



# Fundoplication versus oral proton pump inhibitors for gastroesophageal reflux disease: a systematic review and meta-analysis of randomized clinical trials

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## Abstract

Gastroesophageal reflux disease (GERD) is a widely studied and highly prevalent condition. However, few are reported about the exact efficacy and safety of fundoplication (FPT) compared to oral intake proton-pump inhibitors (PPI). This systematic review and meta-analysis of randomized clinical trials (RCT) aims to compare PPI and FPT in relation to the efficacy, as well as the adverse events associated with these therapies. Search carried out in June 2020 was conducted on Medline, Cochrane, EMBASE and LILACS. Selection was restricted to RCT comparing PPI and FPT (open or laparoscopic) in GERD patients. Certainty of evidence and risk of bias were assessed with GRADE Pro and with Review Manager Version 5.4 bias assessment tool. Ten RCT were included. Meta-analysis showed that heartburn (RD = -0.19; 95% CI = -0.29, -0.09) was less frequently reported by patients that underwent FPT. Furthermore, patients undergoing surgery had greater pressure on the lower esophageal sphincter than those who used PPI (MD = 7.81; 95% CI 4.79, 10.83). Finally, FPT did not increase significantly the risk for adverse events such as postoperative dysphagia and impaired belching. FPT is a more effective therapy than PPI treatment for GERD, without significantly increasing the risk for adverse events. However, before indicating a possible surgical approach, it is extremely important to correctly assess and select the patients who would benefit from FPT to ensure better results.

**Keywords** Gastroesophageal reflux · Fundoplication · Proton pump inhibitors · Systematic review · Meta-analysis

## Introduction

Gastroesophageal reflux disease (GERD) is a highly prevalent condition worldwide, with up to 33% of the population suffering from this condition [1]. The initial treatment is based on changing lifestyle and diet, avoiding foods and

drugs that trigger reflux, such as caffeine and nonsteroidal anti-inflammatory drugs, and maintaining health weight [2].

Since the development of the proton-pump inhibitors (PPI) in the late 1980s, which were designed to block the ultimate step in stomach acid secretion (the H<sup>+</sup>, K<sup>+</sup>-ATPase pump), the GERD management has undergone a drastic change [3]. The PPI has shown clearly superiority over other medical therapies, such as H<sub>2</sub>-receptor antagonists, antacids, anticholinergics, protective agents, gastrin antagonists and prostaglandins [4]. PPI has become one of the most prescribed drugs in the world, and nowadays, are even frequently overprescribed [5].

PPI has limitations, and not all GERD patients respond well to them. Some patients get dependent on the PPI use, and expenditure on these drugs during lifetime is considerably high [4, 5].

For those who do not respond to PPI, the surgical treatment is the main option. Fundoplication (FPT) is the most used anti-reflux surgery. Although some guidelines have been trying to orientate clinicians when to indicate surgery

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for GERD, few are reported about the exact efficacy and safety of FPT compared to oral intake PPI [6, 7].

This systematic review and meta-analysis of randomized clinical trials aims to compare PPI and FPT in relation to the efficacy, as well as the adverse events associated with these therapies.

## Methods

This systematic review was guided by PRISMA statement [8]. The details of the protocol for this systematic review were registered on PROSPERO [9] (CRD42020153448). The following outcomes were evaluated: Heartburn, regurgitation, dysphagia, LES pressure, flatulence, time exposure to pH < 4 in the 24-h pH monitoring, impaired belching, Gastrointestinal Symptom Rating Scale (GSRS), sustained remission, complication and adverse events.

### Database search

A systematic review was performed in Medline (PubMed), EMBASE, Cochrane (CENTRAL) and LILACS (BVS). In Medline (PubMed), the following search strategy was used: (Gastroesophageal Reflux OR Gastric Reflux OR Acid Reflux OR Esophageal Reflux OR GERD OR Gastroesophageal Reflux OR GORD) AND (Proton Pump Inhibitors OR Proton Pump Inhibitor OR PPI OR PPIs OR omeprazole OR lansoprazole OR esomeprazole OR pantoprazole OR rabeprazole OR medical management) AND (Fundoplication OR Nissen OR Toupet). For other databases, the search was performed with the same medical subject headings (MeSH) and keywords in various combinations.

### Study selection

The inclusion criteria were (I) patients with GERD; (II) Randomized clinical trials, comparing oral intake PPI with FPT; (III) relevant outcomes for this review. The exclusion criteria were (I) reviews, case reports, editorials and letters (II) transoral or endoscopic FPT (III) studies with no full text. No restrictions were set for language or period.

### Assessment of study quality

Certainty of evidence and risk of bias were assessed with the GRADE Pro [10] Guideline Development Tool and with Review Manager (RevMan) Version 5.4 bias assessment tool [12].

## Data extraction

Data were extracted manually and WebPlotDigitizer-4.2 [11] was used when the data were informed only in graphs. For the meta-analysis, Review Manager (RevMan) Version 5.4 [12] was used. Comparisons were demonstrated in risk difference (RD), mean difference (MD) and 95% confidence interval (95% CI). Inconsistency of effects on interventions was assessed using  $I^2$ . The random effects model was used if  $I^2 > 50\%$  and the fixed effects model if  $I^2 \leq 50\%$ . To access possible publication bias, we analyzed a funnel plot for asymmetry.

## Results

The search carried out in June 2020 retrieved 1806 articles (Fig. 1) of which 37 were selected to read the abstract. Twenty-five were then selected for full text evaluation. In agreement with the eligibility criteria, ten were included in this systematic review [13–22]. The baseline characteristics of each article are in Table 1, risk of bias for each included study in Fig. 2 and GRADE Pro certainty of evidence in Online Resource 1. Four articles are part of a single study [13–15]. Two other articles are also part of another single study [16, 17]. When more than one article in the same study reported the same outcome, only the article with most complete data was included.

### Heartburn

Heartburn was reported by 3 articles [14, 19, 20], totalizing 913 patients. The analysis showed that there were fewer patients with heartburn in the group that underwent FPT. (RD = -0.19; 95% CI = -0.29, -0.09;  $P = 0.0003$ ;  $I^2 = 73\%$ , random model; Certainty of evidence: moderate) (Fig. 3a).

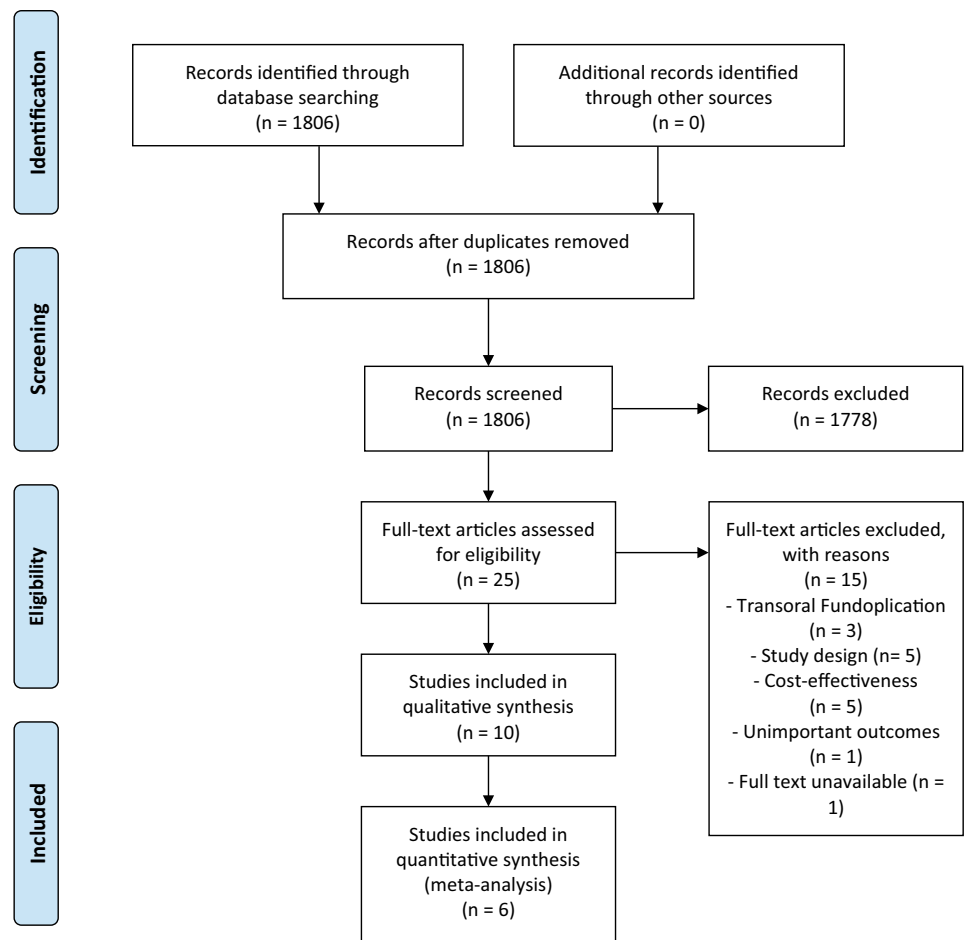
### Regurgitation

The analysis of 3 articles [13, 19, 20], totalizing 968 patients, showed that there was no significant difference between groups for regurgitation. (RD = -0.07; 95% CI = -0.18, 0.04;  $P = 0.18$ ;  $I^2 = 88\%$ , random model; Certainty of evidence: very low) (Fig. 3b).

### Percentage of time with pH lower than 4 in the 24-h pH monitoring

Three articles [13, 17, 18] (494 patients) reported the percentage of time with pH lower than 4 in 24 h measured by

**Fig. 1** PRISMA flow diagram



**Table 1** Studies characteristics

Article	Study design	Intervention (N)	Comparison (N)	Follow-up period
Grant M 2013	RCT	Laparoscopic fundoplication (178)	Omeprazole, lansoprazole or esomeprazole (179)	5 years
Lundell L 2008 <sup>a</sup>	RCT	Laparoscopic fundoplication (288)	Esomeprazole 20 mg/day (up to 40 mg/day) (266)	3 years
Mehta S 2006	RCT	Laparoscopic fundoplication (91)	Omeprazole 20 mg/day (53%) Lansoprazole 28 mg/day (27%) Other PPI (10%) Two or more PPIs (10%) (92)	7 years
Anvari M 2011 <sup>b</sup>	RCT	Laparoscopic fundoplication (52)	PPI <sup>c</sup> (mean: 56.2, 28.8 mg) (52)	3 years
Anvari M 2006 <sup>b</sup>				1 year
Mahon D 2005	RCT	Laparoscopic fundoplication (109)	Rabeprazole 10 mg/day Pantoprazole 20 mg/day Lansoprazole 15 mg/day Omeprazole or esomeprazole 20 mg/day (108)	3 months to 1 year
Lundell L 2009 <sup>d</sup>	RCT	Open fundoplication (144)	Omeprazole 20 mg/day (90%) or 40 mg/day (10%) (155)	12 years
Lundell L 2007 <sup>d</sup>				7 years
Lundell L 2001 <sup>d</sup>				5 years
Lundell L 2000 <sup>d</sup>				3 years

<sup>a</sup>LOTUS trial

<sup>b</sup>From a same study

<sup>c</sup>Does not determine which PPI was used

<sup>d</sup>SOPRAN study

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Anvari M 2006	+	+	-	-	+	+	+
Anvari M 2011	+	+	-	-	-	+	?
Grant M 2013	+	+	-	-	-	+	?
Lundell L 2000	+	+	-	-	-	+	?
Lundell L 2001	+	+	-	-	-	+	?
Lundell L 2007	+	+	-	-	-	+	?
Lundell L 2008	+	+	-	-	-	+	?
Lundell L 2009	+	+	-	-	-	+	?
Mahon D 2005	+	+	-	-	-	+	?
Mehta S 2006	+	+	-	-	+	+	+

**Fig. 2** Risk of bias summary for each included study. +: High risk, -: Low risk, ?: Unclear risk

pHmetry. Mahon et al. [18], in a short-term follow-up (up to 1 year), demonstrated that there was less exposure for those who underwent FPT (MD = -2.40; 95% CI = -4.23, -0.57;  $P=0.01$ ). However, the analysis of two articles [13, 17] in a medium-term follow-up (between 1 and 5 years) showed that there was no significant difference between the groups (MD = 1.81; 95% CI = -5.83, 9.45;  $P=0.64$ ;  $I^2=97%$ , random model). Furthermore, the analysis of the two subgroups showed that there was no significant difference between

treatments (MD = 0.41; 95% CI = -5.89, 6.71;  $P=0.90$ ;  $I^2=98%$ , random model; Certainty of evidence: very low) (Fig. 3c).

### LES pressure (mmHg)

The comparison of manometry performed by two articles, one for short-term [18] and the other for medium-term [17] follow-up, showed that in both there was greater pressure from the LES (mmHg) in those who performed FPT (MD = 7.81; 95% CI 4.79, 10.83;  $P<0.00001$ ;  $I^2=69%$ , random model; Certainty of evidence: moderate) (Fig. 3d).

### Sustained remission

Data analysis showed that there was no significant difference between groups for sustained remission in an analysis of 807 patients from 2 articles [13, 19] (RD = 0.10; 95% CI = -0.19, 0.39;  $P=0.49$ ;  $I^2=96%$ , random model; Certainty of evidence: very low) (Fig. 3e).

### Gastrointestinal symptom rating scale (GSRS)

Analysis of the GSRS, questionnaire applied by two articles [13, 19] with 665 patients in total, showed that there was no significant difference between groups (MD = -0.28; 95% CI = -0.62, 0.07;  $P=0.11$ ;  $I^2=92%$ , random model; Certainty of evidence: very low) (Fig. 4a).

### Dysphagia

The analysis of three articles (totaling 911 patients) [13, 19, 20] demonstrated no significant difference in the presence of postoperative dysphagia in patients (RD = 0.04; 95% CI = -0.03, 0.11;  $P=0.26$ ;  $I^2=72%$ , random model; Certainty of evidence: very low) (Fig. 4b).

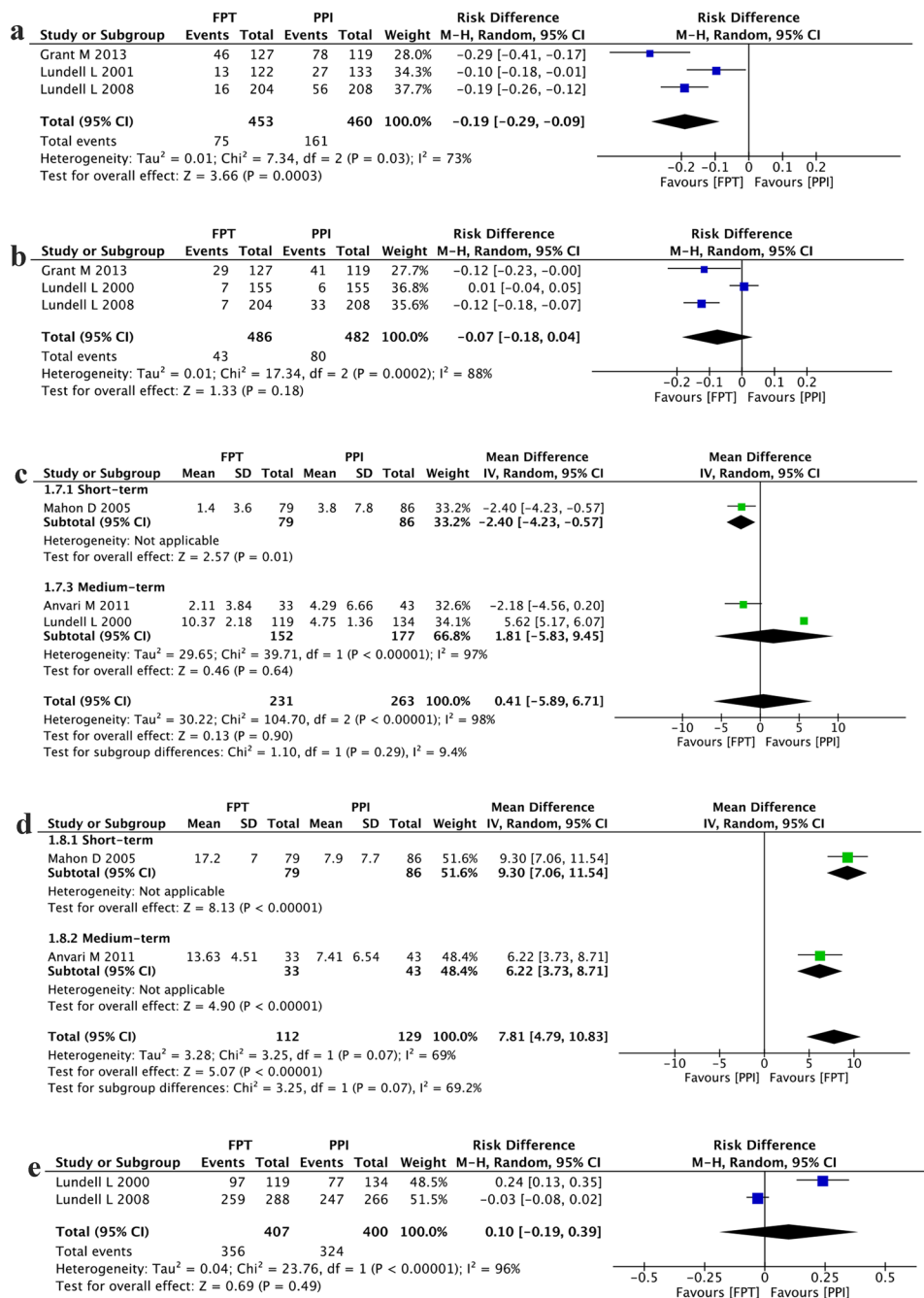
### Adverse events

Two articles [13, 19] that reported flatulence and analyzed a total of 665 patients demonstrated that there was a lower incidence of flatulence in the group that used PPI (RD = 0.36; 95% CI = 0.29, 0.42;  $P<0.00001$ ;  $I^2=44%$ , fixed model; Certainty of evidence: low) (Fig. 4c).

The analysis of two articles [14, 20] (501 patients) that reported impaired belching showed that there was no significant difference between the therapies (RD = 0.02; 95% CI = -0.30, 0.34;  $P=0.91$ ;  $I^2=95%$ , random model; Certainty of evidence: very low) (Fig. 4d).

Three articles reported that 4.5% [20], 2.2% [21] and 3.7% [18] of the patients had to redo the FPT. Other three articles showed that 0.9% [20], 4.0% [17] and 4.4% [21]

**Fig. 3** Forest plots **a** Heartburn **b** Regurgitation **c** Percentage of time with pH lower than 4 in the 24-h pH monitoring **d** LES pressure (mmHg) **e** Sustained remission

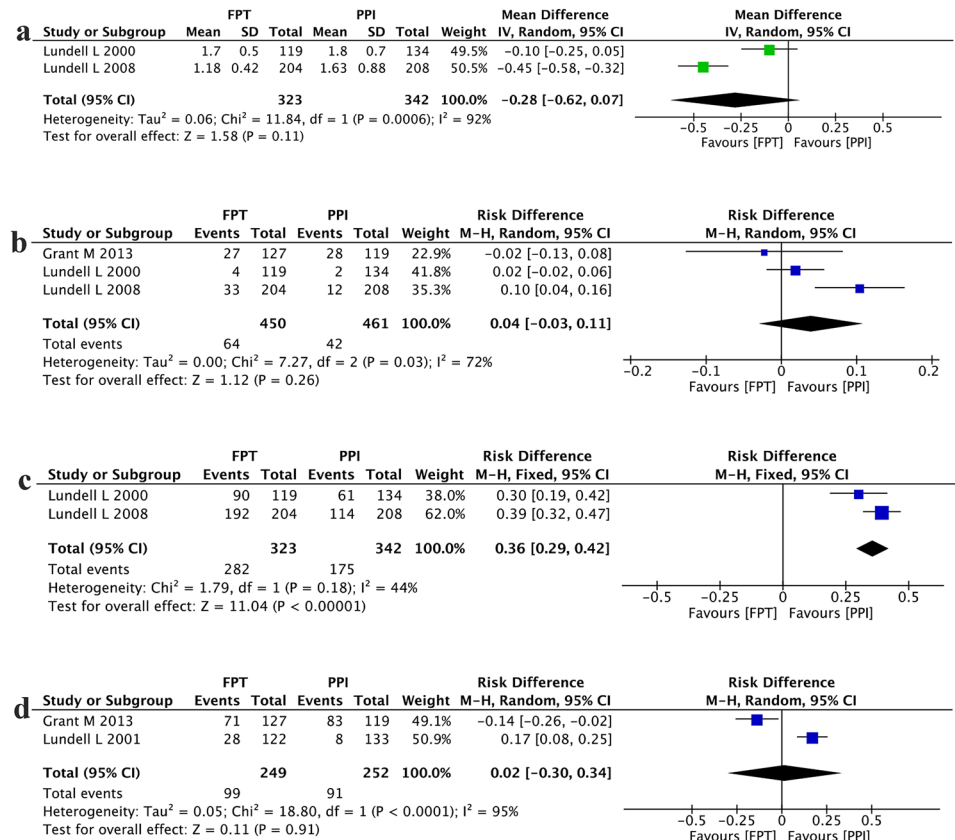


needed to perform esophageal dilation. In the medication arm, in three articles (18% [21], 13.9% [18] and 23.4% [13] an increase in the dose of PPI was reported. Mehta et al.[21] reported that 10% of the patients had to change the type of PPI due to headache, vomiting or abdominal pain. Lundell et al. [19] reported that 14.3% of the patients using PPI and 21% from the surgical arm had serious adverse events, leading to the discontinuation of 3.8% of the patients from the medication arm.

## Discussion

This systematic review and meta-analysis demonstrated that FPT is more effective therapy for the GERD, resulting in a lower number of heartburn complaints, and with higher LES pressure, when compared with patients treated with oral PPI. Furthermore, the risk for adverse events is similar between the groups, without significant difference for dysphagia.

**Fig. 4** Forest Plots **a** GSRS **b** Dysphagia **c** Flatulence **d** Impaired belching



This result can be explained by the fact that the PPI therapy, unlike FPT, does not neutralize de non-acid reflux, such as bile reflux, enzymes or foods [23–25], or by the fact that PPIs are not able to alkalize all gastric contents [26]. In addition, if present, hiatal hernia will not be corrected by PPI. Another hypothesis that may justify the greater effectiveness of FPT compared to PPI therapy is that its efficacy depends on the correct use of the medication, and thus, patients who use it irregularly may have unsatisfactory results.

Nevertheless, proper patient evaluation for better selection of those who would benefit from drug or surgical therapy is paramount for GERD treatment success. A well-done anamnesis, with adequate preoperative exams and shared decision making with the patient is essential for obtaining the best results and greater patient satisfaction.

Once the FPT is more effective than oral PPI, a subgroup of GERD patients that would probably benefit from FPT are those with severe erosive esophagitis. The treatment of erosive esophagitis with PPI demonstrates greater failure in patients with severe degrees than those with milder degrees [27]. On the other hand, Park et al. [28] showed that 88.6% of patients with severe erosive esophagitis had complete resolution of symptoms after FPT.

Another subgroup of GERD patient that would likely benefit from FPT are those with severe respiratory symptoms,

such as asthma attacks known to be related to GERD. Tustumi et al. [29] in a meta-analysis demonstrated that dependence on oral corticosteroids in asthmatic patients with GERD treated with anti-reflux surgery decreased by 58.9%, and that surgical therapy showed better results than drug treatment in this group of patients (RD = -0.46; 95% CI = -0.77, -0.16).

Other group of GERD patients that could benefit from surgical treatment is patients with low adherence to continuous drug treatment and patients with non-acid reflux [30].

In our analysis, there was no difference between surgery and drug treatment for dysphagia. Early postoperative dysphagia usually is related to technical failures, such as twisted valve, tight valve or hiatoplasty, and valve migration [31–34]. Consequently, when indicated, the surgical intervention should be performed by experienced surgeons, avoiding the risk of postoperative dysphagia. Another issue that may impact on the dysphagia is the surgical technique. Toupet's FPT shows less postoperative dysphagia than Nissen's [35–38]. In the present review, we were unable to do subgroup analysis accordingly to the surgical technique due to lack of crucial information for this analysis.

Although PPIs are the most known and used drugs for GERD, other treatments are emerging, such as the potassium-competitive acid blockers. In a network meta-analysis, Miyazaki et al. [39] had shown that vonoprazan is more

effective than most PPIs for patients with severe erosive esophagitis, but it didn't have superior GERD healing effects than PPIs. However, to date, there are no clinical trials comparing Vonoprazan and FPT.

This review has several limitations. All articles were classified as having a high risk of bias, as they did not blind the evaluators, which may influence subjective outcomes, and had major drop-outs during follow-up (Fig. 2). To minimize the risk of selection bias, only randomized controlled trials were selected. The different follow-up times across the studies may also have influenced the results. Only two articles (both from the same series) reported long-term outcomes, publishing results after 7 and 12 years (15, 16). In fact, further studies are needed to assess long-term safety, since the prolonged use of PPIs is not without risks. Islam et al. [40], in a meta-analysis, reported long-term use of PPI has increased risk for gastric cancer, community-acquired pneumonia, hip fracture, and kidney disease. Other meta-analyses also associated long-term PPI intake with fractures [41] and hypomagnesemia [42]. In addition, none of the included studies evaluated Asian population. Future clinical trials are necessary, with well-standardized surgical techniques and well-defined drug dosage, evaluating long-term outcomes, both in Western and in Asian populations.

## Conclusion

FPT is a more effective therapy than PPI treatment for GERD, without significantly increasing the risk for adverse events, although future trials are needed to evaluate long-term outcomes. Before indicating a possible surgical approach, it is extremely important to correctly assess and select the patients who would benefit from FPT, such as patients with severe erosive esophagitis, severe respiratory symptoms, non-acid reflux and those with low adherence to continuous drug treatment, to ensure better results.

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## Compliance with ethical standards

**Ethical Statement** This article does not contain any studies with human or animal subjects performed by any of the authors.

**Conflict of interest** LST reports grants from Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), during the conduct of the study. The other authors declare that they have no conflict of interest.

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