Efficacy and safety of proton pump inhibitors for diabetes mellitus in patients with gastroesophageal reflux disease: A meta-analysis

Keywords
Gastroesophageal reflux disease, Effectiveness, Diabetes mellitus, Safety, M-Analysis

Abstract

Introduction

Gastroesophageal reflux disease (GERD) is prevalent in patients with type 2 diabetes mellitus (T2DM). The use of proton pump inhibitors (PPIs) is recognized as an effective method to reduce gastric acid secretion in patients with GERD. Nevertheless, whether PPIs are effective or safe for the treatment of T2DM complicated by GERD remains unknown.

Material and methods

To assess the efficacy and safety of PPIs in the management of T2DM complicated with GERD, databases including Web of Science, Cochrane Library, PubMed, and Embase, were comprehensively searched for randomized controlled trials (RCTs) focusing on the treatment of T2DM complicated with GERD published before December 2023. Following data extraction and quality assessment, outcomes, including endoscopic efficiency, fasting blood glucose (FBG), symptom relief rates, levels of glycosylated hemoglobin A1c (HbA1c), and the incidence of adverse reactions, were analyzed using RevMan 5.4.

Results

The results suggest that the PPI group exhibited a higher efficacy rate compared to the control group in endoscopic efficiency (69.32% vs. 5.45%, OR: 40.50, 95%CI: 18.77¬–87.39), symptom relief rates (92.94% vs. 54.65%, OR: 6.45, 95%CI: 3.41–12.20). Furthermore, PPI treatment was associated with a significant reduction in HbA1c levels (WMD=-0.41, 95%CI: −0.68 to −0.14) and FBG levels (WMD=−10.15 mg/dL, 95%CI: −19.64 to −0.66) in patients with T2DM complicated with GERD. In terms of safety, the incidence of adverse reactions was not significantly different between the two groups (PPI group: 10.78% vs. control group:11.88%, P>0.05).

Conclusions

PPIs can effectively improve the glycemic index of patients with T2DM complicated with GERD.

Efficacy and safety of proton pump inhibitors for diabetes mellitus in patients with gastroesophageal reflux disease: A meta-analysis

Running Title: PPIs for T2DM in patients with GERD

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Conflict-of-interest statement

All the authors report no relevant conflicts of interest for this article.

Open-Access

Ethic Clearance

Not Applicable.

Conflict of Interest

None.

Funding

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Introduction

Gastroesophageal reflux disease (GERD) is a prevalent digestive system disease that refers to the reflux of duodenal and stomach contents into the esophagus[1], causing clinical signs and symptoms such as heartburn, acid reflux and chest pain[2]. This long-term abnormal reflux can lead to severe damage to the tissues adjacent to the esophagus, such as the mouth, pharynx, and trachea, resulting in extraesophageal symptoms such as bronchial asthma, chronic cough, idiopathic pulmonary fibrosis, hoarseness, and throat inflammation[3]. It may also increase the risk of esophageal stenosis, Barrett's esophagus, and esophageal adenocarcinoma[4]. GERD can be caused by reduced esophageal clearance, abnormal esophageal mucosal barrier function, gastric emptying disorders, and other pathological factors such as diabetes[5].

Approximately 100 million Chinese patients have type 2 diabetes mellitus (T2DM), making China the country with the largest population of individuals with diabetes in the world[6]. Metabolic syndrome, decreased immunity, and microvascular, macrovascular, and autonomic neuropathy caused by diabetes affect gastroesophageal motility[7]. Clinically, approximately 75% of patients with diabetes have abnormal gastrointestinal peristaltic function, acid reflux, heartburn, and other GERD-related symptoms[8,9]. This was significantly higher than that observed in the general population. Compared with GERD alone, due to the influence of nervous system complications of diabetes, patients with diabetes and GERD exhibit weaker pain and lack obvious clinical symptoms[10]. This leads to delayed diagnosis and treatment of the disease, and eventually results in serious GERD[11].

The primary pathophysiological mechanisms linking T2DM and GERD are multifaceted. Firstly, central obesity is a common characteristic among many T2DM patients, leading to increased intra-abdominal pressure that exacerbates the reflux of gastric contents into the esophagus. The accumulation of visceral fat not only promotes insulin resistance but also contributes to lower esophageal sphincter dysfunction, facilitating the occurrence of gastroesophageal reflux[12]. Secondly, autonomic nervous system dysregulation can impair esophageal motility and reduce esophageal sphincter tone, resulting in decreased acid clearance and increased susceptibility to

reflux[13]. Additionally, chronic hyperglycemia observed in diabetes can trigger systemic and localized inflammation, potentially worsening reflux symptoms[14]. Moreover, certain pharmacological treatments for T2DM, such as metformin, have been shown to affect esophageal motility and may lead to GERD symptoms in susceptible patients[15]. Conversely, the use of proton pump inhibitors (PPIs), primarily aimed at controlling reflux symptoms, may have beneficial effects on glycemic control due to their potential role in improving insulin sensitivity and reducing inflammation. These bidirectional interactions highlight the complexity of managing patients with both conditions, emphasizing the need for an integrated treatment approach. In summary, the relationship between T2DM and GERD is complex, involving factors such as obesity, autonomic neuropathy, inflammation, medication effects, and alterations in gut microbiota. Understanding these intricate interactions is essential for optimizing management strategies for patients with both disorders. The exploration of PPIs as a therapeutic option presents a unique opportunity to address these interconnected diseases, potentially improving patient outcomes by alleviating GERD symptoms while also considering the broader implications for glycemic control.

The clinical treatment for patients with gastroesophageal reflux is mainly based on the inhibition of gastric acid and promotion of gastrointestinal motility[16]. Acid-suppressive drugs can reduce the secretion of gastric acid, quickly relieve the symptoms of acid reflux, and reduce further damage to the esophageal mucosa caused by reflux. Among these, proton pump inhibitors (PPIs) are recommended as the first-line therapy for GERD[17]. However, the efficacy and safety of PPI in patients with T2DM and GERD remain unclear. This study aimed to systematically evaluate the effectiveness and safety of PPI in patients with T2DM combined with GRED to provide references for clinical use.

Materials And Methods

Literature retrieval strategy

The Web of Science, Cochrane Library, PubMed, Medline, and Embase databases were available in English from their inception until December 2023. The following retrieval

strategies were used: Proton Pump Inhibitor, Diabetes Mellitus, type 2DM, DM, T2DM, Diabetes, Gastroesophageal reflux disease, Gastroesophageal reflux, PPI, randomized control, PPIs, GERD, Rabeprazole, Omeprazole. Pantoprazole, Dexlansoprazole, Lansoprazole, Ilaprazole， or Esomeprazole. Reviews and references of the included articles were searched extensively.

Inclusion and exclusion criteria

The inclusion criteria[18]: (1) The subjects included were type 2 diabetes patients with GERD symptoms (including acid reflux, heartburn, chest pain, dysphagia, or extraesophageal symptoms); (2) randomized controlled trials; (3) the observation group was a combination of conventional treatment for diabetes PPI, and there was no restriction on the type of PPI; the control group was conventional diabetes treatment alone or combined with placebo treatment. Routine diabetes treatment includes a low-salt and low-fat diet and blood sugar control medications.

The exclusion criteria were as follows: (1) reviews, animal experiments, conference papers, graduation theses, and case reports; (2) duplicate documents; and (3) documents that did not provide original data or had missing data and could not be obtained by contacting the original author.

Extraction of data and assessment of its quality

The following data were extracted individually according to the designed table: the name of the paper, first author, time of publication, method of experimental design, number of subjects, age and sex of subjects, clinical effect, duration of treatment, name and dose of therapeutic drugs, and safety. The inclusion and exclusion of literature, quality evaluation, and data extraction were completed independently by two researchers, and if no consensus could be reached, they discussed and decided with a third researcher.

Statistical methods

Analyses were conducted using RevMan 5.4 software provided by the Cochrane Collaboration. Odds ratios (OR) were used as effect analysis statistics for dichotomous variables; in the case of continuous data, the mean difference (MD) was used. Analyze statistics. Forest plots were constructed, and heterogeneity and publication bias tests were performed. The heterogeneity test between studies was performed using the Q test and I2 value. The study results did not show heterogeneity between them when P>0.10 and F≤50%, otherwise, random effects were used. Statistical significance was determined using a p-value < 0.05.

Risk of bias and certain of evidence

The Risk of Bias Tool 2 (RoB2) and GRADE approaches were used to assess the quality of the articles and our research. The RoB2 tool assessed five key areas: (i) the randomization process, (ii) discrepancies from the planned interventions, (iii) absence of outcome data, (iv) outcome measurement, and (v) the choice of the reported results. In instances of disagreement, the reviewers worked together until they reached a consensus.

Results

Literature retrieval results

Figure 1 illustrates a flow diagram of the study. We obtained 133 articles through preliminary searches and screenings, and after review and evaluation, 73 duplicate articles were excluded. After excluding nine articles whose full text could not be obtained, 64 articles were obtained, and 55 articles whose systematic evaluations, meta-analyses, review articles, animal experiments, and results could not be extracted were further excluded. Finally, nine articles with 950 patients were included, including 445 patients in the basic diabetes treatment combined with PPI group and 505 patients in the control group with basic diabetes treatment alone.

Study characteristics

Table 1 shows the characteristics of the nine studies included.

Included Studies' Methodological Quality

Nine studies were included in this analysis. A summary of the bias in included studies was provided in the Figures 'Risk of bias in included studies' (Figures 2 and 3).

Endoscopic efficiency

Six studies analyzed the endoscopic response rate after eight weeks of treatment. Heterogeneity test results showed that the studies were not statistically heterogeneous (P=0.86, I^2=0%). The meta-analysis study showed that in the PPI group, the endoscopic effective rate was 69.32% (113 cases/163 cases), while in the control group, it was 5.45% (9 cases /163 cases), OR 40.50(95%CI: 18.77-87.39, P < 0.001). and both the groups differed significantly (**Figure 4**).

Symptom relief rates

Symptom remission rates were analyzed in seven studies. According to the heterogeneity test results, no statistical heterogeneity existed among the studies (P=0.83, I^2=0%). The meta-analysis showed that the symptom relief rates of patients in the PPI group were 92.94% (158 cases /170 cases), and those in the control group were 54.65% (94 cases /172 cases). OR 6.45(95%CI:3.41~12.20, P < 0.001), and both groups differed significantly (**Figure 5**).

HbA1C

Changes in HbA1c levels were observed in all nine studies. Both groups showed heterogeneity (P < 0.001, I^2=96%), and overall, PPI group was associated with an additional 0.41% reduction in HbAlc compared with control group (WMD=-0.41; 95% CI: -0.68 to -0.14, P=0.003) (**Figure 6**), the difference between the two groups was statistically significant.

Fasting blood glucose

Changes in FBG levels were analyzed in all nine studies. Both groups showed heterogeneity (P < 0.001; I^2=89%). Overall, the PPI group was associated with an additional 10.15 mg/dL reduction in FBG compared with the control group (WMD=-10.15 mg/dL; 95% CI, -19.64–-0.66; P=0.04), and both groups differed significantly (**Figure 7**).

The incidence of adverse reactions

The incidence of adverse reactions was analyzed in nine studies. According to the heterogeneity test results, no statistical heterogeneity existed among the studies (I^2=36%, P=0.13). The meta-analysis showed that the incidence of adverse reactions in patients in the PPI group was 10.78%

(48 cases /445 cases) and that in the control group was 11.88% (60 cases /505 cases). According to **Figure 8**, there is no statistical significance [OR=0.64, 95%CI (0.40, 1.01), P=0.06].

Discussion

Patients with T2DM often have gastric and esophageal motor dysfunctions, and the incidence of GERD in patients with diabetes is significantly higher than that in the general population[19]. The pathogenesis of diabetes combined with GERD mainly includes the following[20,21]: diabetic autonomic neuropathy causes primary esophageal peristaltic dysfunction, delayed esophageal emptying, and reduced esophageal clearance; gastric acid, pepsin, and bile are the direct damaging factors that cause inflammation, erosion, and ulcers of the esophageal mucosa. Proton pump inhibitors can selectively inhibit the activity of H+-K+ -ATPase in gastric parietal cells, block the excretion of H+ outside the parietal cells, and reduce the secretion of H+, thereby alleviating the direct damage caused by gastric acid to the esophagus. The meta-analysis showed that the endoscopic efficacy and symptom remission rates in the PPI group after 8 weeks were 69.32% and 92.94%, respectively, which were significantly higher than 5.45% and 54.65% in control group without PPI, $p < 0.001$. At the same time, the incidence of adverse reactions of patients in PPI group was 10.78%, while that in the control group was 11.88%, and there was no statistical significance (p=0.06), further indicating that PPI are effective and safe in the treatment of type 2 diabetes mellitus with diabetic nephropathy in T2DM combined with GRED. These results are consistent with those of previous studies[22].

In addition, diabetic microangiopathy causes ischemia, neurotrophic disorders, and degeneration of smooth muscle cells, and affects the normal contraction and relaxation function of smooth muscle[23]. Chronic hyperglycemia causes dyssecretion of gastrointestinal hormones (SP, VIP, MTL, GAS, SS, and CCK), resulting in lower esophageal sphincter relaxation and gastrointestinal motor dysfunction[24]. The results showed that after 8 weeks of treatment, HbAIc and FBG levels in the PPI group decreased by 0.41% and 10.15 mg/dL, respectively, compared to those in the control group without the addition of PPI, and

statistically significant differences were found ($P < 0.05$). This confirms the results of previous studies[25,26]. The reasons may be as follows: First, PPIs are effective drugs that block stomach acid secretion, thereby reducing the stimulation and damage of gastric acid on the esophageal mucosa and improving the symptoms of GERD; by using PPI, patients are able to reduce their pain and discomfort, and may improve their diet and nutrition intake, indirectly affecting the levels of HbAIc and FBG. Second, improved insulin sensitivity and reduced insulin resistance may lower blood sugar levels with PPIs. Third, PPIs may help reduce inflammation by inhibiting gastric acid secretion, thereby improving blood sugar levels in patients.

In conclusion, the findings of this study offer significant insights that could reshape clinical approaches to managing patients with concurrent GERD and metabolic disorders. The implications for patient care are substantial, emphasizing the need for continued investigation into the therapeutic roles of PPIs beyond their traditional use in acid-related disorders. This could ultimately lead to improved overall patient outcomes and pave the way for innovative treatment paradigms in gastroenterology and endocrinology.

Limitations

There are also some limitations to this study, such as clinical heterogeneity, which may have resulted from differences in patient conditions, postoperative care, and treatment in different studies. While this study controlled for bias risks, there may still be some potential deviations that were not considered, which could affect the conclusions of the meta-analysis. Alternatively, to extract relevant data from various studies, different data sources and the limitations of the data extraction methods must be considered, in addition, the subjects included in this study were only patients with type 2 diabetes mellitus complicated with gastroesophageal reflux disease, and only articles published in English were available, so the included literature may not be comprehensive enough, which may lead to inaccurate and incomplete data. The results of this study may have been influenced by these factors. Therefore, when reading the conclusions of

this study, we need to fully understand its limitations and make comprehensive judgments according to the specific situation. Future research should address these limitations by including larger, more homogeneous patient populations and standardized treatment protocols

Conclusion

In summary, for patients with diabetes combined with GRED, compared with the control group, additional PPI treatment was significantly more effective and showed a greater rate of symptom remission; however, adverse effects did not increase. In addition, PPI can significantly reduce HbAlc and FGB levels in patients with diabetes mellitus and GRED, which is worthy of clinical promotion and application.

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Figure Legends

Figure 1: PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram for studies included in and excluded from the meta-analysis.

Figure 2: Risk of bias graph.

Figure 3: Risk of bias summary.

Figure 4: Forest plot of endoscopic efficiency in PPI and control group.

Figure 5: Forest plot of symptom relief rates in PPI and control group.

Figure 6: Forest plot of the mean difference in HbA1c level in PPI and control group.

Figure 7: Forest plot of the mean difference in FBG level in PPI and control group.

Figure 8 Forest plot of the incidence of adverse reactions in PPI and control group.

Figure 9 The funnel plots of each outcome. A, endoscopic efficiency; B, symptom relief rates; C, levels of glycosylated hemoglobin A1c; D, fasting blood glucose; E. incidence of adverse reactions.

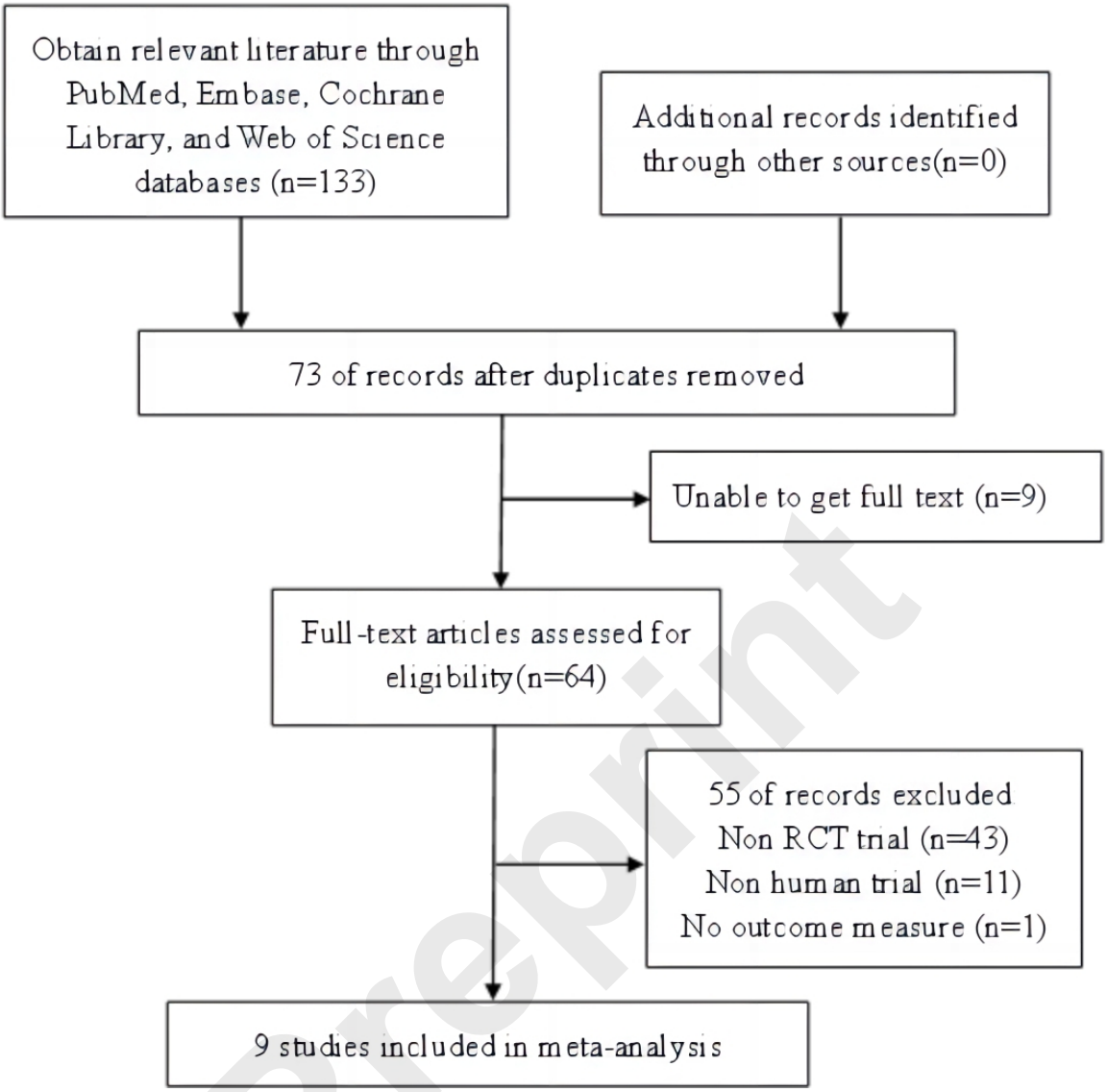
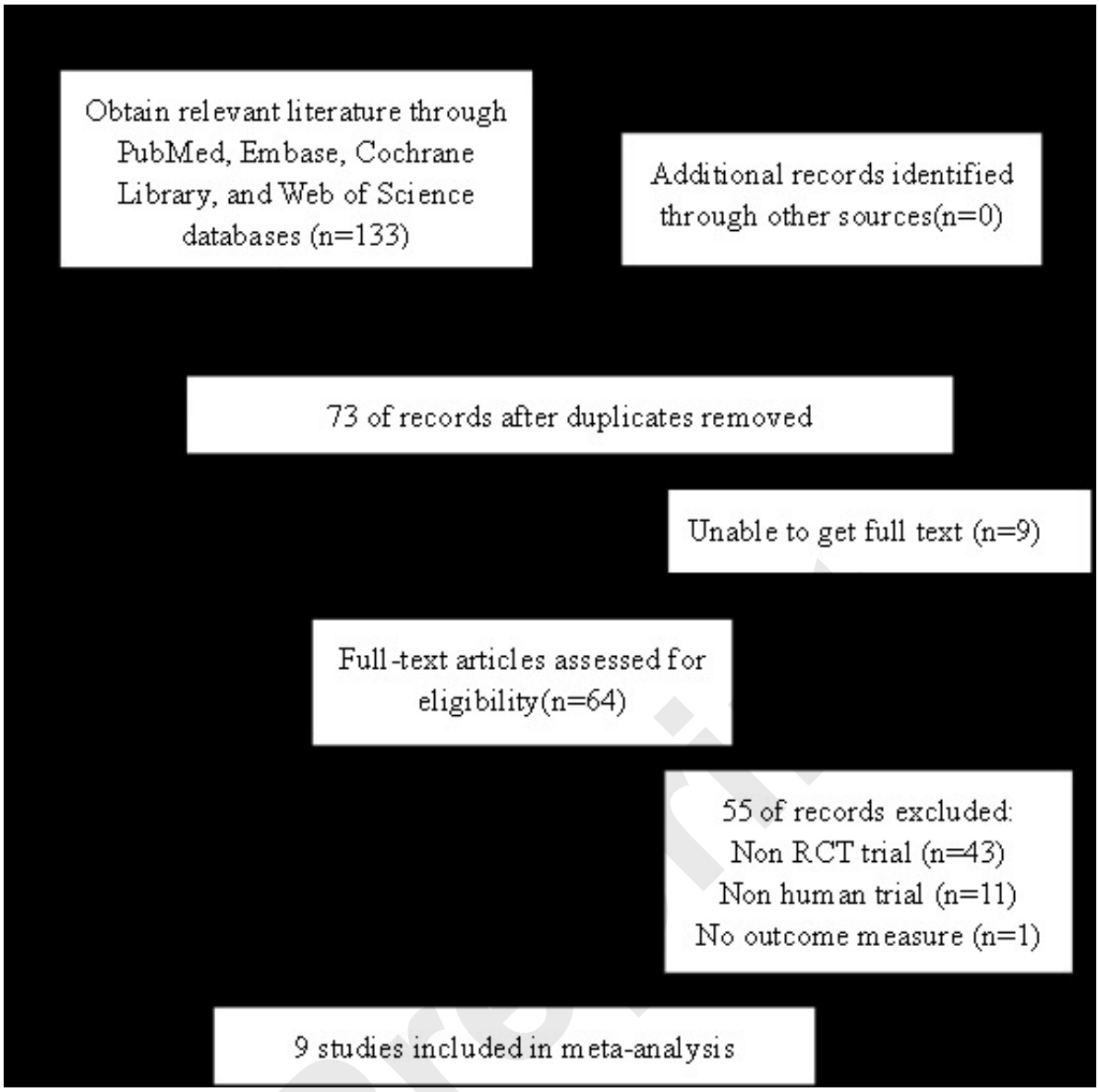

Obtain relevant literature through PubMed, Embase, Cochrane Library, and Web of Science databases (n=133)
Additional records identified through other sources(n=0)
73 of records after duplicates removed
Unable to get full text (n=9)
Full-text articles assessed for eligibility(n=64)
55 of records excluded
Non RCT trial (n=43)
Non human trial (n=11)
No outcome measure (n=1)
9 studies included in meta-analysis

Table 1. Basic characteristics of 9 studies.

First Author	Study design	Region	Total cases	NO. of cases (PPI)	NO. of cases (control)	Intervention (PPI)		Control	Treatment duration
						PPI name	Usage and dosage		
Singh 2012[15]	RCT	India	31	16	15	Pantoprazole	40 mg BID	Placebo	12 weeks
Hove KD 2013[16]	RCT	Denmark	41	20	21	Esomeprazole	40 mg QD	Placebo	12 weeks
Takebayashi K 2014[17]	RCT	Japan	89	46	43	lansoprazole	15 mg QD	None	12 weeks
González-Ortiz M 2015[18]	RCT	Mexico	14	7	7	Pantoprazole	40 mg QD	Placebo	45 days
Agrawal P K 2018[19]	RCT	India	60	30	30	Pantoprazole	40 mg QD	Placebo	24 weeks
Rajput M A 2020[20]	RCT	Pakistan	75	35	40	Omeprazole	20mg BID	None	12 weeks
Bozkuş Y 2020[21]	RCT	Turkey	32	16	16	Esomeprazole	40 mg QD	None	12 weeks
Al-Bachaji IN 2019[22]	RCT	Iraq	60	30	30	Omeprazole, pantoprazole and lansoprazole	/	/	3 months
Barchetta I 2015[23]	RCT	Italy	548	245	303	Omeprazole, esomeprazole, pantoprazole and lansoprazole	/	/	/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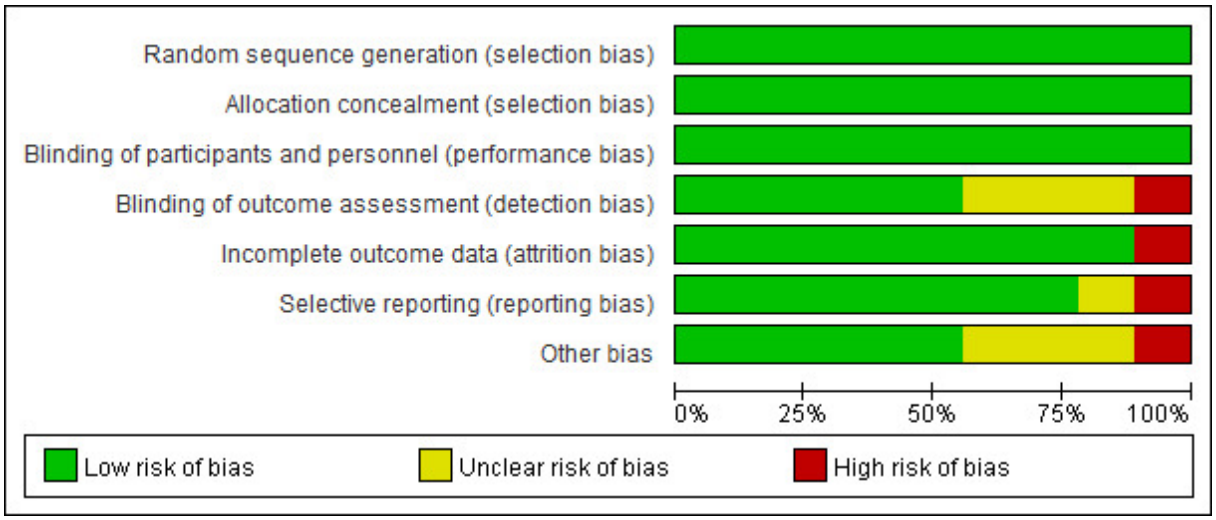
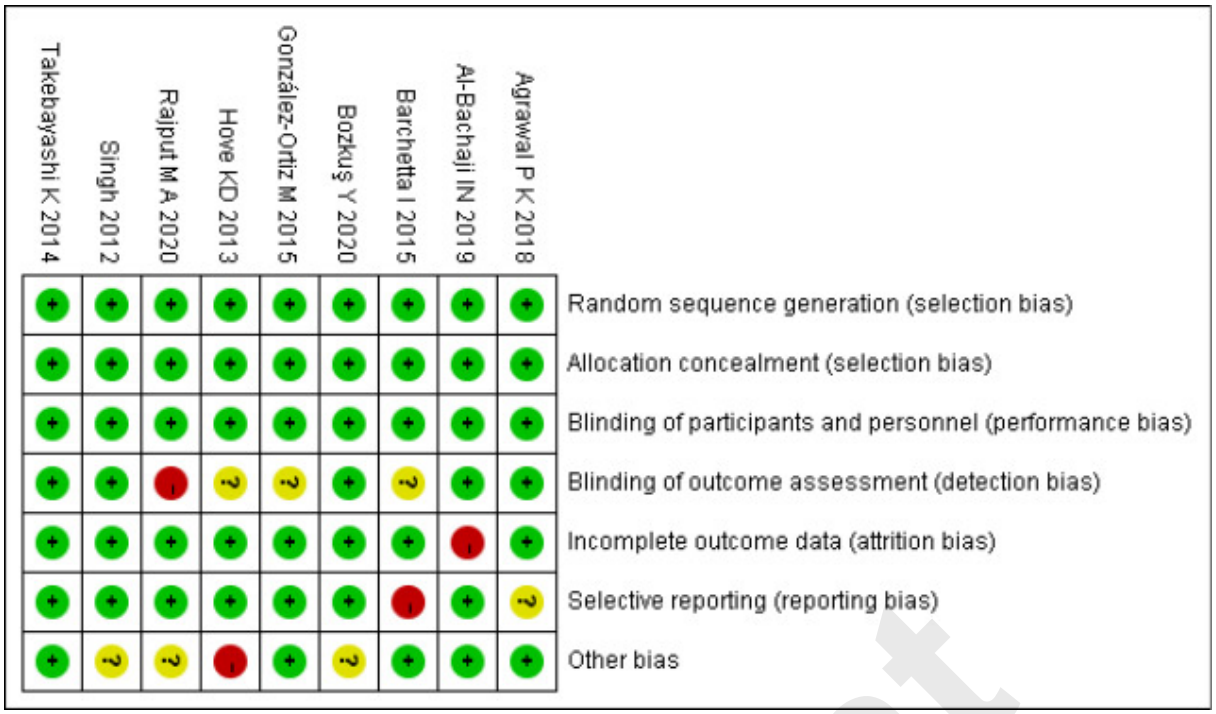

Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Other bias
0%
25%
50%
75%
100%
Low risk of bias
Unclear risk of bias
High risk of bias


Takebayashi K 2014
Singh 2012
Rajput M A 2020
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González-Ortiz M 2015
Bozkuş Y 2020
Barchetta I 2015
Al-Bachaji IN 2019
Agrawal P K 2018
Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
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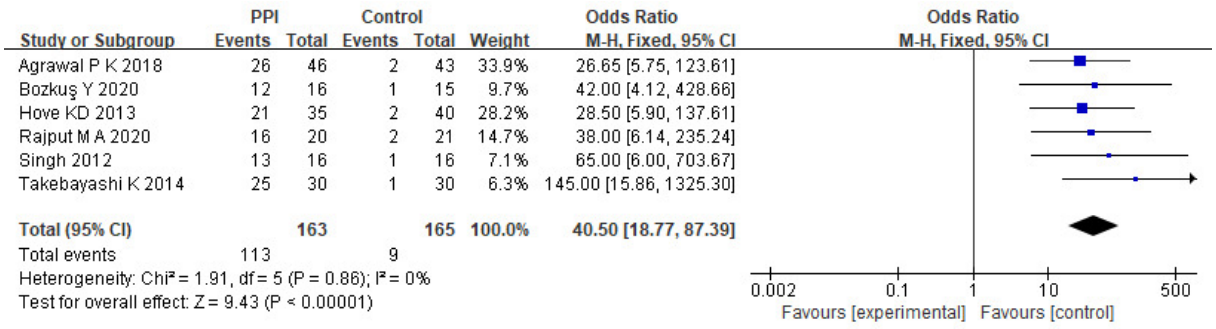
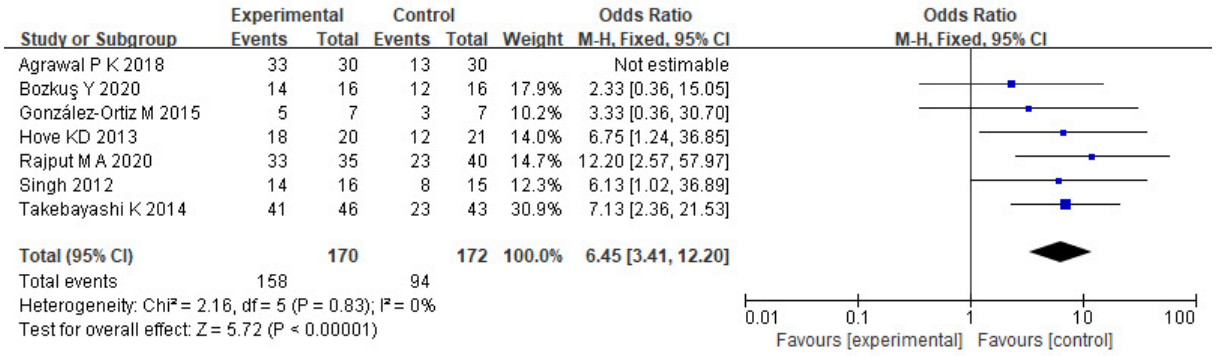
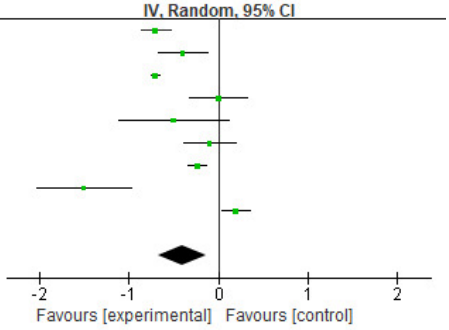
Selective reporting (reporting bias)
Other bias


PPI
Control
Odds Ratio
Odds Ratio
Study or Subgroup
Events
Total
Events
Total
Weight
M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
Agrawal P K 2018 26 46 2 43 33.9% 26.65 [5.75, 123.61]
Bozkuş Y 2020 12 16 1 15 9.7% 42.00 [4.12, 428.66]
Hove KD 2013 21 35 2 40 28.2% 28.50 [5.90, 137.61]
Rajput M A 2020 16 20 2 21 14.7% 38.00 [6.14, 235.24]
Singh 2012 13 16 1 16 7.1% 65.00 [6.00, 703.67]
Takebayashi K 2014 25 30 1 30 6.3% 145.00 [15.86, 1325.30]
Total (95% CI) 163 165 100.0% 40.50 [18.77, 87.39]
Total events 113 9
Heterogeneity: Chi² = 1.91, df = 5 (P = 0.86); I² = 0%
Test for overall effect: Z = 9.43 (P < 0.00001)
0.002
0.1
1
10
500
Favours [experimental]
Favours [control]


Experimental
Control
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
Agrawal P K 2018 33 30 13 30 Not estimable
Bozkuş Y 2020 14 16 12 16 17.9% 2.33 [0.36, 15.05]
González-Ortiz M 2015 5 7 3 7 10.2% 3.33 [0.36, 30.70]
Hove KD 2013 18 20 12 21 14.0% 6.75 [1.24, 36.85]
Rajput M A 2020 33 35 23 40 14.7% 12.20 [2.57, 57.97]
Singh 2012 14 16 8 15 12.3% 6.13 [1.02, 36.89]
Takebayashi K 2014 41 46 23 43 30.9% 7.13 [2.36, 21.53]
Total (95% CI) 170 172 100.0% 6.45 [3.41, 12.20]
Total events 158 94
Heterogeneity: Chi² = 2.16, df = 5 (P = 0.83); I² = 0%
Test for overall effect: Z = 5.72 (P < 0.00001)
0.01
0.1
1
10
100
Favours [experimental]
Favours [control]

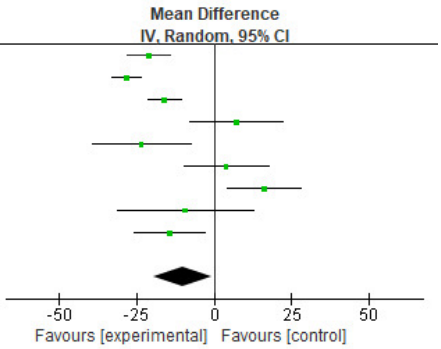
Study or Subgroup	PPI Mean	PPI SD	PPI Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Agrawal P K 2018	-0.5	0.16	30	0.2	0.44	30	12.3%	-0.70 [-0.87, -0.53]
Al-Bachaji IN 2019	-0.7	0.51	30	-0.3	0.58	30	11.4%	-0.40 [-0.68, -0.12]
Barchetta I 2015	-0.6	0.32	245	0.1	0.29	303	12.8%	-0.70 [-0.75, -0.65]
Bozkuş Y 2020	0.1	0.54	16	0.1	0.36	16	10.9%	0.00 [-0.32, 0.32]
González-Ortiz M 2015	-0.9	0.47	7	-0.4	0.69	7	7.7%	-0.50 [-1.12, 0.12]
Hove KD 2013	0.3	0.48	20	0.4	0.48	21	11.2%	-0.10 [-0.39, 0.19]
Rajput M A 2020	-0.4	0.28	35	-0.16	0.15	40	12.6%	-0.24 [-0.34, -0.14]
Singh 2012	-1.1	0.76	16	0.4	0.73	15	8.7%	-1.50 [-2.02, -0.98]
Takebayashi K 2014	-0.8	0.42	46	-1	0.32	43	12.4%	0.20 [0.05, 0.35]
Total (95% CI)			**445**			**505**	**100.0%**	**-0.41 [-0.68, -0.14]**

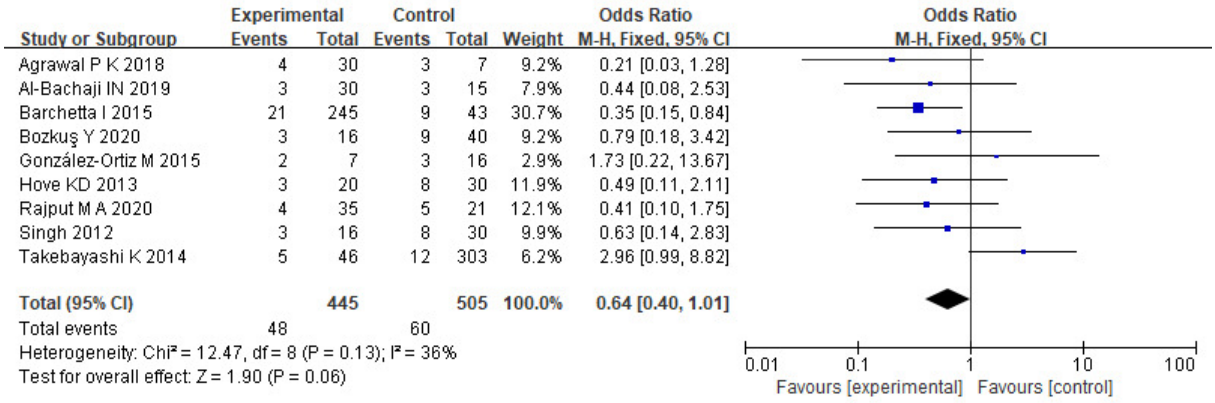
Heterogeneity: Tau² = 0.15; Chi² = 194.04, df = 8 (P < 0.00001); I² = 96%
Test for overall effect: Z = 2.94 (P = 0.003)



Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Takebayashi K 2014	-24.7	21.4	46	-3.6	31.3	303	12.7%	-21.10 [-28.22, -13.98]
Singh 2012	-17.1	7.8	16	11.1	8	30	13.2%	-28.20 [-32.98, -23.42]
Rajput M A 2020	-32	9	35	-16	10.9	21	13.0%	-16.00 [-21.53, -10.47]
Hove KD 2013	10.9	23	20	3.6	31.3	30	10.1%	7.30 [-7.77, 22.37]
González-Ortiz M 2015	-9	17.2	7	14.4	19.9	16	9.8%	-23.40 [-39.44, -7.36]
Bozkuş Y 2020	3	26.7	16	-1	12.4	40	10.6%	4.00 [-9.64, 17.64]
Barchetta I 2015	11	21	245	-5.2	38.3	43	11.3%	16.20 [4.45, 27.95]
Al-Bachaji IN 2019	-15	13.6	30	-5.7	42.6	15	7.8%	-9.30 [-31.40, 12.80]
Agrawal P K 2018	-12.5	12.5	30	1.9	14	7	11.4%	-14.40 [-25.69, -3.11]
Total (95% CI)			**445**			**505**	**100.0%**	**-10.15 [-19.64, -0.66]**

Heterogeneity: Tau² = 172.11; Chi² = 73.47, df = 8 (P < 0.00001); I² = 89%
Test for overall effect: Z = 2.10 (P = 0.04)




Experimental
Control
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
Agrawal P K 2018 4 30 3 7 9.2% 0.21 [0.03, 1.28]
Al-Bachaji IN 2019 3 30 3 15 7.9% 0.44 [0.08, 2.53]
Barchetta I 2015 21 245 9 43 30.7% 0.35 [0.15, 0.84]
Bozkuş Y 2020 3 16 9 40 9.2% 0.79 [0.18, 3.42]
González-Ortiz M 2015 2 7 3 16 2.9% 1.73 [0.22, 13.67]
Hove KD 2013 3 20 8 30 11.9% 0.49 [0.11, 2.11]
Rajput M A 2020 4 35 5 21 12.1% 0.41 [0.10, 1.75]
Singh 2012 3 16 8 30 9.9% 0.63 [0.14, 2.83]
Takebayashi K 2014 5 46 12 303 6.2% 2.96 [0.99, 8.82]
Total (95% CI) 445 505 100.0% 0.64 [0.40, 1.01]
Total events 48 60
Heterogeneity: Chi² = 12.47, df = 8 (P = 0.13); I² = 36%
Test for overall effect: Z = 1.90 (P = 0.06)
0.01
0.1
1
10
100
Favours [experimental]
Favours [control]