

Addition of prokinetics to PPI therapy in gastroesophageal reflux disease: A meta-analysis

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Abstract

AIM: To investigate the efficacy of adding prokinetics to proton pump inhibitors (PPIs) for the treatment of gastroesophageal reflux disease (GERD).

METHODS: PubMed, Cochrane Library, and Web of Knowledge databases (prior to October 2013) were systematically searched for randomized controlled trials (RCTs) that compared therapeutic efficacy of PPI alone (single therapy) or PPI plus prokinetics (combined therapy) for GERD. The primary outcome of those selected trials was complete or partial relief of non-erosive reflux disease symptoms or mucosal healing in erosive reflux esophagitis. Using the test of heterogeneity, we established a fixed or random effects model where the risk ratio was the primary readout for measuring efficacy.

RESULTS: Twelve RCTs including 2403 patients in total were enrolled in this study. Combined therapy was

not associated with significant relief of symptoms or alterations in endoscopic response relative to single therapy (95%CI: 1.0-1.2, $P = 0.05$; 95%CI: 0.66-2.61, $P = 0.44$). However, combined therapy was associated with a greater symptom score change (95%CI: 2.14-3.02, $P < 0.00001$). Although there was a reduction in the number of reflux episodes in GERD [95%CI: -5.96-(-1.78), $P = 0.0003$] with the combined therapy, there was no significant effect on acid exposure time (95%CI: -0.37-0.60, $P = 0.65$). The proportion of patients with adverse effects undergoing combined therapy was significantly higher than for PPI therapy alone (95%CI: 1.06-1.36, $P = 0.005$) when the difference between 5-HT receptor agonist and PPI combined therapy and single therapy (95%CI: 0.84-1.39, $P = 0.53$) was excluded.

CONCLUSION: Combined therapy may partially improve patient quality of life, but has no significant effect on symptom or endoscopic response of GERD.

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Key words: Gastroesophageal reflux diseases; Proton pump inhibitors; Prokinetics; GABA-B receptor agonists; Treatment; Meta-analysis

Core tip: Proton pump inhibitors (PPIs) are generally accepted as the standard treatment of care for gastroesophageal reflux disease (GERD). However, many patients undergoing PPI treatment have no effective symptomatic relief. Although many studies have shown the clinical efficacy of adding prokinetics to PPI therapy in GERD, others have shown no therapeutic benefit. The efficacy and safety of combined prokinetic and PPI therapy for GERD remain controversial. In this retrospective meta-analysis, we find no advantage for the addition of prokinetics to a PPI therapeutic regimen, relative to PPI alone. However, combination therapy may improve symptom score and patient quality of life.

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INTRODUCTION

Gastroesophageal reflux disease (GERD) is a common condition affecting 10%-20% of Europeans^[1] and 3%-7% of Asians^[2]. Based on an endoscopy study, the prevalence of erosive reflux esophagitis (RE), a chronic form of GERD associated with damage to the esophagus, ranges from 6% to 10% in Asia^[3]. Since RE is more likely to be detected by endoscopy than non-erosive reflux disease (NERD), the incidence of RE is higher than that of NERD. Symptoms of GERD, which include heartburn, non-cardiac chest pain, acid regurgitation, chronic cough, bloating and belching, may seriously affect quality of life of some patients. Furthermore, GERD is linked with serious complications, such as hemorrhage, peptic stricture, Barrett's esophagus, and esophageal adenocarcinoma^[3-5]. Both NERD and RE are subtypes of GERD. NERD presents clinically with acid reflux and heartburn with no mucosal break, whereas RE patients have mucosal damage detectable by endoscopy^[6]. The mechanisms underlying GERD may include esophageal hypersensitivity and transient lower esophageal sphincter relaxation (TLESR)^[7]. Studies show that changes in diet, physical activity, and BMI increase the risk for GERD^[3]. NERD may be due to visceral hypersensitivity, prolonged contraction of the lower esophagus, and other psychological factors^[8].

Proton pump inhibitors (PPIs) are generally accepted as the standard treatment paradigm for GERD. Although many patients with RE have symptomatic relief with this drug alone^[9], many patients have no symptomatic resolution^[10-13]. Overall, 30% of GERD patients, 10%-15% of RE patients, and 40%-50% of NERD patients do not experience symptom alleviation with conventional PPI therapy^[14-16]. New PPI formulations and regenerative types of acid-suppressive drugs for GERD are urgently needed.

Prokinetics are agents that increase lower esophageal sphincter pressure (LESP), enhance esophageal peristalsis, and augment gastric emptying. These include 5-hydroxy-tryptamine (5-HT) receptor agonists, GABA-B receptor agonists, dopamine receptor antagonists, and others. Five-HT receptor agonists increase acetylcholine release from parasympathetic nerve roots and promote gastric emptying and bowel motility^[14,17], and are frequently used in combination with PPI therapy. Cisapride is a canonical prokinetic agent with equal efficacy as a 5-HT₄ receptor agonist and a H₂ histamine receptor antagonist. In addition to protecting the esophageal mucosa, it was reported that cisapride increased LEST and esophageal peristaltic amplitude; however, cisapride is now prohibited in Eu-

rope due to its detrimental side effects on the cardiac system^[18]. Mosapride, another 5-HT₄ agonist, is a structural analog of cisapride with less cardiac side effects^[19,20]. It has been approved in Asia for the treatment of some functional gastrointestinal disorders, such as functional dyspepsia. Baclofen and lesogaberan (AZD 3355) were developed as selective GABA-B agonists based on their inhibition of TLESR and reflux episodes^[21]. A phase II study reported that lesogaberan combined with PPI modestly improved GERD symptoms^[22], but its efficacy and safety were not determined.

Although many studies have shown that addition of a prokinetic to PPI can improve the symptoms of GERD, there is still some controversy in the literature. The efficacy and safety profiles of combination prokinetics and PPI therapy regimens relative to PPI monotherapy for GERD remain unclear. Here, we performed a retrospective meta-analysis to identify the efficacy and safety of these two types of treatments in GERD.

MATERIALS AND METHODS

Literature search

All eligible articles in English published prior to October 2013 were searched from PubMed, Cochrane Library, and Web of Knowledge. The search strategy consisted of a combination of the following MESH terms and text words: gastroesophageal reflux diseases, GERD, non-erosive reflux diseases, NERD, reflux esophagitis, RE, proton pump inhibitors, PPI, prokinetics, and GABA-B receptor agonists. A Cochrane filter for identifying randomized controlled trials (RCTs) was applied to the search results, and all potentially relevant abstracts and citations were retrieved for further review. Furthermore, we searched the bibliographies of selected trials obtained through the electronic screen to identify additional studies of interest.

Criteria for inclusion

Articles were eligible for inclusion in this meta-analysis if they met the following criteria: (1) Participants were diagnosed with GERD (RE or NERD); (2) Participants were 18 years or older; (3) Patients receiving PPI monotherapy were compared with patients receiving combined prokinetic and PPI therapy; (4) The study was a RCT; (5) Criteria for successful treatment were clearly defined; and (6) Treatment lasted for two or more weeks.

Criteria for exclusion

Publications were excluded according to the following criteria: (1) Studies comparing H₂ receptor antagonist plus prokinetic to H₂ receptor antagonist; (2) Participants with complications in addition to GERD; and (3) Missing or unclear data for final outcomes of interest.

Data extraction

To avoid bias in the data abstraction process, two investigators (Ren LH and Chen WX) independently abstracted

Table 1 Characteristics of the 12 randomized controlled trials included in this meta-analysis of the effects of combined prokinetic and proton pump inhibitor therapy in gastroesophageal reflux diseases *n* (%)

Ref.	Country	Participants (<i>n</i>)	Duration of study	Female	Age (yr)	BMI (kg/m ²)
Vakil <i>et al</i> ^[23] , 2013	United States	460	6 wk	254 (55.2)	44	28
Cho <i>et al</i> ^[24] , 2013	South Korea	50	4 wk	26 (52.0)	46	21
Shaheen <i>et al</i> ^[28] , 2013	United States	661	4 wk	376 (56.9)	48	28
Ndraha <i>et al</i> ^[29] , 2011	Indonesia	60	2 wk	40 (66.7)	42	24
Hsu <i>et al</i> ^[2] , 2010	Taiwan	96	8 wk	48 (50.0)	47	24
Boeckstaens <i>et al</i> ^[22] , 2011	United States	244	4 wk	82 (33.6)	50	27
Miwa <i>et al</i> ^[12] , 2011	Japan	200	4 wk	120 (60.0)	52	22
Beaumont <i>et al</i> ^[27] , 2009	United States	16	2 wk	8 (50.0)	54	Not reported
Madan <i>et al</i> ^[19] , 2004	India	68	8 wk	23 (33.8)	35	Not reported
Smythe <i>et al</i> ^[30] , 2003	United Kingdom	23	4 wk	3 (13.0)	62	Not reported
van Rensburg <i>et al</i> ^[25] , 2001	United Kingdom	350	8 wk	213 (60.9)	47	28
Vigneri <i>et al</i> ^[26] , 1995	Italy	175	12 mo	58 (33.1)	45	Not reported

Table 2 Symptom response in ten studies

Ref.	Intervention	Combined therapy, improved/treated	Single therapy, improved/treated
Cho <i>et al</i> ^[24] , 2013	Esomeprazole 40 mg/d + mosapride 30 mg <i>tid</i>	19/24	13/19
Hsu <i>et al</i> ^[2] , 2010	Lansoprazole 30 mg/d + mosapride 5 mg <i>tid</i>	39/44	41/50
Madan <i>et al</i> ^[19] , 2004	Pantoprazole 40 mg <i>bid</i> + mosapride 5 mg <i>tid</i>	25/28	23/33
Miwa <i>et al</i> ^[12] , 2011	Omeprazole 10 mg/d + mosapride 5 mg <i>tid</i>	45/97	42/95
van Rensburg <i>et al</i> ^[25] , 2001	Pantoprazole 40 mg/d + cisapride 20 mg <i>bid</i>	120/173	129/177
Vigneri <i>et al</i> ^[26] , 1995	Omeprazole 40 mg/d + cisapride 10 mg <i>tid</i>	31/35	28/35
Beaumont <i>et al</i> ^[27] , 2009	PPI + baclofen 20 mg <i>tid</i>	4/12	6/12
Boeckstaens <i>et al</i> ^[22] , 2011	PPI + lesogaberan 65 mg <i>bid</i>	21/104	11/105
Shaheen <i>et al</i> ^[28] , 2013	PPI + lesogaberan 60/120/180/240 mg <i>bd</i>	110/458	22/122
Vakil <i>et al</i> ^[23] , 2013	PPI + baclofen 20/40/60 mg <i>qd</i>	110/240	21/54

PPIs: Proton pump inhibitors.

the data, recorded the first author, year of study, study design, and study population characteristics, and compared the results. All data were checked by a third reviewer and disagreements were resolved by discussion.

Statistical analysis

Appropriate RCTs were included, and Review Manager Version 5.1 (The Cochrane Collaboration, Oxford, England) was used for preparation of the review. Stata 12.0 software (StataCorp, College Station, TX, United States) was used for statistical analysis. The risk ratio of data was estimated by the Mantel-Haenszel χ^2 method, where *P* values < 0.05 were considered significantly different. Study heterogeneity was evaluated by Cochran *I*² statistics, where *I*² < 50% indicated a lack of heterogeneity. If significant heterogeneity was found, a random effects model was applied for evaluation of the pooled data; otherwise, a fixed effects model was used. Possible publication bias was assessed by Egger's and Begg's funnel plots, where *P* values < 0.05 indicated little publication bias.

RESULTS

Twelve RCTs met the inclusion criteria, and characteristics of each study are presented in Table 1. In total, there were 2403 enrolled participants in the trials who were treated with 5-HT agonists, GABA-B receptor agonists,

dopamine-receptor antagonists, and placebo control. Combination 5-HT agonist and PPI therapy was given in seven trials, combination GABA-B receptor agonist and PPI therapy in four trials, and combination dopamine-receptor antagonist and PPI therapy in one trial. In all RCTs, monotherapy was directly compared with combination PPI therapy. In the 5-HT agonist studies, the doses of PPI and mosapride or cisapride were the same across patients. However, in the GABA-B receptor agonist studies, different kinds of PPI and variable doses of baclofen or lesogaberan were used. All trials included mild to moderate GERD patients, with severe participants divided into a subgroup. The primary endpoints evaluated in these trials were symptom or endoscopic response, and the relief score was used to determine the symptomatic remission.

Symptom response

Table 2 details the symptom response in ten studies. Six trials^[2,13,20,25-27] compared the addition of mosapride or cisapride to PPI therapy to PPI alone therapy, and four trials^[23,24,28,29] compared baclofen or lesogaberan to placebo PPI control. There was no statistically significant difference in symptom response between combined therapy and single therapy in these ten trials (95%CI: 1.0-1.2, *P* = 0.05) (Figure 1A). Furthermore, we divided those ten trials into a 5-HT agonist group and a GABA-B recep-

tor agonist group and found that neither group displayed significant differences between combination and monotherapy for symptom response (95%CI: 1.0-1.2, $P = 0.21$; 95%CI: 0.8-1.7, $P = 0.40$) (Figure 1B and C).

Symptom score change

The 5-HT receptor agonist group showed a change in symptom score in the two treatment groups, even though the symptom assessments were different. Since Ndraha^[29] and Hsu *et al*^[2] used the frequency scale for the symptoms of gastroesophageal reflux (FSSG) score, we combined the two trials to assess the change in symptom score. Combination therapy yielded more symptomatic relief relative to monotherapy (95%CI: 2.1-3.0, $P < 0.00001$) (Figure 1D). Although symptom response in these two treatment groups was not statistically different, the clinical symptoms in the combination therapy group were relieved more than the single therapy group. Overall, these findings suggest that combined therapy may have improved patient quality of life.

Endoscopic response

To explore the mucosal healing in RE patients, we investigated the endoscopic response in two trials^[19,25] where endoscopic response was reported. Overall, the endoscopic response in RE patients was not significantly different between 5-HT agonist and PPI combined therapy and PPI single therapy (95%CI: 0.7-2.6, $P = 0.44$) (Figure 1E).

Reflux wave amplitude and wave duration

Two trials^[24,29] reported LESP, reflux wave amplitude, and wave duration. As shown in Figure 1F, combined therapy may reduce reflux wave amplitude [95%CI: -6.0-(-1.8), $P = 0.0003$] but not wave duration (95%CI: -0.4-0.6, $P = 0.65$) (Figure 1G). Taken together, these findings suggest that combined therapy in GERD may reduce the number of reflux episodes but not the duration of acid exposure time.

Proportion of adverse effects

Combined prokinetic and PPI therapy may be linked to additional side effects, such as reflux, abdominal pain, indigestion, diarrhea, chest pain, and constipation. Since only six of the 12 trials reported adverse effects, we only included these studies in our proportional analysis. The side-effects ratio demonstrated that side effects were elevated in patients with combined relative to single PPI therapy (95%CI: 1.06-1.36, $P = 0.005$) (Figure 1H). To further explore the side-effects of the 5-HT group, we excluded the GABA-B receptor agonists group. However, we found no difference between the two therapies for the 5-HT agonist group (95%CI: 0.84-1.39, $P = 0.53$) (Figure 1I). Single side-effects ratio in the GABA-B receptor agonist group was evaluated, and there were significantly more side effects in the GABA-B receptor agonists combined group than in the group with PPI therapy alone (95%CI: 1.1-1.5, $P = 0.004$) (Figure 1J).

Publication bias

As shown in Figure 2, no publication bias was detected

in symptom response (Egger's test $P = 0.333$; Begg's test $P = 0.721$) or adverse event proportion (Egger's test $P = 0.246$; Begg's test $P = 0.452$).

DISCUSSION

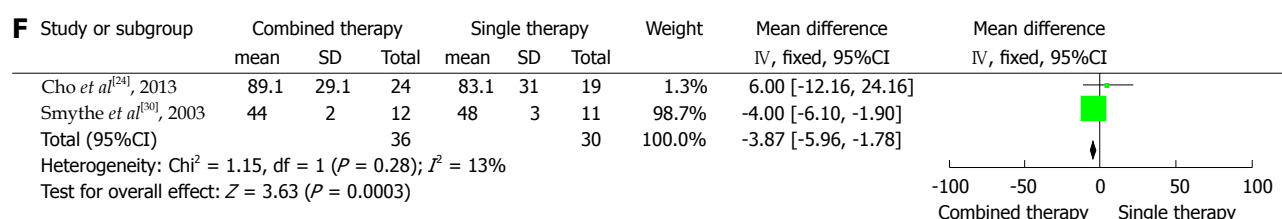
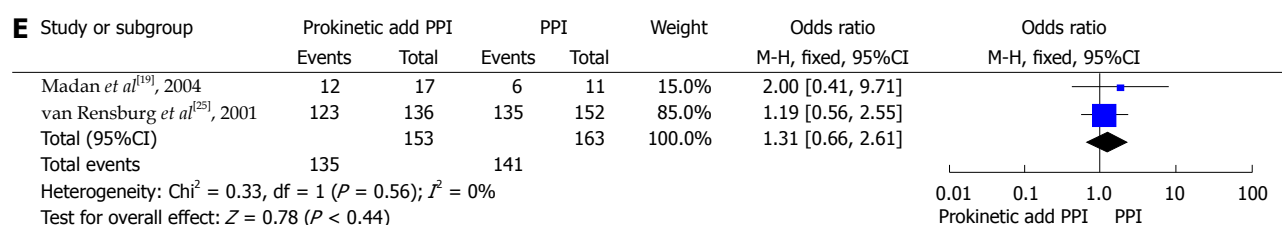
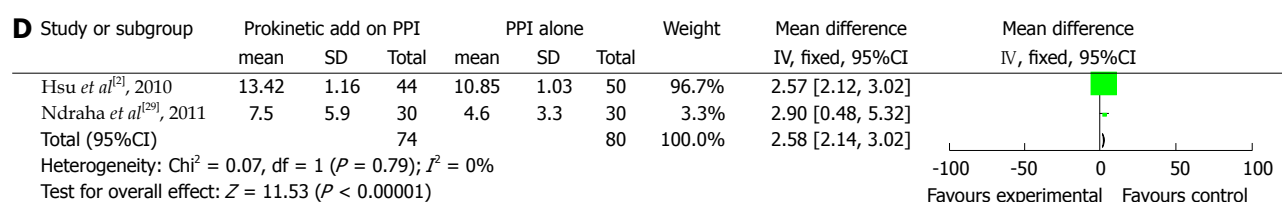
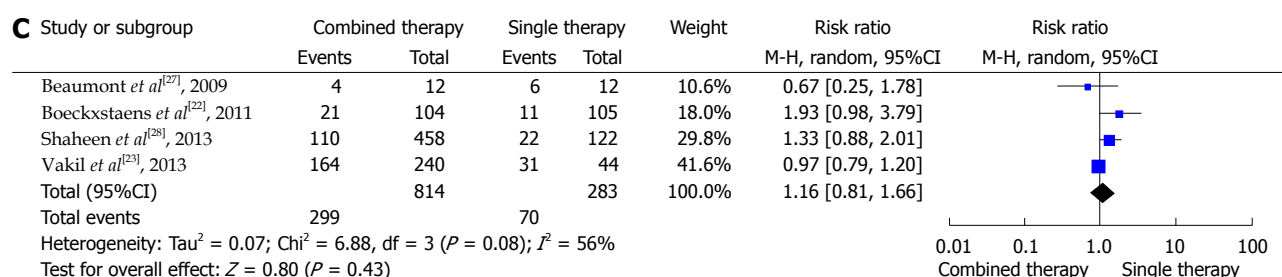
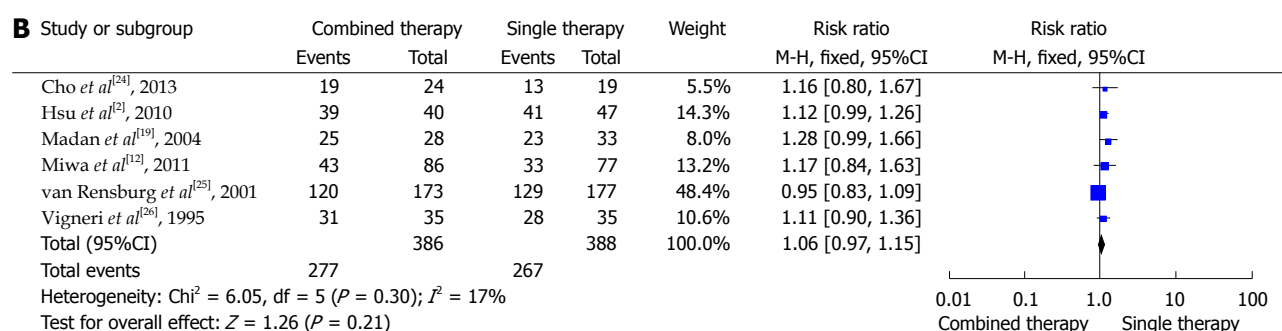
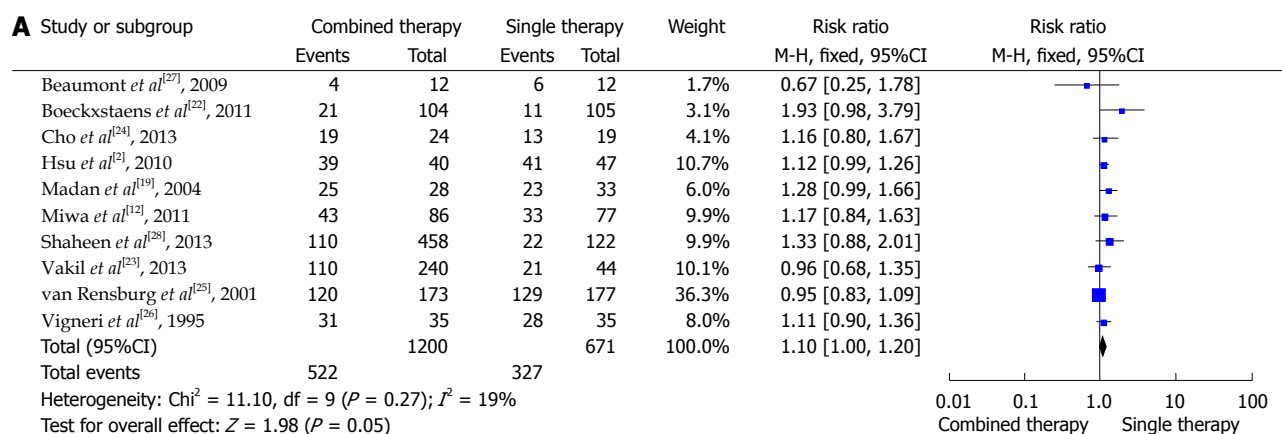
Previous studies have reported that PPI therapy was more effective than H2R agonists and prokinetics for GERD^[4], but none had investigated the efficacy of combined prokinetic and PPI therapy. In this systematic review and meta-analysis, we demonstrated that combination prokinetic and PPI therapy was no more efficacious than PPI alone for GERD. This therapy did improve patients' reported symptoms score, suggesting that it may enhance patient quality of life.

Since the 1990s, PPIs have been the mainstay treatment for GERD^[31] even though a large number of patients fail to improve with a standard single PPI therapy^[7]. Approximately 15% of eosinophilic esophagitis (EE) patients (mainly of Los Angeles grades C and D), 20% of Barrett's esophagus (BE) patients, 40%-50% of NERD patients^[15], and up to 40% of patients with extra-esophageal manifestations of GERD^[32] did not therapeutically benefit from standard PPI therapy. Recently, a number of studies found that PPIs are less effective for NERD than RE^[10,13,15,33], but the underlying mechanism remains unknown.

Hiyama *et al*^[34] evaluated whether *Helicobacter pylori* infection and sex may contribute to attenuated PPI efficacy in NERD. Miyamoto *et al*^[33] identified younger age, constipation, and GI dysmotility as potential influencing factors of PPI non-responsiveness in NERD. Adding a prokinetic to PPI may partly alleviate symptoms of NERD, but there is little evidence available regarding an impact on mucosal healing^[35]. However, Koshino *et al*^[16] demonstrated that mosapride (15 mg/d) did not change salivary secretion and esophageal motility in healthy volunteers.

There are available different PPIs for the treatment of GERD, including omeprazole, lansoprazole, rabeprazole, pantoprazole, esomeprazole, and others. Meta-analyses failed to reveal a difference in efficacy for symptom relief among various PPIs^[36]. Prokinetics in addition to PPI therapy may be a new treatment paradigm for PPI-non responsive patients. The GABA-B agonists, baclofen and lesogaberan, were reported to be effective in treating GERD by reducing LES pressure, LES relaxations, and acid reflux episodes^[37]. Unfortunately, its clinical use is limited by side effects, including dizziness and constipation^[9].

Here, we analyzed 12 RCTs to determine the therapeutic benefit of combination prokinetic and PPI therapy over PPI therapy alone. We found no significant difference between these two groups regarding symptom or endoscopic response. When we divided these 12 trials into two groups, according to 5-HT agonist and GABA-B agonist, we still did not find any difference between the combination and single therapy groups. Regarding adverse events, GABA-B agonists, but not 5-HT agonists, were associated with increased frequency of adverse effects. In



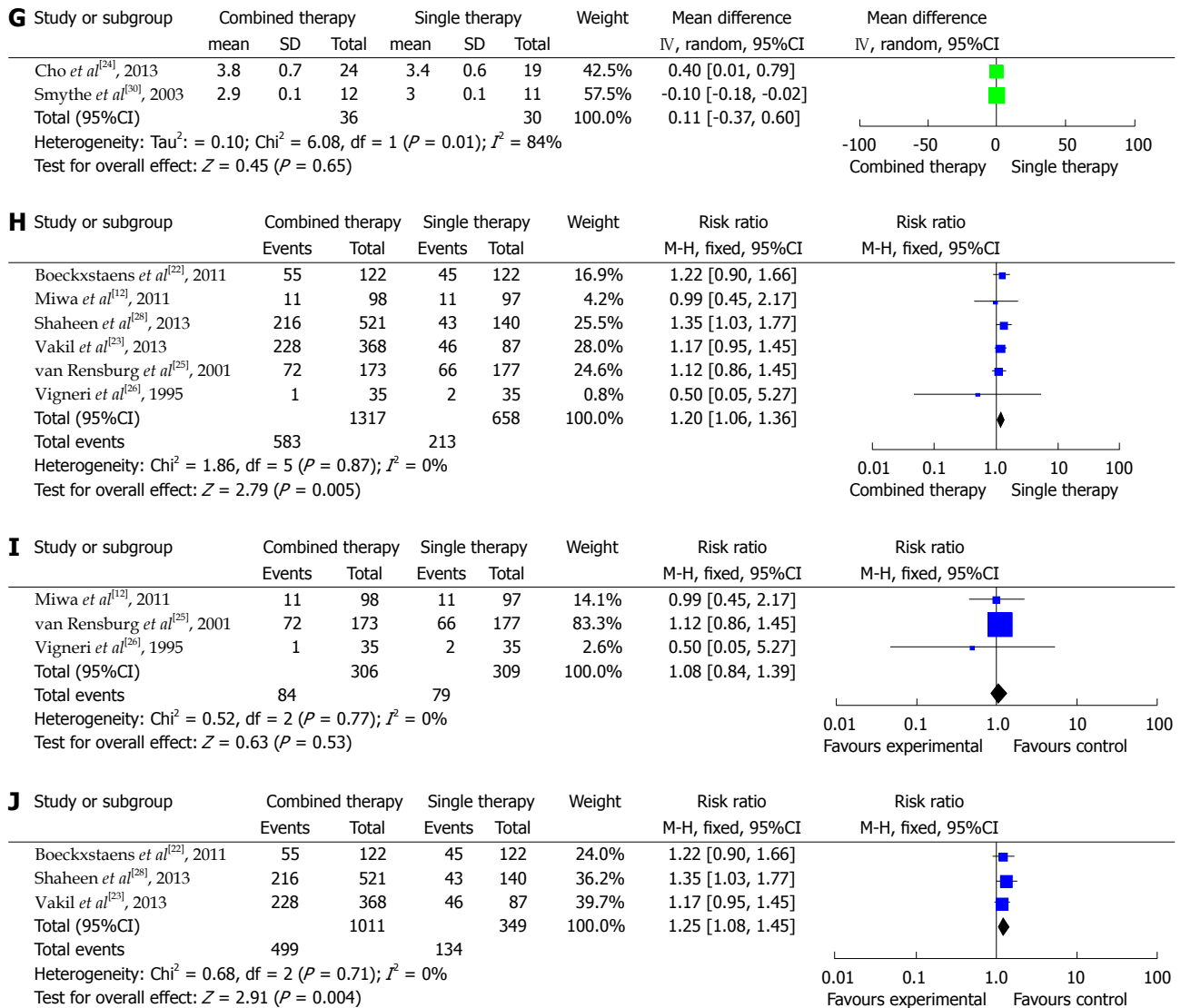


Figure 1 Meta-analysis. A: Symptom response in 5-hydroxytryptamine (5-HT) and GABA-B receptor therapies; B: Symptom response in the 5-HT receptor agonist group; C: Symptom response in the GABA-B receptor agonist group; D: Symptom score change (FSSG) in the two therapies; E: Endoscopic response in 5-HT and GABA-B receptor therapies; F: Wave amplitude in 5-HT and GABA-B receptor therapies; G: Wave duration in 5-HT and GABA-B receptor therapies; H: Adverse events proportion in 5-HT and GABA-B therapies; I: Adverse events in 5-HT agonist group; J: Adverse events in GABA-B receptor agonist group.

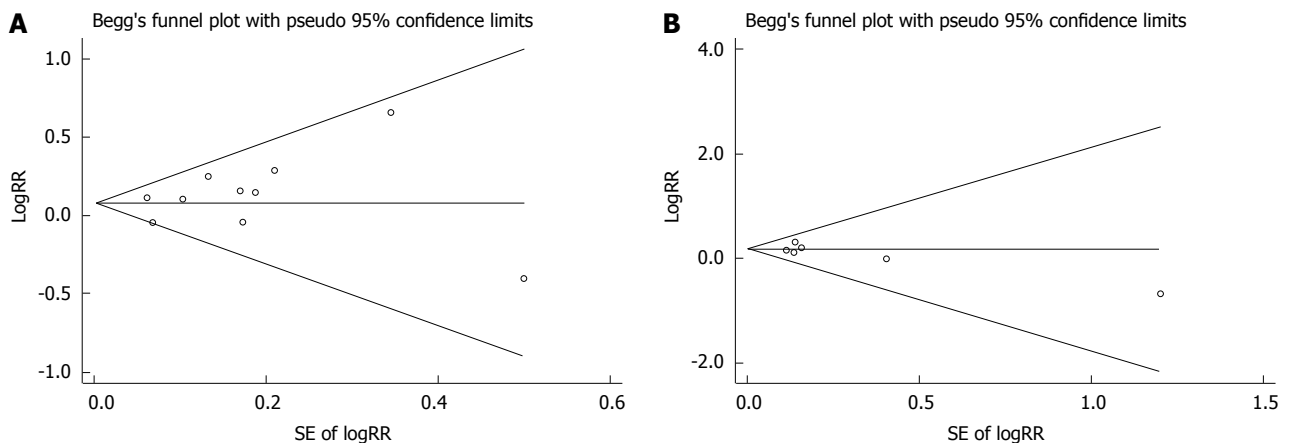


Figure 2 Funnel plots for publication bias in meta-analysis. A: No publication bias was detected in symptom response (Egger's test $P = 0.333$; Begg's test $P = 0.721$); B: Adverse event proportion (Egger's test $P = 0.246$; Begg's test $P = 0.452$).

terms of symptom score change, combined therapy may improve patient quality of life by decreasing the number of reflux episodes, although acid exposure time was unaltered.

There are some limitations of our meta-analysis to consider. First, PPI and prokinetic therapies in the 12 trials were not identical. Although one study found little impact on symptom response^[36], we cannot rule out the possibility of treatment course affecting this measure. To limit this complication, we only chose studies for this analysis with a treatment course for GERD longer than two weeks. Second, an inherent weakness of all systematic reviews and meta-analyses is the possibility that some studies failed to find significant symptom improvement in the peer-reviewed literature^[38], thereby leading us to underestimate the main effect. To overcome these limitations, long-term RCTs need to be performed with a larger quantity of participants to more effectively determine efficacy and safety profiles of combined prokinetic and PPI therapy.

In summary, patients with GERD respond to combined prokinetic and PPI therapy. Combination therapy may improve patient quality of life, although there was no significant difference in symptom or endoscopic responses. Side effects of combined therapy may be greater than single therapy, especially with GABA-B agonists. Whether prokinetic plus PPI is indeed therapeutically efficacious for GERD will require future trials.

COMMENTS

Background

Gastroesophageal reflux disease (GERD) is a common disease, affecting individuals of all nationalities. The standard treatment regimen is proton pump inhibitors (PPIs). Despite this therapy, many patients remain symptomatic. The addition of prokinetics to PPI therapy may improve the symptoms of GERD in these patients, but the efficacy and safety of prokinetics remain to be established.

Research frontiers

This meta-analysis was performed to assess the efficacy and safety of PPI mono-therapy versus combined therapy in patients with GERD. The main measured outcomes are as follows: symptom response, symptoms score change, endoscopic response, wave amplitude, wave duration, and adverse events.

Innovations and breakthroughs

Authors found with this meta-analysis no demonstrable effect of either combination therapy for relief of symptoms or alteration in endoscopic response. However, with combination therapy there was a greater symptom score change, suggesting that this therapy did improve patient quality of life.

Applications

Authors' results suggest that combination therapy may have some advantages for symptomatic or endoscopic response relative to PPI alone. There is some evidence that combination therapy may partially improve patient quality of life. Until further randomized controlled trials with a large population number are carried out, authors suggest use of combination therapy on an individual basis.

Terminology

FSSG score: a questionnaire given to GERD patients in order to assess severity of symptoms, based on a frequency scale for symptoms of GERD.

Peer review

The efficacy and safety for the use of prokinetics plus PPI compared to PPI monotherapy for GERD remain unclear. Therefore, the authors conducted a meta-analysis to determine the efficacy and safety of these two treatment regimens for GERD. The authors concluded that combination therapy may partially improve the patient quality of life (symptoms score change, reflux wave amplitude, and wave duration).

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