Systematic Review and Meta-Analysis

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Comparative effectiveness and acceptability of the FDA-licensed proton pump inhibitors for erosive esophagitis

A PRISMA-compliant network meta-analysis

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Abstract

Background: This study compared the effectiveness and acceptability of all Food and Drug Administration (FDA)-recommended dose proton pump inhibitors (PPIs) in erosive esophagitis (EE): Dexlansoprazole 60 mg, Esomeprazole 40 mg, Esomeprazole 20 mg, Pantoprazole 40 mg, Lansoprazole 30 mg, Rabeprazole 20 mg, Omeprazole 20 mg.

Methods: A systematic literature search was performed using PubMed, Embase, and Cochrane Library. Totally, 25 randomized controlled trials (RCTs) met study selection criteria and were incorporated in this network meta-analysis (NMA) study.

Results: For the NMA, eligible RCTs of adults with EE verified by endoscopic examination were randomly assigned to the licensed PPIs at least 4 weeks of continuous therapy. The primary efficacy outcome was the endoscopic healing rates at 4 and 8 weeks. Heartburn relief rates were a secondary efficacy outcome. The rates of withdrawal were analyzed as a safety outcome. In comparison to the common comparator omeprazole 20 mg, esomeprazole 40 mg provided significantly healing rates at 4 weeks [odds ratio (OR), 1.46 (95% confidence interval, 95% CI, 1.24–1.71)] and 8 weeks [1.58 (1.29–1.92)], and improved the heartburn relief rates [1.29 (1.07–1.56)]. In comparison to lansoprazole 30 mg, esomeprazole 40 mg provided significantly healing rates at 4 weeks [1.30 (1.10–1.53)] and 8 weeks [1.37 (1.13–1.67)], and improved the heartburn relief rates [1.29 (1.03–1.62)]. In terms of acceptability, only dexlansoprazole 60 mg had significantly more all-cause discontinuation than omeprazole 20 mg [1.54 (1.03–2.29)], pantoprazole 40 mg [1.68 (1.08–2.63)], and lansoprazole 30 mg [1.38 (1.02–1.88)].

Conclusion: The standard-dose esomeprazole 40 mg had more superiority in mucosal erosion healing and heartburn relief. Esomeprazole 40 mg, pantoprazole 40 mg, esomeprazole 20 mg, and lansoprazole 30 mg showed more benefits in effectiveness and acceptability than other interventions.

Abbreviations: EE = erosive esophagitis, FDA = Food and Drug Administration, GERD = gastroesophageal reflux disease, H_2RAs = histamine-2 receptor antagonists, NMA = network meta-analysis, OR = odds ratio, PPIs = proton pump inhibitors, RCTs = randomized clinical trials, ROR = the ratio of two odd ratios, SUCRA = the surface under the cumulative ranking curves.

Keywords: acceptability, effectiveness, erosive esophagitis, network meta-analysis, proton pump inhibitors

1. Introduction

Gastroesophageal reflux disease (GERD) can be defined as the troublesome complications that result from the retrograde flow of gastric contents into the esophagus.[1,2] The prevalence of GERD in western countries is 18% to 28%, compared with the increasing incidence in the Asia-Pacific region.[3–5] GERD is a prevalent public digestive disease that frequently results in the development of erosive esophagitis (EE), responsible for 10% of GERD.[6] EE is relative to the presence of esophageal mucosal

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MJL, QL, and MS have contributed equally to this work.

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Ethical approval was not necessary, because this article is a network meta-analysis and it does not involve any confidential personal data.

The authors declare that they have no conflict of interest.

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erosions at conventional endoscopy and heartburn symptom, considered to be a moderate to severe symptom that occurs one or more days per week.

With regard to mucosal healing and heartburn symptom relief, several approaches have been proposed and tested, such as lifestyle and dietary modifications (losing weight, elevating the head of bed, and quitting alcohol and tobacco), surgery, and medications.[7,8] Lifestyle and dietary modifications have little effectiveness in relieving reflux symptom.[9] Alternatively, surgical therapy is a cost-effective method and recommended for GERD patients in need of a long-term treatment or with year-long reflux history.[10–12] In the end, the mainstay of treatment is medication.[7,8]

Currently, in the light of the acid suppression, medications include sucralfate, antacids, prokinetics, histamine-2 receptor antagonists (H_2RAs), and proton pump inhibitors (PPIs). PPIs have been demonstrated to be the most common first-line treatment to heal erosions and symptom control in clinical trials.[7,13,14] It is surprising that only 1 single agent, esomeprazole, could cost about $2.5 billion in 2013.[15] Now, there are 7 different dosages of PPIs, Dexlansoprazole 60 mg, Esomeprazole 40 mg, Esomeprazole 20 mg, Pantoprazole 40 mg, Lansoprazole 30 mg, Rabeprazole 20 mg, Omeprazole 20 mg, which are recommended by the US Food and Drug Administration (FDA) for EE between 4 and 8 weeks.[16–21]

Recently, numerous traditional meta-analyses have been performed comparing different PPIs for EE patients.[22–24] Only 1 indirect meta-analysis was compared between dexlansoprazole and esomeprazole interventions.[25] In addition, no data were available from RCTs for dexlansoprazole in relation to other PPI interventions in the EE patients, just compared with lansoprazole.[26] To date, there were no studies that simultaneously included all interventions by a network meta-analysis method to assess the effectiveness and acceptability between any 2 of the FDA-licensed PPIs in the management of EE.

2. Methods

2.1. Study outcomes

To compare PPI monotherapy in terms of:

(1) The primary efficacy outcome, measured by the proportion of patients with healed EE (complete re-epithelialization of all ulcers and erosions) through 4 and 8 weeks who were determined by endoscopic examination by specialist physicians.
(2) The secondary efficacy outcome, measured by the proportion of patients who showed complete resolution of diary or investigator-assessment heartburn at 4 weeks, which was most frequently reported as the predominant troublesome clinical manifestation.
(3) Acceptability of treatment, defined as the proportion of patients who withdrew from the study during the therapy by any reason.

2.2. Eligibility criteria

We only included RCTs comparing with any of the FDA-approved PPIs (at least 2 licensed-dose design or 1 licensed-dose and 1 placebo design would be allowed) in patients with at least 4 weeks of continuous therapy. Patients aged 18 years or older of both sexes with EE diagnosed by endoscopic examination required the same operation to confirm healing after a 4 or 8-week course and investigator assessments on the heartburn symptom relief after a 4-week course. Most commonly used measures were the Grading of Esophagitis according to the Los Angeles Classification System, the Savary–Miller scale, and the Modified Hetzel–Dent scale by endoscopic examination. All included RCTs were reported in English language. Those studies assessing patients with the presence of oesophageal strictures or Barrett oesophagus would be excluded. We also excluded RCTs with obvious bias and only obtained the abstract data.

2.3. Study selection, data extraction, and risk of bias

We searched PubMed, Embase, and the Cochrane library from the inception to November 2016, as well as manually searched the reference lists of published systematic reviews to identify additional pertinent studies. All citations were imported into an electronic database (EndNote 7). All titles and abstracts were independently scanned by 2 investigators (MJL and LQL) for excluding the irrelevant reviews. Then, we screened the eligible studies by reading the remaining full texts. Any disagreements would be consulted with another 2 members (QL and MS). We then abstracted the key features to the prepared electronic data table. The Cochrane Collaboration Risk of Bias Tool was used independently by the first 2 reviewers to assess the quality of included trials.

2.4. Statistical analysis

NMA was simultaneously performed by both direct and indirect RCT comparisons by applying a series of STATA software (version 14; StataCorp LP, College Station, TX) network commands, which were a suite of numerical and graphical programs built by Chaimani et al.[27] Network suite included commands to automatically introduce and run mvmeta models (including consistency and inconsistency models) for a contrast-based NMA. The network plot of interventions was visually described by the relationship between any of comparisons. A comparison-specific random-effects model was used for assessing the contribution percentage of each direct comparison to the network summary estimates and in the entire network.

For assessing the inconsistency, node-splitting model was employed to calculate the differences between the direct comparisons (only pairwise meta-analysis) with indirect comparisons (network meta-analysis excluding the direct estimates). If the differences were fewer than 5%, the network model was regarded as consistent. Simultaneously, we made judgments about the loop-specific heterogeneity in the network by computing the ratio of the 2 odd ratios (ROR) from direct and indirect evidence for each paired-comparison in each loop. ROR values close to 1 indicate the 2 sources are in agreement. Moreover, we assessed the absence of the small-study effects based on whether the comparing-adjusted funnel plot was symmetric around the zero line in this study.

Be different with the pairwise meta-analysis, the between-study variance tau-squared often assumed to be common across comparisons was typically used to present the heterogeneity across the network. In addition, the mean summary effects facilitate the interpretation of the results. All outcomes were calculated by odds ratios (ORs) with 95% credible intervals (CIs). $P < .05$ was considered to be statistically significant between the mean effect sizes.

The surface under the cumulative ranking curves (SUCRA) was performed to rank the interventions for every outcome. The larger the SUCRA value, the better the rank of the treatment. We

employed the 2-dimensional plots and the clustering methods to simultaneously express the 2 primary outcomes.

3. Results

3.1. Evidence base

In total, we included 25 trials with 57 study arms for the network meta-analysis (Fig. 1). These studies included 25,088 EE patients with an average age of 48.6 years; 60% were males. The main characteristics of the eligible RCT studies are reported in Table 1.[26,28–51] Figure 2 shows network plots of different endpoints in patients with EE. Twenty thousand four hundred forty-one patients were contributed to the endoscopic healing rate analysis at 4 weeks (21 studies, 7 treatments, Fig. 2A), 24,625 to the endoscopic healing rate analysis at 8 weeks (24 studies, 8 treatments, Fig. 2B), 14,375 to the heartburn relief rate at 4 weeks (11 studies, 6 treatments, Fig. 2C), and 24,610 to the acceptability analysis (23 studies, 8 treatments, Fig. 2D). Omeprazole 20 mg, the first PPI, was the most frequent control intervention across the 25 trials. Only 1 usable trial was included for dexlansoprazole 60 mg that just provided data for the endoscopic healing rate analysis at 8 weeks and the acceptability analysis. Some included RCTs did not provide sufficient information about randomization and allocation concealment. Six trials were only recorded if there was a difference for some 1 endpoint, but not reported the specific value. All trials used intention-to-treat analysis (Table 2).

3.2. Assumption of the network meta-analysis

The node-split method indicated that there was no inconsistency between direct and indirect estimates on node (Supplementary Table 1, http://links.lww.com/MD/B886). In our NMA, most loops were consistent as their 95% CI for RoR including the 1 according to the forest plots (Fig. 3), but finding 1 inconsistency loop (omeprazole 20mg-placebo-pantoprazole 40 mg, RoR >2) in the healing rates at 4 weeks. The comparison-adjusted funnel plots (Fig. 4) of direct comparisons showed no apparent publication bias being relatively symmetric.

3.3. Comparative effectiveness of intervention to the esophageal mucosal erosions

Network meta-analysis generated 12 mixed comparisons and 9 indirect comparisons in the healing rates at 4 weeks, 13 mixed comparisons and 15 indirect comparisons in the healing rates at 8 weeks (contribution matrix in Supplementary Figure 1 and 2, http://links.lww.com/MD/B886). Figures 5 and 6, respectively, presented their NMA mean summary effects. All the agents included in this review were statistically superior than placebo for endoscopic healing rates both at 4 and 8 weeks (at least increased

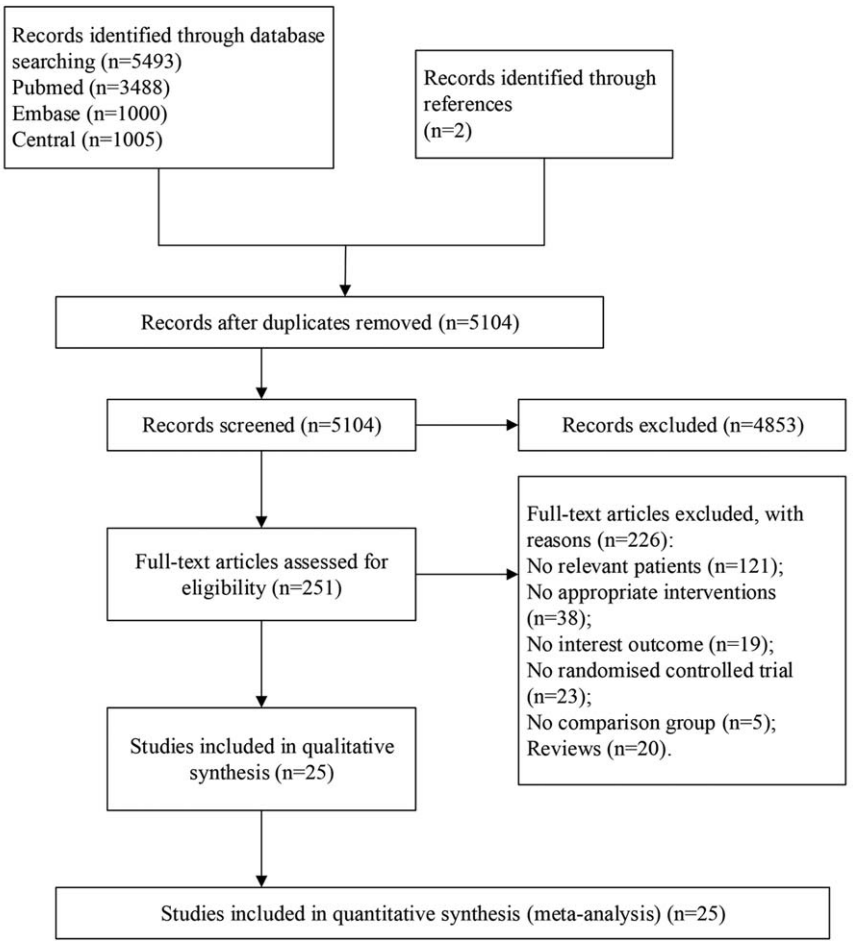

Figure 1. Flow chart of study selection.

Table 1

Baseline characteristics of the included trials.

Ref.	N of centers country	Fund	Patient's characteristic					Intervention	Outcome			
			N of patients	Median age±SD	N male (%)	Follow-up	Diagnosis level	Drug, Dosage, Usage	Healing rates 4 wk (n/n)	Healing rates 8 wk (n/n)	Heartburn Relief 4 wk (n/n)	Acceptability (n/n)
Sontag et al[28]	15	No	139	NA	NA	8 wk	HD II-IV	Omeprazole 20 mg od	36/93	68/93	NA	14/93
	US							Placebo	3/46	7/46		5/46
Hatlebakk et al [29]	7 Norway	Yes	225	54.3	77 (66.4)	8 wk	Other 1–2	Lansoprazole 30 mg qd	71/113	95/112	NA	NA
	2 Sweden			55.4	74 (65.5)			Omeprazole 20 mg qd	73/112	96/111		
Corinaldesi et al[30]	30	No	241	50	78 (65)	8 wk	SM II-III	Pantoprazole 40 mg qd	81/120	97/120	87/99	19/120
	Belgium, Netherland			52	75 (62)			Omeprazole 20 mg qd	83/121	96/121	83/101	18/121
Mossner et al[31]	44	Yes	286	53	133 (70)	8 wk	SM II-III	Pantoprazole 40 mg qd	126/191	153/191	149/165	23/191
	Germany			55	66 (69)			Omeprazole 20 mg qd	67/95	81/95	81/86	10/95
Castell et al[32]	multiple centers	No	1065	48.6	88 (68.4)	8 wk	Other II-IV	Lansoprazole 30 mg qd	336/421	367/421	NA	26/422
	USA			47.5	260 (60.3)			Omeprazole 20 mg qd	343/431	375/431		22/431
				47.6	142 (66.7)			placebo	62/213	74/213		17/213
Mee and Rowley [33]	54	No	604	53.4	198 (66)	8 wk	SM I-IV	Lansoprazole 30 mg qd	186/300	226/300	NA	34/300
	UK, Ireland			52.4	204 (67)			Omeprazole 20 mg qd	172/304	216/304		33/304
Dekkers et al[34]	10	Yes	202	54±15.70	53 (53)	8 wk	HD II-IV	Rabeprazole 20 mg qd	81/100	92/100	29/98	5/100
	European			52±15.56	73 (71.6)			Omeprazole 20 mg qd	83/102	96/102	27/102	5/102
Delchier et al[35]	50	Yes	207	55±15.7	47 (45)	8 wk	HD II-IV	Rabeprazole 20 mg qd	92/104	95/104	NA	6/104
	European			53±15.1	40 (39)			Omeprazole 20 mg qd	94/103	97/103		5/103
Kahrilas et al[36]	140	Yes	1960	44.8±13.0	384 (58.7)	8 wk	LA I-IV	Esomeprazole 40 mg qd	496/654	615/654	402/621	48/654
	United States			45.3±13.3	391 (59.6)			Esomeprazole 20 mg qd	462/656	590/656	382/626	60/656
				46.5±13.5	399 (61.4)			Omeprazole 20 mg qd	421/650	565/650	357/624	51/650
Richter and Bochenek[37]	47	Yes	255	49.3±13.6	121 (69.9)	8 wk	HD II-IV	Pantoprazole 40 mg qd	125/173	152/173	NA	NA
	US			48.3±14.0	53 (64.6)			Placebo	11/82	27/82		
Dupas et al[38]	74	Yes	461	53±14.5	165 (73)	8 wk	SM II-III	Pantoprazole 40 mg qd	184/226	203/226	204/226	3/226
	France			55±14.7	178 (58)			Lansoprazole 30 mg qd	189/235	201/235	216/235	6/235
Richter et al[39]	163	No	2425	NA	722 (59.4)	8 wk	LA I-IV	Esomeprazole 40 mg qd	956/1216	1093/1216	831/1216	55/1216
	United States				760 (62.9)			Omeprazole 20 mg qd	805/1209	978/1209	702/1209	54/1209
Castell et al[40]	228	Yes	5241	47.0±13.0	1504 (57.3)	8 wk	LA I-IV	Esomeprazole 40 mg qd	1986/2624	2299/2624	1650/2624	48/2624
	United States			47.4±13.1	1501 (57.4)			Lansoprazole 30 mg qd	1876/2617	2204/2617	1575/2617	50/2617
Howden et al[41]	multiple centers	Yes	284	47±12	57 (82)	8 wk	Other II-IV	Esomeprazole 40 mg qd	107/143	127/143	NA	7/143
	USA			46±13	54 (76)			Lansoprazole 30 mg qd	108/141	123/141		6/141
Mulder et al[42]	31	No	461	51.6±15.0	88 (58)	8 wk	SM I-IV	Omeprazole 20 mg qd	NA	NA	127/151	7/151
	Netherlands			51.2±14.4	94 (61)			Lansoprazole 30 mg qd			122/156	11/156
				50.8±14.5	90 (58)			Pantoprazole 40 mg qd			129/154	5/154
Gillessen et al[43]	27	Yes	227	53±15	64 (57)	8 wk	LA II-III	Pantoprazole 40 mg qd	55/113	94/113	NA	19/113
	Germany			54±14	57 (50)			Esomeprazole 40 mg qd	68/114	92/114		11/114
Fennerty et al[44]	163	Yes	999	47.3±13.2	327 (65.7)	8 wk	LA III-IV	Esomeprazole 40 mg qd	278/498	386/498	344/478	31/498
	United States			47.1±12.9	333 (66.5)			Lansoprazole 30 mg qd	238/501	367/501	307/483	29/501
Labenz et al[45]	263	No	3151	50.6±14	969 (62.0)	8 wk	LA I-IV	Esomeprazole 40 mg od	1231/1562	1431/1562	NA	33/1562
	Germany			50.5±13.8	1102 (63.7)			Pantoprazole 40 mg od	1157/1589	1413/1589		29/1589
Pace et al[46]	71	Yes	560	47.7±14.2	190 (68.6)	8 wk	SM I-III	Rabeprazole 20 mg qd	212/283	228/283	NA	25/283
	Italy			47.1±14.9	184 (67.7)			Omeprazole 20 mg qd	213/277	231/277		22/277
Lightdale et al[47]	80	Yes	1175	44.7±13.2	372 (63.3)	8 wk	LA I-IV	Esomeprazole 20 mg qd	NA	508/587	356/587	9/587
	US			45.3±13.0	376 (63.9)			Omeprazole 20 mg qd		484/588	356/588	10/588
Schmitt et al[48]	72	No	1148	47.1±13.3	346 (60.1)	8 wk	LA I-IV	Esomeprazole 40 mg qd	393/576	501/576	366/563	18/576
	USA			46.2±13.6	335 (58.6)			Omeprazole 20 mg qd	379/572	491/572	357/566	10/572
Vcev et al[49]	3	Yes	180	51.2±14.5	57 (63.3)	8 wk	LA I-III	Esomeprazole 40 mg od	70/90	84/90	NA	11/90
	Croatia			49.4±13.9	59 (65.6)			Pantoprazole 40 mg od	65/90	82/90		10/90
Bardhan et al[50]	Multicenter	Yes	581	53±14	141 (49)	8 wk	LA I-IV	Pantoprazole 40 mg qd	199/288	248/288	NA	28/289
	Germany			54±14	154 (53)			Esomeprazole 40 mg qd	202/293	243/293		44/293
Sharma et al[26]	188 us centers	No	1370	47.8±13.71	380 (55.9)	8 wk	LA I-IV	Dexlansoprazole MR 60 mg qd	NA	545/680	NA	51/680
	118 non-us centers			47.3±13.74	365 (52.9)			Lansoprazole 30 mg qd				
										518/690		46/690
			1367	48.7±13.53	377 (54.3)	8 wk	LA I-IV	Dexlansoprazole MR 60 mg qd	NA	571/694	NA	53/694
				47.3±13.65	362 (53.8)			Lansoprazole 30 mg qd				
										548/673		30/673
Zheng[51]	1	No	274	57.9±14.1	33 (48.5)	8 wk	LA I-IV	Omeprazole 20 mg qd	NA	57/68	NA	3/68
	China			58.1±13.0	35 (50.7)			Lansoprazole 30 mg qd		60/69		2/69
				57.8±13.2	34 (49.3)			Pantoprazole 40 mg qd		61/69		2/69
				57.4±12.8	33 (48.5)			Esomeprazole 40 mg qd		62/68		3/68

HD = the Modified Hetzel-Dent scale, LA = the Los Angeles Classification System, NA = not available, od = omne in die, qd = quaque die, SM = the Savary–Miller scale, wk = week.

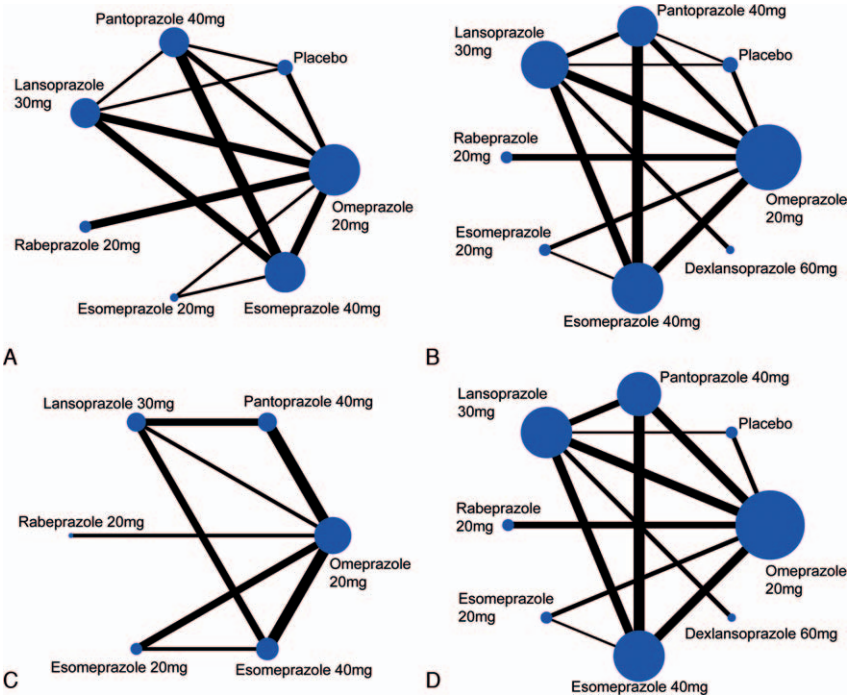

Figure 2. Network plots for the primary efficacy outcome healing rates at 4 and 8 weeks (A and B), secondary efficacy outcome heartburn relief rates (C), and primary safety outcome (D). Nodes show interventions being compared, surface areas of circles represent the number of patients included studies, and edges indicate head-to-head comparisons in the eligible RCTs.

9-fold). Esomeprazole 40 mg separately increased the erosion healing by an additional 46% at 4 weeks and 58% at 8 weeks above omeprazole 20 mg. Compared with lansoprazole 30 mg, esomeprazole 40 mg improved the efficacy by around 30% both at 4 and 8 weeks. For rabeprazole 20 mg, esomeprazole 40 mg provided greater mucosal erosions up to 8 weeks as the healing rate increased doubled. Moreover, esomeprazole 40 mg seems to have greater efficacy only at 4 weeks compared with pantoprazole 40

Table 2

Risk of bias in the included trials.

Ref.	Adequate random sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Free selective reporting	Other bias	Sum bias
Sontag et al[28]	Unclear	Low	Low	Low	Low	Low	Low
Hatlebakk et al [29]	Unclear	Low	Low	Unclear	Low	High	Unclear
Corinaldesi et al[30]	Low	Low	Low	Low	Low	Low	Low
Mossner et al[31]	Low	Low	Low	Low	Low	Low	Low
Castell et al[32]	Unclear	Unclear	Unclear	Unclear	Low	Low	Unclear
Mee and Rowley [33]	Low	Low	Low	Low	Low	High	Low
Dekkers et al[34]	Unclear	Low	Unclear	Unclear	Low	High	Unclear
Delchier et al[35]	Unclear	Unclear	Low	Low	Unclear	Low	Unclear
Kahrilas et al[36]	Unclear	Low	Low	Low	Low	Low	Low
Richter and Bochenek [37]	Low	Low	Low	Low	Low	Low	Low
Dupas et al[38]	Low	Low	Low	Low	Low	Low	Low
Richter et al [39]	Low	Low	Low	Low	Low	Low	Low
Castell et al[40]	Low	Low	Low	Low	Low	Low	Low
Howden et al[41]	Low	Low	Low	Low	Low	Low	Low
Mulder et al[42]	Low	Low	Low	Low	Low	Low	Low
Gillessen et al[43]	Low	Unclear	Low	Low	Low	Low	Low
Fennerty et al[44]	Low	Low	Low	Low	Low	Low	Low
Labenz et al[45]	Unclear	Unclear	Low	Low	Unclear	Low	Unclear
Pace et al[46]	Low	Low	Low	Low	Low	Low	Low
Lightdale et al[47]	Low	Low	Low	Low	Unclear	Low	Low
Schmitt et al[48]	Low	Low	Low	Low	Low	Low	Low
Vcev et al[49]	Unclear	Unclear	Low	Low	Unclear	Low	Unclear
Bardhan et al[50]	Low	Low	Low	Low	Low	Low	Low
Sharma et al[26]	Unclear	Low	Low	Low	Unclear	Low	Low
Zheng[51]	Unclear	Low	Low	Low	Unclear	Low	Low

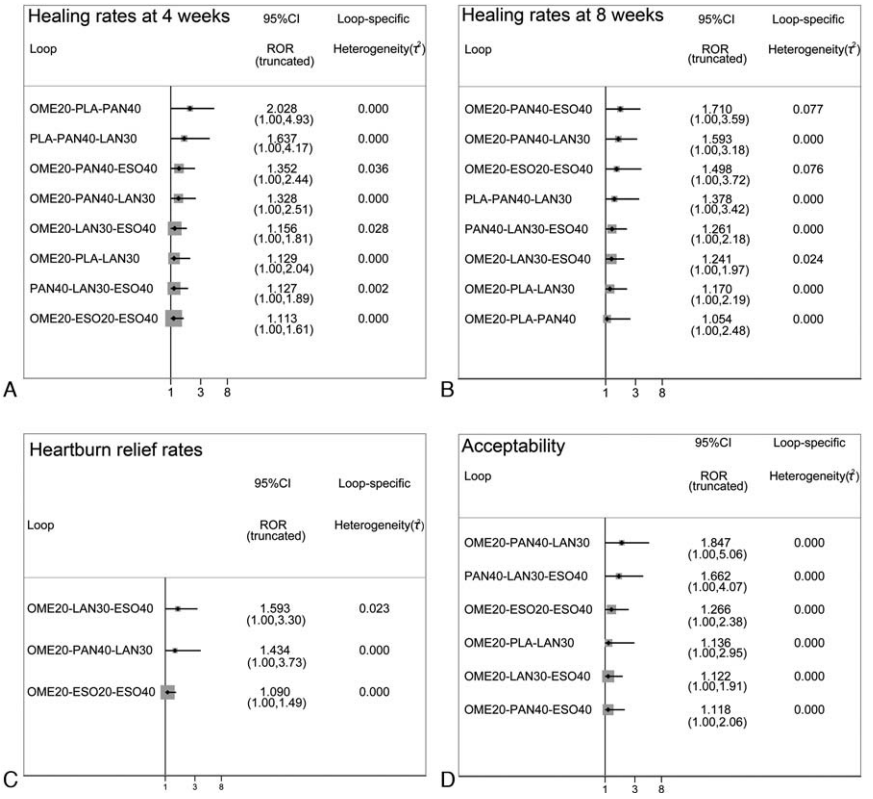

Figure 3. Inconsistency plots for primary efficacy outcome healing rates at 4 and 8 weeks (A and B), secondary efficacy outcome heartburn relief rates (C), and the safety outcome acceptability (D). Forest plots present the RoRs with their 95% CI. DEX60 = dexlansoprazole 60 mg, ESO20 = esomeprazole 20 mg, ESO40 = esomeprazole 40 mg, LAN30 = lansoprazole 30 mg, OME20 = omeprazole 20 mg, PAN40 = pantoprazole 40 mg, RAB20 = rabeprazole 20 mg.

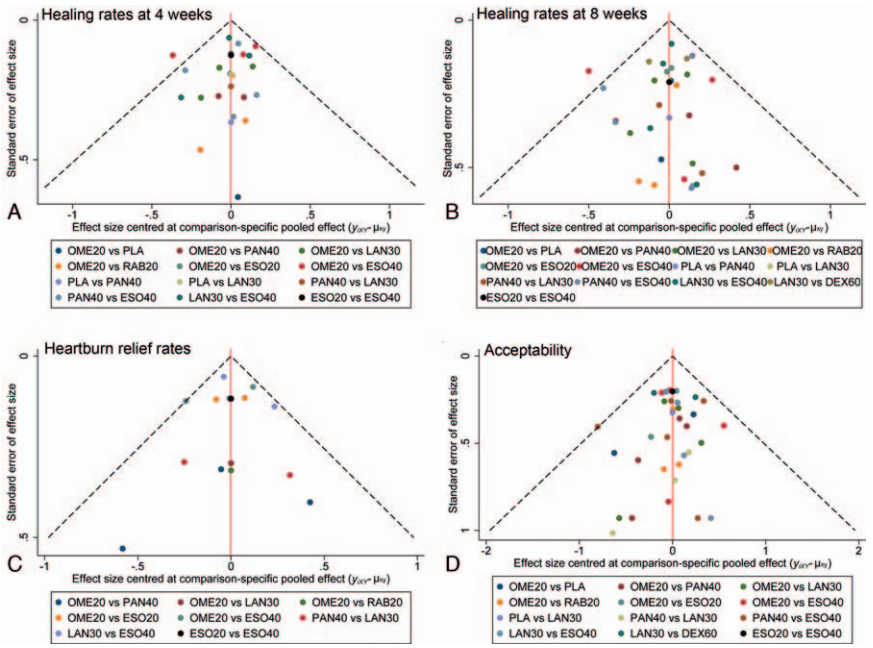

Figure 4. Funnel plots for primary efficacy outcome healing rates at 4 and 8 weeks (A and B), secondary efficacy outcome heartburn relief rates (C), and the safety outcome acceptability (D). Different colors represent different comparisons.

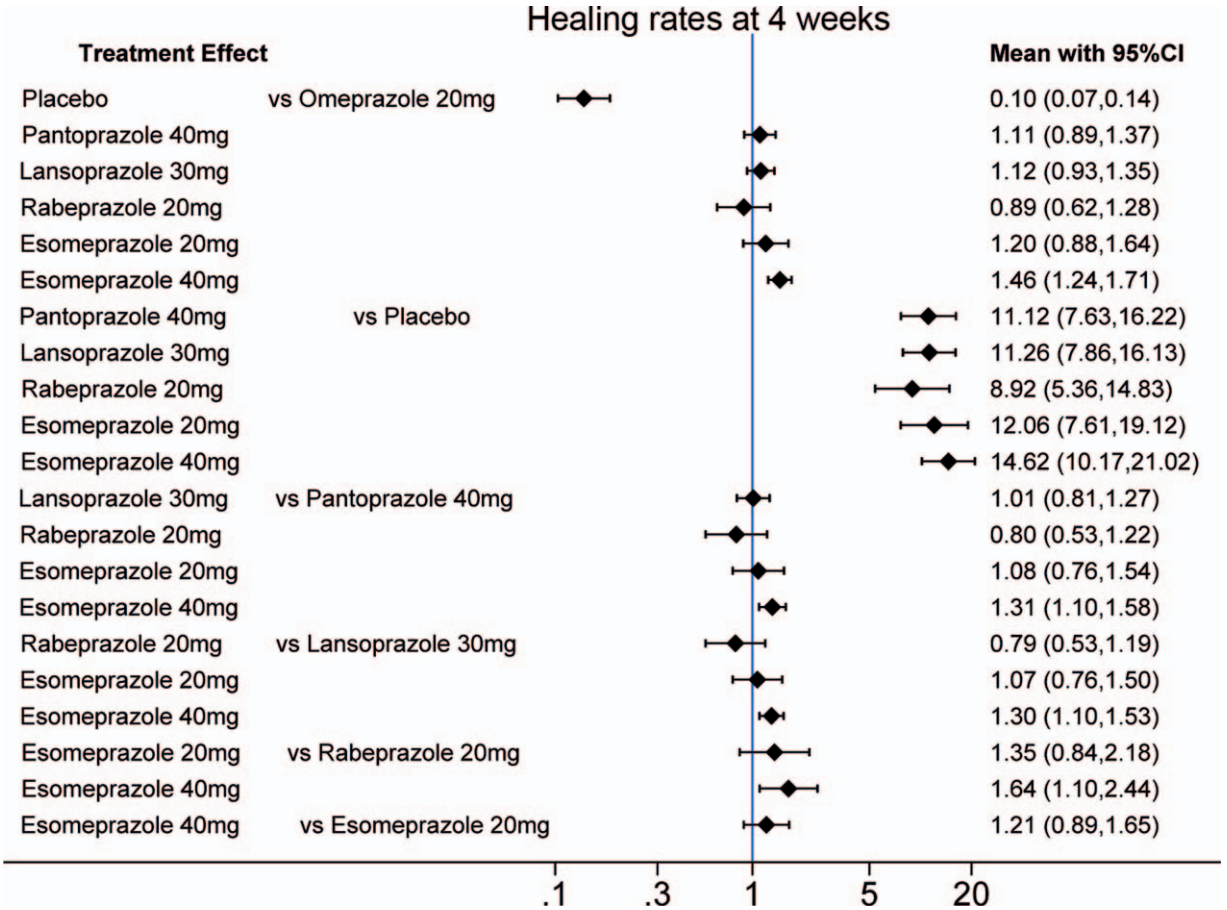

Figure 5. Network meta-analysis results: healing rates at 4 weeks.

mg. For the rest, no significant differences exist for each of PPIs in comparison to one another. Although pantoprazole 40 mg had a difference with the 2 agents (omeprazole 20 mg and rabeprazole 20 mg) at 8 weeks, the effect was almost borderline.

3.4. Comparative effectiveness of intervention to the heartburn relief

Eight mixed comparisons and 7 indirect comparisons in heartburn relief were generated in NMA (contribution matrix in Supplementary Figure 3, http://links.lww.com/MD/B886). Figure 7 graphically described the summary effects for the heartburn relief. Favourable and statistical significant results were observed for esomeprazole 40 mg compared with omeprazole 20 mg (OR = 1.29, 95% CI: 1.07–1.56) and lansoprazole 30 mg (OR = 1.29, 95% CI: 1.03–1.62). Generally, none of the rest treatment comparisons in the NMA controlling for heartburn relief produced any statistically meaningful difference.

3.5. Comparative acceptability of interventions

Twelve mixed comparisons and 16 indirect comparisons in acceptability were generated in NMA (contribution matrix in Supplementary Figure 4, http://links.lww.com/MD/B886). The summary effects for the acceptability outcome are shown in Fig. 8. Only dexlansoprazole 60 mg had more statistically discontinuations than did omeprazole 20 mg, pantoprazole 40 mg, and lansoprazole 30 mg. For analysis of the rest comparisons, no significant estimates were yielded for any agents on acceptability. Furthermore, we progressed network meta-analysis for withdrawals due to adverse events between each intervention (Supplementary Figure 5, http://links.lww.com/MD/B886). Compared with omeprazole 20 mg, pantoprazole 40 mg, lansoprazole 30 mg, and rabeprazole 20 mg, dexlansoprazole 60 mg exhibited the significantly increased withdrawal rates because of adverse events by 2 to 3-folds. There was little variation in withdraw rates and no significant differences among other treatments founded no change in direction.

3.6. Ranking of the interventions on a single outcome

The ranking of PPIs in each endpoint is respectively conducted in Table 3. In the existing data, esomeprazole 40 mg, with a probability of around 98%, was ranked as the best for the endoscopic healing rates at 4 weeks, followed by esomeprazole 20 mg and lansoprazole 30 mg. After adding dexlansoprazole 60 mg in the healing rates at 8 weeks, esomeprazole 40 mg was still ranked the first, with a probability of around 94.4%, followed by dexlansoprazole 60 mg and pantoprazole 40 mg. As a result of dexlansoprazole 60 mg lacking data, esomeprazole 40 mg (86.9%) appeared to be the best agent for heartburn symptom relief at 4 weeks, and the probability of the rest any intervention did not exceed 50%. Pantoprazole 40 mg had the best compliance, with a probability of around 88.4%.

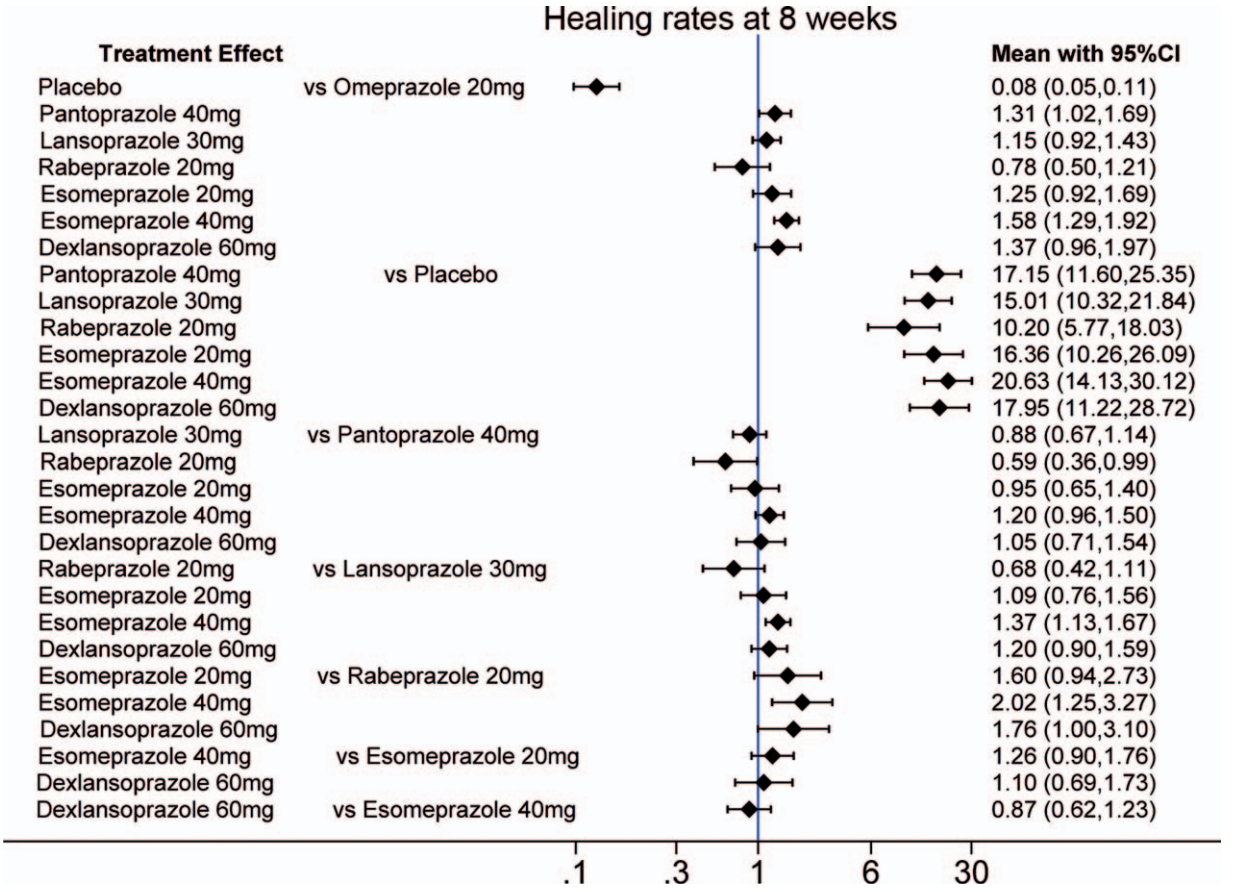

Figure 6. Network meta-analysis results: healing rates at 8 weeks.

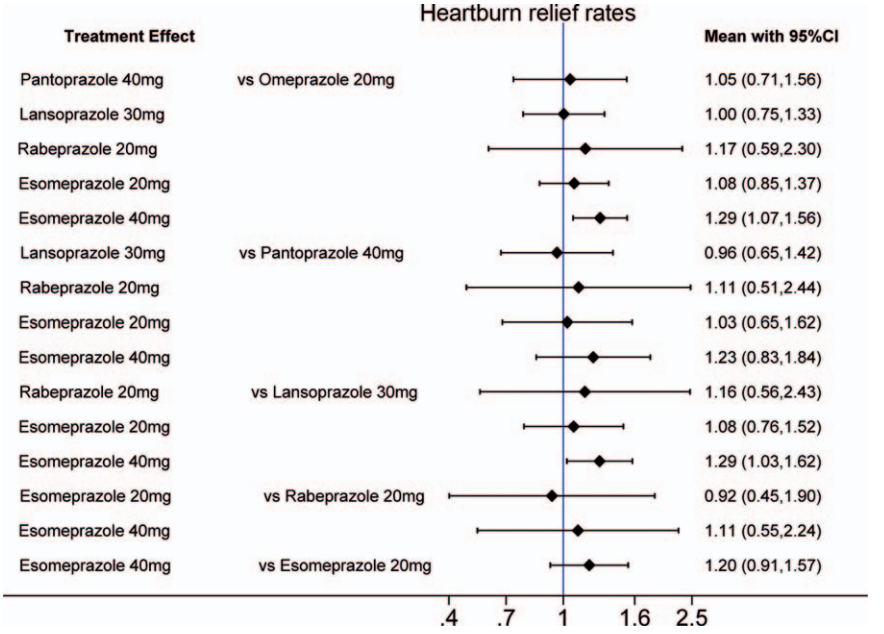

Figure 7. Network meta-analysis results: heartburn relief rates.

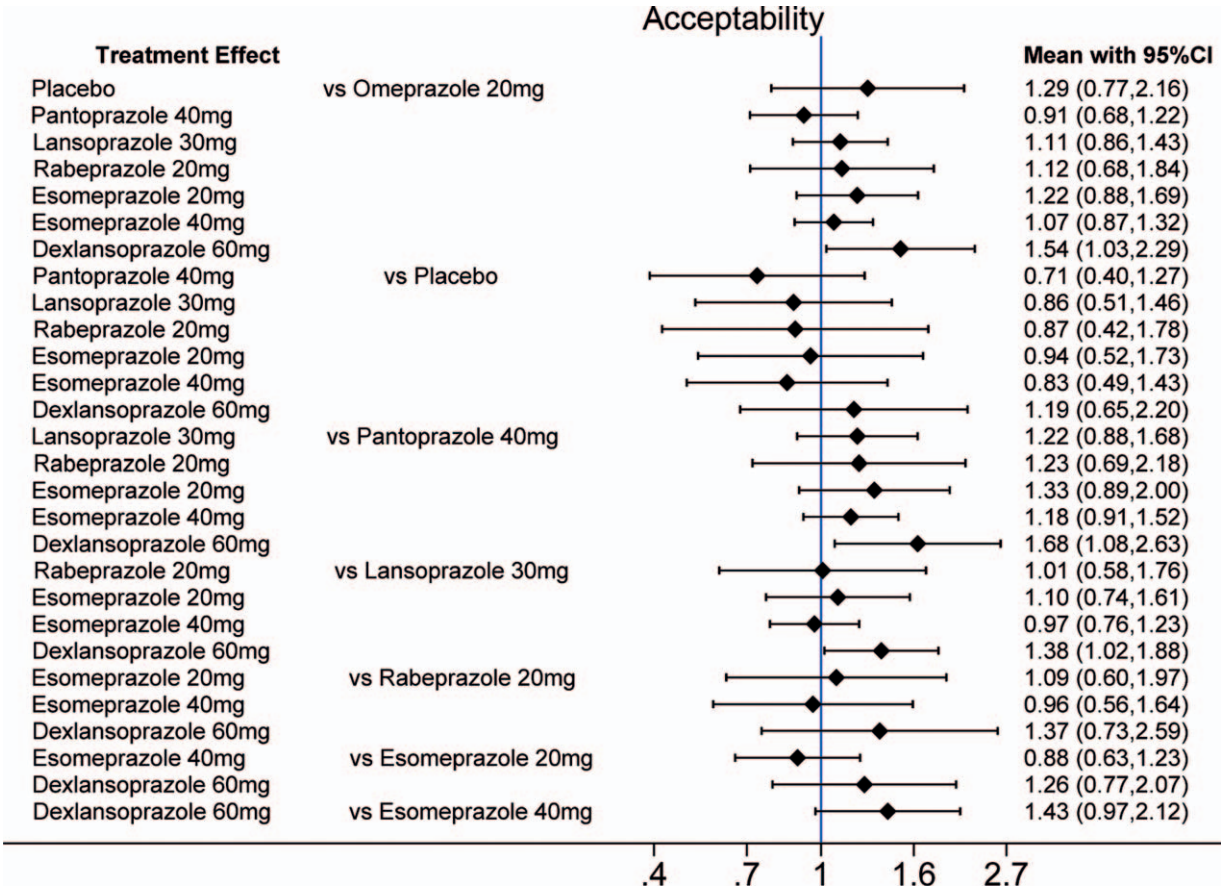

Figure 8. Network meta-analysis results: acceptability.

3.7. Simultaneous ranking of the interventions for 2 primary outcomes

Considering the integrity of the data on all interventions, we only performed the clustering analysis for the endoscopic healing rates at 8 weeks and the acceptability (Fig. 9). The cluster ranking plot shows 4 separate clusters. Esomeprazole 40 mg, pantoprazole 40 mg, esomeprazole 20 mg, and lansoprazole 30 mg formed a cluster of "the most effective and reasonable compliance" agents in the upper right corner. Omeprazole 20 mg and rabeprazole 20 mg represented the "low effective and withdrawal rate" cluster. Moreover, placebo was the ineffective and low compliance agent in the most left position. Dexlansoprazole 60 mg formed a single cluster of "the moderate effective but the poorest compliance" agent in the bottom right corner.

4. Discussion

Despite the current nationally trusted guidelines about GERD pointed out, there were no major differences in efficacy among different PPIs (not included dexlansoprazole), based on the results of the old traditional pairwise meta-analysis in 2006.[7,22] Then, we made a further network meta-analysis to access the effectiveness and acceptability of FDA-licensed PPIs for the

Table 3

Ranking of the PPI interventions.

Treatment	Healing rates at 4 wk			Healing rates at 8 wk			Heartburn relief			Acceptability		
	SUCRA	Pr. best	MeanRank	SUCRA	Pr. best	MeanRank	SUCRA	Pr. best	MeanRank	SUCRA	Pr. best	MeanRank
Omeprazole 20 mg	35.9	0	4.8	30.1	0	5.9	30.3	0.1	4.5	74.3	11.4	2.8
Placebo	0	0	7	0	0	8	NA	NA	NA	34	8.7	5.6
Pantoprazole 40 mg	58	0.4	3.5	69.4	4.4	3.1	44.1	10.3	3.8	85.2	50.6	2
Lansoprazole 30 mg	61.1	0	3.3	49.3	0	4.5	31.1	0.3	4.4	51.6	3.7	4.4
Rabeprazole 20 mg	27.4	0.2	5.4	18.3	0.3	6.7	57.1	35.3	3.1	51.2	19.8	4.4
Esomeprazole 20 mg	69.6	11.3	2.8	62.6	7.6	3.6	50.4	5.6	3.5	36.4	3.5	5.5
Esomeprazole 40 mg	98	88.1	1.1	94.7	68	1.4	86.9	48.4	1.7	57.6	2.2	4
Dexlansoprazole 60 mg	NA	NA	NA	75.6	19.7	2.7	NA	NA	NA	9.7	0.1	7.3

Pr. Best = probability of being the best; SUCRA = the surface under the cumulative ranking curve.

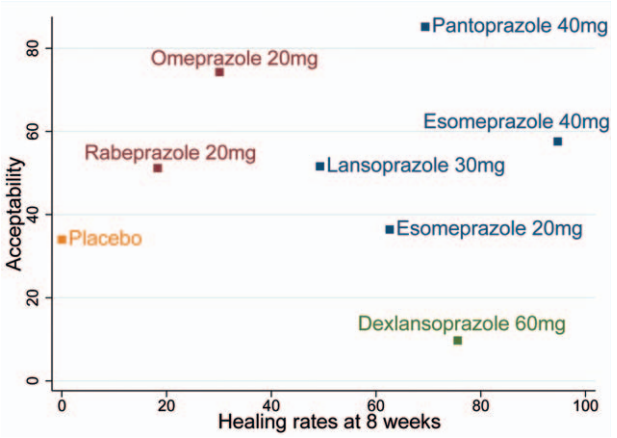

Figure 9. Clustered ranking plot representing simultaneously the primary outcomes: healing rates at 8 weeks (*x* axis) and acceptability (*y* axis) of the 8 therapeutic agents. The same color represents 1 cluster of treatments.

prevention of mucosal erosions and heartburn symptom in EE patients.

Simultaneous ranking of PPI interventions on 2 primary outcomes revealed that a single most effective and safest intervention does not exist. In terms of the effectiveness for prevention of mucosal breaks of the oesophagus at 8 weeks, esomeprazole 40 mg outperformed other PPIs. On the basis of the limited data of dexlansoprazole 60 mg, esomeprazole 40 mg seemed to produce a highest probability for the mucosal healing at 4 weeks (98%). The greater efficacy could be interpreted by its property of acid control. Esomeprazole 40 mg produced significantly longer time of intragastric acid suppression maintaining PH >4 compared with the stand-dose pantoprazole, lansoprazole, rabeprazole, and omeprazole,[52,53] and longer than the low-dose esomeprazole [54] in GERD patients. But dexlansoprazole 60 mg provided higher intragastric PH and significant difference in the time of acid control than esomeprazole 40 mg in healthy subjects.[55] It may be that the drug efficacy in clinical practice was affected by many confounding factors.

Dexlansoprazole, a right-handed(R)-isomer of lansoprazole and a novel dual delayed-release formulation, is the newest addition to the PPI class, which has been approved for GERD by FDA since 2009.[56] Similar to 1 recent indirect meta-analysis, this NMA estimated no difference between esomeprazole and dexlansoprazole in healing rates at 8 weeks.[25] Furthermore, we found that there were no significant differences between dexlansoprazole with each of PPIs in clinical settings, although the new formulation drug was released twice daily at several-hour interval with the longer time of intragastric acid suppression.[53,55] The finding could be probably interpreted that the number of the included studies tended to be small.

For the secondary outcome, esomeprazole 40 mg seemed to be the highest probability for heartburn relief (86.9%) and no significant results were seen among almost all interventions. Our NMA summarized that rabeprazole 20 mg and omeprazole 20 mg were not found statistically different, which was in contrast with 1 earlier review that showed that rabeprazole 20 mg had higher symptom relief rates than omeprazole 20 mg.[57] Only 1 trial was included in our study to evaluate the difference for these 2 interventions with the identical estimated time and explicit endpoint. Nevertheless, a single RCT reported that rabeprazole 20 mg was significantly superior to omeprazole 20 mg (32.2% of patients compared with 18.9%, $P = .001$) for complete heartburn relief after 1 week of therapy.[46]

In terms of the measure of acceptability, we directly investigated the discontinuation rather than the side effects or toxic effects, which showed that dexlansoprazole 60 mg was a "better efficacy but highest drop-out rate" treatment in the all PPIs because of both all causes and adverse events. The percentage of patients with adverse events leading to discontinuation was 2.3% in dexlansoprazole 60 mg therapy group, a higher incidence than shown in other groups. In summary, dexlansoprazole 60 mg demonstrated the better efficacy in increasing the mucosal healing, but were accompanied with the potential risks of the adverse events. More relative head-to-head comparisons will be needed. All agents included in the review did not differ from placebo with regard to all-caused discontinuations. Generally, the most common adverse reactions reported in short term of PPI treatment included diarrhea, nausea, vomiting, abdominal pain, headache, upper respiratory tract infections, flatulence, and constipation, be regarded as relative safety medications.

Overall, no significant correlation was synthesized in almost all analyses comparing the healing rates, heartburn relief rates, and discontinuation rates between omeprazole 20 mg, pantoprazole 40 mg, lansoprazole 30 mg, rabeprazole 20 mg, and esomeprazole 20 mg, which was similar to the traditional meta-analyses.[57–60]

4.1. Strengths and limitations of this study

The previous pairwise meta-analyses always compared 1 agent at both the upper dose and lower dose of its therapeutic range as a group with another agent within the same study.[22,24] In this NMA, we only considered studies randomizing patients to the standard- and low-dose PPIs and provided a formal rank order for each outcome. Meanwhile, the primary results in this NMA are also presented by simultaneous clustered ranking outcome. There are several limitations in this NMA. First, disease severity at baseline is thought to be a source of between-study heterogeneity, as the endoscopic healing effect sizes decreased with increasing severity. Only 7 RCTs reported the healing rates at 4 weeks for a high grade of oesophagitis: omeprazole 20 mg (4 RCTs, 383 cases), pantoprazole 40 mg (3 RCTs, 447 cases), lansoprazole 30 mg (3 RCTs, 711 cases), esomeprazole 40 mg (4 RCTs, 1074 cases). Ten RCTs reported the healing rates at 8 weeks for a high grade of oesophagitis: omeprazole 20 mg (4 RCTs, 505 cases), pantoprazole 40 mg (2 RCTs, 411 cases), lansoprazole 30 mg (5 RCTs, 1130 cases), esomeprazole 20 mg (1 RCT, 158 cases), esomeprazole 40 mg (5 RCTs, 1129 cases), dexlansoprazole 60 mg (2 RCTs, 373 cases). It is difficult to extract the quantitative data of the severe erosive reflux disease to make a sensitive analysis. The second limitation is the measurement of outcome; compared with the primary endpoint based on endoscopy examination, the secondary endpoint based on the diary or investigator-assessment was more subjective to cause the uncertainty of heartburn relief rates. In addition, it should be caution to interpret the relationship among all PPI interventions for preventing the relapse in a longer period of time, as all trials just invariably reported the short-term data of 4 to 8 weeks.`

5. Conclusion

This comprehensive NMA showed that the standard-dose esomeprazole had substantial advantages compared with other

licensed PPIs in mucosal erosion healing and heartburn relief. After clustering analysis of the 2 primary outcomes, esomeprazole 40 mg, pantoprazole 40 mg, esomeprazole 20 mg, and lansoprazole 30 mg showed more benefits in effectiveness and acceptability than other interventions.

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