



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

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**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)

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## 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 severe 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

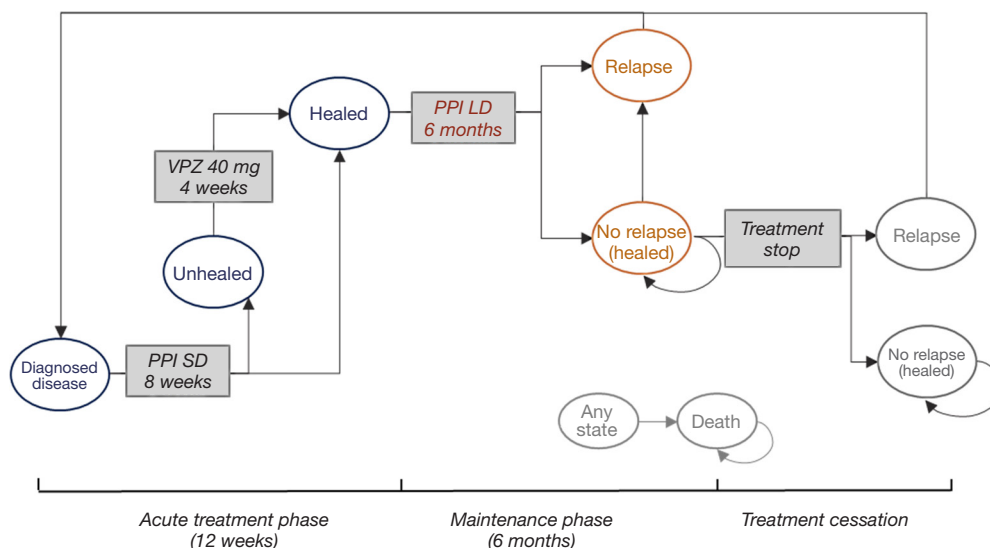
the VPZ 20 mg group at week 4 was higher than that in the LAN 30 mg group at week 8 (at 4 weeks 96.1% *vs.* 90.9%,  $P < 0.05$ ; at 8 weeks 98.9% *vs.* 94.5%,  $P < 0.03$ ) (13). Another phase III study based on an Asian population in which Chinese patients comprised >50% of the total study population, 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**

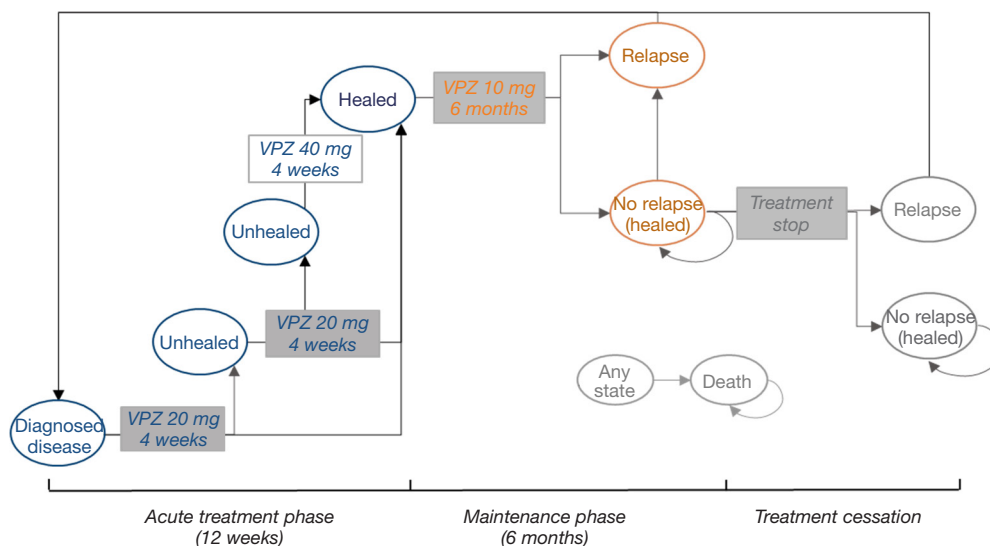
The simulated cohort in the PPI strategy started receiving a standard-dose PPI for 8 weeks. If patients were not healed after initial treatment, continuous therapy on VPZ 40 mg once daily for an additional 4 weeks was added. After

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<sup>®</sup> 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  $\pm 20\%$  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).

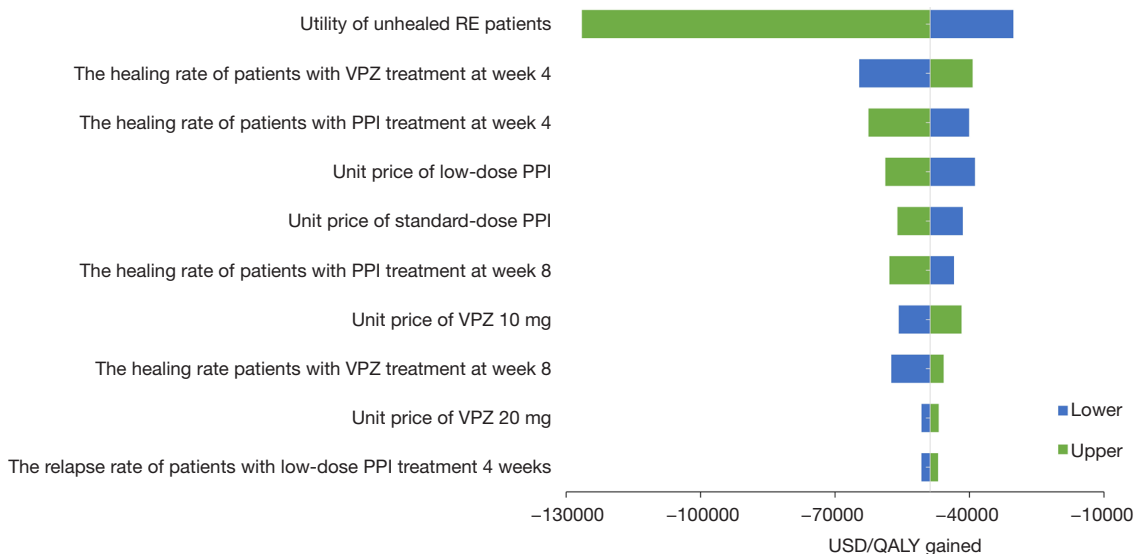
**Sensitivity analysis**

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.

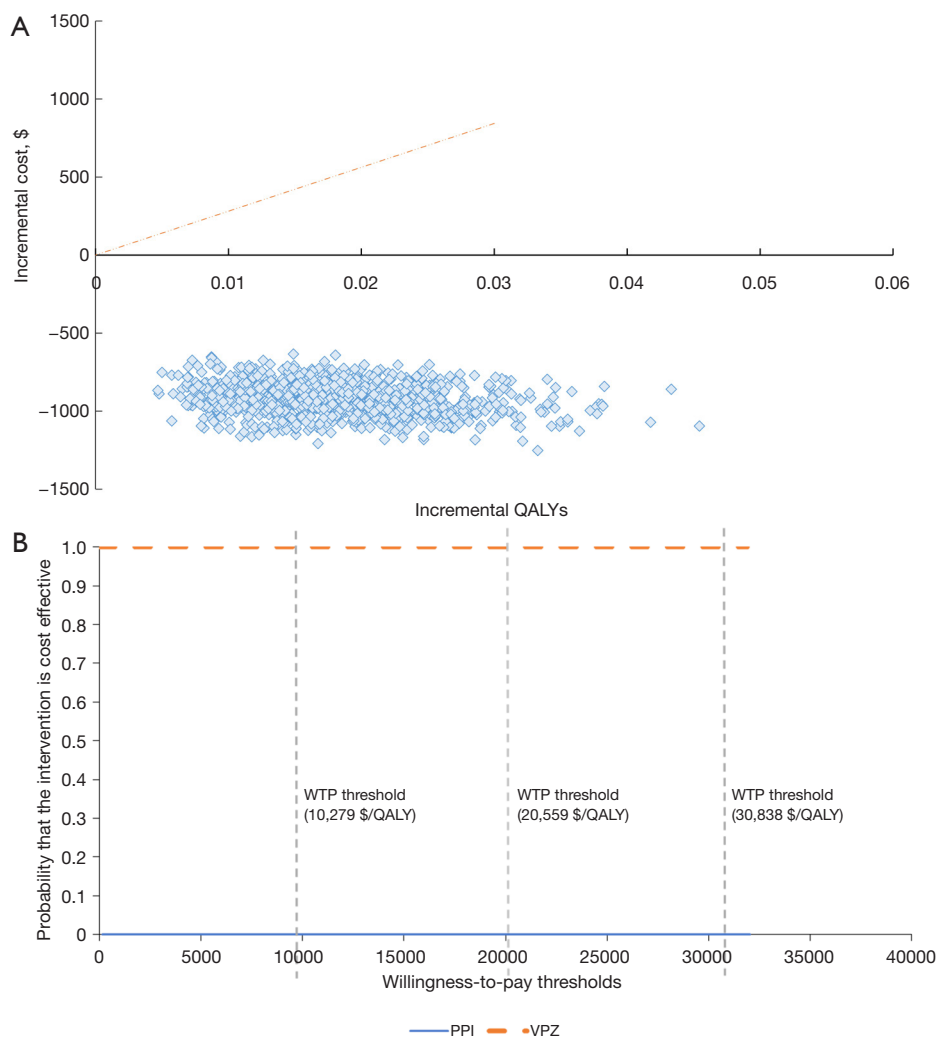
Results of PSA are summarized as a scatter plot in Figure 4A. The acceptability curve in Figure 4B shows that the likelihood of VPZ being considered cost-saving at a WTP threshold of USD30,838 per QALY gained was 100% compared with the PPI group.

**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 assess 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.

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## 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>

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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.

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