Cost-effectiveness Analysis Comparing Vonoprazan-based Triple Therapy with Proton Pump Inhibitor-based Therapy in the Treatment of *Helicobacter pylori* Infection in Thailand

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ABSTRACT

Objective: *Helicobacter pylori (H. pylori)* infection is one of the leading causes of gastrointestinal diseases such as dyspepsia, peptic ulcers. Thailand has a 45.9% prevalence of the infection and an increasing rate of resistance to clarithromycin, leading to standard treatments being less successful. Vonoprazan represents a novel drug offering a new treatment regimen. Although vonoprazan has been available in Thailand since 2019, its cost-effectiveness has not been studied previously.

Materials and Methods: This study analysed the cost-effectiveness of vonoprazan-based triple therapy compared with PPI-based therapy, in treating clarithromycin resistant *H. pylori*, by using the markov model from a societal perspective.

Results: The total cost of vonoprazan-based triple therapy, levofloxacin-PPI based triple therapy and concomitant-PPI therapy were 784,932.08 baht, 783,863.65 baht and 783,874.55 baht respectively. The quality-adjusted life years (QALYs) of vonoprazan-based triple therapy, levofloxacin-PPI based triple therapy and concomitant-PPI therapy were 25.1118 years, 25.1147 years and 25.1054 years respectively. The cost-effectiveness ratio (CER) of vonoprazan-based triple therapy, levofloxacin-PPI based triple therapy and concomitant-PPI therapy were 31,257.50 baht/QALYs, 31,211.35 baht/QALYs and 31,223.34 baht per QALYs respectively.

Conclusion: Therefore, levofloxacin-PPI based triple therapy was found to be the most cost-effective regimen and the dominant strategy compared with concomitant-PPI or vonoprazan-based triple therapy. It provided higher QALYs and lower treatment costs. Levofloxacin-PPI based triple therapy should be the first choice of an alternative strategy in treating clarithromycin-resistant *H. pylori*. The results of this study can be used by policymakers to help inform their decisions.

Keywords: Cost-effectiveness; Vonoprazan; Proton pump inhibitors; Levofloxacin; Concomitant; *Helicobacter pylori infection* (Siriraj Med J 2021; 73: 823-831)

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INTRODUCTION

Helicobactor pylori (H. pylori) is one of the leading causes of gastrointestinal diseases such as peptic ulcers and peptic cancer. This bacterium was found in the gastrointestinal tract of more than 90% of peptic ulcer patients. The worldwide prevalence of *H. pylori* infection is about 66%. The prevalence in developing countries is significantly higher than in developed countries. At present, Thailand has a 45.9% prevalence of infection.[1] The incidence of infection in the Bangkok metropolitan region is 74%, of which 50-80% are infections in adults.[2] For the treatment of *H. pylori* infection, the Thailand Consensus on *Helicobacter pylori* Management 2015 recommended using standard PPI-based triple therapy for the first regimen, including a proton pump inhibitor and 2 antibiotics for 7-14 days. However, the eradication rate of this regimen has since decreased below 80% due to clarithromycin resistance.[3,4]

In the Southeast Asia region, the country with the highest rate of clarithromycin resistance has a resistance rate of 43%, while Thailand's rate is about 14%.[5] In 2017, there was a conference to find new guidelines for *H. pylori* management in Asia called "*Helicobacter pylori* management in ASEAN: The Bangkok consensus report". The conclusion of the report recommended that any countries which have a clarithromycin resistance rate of more than 10% should not use the standard regimen and should switch to other non-clarithromycin regimens instead.[6,7] This was in contrast to the 2015 Thailand Consensus on *Helicobacter pylori* Management's recommendation of only using alternative first-line regimens (sequential therapy and concomitant-PPI therapy) in patients whose first-line regimen therapy had been unsuccessful. Furthermore, the 2017 Bangkok consensus report also recommended using concomitant-PPI therapy over sequential therapy, due to the concern that sequential therapy will have a lower efficacy if *H. pylori* becomes resistant to clarithromycin and metronidazole at the same time. The recommended second-line regimens are levofloxacin-PPI based triple therapy and bismuth quadruple therapy, neither of which use clarithromycin. However, following with the recommendation, bismuth quadruple therapy has limitations of salt form of bismuth and dosage. Therefore, concomitant-PPI therapy and levofloxacin-PPI based triple therapy are more suitable regimens for *H. pylori* infected patients in Thailand.

It is not only drug resistance that affects the treatment of *H. pylori*, but also pH levels in the stomach. Using an anti-gastric acid secretion drug is essential for maintaining stomach pH at 5 and for inhibiting *H. pylori* growth.[8,9] The novel drug Vonoprazan was first used in a new treatment regimen in Thailand in 2019. The mechanism is reversible H_+,K_+-ATPase inhibitor.[10] A meta-analysis study showed that vonoprazan-based triple therapy has an era dication rate almost two-times higher than PPI-based Triple Therapy, especially in clarithromycin resistant *H. pylori* infected patients.[11] Thus, vonoprazan-based triple therapy represents an interesting alternative regimen to eradicate clarithromycin resistant *H. pylori*. Until now there has been no cost-effectiveness study carried out comparing concomitant-PPI therapy, levofloxacin-PPI based triple therapy and vonoprazan-based triple therapy in Thailand. Consequently, the purpose of this study was to assess the cost-effectiveness of vonoprazan-based triple therapy compared with concomitant-PPI therapy and levofloxacin-PPI based triple therapy in the treatment of clarithromycin resistant *H. pylori* infection.

MATERIALS AND METHODS

Study design

This study was a health economic evaluation using a model-based structure and presented humanistic outcomes in quality-adjusted life years (QALYs). The analysis was assessed using cost-effectiveness ratio (CER) and incremental cost-effectiveness ratio (ICER). The perspective of this study was societal. Future costs and utilities were discounted at 3% per year.[12]

Intervention

This study compared three regimes of clarithromycin resistant *Helicobacter pylori* infection treatment, approved for use by the Thailand Consensus of *Helicobacter pylori* Management in 2015. The treatment included vonoprazan-based triple therapy[13] (vonoprazan 20 mg, amoxicillin 750 mg and clarithromycin 250 mg, twice a day for 7 days) , levofloxacin-PPI based triple therapy (levofloxacin 500 mg once daily, amoxicillin 1 g twice daily, and standard dose PPI twice daily for 14 days) and concomitant-PPI therapy (standard dose PPI, amoxicillin 1 g, clarithromycin 500 mg and metronidazole 500 mg, twice a day for 10 days).[3]

Decision model

This study used a Markov model to perform decision analysis through Microsoft Excel 2016. The model was developed from the 2015 Thailand Consensus on *Helicobacter pylori* Management[3] and the *Helicobacter pylori* management in ASEAN: The Bangkok consensus report.[7] This model was validated by two clinical experts in gastrointestinal diseases, to ensure its appropriateness for the treatment of *H. pylori* infection in Thailand. Initially, all patients were in a health status of *H. pylori* infection.

After treatment, patients who returned a negative urea breath test would have their health status recorded as 'successful eradication'. If a positive urea breath test result was returned, the health status was recorded as 'failure from the first regimen state' and the patient would go on to receive hybrid therapy. If a patient in a successful eradication health state suffered a reinfection, they would return to the *H. pylori* infection health state again. Patients in all health status could be changed to the health status of death during the study. The model is demonstrated in Fig 1.

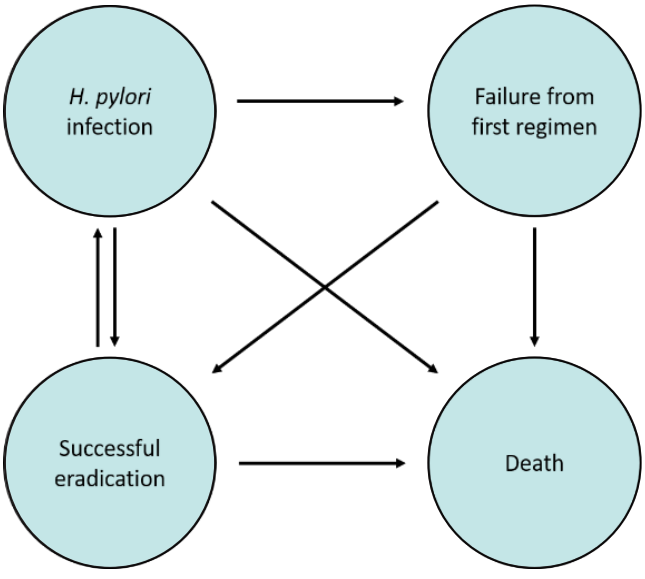

Fig 1. Markov model structure of treatment for patients with *H. pylori* infection

Assumption of the model

1. Patient did not withdraw from any treatment during the study and remained until the end of the treatment.

2. Asymptomatic patients or patients with dyspepsia, who were confirmed to be infected with *H. pylori* and failed from the standard first-line treatment, were recruited.

3. Patients with *H. pylori* infection health status who failed the standard first-line treatment (Amoxicillin, Clarithromycin and PPI[3] and treated by vonoprazan-based triple therapy, levofloxacin-PPI based triple therapy or concomitant-PPI therapy.

4. A successful eradication health status was confirmed by the negative results of a urea breath test conducted at least 4 weeks after treatment.[14,15]

5. Patients whose vonoprazan-based triple therapy, levofloxacin-PPI based triple therapy or concomitant-PPI therapy treatment failed, were switched to a hybrid therapy regimen (standard dose PPI and amoxicillin 1 g for 7 days, followed by a standard dose PPI, amoxicillin 1 g, clarithromycin 500 mg and metronidazole 500 mg twice a day for 7 days) because it is an effective therapy in high clarithromycin resistant areas.[16]

6. No treatment of side effects from any of the regimens (diarrhea and taste disturbance in vonoprazan-based triple therapy[15,17], nausea and diarrhea in levofloxacin-PPI based triple therapy[18], diarrhea and taste disturbance in concomitant-PPI therapy[19-26]) was required as side effects were mild.[27]

7. All patients treated with hybrid therapy regimen were assumed that have successful eradication.

8. The mortality rate of *H. pylori* infection was determined by the age range according to the Thai mortality rate[28] due to *H. pylori* is not a significant risk factor for death from any cause.[29]

Time Horizon

As most previous studies have examined *H. pylori* induced dyspepsia or peptic ulcers in patients aged 18-65 years[19,30], the Markov model used in this study was developed to follow the treatment of *H. pylori* infection over a lifetime, from age 18 until death. In 2020, the average life expectancy in Thailand was 75.7 years.[31] A cycle length of 6 weeks was considered appropriate to cover the period of clinical treatment, adverse drug reactions and *H. pylori* eradication, that was evaluated through the urea breath test at 4-6 weeks after the completion of treatment. *H. pylori* infection could relapse within 1 year.[32]

Probability of clinical outcomes

A systematic search up to September 2020 was conducted in Pubmed, Cochrane library, Science Direct and Scopus databases. The keywords were "Vonoprazan, Levofloxacin triple therapy, Concomitant-PPI therapy, *H. pylori* or *Helicobacter pylori*" with "And" and filtered by randomized controlled trial, meta-analysis, full text and English published literature. Studies were identified as eligible for inclusion if they met the following criteria (i) published in English (ii) randomized control trial, systematic review, or meta-analysis. The studies were excluded if they met any of the following exclusion criteria (i) the outcome was not eradication rate (ii) prevalence of clarithromycin-resistant *H. pylori* was not similar to that found in Thailand (iii) not one of the treatment regimens recommended for use in Thailand (iv) did not analyse eradication rate by intention to treat analysis. All searched literature was evaluated and given a JADAD quality assessment score. The transitional probabilities are shown in Table 1.

TABLE 1. Parameters used in Markov model.

Parameters	Distribution	Mean ± SE	References
Transitional probabilities			
Levofloxacin-PPI based triple therapy			
Success	Beta	0.8481 ± 0.0404	18
Failure	Beta	0.1519 ± 0.0404	18
Relapse	Beta	0.0061 ± 0.0041	32
Vonoprazan-based triple therapy			
Success	Beta	0.7809 ± 0.0310	14, 15, 33
Failure	Beta	0.2191 ± 0.0310	14, 15, 33
Relapse	Beta	0.0061 ± 0.0041	32
Concomitant-PPI therapy			
Success	Beta	0.8286 ± 0.0083	19-26, 34
Failure	Beta	0.1714 ± 0.0083	19-26, 34
Relapse	Beta	0.0061 ± 0.0041	32
Probabilities of side effects			
Levofloxacin-PPI based triple therapy			
Nausea	Beta	0.0253 ± 0.0177	18
Diarrhea	Beta	0.0380 ± 0.0215	18
Vonoprazan-based triple therapy			
Diarrhea	Beta	0.1172 ± 0.0161	15, 17
Taste disturbance	Beta	0.0399 ± 0.0098	15, 17
Concomitant-PPI therapy			
Diarrhea	Beta	0.1639 ± 0.0089	19-26
Taste disturbance	Beta	0.2212 ± 0.0100	19-26
Costs (Baht)			
Medicine costs			
Omeprazole 20 mg (per tablet)	Gamma	0.6245 ± 0.0624	35
Amoxicillin 250 mg (per tablet)	Gamma	6.0432± 0.6043	36
Amoxicillin 500 mg (per tablet)	Gamma	1.7122 ± 0.1712	35
Clarithromycin 250 mg (per tablet)	Gamma	31.0200 ± 3.1020	35
Clarithromycin 500 mg (per tablet)	Gamma	13.5368 ± 1.3537	35
Levofloxacin 500 mg (per tablet)	Gamma	18.1296 ± 1.8130	35
Vonoprazan 20 mg (per tablet)	Gamma	112.6251 ± 11.2625	36
Metronidazole 250 mg (per tablet)	Gamma	0.3324 ± 0.0332	36
Laboratory cost			
Urea Breath Test (per test)	Gamma	3,100.00 ± 310.00	37-39
Gastrointestinal Endoscopy (per test)	Gamma	1,712.24 ± 171.22	40
Biopsy (per test)	Gamma	805.76 ± 80.58	40
Urease (per test)	Gamma	40.29 ± 4.03	40
Treatment and additional procedures			
OPD service (per visit)	Gamma	120.86 ± 12.09	40
OPD prescription (per visit)	Gamma	70.50 ± 7.05	40
Direct non-medical cost			
Travel (per visit)	Gamma	315.49 ± 31.55	41
Food (per visit)	Gamma	63.14 ± 6.31	41
Utility			
H. pylori Infection	Beta	0.9000 ± 0.0006	42
Nausea	Beta	0.6000 ± 0.0500	43
Diarrhea	Beta	0.8970 ± 0.0157	44
Taste disturbance	Beta	0.9410 ± 0.2356	45

Costs

All costs were expressed in Thai Baht and are shown in Table 1. Drugs and laboratory costs were obtained from the drug's median price in Thailand and National Drug Information and the service charge of public health services affiliated with the Ministry of Public Health, Thailand.[35,40] The costs of metronidazole 250 mg, amoxicillin 250 mg and vonoprazan 20 mg, were obtained from the Department of Internal Trade, Ministry of Commerce, Thailand.[36] The urea breath test cost was obtained from 3 hospitals and the mean cost calculated.[37-39] Direct non-medical costs were obtained from the standard cost lists for health technology assessment.[41] All costs were adjusted to 2021 values using the consumer price index from the Bureau of Trade and Economic indices, The Ministry of Commerce, Thailand.[46]

Utility values

The health outcomes were measured in utility weights for different health states and adverse drug reactions, ranging from 0 (death) to 1 (perfect health). Utility weights were multiplied by life expectancy to generate quality-adjusted life-years (QALYs).

Utility values of diarrhea and taste disturbance were estimated based on the disability weights (DW) of diarrhea and taste disturbance from the previous study[44,45] that using the calculation, utility weight = 1-DW. Utility values of *H. pylori* Infection and nausea were obtained from a previous study.[42,43] All utility values are shown in Table 1.

Sensitivity analysis

The one-way sensitivity analysis was performed through Microsoft Excel 2016. The parameter values were changed one by one, usually to a low and a high value. The results are presented in a tornado diagram to demonstrate how a change in the value of one parameter impacts the model results shown as the ICER values. A Monte Carlo Simulation was used for probabilistic sensitivity analysis in Microsoft Excel 2016. All variables were randomized 1,000 times by probability distribution, and the incremental cost-effectiveness ratio (ICER) estimated. The net monetary benefit (NMB) was used to assess the cost-effectiveness in probabilistic sensitivity analyses. The NMB calculation of vonoprazan-based triple therapy compared with proton pump inhibitor-based therapy was formulated as follows[12]

$$NMB = ([QALYs_{\text{Vonoprazan-based triple therapy}} - QALYs_{\text{Proton pump inhibitor-based therapy}}] \times \text{Willingness to Pay [WTP]}) - (Costs_{\text{Vonoprazan-based triple therapy}} - Costs_{\text{Proton pump inhibitor-based therapy}})$$

The results were presented as a cost-effectiveness plane between incremental QALYs and incremental cost, and the cost-effectiveness acceptability curve between probabilities of vonoprazan-based triple therapy and proton pump inhibitor-based therapy, and willingness to pay (WTP).

RESULTS

Cost-effectiveness Analysis

The results in Table 2 show that the total costs of vonoprazan-based triple therapy, levofloxacin-PPI based triple therapy and concomitant-PPI therapy were 784,932.08 baht, 783,863.65 baht and 783,874.55 baht respectively while the quality-adjusted life years (QALYS) were 25.1118 years, 25.1147 years and 25.1054 years respectively. The cost-effectiveness ratio (CER) of vonoprazan-based triple therapy with levofloxacin-PPI based triple therapy were 31,257.50 baht/QALYs, 31,211.35 baht/QALYs and 31,223.34 baht per QALYs respectively. When comparing vonoprazan-based triple therapy with levofloxacin-PPI based triple therapy, the results revealed that levofloxacin-PPI based triple therapy is a dominant strategy because it delivers greater QALYs and has a lower cost. When comparing vonoprazan-based triple therapy with concomitant-PPI therapy, the results revealed that the ICER was 165,239.06 baht per QALYs. When compared levofloxacin-PPI based triple therapy and concomitant-PPI therapy, the results revealed that levofloxacin-PPI based triple therapy was a dominant strategy because of greater QALYs and lower cost.

TABLE 2. Results

Treatment regimens	Total costs (Baht)	QALYs (Years)	CER (Baht/QALY)
Vonoprazan-based triple therapy	784,932.08	25.1118	31,257.50
Levofloxacin-PPI based triple therapy	783,863.65	25.1147	31,211.35
Concomitant-PPI therapy	783,874.55	25.1054	31,223.34

Sensitivity analysis

The one-way sensitivity analysis in Fig 2 is presented in a tornado diagram. The probability of relapse from levofloxacin-PPI based triple therapy had the most impact on the ICER. The probabilistic sensitivity analysis in Fig 3 presents the incremental cost and the QALYs of vonoprazan-based triple therapy compared with levofloxacin-PPI based therapy as a cost-effectiveness plane. Each variable was randomized 1,000 times by the Monte Carlo simulations. The base-case ICER is represented by a yellow dot in the figure and falls in quadrant 2 which mean levofloxacin-PPI based triple therapy was a dominant strategy because of greater QALYs and lower cost. This revealed that levofloxacin-PPI based therapy was more cost-effective than vonoprazan-based triple therapy. Nevertheless, the widely distributed ICERs in the cost-effectiveness plane shows uncertain results.

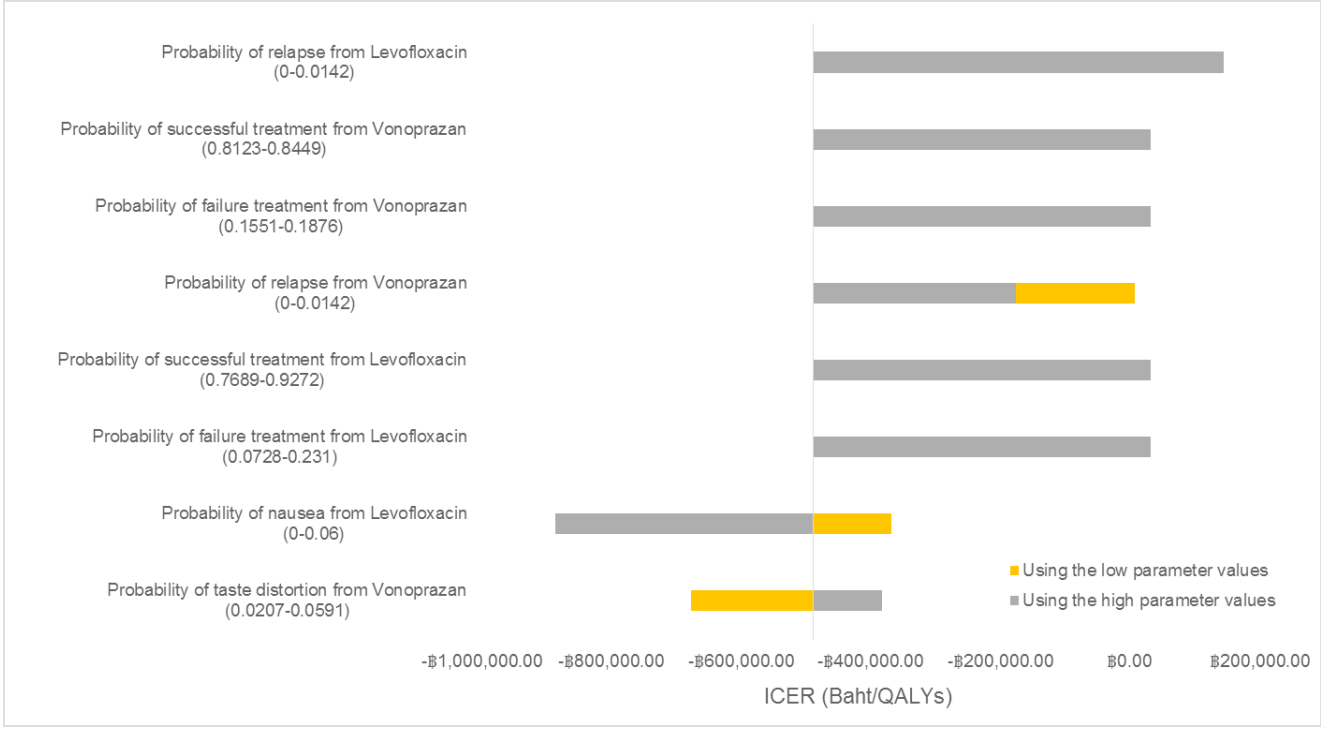

Fig 2. Tornado diagram showing the results of one-way sensitivity analysis

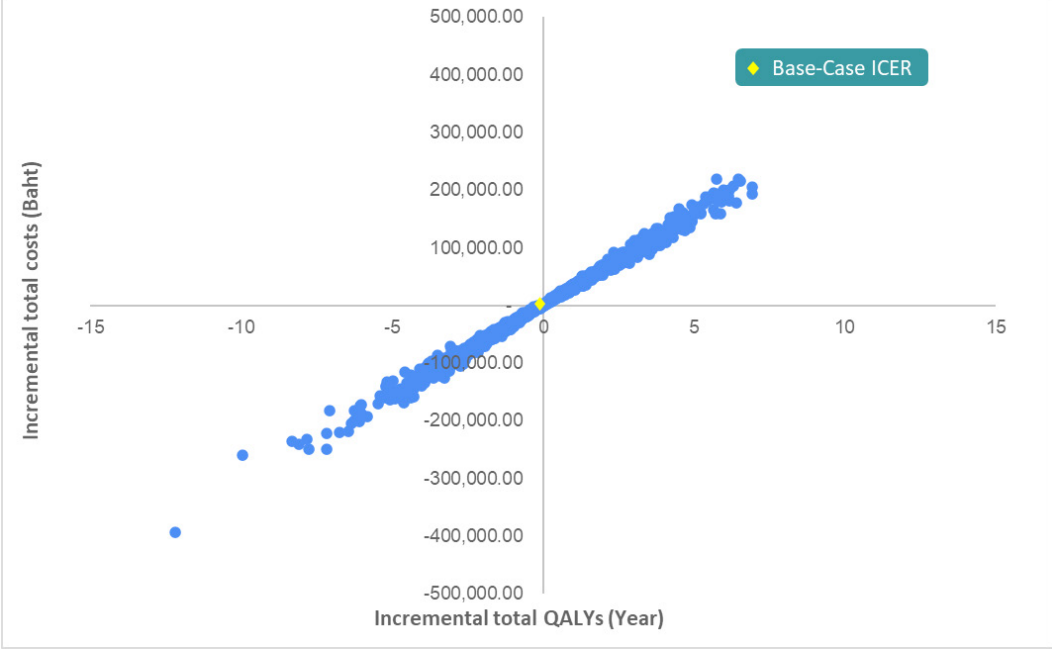

Fig 3. Cost-effectiveness plane between vonoprazan-based triple therapy and levofloxacin-PPI based triple therapy

DISCUSSION

This study is the first economic evaluation of the use of vonoprazan-based triple therapy and proton pump inhibitor-based therapy in clarithromycin-resistant *H. pylori* eradication. An increasing rate of resistance to clarithromycin has led to standard treatments being less successful in Thailand. The results showed that levofloxacin-PPI based triple therapy is the most cost-effective regimen. Although levofloxacin-PPI based triple therapy has a high eradication rate, it also increases the chances of levofloxacin resistance, which is now a reserved antibiotic for the treatment of drug-resistant tuberculosis and other infection diseases. In order to prevent drug resistance, this drug is not widely used.[3] Therefore, vonoprazan-based triple therapy represents an interesting alternative therapy. Although it is not a cost-effective regimen at present, vonoprazan-based triple therapy will become more cost effective if it contributes to an increased eradication rate. A study by Yamasaki T. found that if the dosage of clarithromycin was increased from 400 mg to 800 mg, the eradication rate would be increased from 86.7% to 97.8%[47] and a randomized controlled trial phase 3[15] confirmed that the efficacy of vonoprazan-based triple therapy in clarithromycin resistant *H. pylori* was higher than PPI-based triple therapy. Whereas, a study involving Thai people found that the *H. pylori* eradication rate of vonoprazan-based triple therapy was 63.2%[14], which is lower than that reported in foreign studies. This could be because vonoprazan is mainly metabolized via CYP3A4. As the genes of Thai people may include enzyme enhancers, this would render Vonoprazan-based triple therapy less effective.[48] Therefore, a possible area for further study is to compare the efficacy or the cost-effectiveness of using vonoprazan, with high dose clarithromycin (greater than 800 mg per day). The limitation of this study was scope to focusing on the efficacy of vonoprazan-based triple therapy and the proton pump inhibitor-based therapy. Other factors such as compliance[4] and gastrointestinal pH while taking the drug[49] which could affect the treatment were not considered.

CONCLUSION

Levofloxacin-PPI based triple therapy in clarithromycin-resistant *H. pylori* is a more cost-effective and dominant strategy. It was found to deliver higher QALYs at lower treatment costs from a societal perspective. Levofloxacin-PPI based triple therapy should be the first-choice alternative strategy in treating clarithromycin-resistant *H. pylori*. The results of this study could contribute to informed decision making by policymakers.

This study has been reviewed and approved by the Human Research Ethics Committee of Silpakorn University (COE Number: COE 64.0113-003)

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