Cost-effectiveness analysis of vonoprazan versus proton pump inhibitors in the treatment of reflux esophagitis in China

Zhenhua Wang[1], Ruixiaotong Sun[2], Yanan Sheng[3], Shuli Qu[2], Lu Dong[3], Bin Wu[4]

[1]Department of Gastroenterology, Ren Ji Hospital, School of Medicine, Shanghai Jiaotong University, Shanghai, China; [2]Real-World Solutions, IQVIA, Beijing, China; [3]Medical Affairs, Takeda (China) International Trading Company, Beijing, China; [4]Medical Decision and Economic Group, Department of Pharmacy, Ren Ji Hospital, South Campus, School of Medicine, Shanghai Jiaotong University, Shanghai, China

Contributions: (I) Conception and design: Z Wang, R Sun, Y Sheng, S Qu, B Wu; (II) Administrative support: Y Sheng, L Dong; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Professor Bin Wu. Medical Decision and Economic Group, Department of Pharmacy, Ren Ji Hospital, South Campus, School of Medicine, Shanghai Jiaotong University, Shanghai, China. Email: scilwsjtu-wb@yahoo.com.

Background: Proton pump inhibitors (PPIs) have been recommended as standard of care for reflux esophagitis (RE). Vonoprazan (VPZ), a novel potassium-competitive acid blocker (P-CAB), has been approved in China after demonstrating clinical benefit in RE. However, there are not any published literature reported the cost-effectiveness of VPZ compared with PPI in Chinese healthcare setting. Thus, this study aimed to estimate the cost-effectiveness of VPZ compared with PPIs for the treatment of RE patients in China and take advantage of this result to inform healthcare decision-making.

Methods: A Markov model was developed to predict the effectiveness and costs of VPZ for 4 weeks and PPI group for 8 weeks in RE treatment over a 5-year time horizon from a healthcare system perspective. Four health states within healing and maintenance phases were defined in the model: mucosa healed, mucosa unhealed, relapse, and death. Transition probabilities including healing rate and relapse rate were derived from a single-arm meta-analysis and mortality were obtained from Chinese life table. Drug costs and other medical expenses were retrieved from China tendering prices and local clinical expert estimation. Utility parameters were derived from published literature. Both health outcomes and costs were discounted at a rate of 5% annually. Quality-adjusted life years (QALYs), direct medical costs and incremental cost-effectiveness ratios were evaluated. Uncertainty was assessed by one-way and probabilistic sensitivity analysis (PSA).

Results: The healing rate for VPZ and PPI were 90% (95% CI: 82–97%) and 74% (95% CI: 71–76%) at week 4 respectively and were 94% (95% CI: 88–99%) and 87% (95% CI: 85–88%) at week 8 respectively. Treatment with VPZ resulted in 4.35 QALYs at a total cost of USD 1,354 over 5 years. Compared with the PPI group, treating RE with VPZ was associated with 0.02 QALYs gained and a cost saving of USD 943. Thus, VPZ should be considered as the dominant treatment option. The model results were deemed robust in sensitivity analyses.

Conclusions: VPZ generates incremental QALYs at a lower cost compared with PPI, thus could be considered as an optional choice in the treatment of patients with RE.

Keywords: China; cost-effectiveness; proton pump inhibitors (PPIs); reflux esophagitis (RE); vonoprazan (VPZ)

Submitted Jan 17, 2022. Accepted Apr 20, 2022.

doi: 10.21037/atm-22-1722

View this article at: https://dx.doi.org/10.21037/atm-22-1722

Introduction

Reflux esophagitis (RE) is an esophageal mucosal injury that occurs secondary to retrograde flux of gastric contents into the esophagus and referred as one of phenotypes of gastroesophageal reflux disease (GERD). It is considered a common disease worldwide with increasing prevalence. The estimated prevalence of RE in China was 6.4% based on a population-based study, of whom 3% had sever diseases categorized as Los Angeles (LA) grades C/D (1). The typical symptoms of RE include heartburn and/or regurgitation. Patients may also have other symptoms such as epigastric pain or sleep disturbance, which subsequently affect their quality of life (QOL) (2). Anxiety and depression levels were also significantly higher in people with reflux symptoms, which could result in reduced work productivity and poses a great burden on the society (3).

The main treatment goals of RE are to heal the breaking mucosal and relieve symptoms, as well as to prevent complications and improve QOL (4). Current guidelines recommended proton pump inhibitors (PPIs) for 8 weeks as an initial treatment for RE patients. Once healing of mucosal erosions and symptom relief have been achieved by initial therapy, long-term maintenance treatment with the lowest effective dose of PPIs is also recommended (4-6). In China, approved PPI treatment for RE includes omeprazole (OME), esomeprazole (ESO), rabeprazole (RAB), pantoprazole (PAN), lansoprazole (LAN) and ilaprazole (ILAP). However, PPIs have notable limitations: they do not provide complete acid control and exhibit nocturnal acid breakthrough. A nationwide survey demonstrated that over 80% of adults taking PPIs for reflux diseases reported nocturnal symptoms, which affected their QOL (7). The healing rate with PPIs is also low. A previous study has reported that approximately 4–15% of RE patients fail to achieve complete healing esophageal inflammation after the 8-week standard-dose PPI treatment (8). Also, available evidence shows that a considerable number of patients relapse during maintenance PPI treatment (9).

Vonoprazan (VPZ) is a potassium-competitive acid blocker (P-CAB) for the treatment of gastric acid-related diseases. It has been approved in China for RE treatment since 2019. VPZ exerts faster, more potent and more sustainable acid inhibitory effects than PPIs due to its excellent pharmacological characteristics (10,11). A 4-week treatment with VPZ and 8-week treatment with a PPI has been recommended as initial therapies for RE patients (12). A phase III study found that the mucosal healing rate of the VPZ 20 mg group at week 4 was higher than that in the LAN 30 mg group at week 8 (at 4 weeks 96.1% *vs*. 90.9%, P<0.05; at 8 weeks 98.9% *vs*. 94.5%, P<0.03) (13). Another phase III study based on an Asian population in which Chinese patients comprised >50% of the total study population, also reported non-inferiority between of VPZ 20 mg and LAN 30 mg based on the endoscopic erosion healing rate at week 8, and the incidence of treatment-emerging adverse events was similar between the VPZ 20 mg group and LAN 30 mg group (38.1% *vs*. 36.6%, respectively) (14).

As of now, only three cost-effectiveness of VPZ in the treatment of RE have been published (15-17). However, all these studies evaluated the cost-effectiveness of VPZ from Japanese healthcare payer's perspective and found that VPZ is a cost-effective treatment compared with target PPI. Due to the healthcare system is significantly different between Japan and China, and the commonly used PPI is also different between these two countries, these make them of little use in terms of obtaining plausible conclusions for patients in China. Meanwhile, VPZ along with 70 other innovative drugs were successfully incorporated into the China National Reimbursement Drug List (NRDL) in December 2020. The daily costs for PPIs and VPZ were close. Thus, health economic evidence balancing efficacy and cost will play an important role to inform clinical medication choice and hospital listing. Therefore, this study aimed to estimate the cost-effectiveness of VPZ compared with all available PPIs for the treatment of RE patients in China from the healthcare system perspective. We present the following article in accordance with the CHEERS reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-1722/rc).

Methods

Model development

A Markov model was developed in Microsoft Excel to predict the effectiveness and costs of VPZ versus other PPIs for RE treatment in China (18). Markov models are well studied for modeling the progression of chronic diseases and have been widely used in economic evaluations of GERD treatment (15,19-21). The model incorporated two treatment strategies: VPZ and a group of PPIs including OME, PAN, ESO, RAB, LAN and ILAP. Based on the results of published pairwise meta-analyses, there is no significant difference in the efficacy among different

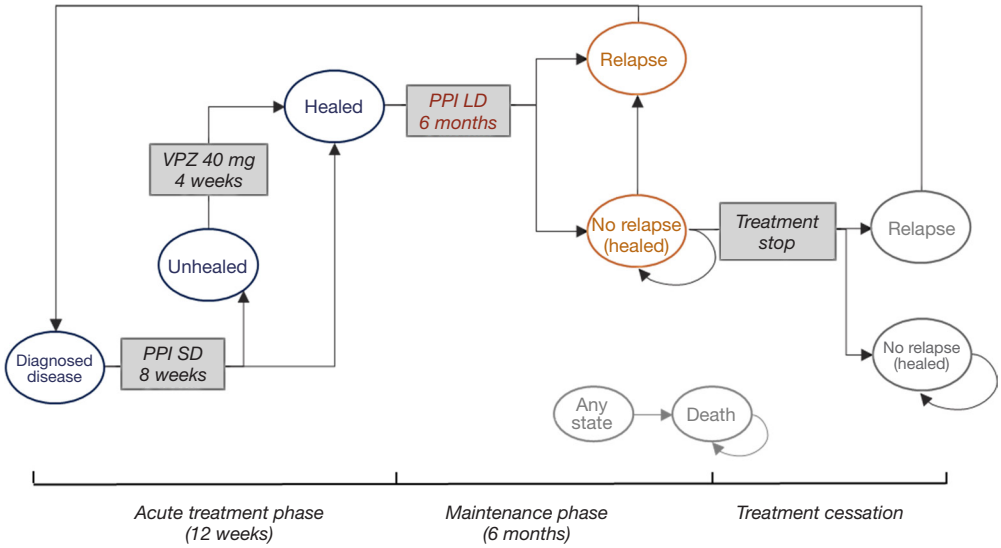

Figure 1 Overview of model structure of PPI strategy. SD, standard dose; LD, low dose; PPI, proton pump inhibitors; VPZ, vonoprazan.

PPIs (22). Therefore, we chose a PPI group, rather than any single PPI, as the comparator.

We defined four disease states to represent possible consequences of RE treatment: mucosa healed, mucosa unhealed, relapse and death. A numeric QOL value and direct medical costs were assigned for each health states. QOL was calculated by quality-adjusted life years (QALYs), which is widely acknowledged as a measure of health outcome for economic assessment. A mean age of 40 years was used as the starting age of patients entering the model (1,23). The time horizon was 5 years and we used a 4-week cycle length (17) with half-cycle correction to accommodate the gradual transition of the population between health states. A discount rate of 5% (24) was applied for QALY and costs.

The model included an acute treatment phase and a maintenance phase, which reflects the general treatment pattern of all RE patients, as well as RE patients with moderate-to-severe disease. The flows of treatments, doses, and length of treatment for different strategies were based on the Chinese clinical practice guideline for GERD (5) and verified with clinical experts' opinions.

Acute treatment and maintenance phase

The simulated cohort in the PPI strategy started receiving a standard-dose PPI for 8 weeks. If patients were not healed after initial treatment, continuous therapy on VPZ 40 mg once daily for an additional 4 weeks was added. After that, all patients were assumed to achieve endoscopically confirmed mucosal healing (25). The acute treatment phase lasted a maximum of 12 weeks. For patients healed at week 8 or 12, 6-month maintenance treatment with low-dose PPI was instituted.

The model structure of the VPZ strategy was slightly different. The simulated cohort of patients was initially treated with VPZ 20 mg once daily for 4 weeks. Patients who were not healed at week 4 continued on VPZ 20 mg once daily for an additional 4 weeks. For unhealed patients at week 8, VPZ 40 mg/day was given for 4 weeks to achieve mucosal healing. Patients who were healed at week 4, 8 and week 12 would progress to 6-month maintenance treatment with VPZ 10 mg.

Treatment cessation and relapse

Patients could stop treatment and remained in the "mucosa healed" state if they completed maintenance therapy without relapse. However, after initial healing of esophageal inflammation, 50–80% of RE patients experience relapse within 6 to 12 months after treatment cessation (26). Patients may experience multiple relapses. In all evaluated strategies, it was assumed that relapsed patients were reintroduced to acute treatment and remained in the same state. Although RE is associated with a low mortality rate (27), we still modeled death as a terminal state in the patient journey. The model structures of the PPI and VPZ strategies are shown in *Figures 1,2* respectively.

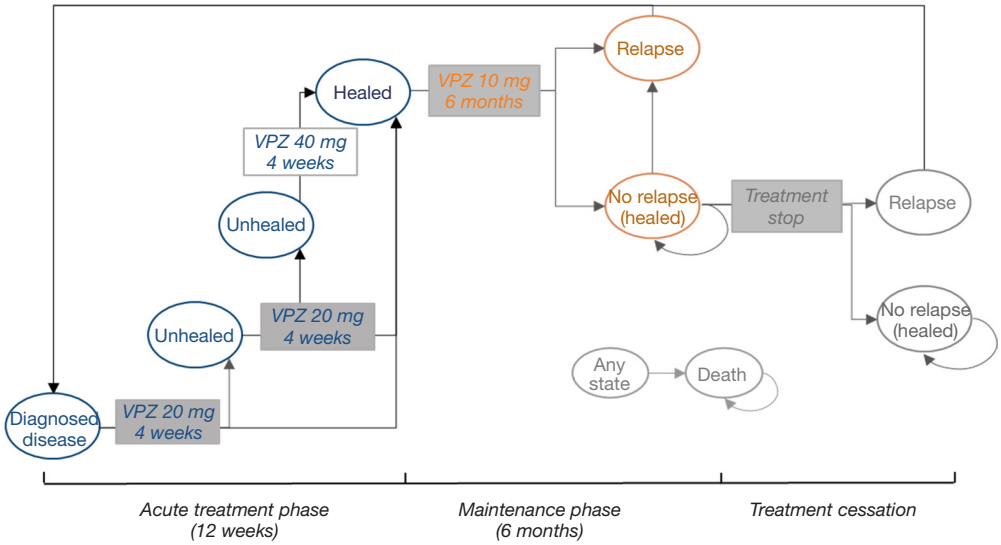

Figure 2 Overview of model structure of VPZ strategy. VPZ, vonoprazan.

Clinical inputs and transition probabilities

Clinical inputs of this model included (I) healing rates measured by the proportion of patients with endoscopically confirmed healing at weeks 4 and 8 during the acute treatment phase, and (II) relapse rates measured by the proportion of patients with endoscopically confirmed relapse during the 6-month maintenance phase. To measure the treatment efficacy of the PPI and VPZ groups, we conducted a systematic review with a series of meta-analyses.

Systematic review

Search Strategy and Eligible Criteria. A structured search was conducted up to March 2019 in PubMed, Cochrane Library, China National Knowledge Infrastructure and WanFang to identify randomized controlled trials of PPIs and VPZ for RE treatment. The population of interest was adult patients with diagnosed RE. The healing and relapse rates had to be based endoscopically confirmed results. Full search strategies and the population, intervention, comparators, outcomes and study design criteria for inclusion in this systematic review are presented in the supplementary files (Tables S1,S2).

Data Extraction and Quality Assessment. Two investigators (SQ and RS) independently extracted all data, which were subsequently validated by a third independent reviewer (YS). All the included studies were critically appraised using a comprehensive assessment criterion based on the recommendations in the Cochrane Handbook (28).

Meta-analyses

For studies meeting the inclusion criteria, the number of patients healed or relapsed at each time interval and the number of patients initially at risk (i.e., intent-to-treat principle) were extracted.

We performed a single-arm meta-analysis for rates of healing and relapse by different treatment strategies, using the *metaprop* package in R software version 3.4 to obtain the pooled estimate of treatment effects of the PPI and VPZ groups. Logit transformation was implemented to normalize the distribution of a single rate calculated based on raw data before calculating the overall rate (29). Heterogeneity among the studies was assessed using the Chi-square test and measured by the I^2 statistic. If the test for heterogeneity was not statistically significant (i.e., $P<0.05$, $I^2<25\%$), a fixed-effects model was assumed for estimating the pooled rates of healing or relapse and the 95% confidence intervals (CI) for different treatment strategies. Otherwise, a random-effects model was used.

Transition probability

The meta-analysis measured the pooled healing rate at weeks 4 and 8, and the relapse rate in the 6-month maintenance phase, which was used to calculate the

transition probability corresponding to a Markov cycle length of 4 weeks as follows: P= 1 – exp(–rt), where e = event rates and t = time (30). Background mortality was considered in this model. The age- and sex-adjusted all-cause death rates of the population aged over 40 years were extracted from the China life table as inputs (31).

Cost and utility

The analysis was conducted from a healthcare system perspective, thus only direct medical costs of patients were considered, including drug costs, outpatient treatment costs, and laboratory test costs. The PPI group's drug cost was calculated based on average tender prices of each PPI available in China weighted by corresponding market shares. We only considered the prices of branded PPIs. The average tender prices of each PPI were extracted from the YAOZHI® database. Market shares were collected from a panel of nationwide hospital surveys (n=12). Other medical expenses were estimated via local clinical expert interviews (n=10). Detailed calculation methods and interview results are presented in the supplementary material (Tables S3,S4). All costs are expressed in US dollars (USD) using an exchange rate of 1 CNY =0.145 USD, which was the average in 2020.

Utility was derived from a cross-sectional survey, using the five-level EuroQol five-dimensional questionnaire (EQ-5D-5L) to elicit preferences for RE patients in China (32). Utility for unhealed RE patients was 0.86. For severe RE patients, the utility was 0.69.

Sensitivity analysis

One-way sensitivity analysis (OWSA) was performed to test the robustness of the study results. We varied the healing/relapse rates, drug costs, utilities, and the discount rate according to the 95% CI for each value or by ±20% if the 95% CI was not available/estimable for the OWSA.

Probabilistic sensitivity analysis (PSA) with 1,000-time Monte-Carlo simulations was also conducted, with a gamma distribution being assigned for cost parameters and a beta distribution being assigned for utilities and transition probabilities, PSA allows all model variables to be varied simultaneously within a plausible range to estimate the probability that the intervention in question is cost-effective at different willingness to pay (WTP) thresholds.

A scenario analysis was undertaken to investigate the cost-effectiveness of VPZ and the PPI group in treating severe RE patients with Los Angeles grade C/D (LA C/D).

Results

Clinical inputs and transition probabilities

Systematic review and meta-analysis

We screened the titles of 911 potentially eligible studies. After de-duplication, abstract and full-text screening, we included 56 studies in the systematic review (Figure S1). The data extraction and risk of bias assessment for the included studies is presented in the supplementary files (Tables S5-S7, Figures S2,S3).

There were 38 studies (65 arms) with 24,020 RE patients with reported endoscopic healing rates for PPI treatment or VPZ treatment. Meta-analysis showed that rates of healing at weeks 4 and 8 tended to be higher in those who receiving VPZ 20 mg compared with those receiving standard-dose PPIs. At week 4, the healing rate with VPZ treatment and PPI treatment was 90% (95% CI: 82–97%) and 74% (95% CI: 71–76%), respectively. After 8-week treatment of RE, the healing rate was 94% (95% CI: 88–99%) for VPZ and 87% (95% CI: 85–88%) for the PPI group.

VPZ was also found to be more effective in patients with moderate-to-severe RE. We included 17 studies that reported endoscopic healing rates of 3,398 patients with moderate-to-severe RE categorized as LA C/D. Results showed that at week 4, the healing rate of patients with LA C/D was 90% (95% CI: 81–100%) for VPZ and 61% (95% CI: 55–67%) for the PPI group. At week 8, the healing rate of patients with LA C/D was 96% (95% CI: 90–100%) for VPZ and 79% (95% CI: 75–83%) for the PPI group.

There were 17 studies that evaluated the efficacy of low-dose PPIs as maintenance therapy for healed RE. Results showed that during 6-month maintenance therapy, 82% (95% CI: 80–85%) of all patients and 71% (95% CI: 65–77%) of LA C/D patients remained healed when treated with low-dose PPIs. Therefore, the relapse rate of all patients and those with LA C/D treated with PPIs was 18% and 29%, respectively. There was only one study that reported rates of RE recurrence following treatment with VPZ 10 mg: 5.1% for all patients and 13.2% for patients with LA C/D during 6-month maintenance therapy (33). Detailed meta-analysis results are summarized in the supplementary files (Figures S4-S13).

Transition probability

We converted the event rates (r) over a time period (t) to transition probabilities (p) using the formula p = 1 – exp(–rt). The estimated healing probabilities and relapse

Table 1 Transition probabilities

Phase and population	Parameters	VPZ 20 mg QD	PPI standard dose QD	VPZ 10 mg QD	PPI low dose QD	Treatment cessation
Healing rate during healing therapy						
All RE patients	Healing rate at week 4	90%	74%			
	Healing rate at week 8	94%	87%			
	Healing rate at weeks 4–8*	40%	50%			
LA C/D RE patients	Healing rate at week 4	90%	61%			
	Healing rate at week 8	96%	79%			
	Healing rate at weeks 4–8*	60%	46%			
Relapse rate during maintenance therapy						
All RE patients	Relapse rate in 6 months			5%	18%	
	Relapse rate in 4 weeks			0.87%	3.25%	
LA C/D RE patients	Relapse rate in 6 months			13%	29%	
	Relapse rate in 4 weeks			2.33%	5.55%	
Relapse rate after treatment cessation						
All RE patients and LA C/D RE patients	Relapse rate in 6 months					80% [9]
	Relapse rate in 4 weeks					23.5%

*, healing rate at weeks 4–8 calculated by (healing rate at week 8 – healing rate at week 4)/(1 – healing rate at week 4). LA C/D, as Los Angeles grade C/D; PPI, proton pump inhibitors; QD, once daily; RE, reflux esophagitis; VPZ, vonoprazan.

Table 2 Cost and health resource utilization

Medical expense	Items	Cost (USD)	Notes
Drug cost (cost per cycle)	PPI group (standard dose, QD)	65	Unit cost ×28 days*
	VPZ 20 mg QD	40	
	PPI group (low dose, QD)	34	
	VPZ 10 mg QD	20	
Outpatient visit	Visit during healing phase	15	Twice a month
	Visit during maintenance phase	7	Once a month
Endoscopy	For diagnosis	84	Once
24-hour pH monitoring	For patients who were unhealed after 8-week treatment	116	Once

*, cycle costs for PPI group and VPZ can be calculated by multiplying the unit cost by 28 days. PPI, proton pump inhibitors; QD, once daily; VPZ, vonoprazan.

probabilities at different time points are presented in *Table 1*.

Cost and health resource utilization

Drug costs and other medical expenses associated with RE treatment are listed in *Table 2*. The drug cost for VPZ used in the model was the price after NRDL negotiation updated in December 2020. The initiation of acute treatment included one outpatient visit and several follow-up visits every 2 weeks for drug prescription. During 6-month maintenance treatment, the outpatient visit was made every 4 weeks. Patients were required to undergo

endoscopy at the first outpatient visit for diagnosis. For patients who were unhealed after the 8-week treatment, esophageal manometry and 24-hour pH monitoring were initiated.

Base-case analysis

Over the 5-year time horizon, a 40-year-old RE patient treated with VPZ was associated with 0.02 QALYs gained and a cost saving of USD943 compared with the PPI group. Therefore, VPZ appears to be a dominant strategy compared with PPIs (more QALYs gained and less cost incurred) (*Table 3*).

Table 3 Total cost and QALYs associated with VPZ and PPIs

Scenario	QALYs	ΔQALYs	Cost (USD)	ΔCost(USD)	ICER(USD)
Base case					
PPI group	4.33		2,297		
VPZ	4.35	0.02	1,354	−943	Dominant
Scenario analysis–LA C/D patients					
PPI group	4.19		2,288		
VPZ	4.27	0.08	1,352	−936	Dominant

Δ, represents the difference between the two groups. ICER, incremental cost-effectiveness ratios; LA C/D, Los Angeles (LA) grade C/D; PPI, proton pump inhibitor; QALY, quality-adjusted life year; VPZ, vonoprazan.

Scenario analysis

The scenario analysis showed VPZ was also a cost-saving option compared with the PPI group for LA C/D patients (*Table 3*).

Sensitivity analysis

Results of OWSA are presented as a tornado diagram (*Figure 3*). VPZ remained cost-saving under each scenario investigated. Utility of unhealed RE patients, and the healing rate at week 4 for the VPZ and PPI groups had the greatest effects on the result.

Results of PSA are summarized as a scatter plot in *Figure 4A*. The acceptability curve in *Figure 4B* shows that the likelihood of VPZ being considered cost-saving at a WTP threshold of USD30,838 per QALY gained was 100% compared with the PPI group.

Discussion

Several clinical trials have demonstrated that compared with other PPIs that available for RE patients, VPZ, a novel P-CAB, can provide rapid and sustained acid inhibition with good safety profile (13,14,33). However, no systematic comparison of the clinical effects and cost-effectiveness of VPZ and PPIs has been reported to date. This study, to the best of our knowledge, is the first to assess the treatment of

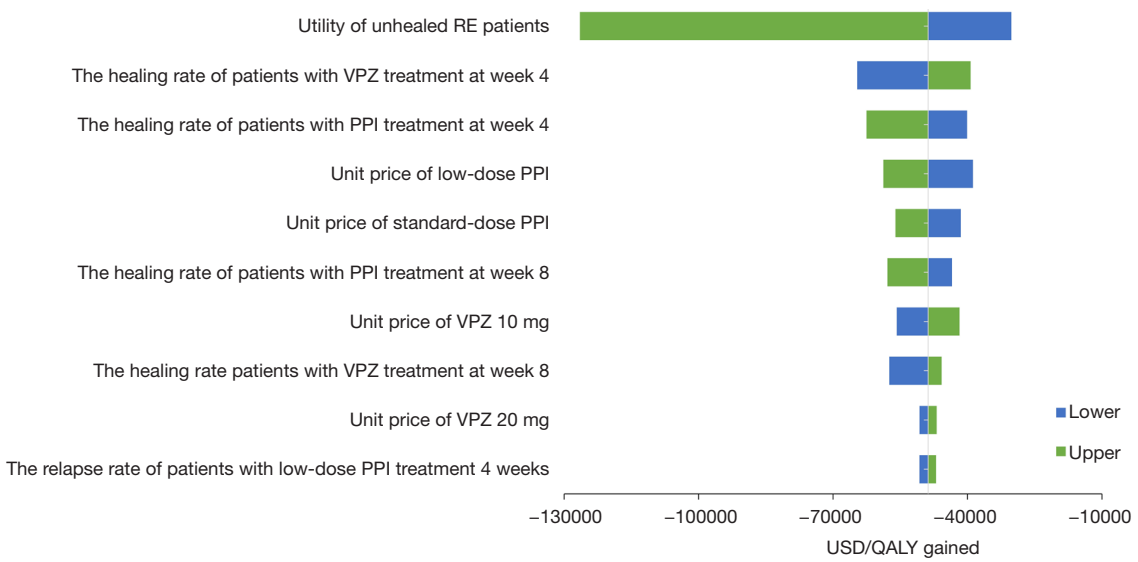

Figure 3 One-way sensitivity analysis: incremental costs and QALYs for the comparison of VPZ with the PPI group. PPI, proton pump inhibitor; QALY, quality-adjusted life year; VPZ, vonoprazan; RE, reflux esophagitis.

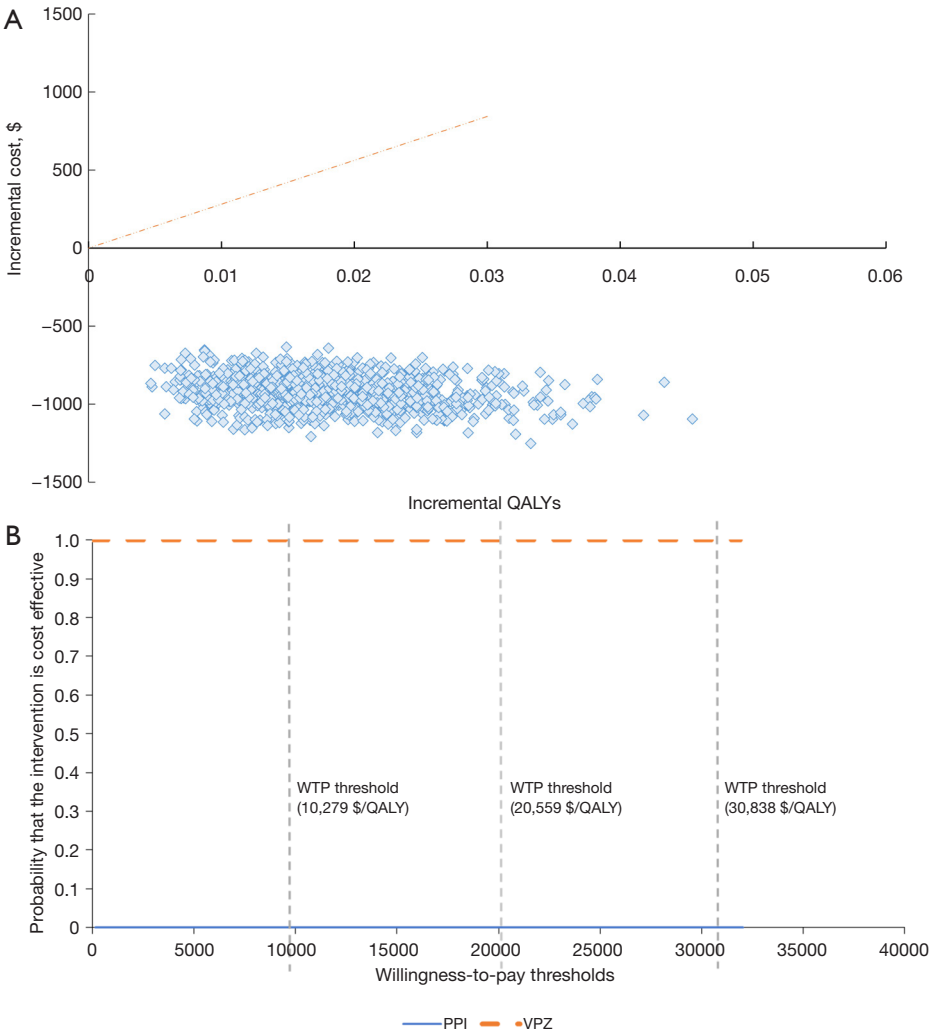

Figure 4 Probabilistic sensitivity analysis. (A) Cost-effectiveness planes for the comparison of VPZ with the PPI group, which illustrates the incremental costs (vertical axis) versus incremental QALYs (horizontal axis) for the individual 10,000-time Monte-Carlo simulations. Each diamond represents the base case analysis, and the line represents the WTP threshold of USD 30,838 per QALY (3-time GDP per capita). (B) Cost-effectiveness acceptability curve, which plots the probability of cost-effectiveness (vertical axis) against a range of WTP thresholds (horizontal axis). The dotted vertical lines represent the probability of cost-effectiveness at the WTP threshold of threshold of USD 10,279 per QALY (1-time GDP per capita), USD 20,559 per QALY (2-time GDP per capita) and USD 30,838 per QALY (3-time GDP per capita), respectively. PPI, proton pump inhibitor; QALY, quality-adjusted life year; VPZ, vonoprazan; WTP, willingness to pay.

RE patients in China.

The model we used incorporated both acute treatment and maintenance phases, which reflects current guidelines and treatment patterns in China. Our results demonstrated that treating RE with VPZ is an efficacious and cost-saving option compared with conventional PPIs. Subgroup analysis results further demonstrated that treatment with VPZ is cost-saving for patients with severe esophagitis. These results are in line with previous studies. A study in Japan evaluated the cost-effectiveness of VPZ versus LAN for the acute treatment of RE (15). It demonstrated that VPZ was consistently superior to LAN in terms of cost-effectiveness and medication duration. Another Japanese study evaluated the long-term cost and effectiveness of a VPZ-first strategy compared with the ESO-first and RAB-first strategies. Results showed that the VPZ-first strategy increased QALYs and appeared to be cost-effective for GERD patients compared with the ESO- or RAB-first strategy (17). Our

findings now supersede these and indicated the superiority of VPZ over the PPI group in treating and maintaining RE.

Some limitations of our analysis should be noted. First, there is no head-to-head trial that has compared VPZ with most PPIs except LAN, and there is not a single trial comparing all available PPIs. Therefore, we used meta-analysis with further assumptions to combine data. However, most studies included in meta-analyses do not have a Chinese cohort. To make sure the pooled estimates can reflect treatment efficacy of Chinese patients all data inputs were validated by local clinical experts. Furthermore, sensitivity analyses were performed to access uncertainties. Second, we did not include the costs of adverse events in the analysis due to lack of data. Nonetheless, the costs associated with adverse events would not be an influential or differentiating feature of this study. Third, although generic PPIs have been used in RE treatment in clinical practice in China, we only considered original PPIs. Whether generic drugs have the same quality, therapeutic effect, and safety profile as the original drugs is a matter of concern.

Conclusions

In the current setting of the Chinese healthcare system, our analysis suggested that VPZ could be a cost-saving strategy in the treatment of RE patients in China. The findings of this study, which were based on local data, can inform treatment decision makers at both the level of the individual patient and the policy level.

Acknowledgments

Funding: This study was funded by Takeda (China) International Trading Company.

Footnote

Reporting Checklist: The authors have completed the CHEERS reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-1722/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-1722/coif). The authors report that this study was funded by Takeda (China) International Trading Company. RS and SQ are employees of IQVIA (China). YS and LD are employees of Takeda (China) International Trading Co. Ltd. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Zou D, He J, Ma X, et al. Epidemiology of symptom-defined gastroesophageal reflux disease and reflux esophagitis: the systematic investigation of gastrointestinal diseases in China (SILC). Scand J Gastroenterol 2011;46:133-41.
2. Vakil N, van Zanten SV, Kahrilas P, et al. The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. Am J Gastroenterol 2006;101:1900-20; quiz 1943.
3. Choi JM, Yang JI, Kang SJ, et al. Association Between Anxiety and Depression and Gastroesophageal Reflux Disease: Results From a Large Cross-sectional Study. J Neurogastroenterol Motil 2018;24:593-602.
4. Iwakiri K, Fujiwara Y, Manabe N, et al. Evidence-based clinical practice guidelines for gastroesophageal reflux disease 2021. J Gastroenterol 2022;57:267-85.
5. Xiao YL, Zhou LY, Hou XH, et al. Chinese expert consensus on gastroesophageal reflux disease in 2020. J Dig Dis 2021;22:376-89.
6. Katz PO, Dunbar KB, Schnoll-Sussman FH, et al. ACG Clinical Guideline for the Diagnosis and Management of Gastroesophageal Reflux Disease. Am J Gastroenterol 2022;117:27-56.
7. Chey WD, Mody R, Chen L, et al. M1033 Nighttime Symptoms and Sleep Impairment Among Patients with Gastro-Esophageal Reflux Disease (GERD) Receiving Prescription (Rx) Proton Pump Inhibitors (PPIs). Gastroenterol 2008;134.
8. Fass R, Sifrim D. Management of heartburn not responding to proton pump inhibitors. Gut 2009;58:295-309.

9. Dickman R, Maradey-Romero C, Gingold-Belfer R, et al. Unmet Needs in the Treatment of Gastroesophageal Reflux Disease. J Neurogastroenterol Motil 2015;21:309-19.
10. Matsukawa J, Inatomi N, Nishida H, et al. Pharmacological characteristics and clinical efficacies of a novel potassium-competitive acid blocker, vonoprazan fumarate. Nihon Yakurigaku Zasshi 2018;152:104-10.
11. Oshima T, Miwa H. Potent Potassium-competitive Acid Blockers: A New Era for the Treatment of Acid-related Diseases. J Neurogastroenterol Motil 2018;24:334-44.
12. Mori H, Suzuki H. Role of Acid Suppression in Acid-related Diseases: Proton Pump Inhibitor and Potassium-competitive Acid Blocker. J Neurogastroenterol Motil 2019;25:6-14.
13. Ashida K, Sakurai Y, Hori T, et al. Randomised clinical trial: vonoprazan, a novel potassium-competitive acid blocker, vs. lansoprazole for the healing of erosive oesophagitis. Aliment Pharmacol Ther 2016;43:240-51.
14. Xiao Y, Zhang S, Dai N, et al. Phase III, randomised, double-blind, multicentre study to evaluate the efficacy and safety of vonoprazan compared with lansoprazole in Asian patients with erosive oesophagitis. Gut 2020;69:224-30.
15. Habu Y. Vonoprazan versus Lansoprazole for the Initial Treatment of Reflux Esophagitis: A Cost-effectiveness Analysis in Japan. Intern Med 2019;58:2427-33.
16. Habu Y, Hamasaki R, Maruo M, et al. Treatment strategies for reflux esophagitis including a potassium-competitive acid blocker: A cost-effectiveness analysis in Japan. J Gen Fam Med 2021;22:237-45.
17. Yokoya Y, Igarashi A, Uda A, et al. Cost-utility analysis of a 'vonoprazan-first' strategy versus 'esomeprazole- or rabeprazole-first' strategy in GERD. J Gastroenterol 2019;54:1083-95.
18. Briggs A, Sculpher M. An introduction to Markov modelling for economic evaluation. Pharmacoeconomics 1998;13:397-409.
19. Heudebert GR, Marks R, Wilcox CM, et al. Choice of long-term strategy for the management of patients with severe esophagitis: a cost-utility analysis. Gastroenterology 1997;112:1078-86.
20. Habu Y, Maeda K, Kusuda T, et al. "Proton-pump inhibitor-first" strategy versus "step-up" strategy for the acute treatment of reflux esophagitis: a cost-effectiveness analysis in Japan. J Gastroenterol 2005;40:1029-35.
21. Romagnuolo J, Meier MA, Sadowski DC. Medical or surgical therapy for erosive reflux esophagitis: cost-utility analysis using a Markov model. Ann Surg 2002;236:191-202.
22. Gralnek IM, Dulai GS, Fennerty MB, et al. Esomeprazole versus other proton pump inhibitors in erosive esophagitis: a meta-analysis of randomized clinical trials. Clin Gastroenterol Hepatol 2006;4:1452-8.
23. He J, Ma X, Zhao Y, et al. A population-based survey of the epidemiology of symptom-defined gastroesophageal reflux disease: the Systematic Investigation of Gastrointestinal Diseases in China. BMC Gastroenterol 2010;10:94.
24. Xie Z, Li H. Discussion on Discount Rate in Pharmacoeconomic Evaluation for China. Chin Health Econ 2019;38:74-7.
25. Umezawa M, Kawami N, Hoshino S, et al. Efficacy of On-Demand Therapy Using 20-mg Vonoprazan for Mild Reflux Esophagitis. Digestion 2018;97:309-15.
26. Miwa H, Igarashi A, Teng L, et al. Systematic review with network meta-analysis: indirect comparison of the efficacy of vonoprazan and proton-pump inhibitors for maintenance treatment of gastroesophageal reflux disease. J Gastroenterol 2019;54:718-29.
27. Rantanen TK, Salo JA. Gastroesophageal reflux disease as a cause of death: analysis of fatal cases under conservative treatment. Scand J Gastroenterol 1999;34:229-33.
28. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 2019;366:l4898.
29. Rousseau MJ, Evans JC. Key statistical assumptions and methods in one-arm meta-analyses with binary endpoints and low event rates, including a real-life example in the area of endoscopic colonic stenting. Cogent Medicine 2017;4:1334318.
30. Sonnenberg FA, Beck JR. Markov models in medical decision making: a practical guide. Med Decis Making 1993;13:322-38.
31. National Bureau of Statistics of China. China Statistical Yearbook 2019. Available online: http://www.stats.gov.cn/tjsj/ndsj/2019/indexeh.htm
32. Wang ZH, Yan YQ, Tong TY, et al. Estimating health-state utility values in reflux esophagitis using the EQ-5D-5L. ISPOR 2020, Orlando, FL, USA. Available online: https://www.ispor.org/heor-resources/presentations-database/presentation/intl2020-3182/100960
33. Ashida K, Iwakiri K, Hiramatsu N, et al. Maintenance for healed erosive esophagitis: Phase III comparison of vonoprazan with lansoprazole. World J Gastroenterol 2018;24:1550-61.

Cite this article as: Wang Z, Sun R, Sheng Y, Qu S, Dong L, Wu B. Cost-effectiveness analysis of vonoprazan versus proton pump inhibitors in the treatment of reflux esophagitis in China. Ann Transl Med 2022;10(8):480. doi: 10.21037/atm-22-1722

Supplementary

Table S1 Literature Search Strategies in English for the SLR

#	Search Terms
1.	"erosive esophagitis[Title/Abstract] OR "erosive oesophagitis"[Title/Abstract] OR "erosive gastroesophageal reflux disease "[Title/Abstract] OR "erosive reflux esophagitis"[Title/Abstract] OR " erosive gastro-oesophageal reflux disease"[Title/Abstract] OR "erosive gastrooesophageal reflux disease"[Title/Abstract] OR "reflux oesophagitis"[Title/Abstract] OR "reflux esophagitis"[Title/Abstract] OR "EE"[Title/Abstract] OR "RE"[Title/Abstract]
2.	" proton pump inhibitors "[Title/Abstract] OR "PPI"[Title/Abstract]
3.	" potassium-competitive acid blockers"[Title/Abstract] OR " P-CAB "[Title/Abstract]
4.	" vonoprazan "[Title/Abstract]
5.	" pantoprazole"[Title/Abstract]
6.	" esomeprazole"[Title/Abstract]
7.	" lansoprazole "[Title/Abstract]
8.	" omeprazole "[Title/Abstract]
9.	" rabeprazole"[Title/Abstract]
10.	" Ilaprazole"[Title/Abstract]
11.	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10
12.	randomized controlled trial [pt]
13.	controlled clinical trial [pt]
14.	randomized [TIAB]
15.	randomised [TIAB]
16.	“random allocation” [TIAB]
17.	clinical trials as topic [mesh: noexp]
18.	randomly [TIAB]
19.	trial [ti]
20.	“double blind” OR “double blinded” OR “double masked”
21.	“single blind” OR “single blinded” OR “single masked”
22.	#12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21
23.	#1 AND #11 AND #22
24.	#23 Limits: Humans
25.	#24 Limits: Adult: 19+ Years
26.	#25 Limits: English
27.	#27 Limits: Publication Date 1995-2019

Abbreviations: SLR, systematic literature review; EE, erosive esophagitis; RE, reflux esophagitis; PPI, proton pump inhibitor; P-CAB, potassium-competitive acid blocker

https://dx.doi.org/10.21037/atm-22-1722

Table S2 PICOS criteria to assess studies for the SLR

PICOS elements	
Population	Adult patients with RE diagnosed by endoscopic examination
Interventions	• VPZ monotherapy (standard dose in acute treatment phase and low dose in maintenance phase) • Any PPI monotherapy (standard dose in acute treatment phase and low dose in maintenance phase) approved by National Medical Products Administration in China
Comparators	Any PPI monotherapy (standard dose in acute treatment phase and low dose in maintenance phase) approved by National Medical Products Administration in China
Outcomes	• Healing rate at week 4 in treatment phase • Healing rate at week 8 in treatment phase • Relapse rate at week 24 in maintenance phase
Study design	RCT

Abbreviations: SLR, systematic literature review; RE, Reflux esophagitis; PPI, proton pump inhibitors; VPZ, Vonoprazan; RCT, randomized controlled trial.

Table S3 Cost calculation for proton pump inhibitors (PPI) group drug cost

Original PPI Brand	The average tender price of each PPI in 2020 was collected from YAOZHI® database*		Market shares were collected from a panel of nationwide hospital survey (n=12); The market share of original PPIs is in 2019Q2 was used to calculate the weighted average price#
	Price of Standard Dose (CNY)	Price of Half Dose (CNY)	Market share by Prescriptions
Omeprazole (Losec)	8.71	5.06	3.6%
Esomeprazole (Nexium)	15.00	9.01	13.9%
Pantoprazole (Protonix)	9.62	4.81	4.0%
Lansoprazole (Prevacid, Takepron)	8.67	4.34	2.2%
Rabeprazole (Pariet)	20.81	10.54	11.0%
Ilaprazole	27.06	13.53	0.70%

PPI group drug cost was calculated based on average tender prices of each PPI available in China weighted by corresponding market shares. Note: *, average price of standard dose of $PPI = \frac{Price\ of\ Standard\ Dose + 2 * Price\ of\ Half\ Dose}{2}$. Each PPI has both standard dose and half dose. In clinical practice, PPI could be taken as 1 tablet with standard dose per day or 2 tablets with half dose per day. #, Market-share weighted average price of standard/half dose of $PPI\ group = \frac{\sum Price\ of\ PPI_i^j * Market\ Share\ of\ PPI_i^j}{\sum Market\ Share\ of\ PPI_i^j}$.

Table S4 Cost of other healthcare resources in a treatment course (Interview results)

Questionnaire	Answer
1 The frequency of outpatient visit and cost	• The Initiation of acute treatment needs one outpatient visit and several follow-up visits every 2 weeks for drug prescription. During 6-month maintenance treatment, the outpatient visit should be made every 4 weeks. • The average cost of an outpatient visit is 7$.
2 The frequency of lab test and cost	• Patients were required to take an endoscopy test in the first outpatient visit for diagnosis. For patients who were unhealed after 8-week treatment, esophageal manometry and 24-hour pH monitoring were needed. • The average cost of an endoscopy test is 84$. • The average cost of 24-hour pH monitoring is 116$.

Other medical expenses associate with RE treatment were collected via local clinical expert interviews (n=10). RE, reflux esophagitis.

https://dx.doi.org/10.21037/atm-22-1722

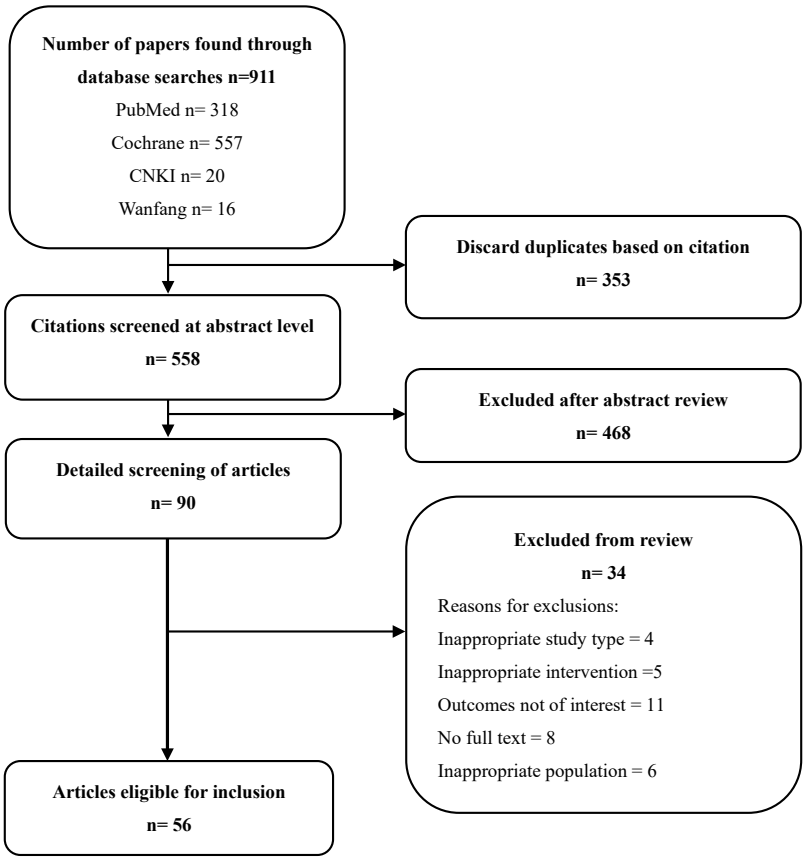

Figure S1 Flowchart of study selection.

https://dx.doi.org/10.21037/atm-22-1722

Table S5 Baseline characteristics of included trials

First author	Publication year	Study Sample (N)	Treatment	Initial duration	Diagnosis level	Evaluable population (N)	Age (year)		Male (%)
							Mean	SD	
Corinaldesi, R., *et al.* (1)	1995	241	pantoprazole40mg	8 weeks	SM 2-3	120	50	-	78 (65)
			omeprazole20mg	8 weeks	SM 2-3	121	52	-	75 (62)
MöSsner, J., *et al.* (2)	1995	286	pantoprazole40mg	8 weeks	SM 2-3	191	53	-	133 (70)
			omeprazole20mg	8 weeks	SM 2-3	95	55	-	66 (69)
Castell, D. O., *et al.* (3)	1996	1284	lansoprazole30mg	8 weeks	other 2-4	422	-	-	-
			omeprazole20mg	8 weeks	other 2-4	431	-	-	-
Mee, A. S., *et al.* (4)	1996	604	lansoprazole30mg	8 weeks	SM 1-4	300	53.4	-	198 (66)
			omeprazole20mg	8 weeks	SM 1-4	304	52.4	-	204 (67)
Dekkers, C. P., *et al.* (5)	1999	202	rabeprazole20mg	8 weeks	HD 2-4	100	54	15.7	53 (53)
			omeprazole20mg	8 weeks	HD 2-4	102	52	15.56	73 (72)
Delchier, J. C., *et al.* (6)	2000	310	rabeprazole20mg	8 weeks	HD 2-4	104	55	15.7	47 (45)
			omeprazole20mg	8 weeks	HD 2-4	103	53	15.1	40 (39)
Kahrilas, P. J., *et al.* (7)	2000	1960	esomeprazole40mg	8 weeks	LA A-D	654	44.8	13	384 (58.7)
			omeprazole20mg	8 weeks	LA A-D	650	46.5	13.5	399 (61.4)
Richter, J. E., *et al.* (8)	2000	603	pantoprazole40mg	8 weeks	HD 2-4	173	49.3	13.6	121 (69.9)
Dupas, J. L., *et al.* (9)	2001	461	pantoprazole40mg	8 weeks	SM 2-3	225	53	14.5	165 (73)
			lansoprazole30mg	8 weeks	SM 2-3	236	55	14.7	178 (58)
Richter, J. E., *et al.* (10)	2001	2425	esomeprazole40mg	8 weeks	LA A-D	1216	-	-	772 (59.4)
			omeprazole20mg	8 weeks	LA A-D	1209	-	-	760 (62.9)
Castell, D. O., *et al.* (11)	2002	5241	esomeprazole40mg	8 weeks	LA A-D	2624	47	13	1504 (57.3)
			lansoprazole30mg	8 weeks	LA A-D	2617	47.4	13.1	1501 (57.4)
Howden, C. W., *et al.* (12)	2002	284	lansoprazole30mg	8 weeks	other 2-4	143	47	-	57 (82)
			esomeprazole40mg	8 weeks	other 2-4	141	46	-	54 (76)
Körner, T., *et al.* (13)	2003	669	pantoprazole40mg	8 weeks	SM 2-3	337	53.7	14.3	216 (64)
Gillessen, A., *et al.*(14)	2004	227	pantoprazole40mg	8 weeks	LA B-C	113	53	15	64 (57)
			esomeprazole40mg	8 weeks	LA B-C	114	54	14	57 (50)
Pace, F., *et al.*(15)	2005	560	rabeprazole20mg	8 weeks	SM 1-3	283	47.7	14.2	190 (67)
			omeprazole20mg	8 weeks	SM 1-3	277	47.1	14.9	184 (66)
Fennerty, M. B., *et al.* (16)	2005	999	esomeprazole40mg	8 weeks	LA C-D	498	47.3	13.2	327 (65.7)
			lansoprazole30mg	8 weeks	LA C-D	501	47.1	12.9	333 (66.5)
Labenz, J., *et al.*(17)	2005	3151	esomeprazole40mg	8 weeks	LA A-D	1562	50.6	14	969 (62)
			pantoprazole40mg	8 weeks	LA A-D	1589	50.5	13.8	1102 (63.7)
Lightdale, C. J., *et al.*(18)	2006	1175	omeprazole20mg	8 weeks	LA A-D	588	45.3	13	376 (63.9)
Schmitt, C., *et al.*(19)	2006	1148	esomeprazole40mg	8 weeks	LA A-D	576	47.1	13.3	346 (60.1)
			omeprazole20mg	8 weeks	LA A-D	572	46.2	13.6	335 (58.6)
Vcev, A., *et al.*(20)	2006	180	esomeprazole40mg	8 weeks	LA A-C	90	51.2	14.5	57 (63.3)
			pantoprazole40mg	8 weeks	LA A-C	90	49.4	13.9	59 (65.6)
Bardhan, K.D., *et al.*(21)	2007	581	pantoprazole40mg	8 weeks	LA A-D	288	53	13	141 (49)
			esomeprazole40mg	8 weeks	LA A-D	293	54	14	154 (53)
Sharma, P., *et al.*(22)	2009	2038	lansoprazole30mg	8 weeks	LA A-D	690	47.3	13.74	365 (52.9)
Sharma,P., *et al.*(22)	2009	2054	lansoprazole30mg	8 weeks	LA A-D	673	47.3	13.65	362 (53.8)
Zheng, R.N., *et al.*(23)	2009	274	omeprazole20mg	8 weeks	LA A-D	68	57.9	14.1	33 (48.5)
			lansoprazole30mg	8 weeks	LA A-D	69	58.1	13	35 (50.7)
			pantoprazole40mg	8 weeks	LA A-D	69	57.8	13.2	34 (49.3)
			esomeprazole40mg	8 weeks	LA A-D	68	57.4	12.8	33 (48.5)
Ashida, K., *et al.*(24)	2015	733	lansoprazole30mg	8 weeks	LA A-D	140	55.8	13.92	99 (70.7)
			vonoprazan20mg	8 weeks	LA A-D	154	58.3	13.86	115 (74.7)
Ashida, K., et al(25)	2016	409	vonoprazan20mg	8 weeks	LA A-D	207	58.3	13.8	137 (66.2)
			lansoprazole30mg	8 weeks	LA A-D	202	57.4	13.2	154 (76.2)
Chen, M.H., et al(26)	2018	274	vonoprazan20mg	8 weeks	LA A-D	143	51.8	13.7	105 (73.4)
			lansoprazole30mg	8 weeks	LA A-D	131	51.5	12.5	110 (82.7)
Bardhan, K. D. et al(27)	1995	239	lansoprazole30mg	8 weeks	Endoscopic appearance 0-3	77	48	-	50 (65)
Mulder, C. J. et al(28)	1996	211	lansoprazole30mg	8 weeks	SM 2-4	106	54.4	14.3	73 (70)
Rensburg, C.V., et al (29)	1996	192	pantoprazole40mg	8 weeks	SM 1-4	97	46	-	57 (59)
Jansen, J.B., et al(30)	1999	133	lansoprazole30mg	8 weeks	SM 2-3	68	53.7	14.8	42 (61)
Festen, H. P., et al(31)	1999	446	omeprazole20mg	8 weeks	SM 1-2	222	51.1	14.5	118 (53)
Farley, A., et al(32)	2000	338	rabeprazole20mg	8 weeks	HD 0-5	167	51.4	14.9	118 (70)
Kovacs, T. O. G., et al(33)	2002	221	pantoprazole40mg	8 weeks	HD 0-5	76	49.4	13.8	52 (68)
Kawano, S., et al(34)	2002	47	omeprazole20mg	8 weeks	LA A-D	-	56	18	14 (58)
Meneghelli, U. G., et al(35)	2002	256	pantoprazole40mg	8 weeks	SM 2-3	128	46.5	-	80 (63)
Cho, Y. K., et al(36)	2012	129	pantoprazole40mg	8 weeks	LA A-C	74	50	13	61 (82)
Song, F., *et al.*(37)	2012	180	Ilaprazole10mg	8 weeks	LA A-D	60	-	-	-
			esomeprazole40mg			60			
Xue, Y., *et al.*(38)	2016	318	Ilaprazole10mg	8 weeks	LA A-D	107	48.9	12.6	75 (70)
			esomeprazole40mg			105	47.9	11.7	72 (69)
Ashida, K., *et al.*(39)	2018	607	Lansoprazole15mg	24 W	LA A-D	196	57.8	12.9	69.70%
			Vonoprazan10mg			197	55.2	13.8	79.20%
Bate, C. M., *et al.*(40)	1995	193	Omeprazole10mg	52 W	LA A-D	60	53	-	44%
DeVault, K.R., *et al.*(41)	2006	1026	Esomeprazole20mg	24 W	LA A-D	501	47.5	-	59.30%
			Lansoprazole15mg			500	47.9	-	58.60%
Robinson,M., *et al.*(42)	1996	115	Lansoprazole15mg	52W	LA A-D	59	-	-	-
Labenz, J., *et al.*(43)	2005	3170	Esomeprazole20mg	24W	LA A-D	1377	50.2	14.1	64.50%
			Pantoprazole20mg			1389	50.7	13.8	61.60%
Lauritsen, K., *et al.*(44)	2003	1224	Esomeprazole20mg	24W	LA A-D	615	49.3	-	63.10%
			Lansoprazole15mg			609	49.2	-	58.50%
Richter, J. E., *et al.*(45)	2004	176	Pantopraole20mg	52W	LA A-D	88	48.99	13.35	69.30%
Vakil, N. B., *et al.*(46)	2001	281	Esomeprazole20mg	24W	LA A-D	98	45.2	12.8	59.00%
Metz, D.C., *et al.*(47)	2003	274	Pantoprazole20mg	52W	Grade 2-5	91	49.19	13.39	61.30%
Gough, A. L., *et al.*(48)	1996	185	Lansoprazole15mg	52W	-	96	57.8	-	68.80%
Kovacs,T.O., *et al.*(49)	2009	100	Lansoprazole15mg	52W	HD 0-4	100	49.6	13.4	72%
Escourrou, J., et al(50)	1999	396	Pantoprazole20mg	52W	Grade 2-3	203	50	-	72%
Plein, K., *et al.*(51)	2000	433	Pantoprazole20mg	52W	Grade 2-3	221	-	-	-
Johnson, D.A., *et al.*(52)	2001	82	Esomeprazole20mg	52W	-	82	-	-	-
Goh, K.L., *et al.*(53)	2007	1303	Pantoprazole20mg	24W	-	636	49	14.1	58.60%
			Esomeprazole20mg			667	48.8	14.5	85%
Caos, A., *et al.*(54)	2005	70	Rabeprazole10mg	24W	HD 0-2	70	-	-	-
Birbara, C., *et al.*(55)	2000	95	Rabeprazole10mg	24W	-	95	-	-	-
Bardhan, K.D., *et al.*(56)	1998	130	Omeprazole10mg	24W	-	130	-	-	-

Abbreviations: SD, standard deviation; LA, Los Angeles grade ; HD, Hetzel–Dent scale ; SM, Savary–Miller scale

https://dx.doi.org/10.21037/atm-22-1722

Table S6 Main outcomes of included trials for treatment studies

First author	Publication Year	Study Sample (N)	Treatment (n)	Evaluable population (All), N	All patients Healing rates at week 4	All patients Healing rates at week 8	Evaluable population (Moderate-severe), N	Moderate-severe patients Healing rate at week 4	Moderate-severe patients Healing rate at week 8
Corinaldesi, R., *et al.* (1)	1995	241	pantoprazole 40 mg	120	81/120	97/120	/	/	/
			omeprazole 20 mg	121	83/121	96/121	/	/	/
MöSsner, J., *et al.* (2)	1995	286	pantoprazole 40 mg	191	126/191	153/191	/	/	/
			omeprazole 20 mg	95	67/95	81/95	/	/	/
Castell, D. O., *et al.* (3)	1996	1284	lansoprazole 30 mg	422	352/422	380/422	/	/	/
			omeprazole 20 mg	431	353/431	391/431	/	/	/
Mee, A. S., *et al.* (4)	1996	604	lansoprazole 30 mg	300	186/300	226/300	40	18/40	26/40
			omeprazole 20 mg	304	172/304	216/304	42	24/42	25/42
Dekkers, C. P., *et al.* (5)	1999	202	rabeprazole 20 mg	100	81/100	92/100	/	/	/
			omeprazole 20 mg	102	83/102	96/102	/	/	/
Delchier, J. C., *et al.* (6)	2000	310	rabeprazole 20 mg	104	92/104	95/104	/	/	/
			omeprazole 20 mg	103	94/103	97/103	/	/	/
Kahrilas, P. J., *et al.* (7)	2000	1960	esomeprazole 40 mg	654	496/654	615/654	/	/	/
			omeprazole 20 mg	650	411/650	565/650	/	/	/
Richter, J. E. *et al.* (8)	2000	603	pantoprazole 40 mg	173	125/173	152/173	/	/	/
Dupas, J. L., *et al.* (9)	2001	461	pantoprazole 40 mg	225	184/225	203/225	/	/	/
			lansoprazole 30 mg	236	189/236	201/236	/	/	/
Richter, J. E., *et al.* (10)	2001	2425	esomeprazole 40 mg	1216	993/1216	1139/1216	/	/	/
			omeprazole 20 mg	1209	831/1209	1018/1209	/	/	/
Castell, D. O., *et al.* (11)	2002	5241	esomeprazole 40 mg	2624	2083/2624	2430/2624	/	/	/
			lansoprazole 30 mg	2617	1965/2617	2324/2617	/	/	/
Howden, C. W., *et al.* (12)	2002	284	lansoprazole 30 mg	143	107/143	127/143	52	/	48/52
			esomeprazole 40 mg	141	108/141	123/141	57	/57	47/57
Körner, T., *et al.* (13)	2003	669	pantoprazole 40 mg	337	220/337	284/337	/	/	/
Gillessen, A., *et al.*(14)	2004	227	pantoprazole 40 mg	113	55/113	94/113	/	/	/
			esomeprazole 40 mg	114	68/114	92/114	/	/	/
Pace, F., *et al.*(15)	2005	560	rabeprazole 20 mg	283	212/283	228/283	/	/	/
			omeprazole 20 mg	277	213/277	231/277	/	/	/
Fennerty, M. B., *et al.* (16)	2005	999	esomeprazole 40 mg	498	278/498	386/498	498	278/498	386/498
			lansoprazole 30 mg	501	/	/	501	238/501	367/501
Labenz, J., *et al.*(17)	2005	3151	esomeprazole 40 mg	1562	1231/1562	1493/1562	374	259/374	340/374
			pantoprazole 40 mg	1589	1157/1589	1463/1589	395	219/395	333/395
Lightdale, C. J., *et al.*(18)	2006	1175	omeprazole 20 mg	588	/	484/588	154	/154	110/154
Schmitt, C., *et al.*(19)	2006	1148	esomeprazole 40 mg	576	393/576	501/576	189	115/189	167/189
			omeprazole 20 mg	572	379/572	491/572	169	81/169	131/169
Vcev, A., *et al.*(20)	2006	180	esomeprazole 40 mg	90	70/90	83/90	13	8/13	10/13
			pantoprazole 40 mg	90	65/90	82/90	16	8/16	12/16
Bardhan, K.D., *et al.*(21)	2007	581	pantoprazole 40 mg	288	199/288	248/288	/	/	/
			esomeprazole 40 mg	293	202/293	243/293	/	/	/
Sharma, P., *et al.*(22)	2009	2038	lansoprazole 30 mg	690	/	518/690	210	/210	130/210
Sharma, P., *et al.*(22)	2009	2054	lansoprazole 30 mg	673	/	548/673	194	/194	150/194
Zheng, R.N., *et al.*(23)	2009	274	omeprazole 20 mg	68	/	57/68	/	/	/
			lansoprazole 30 mg	69	/	60/69	/	/	/
			pantoprazole 40 mg	69	/	61/69	/	/	/
			esomeprazole 40 mg	68	/	62/68	/	/	/
Ashida, K., *et al.*(24)	2015	733	lansoprazole 30 mg	140	123/140	126/140	47	40/47	43/47
			vonoprazan20 mg	154	136/154	139/154	51	50/51	50/51
Ashida, K., et al(25)	2016	409	vonoprazan20 mg	207	198/207	203/207	75	72/75	74/75
			lansoprazole 30 mg	202	184/202	190/202	73	58/73	63/73
Chen, M.H., et al(26)	2018	274	vonoprazan20 mg	143	120/143	131/143	54	38/54	45/54
			lansoprazole 30 mg	131	109/131	116/131	46	32/46	36/46
Bardhan, K. D., et al(27)	1995	239	lansoprazole 30 mg	77	63/77	70/77	58	45/58	51/58
Mulder, C. J., et al(28)	1996	211	lansoprazole 30 mg	106	91/106	99/106	29	24/29	27/29
Rensburg, C.V., et al (29)	1996	192	pantoprazole 40 mg	97	67/97	82/97	/	/	/
Jansen, J.B., et al(30)	1999	133	lansoprazole 30 mg	68	54/68	62/68	/	/	/
Festen, H. P., et al(31)	1999	446	omeprazole 20 mg	222	135/222	165/222	/	/	/
Farley, A., et al (32)	2000	338	rabeprazole 20 mg	167	98/167	146/167	/	/	/
Kovacs, T. O. G., et al(33)	2002	221	pantoprazole 40 mg	76	48/76	58/76	30	11/30	16/30
Kawano, S., et al(34)	2002	47	omeprazole 20 mg	/	/	/	7	/	4/7
Meneghelli, U. G., et al(35)	2002	256	pantoprazole 40 mg	128	69/128	96/128	24	12/24	17/24
Cho, Y. K., et al(36)	2012	129	pantoprazole 40 mg	74	52/74	60/74	/	/	/
Song, F., *et al.*(37)	2012	180	Ilaprazole 10 mg	60	51/60	54/60	/	/	/
			esomeprazole 40 mg	60	52/60	55/60	/	/	/
Xue, Y., *et al.*(38)	2016	318	Ilaprazole 10 mg	107	87/107	95/107	/	/	/
			esomeprazole 40 mg	105	75/105	89/105	/	/	/

https://dx.doi.org/10.21037/atm-22-1722

Table S7 Main outcomes of included trials for maintenance studies

First author	Publication year	Study Sample (N)	Treatment (n)	Evaluable population (All), N	All patients Remission rate* at week 24	Evaluable population (Moderate-severe), N	Moderate-severe patients Remission rate* at week 24
Ashida, K., *et al.*(39)	2018	607	Lansoprazole 15 mg	196	172/196	41	25/41
			Vonoprazan 10 mg	197	192/197	40	33/38
Bate, C. M., *et al.*(40)	1995	193	Omeprazole 10 mg	60	/	/	/
DeVault, K.R., *et al.*(41)	2006	1026	Esomeprazole 20 mg	501	432/501	121	96/121
			Lansoprazole 15 mg	500	388/500	131	91/131
Robinson,M., *et al.*(42)	1996	115	Lansoprazole 15 mg	59	48/59		
Labenz, J., *et al.*(43)	2005	3170	Esomeprazole 20 mg	1377	1198/1377	323	263/323
			Pantoprazole 20 mg	1389	1040/1389	317	208/317
Lauritsen, K., *et al.*(44)	2003	1224	Esomeprazole 20 mg	615	510/615	114	86/114
			Lansoprazole 15 mg	609	451/609	102	60/102
Richter, J. E., *et al.*(45)	2004	176	Pantopraole 20 mg	88	/	/	/
Vakil, N. B., *et al.*(46)	2001	281	Esomeprazole 20 mg	98	77/98	/	/
Metz, D.C., *et al.*(47)	2003	274	Pantoprazole 20 mg	91	/	23	16/23
Gough, A. L., *et al.*(48)	1996	185	Lansoprazole 15 mg	96	78/96	/	/
Kovacs,T.O., *et al.*(49)	2009	100	Lansoprazole 15 mg	100	/	/	/
Escourrou, J., et al(50)	1999	396	Pantoprazole 20 mg	203	171/203	/	/
Plein, K., *et al.*(51)	2000	433	Pantoprazole 20 mg	221	177/221	/	/
Johnson, D.A., *et al.*(52)	2001	82	Esomeprazole 20 mg	82	76/82	/	/
Goh, K.L., *et al.*(53)	2007	1303	Pantoprazole 20 mg	636	534/636	/	/
			Esomeprazole 20 mg	667	567/667	/	/
Caos, A., *et al.*(54)	2005	70	Rabeprazole 10 mg	70	54/70	/	/
Birbara, C., *et al.*(55)	2000	95	Rabeprazole 10 mg	95	81/95	/	/
Bardhan, K.D., *et al.*(56)	1998	130	Omeprazole 10 mg	130	107/130	/	/

*Remission rate is the proportion of patients who remained healed during the 6 months. This is the widely reported endpoint in majority clinical trials' *Relapse rate = 1 – remission rate

https://dx.doi.org/10.21037/atm-22-1722

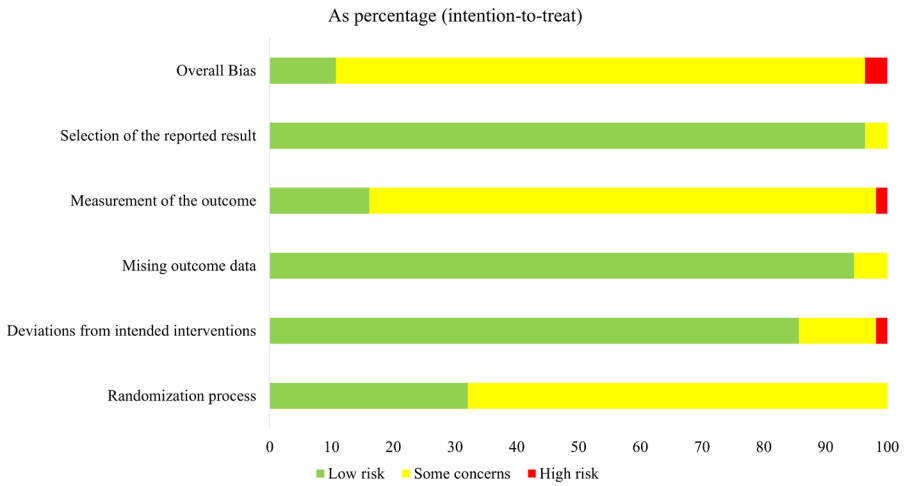

Figure S2 Risk of bias assessment for included clinical trials: overall judgements at each level per domain.

https://dx.doi.org/10.21037/atm-22-1722

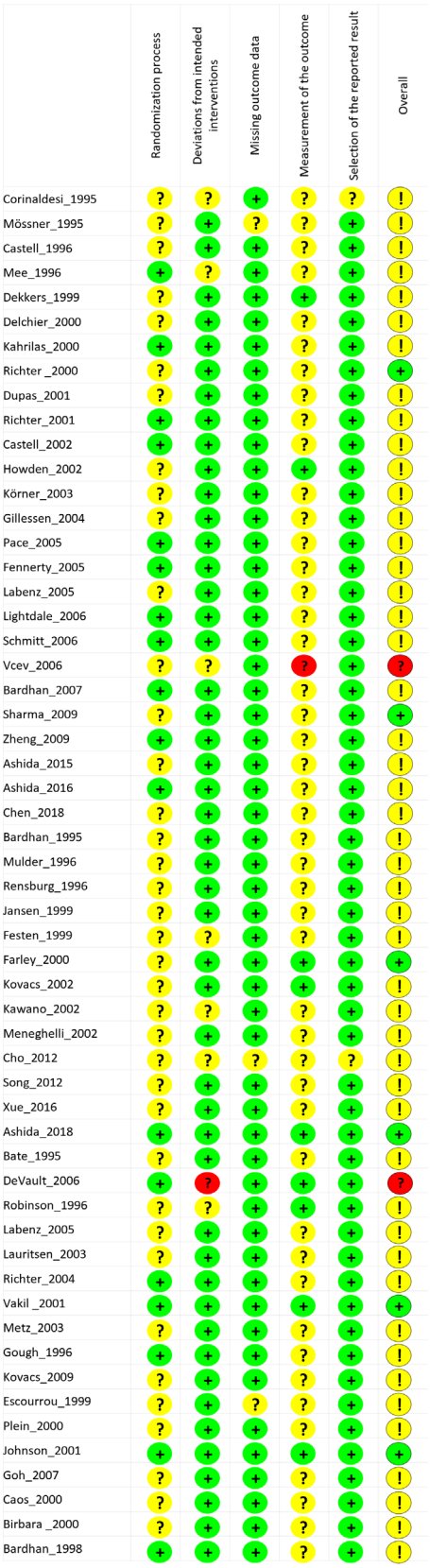

Figure S3 Risk of bias assessment for included clinical trials: judgements at each level per domain, study-by-study.

https://dx.doi.org/10.21037/atm-22-1722

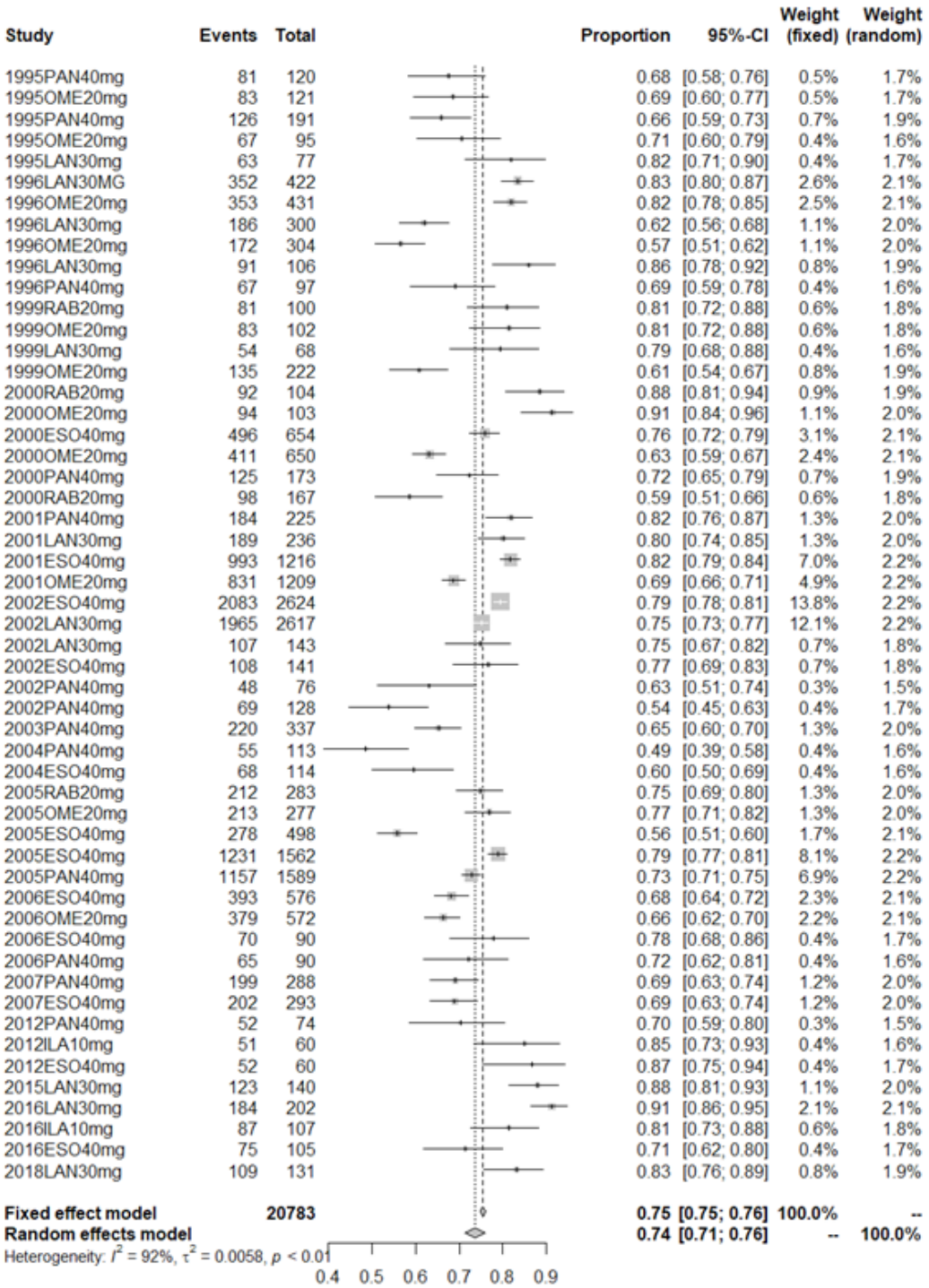

Figure S4 Meta-analysis results – Healing rate of PPI group at week 4 for all patients.

https://dx.doi.org/10.21037/atm-22-1722

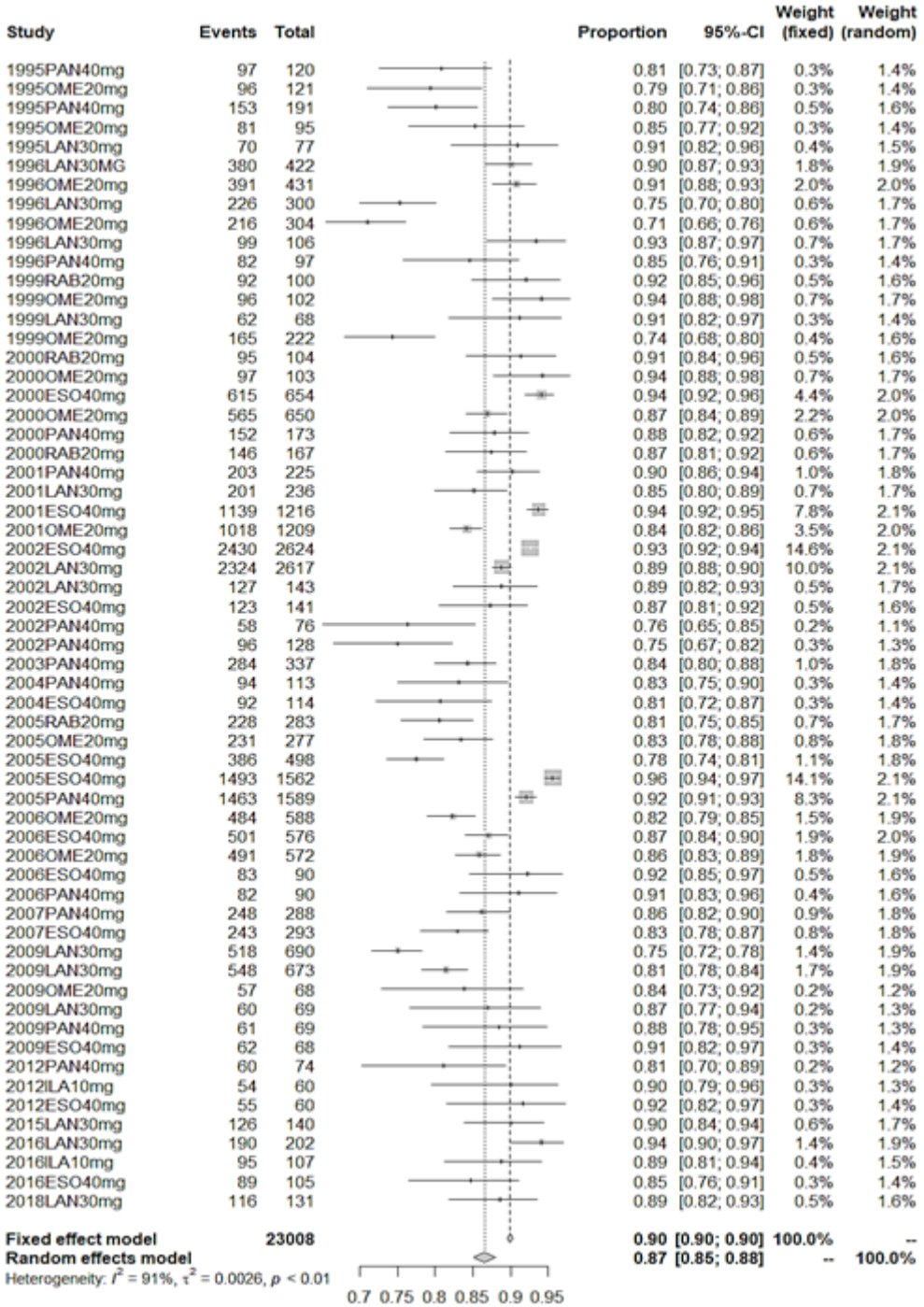

Figure S5 Meta-analysis results – Healing rate of PPI group at week 8 for all patients.

https://dx.doi.org/10.21037/atm-22-1722

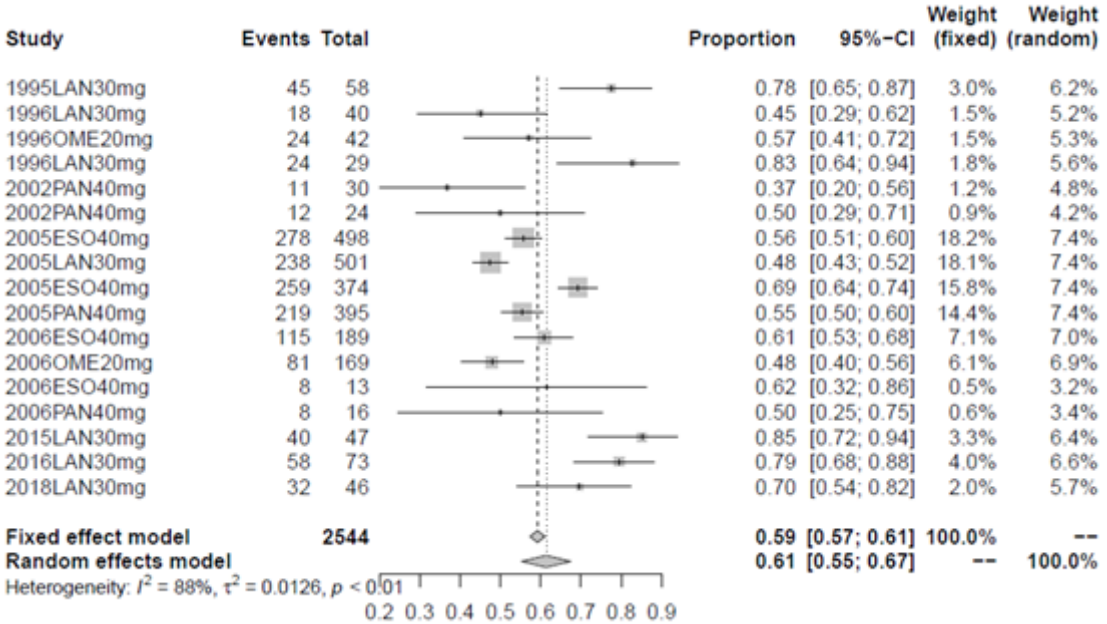

Figure S6 Meta-analysis results – Healing rate of PPI group at week 4 for moderate-to-severe patients.

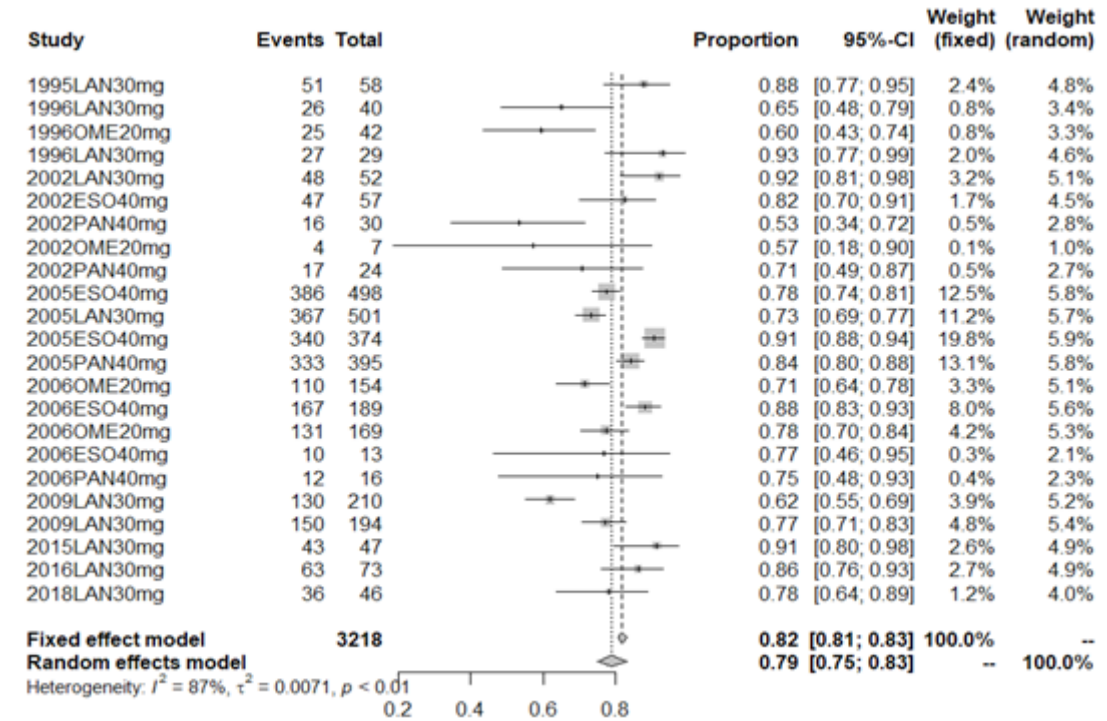

Figure S7 Meta-analysis results – Healing rate of PPI group at week 8 for moderate-to-severe patients.

https://dx.doi.org/10.21037/atm-22-1722

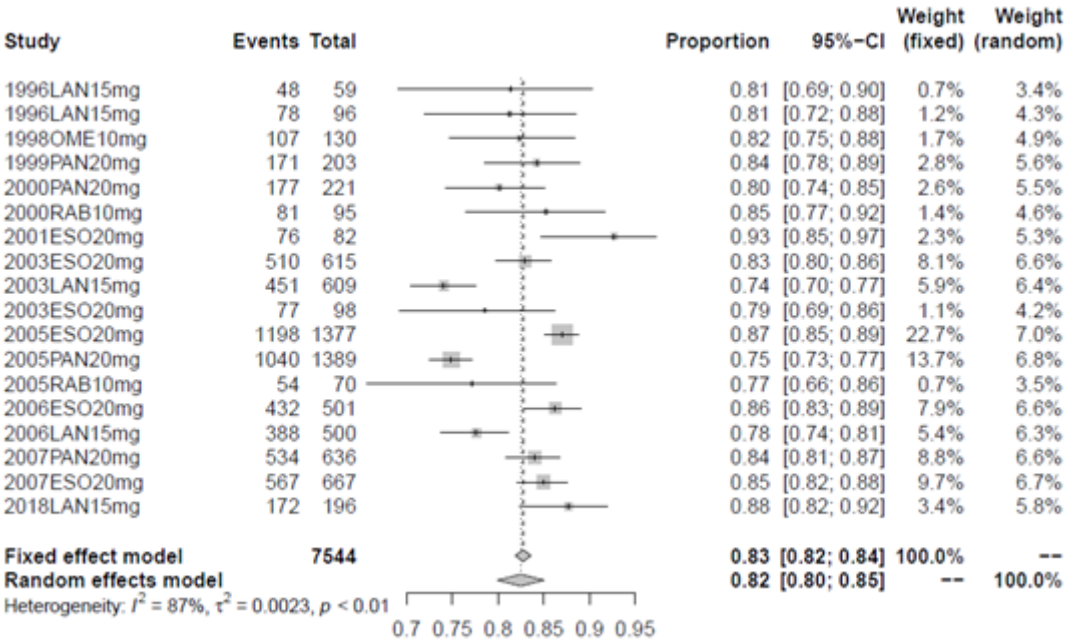

Figure S8 Meta-analysis results – Remission rate of PPI group at week 24 for all patients.

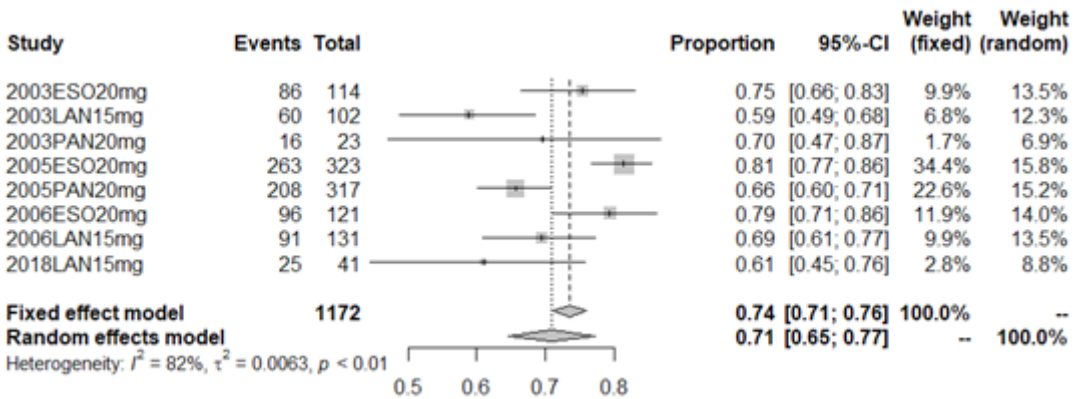

Figure S9 Meta-analysis results – Remission rate of PPI group at week 24 for moderate-to-severe patients.

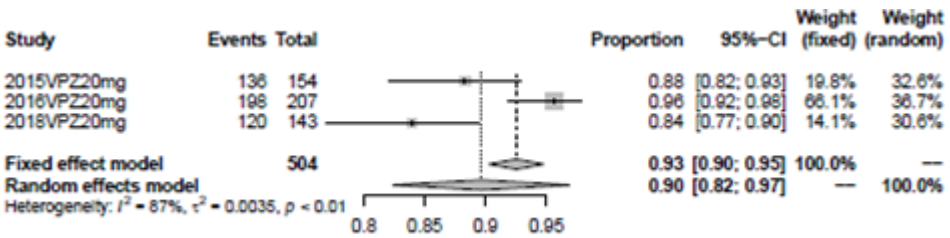

Figure S10 Meta-analysis results - Healing rate of VPZ at week 4 for all RE patients.

https://dx.doi.org/10.21037/atm-22-1722

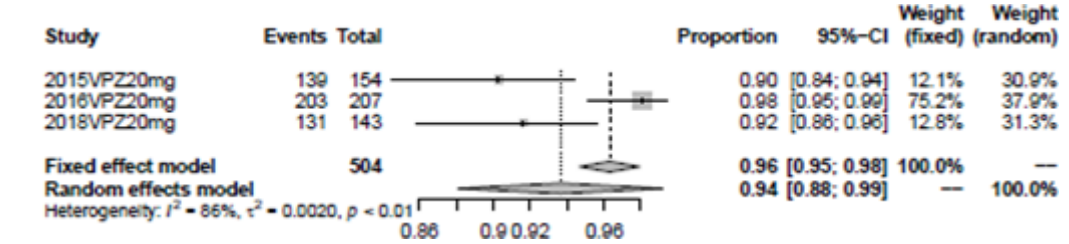

Figure S11 Meta-analysis results - Healing rate of VPZ at week 8 for all RE patients.

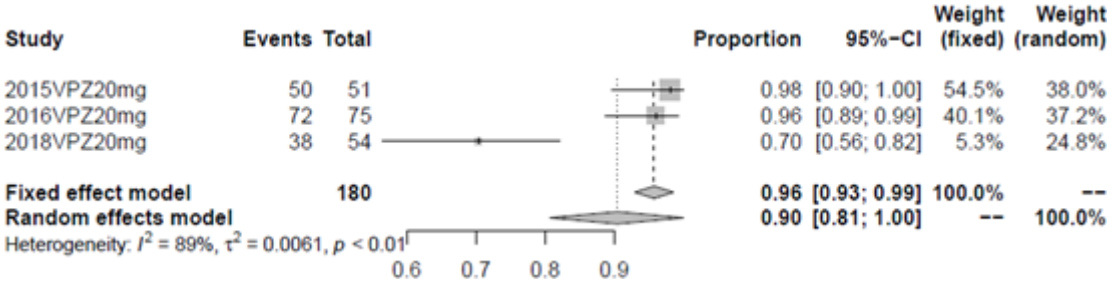

Figure S12 Meta-analysis results - Healing rate of VPZ at week 4 for moderate-to-severe patients.

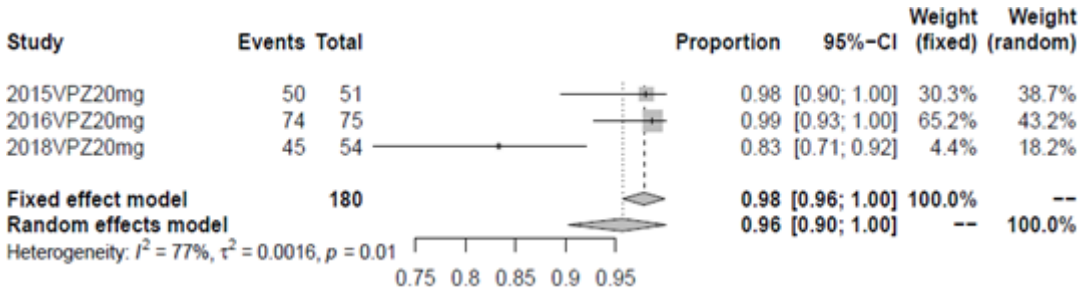

Figure S13 Meta-analysis results - Healing rate of VPZ at week 8 for moderate-to-severe patients.

https://dx.doi.org/10.21037/atm-22-1722

References

1. Corinaldesi R, Valentini M, Belaïche J, et al. Pantoprazole and omeprazole in the treatment of reflux oesophagitis: a European multicentre study. Aliment Pharmacol Ther. 1995 Dec;9(6):667-671.
2. Mössner J, Hölscher AH, Herz R, et al. A double-blind study of pantoprazole and omeprazole in the treatment of reflux oesophagitis: a multicentre trial. Aliment Pharmacol Ther. 1995 Jun;9(3):321-6.
3. Castell DO, Richter JE, Robinson M, et al. Efficacy and safety of lansoprazole in the treatment of erosive reflux esophagitis. The Lansoprazole Group. Am J Gastroenterol. 1996 Sep;91(9):1749–57.
4. Mee AS, Rowley JL, THE LANSOPRAZOLE CLINICAL RESEARCH GROUP. Rapid symptom relief in reflux oesophagitis: a comparison of lansoprazole and omeprazole. Aliment Pharmacol Ther. 1996 Oct;10(5):757–63.
5. Dekkers CP, Beker JA, Thjodleifsson B, et al. Double-blind, placebo-controlled comparison of rabeprazole 20 mg vs. omeprazole 20 mg in the treatment of erosive or ulcerative gastro-oesophageal reflux disease. Aliment Pharmacol Ther. 1999 Jan;13(1):49–57.
6. Delchier JC, Cohen G, Humphries TJ. Rabeprazole, 20 mg once daily or 10 mg twice daily, is equivalent to omeprazole, 20 mg once daily, in the healing of erosive gastrooesophageal reflux disease. Scand J Gastroenterol. 2000 Dec;35(12):1245–50.
7. Kahrilas PJ, Falk GW, Johnson DA, et al. Esomeprazole improves healing and symptom resolution as compared with omeprazole in reflux oesophagitis patients: a randomized controlled trial. Aliment Pharmacol Ther. 2000 Oct;14(10):1249–58.
8. Richter JE. Oral Pantoprazole for Erosive Esophagitis: A Placebo-Controlled, Randomized Clinical Trial. 2000;95(11):10.
9. Dupas JL, Houcke P, Samoyeau R. Pantoprazole versus lansoprazole in French patients with reflux esophagitis. Gastroenterol Clin Biol. 2001 Mar;25(3):245-50.
10. Richter JE, Breiter JR, Levine JG. Efficacy and Safety of Esomeprazole Compared With Omeprazole in GERD Patients With Erosive Esophagitis: A Randomized Controlled Trial. 2001;96(3):10.
11. Castell DO, Johnson DA. Esomeprazole (40 mg) Compared With Lansoprazole (30 mg) in the Treatment of Erosive Esophagitis. 2002;97(3):9.
12. Howden CW, Ballard ED, Robieson W. Evidence for Therapeutic Equivalence of Lansoprazole 30mg and Esomeprazole 40mg in the Treatment of Erosive Oesophagitis: Clin Drug Investig. 2002;22(2):99–109.
13. Körner T, Schütze K, van Leendert RJM, et al. Comparable Efficacy of Pantoprazole and Omeprazole in Patients with Moderate to Severe Reflux Esophagitis. Digestion. 2003;67(1–2):6–13.
14. Gillessen A, Beil W, Modlin IM, et al. 40 mg Pantoprazole and 40 mg Esomeprazole Are Equivalent in the Healing of Esophageal Lesions and Relief from Gastroesophageal Reflux Disease–related Symptoms. J Clin Gastroenterol. 2004 Apr;38(4):332–40.
15. Pace F, Annese V, Prada A, et al. Rabeprazole is equivalent to omeprazole in the treatment of erosive gastro-oesophageal reflux disease. Dig Liver Dis. 2005 Oct;37(10):741–50.
16. Fennerty MB, Johanson JF, Hwang C, et al. Efficacy of esomeprazole 40 mg vs. lansoprazole 30 mg for healing moderate to severe erosive oesophagitis. Aliment Pharmacol Ther. 2005 Feb;21(4):455–63.
17. Labenz J, Armstrong D, Lauritsen K, et al. A randomized comparative study of esomeprazole 40 mg versus pantoprazole 40 mg for healing erosive oesophagitis: the EXPO study. Aliment Pharmacol Ther. 2005 Mar 15;21(6):739–46.
18. Lightdale CJ, Schmitt C, Hwang C, et al. A Multicenter, Randomized, Double-Blind, 8-Week Comparative Trial of Low-Dose Esomeprazole (20 mg) and Standard-Dose Omeprazole (20 mg) in Patients with Erosive Esophagitis. Dig Dis Sci. 2006 May;51(5):852–7.
19. Schmitt C, Lightdale CJ, Hwang C, et al. A Multicenter, Randomized, Double-Blind, 8-Week Comparative Trial of Standard Doses of Esomeprazole (40 mg) and Omeprazole (20 mg) for the Treatment of Erosive Esophagitis. Dig Dis Sci. 2006 May;51(5):844–50.
20. Vcev A, Begić I, Ostojić R, et al. Esomeprazole versus pantoprazole for healing erosive oesophagitis. Coll Antropol. 2006 Sep;30(3):519-22.
21. Bardhan KD, Achim A, Riddermann T, et al. A clinical trial comparing pantoprazole and esomeprazole to explore the concept of achieving 'complete remission' in gastro-oesophageal reflux disease: ACHIEVING 'COMPLETE REMISSION' IN GASTRO-OESOPHAGEAL REFLUX DISEASE. Aliment Pharmacol Ther. 2007 Apr 9;25(12):1461–9.
22. Sharma P, Shaheen NJ, Perez MC, et al. Clinical trials: healing of erosive oesophagitis with dexlansoprazole MR, a proton pump inhibitor with a novel dual delayed-release

https://dx.doi.org/10.21037/atm-22-1722

formulation - results from two randomized controlled studies. Aliment Pharmacol Ther. 2009 Apr;29(7):731–41.
23. Zheng RN. Comparative study of omeprazole, lansoprazole, pantoprazole and esomeprazole for symptom relief in patients with reflux esophagitis. World J Gastroenterol WJG. 2009 Feb 28;15(8):990–5.
24. Ashida K, Sakurai Y, Nishimura A, et al. Randomised clinical trial: a dose-ranging study of vonoprazan, a novel potassium-competitive acid blocker, vs. lansoprazole for the treatment of erosive oesophagitis. Aliment Pharmacol Ther. 2015 Sep;42(6):685–95.
25. Ashida K, Sakurai Y, Hori T, et al. Randomised clinical trial: vonoprazan, a novel potassium-competitive acid blocker, vs. lansoprazole for the healing of erosive oesophagitis. Aliment Pharmacol Ther. 2016 Jan;43(2):240–51.
26. Chen MH, Dai N, Fei GJ, et al. A Phase 3, Randomized, Double-Blind, Multicenter Study to Evaluate the Efficacy and Safety of Vonoprazan 20 mg Once Daily Compared to Lansoprazole 30 mg Once Daily in Patients with Erosive Esophagitis: Results from a Chinese Cohort. 2018 United European Gastroenterology Week, October 20-24, Vienna, Austria. P1154.
27. Bardhan KD, Hawkey CJ, Long RG, et al. Lansoprazole versus ranitidine for the treatment of reflux oesophagitis. UK Lansoprazole Clinical Research Group. Aliment Pharmacol Ther. 1995 Apr;9(2):145–51.
28. Mulder CJ, Dekker W, Gerretsen M. Lansoprazole 30 mg versus omeprazole 40 mg in the treatment of reflux oesophagitis grade II, III and IVa (a Dutch multicentre trial). Dutch Study Group. Eur J Gastroenterol Hepatol. 1996 Nov 1;8(11):1101–6.
29. Rensburg CV, Honiball PJ, Grundling HD, et al. Efficacy and tolerability of pantoprazole 40 mg versus 80 mg in patients with reflux oesophagitis. Aliment Pharmacol Ther. 1996;10(3):397–401.
30. Jansen JB, Van Oene JC. Standard-dose lansoprazole is more effective than high-dose ranitidine in achieving endoscopic healing and symptom relief in patients with moderately severe reflux oesophagitis. The Dutch Lansoprazole Study Group. Aliment Pharmacol Ther. 1999 Dec;13(12):1611–20.
31. Festen HP, Schenk E, Tan G, et al. Omeprazole versus high-dose ranitidine in mild gastroesophageal reflux disease: short- and long-term treatment. The Dutch Reflux Study Group. Am J Gastroenterol. 1999 Apr;94(4):931–6.
32. 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 Aug;95(8):1894–9.
33. Kovacs TOG, Wilcox CM, Devault K, et al. Comparison of the efficacy of pantoprazole vs. nizatidine in the treatment of erosive oesophagitis: a randomized, active-controlled, double-blind study. Aliment Pharmacol Ther. 2002;16(12):2043–52.
34. Kawano S, Murata H, Tsuji S, et al. Randomized comparative study of omeprazole and famotidine in reflux esophagitis. J Gastroenterol Hepatol. 2002;17(9):955–9.
35. Meneghelli UG, Boaventura S, Moraes-Filho JPP, et al. Efficacy and tolerability of pantoprazole versus ranitidine in the treatment of reflux esophagitis and the influence of Helicobacter pylori infection on healing rate. Dis Esophagus Off J Int Soc Dis Esophagus. 2002;
36. Cho YK, Choi M-G, Bak Y-T, et al. Efficacy of S-Pantoprazole 20 mg Compared with Pantoprazole 40 mg in the Treatment of Reflux Esophagitis: A Randomized, Double-Blind Comparative Trial. Dig Dis Sci. 2012 Dec 1;57(12):3189–94.
37. Song F, He H, Shen L, et al. Efficacy and Safety of ilaprazole in the treatment of 180 patients with reflux esophagitis. Chin J New Drugs. 2012(21(8):905–7.
38. Xue Y, Qin X, Zhou L, et al. A Randomized, Double-blind, Active-Controlled, Multi-center Study of Ilaprazole in the Treatment of Reflux Esophagitis. Clin Drug Investig. 2016 Dec;36(12):985–92.
39. Ashida K, Iwakiri K, Hiramatsu N, et al. Maintenance for healed erosive esophagitis: Phase III comparison of vonoprazan with lansoprazole. World J Gastroenterol. 2018 Apr 14;24(14):1550–61.
40. Bate CM, Booth SN, Crowe JP, et al. Omeprazole 10 mg or 20 mg once daily in the prevention of recurrence of reflux oesophagitis. Solo Investigator Group. Gut. 1995 Apr;36(4):492-8.
41. DeVault KR, Johanson JF, Johnson DA, et al. Maintenance of Healed Erosive Esophagitis: A Randomized Six-Month Comparison of Esomeprazole Twenty Milligrams With Lansoprazole Fifteen Milligrams. Clin Gastroenterol Hepatol. 2006 Jul;4(7):852–9.
42. Robinson M, Lanza F, Avner D, et al. Effective maintenance treatment of reflux esophagitis with low-dose lansoprazole. A randomized, double-blind, placebo-controlled trial. Ann Intern Med. 1996 May 15;124(10):859–67.
43. Labenz J, Armstrong D, Lauritsen K, et al. Esomeprazole 20 mg vs. pantoprazole 20 mg for maintenance therapy

 https://dx.doi.org/10.21037/atm-22-1722

of healed erosive oesophagitis: results from the EXPO study1. Aliment Pharmacol Ther. 2005 Nov;22(9):803–11.
44. Lauritsen K, Deviere J, Bigard M-A, et al. Esomeprazole 20 mg and lansoprazole 15 mg in maintaining healed reflux oesophagitis: Metropole study results. Aliment Pharmacol Ther. 2003 Feb;17(3):333–41.
45. Richter JE, Fraga P, Mack M, et al. Prevention of erosive oesophagitis relapse with pantoprazole. Aliment Pharmacol Ther. 2004 Sep 1;20(5):567–75.
46. Vakil NB, Shaker R, Johnson DA, et al. The new proton pump inhibitor esomeprazole is effective as a maintenance therapy in GERD patients with healed erosive oesophagitis: a 6-month, randomized, double-blind, placebo-controlled study of efficacy and safety. Aliment Pharmacol Ther. 2001 Jul;15(7):927–35.
47. Metz DC, Bochenek WJ. Pantoprazole maintenance therapy prevents relapse of erosive oesophagitis. Aliment Pharmacol Ther. 2003;17(1):155–64.
48. Gough AL, Long RG, Cooper BT, et al. Lansoprazole versus ranitidine in the maintenance treatment of reflux oesophagitis. Aliment Pharmacol Ther. 1996;10(4):529–39.
49. Kovacs TO, Freston JW, Haber MM, et al. Long-Term Efficacy of Lansoprazole in Preventing Relapse of Erosive Reflux Esophagitis. Dig Dis Sci. 2009 Mar 7;54(8):1693.
50. Escourrou J, Deprez P, Saggioro A, et al. Maintenance therapy with pantoprazole 20 mg prevents relapse of reflux oesophagitis. Aliment Pharmacol Ther. 1999 Nov;13(11):1481–91.
51. Plein K, Hotz J, Wurzer H, et al. Pantoprazole 20 mg is an effective maintenance therapy for patients with gastro-oesophageal reflux disease. Eur J Gastroenterol Hepatol. 2000 Apr;12(4):425–32.
52. Johnson DA, Benjamin SB, Vakil NB, et al. Esomeprazole once daily for 6 months is effective therapy for maintaining healed erosive esophagitis and for controlling gastroesophageal reflux disease symptoms: a randomized, double-blind, placebo-controlled study of efficacy and safety. Am J Gastroenterol. 2001 Jan;96(1):27–34.
53. Goh K-L, Benamouzig R, Sander P, et al. Efficacy of pantoprazole 20mg daily compared with esomeprazole 20???mg daily in the maintenance of healed gastroesophageal reflux disease: a randomized, double-blind comparative trial –the EMANCIPATE study: Eur J Gastroenterol Hepatol. 2007 Mar;19(3):205–11.
54. Caos A, Moskovitz M, Dayal Y, et al. Rabeprazole for the prevention of pathologic and symptomatic relapse of erosive or ulcerative gastroesophageal reflux disease. Rebeprazole Study Group. Am J Gastroenterol. 2000 Nov 1;95(11):3081–8.
55. Birbara C, Breiter J, Perdomo C, et al. Rabeprazole for the prevention of recurrent erosive or ulcerative gastro-oesophageal reflux disease. Rabeprazole Study Group. Eur J Gastroenterol Hepatol. 2000 Aug;12(8):889–97.
56. Bardhan KD, Cherian P, Vaishnavi A, et al. Erosive oesophagitis: outcome of repeated long term maintenance treatment with low dose omeprazole 10 mg or placebo. Gut. 1998 Oct;43(4):458–64.

https://dx.doi.org/10.21037/atm-22-1722