Efficacy and safety of proton pump inhibitors and H2 receptor antagonists in the initial non-eradication treatment of duodenal ulcer: A network meta-analysis

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Abstract. The present network meta-analysis aimed to enhance the corresponding evidence with respect to the efficacy and safety of pharmaceuticals treatments. Frequentist network meta-analysis was used. Medical literature up to November 2022 was searched for randomized clinical trials assessing the efficacy and safety of these pharmaceuticals, either compared with each other or compared with placebo. With the exception of ranitidine (300 mg four times daily) and vonoprazan (20 mg once daily) having lower safety than placebo, the efficacy and safety of the remaining treatments were superior to placebo. Cimetidine (400 mg four times daily) and pantoprazole (40 mg once daily) were ranked first in terms of efficacy. The frequentist network meta-analysis shows that for cimetidine (except 400 mg once daily), famotidine, rabeprazole, ilaprazole, lansoprazole (except 7.5 mg once daily) and omeprazole (except 10 mg once daily or 30 mg once daily), the efficacy comparison between the different doses of each of the aforementioned pharmaceuticals did not indicate statistically significant differences. In conclusion, pantoprazole (40 mg once daily) was the best choice for the initial non-eradication treatment of patients with duodenal ulcer, and cimetidine (400 mg twice daily), omeprazole (20 mg once daily), lansoprazole (15 mg once daily), ilaprazole (5 mg once daily) and rabeprazole (10 mg once daily) could be used as the first choice. If the aforementioned pharmaceuticals cannot be prescribed, famotidine (40 mg twice daily) is recommended.

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Abbreviations: DU, duodenal ulcer; PPIs, proton pump inhibitors; H2RAs, H2 receptor antagonists; RCT, randomized controlled trial; RR, risk ratio; CI, confidence interval; SUCRA, surface under the cumulative ranking curve; CIM, cimetidine; FAM, famotidine; ILA, ilaprazole; LAN, lansoprazole; OME, omeprazole; PAN, pantoprazole; RAB, rabeprazole; RAN, ranitidine; VON, vonoprazan

Key words: DU, non-eradication therapy, PPIs, H2RAs, network meta-analysis

Introduction

Duodenal ulcer (DU) is a common digestive system disease in the worldwide (1,2). Its complications, such as upper gastrointestinal bleeding or perforation, can cause death in patients with DU (3-5). In China, the duodenal ulcer is more common than gastric ulcer (44.69% vs. 37.42%). Approximately 61% of hospitalized patients with peptic ulcers have complications (46.45% of bleeding and 14.66% of perforation), and the average in-hospital mortality was 0.35% (6).

Although *Helicobacter pylori* eradication is beneficial to the healing of duodenal ulcer and reduce recurrence, non-eradication therapy is suitable for *Helicobacter pylori*-negative patients or without Hp examination (7,8). DU develops when the protective mechanisms of the gastrointestinal mucosa, such as mucus and bicarbonate secretion, are overwhelmed by the damaging effects of gastric acid and pepsin (9). Proton pump inhibitors (PPIs) and H2 receptor antagonists (H2RAs) are the leading pharmaceuticals for the initial non-eradication treatment of DU patients (10). The PPIs specifically inhibit the H+/K+-ATP enzymes of gastric parietal cells, resulting in the continuous and robust inhibition of gastric acid secretion and accelerated healing of ulcers (11). H2RAs mainly act on H2 receptors on gastric parietal cells, competitively inhibiting histamine and inhibiting basal gastric acid secretion (12).

Many systematic reviews and trials compared the effect of different H2RAs and PPIs, but there is no head-to-head comparison of different doses of these pharmaceuticals (13-19). The Japanese Society of Gastroenterology (JSGE) developed the evidence-based clinical practice guidelines for DU's initial non-eradication treatment, but there are no recommended doses of PPIs and H2RAs (10). A reappraisal of the available evidence to support clinical decision-making is timely.

Therefore, we did a contemporaneous systematic review and network meta-analysis of RCTs of pharmaceuticals in non-eradication treatment DU.

Materials and methods

International certification registration. The study protocol is available on the International Prospective Register of Systematic Reviews with a registration number of CRD42020219564 and was prepared according to the guidelines of the Cochrane Multiple Interventions Methods Group (20).

Data sources and searches. We searched Cochrane Library, Embase, Medline, Web of Science, and Clinical Trials.gov databases from their inception until November 2022 for randomized clinical trials (RCTs) investigating different PPIs and H2RAs in initial non-eradication treatment of DU patients with no language restrictions. Additional studies were searched in the reference lists of all identified publications, including relevant meta-analyses. Regarding the search strategy, terms included the following items: ('Proton Pump Inhibitors' or 'PPI' or 'PPIs') and ('H2 Receptor Antagonists' or 'H2-receptor antagonists' or 'H2RAs') and ('Initial Non-eradication Treatment of DU patients' or 'Non-eradication of DU patients').

Study selection. All superiority, non-inferiority, phase II and III, single-blinded, and double-blinded trials were included. RCTs examining the effect of drugs (omeprazole, lansoprazole, rabeprazole, vonoprazan, pantoprazole, ilaprazole, ranitidine, cimetidine, famotidine) in adult patients (aged >18 years) with DU were eligible. The first period of randomized crossover trials was eligible for inclusion if they provided efficacy data before crossover. The definitions of DU considered within this network meta-analysis included endoscopically confirmed active DU. Trials that examined the efficacy of any dose of the drugs of interest and compared them with each other or placebo were considered eligible.

Two investigators (X. Zhu and X. Meng) did the literature search independently from one another. Two investigators (B. Li and Y. Su) evaluated all abstracts identified by searching for eligibility independently from one another. They obtained all potentially relevant papers and evaluated them in more detail, using pre-designed forms, to assess eligibility independently, according to the predefined criteria. We translated papers that were not in the English language. We resolved disagreements between investigators by discussion.

Data extraction and quality assessment. Two reviewers (J. Zhao and J. Liu) independently extracted data from original trial reports using a standardized form and then double-checked the extraction. We assessed the sources of bias using the Cochrane Collaboration's risk-of-bias tool addressing six domains (21). Two investigators (H. Wang and Q. Feng) independently completed the assessments, and discrepancies were discussed with a third party and resolved by consensus. Additionally, the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework were used to assess the quality of evidence contributing to each estimated network (22).

League table of all comparisons of efficacy and safety. Two independent reviewers (X. Meng and B. Li) assessed the risk of bias of these studies included in our analysis. Consistancy between the two reviewers was reported. Any disagreement was solved by a third senior investigator (X. Zhu or J. Zhao). Studies were classified as having high risk of bias if one or more domains were rated as high risk of bias; low if five or more were rated as low risk of bias and none was rated as high risk of bias, and all other cases were assumed to regard as moderate risk.

Statistical analysis. We used frequentist network meta-analysis (23). The risk ratio (RR) and mean difference, with a 95% confidence interval (CI), for outcomes were summarized. The results were combined and analyzed, and the P-score of each treatment scheme was compared using the Haas ranking method (24). P-scores are based solely on point estimates and standard errors from the network estimates, and measure the mean extent of certainty that one intervention is better than another, averaged over all competing interventions (25). A design-by-treatment approach was used to verify the assumption of consistency in the analytical network (26).

Additionally, a funnel plot was drawn and a deviation test in combination with Egger test was conducted. A comparison-adjusted funnel plot was used to detect potential publication biases in the results between small and large studies. Global heterogeneity was assessed using the I^2 statistics, which incorporated the extent of heterogeneity and evaluated the extent of uncertainty in the estimated effect size locally. To assess whether the results were impacted by study characteristics (effect modifiers), the risk of bias (high, unclear, or low) was assessed. Additionally, to assess the robustness of the results, we used random effect models for sensitivity analysis. Comparison-adjusted funnel plots were obtained to investigate whether the integrated results were different between the imprecise and precise trials (27). All analyses were conducted using R 3.6.2 via the netmeta, version 1.1-0.

Results

Study characteristics. Sixty-five eligible studies, published between 1976 and 2022, corresponding to 15381 adults, were selected for pooled analyses (18,19,28-90). The literature search process is shown in Fig. 1. These trials evaluated 6 different PPIs (ilaprazole, omeprazole, lansoprazole, pantoprazole, rabeprazole, and vonoprazan) and 3 different H2RAs (cimetidine, ranitidine and famotidine). These studies have come from many countries (mainly China, Japan, United States, United Kingdom, Germany) and centers. Endoscopic examination was used to define the healing of duodenal ulcers after treatment. The patients' treatment courses were divided into three types: 46 studies were treated for four weeks, 14 studies were treated for six weeks, and five studies were treated for eight weeks. The baseline characteristics of the RCTs included are provided in Table SI (Supplementary File). We found a total of 89 studies about the application PPIs and H2RAs in initial non-eradication treatment of DU patients in the past five years. Most of them are non-RCT, data not extractable and no fixed dose of the drug used. Therefore, only one study was included in the criteria, and the others were not included in this study.

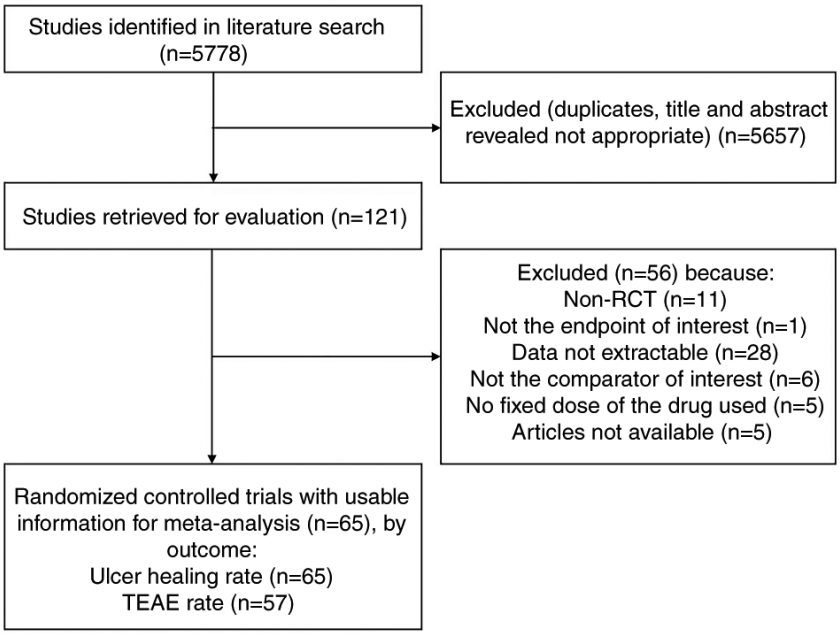

Figure 1. Study selection process. RCT, randomized controlled trial; TEAE, treatment-emergent adverse event.

Quality of the included studies. According to the Cochrane Collaboration's tool, all of the studies were judged to be at low or unclear risk of bias for six domains. Disagreements were resolved by discussion. The method used to generate the randomization schedule and conceal treatment allocation was recorded and whether blinding was implemented for participants, personnel, and outcomes assessment, whether there was evidence of incomplete outcomes data and whether there was evidence of selective reporting of outcomes.

Risk of bias table of included studies. Two independent reviewers (X. Meng and B. Li) assessed the risk of bias of these studies included in our analysis. Consistancy between the two reviewers was reported. Any disagreement was solved by a third senior investigator (X. Zhu or H. Wang). Studies were classified as having high risk of bias if one or more domains were rated as high risk of bias; low if five or more were rated as low risk of bias and none was rated as high risk of bias, and all other cases were assumed to regard as moderate risk. The risk of bias assessment of the trials included in this study is presented in Table SII.

Network meta-analysis results. We assessed the efficacy and safety of 6 different PPIs (ilaprazole, omeprazole, lansoprazole, pantoprazole, rabeprazole, and vonoprazan) and 3 different H2RAs (cimetidine, ranitidine and famotidine) for initial non-eradication treatment of DU. There are different doses of the ilaprazole, omeprazole, lansoprazole, pantoprazole, rabeprazole, vonoprazan, cimetidine, ranitidine, and famotidine (3, 5, 4, 1, 2, 1, 6, 3, 4, respectively). Fig. 2 shows the network of eligible comparisons for ulcer healing rate.

Efficacy of the ulcer healing rate. Concerning an increase in the ulcer healing rate, our network meta-analysis included 65 RCTs involving the administration of 6 different PPIs and three different H2RAs patients. A placebo was used as a reference. We found significant differences in efficacy between all the drugs and the placebo. Compared with the placebo, the included pharmaceuticals significantly increased the ulcer healing rate (Fig. 3). CIM 400 mg four times daily and PAN 40 mg once daily were ranked first (P-score=0.88) in 65 RCTs (RR 3.27, 95% CI 1.18-9.07; RR 1.95, 95% CI 1.72-2.22 respectively). Quantifying heterogeneity/inconsistency: tau^2=0.0006; tau=0.0254; I^2=24.4% [0.0%; 44.1%]. Results of the pairwise comparison are indicated by the RRs and 95% CIs in Table SIII. There were no significant statistical differences in different doses of the CIM (300 mg four times daily, 400 mg four times daily, 400 mg twice daily), FAM (20 mg twice daily, 40 mg once daily, 40 mg twice daily, 80 mg once daily), RAB (10 mg once daily, 20 mg once daily), ILA (5 mg once daily, 10 mg once daily, 20 mg once daily), LAN (15 mg once daily, 30 mg once daily, 60 mg once daily), OME (20 mg once daily, 40 mg once daily, 60 mg once daily).

Safety of TEAE (Treatment-emergent adverse event). Our network meta-analysis included 57 RCTs, reporting the administration of 6 different PPIs and three different H2RAs among 14788 DU patients. There was no statistically significant association between the nine drugs and the treatment-emergent adverse event compared with the placebo (Fig. 4). Results of the pairwise comparisons are indicated by the RRs and 95% CIs in Table SIII. FAM 20 mg twice daily was significantly less likely to lead to adverse events than RAN 300 mg four times daily, VON 20 mg once daily, and placebo. FAM 40 mg once daily was significantly less likely lead to adverse events than RAN 150 mg twice daily, RAN 300 mg four times daily, RAN 300 mg once daily, VON 20 mg once daily and placebo. FAM 40 mg twice daily was significantly less likely to lead to adverse events than VON 20 mg once daily. ILA 10 mg once daily was significantly less likely to lead to adverse events than RAN 300 mg four times daily, RAN 300 mg once daily, and VON 20 mg once daily.

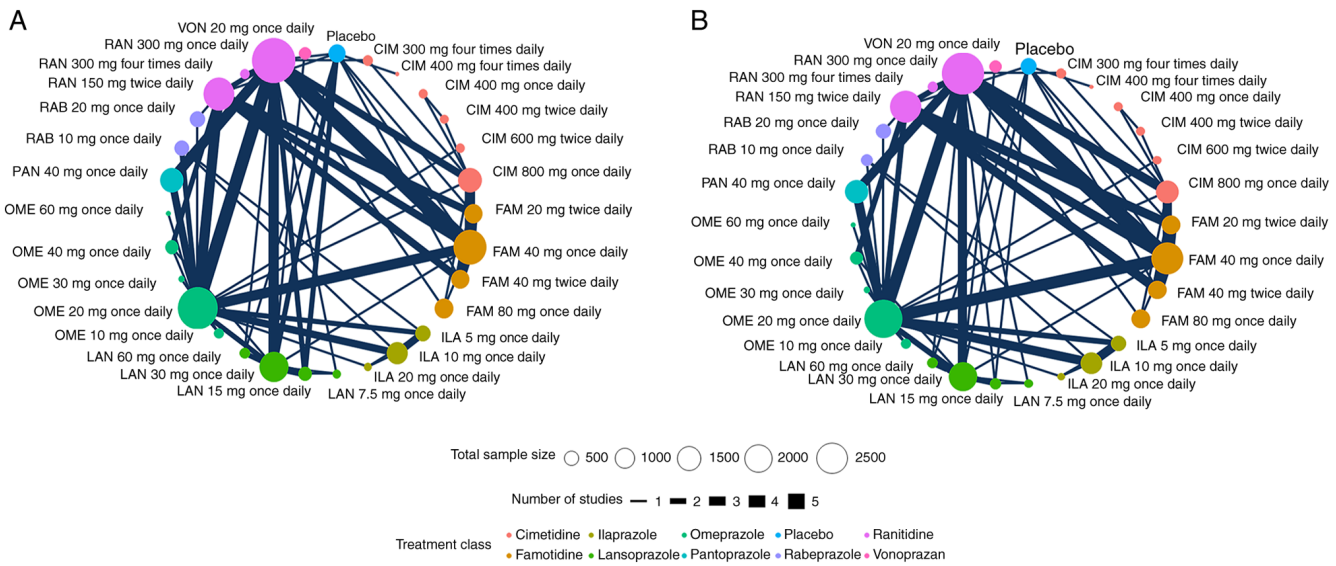

Figure 2. Network meta-analysis of eligible comparisons for efficacy and safety. (A) Efficacy. (B) Safety. The width of represents the number of studies and the size of the node represents the total CIM, cimetidine; FAM, famotidine; ILA, ilaprazole; LAN, lansoprazole; OME, omeprazole; PAN, pantoprazole; RAB, rabeprazole; RAN, ranitidine; VON, vonoprazan.

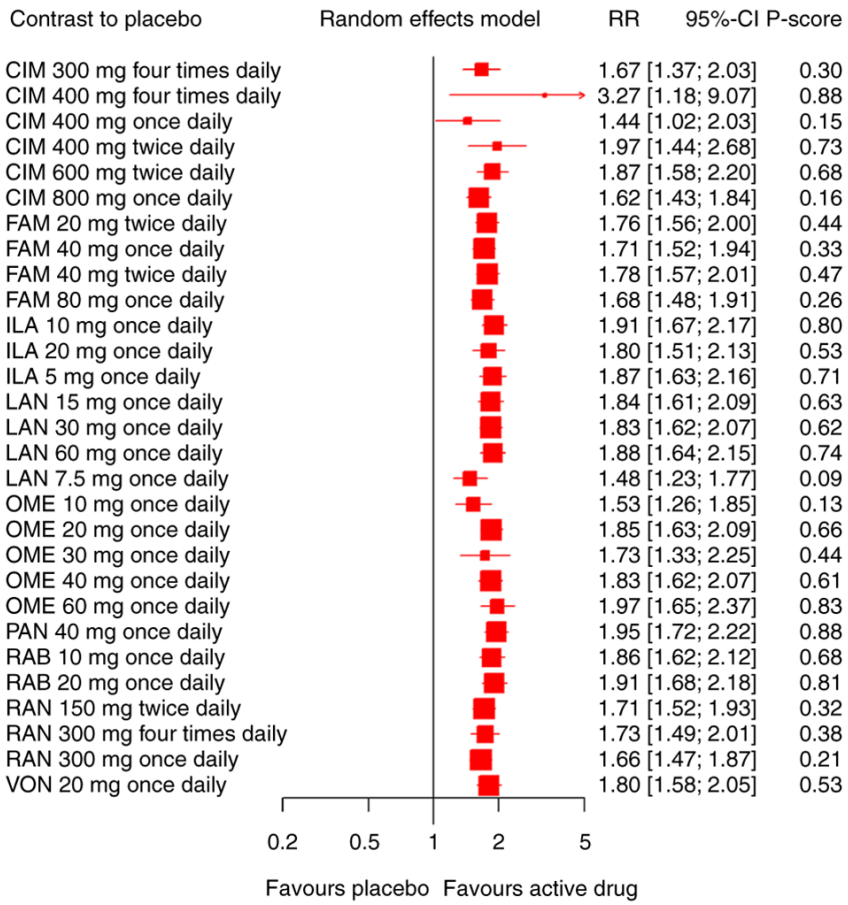

Figure 3. Result of network meta-analysis for efficacy. Contrast to Placebo meant that all patients taking active drugs were compared with those taking placebo. CIM, cimetidine; FAM, famotidine; ILA, ilaprazole; LAN, lansoprazole; OME, omeprazole; PAN, pantoprazole; RAB, rabeprazole; RAN, ranitidine; VON, vonoprazan; RR, risk ratio; CI, confidence interval.

Ranking of efficacy and safety of all included pharmaceuticals. We used the calculated p-scores to rank the efficacy and safety of the nine drugs included in our study (Table I; Fig. 5). A higher p-score indicated higher efficacy or safety. Among all the drug pharmaceuticals, CIM 400 mg four times daily and PAN 40 mg once daily had the highest efficacy, with a p-score

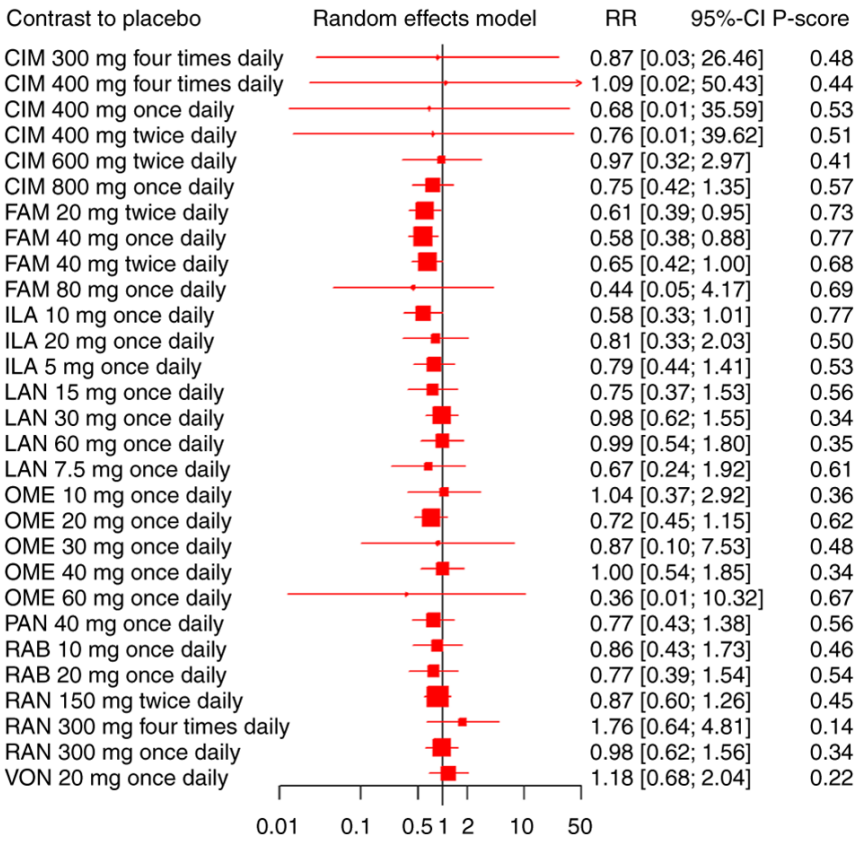

Figure 4. Result of network meta-analysis for the safety of treatment-emergent adverse events. Contrast to Placebo meant that all patients taking active drugs were compared with those taking placebo. CIM, cimetidine; FAM, famotidine; ILA, ilaprazole; LAN, lansoprazole; OME, omeprazole; PAN, pantoprazole; RAB, rabeprazole; RAN, ranitidine; VON, vonoprazan; RR, risk ratio; CI, confidence interval.

of 0.88, while FAM 40 mg once daily and ILA 10 mg once daily were associated with the highest safety (p-score=0.64). RAN 300 mg four times daily (p-score=0.14) and VON 20 mg once daily (p-score=0.22) had lower safety than placebo (p-score=0.33).

Small-study effect analysis. The results of the comparison-adjusted funnel plots suggested that there may not be small-study effects for efficacy and safety (Egger test; P>0.05) (Fig. 6).

Discussion

This study is the first network meta-analysis to specifically evaluate the efficacy and safety of different doses of PPIs and H2RAs for the initial non-eradication treatment of duodenal ulcer (DU) patients. The direct and indirect comparison results showed some evidence from RCTs. Firstly, H2RAs and PPIs were found to perform significantly better than the placebo for increasing the ulcer healing rate. Concerning the TEAE rate, the pharmaceuticals included in this study were comparable to the placebo. Secondly, as refer to the ulcer healing rate, we did find there was no significant statistical differences in different doses of the CIM, FAM, RAB, ILA, LAN, OME. For these different pharmaceuticals, FAM 20 mg twice daily, RAB 10 mg once daily, ILA 5 mg once daily, LAN 15 mg once daily, and OME 20 mg once daily should be prescribed in the clinic considering the economy and convenience of taking medicine. Thirdly, 150 mg twice daily is the best choice for RAN, RAN 300 mg four times daily and VON 20 mg once daily needs more studies to confirm its safety. Lastly, CIM 400 mg four times daily and PAN 40 mg once daily had the highest P-scores of ulcer healing rate, but there is a significant heterogeneity of CIM 400 mg four times daily treatment. Moreover, PAN 40 mg once daily treatment was ranked twelfth for the TEAE rate.

PPI is not only the most recommended drug in the guide, but also the first drug in clinical practice. Although it is accompanied by long-term side effects, such as long-term administration of PPI will lead to gland atrophy, atrophic gastritis and gastric polyps. But its side effects are completely avoidable. In order to avoid such side effects or reduce the chance of occurrence, we can also take orally rebapide tablets, teprenone capsules and other drugs that promote the synthesis of endogenous prostaglandins, improve gastric circulation and protect gastric mucosa. If atrophic gastritis occurs, it can also be reversed or prevented from further development by drugs. Gastric polyps can be treated by endoscopic forceps, argon ion coagulation, ligation, submucosal dissection or resection (91). Therefore, the purpose of this study is to seek the appropriate dose and the best clinical dose to avoid the side effects of overuse and overuse. If PPIs cannot be prescribed, H2RAs are recommended (10). And Dr. Shi believes that with the progress of treatment, it is very necessary to adjust the drug dosage to obtain higher clinical efficacy (92). So this study focuses on the best dose of PPI for DU. But there are no recommended doses of PPIs and H2RAs. In our study, according to the P-scores of efficacy and safety,

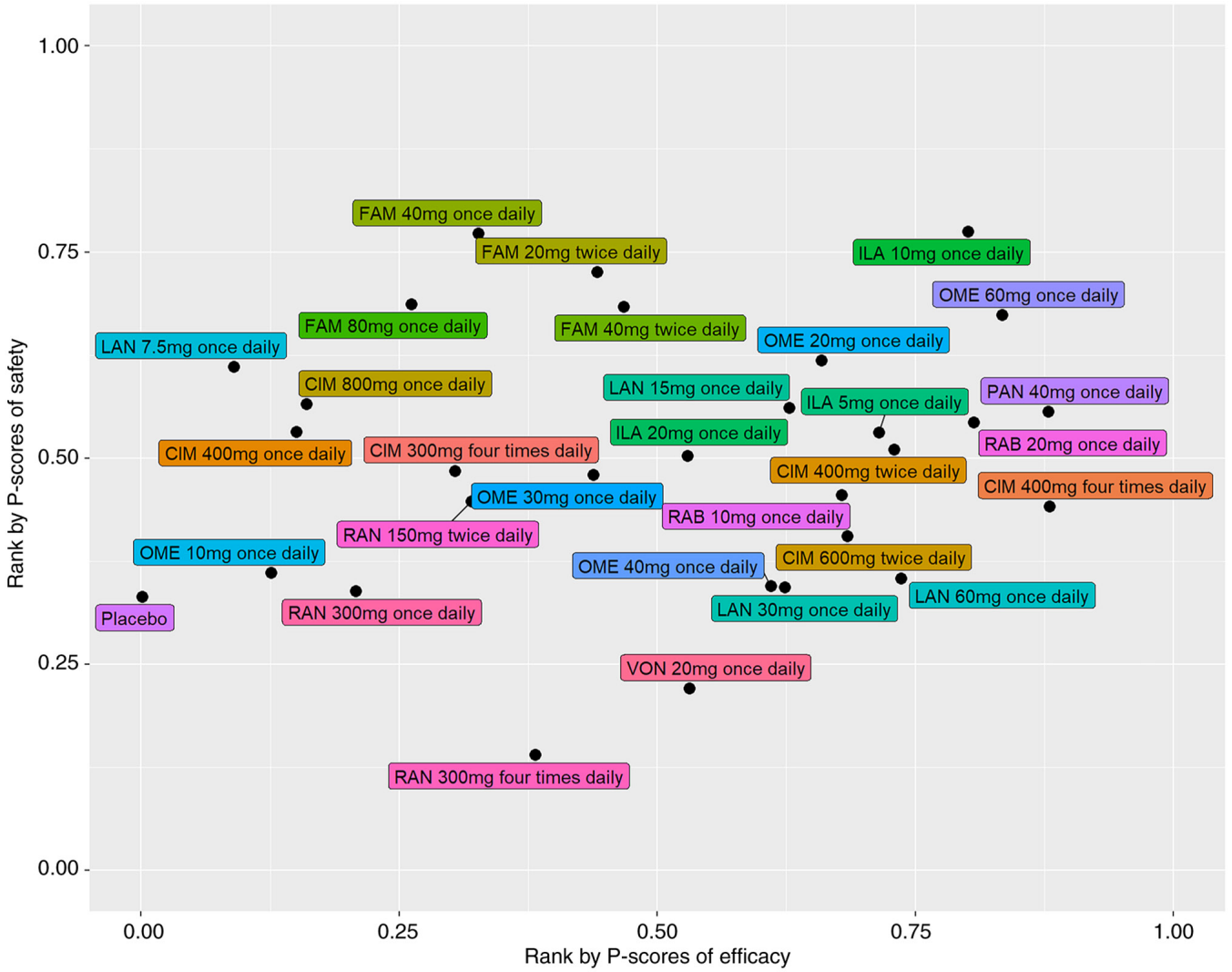

Figure 5. P-score values of total efficacy and safety. CIM, cimetidine; FAM, famotidine; ILA, ilaprazole; LAN, lansoprazole; OME, omeprazole; PAN, pantoprazole; RAB, rabeprazole; RAN, ranitidine; VON, vonoprazan.

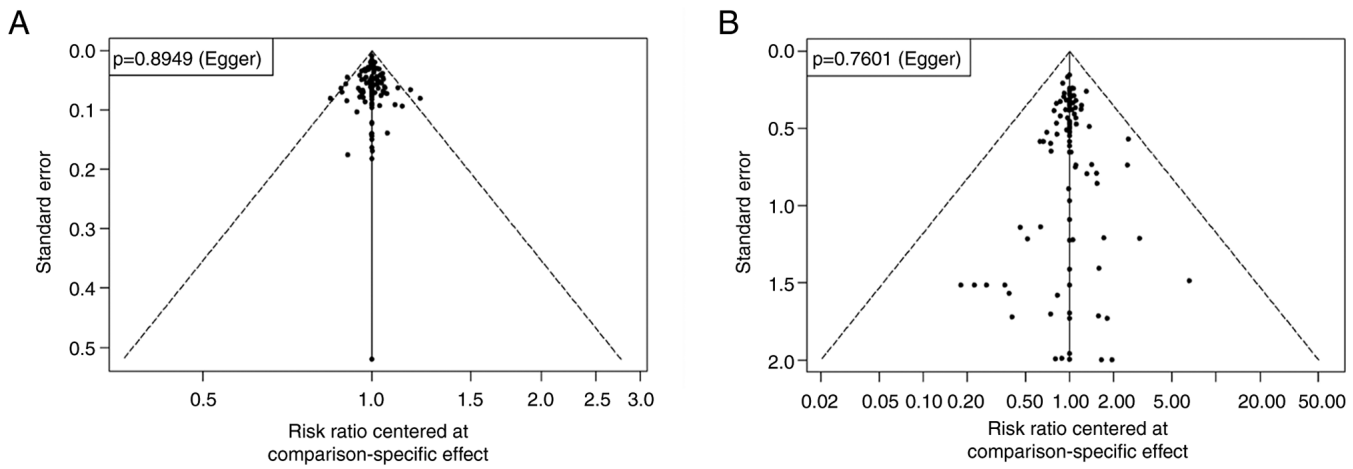

Figure 6. Comparison-adjusted funnel plots of total efficacy and safety. (A) Total efficacy. (B) Safety.

we recommend PAN 40 mg once daily (4 weeks) as the best choice treatment for DU patients. This is also confirmed by the research results of Dr. Huang and Dr. Li which suggested that pantoprazole 40 mg once daily was the best choice for the treatment of DU patients (92,94). Similarly, a previous meta-analysis did find PAN (40 mg/day) seems to be the most cost-effective

Table I. P-score values of total efficacy and safety.

Treatments	P-scores of efficacy	P-scores of safety
CIM (300 mg four times daily)	0.3040679	0.4848278
CIM (400 mg four times daily)	0.8802221	0.4416666
CIM (400 mg once daily)	0.1501962	0.5319926
CIM (400 mg twice daily)	0.7292859	0.5109288
CIM (600 mg twice daily)	0.6841244	0.4053628
CIM (800 mg once daily)	0.1604934	0.5654400
FAM (20 mg twice daily)	0.4414836	0.7262596
FAM (40 mg once daily)	0.3268190	0.7723887
FAM (40 mg twice daily)	0.4674790	0.6834608
FAM (80 mg once daily)	0.2618819	0.6866390
ILA (10 mg once daily)	0.8006744	0.7749225
ILA (20 mg once daily)	0.5291277	0.5026243
ILA (5 mg once daily)	0.7145607	0.5314908
LAN (15 mg once daily)	0.6276334	0.5608376
LAN (30 mg once daily)	0.6235095	0.3432118
LAN (60 mg once daily)	0.7361912	0.3544614
LAN (7.5 mg once daily)	0.0897389	0.6112681
OME (10 mg once daily)	0.1256739	0.3609625
OME (20 mg once daily)	0.6589973	0.6184667
OME (30 mg once daily)	0.4380268	0.4796125
OME (40 mg once daily)	0.6097252	0.3449109
OME (60 mg once daily)	0.8340756	0.6738167
PAN (40 mg once daily)	0.8788211	0.5564456
Placebo	0.0010943	0.3321135
RAB (10 mg once daily)	0.6785481	0.4551692
RAB (20 mg once daily)	0.8067308	0.5436169
RAN (150 mg twice daily)	0.3199518	0.4475938
RAN (300 mg four times daily)	0.3816410	0.1400162
RAN (300 mg once daily)	0.2079667	0.3385505
VON (20 mg once daily)	0.5312583	0.2209416

CIM, cimetidine; FAM, famotidine; ILA, ilaprazole; LAN, lansoprazole; OME, omeprazole; PAN, pantoprazole; RAB, rabeprazole; RAN, ranitidine; VON, vonoprazan.

option in China (95). We also recommend CIM 400 mg twice daily (4 weeks), OME 20 mg once daily (4 weeks or 6 weeks), LAN 15 mg once daily (4 weeks), ILA 5 mg once daily (4 weeks), and RAB 10 mg once daily (4 weeks or 6 weeks) can be used as the first choice in the treatment of patients with duodenal ulcer. If the pharmaceuticals mentioned above cannot be prescribed, FAM 40 mg twice daily (8 weeks) is recommended. Our study provides a reasonable dosage and optimal choice for initial non-eradication treatment of duodenal ulcers.

This study is a network meta-analysis to explore the efficacy and safety of different doses of pharmaceuticals containing PPIs, H2RAs, and a placebo. Based on direct and indirect evidence, we provide a comprehensive preliminary ranking of these drugs regarding their effects on duodenal ulcer healing rate and TEAE rate, which could provide a basis for future clinical research. However, this study has some limitations, the allocation concealment are assessed unclear in most of the studies; the incomplete outcome data and selective reporting are assessed unclear in some studies, there are two studies assessed as high risk. The quality of these studies potentially threatened the validity of our study. Notwithstanding these limitations, the findings from this network meta-analysis represent the most comprehensive currently available evidence base to guide the initial non-eradication treatment of DU in adults.

At present, some studies have shown that mucosal protection therapy combined with PPI has a good effect on DU, but in terms of single efficacy, PPI is better than mucosal protection therapy (96). According to 'Evidence-based Clinical Practice Guidelines for Peptic Ulcer Disease 2015', PPI is recommended for line drugs (97). If PPI cannot be prescribed, H2RA is recommended. So this study focuses on the best dose of PPI for DU. In conclusion, these PPIs and H2RAs are effective and safe for initial non-eradication treatment of DU. The results suggested that pantoprazole 40 mg once daily (4 weeks) was the best choice for the initial non-eradication treatment of DU patients, cimetidine 400 mg twice daily (4 weeks), omeprazole 20 mg once daily

(4 weeks or 6 weeks), lansoprazole 15 mg once daily (4 weeks), ilaprazole 5 mg once daily (4 weeks), and rabeprazole 10 mg once daily (4 weeks or 6 weeks) could be used as the first choice. If the pharmaceuticals mentioned above cannot be prescribed, famotidine 40 mg twice daily (8 weeks) is recommended.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

XM and XZ confirm the authenticity of all the raw data. XM, XZ, QF and YS conceived and designed the current study, defined the content of the research, conducted literature search, performed statistical analysis, and prepared and edited the manuscript. BL and HW are the guarantors of study integrity, designed the current study, defined the content of the research and reviewed the manuscript. JL and JZ conducted the literature search, acquired data and performed statistical analysis. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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