Proton pump inhibitor for non-erosive reflux disease: A meta-analysis

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Abstract

AIM: To evaluate the efficacy, safety and influential factors of proton pump inhibitor (PPI) treatment for non-erosive reflux disease (NERD).

METHODS: PubMed, MEDLINE, EMBASE and the Cochrane Library were searched up to April 2013 to identify eligible randomized controlled trials (RCTs) that probed into the efficacy, safety and influential factors of PPI treatment for NERD. The rates of symptomatic relief and adverse events were measured as the outcomes. After RCT selection, assessment and data collection, the pooled RRs and 95%CI were calculated. This meta-analysis was performed using the Stata 12.0 software (Stata Corporation, College Station, Texas, United States). The level of evidence was estimated by the Grading of Recommendations Assessment, Development and Evaluation system.

RESULTS: Seventeen RCTs including 6072 patients met the inclusion criteria. The results of the meta-analysis showed that PPI treatment was significantly superior to H2 receptor antagonists (H2RA) treatment (RR = 1.629, 95%CI: 1.422-1.867, P = 0.000) and placebo (RR = 1.903, 95%CI: 1.573-2.302, P = 0.000) for the symptomatic relief of NERD. However, there were no obvious differences between PPI and H2RA (RR = 0.928, 95%CI: 0.776-1.110, P = 0.414) or PPI and the placebo (RR = 1.000, 95%CI: 0.896-1.116, P = 0.997) regarding the rate of adverse events. The overall rate of symptomatic relief of PPI against NERD was 51.4% (95%CI: 0.433-0.595, P = 0.000), and relief was influenced by hiatal hernia (P = 0.030). The adverse rate of PPI against NERD was 21.0% (95%CI: 0.152-0.208, P = 0.000), and was affected by hiatal hernia (P = 0.081) and drinking (P = 0.053).

CONCLUSION: PPI overmatched H2RA on symptomatic relief rate but not on adverse rate for NERD. Its relief rate and adverse rate were influenced by hiatal hernia and drinking.

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Key words: Proton pump inhibitor; Non-erosive reflux disease; Symptomatic relief; Adverse event; Meta-analysis

Core tip: As a kind of powerful and effective acid-suppressive drugs, proton pump inhibitor (PPI) has been used for patients with non-erosive reflux disease (NERD), but its efficacy, safety and their influential factors are inconclusive. We performed this systematic review and meta-analysis of randomized controlled trials to assess its efficacy, safety and influential factors. Based on the results of the meta-analysis, we conclude that PPI has a higher symptomatic relief rate and roughly the same adverse rate for NERD. Hiatal hernia and drinking could influence symptomatic relief rate and adverse rate of PPI on NERD.
INTRODUCTION

Non-erosive reflux disease (NERD) is a heterogeneous group of disorders, which present with the typical gastroesophageal reflux symptoms of heartburn, regurgitation or both in the absence of visible esophageal injury upon endoscopy. Patients with NERD are more likely to be female, young, thin, and without hiatal hernias, and over time, the regurgitation of gastric juice associated with NERD can have significant and comparable negative effects on their quality of life that correlate with heartburn severity. To improve these patients’ quality of life, provide a rapid relief of symptoms and reduce the severity and number of recurrent episodes, acid-suppressive drugs have been used to combat NERD.

Proton pump inhibitors (PPI) are a type of acid-suppressive drugs that inhibit the secretion of gastric acid by restraining the exchange of H⁺-K⁺. Due to their powerful inhibition of the secretion of gastric acid, PPIs have been widely used to treat gastroesophageal diseases that result from too much acid, including gastroesophageal reflux disease, gastritis and gastric and duodenal ulcers. However, the efficacy, safety and influential factors of PPI use remain inconclusive, especially for NERD.

Although two papers have previously discussed the efficacy and influential factors of PPI use against NERD, neither paper used randomized controlled trials (RCTs) as the source of their data or used H₂ receptor antagonists (H₂RA) or placebos as control groups. Meanwhile, the clinical safety of PPIs was not addressed by the authors of these two papers. In view of the importance of understanding their clinical implications, we determined that the quality of the previous two papers was insufficient and performed the present meta-analysis.

MATERIALS AND METHODS

Search strategy

We conducted a computer-aided search for RCTs which probed into the efficacy, safety and influential factors of PPI for NERD. Source databases were PubMed (1966 to April 2013), the Cochrane Library (1997 to April 2013), MEDLINE (1966 to April 2013) and EMBASE (1985 to April 2013). The medical subject headings which were used in retrieving citation were: non-erosive reflux disease or NERD, proton pump inhibitors or PPI or esomeprazole or pantoprazole or omeprazole or rabeprazole or lansoprazole. We also searched the references in retrieved articles manually in order to prevent missing relevant publications.

Study selection

The titles and abstracts were independently screened by two reviewers (Zhang JX and Song J), and studies were chosen for the meta-analysis if they fit the following criteria: (1) randomized controlled trials; (2) comparing PPI with other acid-suppressive drugs or placebo; and (3) probing into the efficacy, safety and influential factors of PPI on the symptomatic relief of NERD. We did not consider the restriction on language of publication. Exclusion criteria were: (1) no human subjects in the study; (2) without control group; (3) comparing a PPI with another one; (4) incomplete outcome data; (5) selective reporting; and (6) duplicate publication.

Data extraction and quality assessment

Independently, three reviewers (Qiu S, Ai MH and Wang J) extracted data including the following items: first author, year of publication, country, type of publication, study duration, age, gender, medication duration, drug dose, follow-up time, methods of treatment, H. pylori infection and primary outcomes. Based on the adequate sequence generation, allocation concealment, blinding, incomplete outcome data addressed, free of selective reporting, free from baseline imbalance, sample size calculation and free from sources of funding bias, the risk of bias was evaluated in detail. Each quality component was judged as high, unclear, or low. On the basis of each separate component, the quality of the trials was assessed. When difference appeared, a forth reviewer (Lei HB) joined in the discussion.

Statistical analysis

We treated the rates of symptomatic relief of PPI vs placebo and PPI vs H₂RA as the primary endpoints and the rates of adverse events as the secondary endpoints. Meanwhile, factors influencing rates of symptomatic relief and adverse events of PPI against NERD were analyzed. The RRs, to summary statistics in meta-analysis, were strongly recommended for dichotomous data. So we used Stata12.0 to calculate RR for the rates of symptomatic relief and the rates of adverse events in this meta-analysis. When the P value was less than 0.05, it was considered significant. The data was pooled according to the Mantel-Haenszel fixed-effects model and the DerSimonian and Laird random-effects model. The differences were shown as pooled RRs and 95%CI between different groups. The statistical heterogeneity among trials was assessed by the χ² test and I² test. The percentage of the variability in the estimates of effect, caused by heterogeneity but not chance, was described by I² test. When the values were greater than 50%, it was considered having substantial heterogeneity. If there was no statistically significant heterogeneity, the fixed-effects model was chosen. According to the drug dose and therapeutic duration, subgroup analysis was performed.
RESULTS

Risk of bias and publication bias
We assessed the risks of bias according to assessment of study quality in Cochrane Handbook 4.2.2. Egger’s test and Begg’s test were used to check the publication bias, and P < 0.05 indicated that there was a risk of bias.

Sensitivity analysis
Sensitivity analysis was performed to identify the studies which influence the result obviously.

Meta-regression analysis
Meta-regression analysis was performed to study the relationship between covariates and the outcomes and to find the source of heterogeneity.

Assessment of quality evidence
Grade system was applied to assess the quality of these outcomes.

PPI vs H:RA on the rate of symptomatic relief
Seven studies,[23,26,29,30,32,34,39] which involved 1882 patients, compared PPI with H:RA on the rate of symptomatic relief of NERD. There are 935 patients who received PPI and 947 patients who received H:RA. Heterogeneity analysis showed that there was obviously statistical heterogeneity among these studies (I$^2$ = 42.4%, P = 0.096). Sensitivity analysis indicated that one study[30] influenced the result apparently, and after excluding this study, the heterogeneity disappeared (I$^2$ = 0.1%, P = 0.422). The result showed that PPI was significantly superior to H:RA on the rate of symptomatic relief of NERD (RR = 1.629, 95% CI: 1.422-1.867, P = 0.000), (Figure 2A).

In the subgroup analysis of short duration (PPI 158/372, placebo 112/384, F = 0%, P = 0.640), PPI advanced over H:RA (RR = 1.521, 95% CI: 1.303-1.775, P = 0.000). In the subgroup analysis of long duration (PPI 90/186, placebo 43/184, F = 0.737), similar result was found (RR = 2.063, 95% CI: 1.544-2.756, P = 0.000).

In the subgroup analysis of low dose (PPI 130/308, placebo 78/307, F = 0%, P = 0.422), PPI significantly overmatched H:RA (RR = 1.656, 95% CI: 1.320-2.078, P = 0.000). In the subgroup analysis of high dose (PPI 220/526, placebo 141/537, F = 23.5%, P = 0.365), PPI was also superior to H:RA (RR = 1.614, 95% CI: 1.561-1.914, P = 0.000).

In the subgroup analysis of lansoprazole (PPI 227/585, placebo 141/584, F = 0%, P = 0.003), PPI advanced over H:RA (RR = 1.866, 95% CI: 1.435-2.448, P = 0.000), But compared with groups of omeprazole (PPI 41/67, placebo 31/64, F = 0%, P = 0.434), there were no statistical differences (P = 0.149).

PPI vs placebo on the rate of symptomatic relief
There were 11 studies,[29,25,27,30,31,33-38] which compared PPI with placebo on the rate of symptomatic relief of NERD. In the 5416 patients of the 11 trials, there are 3287 patients who received PPI and 2129 patients received placebo. Heterogeneity analysis showed that there was obviously statistical heterogeneity among these studies (I$^2$ = 84.3%, P = 0.000). Sensitivity analysis did not find studies that influenced the result obviously. The result showed that PPI was significantly superior to placebo on the rate of symptomatic relief of NERD (RR = 1.903, 95% CI: 1.573-2.302, P = 0.000), (Figure 2B).

In the subgroup analysis of long duration (PPI 407/855, placebo 114/315, F = 65.4%, P = 0.034), PPI advanced over placebo (RR = 1.442, 95% CI: 1.034-2.010, P = 0.031). In short duration (PPI 1139/2432, placebo 459/1241, F = 78.6%, P = 0.000), similar result was also found (RR = 2.029, 95% CI: 1.665-2.473, P = 0.000).

In the subgroup analysis of high dose (PPI 486/1098, placebo 131/718, F = 0%, P = 0.509), PPI significantly overmatched placebo (RR = 2.664, 95% CI: 2.251-3.154, the 2135 patients in PPI alone group. The details of these studies are listed in Table 1.
### Table 1: Details of these studies (\%)  

| First author | Country | Year | Study design | Arms of treatment | Age (yr) | Gender (M/F) | n (\%) | BMI (kg/m²) | Hiatal hernia | Smoking | Alcohol users | Therapeutic duration | Adverse events | Effective (\%) |
|--------------|---------|------|--------------|-------------------|----------|--------------|--------|-------------|--------------|----------|---------------|---------------------|---------------|---------------|
| Talley et al. | United Kingdom | 2002 | RCT | Esomeprazole 20 mg | 48.0 | 135/138 | 203 - | 90/89 | - | 6 mo | 5 | 101 (54.6) |
| Fass et al. | United States | 2009 | RCT | Esomeprazole 40 mg | 48.4 | 135/147 | 282 - | 101/92 | - | 6 mo | 6 | 84 (29.7) |
| Juhl-Hansen et al. | Norway | 2009 | RCT | Ranitidine 75 mg | 48.2 | 58/88 | 146 - | 57/39 | - | - | 2 | 30 (17.8) |
| Kinoshita et al. | Japan | 2011 | RCT | Ranitidine 5 mg | 46.3 | 38/55 | 93 - | 42/42 | - | 4 wk | 1 | 14 (4.5) |
| Kobissi et al. | Lebanon | 2012 | RCT | Ranitidine 300 mg | 49.7 | 40/51 | 91 - | 23/23 | - | 4 wk | 1 | 19 (21.0) |
| Talley et al. | Australia | 2001 | RCT | Esomeprazole 20 mg | 45.5 | 16/28 | 44 - | - | - | 4 wk | 1 | 20 (45.5) |
| Fuss et al. | United States | 2009 | RCT | Famotidine 20 mg | 55.0 | 20/30 | 50 - | 22/22 | - | 4 wk | 1 | 44 (80.0) |
| Nakamura et al. | Japan | 2010 | RCT | Ranitidine 75 mg | 46.8 | 9/7 | 16 - | - | - | - | 0 | 51 (70.6) |
| Miner et al. | United States | 2002 | RCT | Ranitidine 10 mg | 49.1 | 20/25 | 48 - | 22/22 | - | 4 wk | 1 | 91 (18.5) |
| Armstrong et al. | Canada | 2001 | RCT | Ranitidine 50 mg | 47.3 | 57/51 | 106 - | 36/36 | - | - | 4 wk | 1 | 20 (45.5) |
| Lind et al. | Sweden | 1999 | RCT | Nizatidine 150 mg | 47.6 | 51/51 | 102 - | 36/36 | - | - | 4 wk | 1 | 118 (83.5) |
| Richter et al. | United States | 2000 | RCT | Famotidine 20 mg | 52.0 | 53/86 | 139 - | - | - | 4 wk | 1 | 6 (97.9) |
| Bytzer et al. | Denmark | 2004 | RCT | Ranitidine 10 mg | 47.0 | 123/156 | 279 - | 26/26 | - | - | 6 mo | 1 | 113 (86.4) |
| Kahrilas et al. | United States | 2009 | RCT | Ranitidine 20 mg | 43.1 | 40/89 | 129 - | 29/29 | - | 58 | 4 wk | 1 | 47 (67.6) |
| Lind et al. | Sweden | 1997 | RCT | Ranitidine 10 mg | 44.0 | 45/87 | 132 - | 30/30 | - | 51 | 4 wk | 1 | 5 (5.8) |
| Uemura et al. | Japan | 2008 | RCT | Ranitidine 10 mg | 43.5 | 34/49 | 93 - | - | - | - | 11 | 22 (23.9) |
| Talley et al. | Australia | 2002 | RCT | Pantoprazole 20 mg | 30.0 | 85/70 | 133 - | 26/26 | - | - | 8 mo | 1 | 83 (56.0) |

RCT: Randomized controlled trials; M: Male; F: Female; BMI: Body mass index.
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A Study

| ID       | RR (95%CI) | Events, treatment | Events, control | % weight |
|----------|------------|-------------------|-----------------|----------|
| Richter (2000) | 1.59 (1.22, 2.08) | 102/276          | 64/276          | 29.57    |
| Richter (2000) | 1.52 (1.16, 1.98) | 97/277           | 64/277          | 29.57    |
| Talley (2002)  | 2.12 (1.45, 3.11) | 62/154           | 29/153          | 13.44    |
| Fujiwara (2005)| 1.17 (0.80, 1.72) | 28/50            | 23/48           | 10.84    |
| Juul-Hansen (2009) | 1.94 (1.29, 2.92) | 28/32            | 14/31           | 6.57     |
| Nakamura (2010) | 1.53 (0.88, 2.67) | 13/17            | 8/16            | 3.81     |
| Kobeissy (2012)| 1.81 (1.17, 2.80) | 20/28            | 17/43           | 6.20     |
| Overall ($I^2 = 0.1\%, P = 0.422$) | 1.63 (1.42, 1.87) | 350/834         | 219/844        | 100.00   |

B Study

| ID       | RR (95%CI) | Events, treatment | Events, control | % weight |
|----------|------------|-------------------|-----------------|----------|
| Lind (1997) | 2.34 (1.38, 3.97) | 62/199           | 14/105          | 4.61     |
| Lind (1997) | 3.48 (2.09, 5.78) | 95/205           | 14/105          | 4.74     |
| Lind (1999) | 1.49 (1.27, 1.76) | 116/139          | 80/143          | 6.81     |
| Richter (2000) | 1.26 (1.04, 1.49) | 99/142          | 80/143          | 6.73     |
| Richter (2000) | 2.48 (1.37, 4.48) | 102/276          | 10/67           | 4.24     |
| Talley (2001) | 2.35 (1.30, 4.25) | 97/277          | 10/67           | 4.23     |
| Talley (2002) | 1.90 (1.13, 3.21) | 83/238          | 13/71           | 4.67     |
| Talley (2002) | 1.63 (0.96, 2.76) | 70/235          | 13/71           | 4.62     |
| Miner (2002) | 1.74 (1.16, 2.61) | 36/64           | 22/68           | 5.41     |
| Miner (2002) | 1.75 (1.17, 2.62) | 38/67          | 22/68           | 5.43     |
| Bytzer (2004) | 1.14 (1.01, 1.30) | 209/242         | 71/94           | 6.95     |
| Uemura (2008) | 2.70 (1.44, 5.05) | 31/96           | 11/92           | 4.04     |
| Uemura (2008) | 2.16 (1.12, 4.15) | 24/93           | 11/92           | 3.89     |
| Fass (2009) | 2.94 (2.26, 3.82) | 161/294         | 54/290          | 6.31     |
| Fass (2009) | 2.69 (2.06, 3.52) | 145/289         | 54/290          | 6.28     |
| Kahrilas (2009) | 2.29 (1.33, 3.94) | 34/105         | 15/106          | 4.52     |
| Kinoshita (2011) | 1.44 (1.01, 2.04) | 44/88           | 31/89           | 5.75     |
| Kinoshita (2011) | 1.61 (1.15, 2.25) | 55/98          | 31/89           | 5.87     |
| Overall ($I^2 = 84.3\%, P = 0.000$) | 1.90 (1.57, 2.30) | 1546/3287       | 573/2129       | 100.00   |

NOTE: Weights are from random effects analysis

C Study

| ID       | RR (95%CI) | Events, treatment | Events, control | % weight |
|----------|------------|-------------------|-----------------|----------|
| Armstrong (2001) | 0.76 (0.53, 1.11) | 32/101          | 39/94          | 31.63    |
| Talley (2002)  | 1.03 (0.84, 1.26) | 86/154          | 83/153          | 65.19    |
| Juul-Hansen (2009) | 0.48 (0.10, 2.46) | 2/32            | 4/31           | 3.18     |
| Overall ($I^2 = 25.1\%, P = 0.263$) | 0.93 (0.78, 1.11) | 120/287         | 126/278        | 100.00   |

NOTE: Weights are from random effects analysis
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Study

| ID         | RR (95%CI) | Events, treatment | Events, control | %  |
|------------|------------|-------------------|-----------------|----|
| Lind (1997)| 0.45 (0.16, 1.31) | 6/199            | 7/105           | 2.05|
| Lind (1997)| 0.80 (0.32, 2.02) | 11/205           | 7/105           | 2.07|
| Talley (2001)| 1.61 (1.07, 2.44) | 60/140           | 21/79           | 5.99|
| Talley (2002)| 0.75 (0.15, 3.76) | 5/238            | 2/71            | 0.69|
| Talley (2002)| 0.91 (0.19, 4.39) | 6/235            | 2/71            | 0.69|
| Miner (2002)| 0.88 (0.47, 1.63) | 14/64            | 17/68           | 3.68|
| Miner (2002)| 1.01 (0.57, 1.82) | 17/67            | 17/68           | 3.77|
| Bytzer (2004)| 1.20 (0.91, 1.57) | 113/279          | 47/139          | 14.01|
| Uemura (2008)| 0.69 (0.35, 1.37) | 12/96            | 17/94           | 3.83|
| Uemura (2008)| 1.31 (0.74, 2.30) | 22/93            | 17/94           | 3.77|
| Fass (2009)| 1.09 (0.87, 1.37) | 103/294          | 93/290          | 20.90|
| Fass (2009)| 0.74 (0.58, 0.94) | 92/389           | 93/290          | 23.79|
| Kinoshita (2011)| 0.98 (0.66, 1.45) | 32/93            | 32/91           | 7.22|
| Kinoshita (2011)| 1.03 (0.71, 1.51) | 37/102           | 32/91           | 7.55|
| Overall (I² = 27.9%, P = 0.156) | 1.00 (0.90, 1.12) | 530/2494        | 404/1656       | 100.00|

NOTE: Weights are from random effects analysis
P = 0.000). In low dose (PPI 1060/2189, placebo 442/1411, \( I^2 = 75.1\%, P = 0.000 \)), PPI was significantly superior to placebo (RR = 1.726; 95%CI: 1.451-2.054, \( P = 0.000 \)).

In the subgroup analysis of lansoprazole (PPI 505/1136, placebo 128/714, \( I^2 = 0\%, P = 0.879 \)), pantoprazole (PPI 252/649, placebo 88/320, \( I^2 = 0\%, P = 0.844 \)), omeprazole (PPI 427/874, placebo 210/680, \( I^2 = 81.4\%, P = 0.000 \)) and rabeprazole (PPI 317/478, placebo 130/336, \( I^2 = 81.3\%, P = 0.001 \)), PPI advanced over placebo (\( P = 0.000 \)).

PPI vs \( H_2 \)RA on the rate of adverse events

Three studies\(^{[24,32,39]} \), which involved 565 patients, compared PPI with \( H_2 \)RA on the rate of adverse events of NERD. There were 287 patients who received PPI and 278 patients who received \( H_2 \)RA. Because there was no obviously statistical heterogeneity among these studies (\( I^2 = 25.1\%, P = 0.263 \)), fixed-effects model was chosen to perform the meta-analysis. The result showed that there was no significantly difference between PPI and \( H_2 \)RA on the rate of adverse events of NERD (RR = 0.928; 95%CI: 0.776-1.100, \( P = 0.414 \), Figure 2C).

PPI vs placebo on the rate of adverse events

There were eight studies\(^{[23,25,27,28,31,36]} \) which compared PPI with placebo on the rate of adverse events of NERD. Among the 4150 patients, 2494 patients received PPI and 1656 patients received placebo. Because there was no obviously statistical heterogeneity among these studies (\( I^2 = 27.9\%, P = 0.156 \)), fixed-effects model was chosen to perform the meta-analysis. The result showed that there was no significant difference between PPI and placebo on the rate of adverse events of NERD (RR = 1.000; 95%CI: 0.896-1.116, \( P = 0.997 \), (Figure 2D).

In the subgroup analysis of long duration (PPI 184/892, placebo 72/360, \( I^2 = 8.5\%, P = 0.364 \)), there was no significant difference between PPI and placebo (RR = 0.921, 95%CI: 0.812-1.046, \( P = 0.206 \)). In short duration (PPI 346/1602, placebo 332/1296, \( I^2 = 0\%, P = 0.565 \)), PPI was significantly superior to placebo (RR = 1.290, 95%CI: 1.032-1.613, \( P = 0.025 \)). In low dose (PPI 214/833, placebo 152/588, \( I^2 = 2.9\%, P = 0.398 \), no significant difference was found either (OR = 1.002, 95%CI: 0.841-1.195, \( P = 0.979 \)).

In the subgroup analysis of lansoprazole (PPI 308/962, placebo 233/719, \( I^2 = 75.4\%, P = 0.017 \)), pantoprazole (PPI 80/668, placebo 68/224, \( I^2 = 0\%, P = 0.997 \), (Figure 2D).
I - 0.2591453 0.3296374 0.303 0.733 0.0003684 -0.0127987 0.186 -0.528 0.0177315 -0.2213605 , 0.665 0.857 0.154 0.1326016 -0.0015192 -0.0005643 - P - 0.6776039 0.030 0.053 0.897 0.484 0.217 -

was obviously statistical heterogeneity among these studies ($I^2 = 97.5\%$, $P = 0.000$). Sensitivity analysis indicated that no study influenced the result apparently. The result showed that the adverse rate of PPI against NERD was 21.0% (95%CI: 0.152-0.208, $P = 0.000$), (Figure 2F).

In the subgroup analysis of long duration, the adverse rate of PPI against NERD was 18.0% (95%CI: 0.094-0.265, $P = 0.000$). In short duration, the rate was 23.3% (95%CI: 0.145-0.322, $P = 0.000$).

In the subgroup analysis of high dose, the adverse rate of PPI against NERD was 21.1% (95%CI: 0.152-0.268, $P = 0.000$). In low dose, the rate was 20.8% (95%CI: 0.100-0.317, $P = 0.000$).

In the subgroup analysis of lansoprazole, the adverse rate of PPI against NERD was 21.5% (95%CI: 0.121-0.309, $P = 0.000$). In that of pantoprazole, omeprazole and rabeprazole, the effective rate respectively were 62.6% (95%CI: 0.000), 9.8% (95%CI: 0.000), and 29.5% (95%CI: 0.165-0.426, $P = 0.000$).

Univariate meta-regression analysis found that the rate of hiatal hernia ($P = 0.081$) and drinking ($P = 0.053$) were associated with the rate of adverse events of PPI against NERD, but not with the other factors (Table 2).

### Sensitivity analysis

In the analysis of PPI vs H2RA on the rate of symptomatic relief, sensitivity analysis indicated that one study [32] influenced the result apparently, and after excluding the this study, the heterogeneity disappeared ($I^2 = 0.1\%$, $P = 0.422$). And in other analysis, there was no study which influenced the results.

### Risk of bias and publication bias

Three studies [26,28,33] performed adequate sequence generation with the others unclear. No study carried out allocation concealment. Two studies [24,26] were open-label trials without blinding of participants and personnel and 11 studies [23,25,27,28,31-36,39] mentioned blinding of participants and personnel. All the studies had complete data, without selective reporting and other bias. According to the Egger’s test and Begg’s test, we did not find obvious publication bias in the outcome of PPI vs H2RA on the rate of symptomatic relief (Egger’s test: $P = 0.711$ and Begg’s test: $P = 0.045$), PPI vs H2RA on the rate of adverse events (Egger’s test: $P = 0.09$ and Begg’s test: $P = 0.056$). But in the outcome of PPI vs placebo on the rate of symptomatic relief, the potential publication bias may exist (Egger’s test: $P = 0.011$ and Begg’s test: $P = 0.013$). A language bias, inflated estimates by a flawed methodologic design in smaller studies, and/or a lack of publication of small trials with opposite results may be the causes.

### Quality of evidence

Following the classification of the Grading of Recommendations Assessment, Development and Evaluation,
the quality of evidences and their causes are shown in Table 3.

### DISCUSSION

PPIs have been widely used to treat NERD, but their efficacy, safety and influential factors are unclear. Our meta-analysis, including 17 well-designed randomized controlled trials, 12 of which were multi-center and 5 of which were single-center, had systematically and comprehensively evaluated the evidence concerning the efficacy, safety and influential factors of PPIs against NERD.

The first major finding revealed by this comprehensive approach was that the activity of PPIs is obviously superior to that of H₂RA in its efficacy and safety against NERD. Because heartburn, the main symptom of patients with NERD, results from erosion due to gastric acid reflux into the esophagus, acid-suppressive drugs, including PPI and H₂RA, have been deemed effective treatments for NERD\(^{[40,41]}\). After a meal, gastrin secretion stimulates the release of histamine by enterochromaffin-like cells, which binds to histamine H₂ receptors, leading to acid release via the hydrogen potassium ATPase (H⁺-K⁺-ATPase) pump\(^{[42]}\). Compared to the mechanism of H₂RA, which acts against one of the three histamine-H₂ receptors, PPI acts against the H⁺-K⁺-ATPase\(^{[43]}\). To control for the influences of different dose and therapeutic duration, we performed a subgroup analysis. This analysis showed that PPI treatment against NERD was superior to H₂RA and placebo regardless of the dose or duration. However, only after short durations was PPI treatment safer than placebo.

The second major finding of this meta-analysis was that the overall rate of symptomatic relief of PPI against NERD was 51.4%; this value was influenced by the presence of a hiatal hernia. Compared with the approximate 50% symptomatic relief rate of PPI against ERD\(^{[44,45]}\), the 51.4% rate of PPI against NERD is fairly high. PPIs with a high dose, long duration and from a new generation should be more effective than those with a low dose, short duration and from an older generation; however, according to our subgroup analysis, there were no obvious differences among different doses, durations and PPI types. PPI enacts its role by binding to the binding sites of the saturable enzyme H⁺-K⁺-ATPase; therefore, an excessively high blood concentration of PPI is not only unable to increase but even decreases the acid suppression effect of the enzyme. Univariate meta-regression analysis found that the rate of hiatal hernia was associated with the rate of the symptomatic relief of PPI use.

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**Table 3  Quality of outcomes according to Grade system**

| Outcome | Study design | Risk of bias | Inconsistecy | Indirectness | Imprecision | Publication bias | Quality of evidence |
|---------|--------------|--------------|--------------|-------------|-------------|------------------|---------------------|
| PPI vs H₂RA on the rate of symptomatic relief | RCT | Serious\(^1\) | No | No | No | Serious\(^1\) | Low |
| Long-duration subgroup | RCT | Serious\(^2\) | No | No | No | Serious\(^1\) | Low |
| Short-duration subgroup | RCT | Serious\(^2\) | No | No | No | Serious\(^1\) | Low |
| High-dose subgroup | RCT | Serious\(^2\) | No | No | No | Serious\(^1\) | Low |
| Lose-dose subgroup | RCT | Serious\(^3\) | No | No | No | Serious\(^1\) | Low |
| PPI vs placebo on the rate of symptomatic relief | RCT | No | Series\(^3\) | No | No | No | Moderate |
| Long-duration subgroup | RCT | No | Series\(^3\) | No | No | No | Moderate |
| Short-duration subgroup | RCT | No | No | No | No | No | Moderate |
| High-dose subgroup | RCT | No | No | No | No | No | Moderate |
| Lose-dose subgroup | RCT | No | Series\(^3\) | No | No | No | Moderate |

\(^1\) Allocation concealment and blind method were not offered which resulted in very serious bias; \(^2\) Allocation concealment and blind method were not offered which resulted in very serious bias mild bias; \(^3\) The assessing standard of outcomes maybe contribute to the heterogeneity; \(^4\) Publication bias may be existed. RCT: Randomized controlled trials; NERD: Non-erosive reflux disease; PPI: Proton pump inhibitor; H₂RA: H₂ receptor antagonists.
against NERD. One role of the gastroesophageal junction is to minimize gastroesophageal reflux; hiatal hernias, which are protrusions (or herniations) of the upper part of the stomach into the thorax through a tear or weakness in the diaphragm, can cause reflux and reduce the clear effects of the esophagus[40]. Due to their effects on gastroesophageal reflux and the normal function of the esophagus, the presence of hiatal hernias may influence the symptomatic relief rate of PPIs against NERD.

The third major finding of this meta-analysis was that the adverse rate of PPI treatment against NERD was 21.0%; this value was affected by hiatal hernia and drinking. PPI use was not, however, without shortcomings. Primary adverse events, typically in the order of 1%-5%, included headache, diarrhea, constipation, nausea, and rash[41]. Long-term PPI use was able to cause diminished acid secretion and reduced somatostatin release, resulting in enterochromaffin-like cell hyperplasia and hypergastrinemia[48,49]. As indicated by univariate meta-regression analysis, the adverse rate of PPI use for NERD was influenced by hiatal hernia and drinking. The mechanism through which hiatal hernias influence the adverse rate of PPI for NERD is uncertain, but the reason might be that hiatal hernias cause reflux, stimulating the nausea-inducing receptors in the esophagus and throat, as well as other adverse events. In addition, the metabolism of PPI generates two different CYP isoforms in the liver, which are responsible for the majority of their biotransformation due to their susceptibility to ethyl alcohol (CYP2C19 and CYP3A4)[40,42]. Thus, as drinking increases the blood concentration of ethyl alcohol, adverse events due to the reduced biotransformation of CYP2C19 and CYP3A4 and an increased blood concentration of PPI may arise.

There are a few shortcomings in our meta-analysis that should be mentioned. First, the analytical results are influenced by the reviewers, although we attempted to overcome this drawback. Second, a few differences may exist due to the various assessments of the efficacy and safety of PPI against NERD. Third, the evaluation index resulted from subjective feelings, which may influence the authenticity of these studies.

In conclusion, our meta-analysis showed that PPI is more effective than H2RA or placebo for the treatment of NERD. However, there was no significant difference between the safeties of PPI and H2RA or placebo. In addition, the effective rate of PPI for NERD was associated with hiatal hernia, while the adverse rate was associated with hiatal hernia and drinking. In the clinic, it is necessary to choose a PPI with a suitable dose, therapeutic duration and type for different NERD patients. More multi-center, high-quality randomized controlled trials with larger samples and longer term of follow-up visits are desirable.

**REFERENCES**

1. Chey WD. Endoscopy-negative reflux disease: concepts and clinical practice. *Am J Med* 2004; 117 Suppl 5A: 365-345 [PMID: 15478851 DOI: 10.1016/j.amjmed.2004.07.016]
2. Wang C, Hunt RH. Precise role of acid in non-erosive reflux disease. *Digestion* 2008; 78 Suppl 1: 51-41 [PMID: 18832838 DOI: 10.1159/000151253]
3. Minatsuiki C, Yamamichi N, Shimamoto T, Kakimoto H, Takahashi Y, Fujishiro M, Sakaguchi Y, Nakayama C, Konno-Shimizu M, Matsuda R, Machizuki S, Asada-Hirayama I, Tsuji Y, Kodashima S, Ono S, Niimi K, Mitsushima T, Koike K. Background factors of reflux esophagitis and non-erosive reflux disease: a cross-sectional study of 10,837 subjects in Japan. *PLoS One* 2013; 8: e69891 [PMID: 23922844 DOI: 10.1371/journal.pone.0069891]
4. Moayyedi P, Hunt R, Armstrong D, Lei Y, Bukoski M, White R. The impact of intensifying acid suppression on sleep disturbance related to gastro-oesophageal reflux disease in primary care. *Aliment Pharmacol Ther* 2013; 37: 730-737 [PMID: 23432146 DOI: 10.1111/apt.12254]
5. Shida H, Sakai Y, Hamada H, Takayama T. The daily response for proton pump inhibitor treatment in Japanese reflux esophagitis and non-erosive reflux disease. *J Clin Biochem Nutr* 2013; 52: 76-81 [PMID: 2341702 DOI: 10.3164/jcbn.12-69]
6. Ke MY. How to differentiate non-erosive reflux disease from functional heartburn. *J Dig Dis* 2012; 13: 605-608 [PMID: 23134478 DOI: 10.1111/j.1751-2980.2012.00637.x]
7. Bardhan KD, Müller-Lissner S, Bigard MA, Bianchi Porro G, Ponce J, Hosie J, Scott M, Weir DG, Gillon KR, Peacock RA, Fulton C. Symptomatic gastro-oesophageal reflux disease: double blind controlled study of intermittent treatment with omeprazole or ranitidine. The European Study Group. *BMJ* 1999; 318: 502-507 [PMID: 10024259 DOI: 10.1136/bmj.318.7182.502]
8. Galmiche JP, Bruley des Varannes S. Endoluminal therapies for gastro-oesophageal reflux disease. *Lancet* 2003; 361: 1119-1121 [PMID: 12672327 DOI: 10.1016/S0140-6736(03)12889-9]
9. Mancini V, Ribolzi M, Gentile M, deAngelis G, Bizzarri B, Lindley KJ, Cucchiara S, Cicala M, Borrelli O. Oesophageal mucosal intercellular space diameter and reflux pattern in childhood erosive and non-erosive reflux disease. *Dig Liver Dis* 2012; 44: 981-987 [PMID: 22974565 DOI: 10.1016/j.dld.2012.08.001]
10. Fock KM, Talley N, Hunt R, Fass R, Nandurkar S, Lam SK, Goh KL, Sollano J. Report of the Asia-Pacific consensus on
the management of gastrooesophageal reflux disease. J Gastroenterol Hepatol 2004; 19: 357-367 [PMID: 15012771 DOI: 10.1111/j.1440-1744.2004.03419.x]

10 Fock KM, Yeo EK, Ang TL, Chua TS, Ng TM, Tan YL. Rabeprazole vs esomeprazole in non-erosive gastro-esophageal reflux disease: a randomized, double-blind study in urban Asia. World J Gastroenterol 2005; 11: 3091-3098 [PMID: 15918196]

11 Bytzer P, van Zanten SV, Mattsson H, Wernersson B. Partial symptom-response to proton pump inhibitors in patients with non-erosive reflux disease or reflux oesophagitis - a post hoc analysis of 5796 patients. Aliment Pharmacol Ther 2007; 26: 1057-1066 [PMID: 17784330 DOI: 10.1111/j.1365-2036.2007.03675.x]

12 Linsky A, Hermes JA, Lawler EV, Rudolph JL. Proton pump inhibitor discontinuation in long-term care. J Am Geriatr Soc 2011; 59: 1658-1664 [PMID: 21883102 DOI: 10.1111/j.1532-5415.2011.03545.x]

13 Wilhelm SM, Rjeter RK, Kale-Pradhan PB. Perils and pitfalls of long-term effects of proton pump inhibitors. Expert Rev Clin Pharmacol 2013; 6: 443-451 [PMID: 23927671 DOI: 10.1586/17512433.2013.812126]

14 Fujiiwara Y, Takahashi S, Arakawa T, Sollano JD, Zhu Q, Umegaki E, Takeuchi N, Yoda Y, Kojima Y, Toioka S, Higuchi K. Steptics for peptic ulcer healing after 1 week proton pump inhibitor-based triple Helicobacter pylori eradication therapy in Japanese patients: differences of gastric ulcers and duodenal ulcers. J Clin Biochem Nutr 2012; 58: 189-195 [PMID: 23170046 DOI: 10.3164/jcbn.12-15]

15 Scarpignato C. Poor effectiveness of proton pump inhibitors in non-erosive reflux disease: the truth in the end! Neurogastroenterol Motil 2012; 24: 697-704 [PMID: 22783985 DOI: 10.1111/j.1365-2982.2012.01977.x]

16 Woodland P, Sifrim D. Management of gastro-oesophageal reflux disease symptoms that do not respond to proton pump inhibitors. Curr Opin Gastroenterol 2013; 29: 431-436 [PMID: 23549542 DOI: 10.1097/MOG.0b013e32836d453c]

17 Beijnen JH, Cremonini F, Smout AJ, Bredenoord AJ. PPI therapy is equally effective in well-defined non-erosive reflux disease. Aliment Pharmacol Ther 2005; 21 Suppl 2: 10-18 [PMID: 15943841 DOI: 10.1111/j.1365-2036.2005.02468.x]

18 Mineur P, Orr W, Filippone J, Kojubaitis L, Sloan S. Rabeprazole in nonerosive gastroesophageal reflux disease: a randomized placebo-controlled trial. Am J Gastroenterol 2002; 97: 1332-1339 [PMID: 12094846 DOI: 10.1111/j.1570-0241.2002.00579.x]

19 Armstrong D, Pare P, Pericak D, Pyzyk M. Symptom relief in gastroesophageal reflux disease: a randomized, controlled comparison of pantoprazole and nizatidine in a mixed patient population with erosive esophagitis or endoscopy-negative reflux disease. Am J Gastroenterol 2001; 96: 2849-2857 [PMID: 11695354 DOI: 10.1111/j.1570-0241.2001.0427.x]

20 Arminbo R, Havelund L, Lundell L, Gisle H, Lauritzen K, Pedersen SA, Anker-Hansen O, Stubberød G, Eriksson G, Carlsson R, Junghard O. On demand therapy with omeprazole for the long-term management of patients with heartburn without oesophagitis—a placebo-controlled randomized trial. Aliment Pharmacol Ther 1999; 13: 907-914 [PMID: 10838225 DOI: 10.1046/j.1365-2036.1999.00564.x]

21 Richter JE, Campbell DR, Kahnirasa PJ, Huang B, Fludas C. Lansoprazole compared with ranitidine for the treatment of nonerosive gastroesophageal reflux disease. Arch Intern Med 2000; 160: 1803-1809 [PMID: 10871974 DOI: 10.1001/archinte.160.12.1803]

22 Bytzer P, Blum A, De Herdt D, Dubois D. Trial Investigators. Six-month trial of on-demand rabeprazole 10 mg main-
tains symptom relief in patients with non-erosive reflux disease. *Aliment Pharmacol Ther* 2004; 20: 181-188 [PMID: 15233698 DOI: 10.1111/j.1365-2036.2004.01999.x]

36 **Kahrilas PJ**, Miner P, Johanson J, Mao L, Jokubaitis L, Sloan S. Efficacy of rabeprazole in the treatment of symptomatic gastroesophageal reflux disease. *Dig Dis Sci* 2005; 50: 2009-2018 [PMID: 16240208 DOI: 10.1007/s10620-005-3000-3]

37 **Lind T**, Havelund T, Carlsson R, Anker-Hansen O, Glise H, Hernqvist H, Junghard O, Lauritsen K, Lundell L, Pedersen SA, Stubberød A. Heartburn without oesophagitis: efficacy of omeprazole therapy and features determining therapeutic response. *Scand J Gastroenterol* 1997; 32: 974-979 [PMID: 9361168 DOI: 10.3109/00365529709011212]

38 **Uemura N**, Inokuchi H, Serizawa H, Chikama T, Yamauchi M, Tsuru T, Umezut T, Urata T, Yurino N, Tanabe S, Yoshida T, Kawamura S, Murakami A, Yamamoto M, Chiba T. Efficacy and safety of omeprazole in Japanese patients with nonerosive reflux disease. *J Gastroenterol* 2008; 43: 670-678 [PMID: 18807128 DOI: 10.1007/s00535-008-2214-5]

39 **Talley NJ**, Moore MG, Sprogis A, Katerlais P. Randomised controlled trial of pantoprazole versus ranitidine for the treatment of uninvestigated heartburn in primary care. *Med J Aust* 2002; 177: 423-427 [PMID: 12812512]

40 **Pace F**, Casini V, Pallotta S. Heterogeneity of endoscopy negative heartburn: epidemiology and natural history. *World J Gastroenterol* 2008; 14: 5233-5236 [PMID: 18785272 DOI: 10.3748/wjg.v14.i23]

41 **Katz PO**, Castell DO, Levine D. Esomeprazole resolves chronic heartburn in patients without erosive oesophagitis. *Aliment Pharmacol Ther* 2003; 18: 875-882 [PMID: 14616151 DOI: 10.1046/j.1365-2036.2003.01771.x]

42 **Shin JM**, Munson K, Vagin O, Sachs G. The gastric HK-ATPase: structure, function, and inhibition. *Pflugers Arch* 2009; 457: 609-622 [PMID: 18536934 DOI: 10.1007/s00424-008-0495-4]

43 **Ward RM**, Kearns GL. Proton pump inhibitors in pediatrics: mechanism of action, pharmacokinetics, pharmacogenetics, and pharmacodynamics. *Paediatr Drugs* 2013; 15: 119-131 [PMID: 23512128 DOI: 10.1007/s40272-013-0012-x]

44 **Kahrilas PJ**, Falk GW, Johnson DA, Schmitt C, Collins DW, Whipple J, D’Amico D, Hamelin B, Joelsson B. Esomeprazole improves healing and symptom resolution as compared with omeprazole in reflux oesophagitis patients: a randomized controlled trial. The Esomeprazole Study Investigators. *Aliment Pharmacol Ther* 2000; 14: 1249-1258 [PMID: 11012468 DOI: 10.1046/j.1365-2036.2000.00856.x]

45 **Farley A**, Wruble LD, Humphries TJ. Rabeprazole versus ranitidine for the treatment of erosive gastroesophageal reflux disease: a double-blind, randomized clinical trial. *Rabeprazole Study Group. Am J Gastroenterol* 2000; 95: 1894-1899 [PMID: 10950032 DOI: 10.1111/j.1572-0241.2000.02233.x]

46 **Hata M**, Shiono M, Sekino H, Furukawa H, Sezai A, Iida M, Yoshitake I, Hattori T, Wakai S, Taoka M, Negishi N, Sezai Y. Efficacy of a proton pump inhibitor given in the early postoperative period to relieve symptoms of hiatal hernia after open heart surgery. *Surg Today* 2006; 36: 131-134 [PMID: 16440158]

47 **Chubineh S**, Birk J. Proton pump inhibitors: the good, the bad, and the unwanted. *South Med J* 2012; 105: 613-618 [PMID: 23128806 DOI: 10.1097/SMJ.0b013e31826efbea]

48 **Laine L**, Ahnen D, McClain C, Solcia E, Walsh JH. Review article: potential gastrointestinal effects of long-term acid suppression with proton pump inhibitors. *Aliment Pharmacol Ther* 2000; 14: 651-668 [PMID: 10848649 DOI: 10.1046/j.1365-2036.2000.00768.x]

49 **di Mario F**, Cavallaro LG. Non-invasive tests in gastric diseases. *Dig Liver Dis* 2008; 40: 523-530 [PMID: 18439884 DOI: 10.1016/j.dld.2008.02.028]

50 **Li Y**, Zhang W, Guo D, Zhou G, Zhou H, Xiao Z. Pharmacokinetics of the new proton pump inhibitor ilaprazole in Chinese healthy subjects in relation to CYP3A5 and CYP2C19 genotypes. *Clin Chim Acta* 2008; 391: 60-67 [PMID: 18319058 DOI: 10.1016/j.cca.2008.02.003]

51 **Pereira MA**. The missing linkage: what pharmacogenetic associations are left to find in CYP3A5 and CYP2C19 genotypes. *Clin Chim Acta* 2008; 391: 60-67 [PMID: 18319058 DOI: 10.1016/j.cca.2008.02.003]
