【 ORIGINAL ARTICLE 】

Vonoprazan versus Lansoprazole for the Initial Treatment of Reflux Esophagitis: A Cost-effectiveness Analysis in Japan

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Abstract:

Objective   Gastroesophageal reflux disease (GERD) is a highly prevalent disorder that negatively affects patients' quality of life and reduces their work productivity. The medical expenses associated with the treatment of GERD are the highest among all digestive diseases. Current guidelines recommend the administration of a standard dose of proton pump inhibitor (PPI) for eight weeks as an initial GERD treatment. However, there is growing concern regarding the safety of PPI treatment. Recently, a novel potassium-competitive acid blocker (P-CAB), vonoprazan (VPZ), was approved for the treatment of reflux esophagitis in Japan and may provide clinical benefits in GERD treatment. This study was conducted to evaluate the cost-effectiveness of a P-CAB, VPZ vs. a PPI, lansoprazole (LPZ), for the acute medical treatment of reflux esophagitis.

Methods   A clinical decision analysis was performed using a Markov chain approach to compare VPZ to LPZ in the acute treatment of reflux esophagitis in Japan.

Results   The P-CAB strategy was superior to the PPI strategy in terms of cost-effectiveness (direct cost per patient to achieve clinical success) and the number of days for which medication was required. Sensitivity analyses revealed that this superiority was robust within the plausible range of probabilities. This remained true even when the healing rates in cases of mild esophagitis were applied.

Conclusion   The P-CAB strategy was consistently superior to the conventional PPI strategy using the original LPZ in terms of cost-effectiveness and the number of days for which medication was required. Thus, VPZ appears to be the drug of choice for the acute medical treatment of reflux esophagitis.

Key words: cost-effectiveness, gastroesophageal reflux disease, potassium-competitive acid blocker, proton pump inhibitor, reflux esophagitis, vonoprazan

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Introduction

Gastroesophageal reflux disease (GERD) is a highly prevalent disorder that negatively affects a patient's quality of life and reduces their work productivity (1-4). GERD is the most common gastrointestinal-related diagnosis made in office visits, and the costs associated with its treatment substantially contribute to the cost of healthcare in the United States (5).

In comparison to other drugs, proton pump inhibitors (PPIs) have superior effects on symptom resolution and mu-

cosal healing and are more cost-effective (3, 6, 7). Thus, the administration of a standard dose of PPIs for eight weeks is recommended as an initial treatment for GERD (3, 8). GERD is a chronic, relapsing disease. Thus, a long-term management plan is required for each individual patient. PPI maintenance therapy is also efficient, cost-effective and recommended as an option for the long-term management of GERD (3, 8). However, some patients with GERD can remain asymptomatic after the discontinuation of PPIs, and are well controlled by intermittent or on-demand therapy (3, 8-10).

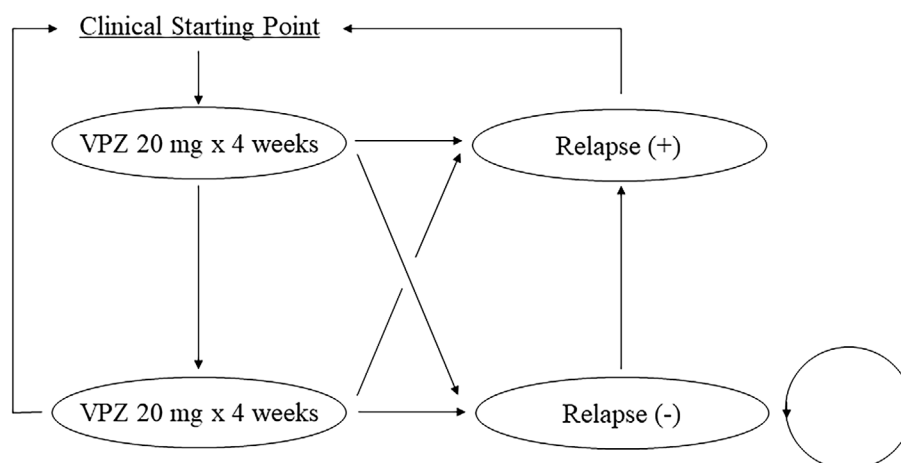Recent studies have linked PPI use to serious adverse ef-

Figure 1.   A schematic overview of the Markov model for the potassium-competitive acid blocker strategy. Circles represent the monthly health states and the treatments that patients underwent. Arrows represent possible probabilistic transitions from one health state to another. VPZ: vonoprazan

fects and safety issues associated with PPI have attracted widespread media and lay attention (11). Although it remains unclear whether PPIs truly cause these adverse effects, this potential has forced physicians to carefully consider the safety and utility of long-term PPI use. This is a topic included in the American Board of Internal Medicine Foundation's Choosing Wisely campaign (12).

Recently, a novel potassium-competitive acid blocker (P-CAB), vonoprazan (VPZ), was approved for the treatment of reflux esophagitis in Japan. VPZ is reported to achieve a more rapid and profound suppression of gastric acid secretion in comparison to PPIs (13). A multicenter randomized trial revealed that the healing rate of erosive esophagitis after four weeks of VPZ treatment (96.6%) was comparable to that of eight weeks treatment using lansoprazole (LPZ), a PPI (95.5%), and demonstrated the remarkably high efficacy of VPZ (14).

Today, efficacy and safety are not the only parameters of interest for assessing medical technology. Cost also plays an increasingly important role in most health care systems. However, simple reliance on the list price of medicine may be misleading and pharmacoeconomic analyses are required to enable prescribers and patients to make an appropriate choice from their available treatment options. This study describes a clinical decision analysis, appropriate for comparing a P-CAB, VPZ and a PPI, LPZ for the acute medical treatment of reflux esophagitis in Japan. The perspective chosen is that of the overall health care budget, implying that direct medical costs are taken into account. Patients' clinical outcomes are described in several ways.

Materials and Methods

Clinical starting points and strategies

The principal decision considered in this analysis is the decision to treat endoscopically verified uncomplicated reflux esophagitis patients with either VPZ (P-CAB strategy) or LPZ (PPI strategy).

Structure of the analysis

The analysis was performed using a decision tree-based state transition model (Markov chain approach) (15). This type of model allowed for a simulation of how patients pass from one health state to another over an extended period of time after initial treatment. Each health state (a four-week period) was assigned several clinical effects, such as the total number of days without esophagitis (disease-free days) and direct medical costs in relation to the health services provided in each state. For every four-week period, the probability of being in a particular state was multiplied by the associated clinical effects and costs. The resultant products for all states were summed and then added to the effects and costs of the previous four weeks. The chains were extended to a 12-month period to estimate clinical effects and costs for 1 year after each initial treatment strategy. Two Markov chains, one for each treatment strategy are shown in Figs. 1 and 2. Table 1 shows the transition probabilities describing the incidence of events with regard to the clinical outcomes.

P-CAB strategy (Fig. 1)

The VPZ package insert stated that the usual treatment period should be up to four weeks, but may be extended for up to eight weeks if the response to the initial treatment course was inadequate for the treatment of reflux esophagitis (16), since a phase III trial reported that the healing rate of erosive esophagitis after four weeks of VPZ treatment (96.6%) was comparable to that of eight weeks of LPZ treatment (95.5%) (14). Thus, in this strategy, patients with endoscopically verified reflux esophagitis were initially treated with VPZ (20 mg/day) for four weeks. After four
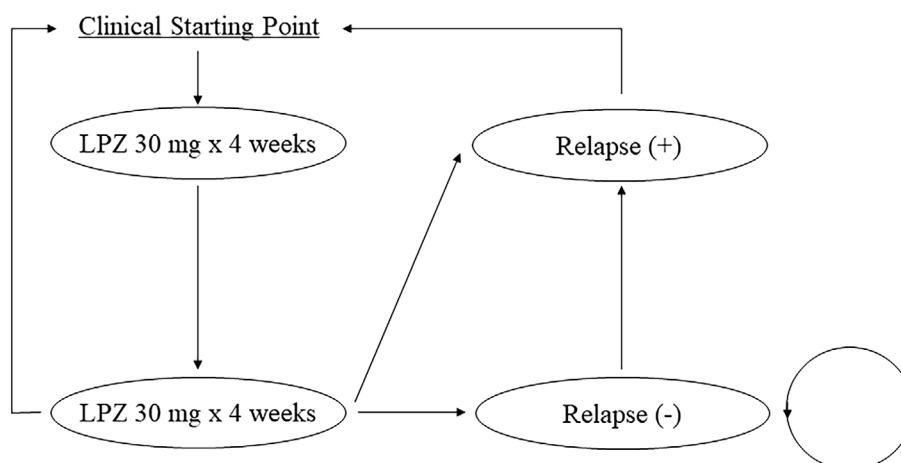
Figure 2. A schematic overview of the Markov model for the proton pump inhibitor strategy. Circles represent the monthly health states and the treatment that patients underwent. Arrows represent possible probabilistic transitions from one health state to another. LPZ: lansoprazole

Table 1. Probability Estimates in the Decision Analysis.

Clinical event or outcome	Probability estimates (Range)	References
Healing rate		(14)
Vonoprazan (20 mg / day)		
4 weeks	0.966 (0.931-0.986)	
cases with grade A/B	0.969	
8 weeks	0.990 (0.965-0.999)	
cases with grade A/B	0.992	
Lansoprazole (30 mg / day)		
4 weeks	0.925 (0.879-0.957)	
cases with grade A/B	0.992	
8 weeks	0.955 (0.916-0.979)	
cases with grade A/B	1	
Relapse after successful healing	0.14 / month (0.075-0.24)	(17 - 21)
Endoscopy to confirm healing	0 (0-0.295)	(23)

weeks of VPZ treatment, healed patients did not require further treatment or follow-up visits, whereas unhealed patients were treated with VPZ (20 mg/day) for another four weeks. After eight weeks of VPZ treatment, healed patients required no further treatment or follow-up visits. Patients who were unhealed after eight weeks of VPZ treatment and patients with symptomatic recurrence after remission went back to the starting point and were treated again.

PPI strategy (Fig. 2)

The current guidelines recommend a standard dose of PPI for eight weeks as an initial GERD treatment (3, 8). Thus, in this strategy, patients with endoscopically verified reflux esophagitis were initially treated with LPZ (30 mg/day) for eight weeks. Patients who were healed after eight weeks of LPZ treatment did not require further treatment or follow-up visits. Patients who were unhealed after eight weeks of LPZ treatment and patients with symptomatic recurrence after remission went back to the starting point and were treated again.

Probability values (Table 1)

The baseline healing probabilities for P-CAB and PPI treatments were obtained from a randomized controlled trial comparing VPZ and LPZ for the treatment of endoscopically confirmed reflux esophagitis [Los Angeles (LA) Classification Grade A-D] in Japan (14). The 95% confidence interval (CI) data and healing rates in mild esophagitis cases (LA Classification Grade A/ B) that were used in the sensitivity analyses were also obtained from this trial.

The rate of relapse after successful healing was obtained from six- to 12-month follow-up studies (17-21). There was

Table 2.   Costs Used in the Decision Analysis.

Type of service	Direct cost (Yen)
Drugs	
vonoprazan 20 mg	201.6
lansoprazole 30 mg	124..8
Treatment	
vonoprazan 20 mg / day x 4 weeks*	6,290
lansoprazole 30 mg / day x 4 weeks*	4,050
Doctor's office visit and physical examination	720
Routine blood tests	3,960
Endoscopic examination	14,500

*involves official charges for prescription and dispensing

Note: one US dollar is equivalent to approximately 110 Japanese yen.

Table 3.   Expected Effects and Costs Per Patient over a 12-months Period.

	P-CAB strategy	PPI strategy
No. of days without esophagitis	298	296
No. of days with medication	65	114
No. of office visits	3.7	5.2
Direct medical costs (Yen)	17,271	20,172
Cost-effectiveness ratio (Yen/day without esophagitis)	58	68

no evidence of a significant difference in relapse rates of healed patients according to the type of acid-suppressing agent (17). Thus, a relapse rate of 0.14 per month, which was the median of the reported probability rates, was used in the base case analysis. Sensitivity analyses were performed within the range of the minimum to the maximum reported probability rates.

Costs

A payer's perspective was chosen for analyzing costs; thus, the analysis only included the direct medical costs reimbursable by the Japanese National Health Insurance system. A list of reimbursable services is summarized in Table 2. The official charges specified by the Japanese National Health Insurance system (as of April 2018) were used in this analysis.

Calculations

The effects evaluated included the total number of disease-free days, the total number of days for which medication was required, and the total number of office visiting days. With regard to the calculation of disease-free days, the healing of esophagitis was assumed to occur according to an exponential function (22). It should be noted that healing probabilities in the analysis were based on the healing rates in a clinical trial where healing was verified by endoscopy. However, in clinical practice, repeated endoscopy cannot be performed in the majority of cases, and patients are usually managed based solely on the relief of symptoms (3, 8, 9). Thus, it was assumed that the healing and recurrence of esophagitis were verified based on the symptomatic state assessed by the physician at the time of office visits in the base case analysis. Endoscopy of the upper gastrointestinal tract has been widely used in Japan and the cost of endoscopy is relatively low in comparison to other countries. A questionnaire survey on the management of GERD in clinical practice, involving 435 physicians in Japan, reported that 29.5% of general practitioners consider endoscopy necessary in the management of GERD (23). Thus, with regard to the

probability of endoscopy to confirm healing, sensitivity analyses were performed within the range from zero to 0.295. It was assumed that there was one office visit for every four weeks during medical therapy. Direct medical costs were also evaluated. Cost-effectiveness ratios were calculated from the cost required to achieve clinical success (healing of esophagitis) per patient. The study model was run for 12 cycles (four-week periods) to simulate a 12-month follow-up period. Discounting was not applied. Sensitivity analyses were performed to assess how the results varied according to the differing probability estimates within an acceptable range of values. All statistical analyses were performed using the Microsoft Excel 2010 software program (Microsoft, Redmond, USA).

Results

Effects

The expected clinical effects for each strategy are presented in Table 3. With regard to the healing of esophagitis, the P-CAB strategy was slightly superior to the PPI strategy. The number of days for which medication was required and the expected number of office visits were fewer with the P-CAB strategy than with the PPI strategy.

Cost-effectiveness

With regard to the expected total direct costs, the PPI strategy was more expensive than the P-CAB strategy over a 12-month follow-up period. The calculated cost-effectiveness ratios showed that the P-CAB strategy was superior to the PPI strategy in terms of cost-effectiveness (Table 3).

Sensitivity analyses

As seen in Table 1, one-way sensitivity analyses regarding the healing probabilities based on the 95% CIs of the efficacy data and relapse rates after healing across the entire range of estimates did not significantly alter the above-described results. The cost-effectiveness advantage of the P-CAB strategy over the PPI strategy was maintained within the entire range of the 95% CIs of the efficacy data (Fig. 3). The superiority of the P-CAB strategy over the PPI strategy in terms of cost-effectiveness remained robust when the healing rates in mild esophagitis cases (LA Classification Grade A/ B) were applied (Fig. 3). Moreover, with regard to
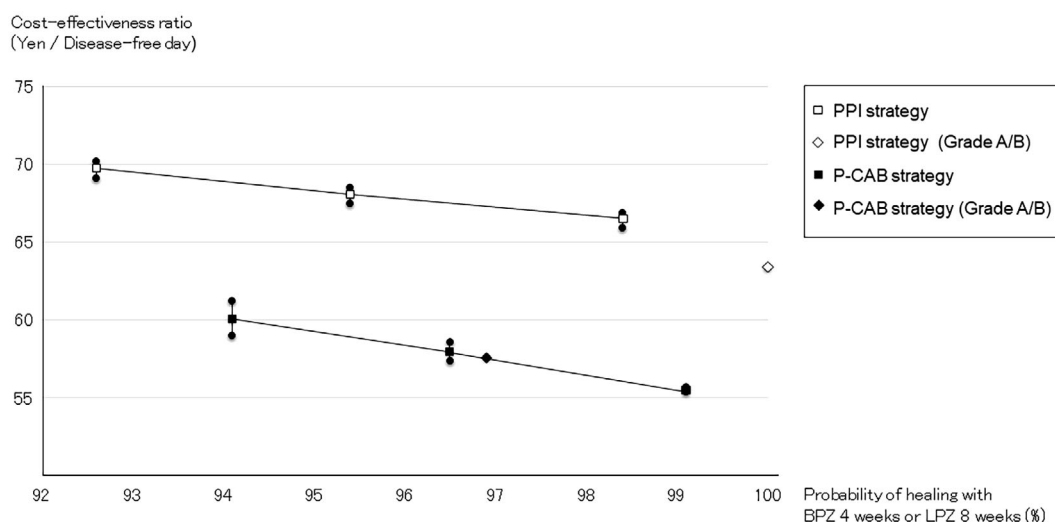
Figure 3. Sensitivity analysis testing the influence of the healing rate achieved with vonoprazan and lansoprazole on cost-effectiveness. Upper and lower limits according to the maximum and minimum probabilities of healing with vonoprazan and lansoprazole based on the 95% confidence interval ranges from a randomized trial, are presented in addition to the base case values. Data based on the results in mild esophagitis cases (Los Angeles Classification Grade A/ B) are also presented. PPI: proton pump inhibitor, P-CAB: potassium-competitive acid blocker, VPZ: vonoprazan, LPZ: lansoprazole
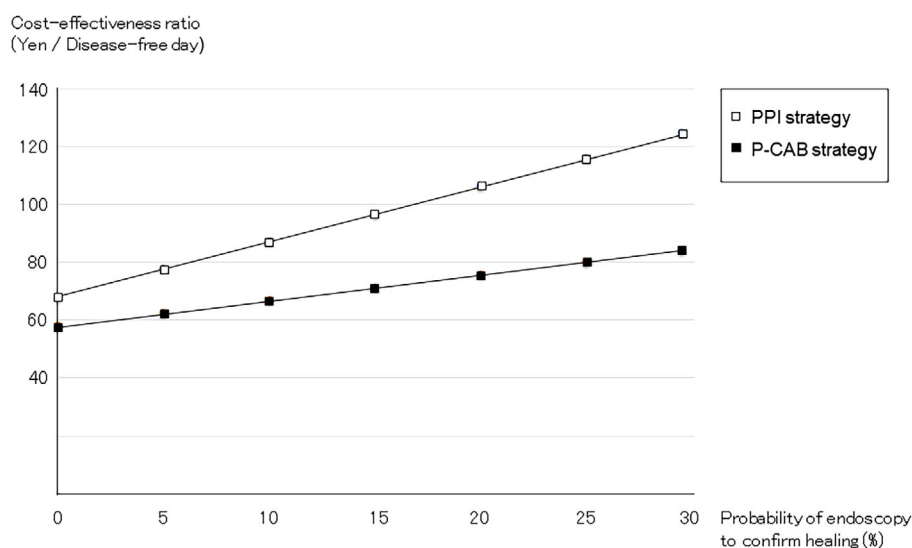

Figure 4. A sensitivity analysis testing the influence of the probability of endoscopy to confirm healing on cost-effectiveness. PPI: proton pump inhibitor, P-CAB: potassium-competitive acid blocker

the probability of performing endoscopy to confirm healing, the cost-effectiveness advantage of the P-CAB strategy over the PPI strategy was maintained within the entire range of estimates (Fig. 4).

Discussion

PPIs have proved to be efficacious and are a mainstay of GERD treatment (3, 6-8). The current guidelines recommend the administration of a standard dose of PPI for eight weeks as an initial treatment for GERD (3, 8). PPIs are among the most commonly prescribed medicines for GERD treatment and are currently ranked in the top 10 medicines for national health-related drug expenditure in the United States (24, 25).

Recently, a P-CAB, VPZ, was approved for the treatment of reflux esophagitis in Japan. A randomized phase III trial reported that the clinical effects of VPZ were stronger and faster in comparison to LPZ, a PPI, which presumably results from its ability to rapidly and strongly suppress gastric acid secretion (13, 14).

There is increasing pressure on today's prescribers to not

only provide effective treatment but also to demonstrate value for money. Thus, comprehensive pharmacoeconomic evaluations based on the results of clinical trials that reflect normal practice are of increasing importance. With regard to PPIs, generic medications are available. Current regulation for generic approval is based on the assessment of average bioequivalence, and very few clinical studies have been reported. Whether approved generic drugs have the same quality and therapeutic effect as the original drug and whether they can be used safely and interchangeably is a matter of concern. Pharmacodynamic studies comparing the acid-suppressive effect of generic PPIs with that of the original PPIs in Japan reported that acid-suppressive effects of some brands of generic PPIs were not the same as those of the original PPIs (26, 27). Moreover, a literature search did not identify any randomized controlled trials comparing generic PPIs to the original PPIs. Thus, in this study, a cost-effectiveness analysis comparing VPZ with the original LPZ for the acute medical treatment of reflux esophagitis under Japanese health insurance scheme was performed.

The aim of reflux esophagitis treatment must include mucosal healing in addition to symptom relief, since leaving patients with an unhealed mucosa seems likely to predispose the damaged structures to continued acid exposure, which carries the risk of esophageal stricture or Barrett's esophagus (3). With regard to the healing of esophagitis, which was used as the chief measure of the clinical effects in this study, the P-CAB strategy was superior to the PPI strategy.

Symptomatic states are also an important measure of clinical efficacy in routine practice. However, a uniform descriptive system for the symptoms of GERD has not been described in the literature and there are no directly comparable data regarding the treatment of GERD symptoms with P-CABs and PPIs. Clinical trials have consistently shown that symptomatic relief usually precedes endoscopic healing, and both symptomatic relief and the healing of esophagitis depend on the degree and duration for which gastric acid secretion is suppressed (28). Based on the assumption that the discrepancies between symptomatic relief and healing are the same for both strategies, the effect regarding the symptom status can be tested by increasing the healing probability in the sensitivity analysis. Since the results of mucosal healing were robust within a broad range of probability estimates, the P-CAB strategy is also suggested to be superior to the PPI strategy with regard to symptomatic relief.

The management of GERD includes other factors in addition to the patient's symptoms. To assess such factors in a clinical setting, the following indices that can be compared quantitatively were identified: the number of days for which medication was required and the number of office visiting days. The P-CAB strategy was superior to the PPI strategy both in terms of the number of days for which medication was required and the expected number of office visits. Moreover, the expected number of days for which medication was required per patient treated with the P-CAB strategy was only 57% of that with the PPI strategy. This infor-

mation may be clinically beneficial given the growing concerns regarding the safety of PPIs (11, 12).

Although VPZ is more expensive in terms of daily use than LPZ, its superior efficacy means that a shorter treatment period is required to achieve clinical success. Consequently, the P-CAB strategy was shown to be less costly and more cost-effective than the PPI strategy. Furthermore, the sensitivity analysis showed that the superiority of the P-CAB strategy over the PPI strategy in terms of cost-effectiveness was robust within the entire range of the 95% CIs of the efficacy data from clinical trials. This was true even when the healing rates in cases of mild esophagitis (LA Classification Grade A/ B) were applied.

The analysis only included direct medical costs because it focused on the effects on the overall healthcare budget. To consider the perspective of society as a whole, it would be desirable to estimate indirect costs, such as lost wages and productivity. Since the P-CAB strategy provides more disease-free days and fewer office visits than the PPI strategy, it is likely that the PPI strategy would be associated with higher indirect costs. Thus, the inclusion of indirect costs would enhance the superiority of the P-CAB strategy over the PPI strategy with respect to cost-effectiveness.

This is the first study to assess the cost-effectiveness of a P-CAB, VPZ for the acute medical treatment of reflux esophagitis. The estimation of the possible clinical and economic impacts of new treatments before practice patterns related to their use are firmly established is one of the challenges of decision analyses for new treatments. This study should help physicians and patients make informed decisions regarding their available treatment options. This study also provides important insights on the cost-effectiveness of GERD treatment and should therefore be of interest to public health payers who make decisions pertaining to formulary and coverage. A limitation of this study is that the study model does not include treatment-related adverse events or discontinuations. However, given that both VPZ and LPZ were similarly well-tolerated, and the reported rates of adverse events and discontinuation were very low in a large-scale clinical trial (14), the costs associated with adverse events would not be an influential or differentiating feature of this study. In addition, like any decision analysis, the results may change if new evidence markedly at odds with the assumptions made in this study were to emerge (29).

In conclusion, this study has shown that the P-CAB strategy was superior to the conventional PPI strategy using the original LPZ with regard to cost-effectiveness and the number of days for which medication was required. Thus, the P-CAB, VPZ, appears to be the drug of choice for the acute medical treatment of reflux esophagitis.

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