J Gastroenterol (2019) 54:1083–1095
https://doi.org/10.1007/s00535-019-01609-2

The Japanese Society of Gastroenterology

ORIGINAL ARTICLE—ALIMENTARY TRACT

Cost-utility analysis of a 'vonoprazan-first' strategy versus 'esomeprazole- or rabeprazole-first' strategy in GERD

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Received: 26 April 2019 / Accepted: 31 July 2019 / Published online: 8 August 2019

Abstract

Background Gastroesophageal reflux disease (GERD) can be treated using a vonoprazan-first strategy (first-line treatment with vonoprazan), or esomeprazole-first/rabeprazole-first strategies (first-line treatment with proton-pump inhibitors [PPIs], esomeprazole/rabeprazole, followed by a switch to vonoprazan). This cost-utility analysis used long-term simulation modeling to evaluate the cost-effectiveness of a vonoprazan-first strategy compared with the esomeprazole-first and rabeprazole-first strategies.

Methods A Markov simulation model was developed to evaluate the cost-effectiveness of vonoprazan-first, esomeprazole-first, and rabeprazole-first strategies, comprising healing and maintenance therapies, over 5 years (4-week cycles). Healing therapy began with the administration of a normal dose of drug per real-world practice. If patients were not healed endoscopically, either a longer duration of healing therapy was provided (vonoprazan), the dose was increased (rabeprazole), or patients were switched to vonoprazan (immediately for esomeprazole, and after dose-escalation for rabeprazole, respectively). Healed patients received maintenance (lower/same dose as healing therapy). Recurrence resulted in re-challenge with healing therapy. Transition probabilities were derived from the results of indirect comparisons (network meta-analysis) and costs calculated from the Japanese payer perspective. Outcomes were defined as quality-adjusted life years (QALYs), with utilities based on published values.

Results Expected costs of the vonoprazan-, esomeprazole-, and rabeprazole-first strategies were ¥36,194, ¥76,719, and ¥41,105, respectively, over 5 years. QALY gains for vonoprazan-first strategy versus the esomeprazole- and rabeprazole-first strategies were 0.014 and 0.003, respectively. Both estimated incremental cost-effectiveness ratios were dominant and robust to two sensitivity analyses.

Conclusions Vonoprazan-first strategy increased QALYs and appeared to be cost-effective for GERD patients

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Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00535-019-01609-2) contains supplementary material, which is available to authorized users.

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compared with the esomeprazole- or rabeprazole-first strategies.

Keywords Cost-utility analysis · Gastroesophageal reflux disease · Proton-pump inhibitor · Vonoprazan

Introduction

Gastroesophageal reflux disease (GERD) is ubiquitous worldwide and evidence suggests an increasing prevalence of this chronic disease, particularly in North America and East Asia [1]. It has been reported in a systematic review that the prevalence of GERD ranges from 18.1 to 27.8% in North America, 8.8–25.9% in Europe, and 2.5–7.8% in East Asia [1].

GERD is characterized by symptoms, such as heartburn and acid regurgitation resulting from the reflux of gastric contents into the esophagus [2]. Although GERD is not life-threatening, its symptoms can have a considerable impact on both the health-related quality of life (QoL) and work productivity of sufferers [3, 4]. For patients with GERD, proton-pump inhibitors (PPIs) are widely recommended as first-line treatment [5, 6]. PPIs are generally effective [7, 8], yet some patients continue to experience ongoing bothersome symptoms, resulting in an impaired QoL and an increased prevalence of anxiety/depression, sleep disorders, and psychological distress [9–11].

Vonoprazan (TAK-438) belongs to a class of acid-inhibitory agents known as potassium-competitive acid blockers (P-CABs) which reversibly inhibit H^+, K^+ ATPase independently of acid pH [12–15]. The P-CAB, vonoprazan, was approved and marketed in Japan in February 2015 for the treatment of acid-related gastrointestinal disorders, including erosive esophagitis (EE), reflux esophagitis (RE) [16–20], and gastric and duodenal ulcers [21, 22], and as an adjunct to *Helicobacter pylori* eradication [23–25]. Phase 2 and phase 3 trials of vonoprazan have recently completed in Europe [26] and Asia [27] in 2018, and there is evidence for increasing clinical use of vonoprazan to treat acid-related diseases in Japan [28].

Vonoprazan has a rapid and sustained acid-inhibitory effect, and is associated with less inter-individual variation in acid suppression compared with other PPI therapy [12, 13, 15, 23, 29]. Clinically, the non-inferiority of vonoprazan to the PPI lansoprazole has been demonstrated in phase 2 and phase 3 studies of Japanese patients with EE-type GERD, when used either as healing or maintenance therapy [30–32]. A recent study has also shown that complete sustained heartburn relief can be achieved sooner with vonoprazan than with lansoprazole [33].

Health economic analyses are important for informing clinicians and payers about the relative affordability of treatments and therapeutic strategies. Therefore, in this cost-utility study, we used long-term simulation modeling to evaluate the cost-effectiveness of a 'top-down' vonoprazan-first strategy compared with two different 'step-up' strategies utilizing PPIs (esomeprazole and rabeprazole) as initial therapy followed by a switch to vonoprazan for non-responding (PPI-resistant) GERD patients. This is the first study to evaluate whether it is more cost-effective to start treatment with PPIs, with vonoprazan reserved for patients with continuing symptoms, or to introduce vonoprazan straight away in patients with symptomatic GERD.

Methods

Model development

A Markov simulation model was developed to evaluate the cost-effectiveness of the vonoprazan-first 'top-down' dosing strategy for symptomatic GERD versus two other PPI-first 'step-up' strategies for esomeprazole and rabeprazole. The analytical model and assumed treatment flows were based on prior research [34, 35], Japanese clinical practice guidelines for GERD [5], regulatory documents, and expert (author) opinion.

A 'top-down' therapeutic strategy was constructed for vonoprazan (Fig. 1a). The base treatment strategy comprised 4 weeks of healing therapy at a dose of 20 mg once daily and, for healed patients, 6 months of maintenance treatment at a dose of 10 mg once daily. Treatment flow was based on the success of healing therapy and recurrence during maintenance. Patients who were healed following 4 weeks of healing therapy with vonoprazan 20 mg once daily progressed to maintenance, while those who are not healed continued on vonoprazan 20 mg once daily for an additional 4 weeks. If patients did not respond to 8 weeks of vonoprazan healing therapy, treatment was stopped. Recurrence during maintenance resulted in the reintroduction of vonoprazan healing therapy for up to 8 weeks. For the other PPI comparators, esomeprazole and rabeprazole, two distinct 'step-up' strategies were developed (Fig. 1b, c). In both cases, the base dosing strategy for the two other PPIs comprised 8 weeks of healing therapy (initial esomeprazole dose, 20 mg once daily; initial rabeprazole dose, 10 mg once daily) and 6 months of maintenance treatment (for healed patients; doses as per healing therapy or lower). For the esomeprazole strategy (Fig. 1b), healed patients who completed 6 months of maintenance therapy at 20 mg once daily without recurrence, received a further 6 months of maintenance treatment at 10 mg once daily. Disease recurrence during

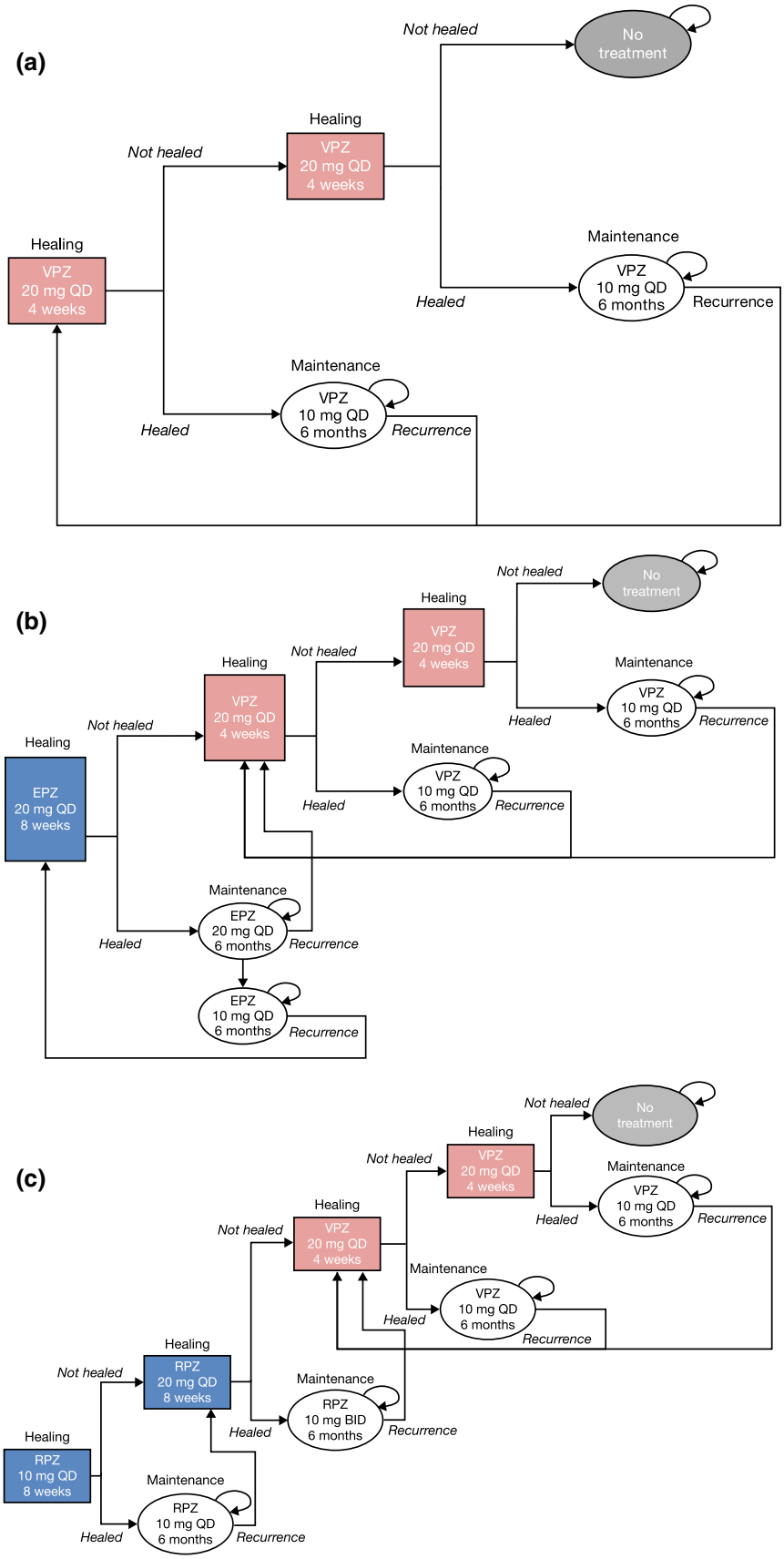


Fig. 1 Overview of model structure **a** 'top-down' vonoprazan strategy; **b** 'step-up' esomeprazole strategy with switch to vonoprazan; and **c** 'step-up' rabeprazole strategy with switch to vonoprazan. A Markov model was used to simulate the therapeutic strategies in 4-week cycles for a period over 5 years. *BID* twice daily, *EPZ* esomeprazole, *QD* once daily, *RPZ* rabeprazole, *VPZ* vonoprazan

maintenance led to the reintroduction of esomeprazole 20 mg once daily healing therapy for 8 weeks (for patients on an esomeprazole maintenance dose of 10 mg once daily, as at the beginning of treatment) or initiation of vonoprazan 20 mg once daily healing therapy for up to 8 weeks (for patients on an esomeprazole maintenance dose of 20 mg once daily). If patients were not healed following 8 weeks' initial healing therapy with esomeprazole 20 mg once daily, they were switched to treatment with vonoprazan, as per the first strategy. For the rabeprazole strategy (Fig. 1c), failure to achieve GERD healing after dosing at 10 mg once daily for 8 weeks resulted in dose escalation to 20 mg twice daily, given for 8 weeks. The dose of rabeprazole maintenance therapy was the same as (10 mg once daily) or half that (10 mg twice daily) at which healing occurred, as shown in Fig. 1c. Recurrence during maintenance at 10 mg once daily led to the reintroduction of rabeprazole healing therapy for 8 weeks at the next dose (20 mg twice daily). If patients were still not healed following treatment with rabeprazole 20 mg twice daily or if they experienced recurrence at the 10 mg twice daily maintenance dose, they were switched to treatment with vonoprazan, as per the first strategy. In all evaluated strategies, it was assumed that all patients started with a clinical and endoscopic diagnosis of GERD and those who completed maintenance therapy without recurrence remained in the same state after cessation of treatment.

All doses and treatment periods for the three medications were based on real-world practices. The overall time frame for the analyses was 5 years (which was considered adequate for the healing and maintenance treatment flow in all evaluated strategies) with cycle lengths of 4 weeks (representing the minimum duration of healing therapy for vonoprazan).

Clinical variables and outcome estimates

Transition probabilities for each drug/dose were derived from the results of published network meta-analysis (NMA) [36, 37], and from Japanese clinical trial data for vonoprazan versus lansoprazole as healing and maintenance treatment for EE (Table 1) [30, 31]. The NMA used an indirect comparison of vonoprazan versus other PPIs to estimate odds ratios for both healing and maintenance therapies in adult patients with GERD [36, 37]**.** Transition probabilities were expressed as the probability of transition to and from endoscopic mucosal healing in RE patients. The transition variables were 'healed' rates for healing therapy (i.e., the percentage of patients who had healed [based on endoscopic investigations] at the end of healing therapy), maintenance rates (i.e., the percentage of patients who remained healed during 6 months' maintenance treatment), and recurrence rates (endoscopic disease recurrence during 6 months' maintenance treatment). While it is expected that rates of healing and maintenance will differ according to when the medications are given along the treatment pathway, the same estimates were used throughout each therapy due to a lack of data showing how the healing and maintenance rates change over the duration of each therapies. Due to insufficient information in the previous NMA for the healing rate of rabeprazole 10 mg once daily and maintenance rate of rabeprazole 10 mg twice daily, we used the healing rate for rabeprazole 20 mg once daily and maintenance rate for rabeprazole 20 mg once daily, respectively, instead.

Costs (in Japanese ¥) were calculated from a Medical Fee Schedule table for healthcare payers in Japan. Drug costs were based on October 2018 prices (Table 2) [38] and were calculated for the duration of treatment by multiplying the unit cost per dose by the number of daily doses and by the number of days of treatment. Additional medical costs included a monthly outpatient treatment fee for all patients during healing and maintenance therapy and the cost of diagnosing disease recurrence (which assumed that a gastroscopy is performed) (April 2018 estimates [39]; Table 2). An annual discount of 2% (95% CI 0–4%) was applied to all costs, in accordance with Japanese guidelines for conducting cost-effectiveness analyses [40].

Clinical outcomes were defined in terms of quality-adjusted life years (QALYs). QALYs were calculated by multiplying the health utility (QoL) of a specific health state (range 0–1, where 1 = perfect health and 0 = death) by the number of years lived in that state. Utility values were derived from the published literature. As utility values based on endoscopic findings were not available, values associated with the presence or absence of RE symptoms were used as an indicator of healing (presence of symptoms, corresponding to the 'not healed' state: 0.56 [95% CI 0.45–0.67]; absence of symptoms, corresponding to the 'healed' state: 0.72 [95% CI 0.58–0.86]) (Table 3) [41].

All authors had access to the study data, and reviewed and approved the final manuscript.

Statistical analysis

Analyses were conducted using TreeAge Pro 2018 software (TreeAge Software, Inc., Williamstown, MA, USA) and Microsoft Excel by CRECON Medical Assessment Inc. (Tokyo, Japan). Incremental cost-effectiveness ratios (ICERs) were calculated for each comparison as the cost per QALY. An ICER of < ¥5 million per QALY (willingness to pay [WTP] threshold) was considered to indicate the cost-effectiveness threshold according to the Japanese ministry guidelines [42].

Table 1 Transition probabilities used in the model

Parameter	Drug and daily dose	Value, %	Plausible range (95% CI)	Distribution[‡]	Source[§]
Rate of healing during healing therapy*	VPZ 20 mg QD (4 weeks)	95.54	90.50–98.00	Log-normal	[31, 36]
	VPZ 20 mg QD (8 weeks)**	56.57	0.00–85.54	Log-normal	[31, 36]
	EPZ 20 mg QD	95.66	92.68–97.46	Log-normal	[31, 36]
	RPZ 10 mg QD***	92.78	85.13–96.65	Log-normal	[31, 36]
	RPZ 40 mg (20 mg BID)	96.23	89.56–98.70	Log-normal	[31, 36]
Maintenance rate during maintenance therapy (per 6 months)[†]	VPZ 10 mg QD	94.95	73.41–99.17	Log-normal	[30, 37]
	EPZ 10 mg QD	64.40	40.73–82.08	Log-normal	[30, 37]
	EPZ 20 mg QD	89.88	77.63–96.05	Log-normal	[30, 37]
	RPZ 10 mg QD	85.57	68.94–94.02	Log-normal	[30, 37]
	RPZ 20 mg (10 mg BID)[††]	93.21	83.16–97.57	Log-normal	[30, 37]
Recurrence rate (per 6 months)	VPZ 10 mg QD	5.05	0.83–26.59	Log-normal	Calculated based on maintenance rate
	EPZ 10 mg QD	35.60	17.92–59.27	Log-normal	Calculated based on maintenance rate
	EPZ 20 mg QD	10.12	3.95–22.37	Log-normal	Calculated based on maintenance rate
	RPZ 10 mg QD	14.43	5.98–31.06	Log-normal	Calculated based on maintenance rate
	RPZ 20 mg (10 mg BID)	6.79	2.43–16.84	Log-normal	Calculated based on maintenance rate

BID twice daily, *CI* credible interval, *EPZ* esomeprazole, *QD* once daily, *RPZ* rabeprazole, *VPZ* vonoprazan

*Percentage of patients who are healed (based on endoscopic investigations) at the end of healing therapy

**Healing rate of vonoprazan 20 mg QD at 8 weeks is calculated based on the non-healing rate of vonoprazan 20 mg QD at 4 weeks

***Healing rate of rabeprazole 20 mg QD is used as alternative parameter instead of 10 mg QD because of lack of sufficient information

†Percentage of patients who remain healed during 6 months' maintenance treatment

††Maintenance rate of rabeprazole 20 mg QD is used as alternative parameter instead of 10 mg BID because of lack of sufficient information

‡Distribution is shown for the odds ratio of indirect comparisons

§Each healing and maintenance rate was calculated from the odds ratio of an indirect comparison with placebo based on the rates for lansoprazole in vonoprazan phase 3 clinical trials

Subgroup and sensitivity analyses

Subgroup analysis according to disease severity

A subgroup analysis to investigate the cost-effectiveness of the 'top-down' versus 'step-up' strategies according to GERD severity (Los Angeles grade A/B and grade C/D esophagitis) was undertaken using the same methodology as the base-case analysis.

Sensitivity analyses

A one-way sensitivity analysis to assess the impact of variations in key parameters on incremental costs and QALYs was performed, varying transition probabilities (Table 1), QoL utilities, and the discount rate according to the 95% CI for each value or by ± 20% if the 95% CI was not available/estimable. Results are presented visually as tornado diagrams to summarize how variations in parameters affect the net monetary and QoL benefit. A probabilistic sensitivity analysis with 10,000-time Monte Carlo simulations was also conducted to test the robustness of the results, assuming a log-normal distribution for the transition probabilities, beta distribution for QALYs, and a fixed value for costs. Parameters were varied according to the standard error (SE) for each value or by ± 10% if the SE was not available/estimable. Results are presented visually as cost-effectiveness planes and acceptability curves.

Table 2 Medical expenses

Medical expense	Unit*	Total cost, ¥	Notes
Drug costs − unit cost	VPZ 10 mg	134.0	Prices correct as of October 2018 [38]
	VPZ 20 mg	201.6	
	EPZ 10 mg	70.0	
	EPZ 20 mg	121.8	
	RPZ 10 mg	99.9	
	RPZ 20 mg	190.1	
Drug costs − Healing therapy	VPZ 20 mg QD for 4 weeks	5645	Unit cost × 28 days
	EPZ 20 mg QD for 8 weeks	6821	Unit cost × 56 days
	RPZ 10 mg QD for 8 weeks	5594	
	RPZ 20 mg BID for 8 weeks	21,291	Unit cost × 2 × 56 days
Drug costs − maintenance therapy	VPZ 10 mg QD for 6 months	24,120	Unit cost × 180 days
	EPZ 10 mg QD for 6 months	12,600	
	EPZ 20 mg QD for 6 months	21,924	
	RPZ 10 mg QD for 6 months	17,982	
	RPZ 10 mg BID for 6 months	35,964	Unit cost × 2 × 180 days
Clinic visit	Visit during healing therapy (¥ per 4 weeks†)	730	Fee assumes one clinic visit per month; April 2018 estimate [39]
	Visit during maintenance therapy (¥ per 6 months)	4380	
Recurrence diagnosis	Diagnosis during maintenance therapy	11,400	Assumes that a gastroscopy is performed; April 2018 estimate [39]

BID twice daily, *EPZ* esomeprazole, *QD* once daily, *RPZ* rabeprazole, *VPZ* vonoprazan

*Drug doses are shown as daily doses

†Cost doubles when duration of healing therapy is 8 weeks

Table 3 Utility values used in the model

Parameter	Base case value	Plausible range (%)	Distribution	Sources
Presence of symptoms	0.56	± 20	Beta	[41]
Absence of symptoms	0.72	± 20	Beta	[41]

Results

Base-case analysis

The expected costs of the vonoprazan-, esomeprazole-, and rabeprazole-first dosing strategies in the base model were ¥36,194, ¥76,719, and ¥41,105, respectively, over the 5-year time frame (Table 4). The QALY gain for the 'top-down' vonoprazan-first strategy relative to that of the 'step-up' esomeprazole-first strategy was 0.014. The vonoprazan-first strategy was dominant, less costly, and more effective than the esomeprazole-first strategy. For the

Table 4 Total costs and QALYs associated with the vonoprazan-, esomeprazole-, and rabeprazole-first therapeutic strategies, their differential values, and the ICERs for the comparisons of vonoprazan- versus the two other PPI-based strategies

Treatment strategy	QALYs	Δ QALYs	Cost, ¥	Δ Cost, ¥	ICER
Comparison: VPZ- vs EPZ-first strategy					
VPZ-first	3.401	0.014	36,194	− 40,525	Dominant
EPZ-first	3.387	–	76,719	–	–
Comparison: VPZ- vs RPZ-first strategy					
VPZ-first	3.401	0.003	36,194	− 4,911	Dominant
RPZ-first	3.398	–	41,105	–	–

Δ difference, *EPZ* esomeprazole, *ICER* incremental cost-effectiveness ratio, *QALY* quality-adjusted life year, *RPZ* rabeprazole, *VPZ* vonoprazan

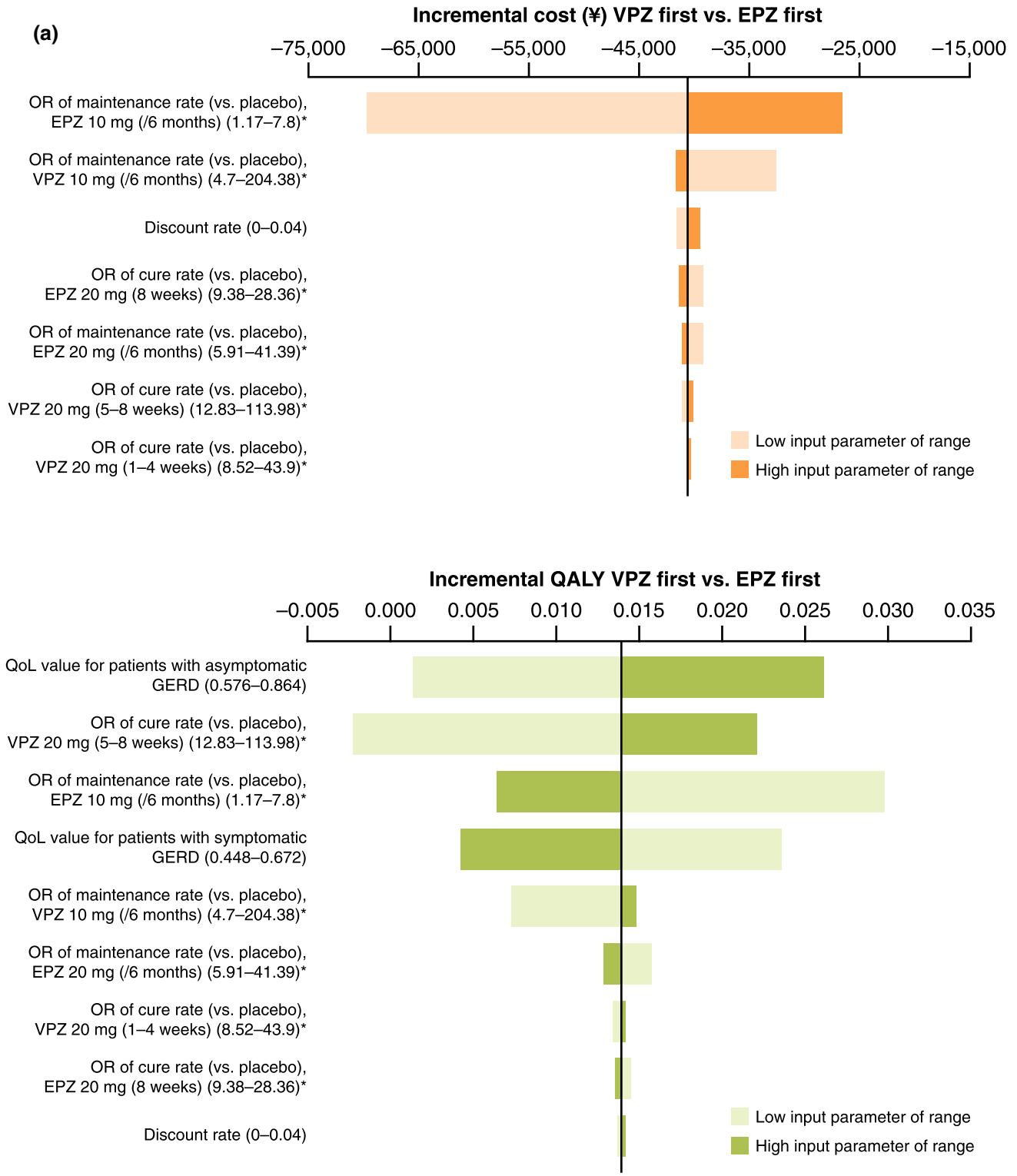


Fig. 2 One-way sensitivity analyses: incremental costs and QALYs for the comparison of the 'top-down' vonoprazan strategy with the **a** 'step-up' esomeprazole strategy and **b** 'step-up' rabeprazole strategy. The parameters on which one-dimensional sensitivity analysis was carried out are summarized in the tornado diagrams. The widths of the bars represent the range of expected incremental monetary or quality of life benefit. The vertical lines indicate the incremental costs or QALYs calculated without changing parameters (i.e., in the base case analysis). *indicates the setting range of the sensitivity analysis, corresponding to the 95% CI for each value or ± 20% if the 95% CI was not available/estimable. *CI* confidence interval, *EPZ* esomeprazole, *QALY* quality-adjusted life-year; *QoL* quality of life, *RPZ* rabeprazole, *VPZ* vonoprazan

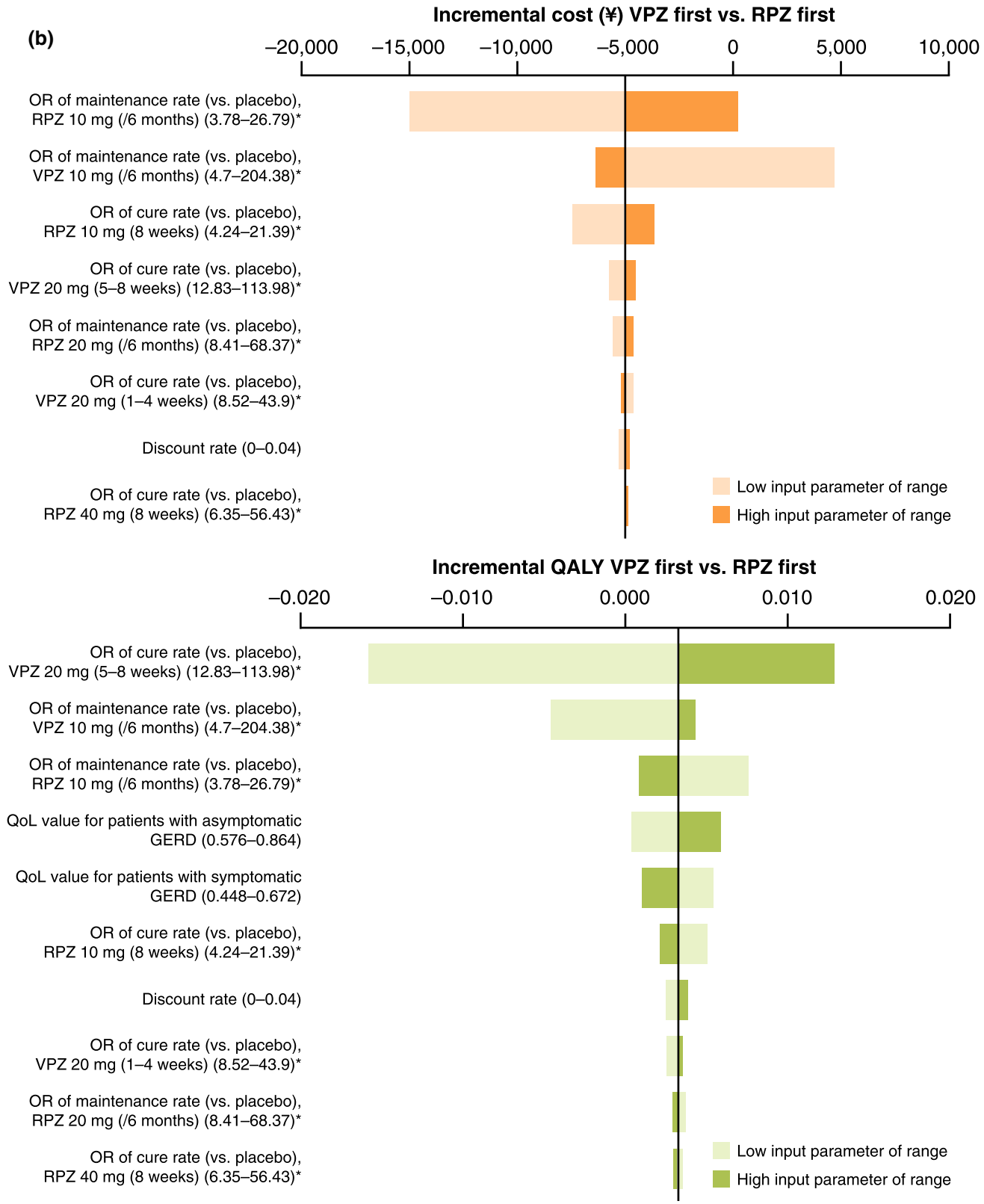


Fig. 2 continued

comparison of the 'top-down' vonoprazan-first strategy versus the 'step-up' rabeprazole-first strategy, the QALY gain was 0.003. Thus, the vonoprazan-first strategy was also dominant over this 'step-up' strategy.

Subgroup and sensitivity analyses

Subgroup analysis according to disease severity

Subgroup analysis of the cost-effectiveness of the 'top-down' versus 'step-up' strategies according to GERD severity (Los Angeles grade A/B vs grade C/D esophagitis) are shown in supplemental Table 1. The expected costs of the vonoprazan- and esomeprazole-first dosing strategies in the base model were ¥36,484 and ¥58,149 for Los Angeles grade A/B esophagitis, and ¥36,385 and ¥56,303 for Los Angeles grade C/D esophagitis (supplemental Table 1). The QALY gain for the 'top-down' vonoprazan-first strategy relative to that of the 'step-up' esomeprazole-first strategy was 0.013 for Los Angeles Grade A/B esophagitis, and 0.012 for Los Angeles Grade C/D esophagitis. The vonoprazan-first strategy remained dominant over the esomeprazole-first strategy for both Los Angeles Grade A/B and C/D esophagitis.

Sensitivity analyses

Results of the one-way sensitivity analysis (Fig. 2), where each parameter was varied by the 95% CI or by ± 20%, showed that the base case was robust with dominance maintained for the vonoprazan-first strategy compared with the esomeprazole-first and rabeprazole-first strategies under each tested scenario. For both comparisons, varying the probability of recurrence at the lowest maintenance dose for other PPIs had the greatest effect on incremental costs and varying the QoL utility values had the greatest effect on incremental health gains (QALYs).

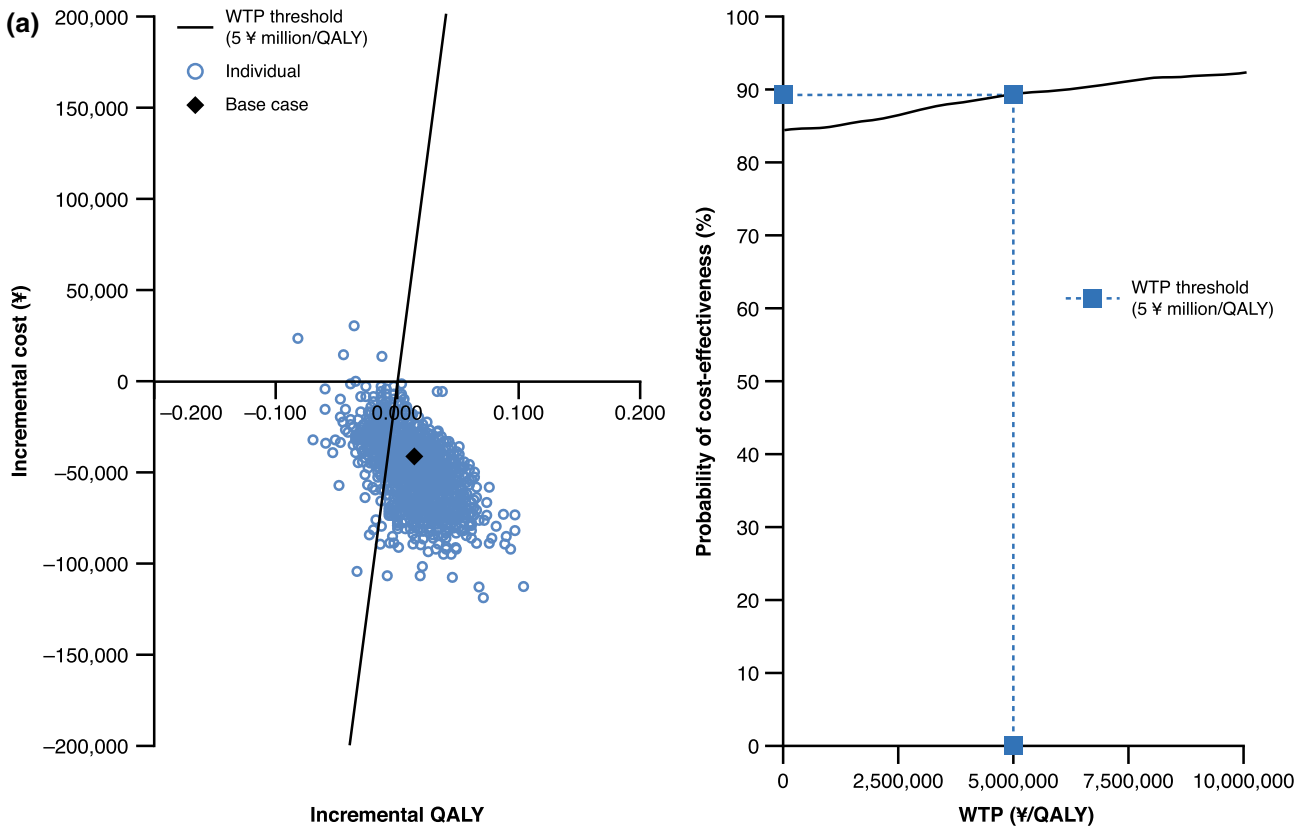
In the probabilistic sensitivity analysis (Fig. 3), 'top-down' vonoprazan-first treatment was dominant in 84.3% and 73.5% of the simulations compared with the 'step-down' esomeprazole- and rabeprazole-first dosing strategies, respectively. The vonoprazan-first strategy remained cost-effective (i.e., below the WTP threshold of ¥5 million per QALY) in 89.0% and 89.5% of the simulations, respectively. The cost-effectiveness planes showed that the vonoprazan-first strategy generated a greater health gain (QALYs) at a lower cost than the two other PPI-based strategies.

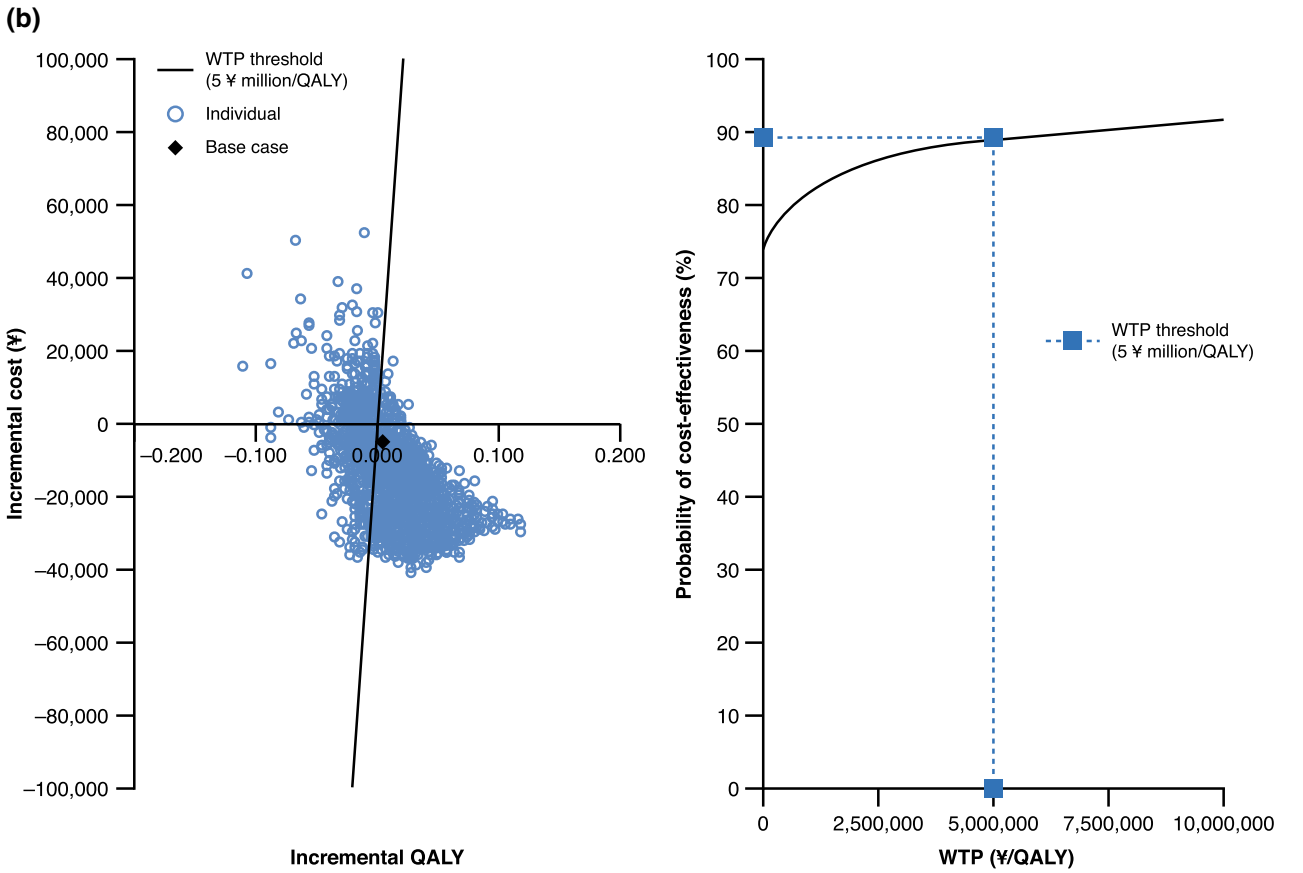
Discussion

This cost-utility analysis showed that application of a 'top-down' strategy for RE patients using the P-CAB, vonoprazan, is cost-effective compared with 'step-up' strategies using the PPIs, esomeprazole or rabeprazole, as initial treatment followed by a switch to vonoprazan for non-responding patients in Japan. These results were robust to two sensitivity analyses: in the one-way analysis and the probabilistic analysis. The results of the subgroup analysis suggest that treatment with vonoprazan can be considered cost-effective regardless of the severity of esophagitis (Los Angeles grades A/B or grade C/D).

Pharmacoeconomic studies comparing the cost-effectiveness of therapeutic strategies for GERD are limited. A recent analysis, using a similar model structure to the present study, demonstrated the cost-effectiveness of vonoprazan-based healing and maintenance treatment relative to esomeprazole-first therapy from a Japanese healthcare payer perspective [34]. The results were consistent with our findings (the ICER for vonoprazan- vs esomeprazole-first therapy was US$9,700 per QALY), and the strategy that was modeled for vonoprazan formed the basis of that used in the present analysis. A Japanese analysis published in 2005, which used a Markov chain approach, reported the superiority of PPI-first strategy for the acute treatment of RE over a histamine H2-receptor antagonist-first 'step-up' strategy with regard to both efficacy and cost-effectiveness [43]. Recently, a cost-effectiveness analysis comparing vonoprazan and lansoprazole, a PPI, has been published [44]. Our findings now supersede these and indicate the superiority of the 'top-down' vonoprazan strategy over PPI-first strategies using second-generation PPIs, esomeprazole and rabeprazole [45, 46], which are metabolized by minimal CYP2C19 involvement [47].

This economic analysis was subject to limitations. First, the same values for healing and maintenance rates were used throughout each therapy since there was a lack of available data showing how these rates change over the duration of the therapies. Second, only drug costs and medical expenses relating to routine outpatient visits and the diagnosis of recurrence (associated primarily with the gastroscopy procedure) were considered during the healing and maintenance periods, and it is possible that additional healthcare expenditure may have been incurred (e.g., expenses relating to further tests at recurrence). Nonetheless, the sensitivity analyses indicate that the model is robust with low levels of uncertainty. Third, we used conservative estimates for the healing rate of rabeprazole 10 mg once daily and maintenance rate of rabeprazole 10 mg twice daily based on the healing rate for rabeprazole 20 mg once daily and maintenance rate for rabeprazole


(a)
WTP threshold
(5 ¥ million/QALY)
Individual
Base case
Incremental cost (¥)
Incremental QALY
Probability of cost-effectiveness (%)
WTP (¥/QALY)
WTP threshold
(5 ¥ million/QALY)


(b)
WTP threshold
(5 ¥ million/QALY)
Individual
Base case
Incremental cost (¥)
Incremental QALY
Probability of cost-effectiveness (%)
WTP (¥/QALY)
WTP threshold
(5 ¥ million/QALY)

◀**Fig. 3** Probabilistic sensitivity analyses: cost-effectiveness planes and acceptability curves for the comparison of the 'top-down' vonoprazan strategy with the **a** 'step-up' esomeprazole strategy and **b** 'step-up' rabeprazole strategy. The left-hand panel shows the cost-effectiveness plane, which illustrates the incremental costs (vertical axis) versus incremental QALYs (horizontal axis) for the individual 10,000-time Monte-Carlo simulations. The diamond represents the base case analysis and the solid line represents the Japanese WTP threshold of ¥5 million per QALY. The right-hand panel shows the cost-effectiveness acceptability curve, which plots the probability of cost-effectiveness (vertical axis) against a range of WTP cost-effectiveness thresholds (horizontal axis). The dotted vertical lines represent the probability of cost-effectiveness at the WTP threshold of ¥5 million per QALY. *QALY* quality-adjusted life-year, *WTP* willingness to pay

20 mg once daily, respectively. Fourth, the three medications included in this study were restricted to branded drugs used in current clinical practice; of these, only rabeprazole had an approved generic version. The cost of generic drugs varies widely and, coupled with clinician and patient preferences, it is a challenge to build a model to encompass generic options. Notably, the parameters used in the study were derived from a previous NMA that involved only branded drugs [36, 37]. Further analysis considering generic drugs, including lansoprazole, will nevertheless be required to show the cost-effectiveness of real-world treatment options for GERD. Lastly, differences in cost-effectiveness between the two strategies according to the severity of GERD symptoms were not analyzed in our study, due to an insufficient number of trials that reported on the outcomes. There were no standardized measures for assessing GERD symptoms, however, a questionnaire evaluating the severity of GERD symptoms and their impact on the patient's daily life has been recently developed [48, 49].

In conclusion, this health-economic analysis demonstrates that 'top-down' vonoprazan-first treatment is a cost-effective therapeutic strategy for symptomatic GERD in Japan. These findings will be informative for Japanese payers evaluating the affordability of acid-suppressing therapeutic strategies for GERD.

Acknowledgements The authors would like to thank Kazuo Ueda, PhD, at the time employed by Takeda Pharmaceutical Co., Ltd., for his contribution to the study design and interpretation of the data. Support in the data analyses was provided, under the direction of the authors, by Sachie Inoue, PhD, an employee of Crecon Medical Assessment. Writing support was provided by Mark Richardson, on behalf of FireKite, and Sabah Farooq of FireKite, an Ashfield company, part of UDG Healthcare plc, during the development of this manuscript, which was funded by Takeda Pharmaceutical Co. Ltd. (Tokyo, Japan), and complied with Good Publication Practice 3 ethical guidelines (Battisti et al., *Ann Intern Med.* 2015;163:461–464).

Author contributions YY: Study conception and design, interpretation of the study data and data analysis, critical revision of the paper, approved the final draft submitted. AI: Study conception and design, interpretation of the study data and data analysis, critical revision of the paper, approved the final draft submitted. AU: Study conception and design, data collection and assembly, interpretation of the study data and data analysis, critical revision of the paper, approved the final draft submitted. HD: Study conception and design, critical revision of the paper, approved the final draft submitted. TT: Interpretation of the study data and data analysis, critical revision of the paper, approved the final draft submitted. KH: Study conception and design, interpretation of the study data and data analysis, critical revision of the paper, approved the final draft submitted.

Funding For this research was provided by Japan Medical Affairs, Takeda Pharmaceutical Company Limited, Tokyo, Japan.

Compliance with ethical standards

Conflict of interest Ataru Igarashi received consulting fees from Novartis Pharma K. K., AbbVie GK, Milliman, Sony Inc., and Eli Lilly Japan K. K., and lecture fees from Chugai Pharmaceutical Company, Ltd., CRECON Research and Consulting Inc., Terumo Corporation, Bristol-Myers Squibb K. K., and Creativ Ceutical K. K. Ataru Igarashi also received research grants from Pfizer Japan Inc., CSL Behring Japan Inc., Gilead Science K. K., and Fuji Film K. K. Akihito Uda and Hisato Deguchi are employees of Takeda Pharmaceutical Company Ltd. Toshihisa Takeuchi received honoraria from AstraZeneca K.K., Daiichi Sankyo Company, Ltd., and Takeda Pharmaceutical Company, Ltd. Toshihisa Takeuchi also received research funding from AstraZeneca K.K. Kazuhide Higuchi received research honoraria and research funding from Takeda Pharmaceutical Company, Ltd., Otsuka Pharmaceutical Company, Ltd., AstraZeneca K.K., Daiichi Sankyo Company, Ltd., and Eisai Company, Ltd. Yuta Yokoya has no conflicts of interest to declare.

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