs (RR = 1.03; 95% CI, 1.00 to 1.07)²⁹ and that vonoprazan is effective, compared with PPIs for healing of grade C/D esophagitis;³⁰ neither of these meta-analyses included earlier, large RCTs that had shown no difference between the P-CAB AZD0865 (linaprazan) and esomeprazole 40 mg daily for erosive

esophagitis³¹ or NERD.³² Furthermore, neither meta-analysis reported any RCT that addressed refractory symptomatic GERD or rRLS^{29,30} and a meta-analysis of vonoprazan therapy for PPI refractory GERD included only one, very small RCT.³³ There was no difference in adverse events between PCABs and PPIs (6 RCTs; N=2001; RR = 0.98; 95% CI, 0.85 to 1.12)^{25,27,28,34-36} or PCABs and placebo^{37,38} in terms of adverse events (Figure 4). One trial (n=607) reported that a PCAB (vonoprazan 10 and 20 mg) was more effective than a low dose PPI (lansoprazole 15 mg od) in preventing relapse of esophagitis, but this is not relevant as these patients did not have refractory reflux disease; furthermore the PPI dosing used in the study was lower than that used for refractory reflux.²⁶

Figure 3: RCTs of PCAB versus PPI in esophagitis²⁵⁻²⁸

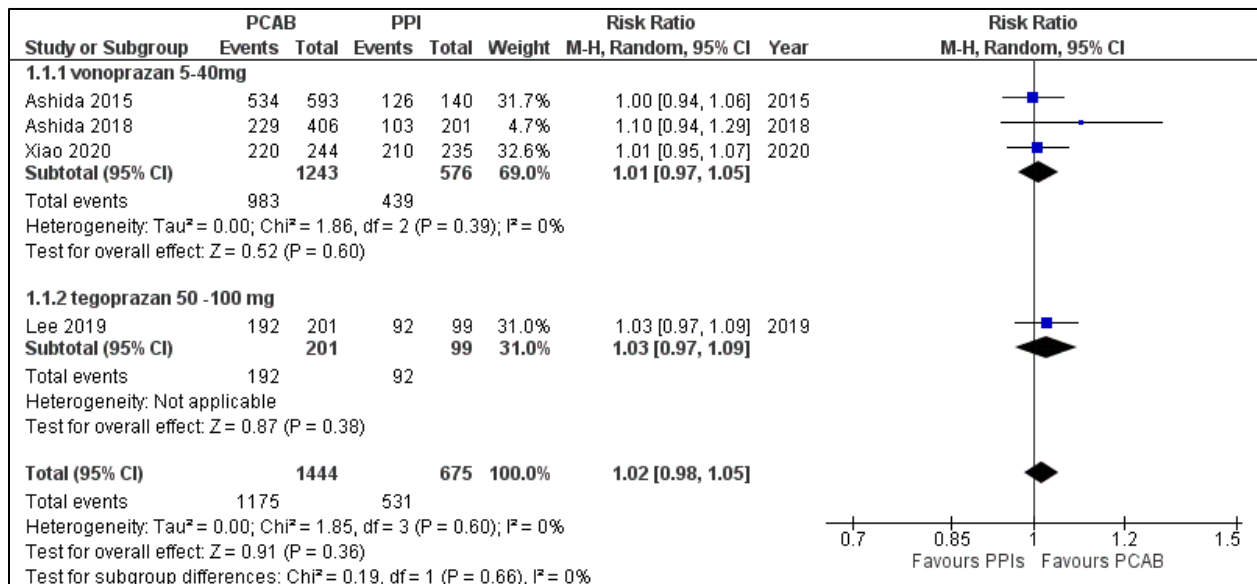
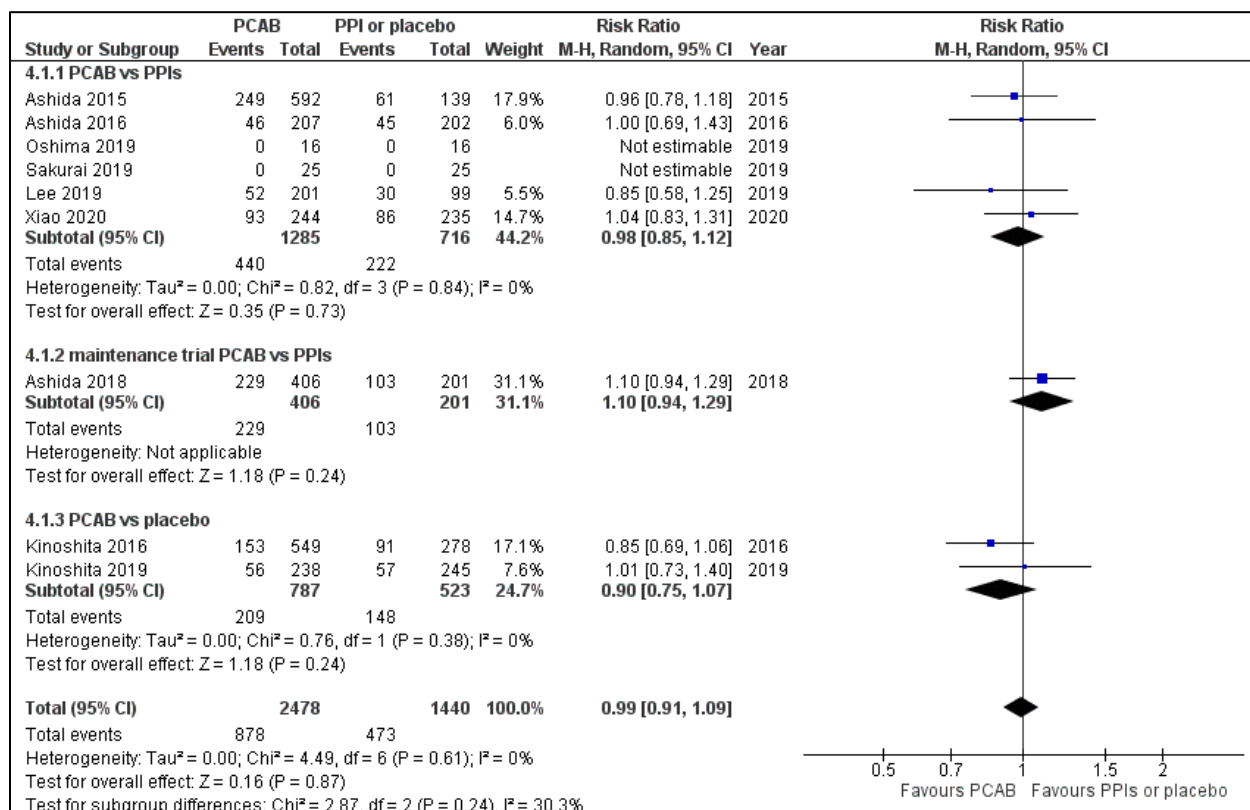


Figure 4; RCTs of adverse events of PCABs versus PPI or placebo ^{25,27,28,34-38}



WITHDRAWN PICO 4.

Does higher dose PPI therapy result in a higher proportion of patients with symptom resolution in those with erosive esophagitis compared with those without erosive esophagitis in patients with refractory reflux-like symptoms on BID PPI therapy?

GRADE: Low quality of evidence supporting this statement

Key evidence: In the analysis described in **Statement 8** there were two RCTs that evaluated once- versus twice-daily PPI therapy in rGERD. One study (Fass et al. 2006)³⁹ did not perform endoscopy at baseline, whereas in the other (Kinoshita et al. 2012) all patients had esophagitis.⁴⁰ Kinoshita et al. did make the observation that twice-daily PPI was primarily more effective than once-daily in the in the LA C and D esophagitis groups. Fass et al. was a negative study whereas Kinoshita et al. had a significant result in favour of bid PPI.^{39,40} However, neither of these studies looked at doses higher than twice-daily.

WITHDRAWN PICO 5.

Does PCAB therapy result in a higher proportion of patients with symptom resolution in those with erosive esophagitis compared with those without erosive esophagitis in patients with refractory reflux-like symptoms on BID PPI therapy?

GRADE: Addressed in Withdrawn PICO 3

Key evidence: This question was addressed in Withdrawn PICO 3. PCABs and PPIs have similar efficacy and this includes the erosive esophagitis group.

WITHDRAWN PICO 6.

Does the addition of an H2RA 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?

GRADE: Neither for or against

Key evidence: No RCTs were identified in rGERD or GERD that addressed this question. Studies did evaluate nocturnal acid breakthrough but these did not provide relevant patient important outcomes.

WITHDRAWN PICO 7.

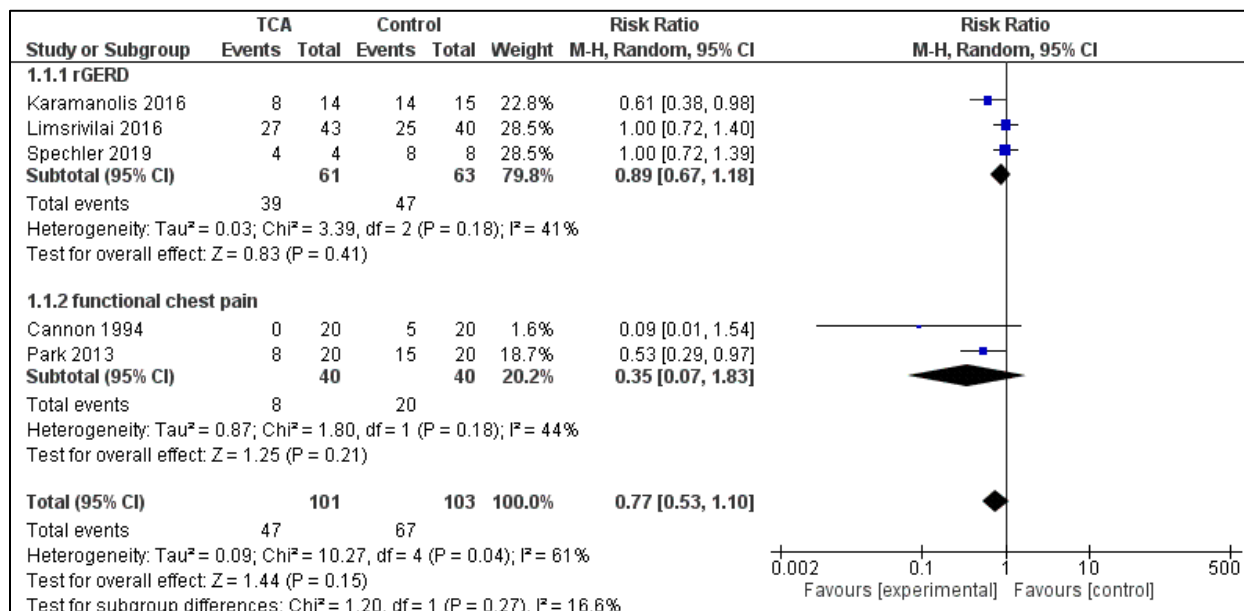
Does the addition of a (tricyclic) antidepressant in a patient with refractory reflux-like symptoms after 8 weeks of therapy with a BID PPI lead to a greater proportion of patients reporting symptom relief than continuing with BID PPI therapy alone?

GRADE: Very low quality of evidence supporting the statement

Key evidence: In 3 RCTs (N=124) evaluating TCAs in rGERD patients (who were not necessarily taking a PPI) there was no significant effect on reflux symptoms (RR = 0.89; 95% CI, 0.67 to 1.18).⁴¹⁻⁴³ Two additional trials (N=80) evaluated TCAs for functional chest pain,

however adding these studies did not produce a statistically significant effect (RR = 0.77; 95% CI, 0.53 to 1.10) (Figure 5).^{44,45} There were other studies that evaluated improvement, however, data were reported on a continuous scale only.

Figure 5: RCTs evaluating TCA in rGERD and functional chest pain



WITHDRAWN PICO 8.

Is an abnormal pH or pH-impedance study result in patients with refractory reflux-like symptoms associated with a greater proportion of patients achieving symptom relief after an anti-reflux procedure than a normal pH or pH-impedance study result?

GRADE: Not collected; surgery not done on patients with normal pH impedance studies

Key evidence: Literature searches were not conducted for the consensus meeting, since it was considered unlikely that a surgical procedure would be performed on patients with normal pH-studies. A recent multi-society consensus conference and guideline on the treatment of GERD did suggest upper endoscopy, manometry, and pH testing for all patients with esophageal symptoms of medically refractory reflux undergoing preoperative evaluation but noted that there was no direct comparative evidence that addressed this⁴⁶ and a recent case series reported that GERD patients with a negative pH study and negative endoscopy responded comparably to anti-

reflux surgery compared with those with a negative pH study and positive endoscopy and this with a positive pH study.⁴⁷ These data are not, however, sufficient to support endorsement or refutation of this PICO question.

Endoscopic or surgical management strategies

WITHDRAWN PICO 9.

Does a surgical anti-reflux procedure (e.g. Linx®) 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?

GRADE: Evidence difficult to interpret. 1 cross-over RCT

Key evidence: One RCT in patients with GERD comparing magnetic sphincter augmentation (MSA: Linx®) to BID PPI, included a subsequent cross-over in patients with rGERD (n=77). However, given the cross-over design, the study was difficult to interpret but it did claim a benefit for MSA.^{48,49} A recent meta-analysis concluded that MSA was safe and effective for rGERD but there were no additional RCTs and it recommended well-designed RCTs to compare MSA with other therapies.⁵⁰ A systematic review and meta-analysis reported that anti-reflux surgery was associated with superior short-term quality of life compared to PPI therapy although short-term symptom control was not significantly superior,⁵¹ and a more recent systematic review reported that the performance of Nissen fundoplication decreases over time.⁵² Although many patients in these studies will have had rGERD, the applicability of the results to rRLS patients is unclear.

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