World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/esps/
bpgoffice@wjgnet.com
doi:10.3748/wjg.v19.i45.8408

World J Gastroenterol 2013 December 7; 19(45): 8408-8419
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

META-ANALYSIS

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

Ji-Xiang Zhang, Meng-Yao Ji, Jia Song, Hong-Bo Lei, Shi Qiu, Jing Wang, Ming-Hua Ai, Jun Wang, Xiao-Guang Lv, Zi-Rong Yang, Wei-Guo Dong

Ji-Xiang Zhang, Meng-Yao Ji, Jia Song, Hong-Bo Lei, Shi Qiu, Jing Wang, Ming-Hua Ai, Jun Wang, Xiao-Guang Lv, Zi-Rong Yang, Wei-Guo Dong, Department of Gastroenterology, Renmin Hospital of Wuhan University, Wuhan 430060, Hubei Province, China

Author contributions: Zhang JX and Dong WG designed the research; Zhang JX, Yang ZR and Lv XG performed the research; Zhang JX, Song J, Qiu S, Ai MH and Wang J analyzed the data; Zhang JX wrote the paper; Yang ZR and Dong WG reviewed and revised the paper.

Correspondence to: Wei-Guo Dong, MD, PhD, Department of Gastroenterology, Renmin Hospital of Wuhan University, Ziyang Road 99, Wuhan 430060, Hubei Province, China. dwg@whu.edu.cn

Telephone: +86-27-88041911 Fax: +86-27-88042292

Received: July 10, 2013 Revised: September 4, 2013
Accepted: September 16, 2013
Published online: December 7, 2013

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 H_2 receptor antagonists (H_2RA) 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 H_2RA (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 H_2RA on symptomatic relief rate but not on adverse rate for NERD. Its relief rate and adverse rate were influenced by hiatal hernia and drinking.

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.

Zhang JX, Ji MY, Song J, Lei HB, Qiu S, Wang J, Ai MH, Wang J, Lv XG, Yang ZR, Dong WG. Proton pump inhibitor for non-erosive reflux disease: A meta-analysis. *World J Gastroenterol* 2013; 19(45): 8408-8419 Available from: URL: http://www.wjgnet.com/1007-9327/full/v19/i45/8408.htm DOI: http://dx.doi.org/10.3748/wjg.v19.i45.8408

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[1-3]. Patients with NERD are more likely to be female, young, thin, and without hiatal hernias[4-6], 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[7-9]. To improve these patients' quality of life, provide a rapid relief of symptoms and reduce the severity and number of recurrent episodes[10-12], 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^+[13,14]. 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[15-18]. However, the efficacy, safety and influential factors of PPI use remain inconclusive, especially for NERD[19,20].

Although two papers[21,22] 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 H_2 receptor antagonists (H_2RA) 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* H_2RA 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 χ^2 test and I^2 test. The percentage of the variability in the estimates of effect, caused by heterogeneity but not chance, was described by I^2 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.

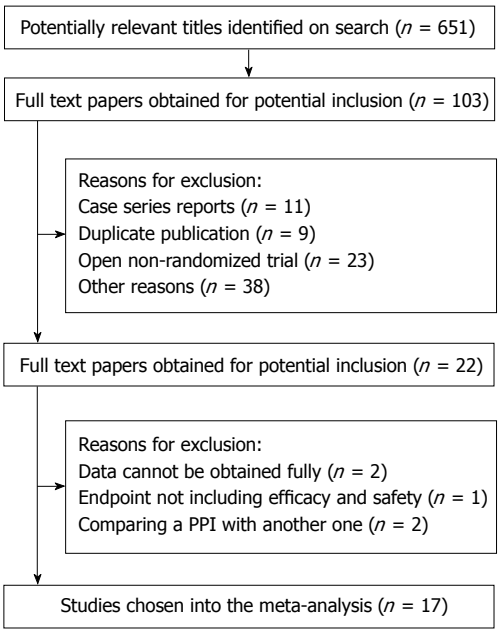


Figure 1 Screening process of studies. PPI: Proton pump inhibitor.

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.

RESULTS

Study identification and selection

Following the searching strategy, we initially acquired 651 studies. Having discarded the studies of repetitive publication and that did not meet the criteria apparently, and after reading the titles and abstracts, there were 51 studies left. To search and read the full text, 34 studies which were not RCTs or without control groups were abandoned and 17 RCTs[23-39] were left finally. The screening process of studies is shown in Figure 1.

Study characteristics

For the 17 RCTs, 5 were single-center studies and 12 were multi-center studies. In the RCTs, there were 6072 patients with 3937 patients in the combination group and the 2135 patients in PPI alone group. The details of these studies are listed in Table 1.

PPI vs H_2RA on the rate of symptomatic relief

Seven studies[24,26,29,30,32,34,39], which involved 1882 patients, compared PPI with H_2RA on the rate of symptomatic relief of NERD. There are 935 patients who received PPI and 947 patients who received H_2RA. 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[32] 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_2RA 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, I^2 = 0%, P = 0.640), PPI advanced over H_2RA (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, I^2 = 0%, P = 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, I^2 = 0%, P = 0.422), PPI significantly overmatched H_2RA (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, I^2 = 23.5%, P = 0.365), PPI was also superior to H_2RA (RR = 1.614, 95%CI: 1.361-1.914, P = 0.000).

In the subgroup analysis of lansoprazole (PPI 227/585, placebo 141/584, I^2 = 0%, P = 0.603), PPI advanced over H_2RA (RR = 1.866, 95%CI: 1.435-2.448, P = 0.000). But compared with groups of omeprazole (PPI 41/67, placebo 31/64, I^2 = 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[23,25,27,28,31,33-38] 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).

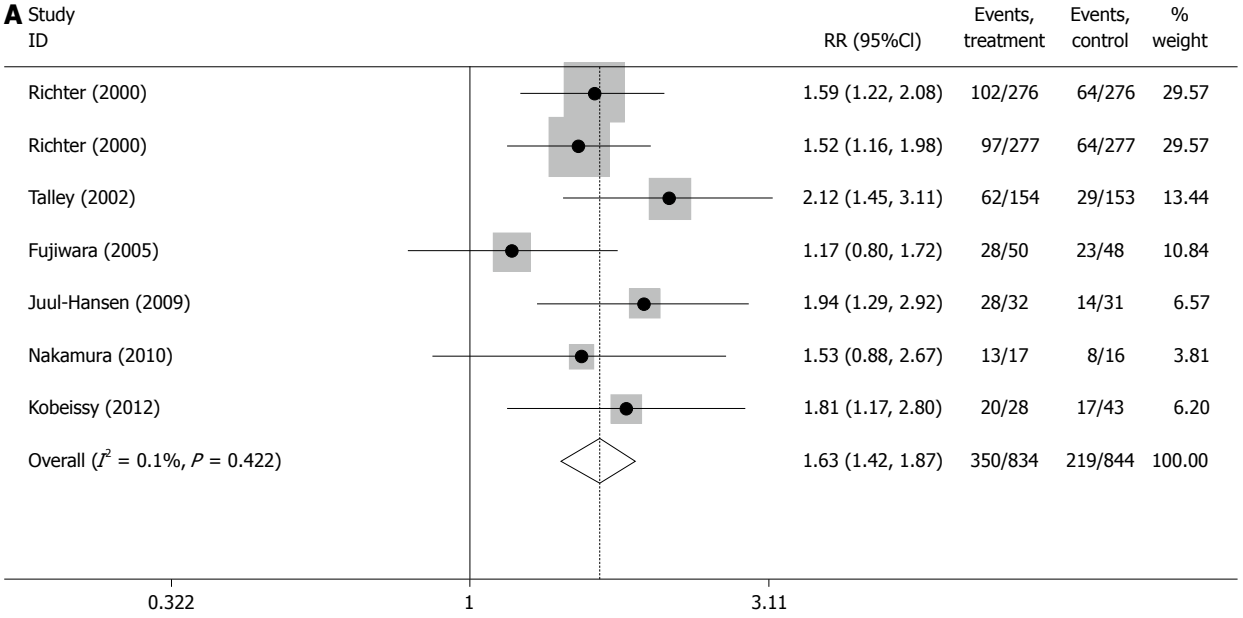
In the subgroup analysis of long duration (PPI 407/855, placebo 114/315, I^2 = 65.4%, P = 0.034), PPI advanced over placebo (RR = 1.442, 95%CI: 1.034-2.010, P = 0.031). In short duration (PPI 1139/2432, placebo 459/1241, I^2 = 78.6%, P = 0.000), similar result was also found (RR = 2.029, 95%CI: 1.665-2.473, P = 0.000).

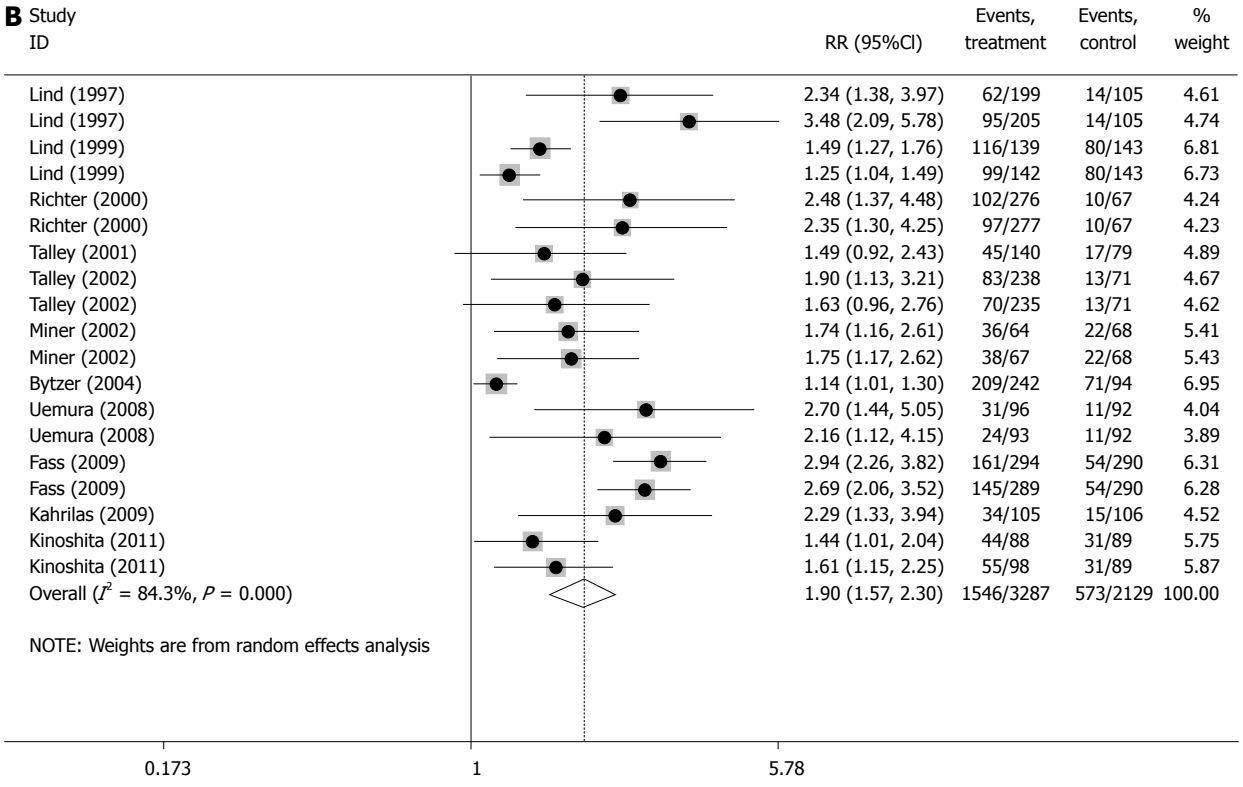
In the subgroup analysis of high dose (PPI 486/1098, placebo 131/718, I^2 = 0%, P = 0.506), PPI significantly overmatched placebo (RR = 2.664, 95%CI: 2.251-3.154,

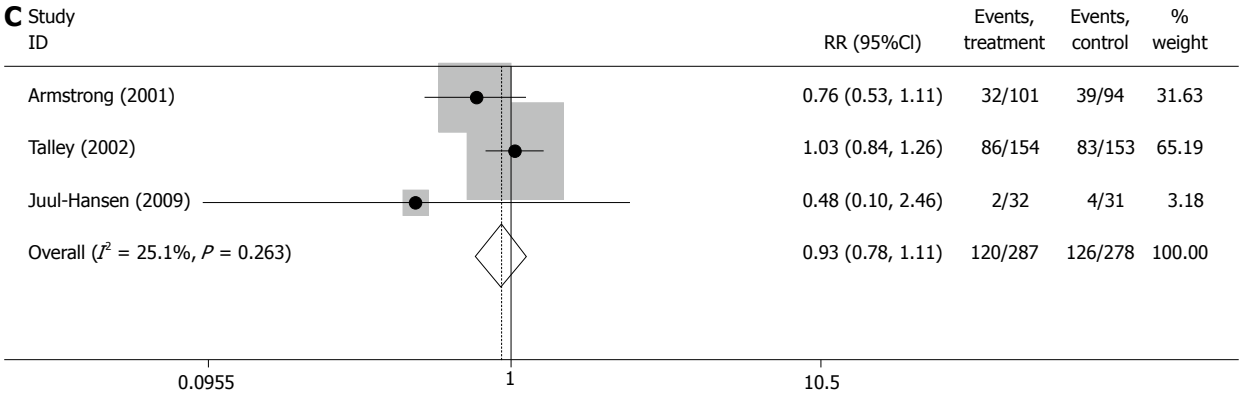
Table 1 Details of these studies *n* (%)

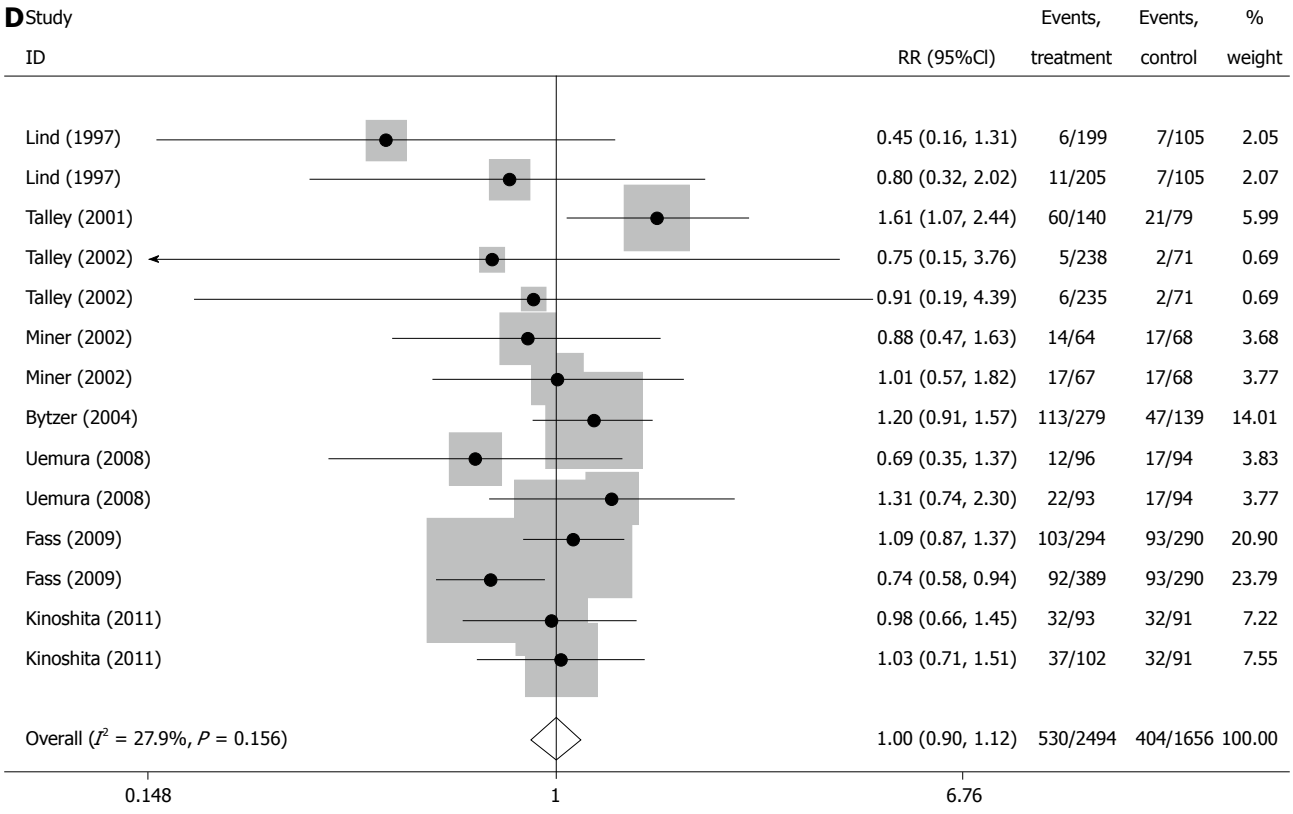
First author	Country	Year	Study design	Arms of treatment	Age (yr)	Gender (M/F)	*n*	BMI	*Helicobacter pylori* infection	Hiatal hernia	Smokers	Alcohol users	Therapeutic duration	Adverse events	Effective
Talley *et al*[23]	United Kingdom	2002	RCT	Esomeprazole 20 mg	48.0	135/158	293	-	90	89	-	-	6 mo	5	101 (34.6)
				Esomeprazole 40 mg	48.4	135/147	282	-	101	92	-	-		6	84 (29.7)
				placebo	48.2	58/88	146	-	57	39	-	-		2	30 (17.8)
Juul-Hansen *et al*[24]	Norway	2009	RCT	Lansoprazole 15 mg	47.5	11/21	32	26.4	6	10	8	-	6 mo	2	28 (87.5)
				Ranitidine 75 mg	48.0	12/19	31	25.2	6	6	8	-		4	14 (45.2)
Kinoshita *et al*[25]	Japan	2011	RCT	Rabeprazole 5 mg	46.3	38/55	93	22.4	35	-	-	-	4 wk	32	36 (35.0)
				Rabeprazole 10 mg	46.8	50/51	101	23.2	42	-	-	-		37	44 (44.0)
				placebo	49.7	40/51	91	23.2	44	-	-	-		32	19 (21.0)
Kobeissy *et al*[26]	Lebanon	2012	RCT	Rabeprazole 20 mg	45.4	16/28	44	-	-	-	-	-	4 wk	-	20 (45.5)
				Ranitidine 300 mg	45.1	16/23	39	-	-	-	-	-		-	17 (43.6)
Talley *et al*[27]	Australia	2001	RCT	Esomeprazole 20 mg	49.0	94/76	170	-	64	65	-	-	6 mo	11	146 (85.0)
				placebo	49.0	98/74	172	-	57	75	-	-		13	83 (48.0)
Fass *et al*[28]	United States	2009	RCT	Dexlansoprazole 30 mg	47.6	84/231	315	29.0	95	-	72	162	4 wk	6	173 (54.9)
				Dexlansoprazole 60 mg	47.5	106/209	315	29.6	90	-	57	181		8	157 (50.0)
				placebo	47.6	84/233	317	29.1	89	-	52	182		1	59 (18.5)
Fujiwara *et al*[29]	Japan	2005	RCT	Omeprazole 20 mg	55.0	20/30	50	22.8	22	14	6	18	4 wk	-	43 (86.0)
				Famotidine 20 mg	56.6	23/25	48	22.2	22	11	11	17		-	36 (75.0)
Nakamura *et al*[30]	Japan	2010	RCT	Omeprazole 20 mg	51.4	8/9	17	-	5	9	-	-	8 wk	0	13 (75.0)
				Roxitidine 75 mg	48.6	9/7	16	-	7	8	-	-		0	11 (70.6)
Miner *et al*[31]	United States	2002	RCT	Rabeprazole 10 mg	44.4	28/37	65	30.9	17	-	22	29	4 wk	14	19 (29.3)
				Rabeprazole 20 mg	45.5	25/33	68	30.3	24	-	21	26		17	19 (28.3)
				placebo	46.1	24/26	70	30.2	28	-	22	30		18	2 (3.4)
Armstrong *et al*[32]	Canada	2001	RCT	Pantoprazole 40 mg	47.1	57/49	106	-	16	-	66	71	4 wk	32	41 (52.8)
				Nizatidine 150 mg	47.6	51/51	102	-	20	-	64	67		39	33 (42.9)
Lind *et al*[33]	Sweden	1999	RCT	Omeprazole 10 mg	52.0	53/86	139	-	-	76	24	88	4 wk	-	116 (83.5)
				Omeprazole 20 mg	51.0	65/77	142	-	-	72	43	85		-	99 (69.7)
				placebo	48.0	61/82	143	-	-	74	57	97		-	80 (55.9)
Richter *et al*[34]	United States	2000	RCT	Lansoprazole 15 mg	44.9	115/161	276	-	66	-	75	132	8 wk	-	37 (13.4)
				Lansoprazole 30 mg	45.1	122/155	277	-	66	-	88	129		-	97 (35.0)
				Ranitidine 150 mg	45.2	108/170	278	-	63	-	69	126		-	64 (23.0)
				placebo	46.3	30/37	67	-	9	-	19	35		-	10 (14.7)
Bytzer *et al*[12]	Denmark	2004	RCT	Rabeprazole 10 mg	47.0	123/156	279	26.0	100	-	-	-	6 mo	113	241 (86.4)
				placebo	48.0	57/82	139	27.0	52	-	-	-		47	94 (67.6)
Kahrilas *et al*[35]	United States	2009	RCT	Rabeprazole 20 mg	43.1	40/89	129	29.3	42	-	35	58	4 wk	-	42 (32.4)
				placebo	44.0	45/87	132	30.0	40	-	36	51		-	5 (3.8)
Lind *et al*[33]	Sweden	1997	RCT	Omeprazole 10 mg	49.0	89/110	199	-	-	-	60	133	4 wk	6	98 (49.2)
				Omeprazole 20 mg	50.0	66/139	205	-	-	-	46	121		11	125 (61.0)
				placebo	51.0	51/54	105	-	-	-	22	64		7	25 (23.8)
Uemura *et al*[36]	Japan	2008	RCT	Omeprazole 10 mg	44.4	47/49	96	-	37	5	-	-	4 wk	12	44 (45.8)
				Omeprazole 20 mg	43.8	53/40	93	-	49	9	-	-		22	43 (46.2)
				placebo	42.4	53/49	92	-	32	2	-	-		17	22 (23.9)
Talley *et al*[27]	Australia	2002	RCT	Pantoprazole 20 mg	53.0	78/76	154	28.9	-	-	65	28	6 mo	86	109 (71.0)
				Ranitidine 150 mg	52.0	83/70	153	28.4	-	-	61	30		83	86 (56.0)

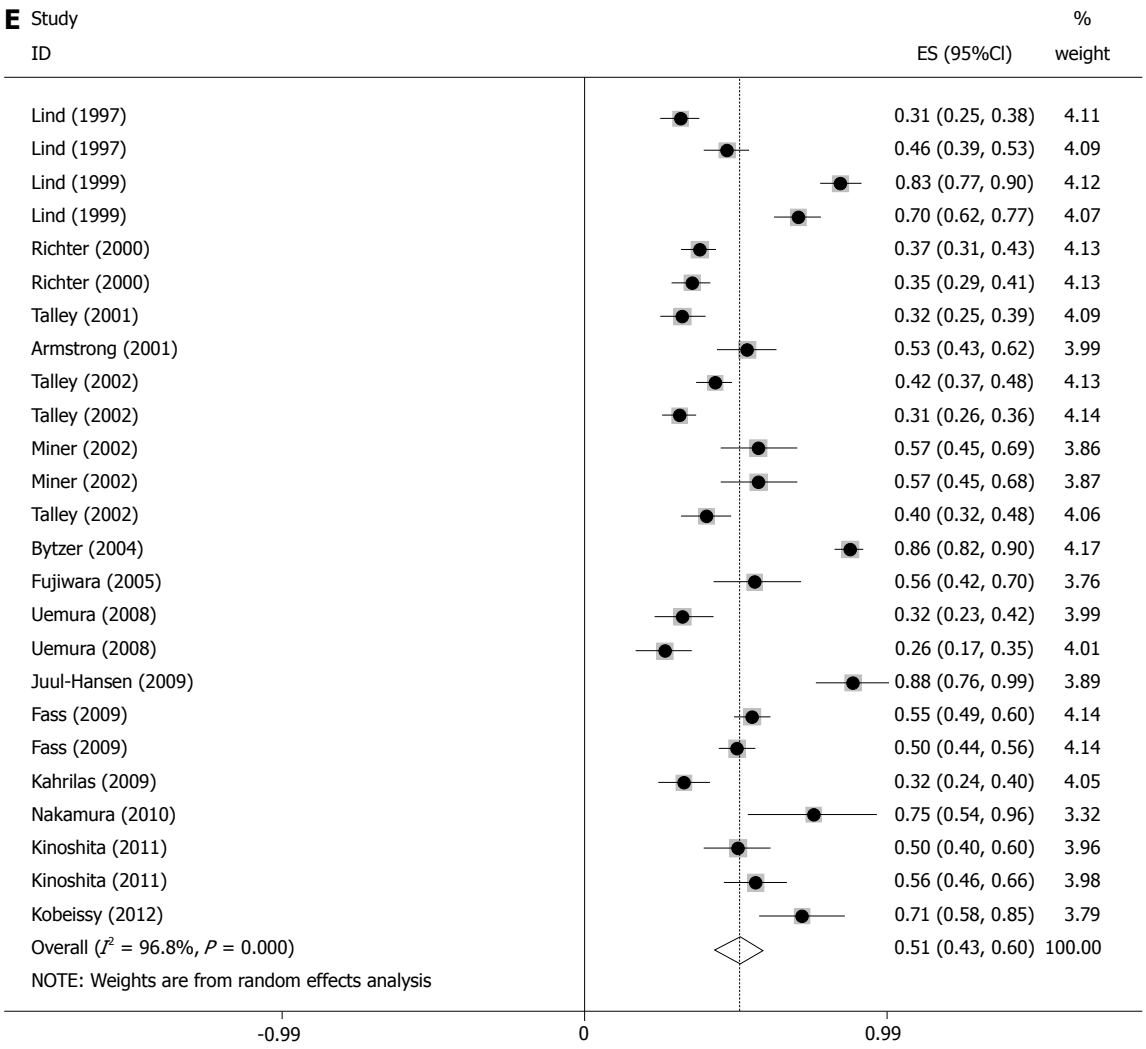
RCT: Randomized controlled trials; M: Male; F: Female; BMI: Body mass index.


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
0.322
1
3.11


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
Lind (1999) 1.25 (1.04, 1.49) 99/142 80/143 6.73
Richter (2000) 2.48 (1.37, 4.48) 102/276 10/67 4.24
Richter (2000) 2.35 (1.30, 4.25) 97/277 10/67 4.23
Talley (2001) 1.49 (0.92, 2.43) 45/140 17/79 4.89
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
0.173
1
5.78


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
0.0955
1
10.5


D
Study ID
RR (95%CI)
Events, treatment
Events, control
% weight
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 (I^2 = 27.9%, P = 0.156) 1.00 (0.90, 1.12) 530/2494 404/1656 100.00
0.148
1
6.76


E
Study ID
ES (95%CI)
% weight
Lind (1997) 0.31 (0.25, 0.38) 4.11
Lind (1997) 0.46 (0.39, 0.53) 4.09
Lind (1999) 0.83 (0.77, 0.90) 4.12
Lind (1999) 0.70 (0.62, 0.77) 4.07
Richter (2000) 0.37 (0.31, 0.43) 4.13
Richter (2000) 0.35 (0.29, 0.41) 4.13
Talley (2001) 0.32 (0.25, 0.39) 4.09
Armstrong (2001) 0.53 (0.43, 0.62) 3.99
Talley (2002) 0.42 (0.37, 0.48) 4.13
Talley (2002) 0.31 (0.26, 0.36) 4.14
Miner (2002) 0.57 (0.45, 0.69) 3.86
Miner (2002) 0.57 (0.45, 0.68) 3.87
Talley (2002) 0.40 (0.32, 0.48) 4.06
Bytzer (2004) 0.86 (0.82, 0.90) 4.17
Fujiwara (2005) 0.56 (0.42, 0.70) 3.76
Uemura (2008) 0.32 (0.23, 0.42) 3.99
Uemura (2008) 0.26 (0.17, 0.35) 4.01
Juul-Hansen (2009) 0.88 (0.76, 0.99) 3.89
Fass (2009) 0.55 (0.49, 0.60) 4.14
Fass (2009) 0.50 (0.44, 0.56) 4.14
Kahrilas (2009) 0.32 (0.24, 0.40) 4.05
Nakamura (2010) 0.75 (0.54, 0.96) 3.32
Kinoshita (2011) 0.50 (0.40, 0.60) 3.96
Kinoshita (2011) 0.56 (0.46, 0.66) 3.98
Kobeissy (2012) 0.71 (0.58, 0.85) 3.79
Overall (I^2 = 96.8%, P = 0.000) 0.51 (0.43, 0.60) 100.00
NOTE: Weights are from random effects analysis
-0.99
0
0.99

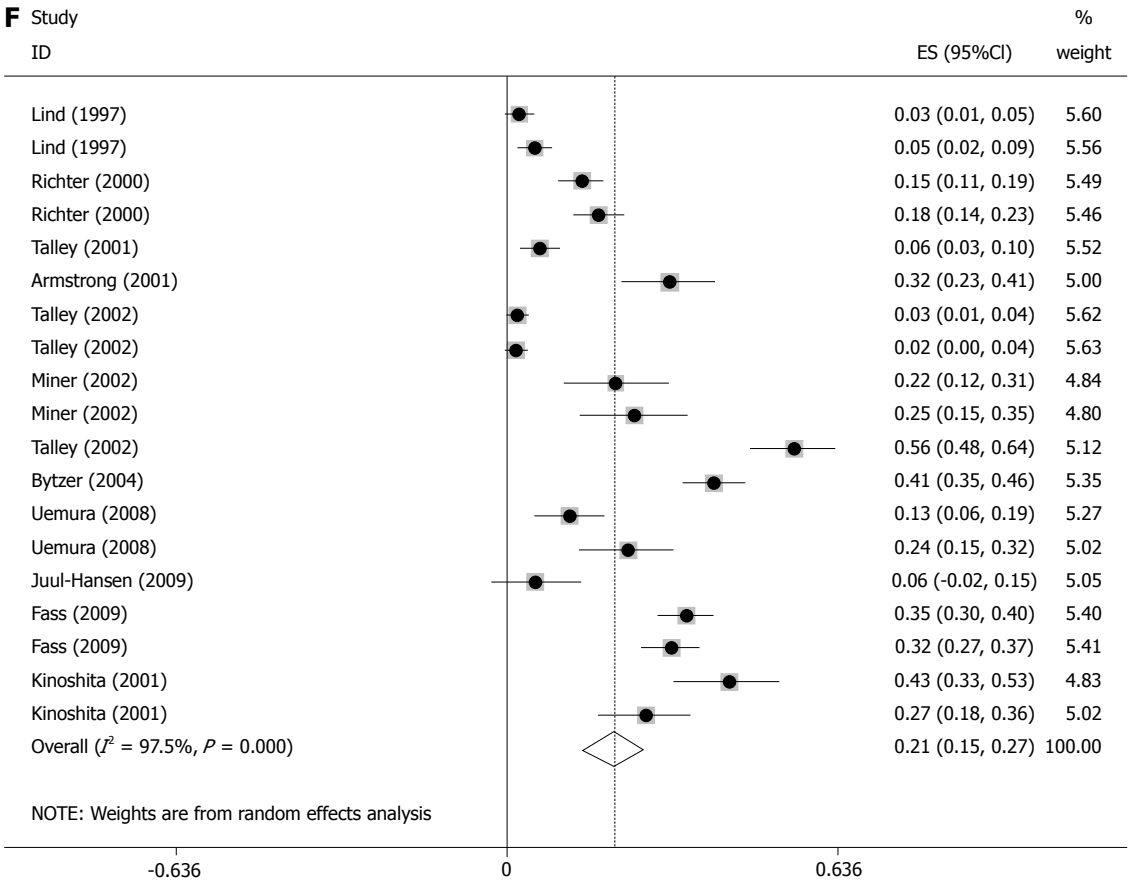


Figure 2 Forest plot. A: Comparison of proton pump inhibitor (PPI) *vs* H_2 receptor antagonists (H_2RA) on the rate of symptomatic relief; B: Comparison of PPI *vs* placebo on the rate of symptomatic relief; C: Comparison of PPI *vs* H2RA on the rate of adverse events; D: Comparison of PPI *vs* placebo on the rate of adverse events; E: Overall efficacy of PPI against non-erosive reflux disease (NERD); F: Adverse rate of PPI against NERD.

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_2RA on the rate of adverse events

Three studies[24,32,39], which involved 565 patients, compared PPI with H_2RA on the rate of adverse events of NERD. There were 287 patients who received PPI and 278 patients who received H_2RA. 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_2RA on the rate of adverse events of NERD (RR = 0.928; 95%CI: 0.776-1.110, 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 the subgroup analysis of high dose (PPI 316/1661, placebo 252/1068, I^2 = 45.6%, P = 0.075), there was no obvious difference between PPI and placebo (RR = 0.999, 95%CI: 0.868-1.150, P = 0.988). 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 =

Table 2 Results of univariate meta-regression analysis exploring factors influencing efficacy and adverse rate of proton pump inhibitor for non-erosive reflux disease

Factors	Efficacy		Adverse rate	
	Coefficient	*P* value	Coefficient	*P* value
Age	0.0177315	0.170	0.0075041	0.665
Gender	-0.2213605	0.186	0.0209630	0.894
BMI	-0.0127987	0.484	-0.0044024	0.808
n	-0.0005643	0.154	-0.0001338	0.733
Helicobacter pylori infection	-0.6007750	0.217	0.1326016	0.736
Hiatal hernia	0.9702707	0.030	-0.4392244	0.081
Smoking	-0.2591453	0.528	0.5030517	0.245
Drinking	0.3296374	0.303	-0.6776039	0.053
Therapeutic duration	0.0008200	0.857	-0.0015192	0.722
Dose	-0.0026090	0.414	0.0003684	0.897

BMI: Body mass index.

0.981), omeprazole (PPI 51/593, placebo 48/398, I^2 = 23.5%, P = 0.270) and rabeprazole (PPI 31/131, placebo 34/136, I^2 = 0%, P = 0.732), the significant difference was also not found (P > 0.05).

Overall efficacy of PPI against NERD and its influential factors

All the 17 studies[23-39] provided the data of the efficacy of PPI against NERD and its influential factors. Heterogeneity analysis showed that there was obviously statistical heterogeneity among these studies (I^2 = 96.8%, P = 0.000). The result showed that the overall rate of symptomatic relief of PPI against NERD was 51.4% (95%CI: 0.433-0.595, P = 0.000), (Figure 2E).

In the subgroup analysis of long duration, the effective rate of PPI against NERD was 51.4% (95%CI: 0.433-0.595, P = 0.000). In short duration, the rate was 51.5% (95%CI: 0.432-0.598, P = 0.000).

In the subgroup analysis of high dose, the effective rate of PPI against NERD was 48.4% (95%CI: 0.404-0.564, P = 0.000). In low dose, the rate was 56.3% (95%CI: 0.395-0.732, P = 0.000).

In the subgroup analysis of lansoprazole, the effective rate of PPI against NERD was 52.1% (95%CI: 0.392-0.650, P = 0.000). In that of pantoprazole, omeprazole and rabeprazole, the effective rate were 44.7% (95%CI: 0.369-0.526, P = 0.000), 52.1% (95%CI: 0.355-0.688, P = 0.000) and 60.8% (95%CI: 0.367-0.849, P = 0.000), respectively.

Univariate meta-regression analysis found that the rate of hiatal hernia (P = 0.030) was associated with the rate of symptomatic relief of PPI against NERD, but not with others.

Overall safety of PPI against NERD and its influential factors

Twelve studies[23-25,27,28,31,32,34,37-39] provided the data of the rate of adverse events of PPI against NERD and its influential factors. Heterogeneity analysis showed that there 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 26.2% (95%CI: 0.150-0.375, P = 0.000), 9.8% (95%CI: 0.036-0.161, P = 0.002) 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[26,28,32] 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 = 0.646), PPI *vs* H2RA on the rate of adverse events (Egger's test: P = 1.000 and Begg's test: P = 0.374) and PPI *vs* placebo on the rate of adverse events (Egger's test: P = 0.125 and Begg's test: P = 0.552). But in the outcome of PPI *vs* placebo on the rate of symptomatic relief, the potential publication bias may exist (Egger's test: P = 0.010 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,

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[4]	Low
Long-duration subgroup	RCT	Serious[2]	No	No	No	Serious[4]	Low
Short-duration subgroup	RCT	Serious[2]	No	No	No	Serious[4]	Low
High-dose subgroup	RCT	Serious[2]	No	No	No	Serious[4]	Low
Lose-dose subgroup	RCT	Serious[2]	No	No	No	Serious[4]	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	High
High-dose subgroup	RCT	No	No	No	No	No	High
Lose-dose subgroup	RCT	No	Series[3]	No	No	No	Moderate
PPI *vs* H2RA on the rate of adverse events	RCT	Serious[2]	No	No	No	Serious[4]	Low
PPI *vs* placebo on the rate of adverse events	RCT	No	Series[3]	No	No	No	Moderate
Long-duration subgroup	RCT	No	No	No	No	No	High
Short-duration subgroup	RCT	No	Series[3]	No	No	No	Moderate
High-dose subgroup	RCT	No	Series[3]	No	No	No	Moderate
Lose-dose subgroup	RCT	No	No	No	No	No	High
Overall efficacy of PPI against NERD	RCT	Serious[1]	Series[3]	No	No	No	Low
Long-duration subgroup	RCT	Serious[2]	Series[3]	No	No	No	Low
Short-duration subgroup	RCT	Serious[2]	No	No	No	No	Moderate
High-dose subgroup	RCT	Serious[2]	Series[3]	No	No	No	Low
Lose-dose subgroup	RCT	Serious[2]	No	No	No	No	Moderate
Overall safety of PPI against NERD	RCT	Serious[2]	Series[3]	No	No	Serious[4]	Low
Long-duration subgroup	RCT	Serious[2]	Series[3]	No	No	Serious[4]	Low
Short-duration subgroup	RCT	No	No	No	No	Serious[4]	High
High-dose subgroup	RCT	No	Series[3]	No	No	Serious[4]	Moderate
Lose-dose subgroup	RCT	Serious[2]	No	No	No	Serious[4]	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.

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

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[46]. 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[47]. 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 hernia influences 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 esophageal 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)[50-52]. 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 H_2RA or placebo for the treatment of NERD. However, there was no significant difference between the safeties of PPI and H_2RA 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.

COMMENTS

Background

Patients with non-erosive reflux disease (NERD) suffer from heartburn due to gastric acid in the reflux content. Acid-suppressive drugs, especially proton pump inhibitor (PPI), have been used widely to manage NERD.

Research frontiers

Though PPI has been used for patients with NERD for years, however, sufficient and convictive evidences concerning its efficacy and safety are lacking and whether its efficacy and safety are influenced by other factors remains unclear.

Innovations and breakthroughs

The meta-analysis and systematic review was conducted according to Cochrane Handbook. The rates of symptomatic relief of PPI *vs* placebo and PPI *vs* H_2 receptor antagonists (H_2RA) were treated as the primary endpoint and the rates of adverse events as the secondary endpoint. Meanwhile, factors influencing rates of symptomatic relief and adverse events of PPI against NERD are analyzed.

Applications

This meta-analysis indicated that PPI overmatched H_2RA on symptomatic relief rate but not on adverse rate for NERD. The rate of symptomatic relief of PPI against NERD was influenced by hiatal hernia and the adverse rate was affected by hiatal hernia and drinking.

Peer review

This is a well written, sufficiently interesting original article in which the authors reviewed the efficacy, safety and their influential factors of PPI against NERD.

REFERENCES

1 **Chey WD**. Endoscopy-negative reflux disease: concepts and clinical practice. *Am J Med* 2004; **117** Suppl 5A: 36S-43S [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: 31-41 [PMID: 18832838 DOI: 10.1159/000151253]

3 **Minatsuki C**, Yamamichi N, Shimamoto T, Kakimoto H, Takahashi Y, Fujishiro M, Sakaguchi Y, Nakayama C, Konno-Shimizu M, Matsuda R, Mochizuki 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: 23341702 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**, Ribolsi M, Gentile M, de'Angelis 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 gastroesophageal reflux disease. *J Gastroenterol Hepatol* 2004; **19**: 357-367 [PMID: 15012771 DOI: 10.1111/j.1440-1746.2004.03419.x]
11 **Fock KM**, Teo 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]
12 **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* 2012; **36**: 635-643 [PMID: 22860764 DOI: 10.1111/apt.12007]
13 **Linsky A**, Hermos 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]
14 **Wilhelm SM**, Rjater RG, 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: 10.1586/17512433.2013.811206]
15 **Fujiwara Y**, Takahashi S, Arakawa T, Sollano JD, Zhu Q, Kachintorn U, Rani AA, Hahm KB, Joh T, Kinoshita Y, Matsumoto T, Naito Y, Takeuchi K, Furuta K, Terano A. A 2008 questionnaire-based survey of gastroesophageal reflux disease and related diseases by physicians in East Asian countries. *Digestion* 2009; **80**: 119-128 [PMID: 19641321 DOI: 10.1159/000226088]
16 **Bruley des Varannes S**, Coudsy B, Waechter S, Delemos B, Xiang J, Lococo J, Ducrotté P. On-demand proton pump inhibitory treatment in overweight/obese patients with gastroesophageal reflux disease: are there pharmacodynamic arguments for using higher doses? *Digestion* 2013; **88**: 56-63 [PMID: 23880545 DOI: 10.1159/000351389]
17 **Chitapanarux T**, Praisontarangkul OA, Lertprasertsuke N. An open-labeled study of rebamipide treatment in chronic gastritis patients with dyspeptic symptoms refractory to proton pump inhibitors. *Dig Dis Sci* 2008; **53**: 2896-2903 [PMID: 18452057 DOI: 10.1007/s10620-008-0255-5]
18 **Takeuchi T**, Umegaki E, Takeuchi N, Yoda Y, Kojima Y, Tokioka S, Higuchi K. Strategies 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; **51**: 189-195 [PMID: 23170046 DOI: 10.3164/jcbn.12-15]
19 **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]
20 **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: 23549342 DOI: 10.1097/MOG.0b013e328360433c]
21 **Weijenborg PW**, Cremonini F, Smout AJ, Bredenoord AJ. PPI therapy is equally effective in well-defined non-erosive reflux disease and in reflux esophagitis: a meta-analysis. *Neurogastroenterol Motil* 2012; **24**: 747-757, e350 [PMID: 22309489 DOI: 10.1111/j.1365-2982.2012.01888.x]
22 **Hiyama T**, Matsuo K, Urabe Y, Fukuhara T, Tanaka S, Yoshihara M, Haruma K, Chayama K. Meta-analysis used to identify factors associated with the effectiveness of proton pump inhibitors against non-erosive reflux disease. *J Gastroenterol Hepatol* 2009; **24**: 1326-1332 [PMID: 19702900 DOI: 10.1111/j.1440-1746.2009.05879.x]
23 **Talley NJ**, Venables TL, Green JR, Armstrong D, O'Kane KP, Giaffer M, Bardhan KD, Carlsson RG, Chen S, Hasselgren GS. Esomeprazole 40 mg and 20 mg is efficacious in the long-term management of patients with endoscopy-negative gastro-oesophageal reflux disease: a placebo-controlled trial of on-demand therapy for 6 months. *Eur J Gastroenterol Hepatol* 2002; **14**: 857-863 [PMID: 12172406]
24 **Juul-Hansen P**, Rydning A. On-demand requirements of patients with endoscopy-negative gastro-oesophageal reflux disease: H2-blocker vs. proton pump inhibitor. *Aliment Pharmacol Ther* 2009; **29**: 207-212 [PMID: 19006541 DOI: 10.1111/j.1365-2036.2008.03877.x]
25 **Kinoshita Y**, Ashida K, Hongo M; Japan Rabeprazole Study Group for NERD. Randomised clinical trial: a multicentre, double-blind, placebo-controlled study on the efficacy and safety of rabeprazole 5 mg or 10 mg once daily in patients with non-erosive reflux disease. *Aliment Pharmacol Ther* 2011; **33**: 213-224 [PMID:21083596 DOI: 10.1111/j.1365-2036.2010.04508.x]
26 **Kobeissy AA**, Hashash JG, Jamali FR, Skoury AM, Haddad R, El-Samad S, Ladki R, Aswad R, Soweid AM. A randomized open-label trial of on-demand rabeprazole vs ranitidine for patients with non-erosive reflux disease. *World J Gastroenterol* 2012; **18**: 2390-2395 [PMID: 22654431 DOI: 10.3748/wjg.v18.i19.2390]
27 **Talley NJ**, Lauritsen K, Tunturi-Hihnala H, Lind T, Moum B, Bang C, Schulz T, Omland TM, Delle M, Junghard O. Esomeprazole 20 mg maintains symptom control in endoscopy-negative gastro-oesophageal reflux disease: a controlled trial of 'on-demand' therapy for 6 months. *Aliment Pharmacol Ther* 2001; **15**: 347-354 [PMID: 11207509 DOI: 10.1046/j.1365-2036.2001.00943.x]
28 **Fass R**, Chey WD, Zakko SF, Andhivarothai N, Palmer RN, Perez MC, Atkinson SN. Clinical trial: the effects of the proton pump inhibitor dexlansoprazole MR on daytime and nighttime heartburn in patients with non-erosive reflux disease. *Aliment Pharmacol Ther* 2009; **29**: 1261-1272 [PMID: 19392864 DOI: 10.1111/j.1365-2036.2009.04013.x]
29 **Fujiwara Y**, Higuchi K, Nebiki H, Chono S, Uno H, Kitada K, Satoh H, Nakagawa K, Kobayashi K, Tominaga K, Watanabe T, Oshitani N, Arakawa T. Famotidine vs. omeprazole: a prospective randomized multicentre trial to determine efficacy in non-erosive gastro-oesophageal reflux disease. *Aliment Pharmacol Ther* 2005; **21** Suppl 2: 10-18 [PMID: 15943841 DOI: 10.1111/j.1365-2036.2005.02468.x]
30 **Nakamura K**, Akiho H, Ochiai T, Motomura Y, Higuchi N, Okamoto R, Matsui N, Yasuda D, Akahoshi K, Kabemura T, Ihara E, Harada N, Ito T, Takayanagi R. Randomized controlled trial: roxatidine vs omeprazole for non-erosive reflux disease. *Hepatogastroenterology* 2010; **57**: 497-500 [PMID: 20698216]
31 **Miner P**, Orr W, Filippone J, Jokubaitis 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.1572-0241.2002.05769.x]
32 **Armstrong D**, Paré 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.1572-0241.2001.4237_a.x]
33 **Lind T**, Havelund T, Lundell L, Glise H, Lauritsen K, Pedersen SA, Anker-Hansen O, Stubberöd A, 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: 10383525 DOI: 10.1046/j.1365-2036.1999.00564.x]
34 **Richter JE**, Campbell DR, Kahrilas 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]
35 **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, Stubberöd 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, Umezu 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, Katelaris 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: 12381251]
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.14.5233]
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. Raberprazole 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, Wakui 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 **Perera MA**. The missing linkage: what pharmacogenetic associations are left to find in CYP3A? *Expert Opin Drug Metab Toxicol* 2010; **6**: 17-28 [PMID: 19968573 DOI: 10.1517/17425250903379546]
52 **Furuta T**, Shirai N, Sugimoto M, Nakamura A, Hishida A, Ishizaki T. Influence of CYP2C19 pharmacogenetic polymorphism on proton pump inhibitor-based therapies. *Drug Metab Pharmacokinet* 2005; **20**: 153-167 [PMID: 15988117 DOI: 10.2133/dmpk.20.153]

P- Reviewers: Jadallah KA, Shimatan T, Tosetti C
S- Editor: Gou SX **L- Editor**: Ma JY **E- Editor**: Wang CH

百世登
Baishideng®

Published by **Baishideng Publishing Group Co., Limited**
Flat C, 23/F., Lucky Plaza,
315-321 Lockhart Road, Wan Chai, Hong Kong, China
Fax: +852-65557188
Telephone: +852-31779906
E-mail: bpgoffice@wjgnet.com
http://www.wjgnet.com

ISSN 1007-9327
9 771007 932045